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A class of breast tumors, known as ER+, contains significant concentrations of ER which functions to regulate cell growth, and mediate the action of estrogen antagonists. There is a need for the development non-invasive and reliable methods for the determination of tumor ER concentration in the identification of patients predicted to respond to hormone therapy. It has been shown that tumor ER concentration can be determined by imaging, using 18F-labeled ER selective ligands, and that the ER concentrations determined by imaging correlate well with those determined by immunoassay methods on surgical biopsies. Because of the short half-life of fluorine-18, this method is costly, with low availability. Thus, the development of an effective ER imaging agent that is of low cost and widespread availability might eliminate the need for tumor biopsy in the treatment selection for breast cancer patients. We propose the development of radiopharmaceutical imaging agents labeled with 99mTc, which is available at most hospitals at a relatively low cost, as a 99Mo/99mTc generator. Studies conducted in this laboratory suggest that an integrated organometallic design in which technetium bonded to carbon forms a part of the core structure will display the stability, as well the requisite affinity to ER.

Breast Cancer

19b. TELEPHONE NUMBER (include area code) USAMRMC
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Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor (ER) Ligands for ER+ Tumor Imaging

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Introduction

It is known that many breast tumors contain significant concentrations of ER. In these tumors, known as ER+ tumors, the role of ER is to regulate cell growth, but it can also function to mediate the anti-proliferative effects of estrogen antagonists, such as tamoxifen. It has been shown that ER concentration correlates well with the efficacy of anti-estrogen use in hormone therapy. Tumors with low ER concentration (i.e., ER- tumors) do not respond well to hormone therapy. As a result, chemotherapy is often used instead of hormone therapy, in spite of the high morbidity associated with its use, because chemotherapy is known to be effective in both ER+ and ER- tumors. Unfortunately, roughly half of patients that are successfully treated with chemotherapy could have been treated equally well with hormone therapy and thereby avoided the deleterious side effects of chemotherapy, provided that a reliable means could be used to identify those patients that would respond to hormone therapy. Thus, there is a great need for the development of a non-invasive and reliable method for the determination of ER concentration in tumors that would allow identification of breast cancer patients having ER+ tumors that are likely to respond well to hormone therapy, so that these patients could be spared the side effects of chemotherapy. It has been shown that the ER concentration in breast tumors can be determined by imaging, using ER selective radiopharmaceutical imaging agents, and that the ER concentrations determined by imaging correlate well with those determined by binding or immunoassay methods on surgical biopsies. Currently, the most effective ER imaging agent is a fluorine-18 labeled estrogen. However, because of the short half-life of this radionuclide, this agent is very expensive and is not widely available. Thus, the development of an effective ER imaging agent that is of low cost and widespread availability might eliminate the need for tumor biopsy to determine whether a patient is a good candidate for hormone therapy. We have proposed the development of a radiopharmaceutical imaging agent labeled with 99mTc, which exhibits a high binding affinity to ER, has high in vivo stability, and functions effectively in vivo for imaging ER levels in breast tumors. Imaging agents labeled with 99mTc would be available at most hospitals and at a relatively low cost, because 99mTc is widely available from a 99Mo/99mTc generator. Previous studies of technetium-99m labeled ER ligands for use as imaging agents have suffered from several problems. Inorganic chelates of 99mTc demonstrated molecular instability under biological conditions; also, the large size of many Tc complexes interferes with cellular uptake. Studies conducted in this laboratory suggest that an integrated organometallic design in which technetium bonded to carbon forms a part of the core structure will display the needed stability, as well the potential for high binding affinity to ER. While significant advances have been made, major improvements in radiolabeling techniques and structural design are still needed before an imaging agent using 99mTc will be effective as a diagnostic tool to identify tumors that will respond to hormone therapy. The structural design motif under investigation is based upon previous work in our laboratory, as well as molecular modeling with comparison to the morphology of the native ER ligand, estradiol.

Body of Report

I. Training

I have attended various organic-chemistry, organometallic-chemistry, and chemical-biology seminars presented by visiting professors and UIUC students.

II. Research

The overall objective of this proposal is to develop a compound bearing a 99mTc label that exhibits both a high relative binding affinity to ER, has good in vivo stability, and functions effectively as an imaging agent for ER in breast tumors. Ultimately, we hope that this compound could be used to image ER+ tumors in a manner that would provide information useful for the selection of the optimal therapy for a breast cancer patient. This aim has been divided into four tasks, which make up the approved Statement of Work.
Task A: (Months 1-18, July 1, 2003 – December 31, 2004)
- Begin model studies for synthesis of compound PyCR (II).
- Begin synthesis of ACR (IV).

Task B: (Months 13-30, August 1, 2004 – December 31, 2005)
- Execute synthesis of PyCR (II), and determine relative binding affinity.
- Execute synthesis of PIRB (VI) analogs and determine relative binding affinity.

Task C: (Months 25-36, July 1, 2005 – June 30, 2006)
- Execute synthesis of analogs of PyCR (II), with various combinations of alkyl and aryl substitution on the central cyclopentadienyl ring.
- Execute synthesis of PIRM (VII) analogs and determine relative binding affinity.
- Execute synthesis of the ACR (IV), and determine relative binding affinity.
- Develop synthesis of CBRN (VIII), and determine relative binding affinity.

Task D: (Months 12-36, July 1, 2004 – June 30, 2006)
- We will develop methods of radiolabeling using $^{94\text{m}}$Tc in place of Re and evaluate the in vivo tissue distribution of all labeled compounds with promising in vitro properties. (To be done through our long-standing collaboration with Professor Michael Welch of the Mallinckrodt Institute of Radiology at Washington University Medical School)

Figure 1. ER Ligand Targets

This final report describes progress made through all thirty-six months of award coverage. A number of unsuccessful synthetic approaches described in annual reports I and II have been omitted, in favor of new approaches to the described statement of work.

Task A Step 1

The model study for the synthesis of $\eta^1\eta^5$-complex PyCR II has been completed with the synthesis of $\eta^1\eta^5$-pyridylmethylcyclopentadienyl rhenium(I) dicarbonyl (5), which forms the core of the phenol substituted PyCR II. Production of 5 proceeds in four steps from commercially available 2-pyridylmethanol (1), as shown in Scheme 1. The essential pyridine to rhenium cyclization occurs via photo-irradiation under inert atmosphere to provide the desired rhenium dicarbonyl complex.1 Alternatively, the production of the
(pyridylmethyl)cyclopentadiene (3) can be accomplished in a one-pot procedure using the lithium anion of picoline (6) and cyclopentenone, as shown in Scheme 2, followed by dehydration.2

\[
\begin{align*}
\text{OH} & \rightarrow \text{OTs} & \text{N} & \rightarrow \text{Li} & \text{N} & \rightarrow \text{Re} \\
1 & \rightarrow 2 & 2 & \rightarrow 3 & 4 & \rightarrow 5 \\
& \text{(99%)} & \text{(59%)} & \text{(28%)} & \text{(42%)}
\end{align*}
\]

(a) TsCl, KOH, THF, RT, overnight. (b) NaCp, THF, -78 °C. (c) n-BuLi, [ReBr(THF)2(CO)3]2, RT, 20 min. (d) hN, 300 nm, 90 min.

**Scheme 1** Synthesis of Pyridyl-Cyclopentadienyl Core

Scheme 2  Anionic Synthesis of Core

**Task A Step 2**

The synthesis of 2,3,5-tris-(4-methoxyphenyl)cyclopentenone (11), as shown in Scheme 3, has been completed in three steps, starting from commercially available methyl 4-methoxyphenylacetate (8). Several methods have been investigated for the addition of a fourth substituent to the central pentacycle, including nucleophilic addition of organometallic reagents, addition of electrophiles to the cyclopentadiene derived from 11, Wittig and titanium mediated olefination, followed by hydride transfer, and zirconocene-mediated cyclopentenone formation.

\[
\begin{align*}
\text{H3CO} & \rightarrow \text{H3CO} & \text{H3CO} & \rightarrow \text{H3CO} \\
8 & \rightarrow 9 & 10 & \rightarrow 11 \\
& \text{(40%)} & \text{(61%)} & \text{(54%)}
\end{align*}
\]

(a) i. LDA, ether, -78 °C, 20 h. ii. AcOH, HCl, reflux, 5h. (b) i. LDA,THF, -78 °C, 1 h. ii. 2-bromo-4'-methoxyacetophenone, 1.5 h. c. methanolic KOH, RT, 20 min.

**Scheme 3** Synthesis of Triarylcyclopentenone

Ultimately, the nucleophilic addition of 1-propynylmagnesium bromide to the carbonyl of enone 11 provided the tetra-substituted 2,3,5-tris-(4-methoxyphenyl)-1-propynylcyclopentadiene (12b), as shown in Scheme 4. Initial attempts to hydrate the triple bond of alkyne 12b using transition metal catalysis have thus far failed to provide the desired ketone 13b. A model study, elucidating potentially successful reaction conditions, is described below as part of Task C.
Scheme 4 Synthesis of Acylcyclopentadiene

Task B Step 1

The completion of the model study in Step 1 of Task A led to attempts to synthesize the phenol substituted PyCR. Early routes to a hydroxyphenyl substituted pyridylmethyl cyclopentadiene, described in Annual Report I, shared the reactivity limitations of enone 4, described above. The Pauson-Khand type reaction, described in Annual Report II (Scheme 5) provided small amounts of the desired acid-enone 15. Ultimately, when attempted on preparative scale the triphasic cyclization reaction to provide the enone carboxylic acid 15 did not provide sufficient material to move beyond the decarboxylative elimination to form dienone 16.

Scheme 5 Pauson-Khand Type Synthesis of PyCR II

Dienone 16 shows impressive structural similarity to the exomethylene enone product of gold catalyzed ring expansion of cyclic propargylic alcohols.3 With this in mind, exo enone 23 was synthesized as shown in scheme 6. The production of dichloroketene from trichloroacetyl chloride (20), followed by 2+2 cyclization with methoxy styrene provided dichlorocyclobutanone 21. Addition of acetylide grignard yielded propargylic alcohol 22, a potential substrate for ring expansion. Upon treatment with the appropriate gold(I) catalyst however, the acetylide moiety was eliminated to again provide cyclobutanone 21 rather than the desired enone 23.
Scheme 6 Ring Expansion

Because literature examples did not contain the \(\alpha,\alpha\)-dichloro moiety\(^3\) it was decided that reduction to the methylene, as shown in scheme 7, would provide a substrate more suitable for expansion. Zinc reduction of dichloride 21 provided cyclobutanone 24. Addition of acetylide yielded propargylic alcohol 25, which decomposed under ring-expansion conditions rather than the eliminating acetylide as previously-observed.

Scheme 7 De-chlorinated Ring Expansion

It was thought that \(\alpha\)-substitution would improve the migratory aptitude of the cyclobutane ring carbon; consequently, production of the \textit{trans} \(\alpha\)-methyl analog (27) of dichloro cyclobutanone 21 was attempted (scheme 8). Reaction of dichloroketene with commercially available \textit{trans}-anethole failed, likely due to the steric requirements of the 2+2 cyclization. Synthesis of \textit{cis}-anethole (29) for the production of \textit{cis}-aryl methyl cyclobutanone 30 (scheme 9) is ongoing.
An alternative approach currently under investigation is the SN2 displacement of a leaving group from a protected hydroxy picoline, using an aryl-substituted cyclopentadienide. The synthesis of bromide 36 is shown in scheme 10. The protection of hydroxypicoline 34 as the radical-stable benzene sulfonate yields picoline 35, which undergoes radical bromination to provide bromide 36.

Alternatively, the hydroxymethyl pyridine 34 can be activated as a trifluoromethane sulfonate 40, as shown in scheme 11. Synthesis of the dihydroxy complexes begins with the protection of the hydroxypicoline 34, as the p-methoxybenzyl ether 37. Oxidation to the N-oxide 38 with peroxy acid, with subsequent rearrangement provides the alcohol 39. Treatment of 39 with triflic anhydride in the presence of base produces triflate 40.
Scheme 11 Synthesis of Pyridylmethyl Triflate

The aryl-substituted cyclopentadiene required as the nucleophilic component for SN2 displacement is potentially synthesized via addition of Grignard reagent to cyclopentenone, followed by dehydration to form. Initial trials of this reaction have demonstrated both its utility in forming product and the instability of the mono-substituted Cp under ambient conditions. Deprotonation using strong acid, followed by SN2 displacement using either bromide or triflate is expected to provide the pyridyl substituted Cp or , suitable for labeling.

Scheme 12 Synthesis of Aryl Pyridyl Cp

Task B Step 2

As discussed in Annual Report I, the synthetic ease of imine formation, as well as the strong coordination of the nitrogen of pyridine makes a pyridyl-imine based scaffold attractive for the bidentate portion of a 2+1 ligand system in the production of radio-labeled ER ligands. The anionic monodentate ligand is bromide for the pyridyl-imine rhenium tricarbonyl bromide (PIRB VI) system. A nomenclature of PIRB ligands is based on whether a hydroxyl appears on the aniline moiety (A-ring mimic), the pyridine (D-ring mimic), and the identity of substituents R1 and R2. As shown in Scheme 6, a variety of commercially available hydroxyaniline derivatives were combined with either pyridinecarboxaldehyde or acetylpyridine in refluxing methanol, followed by addition of a rhenium tricarbonyl salt formed the monohydroxy rhenium complexes , with the aniline moiety forming the A-ring mimic.
Scheme 13 Synthesis of Monohydroxy Imines

Synthesis of the analogous dihydroxy complexes begins with the protection of the hydroxypicoline 34, as the p-methoxybenzyl ether 37. Oxidation to the N-oxide 38 with peroxy acid, with subsequent rearrangement provides the alcohol 39. Benzylc oxidation yields the aldehyde 50 needed for imine formation. Condensation with anisidine derivatives, followed by addition of the rhenium salt causes the protected rhenium complexes 51a-b to precipitate from solution. Deprotection with Lewis acid boron tribromide reveals the dihydroxy complexes 52a-b.

Scheme 14 Synthesis of Bis-Hydroxy Imines

The corollary to monohydroxy 49a, in which the pyridine moiety forms the A-ring mimic, is formed using the above procedure, starting with protected hydroxy aldehyde 50, which undergoes condensation with unsubstituted aniline to form rhenium complex 53. Deprotection reveals the monohydroxy complex 54.

Scheme 15 Synthesis of Isomeric Monohydroxy Imines

For all PIRB complexes synthesized, binding affinities relative to estradiol (100%) are listed in Table 1 for both ERα and β. The highest affinity compound thus far is 52a, ADHH. Among mono-hydroxy compounds 49a-d, 54, substitution in the R2 position increases binding affinity. This is supported by molecular modeling (Figure 2), which for lead compound ADHH (52a), chloro mono-hydroxy ACH (49c), and bis-hydroxy ADCH
(52b), show free space in the receptor opposite the imine carbon. This suggests that a number of bis-hydroxy keto-imines be synthesized in order to improve binding affinity. Substitution in the R₁ position has mixed effects, raising binding affinity for ACH (49c), but lowering binding affinity for AMH (49b), relative to H-substituted AHH (49a). This effect cannot be explained by the difference in halogen versus alkyl, as the substitution of a chloride, which has previously improved binding affinity, lowered it for ADCH (52b) versus ADHH (52a).

Table 1. PIRB Relative Binding Affinity (E2 = 100%)

<table>
<thead>
<tr>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>ERα</th>
<th>ERβ</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a, AHH</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>0.015%</td>
</tr>
<tr>
<td>49b, AMH</td>
<td>CH₃</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>&lt;0.005%</td>
</tr>
<tr>
<td>49c, ACH</td>
<td>Cl</td>
<td>H</td>
<td>OH</td>
<td>H</td>
<td>0.327%</td>
</tr>
<tr>
<td>49d, AHM</td>
<td>H</td>
<td>CH₃</td>
<td>OH</td>
<td>H</td>
<td>0.071%</td>
</tr>
<tr>
<td>52a, ADHH</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>0.271%</td>
</tr>
<tr>
<td>52b, ADCH</td>
<td>Cl</td>
<td>H</td>
<td>OH</td>
<td>OH</td>
<td>&lt;0.01%</td>
</tr>
<tr>
<td>54, DHH</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OH</td>
<td>&lt;0.01%</td>
</tr>
</tbody>
</table>
Synthesis of the keto-imine analog to 49c, ADHM (61a) is shown in scheme 16. Addition of methyl grignard reagent to aldehyde 50 provides secondary alcohol 55a, which is reoxidized using manganese dioxide to ketone 56a. Imine formation, followed by rhenium addition provides ether-protected ADHM (60a), which is deprotected with boron tribromide to form 61a. Binding affinity of ADHM (61a) to the estrogen receptor has yet to be determined.

Scheme 16 Synthesis of Keto-imine Complexes

Task C Step 2

The conversion of bromide complexes PIRB to the methoxy complex PIRM has been initiated. Conversion of ADHH (52a) to the methoxy compound proceeds successfully, according to initial NMR spectroscopy experiments. To date, the high polarity of the resulting methoxy complex has complicated final purification of methoxy complex 59. Future plans include the use of reverse phase HPLC, followed by characterization and binding affinity studies.
Scheme 17  Synthesis of Methoxy Complex

Task C Step 3

As discussed above for Task A, the successful synthesis of ketone 13 depends upon the hydration of alkyne 12 (See Scheme 4). In order to determine the requisite conditions, model compound 63 was synthesized as shown in scheme 18. Enone 62 is synthesized via the dehydrative cyclization of 3-pentanone (60) with 4,4’-dimethoxybenzil (61) to form enone 62, which is converted to alkyne 63 by the addition of propynyl grignard. An investigation of transition metal catalysis revealed that substoichiometric amounts of HgO, in the presence of acetic acid, resulted in clean conversion to acylketone 64. Resynthesis of alkyne 12, the intended substrate for this method, is ongoing.

Scheme 18  Synthesis of Acylcyclopentadiene
Task C Step 4

The lipophilic character of the estrogen receptor, coupled with the lipophilic nature of closo-carboranes make them attractive scaffolds upon which to build ER ligands. Indeed, work in this field by Endo\textsuperscript{4-6} has produced a number of carborane-based ER ligands with good binding affinity (See Figure 3). Radiolabeling under aqueous conditions produces an anionic tricarbonyl species (See Scheme 19).\textsuperscript{7} Use of a di-cationic rhenium-nitroso-dicarbonyl to balance the charge\textsuperscript{8-10} provides the potential for a neutral metallocarborane, capable of binding to the estrogen receptor. To test this hypothesis, Sonogashira coupling of methoxyphenyl acetylene 65 with iodoanisole 66 provides the bis-methoxyphenyl acetylene (67), which is refluxed with decaborane to form the ortho-closo-carborane 68. The closo-carborane is degraded to the nido-carborane potassium salt 69, using potassium hydroxide. Literature methods for the metallation of nido-carbanions such as 69 have only provided metallocarborane 70 in minimal yields. Investigations of alternate counter-ions, bases, solvents and sources of rhenium (I) have in my hands failed to provide increased metallation efficiency.

Figure 3 BE361
The electron density of nido-carborane 69 is high, due to the presence of two electron donating aryl substituents. It was thought that replacing one of these rings with a less donating substituent would increase the acidity of the bridging hydrogen and increase the metallation efficiency. In addition, reducing the steric demand of the carborane substituents could act to improve the facility of approach by the metal complex during metallation. A number of carboranes successfully metallated by Valiant, et. al contain primary alkyl chains, terminated by a Lewis base, which could act as a tether to assist the metal’s approach. With these design features in mind, it was decided to synthesize meta and para arylhydroxymethyl carboranes 74a and 74b for metallation.

The syntheses of the meta- and para- aryl and hydroxymethyl substituted carboranes are shown in scheme 21. Copper catalyzed arylation of the commercially-available carborane 71a-c provides mono-aryl carborane 72a-c, which is converted to ester 73a,b via deprotonation and attack on methyl chloroformate. Reduction with lithium aluminum hydride provides hydroxymethyl carborane 74a,b.
Scheme 21  Synthesis of meta- and para-Carborane Ligands

Mono Aryl ortho-carborane 72c was synthesized via copper catalyzed coupling of methoxyphenyl iodide to the commercially available ortho carborane 71c, as well as by the conversion of methoxyphenyl acetylene to the carborane using decaborane (Scheme 22). Degradation of the closo-carboranes 74a and 72c to the uncapped nido-form, and subsequent attempts at metallation did not provide workable quantities of metallated product.

Scheme 22  Synthesis of Mono Aryl Carborane
Key Research Accomplishments

- Task A Step 1, Model Study for compounds PyCR completed.
- Task A Step 2, Synthesis of ACR two steps from completion.
- Task B Step 1, Synthesis of monoaryl analog to PyCR ongoing using a number of parallel schemes.
- Task B, Step 2, Synthesis of a small library of PIRB ligands accomplished. Lead compound is ADHH with RBA to ER\(\alpha\) of 2.3%.
- Task C Step 2, Synthesis of crude ADHH methoxy analog is awaiting purification.
- Task C Step 3, Model study for Hydration has revealed appropriate conditions for the completion of synthesis of ACR.
- Task C Step 4, A variety of known carborane-based ligands for ER have been synthesized. Metallation has been attempted, yielding minimal amounts of product.

Reportable Outcomes

- Poster Presentation *Cyclopentadienyl Rhenium (Technetium) Tricarbonyl Complexes Integrated in Estrogen Receptor (ER) Ligands for ER+ Tumor Imaging*, at the 9th Congress of the World Federation of Nuclear Medicine & Biology at COEX Seoul, Korea, October 22~27, 2006.

Conclusions

A number of ligands for the Estrogen Receptor have been synthesized, with promising binding affinity among the PIRB family of ligands while the PIRM family of ligands shows increased in vitro stability. Ongoing studies directed towards the further development of this pyridyl-imine class of ligands promise to lead to ligands with both good binding affinity and suitable stability for labeling and in vivo testing. The ACR and PyCR ligand classes are both near completion, with two steps remaining for ACR and multiple synthetic schemes leading to PyCR underway. The CBRN class of ligands has shown low potential for radio-metallation in my hands. As ligands with appropriate binding affinity and stability are completed, radio-labeling and in vivo animal studies will be undertaken with our collaborator, Michael Welch, of the Mallinckrodt Institute of Radiology at Washington University Medical School.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR</td>
<td>1-acetyl-2,3,5-tris-(4-methoxyphenyl)-cyclopentadienylrhenium(I) tricarbonyl (IV)</td>
</tr>
<tr>
<td>ACT</td>
<td>1-acetyl-2,3,5-tris-(4-methoxyphenyl)-cyclopentadienyltechnetium(I) tricarbonyl (V)</td>
</tr>
<tr>
<td>ER</td>
<td>Estrogen Receptor</td>
</tr>
<tr>
<td>ER+</td>
<td>Estrogen Receptor Positive</td>
</tr>
<tr>
<td>ER-</td>
<td>Estrogen Receptor Negative</td>
</tr>
<tr>
<td>CBRN</td>
<td>(3)-1,2-bis-(4-hydroxyphenyl)-1,2-dicarbadodecahydrodecaborate (-2) nitroso rhenium dicarbonyl</td>
</tr>
<tr>
<td>PyCR</td>
<td>(\eta^1,\eta^5)-1-(4-hydroxyphenyl)-3-pyridylmethylcyclopentadienyl rhenium(I) dicarbonyl (II)</td>
</tr>
<tr>
<td>PIRB</td>
<td>{Bromo[N-(2-pyridinylmethylene)-4-hydroxyphenylamine]rhenium(I) tricarbonyl}</td>
</tr>
<tr>
<td>PIRM</td>
<td>{Methoxy[N-(2-pyridinylmethylene)-4-hydroxyphenylamine]rhenium(I) tricarbonyl}</td>
</tr>
<tr>
<td>RBA</td>
<td>Relative Binding Affinity</td>
</tr>
</tbody>
</table>
References

(2) Goldberg, N. N.; Barkley, L. B.; Levine, R. Journal of the American Chemical Society 1951, 73, 4301-3.