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FOREWORD

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Richard Cesati III 11/1/00
PI - Signature Date

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ANNUAL REPORT: October 1, 1999 – September 30, 2000

PRINCIPAL INVESTIGATOR: Richard R. Cesati III

TITLE: Gallium-Containing Estrogens as Receptor-Based Breast Tumor Imaging Agents

ORGANIZATION: University Of Illinois

INTRODUCTION, GOALS OF THE PROJECT AND APPROACH

Radioisotopes of gallium, as the trication Ga^{3+} , are regularly used for medical imaging, and other gallium compounds are being investigated for their potential as radiopharmaceuticals.(1-3) These radiodiagnostic agents consist of ligands chelated to either ^{67}Ga or ^{68}Ga radioisotopes. (4-6) Since the ^{66}Ga and ^{68}Ga isotopes are positron-emitting nuclides with convenient half-lives, we became interested in incorporating gallium into estrogens for imaging of breast tumors by PET.

Breast tumors can be imaged by the binding of appropriately labeled estrogens to the estrogen receptor (ER), which is found in many tumors, and these images provide useful prognostic information concerning cancer stage and tumor responsiveness to hormone therapy. (4,7-12) So far, however, breast tumor imaging through the ER has been accomplished only with a number of radiohalogen-labeled estrogens. The availability of the halogen radionuclides needed to produce these ER-binding agents, however, is limited, either by their short half-lives (e.g., for ^{18}F , $t_{1/2} = 110$ min) or by difficulties in their production (e.g., production of ^{123}I requires high energy cyclotrons). Because ^{66}Ga and ^{67}Ga have relatively long half-lives ($t_{1/2} = 9.4$ h and 3.3 days, respectively) and ^{68}Ga ($t_{1/2} = 68$ min) is available from a long-lived ^{68}Ge ($t_{1/2} = 288$ days) generator, replacing the radiohalogen in these imaging agents with these gallium radionuclides would make them more widely available and might also simplify their preparation.

When gallium is used as the citrate salt of the Ga^{3+} cation, most *in vivo* transport and uptake of this cation is mediated by iron-binding proteins, principally transferrin, because of the similar ionic radii of Ga^{3+} and Fe^{3+} .(13) If undesirable for a given procedure, binding of Ga^{3+} to transferrin can be prevented by the use of high-affinity multidentate ligands, generally hexadentate ones. (14) An alternative form of gallium that has been evaluated for radiopharmaceutical purposes is $(\text{CH}_3)_2\text{Ga}^+$, a cation in which the metal-carbon bonds are highly stable toward hydrolysis.(1,15) The charge and size of this cation apparently make it sufficiently dissimilar to Fe^{3+} to prevent significant binding by plasma proteins.(15) Low affinity for plasma proteins, a tetracoordinate

(rather than hexacoordinate) geometry, and the alkyl ligand environment of the metal suggest that dimethylgallium compounds may be more adaptable to the design of ligands for biological receptors than are multidentate Ga^{3+} complexes.

The highly stable metal-carbon bonds in dimethylgallium hints at further elaboration into actual steroidal and non-steroidal skeletons whereby a single gallium atom would cause minimal perturbation of the estrogenic framework of high affinity ligands. These chemical properties, in combination with the desirable properties of gallium as a radiolabel, should provide an effective means of imaging ER^+ tumors.

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BODY

The following discussion is written as a summary covering the entire three-year research period. The discussion is presented in terms of the four papers that the principal investigator has co-authored during his doctoral research. The first two papers deal with gallium chemistry and the latter two papers cover rhenium and technetium chemistry.

The current research project was designed based upon our initial studies on complexes of the dimethylgallium cation. In this study a number of complexes were prepared by the reaction of dimethylgallium hydroxide with bidentate Lewis bases and then evaluated for their stability towards decomplexation in water, a key property in determining their potential usefulness as radiopharmaceuticals, particularly those targeted at specific receptor proteins. Model compounds from six structural classes, containing bidentate ligands with oxygen-oxygen, oxygen-nitrogen, and sulfur-oxygen donor atoms, were prepared from the ligand and dimethylgallium hydroxide; they were characterized spectroscopically and, in two cases, by X-ray crystallography. The percentage decomplexation of the stable $(\text{CH}_3)_2\text{Ga}^+$ unit from the Lewis base when exposed to 1,000 equivalents of water in acetone- d_6 , determined by ^1H NMR, was used as a measure of the relative hydrolytic stability of each compound. Among the compounds we investigated, the percent hydrolysis under these conditions ranged from 10% to 100%, the most hydrolytically stable compounds proving to be those based on an N-alkylsalicylaldimide donor. Although we were able to make several novel compounds by this strategy, we were unable to obtain any complexes that displayed aqueous stability suitable for in vivo evaluation. In fact, in an unpublished study we were able to prepare our best complexes in radioactive form and demonstrate that not only did these complexes hydrolyze in vivo, but also plasma proteins irreversibly bound the dimethylgallium moiety.

The purpose of the current study was to overcome this undesirable behavior through redesigning the coordination sphere through which gallium is incorporated into the radiopharmaceutical. Over the past three years we have worked diligently to prepare the compounds we designed, but have been unable to incorporate gallium into the ligands we desired. In fact, our synthetic routes to these metallation precursors developed into a powerful methodology for the synthesis of a variety of hexahydrobenzo[*f*]isoquinolines. We have been able to show that through a common cyclization precursor we are able to prepare a variety of heterocycles that contain functional groups, which can be further elaborated. Despite our difficulty in the preparation of the novel gallium complexes, we are still interested in developing a receptor-targeted breast tumor imaging agent which utilizes a metallic radionuclide.

The extensive use of metallic radionuclides in nuclear medicine is dominated by technetium-99m (γ , $t_{1/2} = 6$ h), and radiopharmaceuticals labeled with this isotope are used in approximately 80% of all diagnostic imaging procedures.(16) For tumor radiotherapeutic purposes, rhenium-186 (β , $t_{1/2} = 91$ h) and rhenium-188 (β , $t_{1/2} = 17$ h) have shown great promise.(17,18) Recently, a large number of publications have appeared describing the synthesis of low-valent technetium and rhenium (i.e., $M(\text{CO})_3^+$) and their use for the preparation of new radiopharmaceuticals.(19-24) Our own interest has been focused on the development of novel methods for the generation of stable substituted η^5 -cyclopentadienyltricarbonyl rhenium and technetium (CpTR and CpTT) complexes for radiolabeling biologically interesting molecules, especially small molecule ligands for receptors.

In our ongoing development of the double ligand transfer reaction (DLT), we have extended this methodology toward the direct preparation of cyclopentadienyltricarbonylrhenium (CpTR)-phenyl-tropine conjugates. In the new examples we show, the DLT gives reasonable yields and continues to show broad functional group tolerance. The synthetic utility of this direct synthesis is greater for preparing radioactive rhenium and technetium compounds, where metal incorporation must be close to the final step in the synthesis. Technetium may be predicted to be more reactive chemically, although this is offset with ^{99m}Tc because of the very low concentration of metal under practical conditions of labeling. Initial attempts to synthesize the ^{99m}Tc analog of have in fact shown that high yields of ^{99m}Tc incorporation could be achieved. Of the CpTR-tropine conjugates we have investigated, those substituted at the *N*-8 position seem most promising; their affinity for the dopamine transporter in all cases was high, and their ferrocene precursors can be prepared in a convenient manner. By contrast, the 3β -conjugates were poor DAT binders. The modular nature of these systems, however, allows considerable flexibility, which might be used to further improve the behavior of these compounds.

Impressed by the profile of handling ease, in vivo integrity, and high receptor binding affinity of these CpTR complexes, we desired to develop alternative methods for their synthesis, and to extend their application in breast cancer-related applications. Until recently, the preparation of

these organometallic species has required harsh conditions and multi-step procedures; the DLT reaction described above requires relatively robust substrates.(25) In our final paper, we describe the utility of trialkyltin-substituted cyclopentadienes in the efficient synthesis of substituted CpTR complexes. The reaction is quite complementary to other protocols developed in our laboratories. It is not limited by the need for an electron-withdrawing substituent as in the double ligand transfer reaction, and it does not require the isolation of a reactive cyclopentadienyl source as in the three-component condensation. The reaction can be extended to the use of indenyl ring systems and shows tolerance of a variety of functional groups. The main limitation of the reaction is the yield, which is modest, when the reaction times need to be kept short to achieve efficient radiochemical synthesis with a short-lived radionuclide (e.g., Tc-99m half-life is 6 h). The solvent acetonitrile gives the best yields of CpTR, although this solvent proved to be incompatible with the indenyl ring system. In tetrahydrofuran, the reaction can be carried out in a single pot, and in this solvent it can be extended to more complex systems. We feel that the reaction should provide a very powerful extension of the recent work by Jaouen, who has shown that substituted cyclopentadienes can be produced cleanly by irradiation of cyclopentadienyltricarbonyl manganese complexes. (26)

In summary, our research efforts have lead to a number of discoveries, including new reaction technologies that may prove useful to the design and development of receptor-targeted radiopharmaceuticals. We are focused on advancing the utility of metallic radionuclides in diagnostic imaging and therapy .

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KEY RESEARCH ACCOMPLISHMENTS

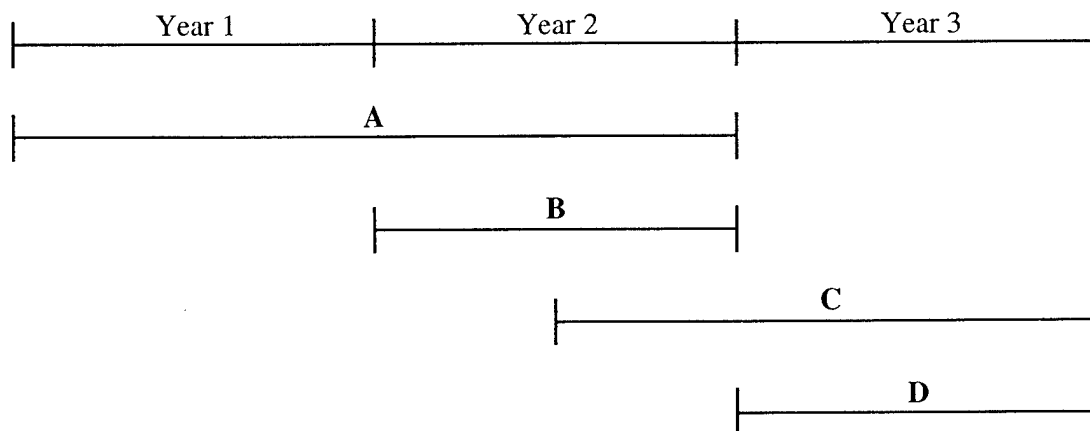
Progress in Relation to the Statement of Work

The complete three year Statement of Work, presented in the original proposal of July 1997, is shown below:

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ORIGINAL STATEMENT OF WORK

Project Period: July 1, 1997– June 30, 2000 (3 years)



Prepare nonradioactive Ga compounds whose structures favor binding with the human estrogen receptor (ER).

- **Task A:** Months 1-24: Develop syntheses for the proposed Receptor-Based Imaging Agents (RBIA's) using non-radioactive ^{69}Ga .

Determine in vitro the estrogenicity of each Ga compound by measuring its Receptor Binding Affinity (RBA) and its non-specific binding.

- **Task B:** Months 13-24: The specific binding of nonradioactive RBIA's to ER will be measured by the standard Receptor Binding Affinity (RBA) assay.

Prepare radiolabeled samples of Ga-containing estrogens that have high RBAs and test their in vitro stability.

- **Task C:** Months 19-36: Synthesis of RBIA's will be achieved by repeating the most efficient techniques from Task A with ^{67}Ga or ^{68}Ga .

Evaluate radiolabeled Ga-containing estrogens as imaging agents for breast tumors.

- **Task D:** Months 25-36: Through our long-standing collaboration with Professor Michael Welch of the Mallinckrodt Institute of Radiology at Washington University Medical School we will evaluate the in vivo tissue distribution of RBIA's with promising in vitro properties.

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It is evident from the results presented in the preceding sections that we have been unable to make further progress in relation to that outlined in the Statement of Work for Year 3. We have shifted our focus during the past year to developing new technologies for the incorporation of rhenium and technetium into receptor-targeted imaging agents. The success of this novel methodology has prompted continued investigation toward its application in systems suitable for breast cancer imaging.

The key outcomes for the third year of this project

- Principal investigator has received his doctoral degree during this past year.
- Three manuscripts describing the completed research have been prepared.
- Completed research has spawned novel application towards breast cancer imaging.

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REPORTABLE OUTCOMES

Manuscripts—The following papers have been prepared during this past year.

Cesati III, R. R. and Katzenellenbogen, J. A. Preparation of Hexahydrobenzo[*f*]isoquinolines Using a Vinylogous Pictet-Spengler Cyclization. *Org. Lett.* Web release date; October 21, 2000.

Cesati III, R. R. and Katzenellenbogen, J. A. One-Pot Formation of Substituted Cyclopentadienyl and Indenyltricarbonyl Rhenium Complexes Through In Situ Generation of Cyclopentadienyl- and Indenyltributylstannanes. *J. Am. Chem. Soc.* In press.

Cesati III, R. R.; Tamagnan, G.; Baldwin, R. N.; Zoghbi, S. S. Innis, R. B.; Kula, N. S.; Baldessarini, R. J. Katzenellenbogen, J. A. Synthesis of Cyclopentadienyl Tricarbonyl Rhenium Phenyl-Tropanes by Methods Applicable to Short-lived Radionuclide Labeling: Organometallic Ligands for the Dopamine Transporter. *Bioconjugate Chem.* Manuscript in preparation.

Degree Obtained—The principal investigator received his doctoral degree on October 13, 2000.

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CONCLUSIONS

Although we failed to achieve all of our goals outlined in the original proposal, we have indeed made significant advances in the organometallic chemistry with which chemists design and synthesize imaging agents which contain metallic radioisotopes. The work reported to date represents the bulk of the research performed by the principal investigator during the course of his doctoral studies. A number of publications have also been generated out of this effort which may prove useful to future endeavors toward organometallic receptor-targeted imaging agents

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APPENDICES

Four-Coordinate Dimethylgallium Compounds Vary in Stability toward Hydrolysis

Robert W. Chesnut,[‡] Richard R. Cesati III,[†] Cathy S. Cutler,[§] Sara L. Pluth,[†] and John A. Katzenellenbogen^{*†}

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Four-coordinate dimethylgallium complexes were prepared by the reaction of dimethylgallium hydroxide with bidentate Lewis bases and evaluated for their stability toward decomplexation in water, a key property in determining their potential usefulness as radiopharmaceuticals, particularly those targeted at specific receptor proteins. Model compounds from six structural classes, containing bidentate ligands with oxygen–oxygen, oxygen–nitrogen, and sulfur–nitrogen donor atoms, were prepared from the ligand and dimethylgallium hydroxide; they were characterized spectroscopically and, in two cases, by X-ray crystallography. The percentage decomplexation of the stable $(\text{CH}_3)_2\text{Ga}^+$ unit from the Lewis base when exposed to 1000 equiv of water in acetone- d_6 , determined by ^1H NMR, was used as a measure of the relative hydrolytic stability of each compound. Among the compounds we have investigated, the percent hydrolysis under these conditions ranged from 10% to 100%, the most hydrolytically stable compounds proving to be those based on an *N*-alkylsalicylaldehyde donor.

Introduction

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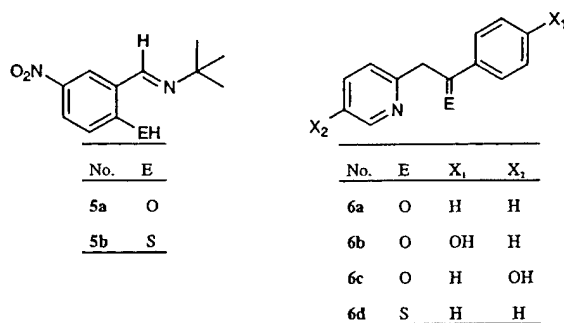
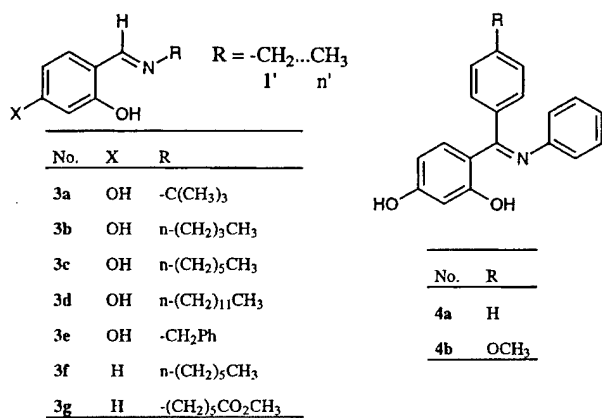
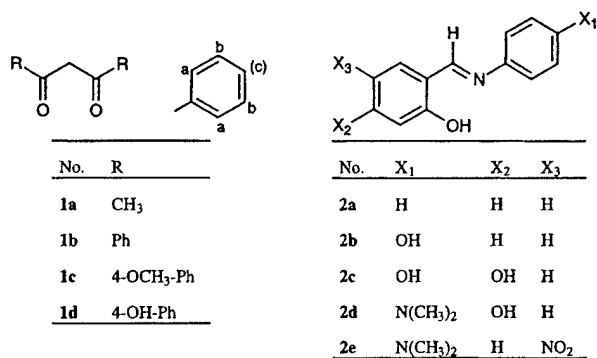


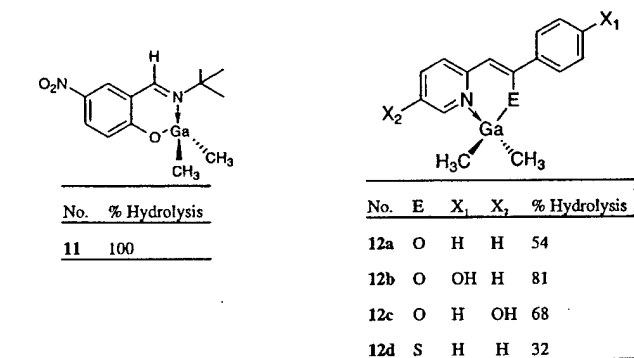
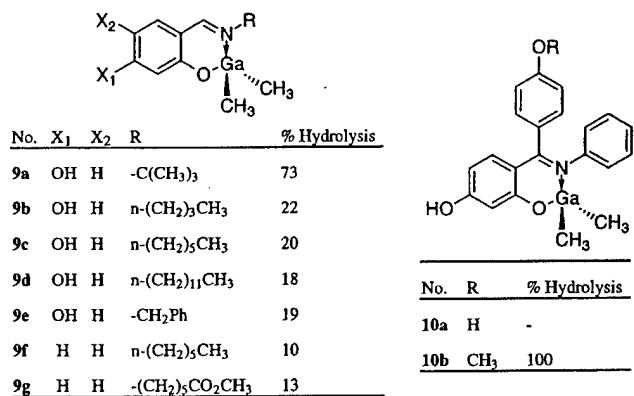
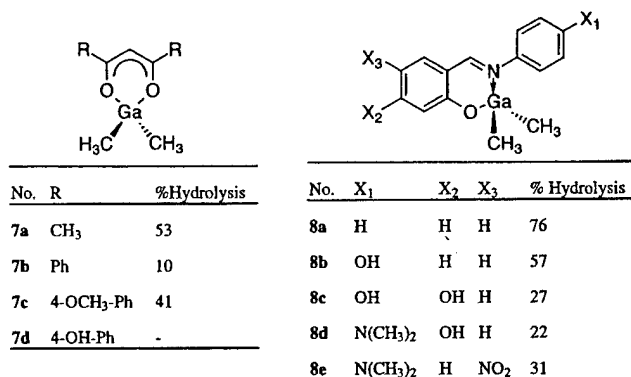
Figure 1. Ligand precursors.

Ga⁺, a cation in which the metal-carbon bonds are highly stable toward hydrolysis.^{1,16} The charge and size of this cation apparently make it sufficiently dissimilar to Fe³⁺ to prevent significant binding by plasma proteins.¹⁶ Low affinity for plasma proteins, a tetracoordinate (rather than hexacoordinate) geometry, and the alkyl ligand environment of the metal suggest that dimethylgallium compounds may be more adaptable to the design of ligands for biological receptors than are multidentate Ga³⁺ complexes.

The goal of this investigation was to prepare a number of tetracoordinate compounds in which the (CH₃)₂Ga moiety is complexed with a bidentate Lewis base and to examine what structural factors affect the stability of these complexes toward decomplexation of the stable (CH₃)₂Ga moiety in the presence of water (i.e., hydrolysis) to determine whether complexes that are stable to hydrolysis can be prepared. Developing stable

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Figure 2. Structure of gallium complexes and percent hydrolysis (after 12–24 h with 1000-fold excess of water in acetone-*d*₆ monitored by ¹H NMR).

gallium-heteroatom bonds rather than stable gallium-carbon bonds proved to be the challenge in this endeavor.

Results and Discussion

Preparation of Ligands and Dimethylgallium Compounds. The six classes of ligands and the six classes of dimethylgallium compounds prepared from them are shown in Figures 1 and 2, respectively. The β -diketonate ligands (1a–d) and their corresponding complexes (7a–d) represent species with two oxygen donor atoms. The *N*-alkylaldimines (2a–e, 5 and 8a–e, 11), *N*-arylalidimines (3a–g and 9a–g), and the related *N*-arylbenzophenonimine analogues (4a,b and 10a,b) are all representatives of N,O-bidentate complexes. Finally, the α -(2-pyridyl)acetophenones and thioacetophenones (6a–d and 12a–d) provide an alternate N,O- and in one case an N,S-chelation geometry. As is mentioned below, the design of several of these

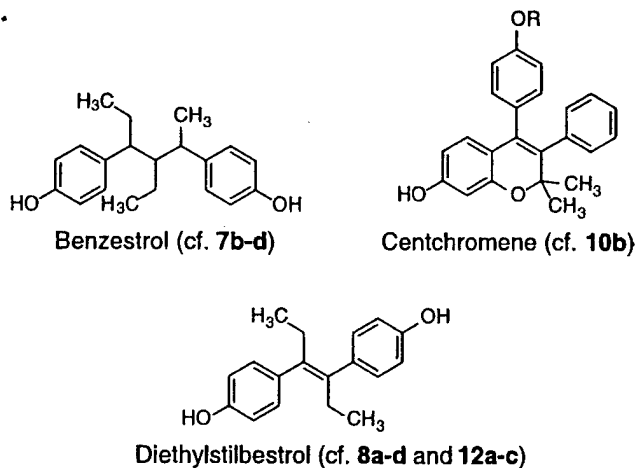
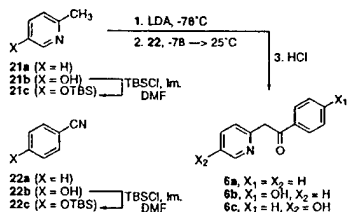


Figure 3. Classes of nonsteroidal estrogens related to dimethyl gallium complexes.

Table 1. Preparation of Gallium Complexes

no.	ligand		(CH ₃) ₂ GaOH			
	mass (mg)	mmol	mass (mg)	mmol	excess (%)	yield (%)
7c	81.3	0.29	35.4	0.30	6	84
7d	23.2	0.09	11.1	0.10	11	74
8a	84.6	0.43	52.7	0.45	6	97
8	81.2	0.38	46.7	0.40	5	100
8d	131.1	0.57	115.3	0.99	70	97
8e	94.8	0.33	63.2	0.54	63	85
9	61.4	0.32	39.4	0.34	6	100
9b	71.7	0.37	45.9	0.39	6	95
9c	72.7	0.33	40.0	0.34	4	92
9d	81.2	0.27	32.4	0.28	5	96
9e	81.8	0.36	45.2	0.39	8	86
9f	64.0	0.31	38.0	0.33	5	100
9g	40.0	0.18	22.0	0.19	4	95
10a	71.6	0.23	28.8	0.25	6	85
10b	122.0	0.38	71.4	0.62	60	76
11	76.1	0.34	42.2	0.36	6	78
12a	115.0	0.58	73.0	0.62	7	97
12b	104.0	0.49	61.0	0.52	6	92
12c	200.0	0.94	117.0	0.99	5	91
12d	50.0	0.23	29.0	0.25	9	89

Scheme 1. Synthesis of α -(2-Pyridyl)acetophenones



gallium compounds was inspired by the structure of certain nonsteroidal ligands for the estrogen receptor (Figure 3). The synthesis of the ligands followed literature precedent or was accomplished using well-precedented methods for aromatic substitution and imine formation reactions. Procedures for the synthesis of new compounds are presented in detail in the Experimental Section and in Scheme 1 and will not be discussed further. The reaction scale and yield of complex formation are given in Table 1.

By all structural comparisons, the dimethylgallium complexes 7–12 are similar to reported compounds. Crystal structures of two of the compounds, the β -diketonate 7c (Figure 4) and the α -(2-pyridyl)acetophenone

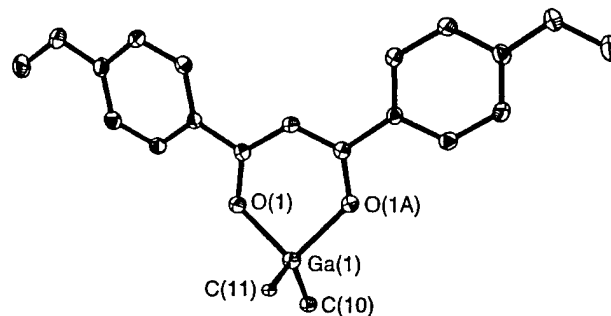


Figure 4. ORTEP plot of β -diketonate compound 7c with thermal ellipsoids at 35%.

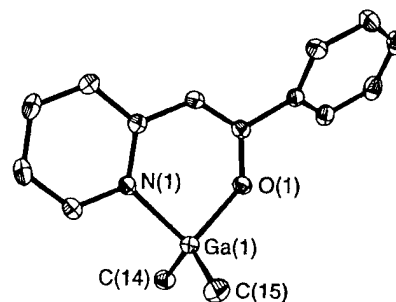


Figure 5. ORTEP plot of α -(2-pyridyl)acetophenone 12a with thermal ellipsoids at 35%.

12a (Figure 5), confirm a four-coordinate environment about the metal and bond lengths to gallium that are similar to those in other known complexes; details are given in Tables 3 and 4.¹⁷ Reflecting the electropositive character of the metal center, NMR spectra of the compounds consistently show the dimethylgallium hydrogens and carbons slightly upfield of TMS. There is, however, remarkably little difference between NMR spectra of the gallium complexes and those of the free ligand and dimethylgallium hydroxide itself. The ¹H NMR resonances of the methyl groups in dimethylgallium hydroxide (δ -0.48) appear at somewhat lower field in the complexes (ca. δ -0.46), the shift in the resonance position of these methyl groups upon hydrolysis of the complex being generally 0.03 ppm downfield. Similarly, the resonances for most of the aromatic and vinylic protons in these systems appear at somewhat higher field in the complexes than in the free ligands; again, the shift is small, ca. 0.05–0.15 ppm. Mass spectra show a peak for the molecular ion (M⁺) or, more commonly, the mass peak resulting from monodemethylation at the gallium center. In either case, the mass peaks corresponding to the two stable isotopes of gallium (⁶⁹Ga and ⁷¹Ga) show the expected relative intensities of 3:2.

Hydrolysis Studies. There are reports that the stability of *trialkylgallium* complexes toward hydrolysis can be improved by intramolecular chelation.^{18,19} There are also qualitative reports of the hydrolytic stability of *dimethylgallium* compounds of the type we studied. For example, dimethylgallium complexes of substituted salicylideneimine and dimethylaminomethyl-3-pyridol-

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Table 2. Crystallographic Details

complex	7c	12a
empirical formula	C ₁₉ H ₂₁ GaO ₄	C ₁₅ H ₁₆ GaNO
fw	383.08	296.01
temp	198(2) K	198(2) K
wavelength	0.710 73 Å	0.710 73 Å
cryst syst	orthorhombic	monoclinic
space group	Pnma	P2 ₁ /n
unit cell dimens	a = 7.915 Å b = 21.0640(4) Å c = 10.5510(2) Å	a = 9.3261(2) Å b = 11.6182(2) Å c = 12.9708(3) Å
volume	1759.08(5) Å ³	1369.14(5) Å ³
Z	4	4
density, calcd	1.446 g cm ⁻³	1.436 g cm ⁻³
abs coeff	1.583 mm ⁻¹	1.997 mm ⁻¹
no. of indep reflns	10688 (R(int) = 0.0384)	8701 (R(int) = 0.0533)
refinement method	full matrix least-squares on F ²	full matrix least-squares on F ²
no. of data/restraints/params	2213/0/115	3297/0/163
goodness-of-fit (GoF) on F ²	1.101	1.124
final R indices (I > 2σ(I))	R1 = 0.0518, wR2 = 0.1420	R1 = 0.0334, wR2 = 0.0652
R indices (all data)	R1 = 0.0635, wR2 = 0.1536	R1 = 0.0496, wR2 = 0.0744

Table 3. Selected Bond Distances and Angles for β-Diketonate Complex 7c

Bond Distances (Å)	
Ga(1)–O(1)	1.921(2)
Ga(1)–C(10)	1.959(4)
Ga(1)–C(11)	2.004(3)
Bond Angles (deg)	
O(1)–Ga(1)–O(1A)	93.89(14)
O(1)–Ga(1)–C(10)	108.88(12)
O(1)–Ga(1)–C(11)	106.43(10)
C(10)–Ga(1)–C(11)	127.2(2)
C(8)–O(1)–Ga(1)	124.4(2)

Table 4. Selected Bond Distances and Angles for α-(2-Pyridyl)Acetophenone Complex 12a

Bond Distances (Å)			
Ga(1)–O(1)	1.899(2)	Ga(1)–C(15)	1.960(3)
Ga(1)–C(14)	1.958(3)	Ga(1)–N(1)	2.027(2)
Bond Angles (deg)			
O(1)–Ga(1)–C(14)	108.99(10)	C(15)–Ga(1)–N(1)	106.40(10)
O(1)–Ga(1)–C(14)	109.78(10)	C(1)–N(1)–Ga(1)	117.4(2)
C(14)–Ga(1)–C(15)	125.71(11)	C(5)–N(1)–Ga(1)	123.3(2)
O(1)–Ga(1)–N(1)	94.10(7)	C(7)–O(1)–Ga(1)	124.0(2)
C(14)–Ga(1)–N(1)	107.13(10)		

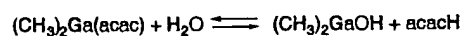
ato ligands are described as "air and moisture sensitive"^{20,21} or "air stable", respectively.^{20,21}

In some quantitative hydrolysis studies of trialkylgallium or dialkylphosphidogallium compounds, the reaction of the complex with small amounts (usually 1 equiv) of water was studied. Aggregated dialkylgallium hydroxides are produced by these reactions.^{22–24} Our experiments were similar, in that [(CH₃)₂GaO]_n was the observed product of hydrolysis; however, our experiments were designed to allow quantitative comparisons of hydrolytic stability in screening for potential radiopharmaceuticals. Thus, in contrast to this earlier work, we added a relatively large quantity of water (1000 equiv) to the gallium compound. Also, the hydroxide product resulted from addition of water across the Ga–

heteroatom bond in our dimethylgallium complexes, rather than from hydrolysis of a Ga–carbon bond in a trialkyl gallium compound.

Because it can be monitored by ¹H NMR, the hydrolysis process can be conveniently followed. Hydrolysis appears to be relatively rapid, and in the cases where the kinetics were followed in some detail, it reached a limiting value within a few hours. So, the extent of hydrolysis was routinely measured after 12–24 h, at which point it had reached an equilibrium value. Because the hydrolysis assay was done at a fixed concentration of dimethylgallium complex (200 mM, see Experimental Section) and a fixed, 1000-fold excess of water, we are measuring the *relative thermodynamic stabilities* of these complexes. The results of the hydrolysis studies on the complexes **7–12** are summarized in Figure 2.

β-Diketonate Compounds 7a–7c. Complexes of this structure were inspired by certain nonsteroidal ligands for the estrogen receptor of the benzestrol class (see Figure 3). Hydrolysis studies on these complexes demonstrated how chelate structure affected hydrolytic stability (see Figure 2). The fact that the published synthesis of **7a** involves an extraction of excess acetylacetonate with a water/diethyl ether system makes (CH₃)₂Ga(acac) appear stable to hydrolysis. By contrast, our measurements show that, in acetone, (CH₃)₂Ga(acac) is more than 50% hydrolyzed by 1000 equiv of water. These observations can be reconciled by the equilibrium



Preferential solubility of (CH₃)₂Ga(acac) in ether and removal of water by bulk partitioning and chemical drying would explain how the unstable (CH₃)₂Ga(acac) can be prepared using an aqueous workup. A second implication of our results is that the *in vivo* distribution of [⁶⁷Ga](CH₃)₂Ga(acac) is probably largely controlled by its hydrolysis product, [⁶⁷Ga](CH₃)₂GaOH.

With identical heteroatom donors, the β-diketonate complexes **7** are a simple model for probing the differences in hydrolytic stability that can result from structural changes distal to the metal (see Figure 2). Electronic influences are most obvious in explaining the relative stabilities of **7a** vs **7b**. Replacing the methyl

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group in **7a** with the more electron-withdrawing phenyl groups in **7b** lowers the basicity and thereby reduces the reactivity of the complexed ligand toward water. Addition of electron-donating methoxy groups in **7c** partially reverses the decrease in basicity and, therefore, increases hydrolytic stability.

N-Arylaldimine Compounds (8a–e). The structure of this class of gallium compounds was inspired by the structure of the nonsteroidal estrogens of the stilbestrol class (see Figure 3). These complexes were the first system in which we separately tuned the basicities of the two different donor atoms of the ligand. Specifically, we designed a series to increase the basicity of the N-donor and decrease the basicity of the O-donor in an attempt to maximize ligand affinity for $(\text{CH}_3)_2\text{Ga}^+$ and minimize reactivity of the dimethylgallium complex toward water. Implementing this trend with substituents generally increased the hydrolytic stability of the compounds (**8a–d**) as desired (see Figure 2). In this series, we used hydroxyl substituents to alter donor atom basicity because estrogenicity, a target property, is often engendered by the phenolic OH functionality.²⁵ The fact that the most acidic oxygen donor ligand (**8e**, bearing a nitro group) did not have the greatest hydrolytic stability suggests that a maximum desirable acidity can be exceeded and that in this ligand the σ -donor character of the oxygen donor toward $(\text{CH}_3)_2\text{Ga}^+$ was diminished.

N-Alkylaldimine Compounds (9a–g). The hydrolytic behavior of these complexes is significant because of the emergence of a new parameter influencing hydrolytic stability. The large hydrolytic labilizing effect of substituting a *tert*-butyl group (**9a**) for an *n*-butyl group (**9b**) is evidence that the bulk of a substituent on the imine nitrogen can compromise hydrolytic stability (see Figure 2). This effect may reflect the relative thermodynamic stabilities of the two complexes. The length of an *n*-alkyl chain, however, had little effect on the reactivity of these compounds (**9b–e**) toward water. Removal of the meta hydroxyl group (**9f**) afforded the most hydrolytically stable member of the series. Addition of an aryl (**9e**) or ester (**9g**) functionality at the ω -carbon did not significantly affect the hydrolytic stability of these complexes.

Approximately the same range of hydrolytic stability is present across series **8** and **9**, but *N*-(*n*-alkyl) groups in complexes **9** stabilize the complexes more than does an unsubstituted *N*-phenyl group in complexes **8**. This difference probably parallels basicity differences at the imine nitrogen. Why a meta OH group should have opposite results on hydrolytic stability in the two series is not clear, however: **8c** (with a *m*-OH) is more stable than **8b**, whereas **9a** (with a *m*-OH) is less stable than **9f**. If these complexes are being stabilized against hydrolysis by formation of micellar structures in which the Ga–O bonds are being sequestered away from water where they are selectively protected from hydrolysis, then micellar destabilization by a polar substituent on the aromatic ring would be understandable.

N-Aryl-Hydroxybenzophenonimine Compounds (10a and 10b). These compounds were prepared because of their similarity to centchromene-type estro-

gens (see Figure 3). The marked hydrolytic instability of **10b** is significant by comparison with that of **8b**. Replacement of the aldimine hydrogen (of **8b**) with a *p*-methoxyphenyl group (as in **10b**) would be expected to reduce the basicity of the imine nitrogen and, consequently, the donor character of the ligand toward $(\text{CH}_3)_2\text{Ga}^+$, increasing its stability, as was observed. Steric crowding in this complex is also expected to twist this phenyl substituent largely out of conjugation with the aldimine.

Compound 11. Complex **11** could be considered in the class of *N*-alkylaldimine complexes (**9**), but was studied separately, for comparative purposes. The low hydrolytic stability of complex **11** is consistent with two earlier observations: (a) the steric crowding caused by a *N*-(*tert*-butyl) group (as in complex **9a**) and (b) the (apparently) low donor character of the *p*-nitrophenoxide ligand (as in complex **8e**). Improvement in stability through a better match of acid/base softness was probed by substituting sulfur for oxygen. We found, however, that the S-donor complex could not be formed from the free thiophenol (**5b**) and $(\text{CH}_3)_2\text{GaOH}$, even in refluxing THF. The sulfur atom may be sufficiently larger than oxygen to cause significant strain in the incipient six-member ring that includes the $(\text{CH}_3)_2\text{Ga}^+$ moiety.

α -Pyridylacetophenone and Thioacetophenone Compounds (12a–d). This system, which provides an alternate geometry for bidentate complexation of the dimethylgallium cation, was systematically modified using hydroxyl groups to probe the effect of increasing the basicity of the N-donor and decreasing the basicity of the O-donor (as was done in the series **8a–d**), in an attempt to maximize ligand affinity for $(\text{CH}_3)_2\text{Ga}^+$ and minimize the reactivity of the complex toward water. However, in contrast to the results in the **8a–d** series, a marked decrease in hydrolytic stability was observed with increasing basicity of the O-donor and decreasing basicity of the N-donor (**12b** and **12c** vs **12a**). Substituting the O-donor for an S-donor increased the acidity of the ligand and hence its σ -donor ability toward $(\text{CH}_3)_2\text{Ga}^+$, affording a somewhat greater stability to this complex (**12d**) than to its oxygen congener (**12a**). The differences in the response of the hydrolytic stability of the dimethylgallium compounds in the series **8a–d** and **12a–c** to hydroxyl substitution could be due to the different paths of conjugation between the hydroxyl groups and the N-, and O-donor atoms in the two complexes, as their structures are rather different.

Conclusion

We have shown that four-coordinate dimethylgallium compounds exhibit marked differences in their hydrolytic stability in the presence of 1000-fold excess of water. In our model systems, stability of substituted salicylideneimine complexes was favored by basicity and steric accessibility of the imine nitrogen. Stability decreased when the acidity of the phenolic oxygen was increased by a *p*-nitro group. Sulfur donor complexes showed only marginal improvement in stability relative to O-donor analogues.

Future efforts to develop hydrolytically stable dimethylgallium complexes as radiopharmaceuticals should concentrate on ligands different from those we have described. Alternatives include five-coordinate gallium

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compounds and dialkyl compounds in which the pharmacophore is included in the alkyl group(s). In this regard, it is of note that none of the dimethylgallium complexes underwent hydrolytic scission of the gallium-alkyl bond.

Experimental Section

Ligand Synthesis. Compounds **1a**, **1b**, and **2a** were purchased from Sigma-Aldrich. Published procedures were employed to synthesize **1c**,^{26,27} **2b**,²⁸ **2c**,²⁹ and **5b**.³⁰ Other ligand precursors (**1d**, **2de**, **3a-g**, **4a,b**, **6a-d**, **21c**, **22c**) were synthesized by the methods described in the Supporting Information.

Gallium Complexes. General Procedure for Formation of Gallium Complexes. Dimethylgallium hydroxide and complex **7a** were prepared by a published procedure.^{31,32} Except where otherwise noted, the remaining gallium complexes were prepared as follows. A 2 mL flask was charged with 70–125 mg of ligand precursor, a 5–8% molar excess (of 1:1 stoichiometry) of $(\text{CH}_3)_2\text{GaOH}$, and 0.5–0.7 mL of THF. The resulting solution was stirred 8–12 h; then MgSO_4 was added, and the mixture was stirred an additional 10 min. Filtration through Celite afforded a clear filtrate from which solvent was removed in vacuo to afford a solid. Since the complexes proved unstable on alumina, silica, and C18 silica, they were washed with three 5 mL portions of boiling petroleum ether to remove excess $(\text{CH}_3)_2\text{GaOH}$ and dried in vacuo. Compounds **9f** and **9g** were soluble in petroleum ether; they were characterized with 4–5% excess $(\text{CH}_3)_2\text{GaOH}$ present.

κ^2O,O -Dibenzoylmethanolatodimethylgallium (7b**).** To 0.53 g (5.21 mmol) of $(\text{CH}_3)_2\text{GaOH}$ dissolved in 5 mL of (1:1) benzene/hexane/ Et_2O was added a solution of 1.17 g (5.21 mmol) of dibenzoylmethane in 7 mL of benzene. The solution was stirred for 12 h at 22 °C. Removal of solvent in vacuo afforded a solid that was subsequently recrystallized from hexane to afford yellow needles. Yield: 0.38 g (22%). Additional product was obtained by concentration of the mother liquor. ^1H NMR (acetone- d_6): δ 8.14 (d, 4H, $J = 7.1$ Hz), 7.62–7.51 (m, 6H), 7.06 (s, 1H), –0.16 (s, 6H). ^{13}C NMR (acetone- d_6): δ 186.8, 138.5, 133.5, 129.5, 129.4, 129.2, 128.6, 128.1, 123.1, –6.8. LRMS (EI): $M - \text{CH}_3^+ = 307$. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{O}_2\text{Ga}$: C, 63.21; H, 5.30. Found: C, 62.84; H, 5.11.

κ^2O,O -1,3-Bis(4-methoxyphenyl)propane-1,3-diolatodimethylgallium (7c**).** ^1H NMR (CDCl_3): δ 7.95 (d, 4H, $J = 9.4$ Hz), 6.92 (d, 4H, $J = 8.8$ Hz), 6.64 (s, 1H), 3.88 (s, 6H), –0.17 (s, 6H). ^{13}C NMR (CDCl_3): δ 184.5, 163.3, 130.8, 130.6, 129.9, 114.3, 114.0, 92.5, 55.7, –6.5. LRMS (EI): $M - \text{CH}_3^+ = 367$. Anal. Calcd for $\text{C}_{19}\text{H}_{21}\text{O}_4\text{Ga}$: C, 59.57; H, 5.33. Found: C, 59.66; H, 5.40.

κ^2O,O -1,3-Bis(4-hydroxyphenyl)propane-1,3-diolatodimethylgallium (7d**).** ^1H NMR (acetone- d_6): δ 9.18 (s, 2H), 8.04 (d, 4H, $J = 8.8$ Hz), 6.94 (d, 4H, $J = 8.8$ Hz), 6.91 (s, 1H), –0.25 (s, 6H). ^{13}C NMR (acetone- d_6): δ 184.9, 162.5, 130.9, 130.0, 123.2, 116.1, 92.2, –7.0. LRMS (EI): $M - \text{CH}_3^+ = 339$. Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{O}_4\text{Ga}$: C, 57.51; H, 4.82. Found: C, 57.16; H, 4.40.

κ^2N,O -2-Phenyliminomethylphenolatodimethylgallium (8a**).** ^1H NMR (acetone- d_6): δ 8.60 (s, 1H), 7.58 (dd, 1H, $J = 8.4, 8.4$ Hz), 6.83 (d, 1H, $J = 8.5$ Hz), 6.76 (ddd, 1H, $J =$

7.3, 7.3, 1.0 Hz), –0.26 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.8, 168.2, 148.0, 137.8, 137.4, 130.6, 130.3, 128.5, 123.0, 122.6, 122.0, 119.7, 116.9, –6.4. LRMS (EI): $M - \text{CH}_3^+ = 280$. HRMS (EI) M^+ Calcd for $\text{C}_{15}\text{H}_{16}\text{NOGa}$: 295.0488. Found: 295.0487.

κ^2N,O -2-[(4-Hydroxyphenylimino)methyl]phenolatodimethylgallium (8b**).** ^1H NMR (acetone- d_6): δ 8.78 (s, 1H), 8.52 (s, 1H), 7.43 (d, 1H, $J = 7.8$ Hz), 7.38 (dd, 1H, $J = 6.8, 6.8$ Hz), 7.29 (d, 2H, $J = 8.8$ Hz), 6.98 (d, 2H, $J = 8.8$ Hz), 6.77 (d, 1H, $J = 8.5$ Hz), 6.71 (dd, 1H, $J = 7.4, 7.4$ Hz). ^{13}C NMR (acetone- d_6): δ 167.3, 167.0, 157.3, 139.4, 136.5, 136.4, 123.0, 122.1, 119.1, 116.4, 116.1, –7.1. LRMS (EI): $M - \text{CH}_3^+ = 296$. HRMS (EI) $M - \text{CH}_3^+$ Calcd for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: 296.0202. Found: 296.0204.

κ^2N,O -4-[(4-Hydroxyphenylimino)methyl]benzene-1,3-diolatodimethylgallium (8c**).** ^1H NMR (1:4 $\text{CD}_3\text{OD}/\text{acetone-}d_6$): δ 8.31 (s, 1H), 7.24 (d, 1H, $J = 8.6$ Hz), 7.17 (d, 2H, $J = 8.9$ Hz), 6.89 (d, 1H, $J = 9.0$ Hz), 6.24 (dd, 1H, $J = 10.0, 2.0$ Hz), 6.17 (d, 1H, $J = 2.7$ Hz), –0.26 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.9, 166.2, 157.4, 140.4, 139.2, 123.5, 117.0, 113.9, 107.4, 106.9, –6.4. LRMS (EI): $M - \text{CH}_3^+ = 312$. HRMS (EI) M^+ Calcd for $\text{C}_{15}\text{H}_{16}\text{NO}_3\text{Ga}$: 327.0386. Found: 327.0382.

κ^2N,O -4-[(4-*N,N*-Dimethylaminophenylimino)methyl]benzene-1,3-diolatodimethylgallium (8d**).** ^1H NMR (acetone- d_6): δ 8.33 (s, 1H), 7.27 (d, 1H, $J = 8.5$ Hz), 7.22 (d, 2H, $J = 8.8$ Hz), 6.82 (d, 2H, $J = 8.8$ Hz), 6.28 (dd, 1H, $J = 8.5, 2.2$ Hz), 6.20 (s, 1H), 3.01 (s, 6H), –0.34 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.1, 163.9, 149.9, 138.2, 136.6, 122.1, 113.3, 112.9, 106.5, 106.2, 39.8, –7.1. LRMS (EI): $M - \text{CH}_3^+ = 339$. Anal. Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_2\text{Ga}$: C, 57.20; H, 5.96; N, 7.89. Found: C, 57.49; H, 6.14; N, 7.59.

κ^2N,O -2-[(4-*N,N*-Dimethylaminophenylimino)methyl]-4-nitrophenolatodimethylgallium (8e**).** ^1H NMR (acetone- d_6): δ 8.81 (s, 1H), 8.53 (d, 1H, $J = 2.9$ Hz), 8.20 (dd, 1H, $J = 9.2, 2.9$ Hz), 7.41 (d, 1H, $J = 9.0$ Hz), 6.87 (d, 1H, $J = 9.0$ Hz), 6.87 (d, 1H, $J = 9.0$ Hz), 3.04 (s, 6H), –0.23 (s, 6H). ^{13}C NMR (acetone- d_6): δ 123.4, 123.2, 113.4, 40.3, –6.1. LRMS (EI) $M - \text{CH}_3^+ = 368$. HRMS (EI) M^+ Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_3\text{Ga}$: 387.0760. Found: 387.0761.

$\kappa^2\text{NO}$ -4-*tert*-Butyliminomethylbenzene-1,3-diolatodimethylgallium (9a**).** ^1H NMR (acetone- d_6): δ 8.34 (s, 1H), 7.17 (d, 1H, $J = 8.6$ Hz), 6.21 (dd, 1H, $J = 8.5, 2.0$ Hz), 6.14 (d, 1H, $J = 1.8$ Hz), 1.43 (s, 9H), –0.34 (s, 6H). ^{13}C NMR (acetone- d_6): δ 172.8, 169.2, 166.3, 138.7, 137.7, 113.3, 106.6, 60.1, –4.0. LRMS (EI): $M - \text{CH}_3^+ = 276$. HRMS (EI) M^+ Calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_2\text{Ga}$: 291.0750. Found: 291.0751.

κ^2N,O -4-*n*-Butyliminomethylbenzene-1,3-diolatodimethylgallium (9b**).** ^1H NMR (acetone- d_6): δ 8.21 (s, 1H), 7.14 (d, 1H, $J = 8.5$ Hz), 6.25 (dd, 1H, $J = 8.5, 2.2$ Hz), 6.19 (d, 1H, $J = 2.0$ Hz), 3.59 (t, 2H, $J = 7.6$ Hz), 1.70 (tt, 2H, $J = 7.3, 7.3$ Hz), 1.41 (tt, 2H, $J = 7.5, 7.5$ Hz), 0.98 (t, 3H, $J = 4.2$ Hz), –0.37 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.5, 169.1, 138.0, 113.0, 106.9, 106.6, 58.4, 32.9, 20.5, 13.9, –7.0. LRMS (EI): $M - \text{CH}_3^+ = 276$. HRMS (EI) M^+ calcd for $\text{C}_{13}\text{H}_{20}\text{NO}_2\text{Ga}$: 291.0750. Found: 291.0748.

κ^2N,O -4-*n*-Hexyliminomethylbenzene-1,3-diolatodimethylgallium (9c**).** ^1H NMR (acetone- d_6): δ 8.18 (s, 1H), 7.10 (d, 1H, $J = 8.6$ Hz), 6.21 (dd, 1H, $J = 8.4, 2.4$ Hz), 6.16 (d, 1H, $J = 2.4$ Hz), 3.56 (t, 2H, $J = 6.4$ Hz), 1.65 (tt, 2H, $J = 7.1, 7.1$ Hz), 1.32–1.34 (m, 6H), 0.89 (t, 3H, $J = 7.1$ Hz), –0.34 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.5, 169.1, 165.5, 138.0, 113.0, 107.0, 106.7, 58.7, 32.1, 30.9, 27.0, 23.1, 14.2, –7.0. LRMS (EI): $M - \text{CH}_3^+ = 304$. HRMS (EI) $M - \text{CH}_3^+$ calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_2\text{Ga}$: 304.0828. Found: 304.0827.

κ^2N,O -4-Dodecyliminomethylbenzene-1,3-diolatodimethylgallium (9d**).** ^1H NMR (acetone- d_6): δ 8.16 (s, 1H), 7.10 (d, 1H, $J = 8.5$ Hz), 6.21 (dd, 1H, $J = 8.4, 2.4$ Hz), 6.17 (d, 1H, $J = 2.4$ Hz), 3.55 (t, 2H, $J = 7.6$ Hz), 1.68 (m, 2H), 1.35–1.20 (m, 18H), 0.88 (t, 3H, $J = 6.4$ Hz), –0.40 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.4, 169.0, 165.4, 137.9, 113.0, 107.0, 106.7, 58.7, 32.6, 30.8, 30.3, 30.1, 27.3, 23.3, 14.3, –6.9.

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LRMS (EI): $M - CH_3^+ = 388$. HRMS (EI) M^+ calcd for $C_{21}H_{36}NO_2Ga$: 403.2002. Found: 403.2003.

$\kappa^2N,O-4$ -Benzyliminomethylbenzene-1,3-diolatodimethylgallium (9c). 1H NMR (acetone- d_6): δ 8.39 (s, 1H), 7.39–7.34 (m, 5H), 7.17 (d, 1H, $J = 8.5$ Hz), 6.24 (d, 1H, $J = 8.5$ Hz), 6.15 (d, 1H, $J = 2.0$ Hz), 4.74 (s, 2H), –0.67 (s, 6H). ^{13}C NMR (acetone- d_6): δ 169.8, 169.4, 138.3, 137.1, 129.8, 129.5, 128.9, 113.1, 106.9, 106.8, 62.4, –7.2. LRMS (EI): $M - CH_3^+ = 310$. HRMS (EI) calcd for $C_{15}H_{15}NO_2Ga$: 310.0359. Found: 310.0358.

$\kappa^2NO-2-n$ -Hexyliminomethylphenolatodimethylgallium (9f). 1H NMR (acetone- d_6): δ 8.37 (s, 1H), 7.31 (ddd, 1H, $J = 8.0, 8.0, 2.0$ Hz), 7.26 (dd, 1H, $J = 7.8, 2.0$ Hz), 6.71 (d, 1H, $J = 8.4$ Hz), 6.64 (ddd, 1H, $J = 8.0, 8.0, 1.0$ Hz). ^{13}C NMR (acetone- d_6): δ 170.5, 167.4, 136.4, 136.0, 122.7, 119.2, 116.4, 59.1, 32.0, 30.6, 27.0, 23.1, 14.2, –6.9. LRMS (EI): $M - CH_3^+ = 288$. HRMS (EI) M^+ calcd for $C_{21}H_{36}NO_2Ga$: 303.1114. Found: 303.1117.

$\kappa^2N,O-2$ -[(6-Methoxycarbonylhexylimino)methyl]phenolatodimethylgallium (9g). 1H NMR (acetone- d_6): δ 8.37 (s, 1H), 7.31 (ddd, 1H, $J = 8.0, 8.0, 2.0$ Hz), 7.26 (dd, 1H, $J = 7.6, 2.0$ Hz), 6.71 (d, 1H, $J = 8.8$ Hz), 6.64 (ddd, 1H, $J = 7.4, 7.4, 1.2$ Hz). ^{13}C NMR (acetone- d_6): δ 173.9, 170.8, 167.6, 136.5, 136.2, 122.8, 119.2, 116.5, 58.9, 51.5, 34.1, 30.4, 26.8, 25.2, –6.9. LRMS (EI): $M - CH_3^+ = 332$. HRMS (EI) M^+ calcd for $C_{21}H_{36}NO_2Ga$: 332.0777. Found: 332.0778.

$\kappa^2N,O-4$ -[(Phenyliminomethyl)benzene-1,3-diolatodimethylgallium (10a). 1H NMR (acetone- d_6): δ 9.04 (s, 1H), 8.74 (s, 1H), 7.22 (t, 2H, $J = 7.6, 7.6$ Hz), 7.05 (m, 1H), 7.02 (d, 2H, $J = 8.5$ Hz), 6.86 (dd, 2H, $J = 8.4, 1.2$ Hz), 6.74 (d, 1H, $J = 9.0$ Hz), 6.73 (d, 2H, $J = 8.5$ Hz), 6.27 (d, 1H, $J = 2.4$ Hz), 6.10 (dd, 1H, $J = 8.9, 2.4$ Hz). ^{13}C NMR (acetone- d_6): δ 169.4, 169.0, 165.4, 137.9, 113.0, 107.0, 106.7, –6.9. LRMS (EI): $M - CH_3^+ = 388$. HRMS (FAB) M^+ Calcd for $C_{21}H_{20}NO_3Ga$: 404.0777. Found: 404.0777.

$\kappa^2N,O-4$ -[(4-Methoxyphenyl)phenyliminomethyl]benzene-1,3-diolatodimethylgallium (10b). 1H NMR (acetone- d_6): δ 9.07 (s, 1H), 7.22 (dd, 2H, $J = 7.6, 7.6$ Hz), 7.11 (d, 2H, $J = 8.8$ Hz), 7.05 (t, 1H, $J = 7.6$ Hz), 6.89 (d, 2H, $J = 7.3$ Hz), 6.82 (d, 2H, $J = 8.8$ Hz), 6.28 (d, 1H, $J = 2.4$ Hz), 6.09 (dd, 1H, $J = 8.9, 2.7$ Hz), 3.75 (s, 3H), –0.48 (s, 6H). ^{13}C NMR (acetone- d_6): δ 176.0, 170.4, 164.3, 159.9, 145.9, 137.1, 131.1, 128.7, 125.3, 124.2, 112.9, 106.8, 105.6, 54.5, –8.8. LRMS (EI): $M - CH_3^+ = 402$. Anal. Calcd for $C_{22}H_{22}NO_3Ga$: C, 63.19; H, 5.30; N, 3.35. Found: C, 63.13; H, 5.44; N, 3.18.

$\kappa^2N,O-2$ -[(*tert*-Butyliminomethyl)-4-nitrophenolatodimethylgallium (11a). 1H NMR (acetone- d_6): δ 8.81 (s, 1H), 8.48 (d, 1H, $J = 2.9$ Hz), 8.18 (dd, 1H, $J = 9.3, 3.1$ Hz), 6.80 (d, 1H, $J = 9.3$ Hz), 1.54 (s, 9H), –0.22 (s, 6H). ^{13}C NMR (acetone- d_6): δ 167.4, 136.5, 133.7, 130.2, 122.1, 117.7, 61.3, 29.3, –3.7. LRMS (EI): $M - CH_3^+ = 305$. HRMS (FAB) $M - CH_3^+$ Calcd for $C_{13}H_{19}N_2O_3Ga$: 305.0413. Found: 305.0417.

$\kappa^2N,O-1$ -Phenyl-2-(2-pyridyl)-1-ethenolatodimethylgallium (12a). Yellow solid. 1H NMR ($CDCl_3$, 500 MHz): δ 7.86 (m, 3H), 7.63 (ddd, 1H, $J = 8.3, 7.3, 1.7$ Hz), 7.38 (m, 3H), 7.04 (dt, 1H, 7.0, 0.98 Hz), 6.99 (ddd, 1H, 7.3, 5.7, 1.3 Hz), 5.93 (s, 1H), –0.19 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.2, 156.9, 143.2, 140.1, 139.0, 129.3, 128.1, 126.4, 123.3, 118.3, 93.9, –7.65. MS (EI, 70 eV): m/z (relative intensity) 297 (M^+ , 5), 295 (M^+ , 8), 282 (68), 280 (100), 266 (8), 264 (12), 163 (8), 161 (11), 71 (90), 69 (14). Anal. Calcd for $C_{15}H_{16}GaNO$: C, 60.86; H, 5.45; N, 4.73. Found: C, 60.84; H, 5.31; N, 4.76.

$\kappa^2N,O-1$ -[(4-Hydroxyphenyl)-2-(2-pyridyl)-1-ethenolatodimethylgallium (12b). Yellow solid. 1H NMR ($CDCl_3$, 500 MHz): δ 8.89 (bs, 1H), 7.70 (dd, 1H, $J = 5.61, 1.65$ Hz), 7.59 (AA' of AA'XX', 2H, $J_{AX} = 8.60$ Hz, $J_{AX} = 2.48$ Hz), 7.47 (ddd, 1H, $J = 8.46, 7.06, 1.85$ Hz), 6.89 (dt, 1H, $J = 8.35, 1.04$ Hz), 6.82 (ddd, 1H, $J = 7.09, 5.76, 1.27$ Hz), 6.724 (XX' of AA'XX', 2H, $J_{AX} = 8.58$ Hz, $J_{XX} = 2.47$ Hz), 5.73 (s, 1H), –0.35 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.9, 158.5, 156.7, 142.7,

138.5, 130.9, 127.7, 122.8, 117.4, 114.8, 92.0, –7.95. MS (EI, 70 eV): m/z (relative intensity) 313 (M^+ , 7), 311 (M^+ , 9), 298 (68), 296 (100), 282 (7), 280 (11), 179 (15), 177 (24), 149 (10), 148 (14), 121 (20), 71 (42), 69 (65). Anal. Calcd for $C_{15}H_{16}GaNO_2 \cdot 0.5H_2O$: C, 56.12; H, 5.34; N, 4.36. Found: C, 56.56; H, 5.32; N, 5.32.

$\kappa^2N,O-2$ -[(5-Hydroxy-2-pyridyl)-1-phenyl-1-ethenolatodimethylgallium (12c). Yellow solid. 1H NMR ($(CD_3)_2CO$, 500 MHz): δ 9.08 (bs, 1H), 7.86 (dd, 2H, $J = 8.14, 1.57$ Hz), 7.72 (d, 1H, $J = 2.80$ Hz), 7.48 (dd, 1H, $J = 8.88, 2.77$ Hz), 7.34 (m, 3H), 7.29 (d, 1H, $J = 8.96$ Hz), 6.11 (s, 1H), –0.29 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.6, 151.6, 150.7, 141.2, 130.8, 129.7, 129.4, 128.7, 126.7, 125.7, 93.6, –7.80. MS (EI, 70 eV): m/z (relative intensity) 313 (M^+ , 5), 311 (M^+ , 6), 298 (60), 296 (88), 282 (10), 280 (121), 212 (4), 184 (10), 163 (13), 161 (18), 149 (4), 148 (5), 105 (31), 77 (34), 71 (65), 69 (100). Anal. Calcd for $C_{15}H_{16}GaNO_2$: C, 57.74; H, 5.17; N, 4.49. Found: C, 57.59; H, 4.94; N, 4.27.

$\kappa^2N,S-1$ -Phenyl-2-(2-pyridyl)-1-ethene-1-thiolatodimethylgallium (12d). Yellow solid. 1H NMR ($(CD_3)_2CO$, 500 MHz): δ 8.46 (dd, 1H, $J = 5.47, 1.87$ Hz), 8.10 (ddd, 1H, $J = 8.15, 7.55, 1.76$ Hz), 7.80 (m, 2H), 7.67 (ddd, 1H, $J = 8.06, 1.30, 0.83$ Hz), 7.55 (ddd, 1H, $J = 7.42, 5.73, 1.33$ Hz), 7.37 (m, 3H), 7.15 (s, 1H), –0.18 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) ($(CD_3)_2CO$, 125 MHz): δ 155.6, 155.4, 146.4, 145.6, 141.5, 129.4, 128.8, 128.2, 128.1, 123.7, 121.2, –6.81. MS (EI, 70 eV): m/z (relative intensity) 313 (M^+ , 2), 313 (M^+ , 2), 298 (73), 296 (100), 212 (86), 180 (36), 152 (12), 78 (26), 71 (17), 69 (27). Anal. Calcd for $C_{15}H_{16}GaNS$: C, 57.73; H, 5.17; N, 4.49; S, 10.27. Found: C, 57.65; H, 5.18; N, 4.55; S, 10.04.

X-ray Structure Determination of 7c. Single crystals of **7c**, grown from a saturated $CHCl_3$ solution, were mounted on glass fibers with Paratone-N oil (Exxon) and immediately cooled to –75 °C in a cold nitrogen gas stream on the diffractometer. Standard peak search and indexing procedures gave rough cell dimensions, and least-squares refinement using 10 688 reflections yielded the cell dimensions given in Table 2. Data were collected with an area detector by using the measurement parameters listed in Table 2. Systematic absences for $0kl$ ($k + l \neq 2n$) and $h0l$ ($h \neq 2n$) were consistent with space groups $Pnma$ and $Pna2_1$. The average values of the structure factors suggest the centri choice $Pnma$, which was verified by the successful refinement of the structure. The measured intensities were reduced to structure factor amplitudes and their esd's by correction for background and Lorentz and polarization effects. While corrections for crystal decay were unnecessary, a face-indexed absorption correction was applied, the maximum and minimum transmission factors being 0.858 48 and 0.570 50. Systematically absent reflections were deleted and symmetry equivalent reflections were averaged to yield the set of unique data. All 10 688 data were used in the least-squares refinement. The structure was solved using direct methods (SHELXL). The correct positions for the C, O, and Ga atoms were deduced from an E-map. Subsequent least-squares refinement and difference Fourier calculations revealed the positions of the remaining non-hydrogen atoms. The quantity minimized by the least-squares program was $\sum w(F_o^2 - F_c^2)^2$, where $w = [(\sigma(F_o^2))^2 + (0.0765P)^2 + 3.6495P]^{-1}$ and $P = (F_o^2 + 2F_c^2)/3$. The analytical approximations to the scattering factors were used, and all structure factors were corrected for both real and imaginary components of anomalous dispersion. In the final cycle of least squares, independent anisotropic displacement factors were refined for the non-hydrogen atoms and the aromatic, vinyl, and methyl hydrogen atoms were fixed in "idealized" positions, with C–H = 0.95 Å for the aromatic and vinyl hydrogens and C–H = 0.98 Å for the methyl hydrogens. Successful convergence was indicated by the maximum shift/error of 0.001 for the last cycle. Final refinement parameters are given in Table 2. The largest peak in the final Fourier difference map (1.966 e Å⁻³) was located 0.88 Å from C10. A final analysis of

variance between observed and calculated structure factors showed no apparent errors.

X-ray Structure Determination of 12a. Single crystals of **12a** were grown and mounted the same as described for compound **7a** above. Standard peak search and indexing procedures gave rough cell dimensions, and least-squares refinement using 8701 reflections yielded the cell dimensions given in Table 2. Data were collected with an area detector by using the measurement parameters listed in Table 2. Systematic absences for $0k0$ ($k \neq 2n$) and $h0l$ ($h + l \neq 2n$) were consistent only with space group $P2_1/n$. The measured intensities were reduced to structure factor amplitudes and their esd's by correction for background and Lorentz and polarization effects. While corrections for crystal decay were unnecessary, a ψ -scan absorption correction was applied, the maximum and minimum transmission factors being 0.990 and 0.861. Systematically absent reflections were deleted and symmetry equivalent reflections were averaged to yield the set of unique data. All 8701 data were used in the least-squares refinement. The structure was solved using direct methods (SHELXTL). The correct positions for the C, N, O, and Ga atoms were deduced from an E-map. Subsequent least-squares refinement and difference Fourier calculations revealed the positions of the remaining non-hydrogen atoms. The quantity minimized by the least-squares program was $\sum w(F_o^2 - F_c^2)^2$, where $w = [(\sigma(F_o^2))^2 + (0.0138P)^2 + 1.3221P]^{-1}$ and $P = (F_o^2 + 2F_c^2)/3$. The analytical approximations to the scattering factors were used, and all structure factors were corrected for both real and imaginary components of anomalous dispersion. In the final cycle of least squares, independent anisotropic displacement factors were refined for the non-hydrogen atoms, and the aromatic, vinyl, and methyl hydrogen atoms were fixed in "idealized" positions, with C-H = 0.95 Å for the aromatic and vinyl hydrogens and C-H = 0.98 Å for the methyl hydrogens. Successful convergence was indicated by the maximum shift/error of 0.001 for the last cycle. Final refinement parameters are given in Table 2. The largest peak in the final Fourier difference map ($0.330 \text{ e } \text{Å}^{-3}$) was located 0.88 Å from C14. A final analysis of variance between observed and calculated structure factors showed no apparent errors.

Hydrolysis Studies. A weighed sample of each gallium complex was dissolved in acetone- d_6 to form a 0.20 M solution. At room temperature, H_2O was added to achieve a $\text{H}_2\text{O}/\text{Ga}$ ratio of 1000. Formation of $(\text{CH}_3)_2\text{GaOH}$ was monitored by ^1H NMR, with the percent hydrolysis measured by integrating the $(\text{CH}_3)_2\text{Ga}^-$ peaks corresponding to the unhydrolyzed complex and to $(\text{CH}_3)_2\text{GaOH}$. The determination of percent hydrolysis was made 12–24 h after the addition of H_2O . These percent hydrolysis values are listed in Figure 2.

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Supporting Information Available: Full crystallographic information, atomic coordinates and isotropic displacement parameters, and intramolecular bond distances and angles can be found on pages S-2–10 for compound **7c** and pages S-11–17 for compound **12a**; experimental procedures and characterization for all ligands can be found on pages S-18–27 (28 pages). Ordering information can be found on any current masthead page.

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Preparation of Hexahydrobenzo[*f*]isoquinolines Using a Vinylogous Pictet–Spengler Cyclization

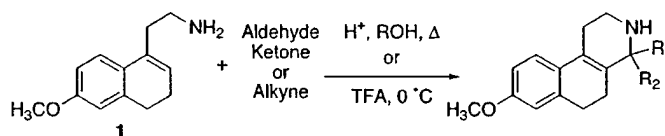
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ABSTRACT



A vinylogous Pictet–Spengler cyclization has been carried out using activated aldehydes, ketones, and alkynes to prepare a variety of substituted hexahydrobenzo[*f*]isoquinolines. A unique set of conditions was utilized to effect efficient cyclization with acid-sensitive electrophiles.

The Pictet–Spengler cyclization has been extensively studied since its discovery in 1911.¹ Over the years, the reaction has been applied in the context of several heterocyclic syntheses,² and it continues to be a significant focus of research. Early applications of the Pictet–Spengler reaction were for the preparation of complex heterocycles such as aza-steroids³ and morphine alkaloids.⁴ However, most of the current literature is focused on the development of diastereo- and enantioselective variants of the Pictet–Spengler reaction, especially for preparing substituted tetrahydroisoquinolines⁵ and tetrahydro- β -carbolines.⁶ Recent mechanistic investigations have provided some insight into the stereochemical course of tetrahydro- β -carboline formation.⁷

For some time, we have been interested in the synthesis of receptor-targeted breast tumor imaging agents, which integrate metallic radionuclides, for use in single photon emission computed tomography (SPECT) and positron emission tomography (PET).⁸ We have recently designed a novel series of compounds that possess steroidal backbones (Figure 1). Our approach to the ligands for these complexes evolved around the use of a vinylogous Pictet–Spengler reaction⁹ in a manner similar to that used previously for the preparation of a variety of 13-aza-steroids.¹⁰ In the course of our studies, we surveyed several electrophiles (aldehydes, ketones, and alkynes) and examined different reaction conditions.

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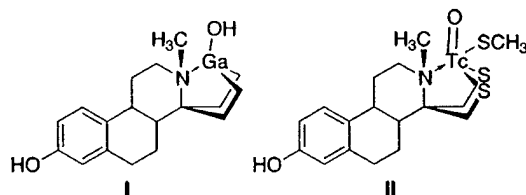
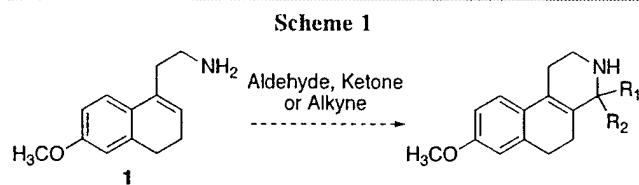


Figure 1. Receptor-targeted breast tumor imaging agents that possess steroidal backbones.

A generic diagram of the vinylogous Pictet–Spengler reaction that we proposed to study for preparing the 13-azasteroid analogues is depicted in Scheme 1. The dihydronaph-



thylamine (**1**) has been reported in the literature and can be prepared in a number of ways.¹¹ For our purposes, we found that homologation of 6-methoxy-1-tetralone via a Horner–Emmons reaction with diethyl cyanomethylphosphonate,¹² followed by Lewis acid mediated reduction (LiAlH₄/AlCl₃), worked well. By this method, we were able to obtain the $\Delta^{8(9)}$ isomer (steroid numbering) exclusively in 70% overall yield after recrystallization of the corresponding hydrochloride salt.

In our initial investigation of this reaction, we utilized a traditional Pictet–Spengler synthetic protocol of heating the dihydronaphthylamine hydrochloride (**1**·HCl) and the carbonyl compound in an alcoholic solvent. We found that although propionaldehyde cyclized readily, acetone did not. In other cases, the products were isolated as mixtures of the $\Delta^{8(9)}$ and $\Delta^{9(11)}$ olefin isomers (steroid numbering), and only upon extended heating, or in those cases where there was additional functionalization, were we able to obtain products consisting only of the $\Delta^{8(9)}$ isomer (see below). If butanol rather than methanol was used as the solvent, reaction times were shortened and product yields improved.¹³

Despite these complications, we were pleased to find that the cyclization worked very well with more electrophilic

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(9) If one considers that a *p*-methoxystyrene is a trienol system and that reactions of enols with imines are termed Mannich reactions, then the reaction described in this report could be considered a vinylogous Mannich reaction. However, this term is currently employed by Martin to illustrate the nucleophilic addition of 2-trialkylsiloxy furans to cyclic iminium ions; cf. Martin, S. F. et al. *J. Am. Chem. Soc.* **1996**, *118*, 3299 and Martin, S. F. et al. *J. Am. Chem. Soc.* **1999**, *121*, 6990. It should also be noted that Overman has described a related intramolecular Mannich reaction; cf. Loegers, M. et al. *J. Am. Chem. Soc.* **1995**, *117*, 9139 and references cited therein.

(10) Refer to ref 3b–d.

(11) Refer to ref 4.

(12) Geier, M.; Hesse, M. *Synthesis* **1990**, 56.

(13) Similar temperature affects have been observed in the Pictet–Spengler reaction of tryptamines carried out in nonacidic, aprotic media; cf. ref 7c.

aldehydes and with cyclic ketones. The details of these investigations are given in Table 1. Ethyl glyoxylate and

Table 1. Cyclization with Aldehydes and Ketones

Carbonyl ^a	Time ^b (h)	Product ^c	Yield (%)
	24		84
	24		97
	72		88
	72		54
	72		51

^a Ar = *p*-OCH₃C₆H₄. ^b Time at reflux in butanol. ^c Compound **8** exists as a 9:1 mixture of olefin isomers.

diethyl ketomalonate both reacted smoothly with **1** in 24 h to yield the corresponding hexahydrobenzo[*f*]isoquinolines in 84% and 97% yield, respectively, as single olefin isomers. Preparation of the spiro-fused compounds **4** and **5** using tetrahydro-4*H*-pyran-4-one and cyclopentanone, respectively, required longer reaction times (72 h). These extended reaction times were needed not to improve reaction yield but rather to isomerize the intermediate mixture of isomers exclusively to the $\Delta^{8(9)}$ isomer.

The preparation of cyclic ketone **8** deserves some additional comment. In our approach to target molecule **II** we desired to synthesize a compound that bore a dithiol functionality of suitable orientation to form a tripartite chelate (S,N,S) for technetium in a [3 + 1] fashion. However, when we attempted to cyclize an acyclic version of ketone **6** (specifically, thioacetic acid *S*-(3-acetylsulfanyl-2-oxo-propyl) ester (**7**)), we were unable to obtain any of the tricyclic product. Hence, we decided to try ketone **6**, which could be readily prepared in two steps from 4-methoxybenzaldehyde and ethyl 2-mercaptoacetate, according to a literature method.¹⁴ We were pleased that compound **6** indeed underwent smooth cyclization under conditions similar to those described above for compound **4**. However, despite an extended reaction time, we could only obtain compound **8** as a 9:1 mixture of isomers favoring the desired $\Delta^{8(9)}$ isomer.

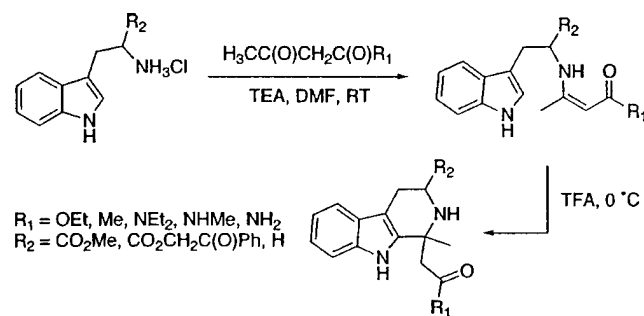
Robust substrates were needed to withstand cyclization under the rather harsh conditions described above. In fact,

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several attempts to achieve cyclization using activated ketones under these conditions were unsuccessful. Specifically, when we attempted the reaction with either a β -ketoester or β -keto- γ -lactone, these substrates were degraded during the reaction. Therefore, we sought to develop a milder protocol for use with these acid-sensitive functionalities.

We were aware of previous work in the tetrahydro- β -carboline literature, which showed that indeed esters, ketones, and amides with a β -carbonyl functionality could be cyclized by acid catalysts (Scheme 2).¹⁵ The two-step protocol

Scheme 2. Two-Step Synthesis of Tetrahydro- β -carbolines



reported in this work consisted of initial enamine formation at room temperature, followed by treatment with acid at low temperature. With this excellent precedent in hand, we proceeded to submit the substrates we desired to the conditions described above. The results of these studies are summarized in Table 2.

When a solution of **1**·HCl and triethylamine in DMF is treated with diethyl 1,3-acetonedicarboxylate at room temperature for 12 h, the desired enamine could be isolated as a single isomer. Although we did not rigorously determine the geometry of the intermediate enamine for compounds **9**, **12**, and **13** (see below), we believe that it is *Z*, on the basis of earlier reports.¹⁶ In this geometry, the enamino ester system would be stabilized via intramolecular hydrogen bonding, and there is evidence for such an interaction by the extreme downfield shift of the amine proton in the NMR (δ 8.58, 7.83, and 8.09, respectively). In contrast, in the case of the intermediate enamine resulting from reaction with dihydropyran-2,4-dione,¹⁷ the cyclic geometry aminodihydropyran requires that the geometry of the enamine be *E*, which is supported by the upfield location (δ 4.56) of the hydrogen atom.

The cyclization of these enamines was effected by treatment of the *neat* oils with excess trifluoroacetic acid at 0 °C for 30 min.¹⁸ The yields of these compounds are given in Table 2. We were gratified to find that, in contrast to the

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(18) TFA is known to cause C(1)–N(2) bond cleavage in methoxy-substituted tetrahydro- β -carbolines through a carbocation-mediated mechanism; cf. ref 7a and Reedy, S. M.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413.

Table 2. Cyclization with Activated Ketones and Alkynes^a

Ketone or Alkyne	Time (h)	Product ^b	Yield (%)
	24		84(92)
	24		27(72)
	120		24(54)
	24		35(60)

^a The reactions shown in this table were performed using a two-step protocol similar to that shown in Scheme 2. The enamine intermediates were used directly in the subsequent cyclization step, but could be isolated by column chromatography if desired. ^b The time refers to the duration with which enamine formation was allowed to occur. A reaction time of 30 minutes was used for all subsequent cyclizations; neat TFA, 0 °C. ^c Yields are combined for the two-step process. Yields in parentheses are for the enamine formation.

results of the one-step protocol reported above, under these milder two-step conditions, the desired $\Delta^{8(9)}$ isomer was produced exclusively. We also found that anhydrous TFA was required for this procedure, because small amounts of water in the reagent caused extensive hydrolysis of the enamines during the cyclization. Unlike what happened in our earlier attempts, we observed no ring opening of the lactone during the formation of the spiro compound (**11**) by the two-step procedure.

Amines are known to undergo conjugate addition with activated alkynes to yield the corresponding enamines.¹⁹ In fact, the use of alkynes in the Pictet–Spengler reaction has been previously documented in the synthesis of several tetrahydro- β -carbolines.²⁰ Upon the basis of these precedents, we reasoned that the alkynes methyl propiolate and dimethyl acetylenedicarboxylate (DMAD) would be suitable substrates for the vinylogous Pictet–Spengler reaction. In the case of methyl propiolate, we found enamine formation to be exceedingly slow. In fact, reasonable yields of the conjugate product were only obtained after 120 h at room temperature. The enamine was isolated as a mixture of *Z*:*E* isomers in a 3:1 ratio, determined by integration of the signals of the vinyl hydrogen atoms. Although the yield was modest, this enamine underwent smooth cyclization upon treatment with TFA to afford the hexahydrobenzo[*f*]isoquinoline (**12**) in 24% overall yield. As expected, conjugate addition with the more

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reactive DMAD was complete after only 24 h. The enamine product was of single configuration, and when submitted to the cyclization conditions, provided the desired tricyclic product (**13**) in 35% overall yield.

The results of this brief investigation of a vinylogous Pictet–Spengler reaction have been encouraging. Not unexpectedly, both aldehydes and ketones can be cyclized using standard Pictet–Spengler conditions with relative ease, and we found that high yields are obtained only when cyclic substrates are used. The harsh conditions required to cyclize unactivated ketones were not suitable for more acid-sensitive substrates, but a milder, two-step protocol was developed for these cases. Suitable enamine cyclization precursors could be prepared by condensation with activated ketones or by conjugate addition with activated alkynes. The vast Pictet–

Spengler cyclization literature provides for further extension of this reaction through a rational choice of electrophiles.

Acknowledgment. We are grateful for support of this research through grants from the Department of the Army (DAMD17-97-1-7292), National Cancer Institute DHHS (PHS 5 T32 CA09067), and the Department of Energy (DE FG02 86ER60401).

Supporting Information Available: Complete experimental procedures and spectral data for compounds **1–9** and **11–13**. This material is available free of charge via the Internet at <http://pubs.acs.org>

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**Synthesis of Cyclopentadienyl Tricarbonyl Rhenium Phenyl-Tropanes
by Direct Double Ligand Transfer with Ferrocene Precursors:
Development of Imaging Agents for the Dopamine Transporter**

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Running Title: Cyclopentadienyl Tricarbonyl Rhenium Phenyl-Tropanes

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ABSTRACT

Cyclopentadienyltricarbonylrhenium (CpTR) systems can be prepared from ferrocenes and perrhenate by a double ligand-transfer (DLT) reaction that gives reasonable yields and shows excellent functional group tolerance. We have used this reaction for the direct preparation of CpTR-phenyl-tropane conjugates. Such agents, when labeled with technetium-99m, might function as imaging agents for the dopamine transporter (DAT) system that would be useful for assessing the onset and severity of Parkinson's disease. Of the CpTR-tropane conjugates we have prepared by the DLT reaction (as well as other analogs prepared by related methods), those substituted at the *N*-8 position seem most promising; their affinity for the DAT in all cases was high, and their ferrocene precursors for the DLT reaction can be prepared in a convenient manner. By contrast, the 3 β -conjugates were poor DAT binders. The modular nature of these systems offers considerable flexibility that could be used to improve the binding characteristics of these compounds further.

INTRODUCTION

The dopamine transporter (DAT) serves a critical modulatory role in dopamine (DA) neurotransmission, removing released transmitter from the synapse by transporting it back into the pre-synaptic terminal.⁽¹⁾ Because of its crucial function, DAT is a target for drug therapy (e.g., Ritalin[®] for attention deficit and hyperactivity disorder) and for drugs of abuse (e.g., cocaine). Not surprisingly, DAT has been extensively studied both by in vitro methods and by in vivo imaging. Because DAT serves as a marker of DA terminal innervation of the striatum, DAT-based images have been proposed as an early diagnostic test for Parkinson's disease.

Parkinson's disease (PD) is a progressive, disabling neurodegenerative disorder characterized clinically by major motor symptoms and pathologically by the degeneration of dopaminergic neurons in the substantia nigra, resulting in an 80-99% reduction in striatal DA concentrations. In the early course of PD, motor deficits can be reversed effectively by DA replacement or DA receptor agonists. However, as the disease progresses, patients develop disabilities from drug-induced side effects, progression of motor dysfunction, and an array of non-motor, non-DA responsive symptoms. The development of DAT imaging as an objective biological marker for PD would be extremely useful for assessing potential agents for neuroprotection and approaches to neuronal restoration.^(2,3) It might also provide a secondary marker in individuals with varying clinical symptoms that would allow for the mapping of disease subsets.⁽⁴⁾ **[RON – SHOULD WE SHORTEN THIS PARAGRAPH?]**

To date, radionuclide imaging of the dopamine transporter has been dominated by compounds such as the iodophenyl-tropane β -CIT (**I**, Figure 1), labeled with iodine-123.⁽⁵⁻⁸⁾ However, production of the I-123 radionuclide requires high-energy cyclotrons, which are not widely available. Because of this limitation, several research groups have developed DAT binding radiotracers that utilize technetium-99m as a practical and widely available, low-cost alternative radionuclide, together with Single Photon Emission Computed Tomography (SPECT) DAT imaging.

Kung and coworkers have reported successful SPECT DAT imaging using a technetium-99m complex of an N_2S_2 chelate conjugated at the 2 β -position of 3 β -(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane (TRODAT-1 (**II**), Figure 1).(9-11) The in vivo pharmacological specificity of this agent was shown in animal experiments by selective blocking with the DAT binding agent, 3 β -(4-chlorophenyl)-8-methyl-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (β -CIT, **I**). The corresponding rhenium analog displayed an inhibition constant (K_i) of 14.1 nM towards DAT. A similar result was reported by Madras and coworkers with one of a series of N_2S_2 chelate analogs of the fluorophenyl-tropane CFT conjugated at the *N*-8 position (Technepine (**III**), Figure 1).(12) These studies demonstrate that technetium-99m can be incorporated into a radiotracer that has high affinity for the target site, crosses the blood-brain barrier, and concentrates in the appropriate target regions in the brain. However, both tracers showed relatively high non-specific uptake, which may be a consequence of the high molecular weight of these agents and their large lipophilic metal complexes.

In a related effort, we have investigated the use of the stable substituted η^5 -cyclopentadienyltricarbonyl rhenium and technetium organometallic complexes for radiolabeling biologically interesting molecules; these complexes are abbreviated collectively as CpTM complexes (M = metal), or individually as CpTR, for the rhenium, and CpTT, for the technetium analogs (**IV**, Figure 1.) Compared to the more widely used high-oxidation state metal-oxo complexes (e.g., **II** and **III**, Fig. 1), CpTM complexes exhibit high chemical and metabolic stability; they are lipophilic and relatively small, and unlike many inorganic chelates, they do not possess additional stereocenters (Figure 1).(13-15) Thus, they appear to be promising for the development of novel metal-labeled DAT imaging agents. However, until recently, the synthesis of these organometallic species has required harsh conditions and multi-step procedures. Recent reports describing the preparation and use of low-valent (i.e., $M(CO)_3^+$) technetium and rhenium has provided some encouragement.(16-23)

The first practical radiochemical preparation of substituted CpTM complexes was the double ligand transfer (DLT) reaction, originally reported by Martin Wenzel in 1992.(24) We

recently reported an improved version of the DLT reaction that minimized formation of unwanted byproducts (Scheme 1).(25) This remarkable transformation involves the in situ reduction/carbonylation of the permethylate species, followed by selective ring transfer from an appropriately substituted ferrocene precursor. It occurs in a single pot, but it requires relatively harsh conditions, and in most cases the DLT is limited to ferrocenes substituted with electron-withdrawing groups. The major drawback in the initial uses of the DLT reaction was that additional steps were needed to conjugate the substituted CpTM to the biological molecule of interest.(25-28)

To extend the DLT methodology further and to prepare novel technetium-labeled DAT imaging agents, we have synthesized a number of appropriately substituted ferrocenyl phenyltropanes for use as substrates in a direct version of the double ligand transfer reaction. In this direct version, the DLT reaction produces the desired radiopharmaceutical agent directly, without need for further conjugations or chemical transformations. We have also prepared some related compounds by methods other than the DLT reaction. All of the compounds prepared here are the rhenium analogs of compounds that might be prepared in technetium-99m labeled form, for SPECT imaging. As a preliminary assessment of the potential of these compounds as DAT imaging agents, we have evaluated the binding affinities of the rhenium complexes for DAT in a competitive binding assay. The preparation of one of the high-affinity compounds in technetium-99m-labeled form, and its evaluation in animal models have been accomplished, but will be described elsewhere.[**REF TO Tc-99m WORK IN PREPARATION OR SUBMITTED?**]

EXPERIMENTAL SECTION

General Comments. In most cases, a general procedure for product isolation and purification was utilized that involved quenching the reaction in an aqueous solution, exhaustive extraction with an organic solvent, drying over an anhydrous salt, filtration, evaporation under reduced pressure and flash chromatography. Such a work-up is indicated by the phrase "product

isolation" (which is then followed, in parentheses, by a listing of quenching agent, extraction solvent and drying agent if not MgSO_4 , which is not listed) and "purification" (which is followed, in parentheses, by the elution solvent used in the flash chromatography).

All reactions were performed under a dry (Drierite) argon atmosphere. Unless otherwise specified, reagents and solvents used in this study were obtained from commercial sources (Aldrich, Strem, or Fluka) and are used without further purification. Temperatures refer to that of the reaction bath. Acetonitrile, triethylamine, methylene chloride and toluene were distilled from calcium hydride under a nitrogen atmosphere. Oxalyl chloride was distilled from and stored over calcium hydride before use. Tetrahydrofuran was distilled from sodium/benzophenone ketal under a nitrogen atmosphere. Dimethylformamide was dried with barium hydroxide and distilled from and stored over 4\AA molecular sieves. Methanol was distilled from magnesium activated with iodine and stored over 3\AA molecular sieves. Hexanes were distilled from CaSO_4 before use in flash chromatography. Butyllithium (Aldrich) was titrated using *N*-pivaloyl-*o*-toluidine according to a literature method.(29)

Reaction progress was monitored using analytical thin-layer chromatography (TLC) on 0.25 mm Merck F-254 silica gel glass plates. Visualization was achieved using potassium permanganate, Dragendorff's reagent or UV illumination. Flash chromatography was performed according to the literature method(30) with Woelm silica gel (0.040-0.063 mm) packing.

Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a U400, U500 or KECK750 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. Both low and high resolution chemical ionization (CI) mass spectra were obtained on a VG Instruments 70-VSE spectrometer. All fast atom bombardment (FAB) mass spectra were obtained on a VG Instruments ZAB-SE

mass spectrometer. Elemental and DSC analyses were performed by the Microanalytical Service Laboratory of the University of Illinois.

4-Bromo-1-ferrocenyl-butan-1-one was prepared by a method analogous to that reported previously.(31) However, in this paper, no characterization data for the aforementioned compound was reported. Ferrocenecarbonyl chloride(32) and cyclopentadienyltricarbonyl rhenium carbonyl chloride(33) have been previously reported. Ferrocenecarboxylic acid is available commercially, whereas cyclopentadienyltricarbonyl rhenium carboxylic acid was prepared by DLT reaction of 1,1'-methoxycarbonylferrocene followed by saponification. Iodocyclopentadienyltricarbonyl rhenium was prepared by an existing method.(34) 8-Methyl-3 β -[4-(trimethylstannanyl)phenyl]-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester(35) and 1-(*tert*-butyldimethylsiloxy)-4-iodobutane(36) were prepared as previously described. Reactions performed using palladium catalysts were degassed using a standard freeze-pump-thaw method

Cautionary Note for the Double Ligand Transfer Reactions: (Taken from Spradau, T. W.; Katzenellenbogen, J. A. Organometallics, 1998, 17, 2009-2017). Pressure tubes were placed within a specially-made solid aluminum block containing holes drilled deep enough to admit the tubes to about 3/4 of their height, and wide enough to allow room for some added mineral oil. The tubes and aluminum base were covered with a matching hollow aluminum screw cap, equipped with a small hole aligned with one drilled in the base (to the same depth as those for the pressure tubes) to hold a metal thermometer. This containment device minimized the potential danger of explosions during heating, allowed for the efficient stirring of the reactions, and enabled the reaction temperature to be monitored readily. All manipulations of sealed reaction tubes during and after the reactions were done in a fume hood with suitable protective equipment: blast shield, full face visor and heavy gloves.

(4-Bromobutanoyl)ferrocene (4). To a suspension of aluminum chloride (1.40 g, 10.5 mmol) in CH₂Cl₂ (4 mL) was added 4-bromobutanoyl chloride (1.16 mL, 10.0 mmol) as a solution in CH₂Cl₂ (4 mL) dropwise via a cannulus at room temperature. After 2 h, the now homogeneous solution was cooled to -10 °C and added via a cannulus to a solution of ferrocene

(1.86 g, 10.0 mmol) in CH_2Cl_2 (24 mL) cooled to 0 °C. The now purple solution was allowed to warm to room temperature and stirred for 16 h. This solution then diluted with CH_2Cl_2 and poured over ice- H_2O . Product isolation (sat NaHCO_3 , CH_2Cl_2), filtration through Celite and purification (R_f 0.45 in CH_2Cl_2) afforded an orange solid (2.78 g, 83%). Mp: 58.0-61.1 °C. This solid should be stored in the freezer to prevent decomposition. ^1H NMR (CDCl_3 , 500 MHz): δ 4.81 (t, 2H, $J = 1.80$ Hz), 4.52 (t, 2H, $J = 1.86$ Hz), 4.22 (s, 5H), 3.57 (t, 2H, $J = 6.23$ Hz), 2.94 (t, 2H, $J = 6.83$ Hz), 2.27 (quin, 2H, $J = 6.54$ Hz). ^{13}C NMR (CDCl_3 , 125 MHz): δ 203.0, 78.8, 72.3, 69.8, 69.2, 37.2, 34.0, 26.9. MS (CI, CH_4): m/z (relative intensity) 337(M+3, 29), 336(M+2, 27), 335(M+1, 29), 334(M⁺, 25), 255(100). HRMS Calcd for $\text{C}_{14}\text{H}_{15}\text{Br}^{56}\text{FeO}$: 333.9656. Found: 333.9656. Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{BrFeO}$: C, 50.19; H, 4.51; Br, 23.85. Found: C, 50.02; H, 4.19; Br, 24.20.

3 β -(4-Chlorophenyl)-8-(4-ferrocenyl-4-oxobutyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (5). To a solution of 3 β -(4-chlorophenyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (nor-CCT, (1) 246.4 mg, 0.881 mmol) and (4-bromobutanoyl)ferrocene (885.2 mg, 2.64 mmol) in toluene (12.3 mL) was added triethylamine (12.3 mL, 88.1 mmol) and KI (27.7 mg, 0.220 mmol) successively. The mixture was then heated to reflux and stirred overnight. After cooling to RT, all volatile material was removed in vacuo. Purification (R_f 0.14 in 2% TEA/18% Et_2O /80% Hexanes) afforded orange solid (318 mg, 68%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.23 (AA' of AA'XX', 2H, $J_{\text{AX}} = 8.78$ Hz, $J_{\text{AA}} = 2.14$ Hz), 7.19 (XX' of AA'XX', 2H, $J_{\text{AX}} = 8.55$ Hz, $J_{\text{XX}} = 2.3$ Hz), 4.80 (m, 2H), 4.48 (m, 2H), 4.22 (s, 5H), 3.73 (dd, 1H, $J = 6.84, 2.67$ Hz), 3.52 (s, 3H), 3.40 (dt, 1H, $J = 6.62, 2.61$ Hz), 2.95 (m, 3H), 2.65 (ddd, 1H, $J = 16.77, 7.63, 5.97$ Hz), 2.59 (td, 1H, $J = 12.60, 3.4$ Hz), 2.33 (m, 2H), 2.11 (m, 1H), 2.01 (m, 1H), 1.85 (tt, 1H, $J = 13.83, 6.71$ Hz), 1.66 (m, 4H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 204.8, 171.8, 141.8, 131.4, 128.6, 128.0, 79.1, 72.1, 72.0, 69.8, 69.4, 69.2, 62.6, 61.5, 52.7, 52.6, 51.0, 36.7, 34.0, 33.8, 26.0, 25.9, 23.4. MS (CI, CH_4): m/z (relative intensity) 534(M+1, 100), 292(40), 255(15), 228(69). HRMS Calcd for $\text{C}_{29}\text{H}_{33}\text{Cl}^{56}\text{FeNO}_3$: 534.1498. Found: 534.1493.

[3 β -(4-Chlorophenyl)-8-(4-ferrocenyl-4-oxobutyl)-8-azabicyclo[3.2.1]oct-2 β -yl]-methanol (6). To a solution of [3 β -(4-chlorophenyl)-8-azabicyclo[3.2.1]oct-2-yl]-methanol (**2**) (36.3 mg, 0.144 mmol) and (4-bromobutanoyl)ferrocene (145 mg, 0.433 mmol) in toluene (1.7 mL) was added triethylamine (1.71 mL, 12.3 mmol) and KI (5.3 mg, 0.032 mmol) successively. The mixture was then heated to reflux and stirred overnight. After cooling to RT, all volatile material was removed in vacuo. Purification (R_f 0.15 in 2% TEA/48% Et₂O/50% Hexanes) afforded an orange solid (68.2 mg, 94%). ¹H NMR (CDCl₃, 500 MHz): δ 7.29 (m, 4H), 4.82 (m, 2H), 4.50 (t, 2H, $J = 1.99$ Hz), 4.21 (s, 5H), 3.77 (dd, 1H, $J = 11.12, 2.06$ Hz), 3.62 (dd, 1H, $J = 6.65, 1.37$ Hz), 3.49 (dt, 1H, $J = 6.48, 3.24$ Hz), 3.37 (dd, 1H, $J = 11.14, 2.53$ Hz), 3.10 (dt, 1H, $J = 12.58, 5.95$ Hz), 2.84 (td, 2H, $J = 7.15, 2.03$ Hz), 2.51 (td, 1H, $J = 13.18, 3.10$ Hz), 2.43 (t, 2H, $J = 7.07$ Hz), 2.10 (m, 2H), 1.95 (quin, 2H, $J = 7.16$ Hz), 1.75 (m, 2H), 1.66 (ddd, 1H, $J = 12.80, 5.40, 3.00$ Hz), 1.52 (dq, 1H, $J = 5.83, 2.61$ Hz). ¹³C NMR (CDCl₃, 189 MHz): δ 204.0, 141.1, 131.8, 129.7, 128.3, 78.8, 72.2, 72.1, 69.8, 69.3, 69.2, 66.9, 65.1, 60.1, 52.9, 45.3, 37.0(2), 36.8, 26.6, 25.4, 23.0. MS (FAB): m/z (relative intensity) 506(M+1, 2), 460(4), 424(2), 366(3), 307(35), 289(17), 154(100), 136(56). HRMS Calcd for C₂₈H₃₃Cl⁵⁶FeNO₂: 506.1549. Found: 506.1548.

3 β -(4-Iodophenyl)-8-(4-ferrocenyl-4-oxobutyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (7). To a solution of 3 β -(4-iodophenyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (nor-CCT, **3**) 180 mg, 0.485 mmol) and (4-bromobutanoyl)ferrocene (812.2 mg, 2.42 mmol) in toluene (20 mL) was added triethylamine (11.5 mL, 82.6 mmol) and KI (13.6 mg, 0.108 mmol) successively. The mixture was then heated to reflux and stirred overnight. After cooling to RT, all volatile material was removed in vacuo. Purification (R_f 0.24 in 2% TEA/28% Et₂O/70% Hexanes) afforded orange solid (210 mg, 69%). ¹H NMR (CDCl₃, 500 MHz): δ 7.29 (AB, 4H, $J_{AB} = 8.45$ Hz), 4.80 (m, 2H), 4.48 (m, 2H), 4.22 (m, 5H), 3.73 (dd, 1H, $J = 6.00, 3.10$ Hz), 3.52 (s, 3H), 3.39 (dt, 1H, $J = 5.80, 2.08$ Hz), 2.94 (m, 3H), 2.64 (ddd, 1H, $J = 16.54, 7.38, 6.00$ Hz), 2.57 (td, 1H, $J = 12.57, 2.43$ Hz), 2.33 (m, 2H), 2.11 (m 1H), 2.00 (m, 1H), 1.84 (tt, 1H, $J = 13.57, 6.79$ Hz), 1.66 (m,

4H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 204.7, 171.8, 143.1, 136.9, 129.5, 127.9, 79.3, 72.2, 72.1, 69.8, 69.4, 69.3, 62.8, 61.4, 52.7, 52.6, 51.0, 36.8, 34.0, 33.9, 26.1, 26.0, 23.5. MS (CI, CH_4): m/z (relative intensity) 626(M+1, 100), 384(61), 228(74). HRMS Calcd for $\text{C}_{29}\text{H}_{33}\text{I}^{56}\text{FeNO}_3$: 626.0855. Found: 626.0846.

{PREPARATION OF COMPOUND 8}

{PREPARATION OF COMPOUND 9}

3β -(4-Chlorophenyl)-8-(4-cyclopentadienyltricarbonyl rhenium butanoyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (10). $(\text{Et}_4\text{N})_2[\text{ReBr}_3(\text{CO})_3]$ (50 mg, 0.065 mmol) was dissolved in acetonitrile (2 mL) and treated with silver trifluoromethanesulfonate (53.4 mg, 0.208 mmol) in one portion. The mixture was stirred for 5 min and the yellow silver bromide precipitate was removed by filtration using a Pasteur pipette fitted with a cotton plug. The resulting colorless solution was added directly to a previously prepared solution containing 8-(3-carboxypropyl)- 3β -(4-chlorophenyl)-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester (**9**) (40.4 mg, 0.110 mmol) and triethylamine (36 μL , 0.260 mmol) in acetonitrile (1 mL). The mixing of the two solutions resulted in the formation of a white precipitate. The polymer-supported diazocyclopentadiene (102.5 mg, 0.195 mmol, 1.90 mmol CpN_2/g polymer) was then added in one portion to the suspension. The mixture was then fitted with a reflux condenser and heated to 80 $^\circ\text{C}$ for 45 min. After cooling to RT, the mixture was concentrated under a stream of nitrogen. Purification (R_f 0.11 in 2% TEA/13% EtOAc/85% Hexanes) afforded a pale yellow oil (38 mg, 70%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.28 (dd, 4H, $J = 8.4$ Hz), 5.55 (t, 2H, $J = 2.3$ Hz), 5.15 (t, 2H, $J = 2.4$ Hz), 3.67 (dd, 1H, $J = 7.3, 3.3$ Hz), 3.45 (s, 3H), 3.37 (dt, 1H, $J = 6.6, 2.5$ Hz), 2.94 (dt, 1H, $J = 12.8, 5.0$ Hz), 2.89 (t, 1H, $J = 4.3$ Hz), 2.58-2.40 (m, 4H), 2.28 (m, 2H), 2.07 (m, 1H), 1.98 (m, 1H), 1.81-1.56 (m, 4H). MS (FAB): m/z (relative intensity) 700(M+1, 4), 460(4), 307(36), 289(17), 154(100), 136(59). HRMS Calcd for $\text{C}_{27}\text{H}_{28}\text{ClNO}_7$ ^{187}Re : 700.1112. Found: 700.1112.

Ferrocenecarbonyl chloride (12). Ferrocenecarboxylic acid (200 mg, 0.869 mmol) was suspended in dry CH_2Cl_2 (5 mL) at 0 $^\circ\text{C}$. Oxalyl chloride (100 μL , 1.13 mmol) was then added

dropwise, followed by several drops of DMF. Vigorous gas evolution ensued, and the mixture became a dark red homogeneous solution. After 1 h, the solution was warmed to RT, and all volatile material was removed under a stream of nitrogen. The residue was dissolved in hot petroleum ether and filtered through paper. The petroleum ether was then removed in vacuo to afford a dark red solid (200 mg, 93%). This compound was used without purification directly in the preparation of compound **14**.

Cyclopentadienyltricarbonyl rhenium carbonyl chloride (13).

Cyclopentadienyltricarbonyl rhenium carboxylic acid (200 mg, 0.527 mmol) was suspended in dry CH_2Cl_2 (5 mL) at 0 °C. Oxalyl chloride (60 μL , 0.685 mmol) was then added dropwise, followed by several drops of DMF. Vigorous gas evolution ensued. After 1 h, the solution was warmed to RT, and all volatile material was removed under a stream of nitrogen. The residue was dissolved in hot hexanes and filtered through paper. The hexanes were then removed in vacuo to afford a white solid (120 mg, 62%). This compound was used without purification directly in the preparation of compound **14a**.

8-Methyl-3 β -(4-ferrocenylphenyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (14). To a solution of ferrocenecarbonyl chloride (**12**) (143 mg, 0.575 mmol) and benzyl bis-(triphenylphosphino) palladium chloride (2.2 mg, 2.9 μmol) in chloroform (1 mL) was added 8-methyl-3 β -[4-(trimethylstannanyl)-phenyl]-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (**11**)(35) (255.1 mg, 0.604 mmol) as a solution in chloroform (1 mL). The flask was fitted with a reflux condenser, and the solution was heated to reflux for 1 h or until palladium black precipitated from the solution. After being cooled to RT, the now red solution was placed directly on a silica column. Purification (R_f 0.26 in 2% TEA/58% Et_2O /40% Hexanes) afforded a red solid (100 mg, 37%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.84 (AA' of AA'XX', 2H, $J_{\text{AX}} = 8.47$ Hz, $J_{\text{AA}} = 1.95$ Hz), 7.35 (XX' of AA'XX', 2H, $J_{\text{AX}} = 8.10$ Hz, $J_{\text{XX}} = 2.28$ Hz), 4.90 (m, 2H), 4.56 (m, 2H), 4.20 (s, 5H), 3.60 (dd, 1H, $J = 7.47, 3.35$ Hz), 3.52 (s, 3H), 3.40 (dt, 1H, $J = 6.62, 3.31$ Hz), 3.06 (dt, 1H, $J = 12.76, 5.06$ Hz), 2.98 (ddd, 1H, $J = 5.01, 3.47, 1.11$ Hz), 2.64 (td, 1H, $J = 12.61, 2.93$ Hz), 2.2⁴ (m, 1H), 2.24 (s, 3H), 2.13 (m, 1H), 1.75 (m, 2H),

1.64 (ddd, 1H, $J = 13.20, 9.43, 4.12$ Hz). ^{13}C NMR (CDCl_3 , 189 MHz): δ 198.7, 172.0, 147.3, 137.3, 128.1, 127.2, 78.5, 72.3, 72.2, 71.6, 71.5, 70.2, 65.3, 62.2, 52.6, 51.2, 42.0, 33.9, 33.8, 25.9, 25.2. MS (EI, 70 eV): m/z (relative intensity) 471(M^+ , 84), 97(64), 83(100). HRMS Calcd for $\text{C}_{27}\text{H}_{29}^{56}\text{FeNO}_3$: 471.1497. Found: 471.1493.

8-Methyl-3 β -[4-(carbonyloxy cyclopentadienyltricarbonyl rhenium)-phenyl]-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (14a). To a solution of cyclopentadienyltricarbonyl rhenium carbonyl chloride (**13**) (38.5 mg, 96.8 μmol) and benzylchloro-bis-(triphenylphosphino) palladium (0.37 mg, 0.48 μmol) in chloroform (1 mL) was added 8-methyl-3 β -[4-(trimethyl-stannanyl)-phenyl]-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester **11** (42.9 mg, 0.102 mmol) as a solution in chloroform (1 mL). The flask was fitted with a reflux condenser, and the solution was heated to reflux for 1 h or until palladium black precipitated from the solution. After being cooled to RT, the yellow solution was placed directly on a silica column. Purification (R_f 0.24 in 2% TEA/68% Et_2O /30% Hexanes) afforded a white solid (55 mg, 92%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.72 (AA' of AA'XX', 2H, $J_{\text{AX}} = 8.32$ Hz, $J_{\text{AA}} = 1.95$ Hz), 7.35 (XX' of AA'XX', 2H, $J_{\text{AX}} = 8.35$ Hz, $J_{\text{XX}} = 2.15$ Hz), 6.06 (t, 2H, $J = 2.26$ Hz), 5.44 (t, 2H, $J = 2.30$ Hz), 3.60 (dd, 1H, $J = 6.56, 2.92$ Hz), 3.51 (s, 3H), 3.39 (m, 2H), 3.04 (dt, 1H, $J = 12.69, 5.20$ Hz), 2.96 (m, 1H), 2.61 (td, 1H, $J = 12.52, 2.78$ Hz), 2.24 (m, 1H), 2.24 (s, 3H), 2.13 (m, 1H), 1.73 (m, 2H), 1.62 (ddd, 1H, $J = 13.29, 9.51, 4.14$ Hz). ^{13}C NMR (CDCl_3 , 125 MHz): δ 192.0, 189.3, 171.9, 148.9, 134.8, 128.3, 127.6, 96.1, 89.7, 89.6, 85.2, 65.2, 62.1, 52.5, 51.2, 41.9, 33.9, 33.7, 25.8, 25.1. MS (EI, 70 eV): m/z (relative intensity) 621(M^+ , 24), 97(53), 83(100). HRMS Calcd for $\text{C}_{25}\text{H}_{24}\text{NO}_6^{187}\text{Re}$: 621.1161. Found: 621.1155.

(7R,5S)-7-(4-Chlorophenyl)-5-pyrrolidin-1-yl-cyclohept-1-enecarboxylic acid methyl ester (15). To a solution of nor-CCT (**1**) (44.4 mg, 0.159 mmol) and 1-bromo-4-chlorobutane (91 mL, 0.794 mmol) in toluene (10 mL) was added triethylamine (250 μL , 1.79 mmol) and KI (6.6 mg, 0.040 mmol) successively. The mixture was then heated to reflux and stirred overnight. After being cooled to RT, all volatile material was removed. Purification (R_f 0.21 in 2% TEA/68% Et_2O /30% Hexanes) afforded a colorless oil (34 mg, 58%). ^1H NMR (CDCl_3 , 500

MHz): δ 7.24 (AA' of AA'XX', 2H, $J_{AX} = 8.49$ Hz, $J_{AA} = 2.30$ Hz), 7.19 (d, 1H, $J = 9.20, 5.95$ Hz), 7.15 (XX' of AA'XX', 2H, $J_{AX} = 8.39$ Hz, $J_{XX} = 2.41$ Hz), 4.02 (ddd, 1H, $J = 11.72, 6.77, 1.55$ Hz), 3.57 (s, 3H), 2.78 (ddtd, 1H, $J = 14.57, 12.35, 6.20, 1.94$ Hz), 2.57 (m, 6H), 2.28 (dddd, 1H, $J = 14.60, 9.06, 5.37, 3.01$ Hz), 2.09 (m, 2H), 1.95 (ddd, 1H, $J = 14.29, 12.06, 9.88$ Hz), 1.77 (m, 5H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 167.9, 143.4, 140.8, 134.7, 131.9, 128.6, 128.6, 59.8, 51.7, 50.7, 45.6, 36.6, 30.0, 23.3, 22.6. MS (EI, 70 eV): m/z (relative intensity) 333(M^+ , 11), 318(4), 304(10), 274(6), 208(48), 97(100). HRMS Calcd for $\text{C}_{19}\text{H}_{24}\text{ClNO}_2$: 333.1496. Found: 333.1491.

Benzoylferrocene (16). To a suspension of aluminum chloride (376.3 g, 2.82 mmol) in CH_2Cl_2 (1 mL) was added benzoyl chloride (312 μL , 2.69 mmol) as a solution in CH_2Cl_2 (1 mL) dropwise via a cannulus at RT. After 2 h, the homogeneous solution was cooled to -10 °C and added via a cannulus to a solution of ferrocene (500 mg, 2.69 mmol) in CH_2Cl_2 (5 mL) cooled to 0 °C. The now purple solution was allowed to warm to RT and stirred for 16 h. This solution then diluted with CH_2Cl_2 and poured over ice- H_2O . Product isolation (sat NaHCO_3 , CH_2Cl_2), filtration through Celite and purification (R_f 0.21 in CH_2Cl_2) afforded red crystals (631 mg, 81%). Mp: 107.3 - 108.9 °C. ^1H NMR (CDCl_3 , 500 MHz): δ 7.90 (m, 2H), 7.55 (m, 1H), 7.47 (m, 2H), 4.91 (t, 2H, $J = 1.88$ Hz), 4.59 (t, 2H, $J = 2.00$ Hz), 4.21 (s, 5H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 199.2, 139.8, 131.5, 128.2, 128.1, 78.1, 72.5, 71.5, 70.2. MS (EI, 70 eV): m/z (relative intensity) 290(M^+ , 100), 197(10), 141(10), 133(14), 56(12). HRMS Calcd for $\text{C}_{17}\text{H}_{14}^{56}\text{FeO}$: 290.0394. Found: 290.0395.

4-tert-Butyldimethylsilyloxy-1-(cyclopentadienyltricarbonyl rhenium)-butane (18). To a solution of cyclopentadienyltricarbonyl rhenium (335.3 mg, 1.00 mmol) in THF (10 mL) at -78 °C, was added BuLi (617 μL , 1.00 mmol). After 3 h at -78 °C, 1-(tert-butyldimethylsilyloxy)-4-iodobutane **17** (628.6 mg, 2.00 mmol) was added and the temperature maintained for an additional 2 h. The solution was then allowed to warm to RT and stirred overnight. Product isolation (H_2O , EtOAc) and purification (R_f 0.23 in 5% EtOAc/Hexanes) afforded a colorless oil (250 mg, 48%). ^1H NMR (CDCl_3 , 500 MHz): δ 5.24 (s, 4H), 3.62 (m, 2H), 2.43 (m, 2H), 1.58-

1.54 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 194.6, 111.6, 83.5, 82.9, 62.7, 32.3, 28.2, 27.9, 25.9, 18.3, -5.3. MS (EI, 70 eV): m/z (relative intensity) 523(M+1, 18), 507(16), 465(41), 409(15), 391(100). HRMS Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_4^{187}\text{ReSi}$: 522.1236. Found: 524.1399.

4-*tert*-Butyldimethylsilyloxy-1-(cyclopentadienyltricarbonyl manganese)butane (19).

To a solution of cyclopentadienyltricarbonyl manganese (408.1 mg, 2.00 mmol) in THF (20 mL) at $-78\text{ }^\circ\text{C}$, was added BuLi (1.23 mL, 2.00 mmol). After 3 h at $-78\text{ }^\circ\text{C}$, 1-(*tert*-butyldimethylsilyloxy)-4-iodobutane **17** (942.8 mg, 3.00 mmol) was added and the temperature maintained for an additional 2 h. The solution was then allowed to warm to RT and stirred overnight. Product isolation (H_2O , EtOAc) and purification (R_f 0.06 in 2.5% EtOAc/Hexanes) afforded a yellow oil (558 mg, 72%). ^1H NMR (CDCl_3 , 500 MHz): δ 4.63(t, 2H, $J = 2.14$ Hz), 4.61 (t, 2H, $J = 2.09$ Hz), 3.62 (m, 2H), 2.27 (m, 2H), 1.56 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). In order to avoid decomposition, this compound was used without further purification in the next step.

4-Hydroxy-1-(cyclopentadienyltricarbonyl rhenium)-butane (20). To a solution of TBS ether **18** (240 mg, 0.460 mmol) in THF (5 mL) was added 1M solution of tetrabutylammonium fluoride in THF (TBAF, 920 μL , 0.920 mmol) dropwise at $0\text{ }^\circ\text{C}$. After 1 h at $0\text{ }^\circ\text{C}$, TLC indicated complete conversion of the starting material to a more polar compound. Product isolation (H_2O , Et_2O) and purification (R_f 0.26 in 50% EtOAc/Hexanes) afforded a colorless oil (180 mg, 96%). ^1H NMR (CDCl_3 , 500 MHz): δ 5.25 (s, 4H), 3.68 (m, 2H), 2.46 (m, 2H), 1.67-1.57 (m, 4H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 194.5, 111.3, 83.6, 82.8, 62.4, 32.2, 27.9(2). MS (EI, 70 eV): m/z (relative intensity) 408(M^+ , 45), 380(23), 348(31), 322(100), 304(23), 263(34), 85(35), 71(48), 57(67). HRMS Calcd for $\text{C}_{12}\text{H}_{13}\text{O}_4^{187}\text{Re}$: 408.0371. Found: 408.0372.

4-Hydroxy-1-(cyclopentadienyltricarbonyl manganese)-butane (21). To a solution of TBS ether **19** (550 mg, 1.41 mmol) in THF (10 mL) was added TBAF (2.82 mL, 2.00 mmol) dropwise at $0\text{ }^\circ\text{C}$. After 1 h at $0\text{ }^\circ\text{C}$, TLC indicated complete conversion of the starting material

to a more polar compound. Product isolation (H_2O , Et_2O) and purification (R_f 0.15 in 30% EtOAc/Hexanes) afforded a yellow oil (240 mg, 62%). ^1H NMR (CDCl_3 , 500 MHz): δ 4.64 (t, 2H, $J = 2.10$ Hz), 4.61 (t, 2H, $J = 2.20$ Hz), 3.68 (q, 2H, $J = 5.53$ Hz), 2.29 (m, 2H), 1.66-1.55 (m, 4H), 1.25 (bt, 1H, 5.15 Hz). ^{13}C NMR (CDCl_3 , 125 MHz): δ 225.2, 107.0, 81.9, 81.7, 62.5, 32.2, 27.9, 27.1. MS (EI, 70 eV): m/z (relative intensity) 276(M^+ , 2), 192(32), 174(32), 150(16), 84(100). HRMS Calcd for $\text{C}_{12}\text{H}_{13}\text{O}_4\text{Mn}$: 276.0194. Found: 276.0190.

4-*p*-Toluenesulfonyloxy-1-(cyclopentadienyltricarbonyl rhenium)-butane (22).

Alcohol **20** (90 mg, 0.221 mmol) was dissolved in pyridine (5 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (63.2 mg, 0.331 mmol) was added in one portion and the solution placed in the freezer overnight. Product isolation (sat CuSO_4 , Et_2O) and purification (R_f 0.33 in 30% EtOAc/Hexanes) afforded a yellow oil (100 mg, 81%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.79 (AA' of AA'XX', 2H, $J_{\text{AX}} = 8.36$ Hz, $J_{\text{AA}} = 2.05$ Hz), 7.36 (m, 2H), 5.24 (t, 2H, $J = 2.16$ Hz), 5.19 (t, 2H, $J = 2.26$ Hz), 4.04 (t, 2H, $J = 6.33$ Hz), 2.46 (s, 3H), 2.37 (m, 2H), 1.71 (m, 2H), 1.53 (m, 2H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 194.3, 144.9, 132.9, 129.9, 127.9, 110.4, 83.7, 82.9, 69.8, 28.4, 27.6, 27.4, 21.6. MS (EI, 70 eV): m/z (relative intensity) 562(M^+ , 68), 534(63), 478(51), 332(100), 91(52). HRMS Calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6\text{S}^{187}\text{Re}$: 562.0460. Found: 562.0458.

4-*p*-Toluenesulfonyloxy-1-(cyclopentadienyltricarbonyl manganese)-butane (23).

Alcohol **21** (240 mg, 0.869 mmol) was dissolved in pyridine (10 mL) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (331.3 mg, 1.74 mmol) was added in one portion and the solution placed in the freezer overnight. Product isolation (sat CuSO_4 , Et_2O) and purification (R_f 0.25 in 20% EtOAc/Hexanes) afforded a yellow oil (374 mg, 99%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.79 (AA' of AA'XX', 2H, $J_{\text{AX}} = 8.33$ Hz, $J_{\text{AA}} = 2.02$ Hz), 7.35 (m, 2H), 4.63 (t, 2H, $J = 2.12$ Hz), 4.55 (t, 2H, $J = 2.11$ Hz), 4.04 (t, 2H, $J = 6.29$ Hz), 2.45 (s, 3H), 2.20 (m, 2H), 1.71 (m, 2H), 1.53 (m, 2H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 225.1, 144.8, 133.0, 29.9, 127.9, 106.2, 81.9, 81.8, 69.9, 28.4, 27.5, 26.8, 21.6. MS (EI, 70 eV): m/z (relative intensity) 430(M^+ , 6), 346(33), 259(100), 203(23), 121(25), 93(35). HRMS Calcd for $\text{C}_{19}\text{H}_{19}\text{O}_6\text{MnS}$: 430.0283. Found: 430.0278.

3 β -(4-Chlorophenyl)-8-(4-cyclopentadienyltricarbonyl rhenium-butyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (24). To a solution of nor-CCT (**1**) (49.8 mg, 0.178 mmol) and tosylate **22** (100 mg, 0.178 mmol) in toluene (10 mL) was added triethylamine (250 μ L, 1.79 mmol) and KI (5.6 mg, 0.045 mmol) successively. The mixture was then heated to reflux and stirred overnight. After the solution had cooled to RT, all volatile material was removed in vacuo. Purification (R_f 0.24 in 2% TEA/28% Et₂O/70% Hexanes) afforded a yellow oil (61 mg, 51%). ¹H NMR (CDCl₃, 500 MHz): δ 7.23 (AA' of AA'XX', 2H, $J_{AX} = 8.59$ Hz, $J_{AA} = 2.29$ Hz), 7.18 (XX' of AA'XX', 2H, $J_{AX} = 8.54$ Hz, $J_{XX} = 2.59$ Hz), 5.24 (m, 4H), 3.66 (dd, 1H, $J = 7.12, 3.29$ Hz), 3.48 (s, 3H), 3.38 (dt, 1H, $J = 6.63, 3.32$ Hz), 2.97 (dt, 1H, $J = 12.80, 5.06$ Hz), 2.89 (m, 1H), 2.54 (td, 1H, $J = 12.37, 2.99$ Hz), 2.39 (m, 2H), 2.25 (ABt, 2H, $J_{AB} = 12.19$ Hz, $J_t = 6.68$ Hz), 2.09 (tdd, 1H, $J = 12.70, 7.10, 4.09$ Hz), 1.99 (tdd, 1H, $J = 12.76, 6.57, 4.66$ Hz), 1.71 (ddd, 1H, $J = 13.35, 9.45, 4.28$ Hz), 1.65 (dddd, 1H, $J = 12.45, 4.74, 3.40, 1.18$ Hz), 1.61 (ddd, 1H, $J = 13.39, 9.43, 4.28$ Hz), 1.52 (m, 2H), 1.43 (m, 2H). ¹³C NMR (CDCl₃, 125 MHz): δ 194.6, 171.9, 141.8, 131.4, 128.7, 128.0, 111.8, 83.6, 82.9, 82.8, 62.9, 61.3, 52.9, 52.8, 51.0, 34.0, 33.8, 29.2, 28.5, 27.9, 26.0. MS (EI, 70 eV): m/z (relative intensity) 669(M⁺, 62), 638(9), 610(14), 458(51), 429(38), 292(100), 97(56). HRMS Calcd for C₂₇H₂₉ClNO₅¹⁸⁷Re: 669.1292. Found: 669.1297.

3 β -(4-Chlorophenyl)-8-(4-cyclopentadienyltricarbonyl manganese-butyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (25). To a solution of nor-CCT (**1**) (194.5 mg, 0.695 mmol) and tosylate **23** (374 mg, 0.869 mmol) in toluene (20 mL) was added triethylamine (500 μ L, 3.59 mmol) and KI (21.9 mg, 0.174 mmol) successively. The mixture was then heated to reflux and stirred overnight. After the solution had cooled to RT, all volatile material was removed in vacuo. Purification (R_f 0.42 in 2% TEA/20% Et₂O/78% Hexanes) afforded a yellow oil (345 mg, 93%). ¹H NMR (CDCl₃, 500 MHz): δ 7.23 (AA' of AA'XX', 2H, $J_{AX} = 8.75$ Hz, $J_{AA} = 2.22$ Hz), 7.18 (XX' of AA'XX', 2H, $J_{AX} = 8.73$ Hz, $J_{XX} = 2.52$ Hz), 4.62 (t, 2H, $J = 2.10$ Hz), 4.60 (t, 2H, $J = 2.15$ Hz), 3.67 (dd, 1H, $J = 7.03, 3.44$ Hz), 3.48 (s, 3H), 3.38 (dt, 1H, $J = 7.00, 3.50$ Hz), 2.97 (dt, 1H, $J = 12.86, 4.98$ Hz), 2.89 (m, 1H), 2.54 (td, 1H, $J =$

12.57, 3.13 Hz), 2.30-2.20 (m, 4H), 2.09 (tdd, 1H, $J = 12.73, 6.92, 4.18$ Hz), 1.99 (tdd, 1H, $J = 12.70, 6.40, 3.78$ Hz), 1.71 (ddd, 1H, $J = 13.34, 9.44, 4.12$ Hz), 1.65 (dddd, 1H, $J = 12.20, 4.82, 3.30, 1.34$ Hz), 1.61 (ddd, 1H, $J = 13.37, 9.73, 4.53$ Hz), 1.52 (m, 2H), 1.42 (m, 2H). ^{13}C NMR (CDCl_3 , 125 MHz): δ 225.2, 171.8, 141.7, 131.3, 128.6, 127.9, 107.4, 81.9, 81.6, 62.8, 61.3, 53.0, 52.7, 51.0, 33.9, 33.7, 28.6, 28.4, 27.9, 25.9, 25.8. MS (EI, 70 eV): m/z (relative intensity) 537(M^+ , 23), 453(100), 421(11), 292(13), 243(11), 174(13). HRMS Calcd for $\text{C}_{27}\text{H}_{29}\text{ClMnNO}_5$: 537.1115. Found: 537.1113.

8-Methyl-3 β -[4-(Cyclopentadienyltricarbonyl rhenium)-phenyl]-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (26). 8-Methyl-3 β -[4-(trimethylstannyl)-phenyl]-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester **11** (70 mg, 0.166 mmol) and iodocyclopentadienyltricarbonyl rhenium (33.4 mg, 0.166 mmol) were dissolved in DMF (5 mL) at RT. Bis(triphenylphosphino)dichloro palladium (2.3 mg, 3.3 μmol) was added to the solution, which was subsequently degassed and stirred overnight. Product isolation (sat LiCl, Et_2O) and purification (R_f 0.22 in 2% TEA/68% Et_2O /30% Hexanes) afforded a white powder (63 mg, 64%). ^1H NMR (CDCl_3 , 400 MHz): δ 7.22 (AA' of AA'XX', 2H, $J_{\text{AX}} = 8.40$ Hz, $J_{\text{AA}} = 2.20$ Hz), 7.14 (m, 2H), 5.64 (m, 2H), 5.29 (m, 2H), 3.49 (dd, 1H, $J = 6.80, 2.80$ Hz), 3.40 (s, 3H), 3.29 (tt, 1H, $J = 6.40, 3.20$ Hz), 2.93 (dt, 1H, $J = 12.40, 5.20$ Hz), 2.83 (m, 1H), 2.50 (td, 1H, $J = 12.40, 2.80$ Hz), 2.15 (s, 3H), 2.12 (m, 1H), 2.03 (m, 1H), 1.64 (m, 2H), 1.54 (ddd, 1H, $J = 13.20, 9.60, 4.40$ Hz). ^{13}C NMR (CDCl_3 , 100 MHz): δ 194.6, 172.5, 144.2, 129.5, 128.1, 126.4, 109.4, 84.6, 84.5, 82.0, 81.9, 65.7, 62.6, 53.1, 51.6, 42.3, 34.3, 33.9, 26.3, 25.5. MS (EI, 70 eV): m/z (relative intensity) 593(M^+ , 73), 565(15), 534(19), 97(68), 83(100). HRMS Calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_5^{187}\text{Re}$: 593.1212. Found: 593.1212.

Typical Experimental Procedure for Double Ligand Transfer Reactions. (*See Cautionary Note at the Start of the Experimental Section.*) Reactions were performed in 4 mL threaded pressure tubes sealed with Teflon screw caps with O-rings (all purchased from Ace Glass). An egg-shaped (1 cm) stir bar was used to stir each reaction. Potassium perrhenate (1 equiv), chromium hexacarbonyl (5.61 eq), chromium chloride (2.01 equiv) and the appropriate

ferrocene (3.13 equiv) were combined in an oven-dried 4 mL pressure tube containing a magnetic stir bar. Dry methanol (500 μ L) was added, the tube was flushed with argon and then rapidly sealed. The heterogeneous mixture was placed in the reaction vessel described above and heated to 160 $^{\circ}$ C for 30 min. The tube was then carefully removed and placed directly into a water bath at RT: the solution is homogeneous when it comes out of the reaction vessel. After 10 min, ice was added to the bath. Following an additional 10 min, the tube was transferred to a -78 $^{\circ}$ C bath before it could safely be opened. The reaction mixture was then diluted with CH_2Cl_2 and transferred to a 20-mL scintillation vial. The volatile components were removed under a stream of nitrogen and the residue purified on silica.

3 β -(4-Chlorophenyl)-8-(4-cyclopentadienyltricarbonyl rhenium-4-oxobutyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (5a). The typical procedure for the DLT reaction, given above, was used with potassium perrhenate (8.7 mg, 0.030 mmol), chromium hexacarbonyl (36.9 mg, 0.168 mmol), chromium chloride (9.5 mg, 0.060 mmol) and ferrocene **5**, (50 mg, 0.094 mmol). Purification (2% TEA/48% Et_2O /50% Hexanes) afforded dark brown oil (9.7 mg, 47%). All spectroscopic data for this compound were identical to that previously reported in the literature. (37)

[3 β -(4-Chlorophenyl)-8-(4-cyclopentadienyltricarbonyl rhenium-4-oxobutyl)-8-azabicyclo[3.2.1]oct-2 β -yl]-methanol (6a). The typical procedure for the DLT reaction, given above, was used with potassium perrhenate (11.0 mg, 0.038 mmol), chromium hexacarbonyl (46.8 mg, 0.213 mmol), chromium chloride (12.1 mg, 0.076 mmol) and ferrocene **6**, (60 mg, 0.119 mmol). Purification (R_f 0.16 in 2% TEA/68% Et_2O /30% Hexanes) afforded a dark brown oil (6.6 mg, 27%). ^1H NMR (CDCl_3 , 500 MHz): δ 7.28 (m, 4H), 6.05 (ddt, 2H, $J = 9.06, 3.14, 1.67$ Hz), 5.40 (m, 2H), 3.75 (dd, 1H, $J = 11.27, 2.23$ Hz), 3.57 (dd, 1H, $J = 6.94, 2.08$ Hz), 3.45 (dt, 1H, $J = 6.48, 2.86$ Hz), 3.33 (dd, 1H, $J = 11.12, 2.58$ Hz), 3.09 (dt, 1H, $J = 12.57, 5.95$ Hz), 2.72 (ABt, 2H, $J_{AB} = 16.88$ Hz, $J_1 = 7.20$ Hz), 2.47 (td, 1H, $J = 13.13, 3.24$ Hz), 2.36 (t, 2H, $J = 6.93$ Hz), 2.08 (m, 2H), 1.91 (quin, 2H, $J = 7.25$ Hz), 1.73 (m, 2H), 1.64 (ddd, 1H, $J = 12.84, 5.59, 2.90$ Hz), 1.50 (dq, 1H, $J = 6.12, 2.37$ Hz). ^{13}C NMR (CDCl_3 , 125 MHz): δ 194.9, 191.9,

141.1, 131.9, 129.7, 128.4, 96.0, 88.0, 87.9, 85.5, 85.3, 66.9, 65.1, 60.2, 52.5, 45.3, 36.9, 36.7, 36.3, 26.5, 25.4, 23.0. MS (FAB): m/z (relative intensity) 656(M+1, 11), 307(31), 289(16), 154(100), 136(72). HRMS Calcd for $C_{26}H_{28}ClNO_5^{187}Re$: 656.1214. Found: 656.1223.

3 β -(4-Iodophenyl)-8-(4-cyclopentadienyltricarbonyl rhenium-4-oxobutyl)-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (7a). The typical procedure for the DLT reaction, given above, was used with potassium perrhenate (4.6 mg, 0.016 mmol), chromium hexacarbonyl (21.1 mg, 0.096 mmol), chromium chloride (5.1 mg, 0.032 mmol) and ferrocene **7**, (10 mg, 0.016 mmol). Purification (R_f 0.26 in 2% TEA/28% Et₂O/70% Hexanes) afforded dark brown oil (6.5 mg, 52%). ¹H NMR (CDCl₃, 500 MHz): δ 7.58 (AA' of AA'XX', 2H, $J_{AX} = 8.46$ Hz, $J_{AA} = 2.15$ Hz), 7.00 (m, 2H), 6.06 (ABt, 2H, $J_{AB} = 3.08$ Hz, $J_t = 1.62$ Hz), 5.39 (dtd, 2H, $J = 10.95, 2.76, 1.72$ Hz), 3.66 (m, 1H), 3.48 (s, 3H), 3.36 (m, 1H), 3.10 (ABd, 2H, $J_{AB} = 7.29$ Hz, $J_d = 4.76$ Hz), 2.92 (m, 2H), 2.83 (dt, 1H, $J = 16.89, 7.38$ Hz), 2.55 (m, 2H), 2.27 (t, 2H, $J = 6.10$ Hz), 2.07 (m, 1H), 1.98 (m, 1H), 1.70 (m, 4H). ¹³C NMR (CDCl₃, 125 MHz): δ 195.9, 192.0, 171.9, 143.0, 136.9, 129.4(2), 96.4, 88.1, 88.0, 85.5, 85.0, 62.9, 61.2, 58.4, 52.5, 52.2, 51.0, 35.9, 33.9, 26.0, 25.9, 23.5. MS (CI, CH₄): m/z (relative intensity) 776(M+1, 95), 650(18), 397(100), 271(19). HRMS Calcd for $C_{27}H_{28}INO_6^{187}Re$: 776.0519. Found: 776.0523.

8-Methyl-3 β -[4-(carbonyloxy cyclopentadienyltricarbonyl rhenium)-phenyl]-8-azabicyclo[3.2.1]octane-2 β -carboxylic acid methyl ester (14a). The typical procedure for the DLT reaction, given above, was used with potassium perrhenate (3.3 mg, 0.011 mmol), chromium hexacarbonyl (14 mg, 0.064 mmol), chromium chloride (3.6 mg, 0.023 mmol) and ferrocene **14**, (5.6 mg, 0.012 mmol). Purification (R_f 0.24 in 2% TEA/68% Et₂O/30% Hexanes) afforded dark brown oil (3.1 mg, 42%). All spectroscopic data for this compound were identical to that shown above for this compound.

Benzoylcyclopentadienyltricarbonyl rhenium (16a). The typical procedure for the DLT reaction, given above, was used with potassium perrhenate (31.9 mg, 0.110 mmol), chromium hexacarbonyl (135.9 mg, 0.618 mmol), chromium chloride (35 mg, 0.221 mmol) and

ferrocene **16**, (100 mg, 0.345 mmol). Purification (R_f 0.06 in 10% EtOAc/Hexanes) afforded an orange solid, (25 mg, 50%), which could be recrystallized from ethanol/water to afford white crystals. Spectroscopic data for this compound matched that previously reported.(38) ^1H NMR (CDCl_3 , 500 MHz): δ 7.78 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 6.06 (t, 2H, $J = 2.46$ Hz), 5.46 (t, 2H, $J = 2.33$ Hz). MS (EI, 70 eV): m/z (relative intensity) 440(M^+ , 50), 412(28), 356(100), 328(51), 302(38). HRMS Calcd for $\text{C}_{15}\text{H}_9\text{O}_4^{187}\text{Re}$: 440.0058. Found: 440.0051.

Dopamine Transporter Affinity Assays. {RON AND ROSS TO CHECK/REVISE}

Stock solutions (1 mM) of test agents were made in 96% ethanol/DMSO (1/1, v/v) and stored at -5 °C until used for transporter affinity assay, by diluting in a large excess of assay buffer. Typically, agents were tested at six concentrations in duplicate, with a crude membrane fraction of homogenates of rat brain corpus striatum in Tris-citrate buffer (pH 7.4) containing Na^+ (120 nM) and Mg^{2+} (4 mM) following the methods reported previously.(7,39,40) For this assay the radioligand was [^3H]GBR-12935 (13 Ci/mmol; $K_d = 1.0$ nM) at a test concentration (L) of 0.4 nM and was incubated for 45 min at 4 °C, with or without 30 μM methylphenidate included to define nonspecific binding (blank) as recommended by Andersen;(39) nonspecific binding averaged 20-25% of total counts bound with this or alternative blanking agents included at ca. 200 times their experimentally determined IC_{50} values (GBR-13069, 100 nM; mazindol, 1 μM ; nomifensine, 10 μM). All radioligands were from DuPont-NEN (Boston, MA). Concentration-inhibition curves were fit with the ALLFIT program(41,42) to determine $\text{IC}_{50} \pm \text{SEM}$ and converted to K_i values from the Cheng and Prusoff(43) equation: $K_i = \text{IC}_{50}/(1 + [L]/K_d)$.(7)

RESULTS AND DISCUSSION

Compound Design. A great number of substituted phenyl-tropanes that target a variety of monoamine reuptake sites are known, many of which have a variety of substituents at the 2 β -, 3 β - and N -8 positions of the azabicyclo[3.2.1]octane cocaine core structure. As exemplified through the structures shown in Figure 1, the dopamine transporter is quite tolerant of steric bulk at these positions. Therefore, to obtain compounds that retain high affinity for the dopamine

transporter, we have chosen to prepare 2 β -, 3 β - and *N*-8 substituted tropane systems. Our initial design also incorporated an electron-withdrawing substituent, such as a ketone or ester, which is needed to facilitate the double ligand transfer (DLT) reaction.⁽²⁵⁾ Later, we prepared tropane analogs without this carbonyl function; these analogs were prepared by other, more recently described methods.⁽⁴⁴⁾

Carbonyl-Linked CpTR-Tropane Systems. The initial set of carbonyl-linked compounds (V-VII) we chose to prepare is shown in Figure 2. In our preliminary investigations, the ester linkage in compounds such as VI proved to be problematic, because it was cleaved by methanolysis under the vigorous conditions of the DLT reaction.⁽³³⁾ Therefore, these esters will not be discussed further. Methanolysis of the C-2 β methoxycarbonyl group in V and VII, on the other hand, regenerates the same compound and is of no consequence.

N-Alkylation of Nor-Tropans. *N*-Alkylation of the nor-tropans is readily accomplished with alkyl halides and sulfonates, using the weak base triethylamine; stronger bases, such as carbonates, result in significant epimerization of the C-2 β methoxycarbonyl group to the thermodynamically more stable C-2 α isomer. Systems with a four-atom linker between the nitrogen and the metallocene (5-7) were prepared using (4-halobutanoyl)ferrocenes (Scheme 2). These alkylating agents can be prepared by Friedel-Crafts monoacylation of ferrocene with the (4-halobutanoyl)chlorides, under carefully controlled conditions.⁽³¹⁾ Although (4-chlorobutanoyl)ferrocene was unreactive in tropane *N*-alkylations, the corresponding 4-bromo compound 4 afforded the desired ferrocenyl phenyl-tropans (5-7) in moderate yields.

Because of its structural relationship to the *N*-linked ketones 5-7 (Scheme 4), we also prepared the ester 10. This ester can be prepared conveniently by a three-component condensation reaction that we have recently described, through which carboxylic acids can be attached directly as acyloxy links to the cyclopentadienyl ring of CpTM systems.^(45,46) The required suitable carboxylic acid precursor 9 was prepared by alkylation of the chlorophenyl-tropane, nor-CCT (1) with benzyl 4-bromobutanate to afford the benzyl ester 8 in moderate yield. We initially had difficulty removing the benzyl ester protecting group, because aromatic

ring dechlorination also occurred during the hydrogenolysis. However, by reducing the catalyst loading, we could remove the benzyl ester group selectively, and the free acid **9** was converted to the desired CpTR phenyl-tropane complex **10** in good yield by the three-component condensation, using *fac*-(CH₃CN)₃Re(CO)₃⁺ and polymer-supported diazocyclopentadiene (Scheme 3).(47)

Substitution at the Para Position of the 3β-Phenyl Group. In general, phenyl-tropanes substituted at the *para* position of the 3β-phenyl group have poor affinity for the dopamine transporter, a notable exception being the *para*-3β-(2-pyridyl)-substituted compound, which exhibits good binding affinity to DAT. Interestingly, the analogous unsymmetrical bisaryl ketones have not been reported as substrates in the DLT reaction.

We initially attempted to prepare the differentially-substituted bisaryl ketones **14** and **14a** (Scheme 4) from β-CIT (**I**) using a Suzuki carbonylative cross-coupling reaction.(48,49) Although ferroceneboronic acid is commercially available, it is a rather hindered compound,(46) and in a model Suzuki reaction of ferroceneboronic acid with 4-iodotoluene in the presence of bis(triphenylphosphine)dichloro palladium and potassium carbonate under one atmosphere of carbon monoxide, we obtained the coupling product in only low yield (20%), with poor conversion (not shown). We attempted this reaction on the hydroxymethyl analog of CIT [**DO WE NEED TO SHOW THIS STRUCTURE – COULD BE A VARIANT ON THE B-CIT STRUCTURE TO BE ADDED**] rather than on β-CIT itself, to avoid the risk of epimerization of a C-2 ester by potassium carbonate, but we did not obtain any cross-coupled product.

We were able to prepare the desired ketones using the Stille reaction, however.(50) 8-Methyl-3β-[4-(trimethylstannanyl)-phenyl]-8-azabicyclo[3.2.1]octane-2β-carboxylic acid methyl ester **11**, which has been used for the preparation of iodine-123 labeled β-CIT (**I**), can be prepared directly from the iodo precursor (the N-methyl analog of **3**) by treatment with hexamethyldistannane in the presence of a palladium catalyst. (35) Ferrocenecarbonyl chloride (**12**) and cyclopentadienyltricarbonyl rhenium carbonyl chloride (**13**) were prepared from the corresponding carboxylic acids. They reacted with the tin precursor **11** and

bis(triphenylphosphino)dichloro palladium to afford the desired biaryl ketones **14** and **14a** (Scheme 4). It should be noted that these reactions were performed on purified (i.e., recrystallized) acid chlorides; reaction yields decreased significantly with unpurified material.

Double Ligand Transfer Reactions of Ferrocenyl Phenyl-Tropans. We used rhenium as the metal in these reactions as a model for technetium to evaluate the utility of these ferrocenyl phenyl-tropans as potential substrates for the direct double ligand transfer reaction. The results are given in Table 1. Several aspects of these reactions deserve comment. The yields of the CpTR products are, as expected, moderate. However, these results are encouraging because rhenium is less reactive than technetium, so higher yields with technetium are anticipated. **[REFER TO TECHNETIUM PAPER SUBMITTED, IN PREPARATION]**

The DLT reaction continues to display an impressive tolerance for functional groups. Previous reports had shown that amides, esters and ketones were unaffected by this reaction, whereas aldehydes and alkynes underwent methanol addition. Through our efforts here, we find that free alcohols, amines and halides also survive the high temperature of this reaction, and, of special note, aryl halide bonds remain intact, even under these reducing conditions. Since the biaryl ketones had up to now not been reported as substrates for the DLT reaction, we examined benzoylferrocene (**16**) and found it to be an excellent substrate for the reaction. Reaction of the analogous tropane system (**14**) proceeded similarly.

Directly Linked CpTR Phenyl-Tropans. To have a more complete profile of our CpTR phenyl-tropane pharmacophore, we modified our original designs by removing the carbonyl functionality in the conjugate side chain. Although it would be difficult to prepare these systems by the DLT reaction, because they lack the activating carbonyl link, our recently described approach using cyclopentadienyl tin precursors could be ultimately be used to prepare them in technetium-99m labeled form.⁽⁴⁴⁾ Here, we have taken a different approach.

The preparation of these new systems by direct deoxygenation of compounds we had already prepared did not seem promising, because of the sensitivity of the tropane skeleton. Therefore, we investigated the alkylation of suitable haloalkyl tropane precursors with the

lithium anions generated from cyclopentadienyltricarbonyl manganese and CpTR. To our surprise, when we attempted to prepare a potential 4-chlorobutyl-tropane alkylating precursor by the reaction of nor-CCT (**1**) with 1-bromo-4-chlorobutane, we isolated the ring-opened material **15** as the exclusive product (Scheme 5), presumably the result of double alkylation to form a spiro ammonium salt that then undergoes β -elimination, forming the unsaturated ester.

To avoid this difficulty, we reversed the sequence of alkylation steps, preparing first a 4-halobutyl CpTM system and then coupling it to the N-8 position of a nor-tropane. The anions of CpTM (rhenium and manganese), generated by treatment with butyllithium, underwent reaction with 1-(*tert*-butyldimethylsiloxy)-4-iodobutane (**17**) to give 4-(*tert*-butyldimethylsilyloxy)-1-(cyclopentadienyltricarbonyl rhenium)-butane (**18**) and the corresponding manganese analog **19**, respectively (Scheme 6). Both compounds underwent smooth deprotection upon treatment with tetrabutylammonium fluoride. The *para*-toluenesulfonate esters of alcohols **20** and **21** underwent reaction with nor-tropane **1**, affording the desired CpTR and CpTM phenyl-tropane conjugates (Scheme 7).

We prepared another directly linked CpTR tropane, an analog of conjugate **14a**, by removal of the carbonyl linkage of the biaryl ketone moiety and its replacement with a direct biaryl link. In a manner analogous to the method described previously (cf. Scheme 4), iodocyclopentadienyltricarbonyl rhenium was coupled with the aryl stannane **11** in the presence of a palladium catalyst, to afford the desired biarene **26** (Scheme 8). The three-component condensation or our more recent approach using cyclopentadienyl tin precursors, might provide an efficient route for preparing this compound in technetium-99m form.^(44,46)

DAT Binding Affinities of CpTR Phenyl-Tropane Conjugates. [NOTE TO RON: THIS SECTION NEEDS YOUR ATTENTION. DO WE HAVE AFFINITIES FOR COMPOUNDS **24** AND **25**?] A competitive in vitro radiometric binding assay was used to determine the binding affinity of the new tropane derivatives for the dopamine-transporter in rat forebrain tissue. A summary of the values is given in Table 2. Compounds are listed in order of decreasing DAT affinity, with linkage type and substituent position indicated: $K_i = 0.96$ nM for

β -CIT (**I**). Affinities for the serotonin (5-HTT) and nor-epinephrine (NET) transporters are also given for comparison.

The compounds conjugated at the *N*-8 position all showed good affinity for the dopamine transporter. Compounds **5a** and **6a** had an affinity that was nearly identical to that of β -CIT (**I**), the current standard for SPECT DAT imaging. The high affinity of compound **5a** was particularly interesting because of its superior performance in the DLT reaction. Compound **10** also showed excellent DAT affinity. This result encourages us to consider in the future design compounds that can be prepared by the three-component condensation methodology or the direct cyclopentadienyl-tin route.⁽⁴⁴⁻⁴⁶⁾

In contrast to the aforementioned results was the low affinity of the 3 β -phenyl conjugate **14a**. The DAT affinity of the analog, compound **28**, was somewhat improved over that of **14a**, ($K_i \sim 10,000$ nM), but the enhancement was too little to warrant further investigations of these types of CpTR phenyl-tropane conjugates. Although these last results were disappointing, they support the observed trends that the dopamine transporter does not tolerate excessive steric bulk at the *para*-position of the 3 β -phenyl substituent.

CONCLUSIONS

In this work we present the first application of the double ligand-transfer (DLT) reaction for the direct preparation of cyclopentadienyltricarbonylrhenium (CpTR)-phenyl-tropane conjugates. In the new examples we show, the DLT gives reasonable yields and continues to show excellent functional group tolerance. The synthetic utility of this direct synthesis will be fully evident in the labeling of these analogs with technetium-99m, to be described elsewhere. [REFERENCE TO TC-99M WORK ELSEWHERE] Of the CpTR-tropane conjugates we have investigated, those substituted at the *N*-8 position seem most promising; their affinity for the dopamine transporter in all cases was high, and their ferrocene precursors can be prepared in a convenient manner. By contrast, the 3 β -conjugates were poor DAT binders. The

modular nature of these systems, however, allows considerable flexibility, which might be used to further improve the behavior of these compounds.

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Table 1. Structures and Isolated yields in the Direct Double Ligand Transfer Reaction

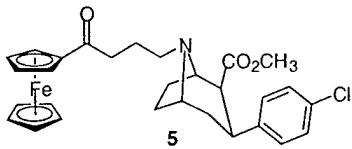
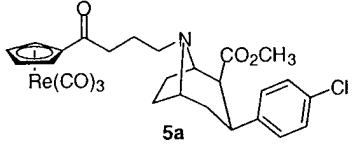
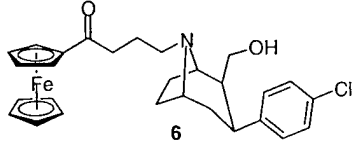
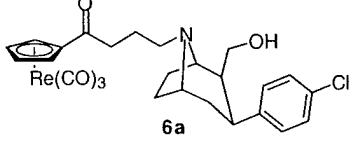
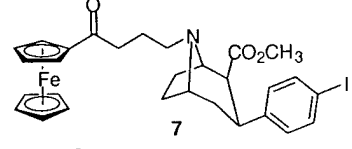
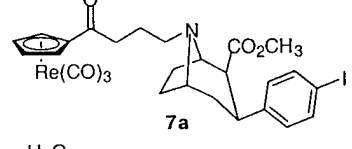
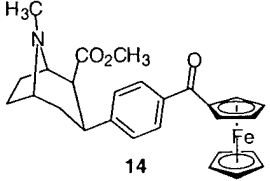
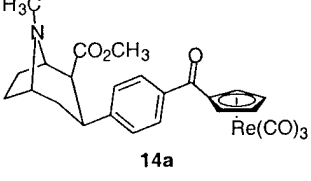
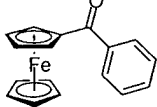
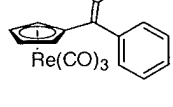
entry	reactant	isolated yield	product
1	 <p>5</p>	47%	 <p>5a</p>
2	 <p>6</p>	27%	 <p>6a</p>
3	 <p>7</p>	52%	 <p>7a</p>
4	 <p>14</p>	42%	 <p>14a</p>
5	 <p>16</p>	50%	 <p>16a</p>

Table 2. Affinities { K_i (nM)} of Phenyl-Tropine Conjugates

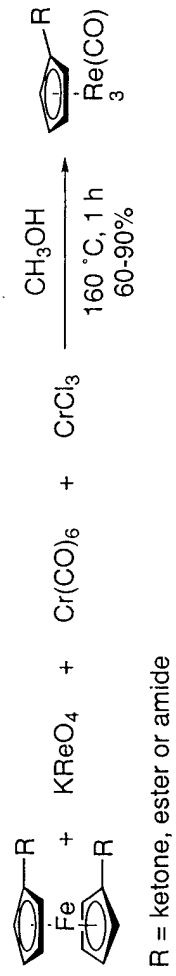
compound	position	linkage	2 β -	5-HTT	DAT	NET
5	<i>N</i> -	Ketone	ester	0.22 \pm 0.03	2.31 \pm 0.16	20.3 \pm 4.7
5a	<i>N</i> -	Ketone	ester	0.63 \pm 0.007	2.81 \pm 0.5	161 \pm 32
6	<i>N</i> -	Ketone	alcohol	5.03 \pm 0.35	3.66 \pm 0.20	2.30 \pm 0.2
10	<i>N</i> -	Carboxylate	ester	5.28 \pm 0.21	4.18 \pm 0.33	74.0 \pm 8.2
26	<i>N</i> -	Alkyl	ester	1.14 \pm 0.16	5.45 \pm 0.64	199 \pm 30
6a	<i>N</i> -	Ketone	alcohol	13.3 \pm 1.0	13.0 \pm 1.8	74.0 \pm 8.2
28	3 β - <i>para</i>	--	ester	~ 10,000	>10,000	>10,000
14a	3 β - <i>para</i>	Ketone	ester	>20,000	>30,000	>30,000
14	3 β - <i>para</i> -	Ketone	ester	>10,000	>30,000	>30,000

FIGURE LEGENDS

Figure 1. Structures of successful technetium-99m dopamine transporter imaging agents TRODAT-1 and Technepine.

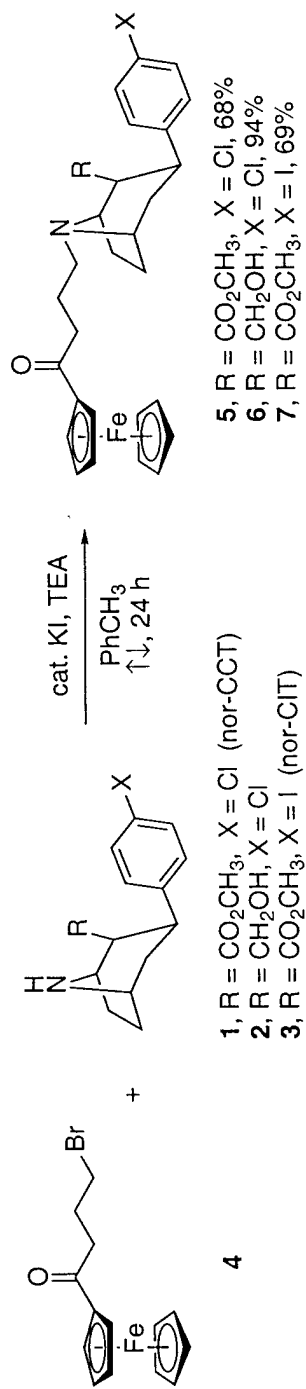
Figure 2. Novel CpTR phenyl-tropane conjugates.

Scheme 1



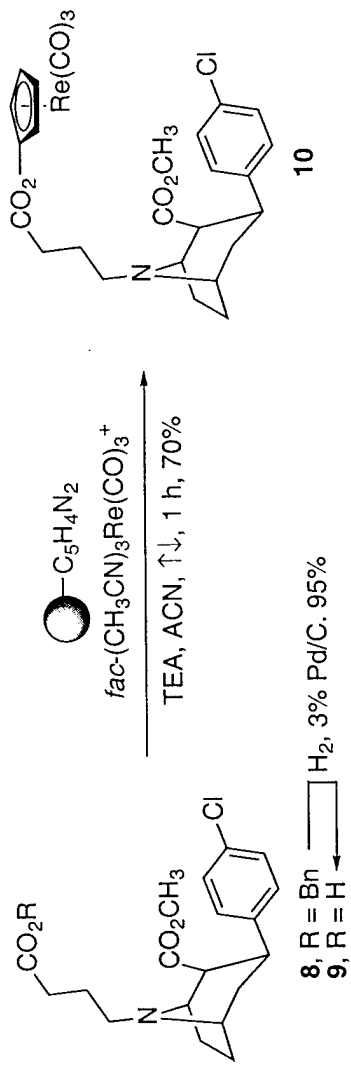
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Scheme 2



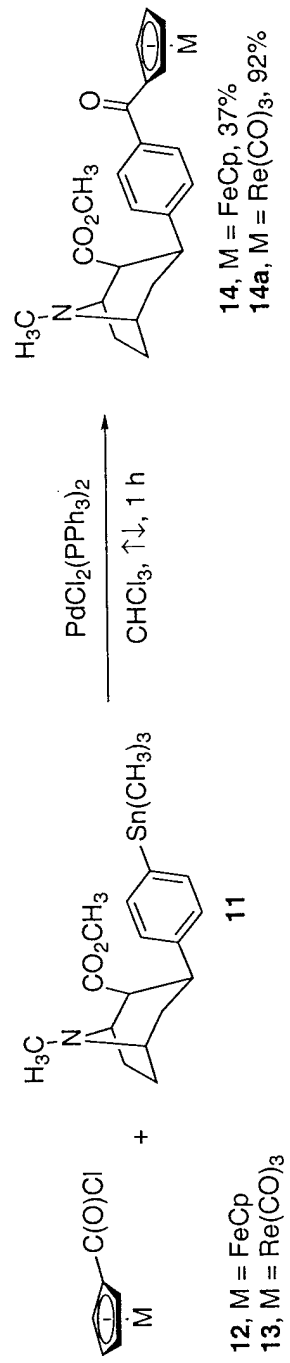
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Scheme 3



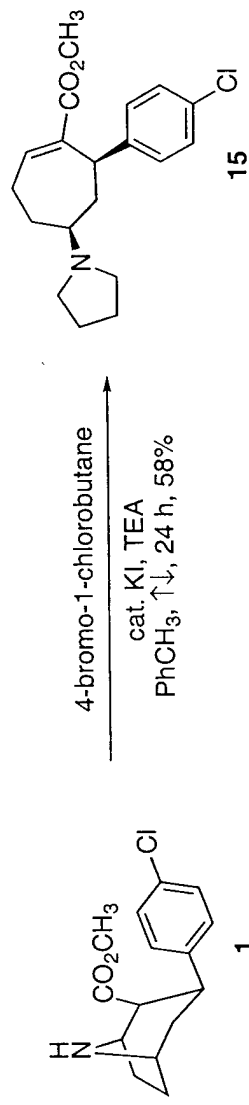
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Scheme 4



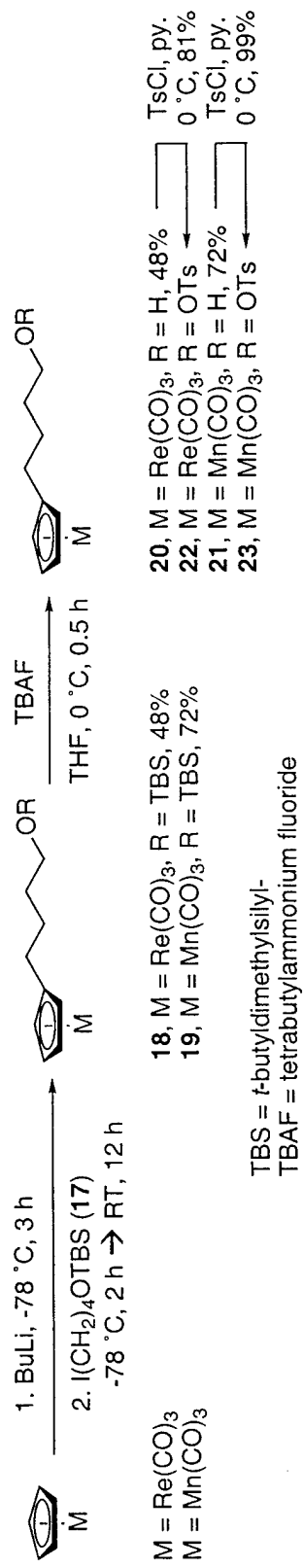
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Scheme 5



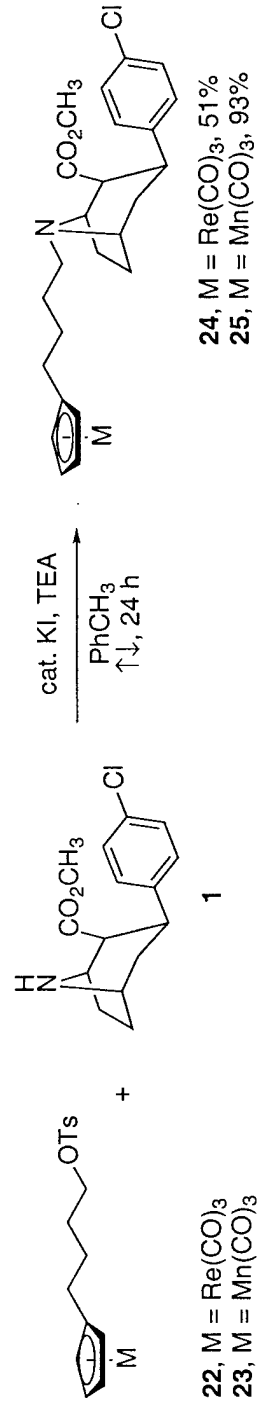
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Scheme 6



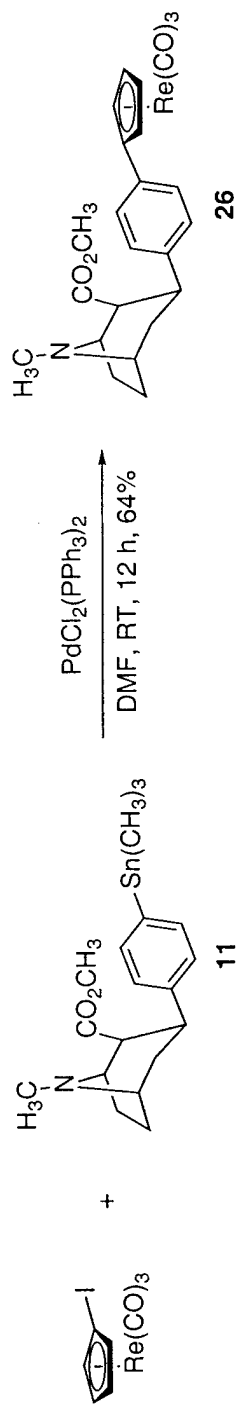
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Scheme 7



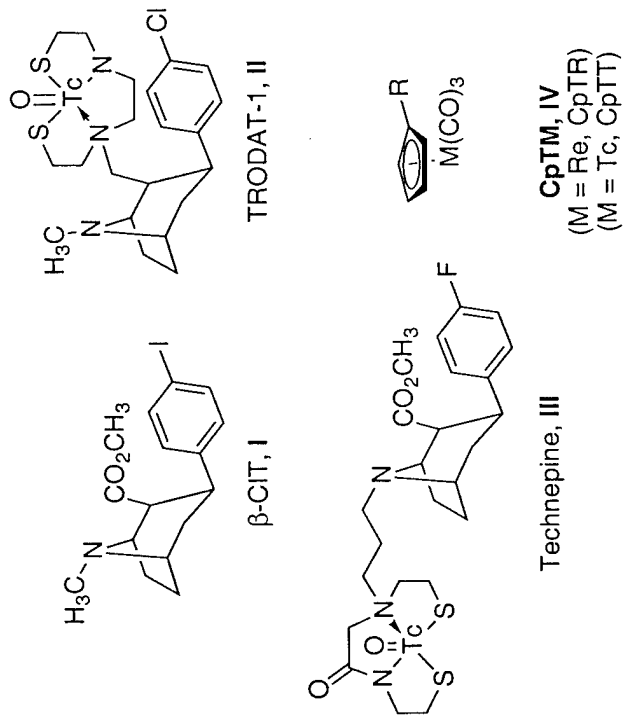
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Scheme 8



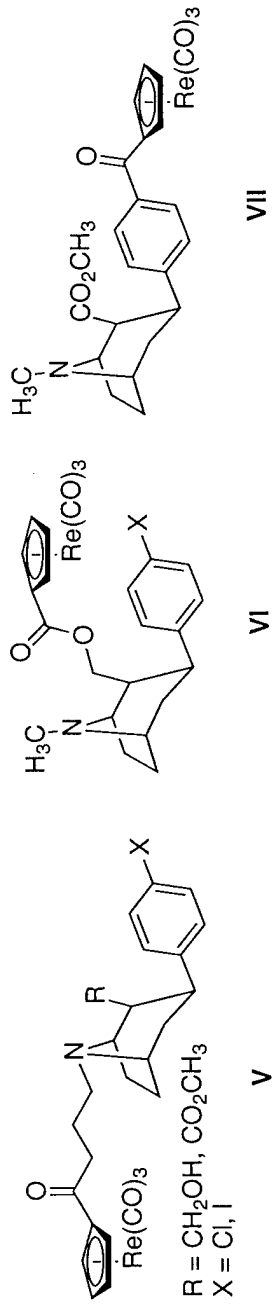
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Figure 1



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Figure 2



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One-Pot Formation of Substituted Cyclopentadienyl and Indenyltricarbonyl Rhenium Complexes Through In Situ Generation of Cyclopentadienyl- and Indenyltributylstannanes.

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RECEIVED DATE

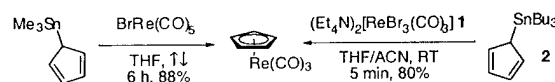
The extensive use of metallic radionuclides in nuclear medicine is dominated by technetium-99m (γ , $t_{1/2} = 6$ h), and radiopharmaceuticals labeled with this isotope are used in approximately 80% of all diagnostic imaging procedures.¹ For tumor radiotherapeutic purposes, rhenium-186 (β , $t_{1/2} = 91$ h) and rhenium-188 (β , $t_{1/2} = 17$ h) have shown great promise.² Recently, a large number of publications have appeared describing the synthesis of low-valent technetium and rhenium (i.e., $M(\text{CO})_3^+$) and their use for the preparation of new radiopharmaceuticals.³ Our own interest has been focused on the development of novel methods for the generation of stable substituted η^5 -cyclopentadienyltricarbonyl rhenium and technetium (CpTR and CpTT) complexes for radiolabeling biologically interesting molecules, especially small molecule ligands for receptors.⁴ However, until recently, the preparation of these organometallic species has required harsh conditions and multi-step procedures.⁵ Herein, we describe the utility of trialkyltin-substituted cyclopentadienes in the efficient synthesis of substituted CpTR complexes.

Reactions of trialkylstannylcyclopentadienes with Group VII pentacarbonyl halides $[\text{MX}(\text{CO})_5]$ for the preparation of unsubstituted CpTR complexes have been reported.⁶ Most reactions utilized the trimethyltin derivative and were complete within 3-7 h, with manganese, as expected, exhibiting a higher rate of reaction than rhenium. However, for this chemistry to be useful for radiolabeling receptor ligands, we needed to be able to include additional functionality in the cyclopentadienyl ring.

Our initial studies focused on the reaction of tributylstannylcyclopentadiene (CpTBT) with $(\text{Et}_4\text{N})_2[\text{ReBr}_5(\text{CO})_3]$ (**1**)^{3a} as the source of $\text{Re}(\text{CO})_3^+$, an approach analogous to that which we used in a related three-component condensation.⁷ Because the

metal precursor **1** is insoluble in THF, it was dissolved in acetonitrile (ACN). CpTBT, being insoluble in ACN, was dissolved in THF, which was used as reaction co-solvent. When a solution of **1** in ACN was treated with a THF solution of CpTBT at RT, formation of CpTR was complete within 5 min, and this material could be isolated in 80% yield, after isolation and chromatography (Scheme 1). The corresponding reaction with $\text{BrRe}(\text{CO})_5$ required 6 h at reflux in THF to achieve a similar yield. It should be noted that under analogous conditions, neither of the other Cp donors, nickelocene nor trimethylsilyl-cyclopentadiene, produced any significant amount of CpTR.

Scheme 1. Comparison of Reactivity of Rhenium Sources



With this promising result in hand, we attempted to prepare a variety of substituted cyclopentadienyl- and indenyltributyltin compounds. Unfortunately, we were unable to isolate most of these compounds, because of the facility with which they underwent protonolysis (destannylation). To circumvent this hydrolysis problem, we chose not to isolate the tributyltin species, but rather to generate them in situ, and use them directly in the reaction with the addition of the metal precursor **1**.

Recently, tin-amines have been used in palladium-catalyzed amination reactions of aryl halides.⁸ However, the tin-amines have long been known for their ability to react with protic solvents, such as alcohols, thiols, and other amines, to form the corresponding tin-alkoxides, sulfides or amines under mild conditions.⁹ They also are known to react with the relatively acidic protons of cyclopentadiene and indene to form the corresponding enyl-tin species.^{5b-10}

Our initial attempt to utilize the tin-amines was in the preparation of unsubstituted CpTR. When we treated a THF solution of freshly cracked cyclopentadiene with diethylamino-tributyltin at RT for 2 h, added this mixture to a solution of **1** in a minimal amount of ACN, and refluxed the resulting solution, we indeed saw formation of CpTR by TLC analysis. After one hour, CpTR was isolated, as above, in 81% yield.

To extend this reaction to other ring systems, we attempted to carry out the analogous reaction using indene rather than cyclopentadiene. In this experiment, a THF solution of indene was treated with diethylamino-tributyltin at reflux for one hour. TLC showed complete consumption of the indene starting material and formation of a new, higher R_f compound.

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⁴ Preliminary accounts of related work: Cesati III, R. R.; Tamagnan, G.; Baldwin, R. M.; Zoghbi, S. S.; Innis, R. B.; Katzenellenbogen, J. A. *J. Label. Comp. Radiopharm.* 1999, 42, S1, 150-152.

⁵ Spradau, T. S.; Katzenellenbogen, J. A. *Organometallics*, 1998, 17, 2009.

⁶ The following citations contain several examples of reactions involving silyl-substituted compounds as well as one example of a methyl substituted compound. (a) Abel, E. W.; Moorhouse, S. *J. Organomet. Chem.* 1971, 28, 211. (b) Abel, E. W.; Moorhouse, S. *J. Chem. Soc., Dalton Trans.* 1973, 1706.

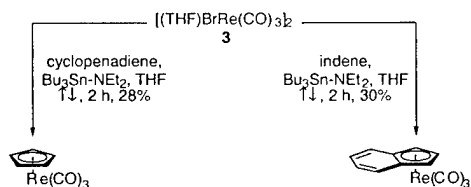
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However, upon addition of the ACN solution of **1** at RT, TLC analysis showed the rapid reappearance of free indene, with no detectable formation of the desired indenyltricarbonyl rhenium (InTR) complex. It is unlikely that adventitious water can account for this complete protonolysis. Rather, because the pK_a values of indene and the solvent ACN are comparable, it is more likely that the indene anion is being protonated by this solvent, although it is not clear why this same protonation would not happen with the more basic Cp-tin species. In any case, we developed as an alternative a strictly aprotic system in THF solvent.

A simple form of the metal precursor that is soluble in THF is $[(\text{THF})\text{BrRe}(\text{CO})_3]_2$ (**3**), which is a halide-bridged dimer in the solid state that becomes a monomer $[(\text{THF})_2\text{BrRe}(\text{CO})_3]$ in THF solution.¹¹ It should be noted that the related technetium complex, $[\text{Tc}^{99m}](\text{THF})_2\text{ClTc}(\text{CO})_3$, can be produced by the reduction of $[\text{Tc}^{99m}]\text{NH}_4\text{TcO}_4$ by $\text{BH}_3 \cdot \text{THF}$ in the presence of a chloride source, according to the methods developed by Alberto.^{3b} Our hope was that precursor **3** would offer similar reactivity in THF as did precursor **1** in ACN.

For this study, we attempted to generate the CpTR in the presence of the $\text{Re}(\text{CO})_3^+$ source, as this would simplify the in situ, two-step procedure used above. We were pleased to find that treatment of a solution of the metal precursor **3** and cyclopentadiene in THF with diethylamino-tributyltin at reflux for 2 h, afforded CpTR in 28% yield. More importantly, when we performed the analogous procedure with indene, we successfully isolated InTR, although in a relatively modest 30% yield (Scheme 2). To our knowledge, this result represents the first *one-pot* synthesis of CpTR and InTR, using an in situ generated enyl-stannane.

Scheme 2. Studies on In Situ Generation of Enyl-stannanes



Several aspects of this reaction deserve comment. First and foremost is that CpTR was not formed under the reaction conditions in the absence of the tin reagent. It is also of note that the yields of both reactions improved somewhat with extended reaction times, although the yields were lower than expected when compared to the results obtained from metal precursor **1** in ACN. We believe that the different reaction temperatures used in the two cases are not as important as the greater polarity and ionizing potential of ACN compared to THF. These factors may become more apparent in future mechanistic studies.

To demonstrate the utility of this reaction, we wished to extend it to more complex substrates. Our results are summarized in Table 1. When the substituted cyclopentadiene **4a** is subjected to the reaction conditions described above, the corresponding *p*-methoxyphenyl-substituted CpTR (**4b**)^{4b} was formed in 65% yield: In three separate trials, the yields of this compound consistently averaged 65%. Similarly, the phenyltropane **5a** gave the highly functionalized alkyl-substituted CpTR **5b** in 26% yield. Although the reaction worked with these substrates, it did not work with several others (e.g., other

diarylindenes). Efforts to make more complex rhenium tricarbonyl complexes, specifically those with estrogenic cores, are currently underway in our laboratories.¹²

Table 1. Structures and Isolated Yields in the Reaction of **3** with Various Cyclopentadienes and Indenes

Entry	Reactant	Yield (%)	Product
1		28	
2		30	
3		65	
4		26	

The mechanism of this reaction is not known; however, the transmetalation to rhenium appears to be the rate-limiting step. During this transmetalation, attack of halide at tin can occur in an inter- or intramolecular fashion, but the exact nature of this transition state is unknown. Based on literature precedent,^{3b} it is likely that the reaction occurs through initial olefin coordination to form a η^2 -intermediate, then directly to a η^3 -intermediate, and finally to the η^5 -product.

In summary, the reaction herein reported has proved to be a mild and efficient method for the preparation of substituted CpTR complexes. The reaction is quite complementary to other protocols developed in our laboratories. It is not limited by the need for an electron-withdrawing substituent as in the double ligand transfer reaction, and it does not require the isolation of a reactive cyclopentadienyl source as in the three-component condensation. The reaction can be extended to the use of indenyl ring systems and shows tolerance of a variety of functional groups. The main limitation of the reaction is the yield, which is modest, when the reaction times need to be kept short to achieve efficient radiochemical synthesis with a short-lived radionuclide (e.g., Tc-99m half-life is 6 h). The solvent ACN gives the best yields of CpTR, although this solvent proved to be incompatible with the indenyl ring system. In THF, the reaction can be carried out in a single pot, and in this solvent it can be extended to more complex systems. We feel that the reaction should provide a very powerful extension of the recent work by Jaouen, who has shown that substituted cyclopentadienes can be produced cleanly by irradiation of cyclopentadienyltricarbonyl manganese complexes.¹³

Acknowledgment. We are grateful for support of this research through grants from the Department of the Army (DAMD17-97-1-7292), National Cancer Institute DHHS (PHS 5 T32 CA09067) and the Department of Energy (DE FG02 86ER60401).

Supporting Information Available: Complete experimental procedures and spectral data for compounds **4a**, **4b**, **5a** and **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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