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Model studies for the total synthesis of vancomycin and related compounds using organoiron and organoruthenium complexes

Park, Jewn-Giew, Ph.D.

Case Western Reserve University, 1992
MODEL STUDIES FOR THE TOTAL SYNTHESIS OF
VANCOMYCIN AND RELATED COMPOUNDS
USING ORGANOIRON AND ORGANORUTHENIUM COMPLEXES

by

JEWN-GIEW PARK

Submitted in partial fulfillment of the requirements
for the Degree of Doctor of Philosophy

Thesis Advisor: Dr. Anthony J. Pearson

Department of Chemistry
CASE WESTERN RESERVE UNIVERSITY
January, 1992
CASE WESTERN RESERVE UNIVERSITY
GRADUATE STUDIES

We hereby approve the thesis of

JEWN-GIEW PARK

candidate for the Ph.D.
degree.*

Signed: 

(Chairman)

Date 8/7/71

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MODEL STUDIES FOR THE TOTAL SYNTHESIS OF VANCOMYCIN AND RELATED COMPOUNDS USING ORGANOIRON AND ORGANORUTHENIUM COMPLEXES

Abstract

by

JEWN-GIEW PARK

In an effort to gain access to the "upper half" of molecules belonging to the vancomycin class, various Fe⁺C₃ complexes of diaryl ethers and triaryl diethers were synthesized in high yield under mild conditions via nucleophilic substitution reactions between (1,3-dichlorobenzene)Fe⁺C₃PF₆⁻ and various aryl oxides, which include aryl amino acids.

The reactions between triaryl diether-Fe⁺C₃ complexes and glycine enolate equivalents and subsequent rearomatization were attempted without success. Photolysis of the Fe⁺C₃ complexes of diaryl ethers and triaryl diethers gave demetallated products with no detectable racemization in the amino acid side chains, providing a useful method for the construction of aryl ethers.

Several (polychlorobenzene)Ru⁺C₃ complexes were synthesized by treatment of polychloroarenes with (CH₃CN)₃Ru⁺C₃PF₆⁻. In a number of cases the analogous iron complexes can not be prepared. Similar reactivity has been found for Fe⁺C₃ and Ru⁺C₃ toward aryloxides, but the chloride attached to the benzene ring in (chloroarene)C₃Fe⁺ complexes could be displaced by carbanions, whereas
(chloroarene)Ru⁺Cp did not undergo nucleophilic substitution reactions with the same carbanions.

In an effort to prepare the “upper right” moiety of a model for ristocetin A, optically active 4-chlorophenylalanine derivatives and 3-hydroxyphenylglycine derivatives were synthesized by the Evans method. Treatment of 4-chlorophenylalanine derivatives with (CH₂CN)₃RuCpPF₆ gave (chloroarylamino acid)Ru⁺Cp in high yield under mild conditions. Ru⁺Cp complexes of 4-chlorophenylalanine derivatives underwent nucleophilic substitution reactions with 3-hydroxyphenylglycine derivatives to give the precursors of the “upper right” section of ristocetin A. Photolytic demetallation in acetonitrile afforded both demetallated diaryl ethers and (CH₂CN)₃Ru⁺Cp in high yield without racemization in the amino acid side chains.

The use of a 2-bromoethyl ester as a protecting group for the amino acid proved to be problematic due to the unexpected formation of 2-hydroxyethyl ester during attempted deprotection. Thus, a more reliable protecting group is desired.

Attempted peptide cyclizations using the standard Curtius method, the active ester method, the DPPA method, and various other coupling methods were unsuccessful.
Dedication

This work is dedicated to

my wife, Gloria, my son, Francisco, and my daughter, Christina
Acknowledgements

Special thanks to Prof. A. J. Pearson, my research advisor. He has patiently supported and encouraged me through this work; his exemplary scholarship, professionalism, and enthusiasm have become a standard by which I aspire to be measured. The financial support provided by the National Institute of Health is greatly appreciated. To my wife, Gloria, and kids, Francisco and Christina more than just thank you is due for their understanding my common preoccupation and many absences, both physical and mental/emotional, that they have endured over the years. I hope they realize my appreciation and I look forward to many years of showing that appreciation. I also thank Mr. Sanku Mallik and Mr. Hunwoo Shin for the many helpful conversations that I had over the years. And I thank Miss Ann Gelormini for helping my English and her funny jokes and Mr. and Mrs. Seok Chan Kim for the warm hospitality which they showed towards my family, and all the students in the lab. Finally, I thank and praise God for all the blessings He has given me. The gifts of life, love, and learning that I have received will continue to be shared with others.
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<tr>
<td>br</td>
<td>Broad</td>
</tr>
<tr>
<td>br d</td>
<td>Broad doublet</td>
</tr>
<tr>
<td>br m</td>
<td>Broad multiplet</td>
</tr>
<tr>
<td>Cp</td>
<td>Cyclopentadienyl</td>
</tr>
<tr>
<td>Cp*</td>
<td>Pentamethylcyclopentadienyl</td>
</tr>
<tr>
<td>CpFe⁺ (Fe⁺Cp)</td>
<td>Cyclopentadienyliron (used for cationic complexes)</td>
</tr>
<tr>
<td>CpFe (FeCp)</td>
<td>Cyclopentadienyliron (used for neutral complexes)</td>
</tr>
<tr>
<td>CpRu⁺ (Ru⁺Cp)</td>
<td>Cyclopentadienylruthenium (used for cationic complexes)</td>
</tr>
<tr>
<td>CpRu (RuCp)</td>
<td>Cyclopentadienylruthenium (used for neutral complexes)</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DCU</td>
<td>N,N'-Dicyclohexylurea</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet</td>
</tr>
<tr>
<td>DDQ</td>
<td>Dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>d.e.</td>
<td>Diastereomeric excess</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide or Methyl sulfoxide</td>
</tr>
<tr>
<td>DPPA</td>
<td>Diphenylphosphoryl azide</td>
</tr>
<tr>
<td>EDC (= EDCI)</td>
<td>1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>e.e.</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>HPLC</td>
<td>High-pressure liquid chromatography</td>
</tr>
<tr>
<td>hr</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>KHMDS</td>
<td>Potassium bis(trimethylsilyl)amide or Potassium hexamethyldisilazide</td>
</tr>
</tbody>
</table>
IR  Infrared
m  Multiplet
mg  Milligram
min  Minute(s)
μL  Microliter
mmol  Millimole
mp  Melting point in °C
MS  Mass spectroscopy
N-Boc  N-(1,1-Dimethylethoxy)carbonyl or N-t-Butyloxy carbonyl
NBS  N-Bromosuccinimide
N-Cbz  N-Benzylxycarbonyl
NMO  N-Methylmorpholine N-oxide
NMR  Nuclear magnetic resonance
PCC  Pyridinium chlorochromate
s  Singlet
t  Triplet
T  Tertiary
TBQ  2,3,5,6-Tetrachloro-p-benzoquinone
THF  Tetrahydrofuran
TLC  Thin-layer chromatography
TMS  Tetramethyldisilane
TPAP  Tetra-n-propylammonium perruthenate
TTN  Thallium trinitrate
uv  Ultraviolet
CHAPTER I

Vancomycin and its Synthetic Approaches
1. Introduction

Vancomycin and ristocetin are related glycopeptide antibiotics that were discovered in the mid-fifties, being respectively isolated from *Streptomyces orientalis*\textsuperscript{1,2} and from *Nocardia luria*.\textsuperscript{3} Vancomycin has been used clinically for over 20 years,\textsuperscript{4} and its structure was reported by Williamson and Williams.\textsuperscript{5} Ristocetin A\textsuperscript{6,7} was first isolated by Phillip and his co-workers\textsuperscript{8} in 1956. The structure was first reported by Williams *et al.*\textsuperscript{9} in 1979 and shortly after that they revised the configuration at 1985.\textsuperscript{10}

A general structure of the aglycone glycopeptide antibiotics can be depicted as in Figure 1.1.

![Figure 1.1. General structure of the aglycone of vancomycin and related antibiotics.](image)

The identity of units F and G can be used to subdivide this class of antibiotics into the main families. In the vancomycin family F and G are side chains of (S)-
Asparagine and (R)-Leucine. Members of this family include vancomycin,\textsuperscript{11} A82846-A, B, and C;\textsuperscript{12} M43-A, B, and D;\textsuperscript{3} A51568;\textsuperscript{13} and orienticin-A, B, C, and D.\textsuperscript{14}

![Chemical structure of vancomycin family](image)

2 a Vancomycin: \( n = 1, X = Y = Cl, R = H \)
b A82486-A: \( n = 1, X = Cl, Y = H, R = \text{sugar} \)
c A82486-B: \( n = 1, X = Y = Cl, R = \text{sugar} \)
d A82486-C: \( n = 1, X = Y = H, R = \text{sugar} \)
e M43-A: \( n = 2, X = Cl, Y = R = H \)
f M43-B: \( n = 2, X = Cl, Y = R = H, \text{CONH}_2 = \text{CO}_2\text{H} \)
g M43-D: \( n = 1, X = Cl, Y = R = H \)
h A51568: \( n = 0, X = Y = Cl, R = H \)
i Orienticin-A: \( n = 1, Y = Cl, R = \text{sugar} \)
j Orienticin-B: \( n = 1, X = H, Y = Cl, R = \text{sugar} \)
k Orienticin-C: \( n = 1, X = Y = H, R = \text{sugar} \)
l Orienticin-D: \( n = 2, X = Y = Cl, R = \text{sugar} \)

Figure 1.2. Vancomycin family

In the ristocetin family, F and G are (S)- and (R)-aryl glycine side chains connected as a diaryl ether. This family includes ristocetin A,\textsuperscript{5-10} aridicin,\textsuperscript{15} A40926,\textsuperscript{16} A35512-B,\textsuperscript{17} actiplanin (A4696),\textsuperscript{18} teichomycin,\textsuperscript{19} and UK-68,697.\textsuperscript{20}
Anomalies include actinoidan,\textsuperscript{21} α- and β-avoparcin,\textsuperscript{22} OA7653,\textsuperscript{23} and complestatin.\textsuperscript{24} The structural variations within each family are summarized in Figures 1.2 and 1.3.

![Chemical structure](image)

3a Ristocetin A: $n = 0$, $T = \text{OH}$, $U = V = \text{Me}$, $W = X = Y = Z = \text{H}$, $R = \text{sugar}$

3b Aridicin: $n = 1$, $T = \text{OH}$, $W = X = Y = Z = \text{Cl}$, $V = U = R = \text{H}$

3c A40926: $n = 1$, $W = \text{Cl}$, $T = V = X = Y = Z = U = R = \text{H}$

3d A35512-B: $n = 0$, $T = \text{OH}$, $W = \text{Cl}$, $V = X = Y = Z = R = \text{H}$, $U = \text{Me}$

3e Actiplanin: $n = 0$, $U = V = \text{Me}$, $X = \text{Cl}$, $T = W = Z = Y = R = \text{H}$

3f Teichomycin: $n = 0$, $X = Z = \text{Cl}$, $T = V = W = Y = U = R = \text{H}$

Figure 1.3. Ristocetin family - general structure.

These compounds function by binding to mucopeptides at a late stage of their biosyntheses.\textsuperscript{25} This binding inhibits completion of the bacterial cell wall and leads to destruction of the bacteria by lysis. The antibiotics target the D-Ala-D-Ala\textsuperscript{26} carboxyl terminus of the mucopeptide, a feature common to a number of bacteria.
The compound can be divided into two portions - the sugars attached to the aryl rings and the linear heptapeptide which features a complex array of aromatic amino acids. Although an *in vitro* antibacterial activity study has not been reported for ristocetin, Nagarajan\(^{27}\) found the disaccharide unit in vancomycin appeared unimportant and its removal had no influence on its *in vitro* activity, however, selective removal of the vancosamine did lead to a small drop in activity (by a factor of 2-4). In contrast the gross structure and precise configurational and conformational arrangements of the heptapeptide is crucial.

For vancomycin, the key role played by the N-terminal N-methylleucine has been demonstrated by the observation of Nagarajan that the removal of this unit by Edman degradation\(^{27}\) leads to zero antibacterial activity.

![Image](image.png)

*Figure 1.4. Schematic representation of the complex formed between vancomycin and a bacterial cell-wall peptide model, N-acetyl-D-alanyl-D-alanine. The broken lines indicate the position of intermolecular hydrogen bonds.*
Consistent with this Williams et al.\textsuperscript{28} found that acetylation of this nitrogen terminus substantially reduces its ability to complex with an Ac-D-Ala-D-Ala model mucopéptide terminus. In addition it was found that deprotonation of the ammonium ion drastically reduces the binding energy in the complex with the model compound.\textsuperscript{29}

Williams et al.\textsuperscript{10,20,26,31} and Hamilton et al.\textsuperscript{30} have described elegant binding studies using NMR spectroscopy. They found that three of the amide N-H groups point directly towards the carboxylate anion from D-Ala-D-Ala and are geometrically disposed so that both oxygens are held by strong hydrogen bonding (Figure 1.4).

Recently, Popieniek and Pratt\textsuperscript{32} have suggested a mechanism of binding between several glycopeptide antibiotics and a peptide ligand, e-N-acetyl-\textalpha-N-dansyl-L-lysyl-D-alanyl-D-alanyl (ADLAA) by measuring rate constants and equilibrium constants. On the titration of the glycopeptide antibiotics in the presence of the peptide, the first dissociation constants were perturbed, and perturbations (\(\Delta\Delta G^*\)) were 0.41, 0.29, and 0.44 Kcal/mol for vancomycin, ristocetin A, and \(\alpha\)-avoparcin, respectively. These values are relatively small compared to the total binding energies, 7.47, 7.47, 7.06 Kcal/mol, respectively. The weak perturbations can be interpreted as the difference in free energy of interaction between the peptide and N-terminal protonated and free amine species. Thus, the significant decreases in binding strength attest to the fragile specificity of the carboxylate binding pocket in glycopeptide antibiotics.

Therefore, the association reaction (binding) of vancomycin and ADLAA must consist of at least two distinct steps. In conclusion, there appears to be a rapid,
diffusion-controlled preequilibrium association of glycopeptide and ligand, followed by a slower, rate-controlling rearrangement of the initial "loose" complex (eq 1.1).\textsuperscript{32}

\[
\begin{array}{ccc}
D + V & \xrightarrow{k_1} & DV_1 \\
& \xleftarrow{k_1} & \\
& \xrightarrow{k_2} & DV_2 \\
\end{array}
\]  \\
(eq 1.1)

D: ε-N-Acetyl-α-N-dansyl-L-lysyl-D-alanyl-D-alanine (ADLAA)  
V: Vancomycin

Also, Nieto and Perkins\textsuperscript{33} and Williams et al.\textsuperscript{28} have studied the energetic consequences of changing the terminal residues (Table 1.1). It is noteworthy that there is a 3.1 Kcal/mol drop in binding energy for vancomycin when the terminal D-Ala is changed to D-Leu. It should also be noted that L-amino acids are the wrong shape

<table>
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<tr>
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<th>Ristocetin-ΔG</th>
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<tbody>
<tr>
<td>Ac\textsubscript{2}-L-Lys-D-Ala-D-Ala</td>
<td>3.5</td>
<td>7.8</td>
</tr>
<tr>
<td>Ac\textsubscript{2}-L-Lys-D-Ala-Gly</td>
<td>7.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Ac\textsubscript{2}-L-Lys-D-Ala-D-Leu</td>
<td>5.4</td>
<td>7.9</td>
</tr>
<tr>
<td>Ac\textsubscript{2}-L-Lys-D-Ala-L-Ala</td>
<td>No combination</td>
<td></td>
</tr>
<tr>
<td>Ac\textsubscript{2}-L-Lys-D-Gly-D-Ala</td>
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<td>7.1</td>
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<tr>
<td>Ac\textsubscript{2}-L-Lys-D-Leu-D-Ala</td>
<td>7.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Ac\textsubscript{2}-L-Lys-L-Ala-D-Ala</td>
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<td></td>
</tr>
<tr>
<td>Ac-D-Ala-D-Ala</td>
<td>6.2</td>
<td>7.5</td>
</tr>
</tbody>
</table>

* Values at 26 °C, in Kcal/mol.
for binding and do not form complexes. From Table 1 it is also apparent that while glycine may be substituted for either D-Ala residue the binding is less effective by ~1.5 Kcal/mol. This would appear to be a result of a looser fit in the pocket and hence some movement of the peptide, which in turn will lead to less effective hydrogen bonding.

The "left hand" half of Ristocetin A plays a less direct role in the binding and the influence of the biphenyl unit is unknown.

2. Synthetic Approaches

From a synthetic standpoint several key issues must be addressed:

1. Formation of the diaryl ether and triaryl diether linkages.
2. Construction of four macrocyclic peptide rings.
3. Preparation of some unusual amino acids.

A. Formation of diaryl ether linkages.

Hamilton et al.\textsuperscript{34} have described an example of diaryl ether formation featuring a standard Ullmann reaction via nucleophilic substitution between 3-hydroxyphenylalanine derivative (1.3) and dinitrotosylate (1.4) in pyridine (eq 1.2). Under these reaction conditions (80 °C, pyridine), racemization is not a serious problem because the only chiral center under consideration is isolated from the phenyl ring by a methylene carbon. But these conditions cannot be used for phenylglycine derivatives due to the highly racemizable chiral center.
For the total synthesis of piperazinomycin, which has similar aryl structure to the vancomycin class, Yamamura et al. developed a new method to synthesize the diaryl ethers by thallium trinitrate (TTN) oxidation of the dibromophenols, followed by zinc reduction. As it was an intramolecular ether formation, this method was used as the later step of the synthesis (eq 1.3).
Zinc reduction was necessary to convert the quinoid intermediate (1.8) to a phenyl ring. Due to the nature of Zn/HOAc conditions, partial loss of many protecting groups such as NHBoc is expected. However, this methodology has been extended to other syntheses, including total synthesis of deoxybouvardin and RA-VII,37 OF4949-III,38 K-13,39 and synthetic studies for vancomycin.40,41

\[
\text{Br} \quad \text{OH} \quad \text{Br} \quad \text{Br} \quad \text{OH} \quad \text{Br}
\quad \text{TTN} \quad \text{MeOH} \quad \text{Br} \quad \text{Br} \quad \text{O} \quad \text{Me}
\]

(eq 1.4)

\[
\text{OH}
\]

Recently Evans et al.41 have modified the reaction conditions by replacing Zn/HOAc with CrCl\(_2\), leading to as much as 40% increase in yield.

Although this methodology is appealing in that it probably mimics a related step in the biosynthesis of these structures, the low yields for macrocyclization as well as the use of large excesses of thallium and chromium reagents detract from the practical utility of these reactions. Also, as mentioned before, special care should be taken on selection of protecting groups for other functionalities in the molecule.
Evans et al.\textsuperscript{42} has reported a different approach to related isodityrosine derivatives by employing an Ullmann reaction to form the diaryl ether subunit prior to the construction of either of the amino acid side chains. Thus, for the total synthesis of OF4949-III and K-13, the carbon framework of the fully differentiated isodityrosine was synthesized in 90\% yield through Ullmann coupling. The side chains were subsequently transformed to amino acid derivatives that are present in the target molecule (eq 1.5).

![Chemical structure](image)

**Steps**

**OF4949-III and K-13** (eq 1.5)

Boger et al.\textsuperscript{43} have reported Ullmann condensation of the selectively-protected L-Dopa derivative (1.12) with sodium p-iodobenzoate (1.13), which provided the diaryl ether (1.14) without amino acid racemization (eq 1.6).

![Chemical structure](image)

**1.12**

**(eq 1.6)**

**1.13**

**1.14**

51\%
This methodology has been extended to intramolecular diaryl ether formation. The yields range from 31 to 58% depending on substituents on the phenyl ring and side chain.

Crimmin and Brown have described the reaction of aryl iodonium salts (1.15) with aryl oxides (1.16) to give an aryl ether (1.17) without loss of stereochemical integrity (eq 1.7). The yield was moderate to good (30–70%), but the reaction cannot be driven to completion. Thus, in almost all cases, 10–30% of the starting tyrosine derivative was recovered, presumably due to side reactions of the iodonium salts.

![Chemical structures](image)

<table>
<thead>
<tr>
<th>1.15</th>
<th>1.16</th>
<th>1.17</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 1.15" /></td>
<td><img src="image" alt="Structure 1.16" /></td>
<td><img src="image" alt="Structure 1.17" /></td>
</tr>
</tbody>
</table>

(eq 1.7)

B. Construction of macrocyclic peptides
The development of the azide coupling method by Curtius\textsuperscript{46} was one of the starting points of peptide synthesis. At the time, the azide method\textsuperscript{47} became the most valuable synthetic tool for peptide segment condensation, when it was recognized that its apparent "racemization-free" performance was not attained by other efficient coupling procedures. While the azide method is not always free from racemization,\textsuperscript{48} there is a consensus that this procedure is still the least racemization-prone among the known methods of peptide bond formation.\textsuperscript{47}

This eminence of the azide procedure over other efficient methods is somewhat offset by several constraints: (1) it is experimentally more laborious and time-consuming in three stages (hydrazide formation $\rightarrow$ azide formation $\rightarrow$ coupling), (2) many side reactions have been observed,\textsuperscript{49} and (3) the rate of acylation is considerably slower than those of the anhydride or carbodiimide methods.

Reaction of diphenylphosphoryl azide (DPPA, \textbf{1.19})\textsuperscript{50} with N-protected amino acid (\textbf{1.18}) in DMF produces an azide (\textbf{1.21}), probably via the intermediate structure (\textbf{1.20}). This method lends yet another dimension of experimental flexibility to the azide method. Hydrazides are altogether circumvented in this most direct route for the preparation of protected peptide azides. The level of racemization is even lower than that of the standard method.\textsuperscript{51} This is the major reason why many macropeptide cyclizations are attempted with this method.

\[
\begin{align*}
\text{RCO}_2^- & + \text{N}_3-\text{P(O}_\text{Ph})_2 \quad \rightarrow \\
\text{1.18} & \quad \text{1.19} \\
\rightarrow & \quad \text{1.20} \\
\rightarrow & \quad \text{1.21} \\
\quad & \quad \text{RCON}_3^- + \text{HOP(O}_\text{Ph})_2
\end{align*}
\]
As a synthetic model for vancomycin, Hamilton et al.\textsuperscript{34} employed diphenylphosphoryl azide (DPPA)\textsuperscript{49} as the peptide coupling reagent under high dilution, low temperature conditions in DMF in the presence of NaHCO\textsubscript{3} (to control pH of the medium). In this cyclization, a remarkable change in the NMR spectrum was observed: A comparison of the aromatic regions in the \textsuperscript{1}H NMR spectra of (1.22) and (1.23) (both in DMSO-d\textsubscript{6}) showed a dramatic upfield shift of the benzylamine aromatic 2-H signal, from $\delta$ 6.92 in (1.22) to $\delta$ 5.84 in (1.23). This is due to the peptide ring which restricts the motion of the benzylamine unit and forces its 2-proton to lie under the dinitrophenyl group.\textsuperscript{34} The equivalent proton in vancomycin is found at $\delta$ 5.69\textsuperscript{52} and in ristocetin A at $\delta$ 5.85.\textsuperscript{53}

This DPPA cyclization has been employed also by Boger et al.\textsuperscript{43,44} and Crimmin and Brown,\textsuperscript{54} who observed the same characteristic changes in NMR spectra.

Boger et al.\textsuperscript{43,44a} investigated macrocyclization of isodityrosines in an effort to determine the optimal strategy and method for the total synthesis of K-13 and OF4949, and structurally related compounds. With a full range of substrates available for examination, comparative studies on the methods (both active ester and DPPA), site,
and substrate structural features affecting the 17-membered macrocyclization were conducted.

![K-13 Model](1.24a) ![OF4949 Model](1.24b)

For K-13, cyclization was optimized through C\(^{11}\)-N\(^{10}\) amide bond formation using the DPPA method (eq 1.10). Presumably, in the C\(^{14}\)-N\(^{13}\) amide bond formation, intramolecular active ester closure to a 5-membered oxazolidinone is competitive with 17-membered ring closure reaction.

![Reactions](eq 1.10)
Similarly, in C\textsuperscript{13}-N\textsuperscript{14} macrocyclization on the OF4949-related substrates, competitive formation of a succinimide was anticipated. Consequently, OF4949-III and OF4949-IV were synthesized by accommodating C\textsuperscript{10}-N\textsuperscript{11} amide bond closure using the DPPA method (eq 1.11).

\[
\begin{align*}
\text{R} &= \text{Me, OF4949-III} \\
\text{R} &= \text{H, OF4949-IV} \\
\text{active ester methods have been examined by Schmidt et al.}\textsuperscript{59} \text{ and Evans et al.}\textsuperscript{42} \\
&\text{for the cyclization step in the total syntheses of OF4949 and K-13. Among all of the} \\
&\text{active esters, pentafluorophenyl ester has been chosen due to their inherently higher} \\
&\text{reactivity over other esters.}\textsuperscript{55,56}
\end{align*}
\]
Shortly after this, Schmidt et al.\textsuperscript{57} reported synthesis of diisotyroline employing pentafluorophenyl ester. To investigate the crucial site of coupling for the successful ring closure via \(\omega\)-amino-pentafluorophenyl ester to the ansa-peptide, two different peptides, (1.31) and (1.32) were synthesized. In this case compound (1.33) was obtained from both starting materials in 80% yield, showing no apparent difference in cyclization (eq 1.13). Edwards et al.\textsuperscript{58} have shown that p-nitrophenyl ester also can be used as active ester for cyclization.
C. Synthesis of amino acids

Biologically, the most important structural component in the vancomycin class consists of a heptapeptide. In this context, Evans et al. have developed asymmetric azidation of phenylacetic acid or hydrocinnamic acids (eq 1.14). The oxazolidinone ring in 1.35 proved to be an excellent chiral auxiliary which provided a new way to synthesize optically active α-amino acids. The acid 1.34 was treated with pivaloyl chloride and triethylamine to yield the mixed anhydride which, on reaction with 1 equivalent of lithiated oxazolidinone at -78 °C, afforded the carboximide 1.35 in

\[
\begin{align*}
\text{PhCOOH} & \xrightarrow{\text{Pivaloyl-Cl}} \text{PhCOCH}_2\text{N} = \text{O} \quad \text{Et}_3\text{N/0 °C; lithiated oxazolidinone}^* \\
& \quad \xrightarrow{\text{KH-MDS Trisyl azide}} \\
\text{1.34} & \quad 99\% \text{ de} \\
\text{1.35} & \quad \text{(eq 1.14)} \\
\text{1.36} & \quad 99\% \text{ ee} \\
\text{1.37} & \quad 99\% \text{ ee}
\end{align*}
\]
excellent yield. The enolate anion of 1.35, formed by addition of a THF solution to 1.1 equivalent of potassium bis(trimethylsilyl)amide (or potassium hexamethyldisilazide, KHMDS) at -78 °C, was then treated with 1.2 equivalent of trisyl azide, followed by a quench with 5 equivalent of acetic acid to give 1.36 in high yield. Lithium hydroxide hydrolysis and reduction of 1.36 gave (S)-phenylglycine in high chemical yield with excellent enantiomeric excess. This method was elegantly applied to the total synthesis of OF4949-III and K-13 (eq 1.15). Upon successful completion of the above experiments, 1.38 was converted into the fully differentiated isodityrosine precursor (1.41).
Williams et al.\textsuperscript{61} prepared (S)-3,5-dihydroxyphenylglycine, which is a naturally occurring amino acid found in the vancomycin class. Thus, commercially available starting material (1.42) was converted to an aromatic acid (1.43), which was transformed to 3,5-dimethoxyphenylglycine (1.44) using Evans’ method (eq 1.16).

\[
\begin{align*}
\text{MeO} & \quad \text{steps} & \quad \text{HO} \quad \text{steps} & \quad \text{MeO} \\
1.42 & \quad \text{HO} & \quad \text{NH}_2 & \quad 1.44 \\
\text{HO} & \quad \text{OH} & \quad \text{MeO} & \quad \text{OMe}
\end{align*}
\]

(eq 1.16)

In the synthesis of diisotyrosine, Schmidt et al.\textsuperscript{57} have utilized asymmetric hydrogenation with the homogeneous catalyst [Rh(dipamp)]\textsuperscript{+}.\textsuperscript{62} Since this catalyst hydrogenates \textit{E} double bonds only very slowly and without high stereoselectivity, the \textit{E} form was converted into \textit{Z}-compound (1.46) by photochemical isomerization. The enantioselectivity for 1.47 was greater than 99%.

\[
\begin{align*}
\text{Br} & \quad \text{O} & \quad \text{Me} & \quad \text{hv} & \quad \text{Br} & \quad \text{O} & \quad \text{Me} & \quad [\text{Rh(dipamp)}]^+ \quad \text{H}_2 \\
\text{BocHN} & \quad \text{CO}_2\text{Bn} & \quad & & & \quad \text{BocHN} & \quad \text{CO}_2\text{Bn} \\
E \text{ and } Z & \quad 1.45 & \quad & & & \quad Z & \quad 1.46 & \quad 1.47 \\
\text{Br} & \quad \text{O} & \quad \text{Me} & \quad \text{CH}_2\text{OH} \quad 20 \degree C \\
\text{BocHN} & \quad \text{CO}_2\text{Bn} & \quad 72 \text{ hr}
\end{align*}
\]

(eq 1.17)
D. Organometallic approach

The thirty year-old finding\textsuperscript{63} that arenes can be complexed to various metals by ligand exchange has led to the synthesis of several hundred cationic complexes of aromatic ligands.

Many of these cationic complexes have attracted considerable attention because of their stability to heat, air, water and some concentrated acids such as H\textsubscript{2}SO\textsubscript{4} (NMR spectra could be recorded using the latter solvent).\textsuperscript{64}

In addition, the chemistry of complexed arenes is completely opposite to that of the free aromatics. Thus, they do not undergo any of the reactions of nucleophilic aromatics such as acylation, arylation, bromination, or substitution by free radicals.\textsuperscript{63} On the contrary, they undergo many useful reactions with nucleophiles. These include the \textit{exo} addition of hydride and carbanions, as well as nucleophilic displacement of chloride by C, N, O, and S anions under mild conditions.\textsuperscript{63,64}

Since simple arenetricarbonylmanganese complexes\textsuperscript{65} had been synthesized for electron rich aromatic compounds, several methods have been investigated in our laboratories in an effort to make compounds such as 1.49 (eq 1.18). To this end, various reaction conditions and reagents were tested but 1.48, as well as protected phenylalanine did not undergo complexation.\textsuperscript{66,67} Nevertheless, despite these limitations, some valuable results have been obtained. After nucleophilic replacement
of chloride in complex 1.51, a chiral glycine enolate equivalent, the Schoellkopf reagent\textsuperscript{68} was reacted with the resulting complex 1.53 (eq 1.19) to afford a precursor of the B-C ring moiety in vancomycin.

In the following chapters, synthetic approaches toward the B-C ring portion of vancomycin using (arene)Fe\textsuperscript{+}Cp and Ru\textsuperscript{+}Cp complexes will be described.
CHAPTER II

$\eta^6$-(Arene)-$\eta^5$-Cyclopentadienyliron

Hexafluorophosphate Complexes
1. Introduction

The discovery of the transition metal sandwich structure\(^{69-71}\) in compounds such as ferrocene\(^{72}\) and bis-benzene chromium\(^{73}\) was a major advance in organic and organometallic chemistry. Their syntheses have been extensively documented, but subsequent reactivity of the coordinated arene is still under exploration.\(^{74}\) Complexes which have proved to be useful in aromatic synthesis are the readily available cationic sandwiches of the type (arene)cyclopentadienyliron cations, 2.1 (Figure 2.1).

![Figure 2.1 General structure of (arene)CpFe\(^+\) complex. X = BF\(_4^–\), PF\(_6^–\) R = alkyl, alkoxy or halogen](image)

(Arene)CpFe\(^+\) complexes were first synthesized using CpFe(CO)\(_2\)Cl (eq 2.1).\(^{75-78}\) The salts were isolated as iodides\(^{75-77}\) or tribromides.\(^{78}\) However this reaction is no longer used because ferrocene was found to be a better starting material under similar conditions; also side products were found in the reaction of eq 2.1, limiting the yields.\(^{74}\)
\[
\text{CpFe(CO)₂Cl} + \text{C₆H₆} \xrightarrow{\text{AlCl₃/Al}} \begin{bmatrix}
\text{Fe⁺C₆H₆} \\
\text{R} \\
\text{2.3}
\end{bmatrix} \text{AlCl₄⁻} \quad (\text{eq 2.1})
\]

But this method has been found to be clean and convenient for the synthesis of (arene)Cp⁺Fe⁺ complexes (eq 2.2) since decamethylferrocene is inert towards ligand exchange by AlCl₃.\(^{79}\)

\[
\text{Cp⁺Fe(CO)₂Br} + \text{C₆H₆} \xrightarrow{\text{2 AlCl₃/80-100 °C}} \begin{bmatrix}
\text{Fe⁺C₆H₆} \\
\text{Cp⁺} \text{C₆H₆} \\
\text{R} \\
\text{2.5}
\end{bmatrix} \text{X} \quad (\text{eq 2.2})
\]

\(\text{Cp⁺} = \text{pentamethylcyclopentadienyl}, \text{X} = \text{BF}_4⁻ \text{or PF}_6⁻\)

The ligand exchange reaction between one ring of ferrocene and arenes has attracted a great deal of attention as it is a straightforward way to complex arenes with the CpFe⁺ unit (eq 2.3).\(^{80}\)

\[
\text{Cp₂Fe} + \text{C₆H₆} \xrightarrow{\text{AlCl₃/Al}} \begin{bmatrix}
\text{Fe⁺C₆H₆} \\
\text{R} \\
\text{2.1a}
\end{bmatrix} \text{AlCl₄⁻} \quad (\text{eq 2.3})
\]

This reaction is carried out at 70-190 °C during 1-16 hr in the arene as solvent; if the arene is a solid the reaction can be carried out neat in a sealed tube or in an inert solvent such as heptane, cyclohexane, methylcyclohexane, octane or decalin. AlCl₃ is
the most common Lewis acid and Al powder is added to inhibit oxidation of ferrocene to ferricinium. The stoichiometry of the reactants is ferrocene : arene : AlCl₃ : Al = 1 : 1 : 2 : 1. However in some cases, the addition of a stoichiometric amount of water increases the yield; then the favorable ratio is ferrocene : arene : AlCl₃ : Al : H₂O = 1 : 1 : 3 : 1. For instance, with benzene, the yield increases from 20 to 90% upon addition of water. After hydrolysis with ice water, the aqueous phase contains the (arene)CpFe⁺ cation. NH₄PF₆ is added to precipitate the nearly water insoluble PF₆⁻ salt. BF₄⁻ salts are hygroscopic in many cases.

Electron releasing methyl groups on the arene increase the yield. However, inhibiting steric effects predominate when the number of methyl groups is larger than two. Conversely, the yields decrease dramatically upon increasing the number of fluorine substituents on the arene ring from 0 to 3.

<table>
<thead>
<tr>
<th>Arene</th>
<th>C₆H₆</th>
<th>C₆H₅F</th>
<th>o-C₆H₄F₂</th>
<th>m-C₆H₄F₂</th>
<th>p-C₆H₄F₂</th>
<th>C₆H₃F₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield(%)</td>
<td>90</td>
<td>45</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Although no ferrocene can be detected before hydrolysis of the ligand exchange reaction between ferrocene and benzene, a large amount of ferrocene is recovered after hydrolysis. This indicates that ferrocene is complexed to aluminium chloride before hydrolysis, which is destroyed by water. The mechanism of ligand exchange between ferrocene and arenes is believed to be as shown in Scheme 2.1.

The ¹H NMR chemical shifts of (Benzene)CpFe⁺ are 5.20 and 6.50 ppm downfield from TMS, thus the Cp hydrogens are 1 ppm downfield from those in ferrocene whereas the benzene hydrogens are 1 ppm upfield from free benzene due to the metal to ligand π-back-donation.
Scheme 2.1. Mechanism of ligand exchange reaction.

Scheme 2.2. General reactions of (arene)Fe\textsuperscript{3+}Cp complexes.

\[ X = H, m-\text{Cl}, p-\text{Cl} \]
(Arene)CpFe\(^{+}\) complexes are remarkably stable towards the action of strong oxidants such as concentrated H\(_2\)SO\(_4\), HNO\(_3\), peroxides, dichromates, permanganate and H\(_2\)O\(_2\)/NaOH. This stability permits the oxidation of alkyl substituents on the arene and Cp ligands to give acids.\(^{86}\) Thus a series of (arene)CpFe\(^{+}\) complexes have been prepared by oxidation of alkyl side chains bearing various substituents.\(^{87}\) The acids (2.10b) were esterified (2.10c) or converted to acid chlorides (2.10d) and thence to amides (2.10e) and nitriles (2.10f, Scheme 2.2).

The reaction of LiAlH\(_4\) or NaBH\(_4\) with the (arene)CpFe\(^{+}\) complex has long been known to give a neutral orange product.\(^{77}\) When the arene is monosubstituted, the hydride attack always occurs at an unsubstituted arene carbon.\(^{84,88,89}\) Directing effects of Me,\(^{84}\) Cl,\(^{88}\) OMe\(^{89}\) and CO\(_2\)Me\(^{90}\) substituents are shown below (Scheme 2.3). Cl and CO\(_2\)Me groups favor ortho attack whereas the OMe group favors meta attack although the latter is rather weak.

### Scheme 2.3. Directing effect of various substituents.

<table>
<thead>
<tr>
<th>R</th>
<th>2.11a</th>
<th>2.11b</th>
<th>2.11c</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH(_3)</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>Cl</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>OMe</td>
<td>0.2</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>CO(_2)Me</td>
<td>12.7</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
The reactions of hydrides and other nucleophiles with the organometallic cations have been rationalized in terms of charge control. Nucleophilic attack occurs at an even numbered aromatic ring rather than at odd one (Cp). Schematically, the even numbered ring (arene) ligand donates electron pairs to the metal whereas the odd ligand accepts one electron from the metal; thus the positive charge is more delocalized onto the even numbered ring. This was confirmed by INDO calculations.

Addition of phenyl-, methyl- and ethyllithium to (benzene)CpFe\(^+\) gives results analogous to the hydride reaction ($\eta^5$-cyclohexadienylCpFe complex). The reaction of Ph\(_3\)C PF\(_6\) (trityl) or NBS with $\eta^5$-cyclohexadienylCpFe complex can give either exo-R abstraction of endo-H abstraction (Scheme 2.4). The tendency for exo-R abstraction increases in the series: R = CH\(_3\) ≈ Ph < C\(_5\)H\(_5\) < C\(_2\)H\(_5\) < PhCH\(_2\). This is confirmed by INDO calculations.

Scheme 2.4. Substituent effect on the selective removal of endo-H

A chlorine substituent is displaced by various nucleophiles (eq 2.4).
The order of reactivity for the displacement of a halogen by nucleophile follows the order: \( \text{Nu} = \text{OH}, \text{OPh}, \text{CN}, \text{SH}, \text{OE}, \text{OAc}, \text{SPh}, \text{N}_3, \text{NR}_2 \)

A dichotomy of behavior is noteworthy between \( \text{CpFe}^+ \) and \( \text{Cr(CO)}_3 \) complexes of chlorobenzene with respect to reactions of carbanions: the chlorine is replaced only in \( \text{Cr(CO)}_3 \) complex (Scheme 2.5).\(^7\)
CpFe⁺ complexes of fluoroarenes show essentially the same behavior as the chloro analogues, e.g., easy displacement of the halogen by amines and ortho addition of H⁻ and carbon nucleophiles. Rate studies have shown that the fluoroacetone complexes are more reactive than the chlorobenzene analogues.⁹⁶a

Decomplexation occurs when (arene)CpFe⁺ complexes are irradiated with uv or sunlight to give free arene.⁹⁷ Photolysis can be done in CH₂Cl₂, acetone, or CH₃CN. In acetonitrile, photolysis of various (arene)CpFe⁺ complexes in the presence of a two-electron donor ligand gives CpFe⁺(CH₃CN)ₓLₙ₋ₓ (L = CO, phosphine, olefin).⁹⁸

Figure 2.2. Schematic representation of general reactions of (arene)Fe⁺Cp complexes.
Thermal decomplexation of (arene)CpFe\(^+\) complexes does not always proceed cleanly since high temperatures are required due to the stability of these complexes. However, it has been found possible for mesitylene-CpFe\(^+\) complex.\(^{99}\) Decomplexation also can be obtained by electrochemical one-electron reduction.\(^{100}\)

This section can be summarized schematically as in Figure 2.2.

2. Nucleophilic substitution reactions

As discussed before, Cl attached to the benzene ring in areneFe\(^+\)Cp complexes can be replaced very easily by various nucleophiles. Based on this reactivity, syntheses of triaryl diether and diaryl ethers have been attempted utilizing halogen replacement by aryloxides having amino acid side chain. The resultant aryl ethers (2.17) are potential intermediates for macropeptide cyclization.

Scheme 2.6. Construction of the "upper half" of the vancomycin class.

To this end, the starting material, m-dichlorobenzeneCpFe\(^+\) complex and related compounds (2.16) were prepared according to the literature procedure.\(^{85, 101-103}\) As the literature yield for m-dichlorobenzeneCpFe\(^+\) complex was only about 20\%, the ligand exchange reaction (eq 2.5) was attempted under somewhat modified conditions in an effort to improve the yield. The results are summarized in Table 2.1.
Table 2.1. Complexation of polychloroaromatics.

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>Lewis acid</th>
<th>Ln</th>
<th>Conditions</th>
<th>Results</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 H</td>
<td>decalin</td>
<td>AlCl₃</td>
<td>Cp</td>
<td>Reflux, 16 hr</td>
<td>2.16a, 17%</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>heptane</td>
<td></td>
<td></td>
<td>* 6 hr</td>
<td>* 12%</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>heptane</td>
<td></td>
<td></td>
<td>72 °C, 16 hr</td>
<td>Decomposition</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>*</td>
<td></td>
<td></td>
<td>Reflux</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>*</td>
<td></td>
<td></td>
<td>Reflux</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>*</td>
<td></td>
<td></td>
<td>Reflux without Al</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CCl₄</td>
<td></td>
<td></td>
<td>Reflux, with Al</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>*</td>
<td></td>
<td></td>
<td>90 °C, 16 hr</td>
<td>2.16a, 15.8%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>*</td>
<td></td>
<td></td>
<td>* 48 hr</td>
<td>14.5%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>*</td>
<td></td>
<td></td>
<td>110 °C, 33 hr</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>*</td>
<td></td>
<td></td>
<td>130 °C, 48 hr</td>
<td>22.7%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>*</td>
<td></td>
<td></td>
<td>80 °C, 24 hr</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>*</td>
<td>(P(OEt)₃)₃</td>
<td></td>
<td>110-120 °C</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Cl decalin</td>
<td>Cp</td>
<td></td>
<td>110 °C, 16 hr</td>
<td>No Reaction</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>*</td>
<td></td>
<td></td>
<td>110-130 °C, 16 hr</td>
<td>2.16a : 2.16b = 1 : 5.5, total 2.5%</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>*</td>
<td>*</td>
<td></td>
<td>* without Al</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>*</td>
<td>*</td>
<td></td>
<td>* with Al and water</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>*</td>
<td>(CO)(CH₃CN)(PPh₃)</td>
<td></td>
<td>115 °C, 5 hr</td>
<td>2.1, 18%</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>CH₂Cl₂</td>
<td></td>
<td></td>
<td>hv, r.t., 1 hr</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>CH₃CN</td>
<td>*</td>
<td></td>
<td>Reflux, 16 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>*</td>
<td>AlBr₃</td>
<td></td>
<td>115 °C, 1.5 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>CH₂Br₂</td>
<td></td>
<td></td>
<td>Reflux, 2 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>CH₂Cl₂</td>
<td>(P(OEt)₃)₃</td>
<td></td>
<td>hv, r.t., 1 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>24OMe</td>
<td>decalin</td>
<td>AlCl₃</td>
<td>Cp</td>
<td>80-110 °C, 30 min</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Hexane</td>
<td>*</td>
<td></td>
<td>Ultrasound, r.t., 24 hr</td>
<td>No Reaction</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>*</td>
<td>*</td>
<td></td>
<td>100 °C, 30 min</td>
<td>Decomposition</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>*</td>
<td>*</td>
<td></td>
<td>* without Al</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>CH₂Cl₂</td>
<td>(CO)(CH₃CN)(PPh₃)</td>
<td></td>
<td>hv, r.t., 1 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>CH₃CN</td>
<td>*</td>
<td></td>
<td>Reflux, 16 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>CH₂Cl₂</td>
<td>(P(OEt)₃)₃</td>
<td></td>
<td>hv, r.t., 1 hr</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>*</td>
<td>(m-dichlorobenzene)</td>
<td></td>
<td>hv, r.t., 1 hr</td>
<td>No Reaction</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{a}\) Arene was used as solvent. \(^{\text{b}}\) Order of addition: arene, ferrocene, Al, then AlCl₃. \(^{\text{c}}\) Order of addition: ferrocene, Al, AlCl₃, then arene. \(^{\text{d}}\) For the synthesis see ref 36. \(^{\text{e}}\) For the synthesis see ref 37. \(^{\text{f}}\) uv (sunlamp, 275 W), pyrex.
For m-dichlorobenzene, choice of solvent seems to be the most important over other factors (entries 1-13). Thus the only productive solvents were decalin and m-dichlorobenzene itself.

The effect of reaction temperature was not distinctive. When ferrocene was replaced by CpFe⁺(P(OEt)₃)₃PF₆₁⁰⁴ it resulted in decomposition (entry 13).

For the complexation of 1,3,5-trichlorobenzene, as was expected, the yield was very low (~2%, entry 15). Also dehalogenated product was detected in the mixture of product at the ratio of (trichloro) : (dichloro) = 1 : 5.5 in the presence of Al powder. This phenomenon also has been observed by Nesmeynov et al.₁⁰³ and Astruc et al.₇⁴ When this reaction was repeated without Al powder decomposition occurred (entry 16). Addition of an equimolar amount of water also led to decomposition (entry 17). Interestingly, the reaction with CpFe⁺(CO)(CH₃CN)(PPh₃)₁⁰⁵ gave only (benzene)CpFePF₆, i.e., totally dehalogenated product in 18% yield. Photolytic or thermal reaction between 1,3,5-trichlorobenzene and CpFe⁺(CO)(CH₃CN)(PPh₃) also led to decomposition (entries 19, 20, 23). Replacement of the Lewis acid, from AlCl₃ to AlBr₃ led to even faster decomposition (entries 21 and 22). Thus, complexation of polychloroaromatics is highly problematic.

Also an attempted photolytic ligand exchange₁⁰⁵ between a more electron rich arene (3,5-dichloroanisole) and an electron deficient complex (m-dichloroCpFePF₆) was unsuccessful (entry 31).

Although the chemical yield was low, starting materials are readily available at low cost, both starting materials (ferrocene and m-dichlorobenzene) are easily recovered, and the reaction can be scaled up to hundred gram scale without difficulties.
The (m-dichlorobenzene)CpFe⁺ complex was subjected to reaction with various nucleophiles. Thus as a model study, 2 equivalents of 4-methoxyphenol was reacted with the starting complex using K₂CO₃ as the base to give disubstituted complex (eq 2.6) in 43% yield (Table 2.2, entry 1). The yield was improved using lower temperature and shorter reaction time using NaH as base (entry 4).

![Reaction scheme]

**Table 2.2.** Nucleophilic disubstitution of m-dichlorobenzeneFe⁺Cp complex.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
<td>THF/50 °C/16 hr</td>
<td>43.4</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>CH₃CN/reflux/30 min</td>
<td>69.7</td>
</tr>
<tr>
<td>3</td>
<td>NaH</td>
<td>THF/0 °C (20 min) r.t. (2 hr)</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>THF/0 °C (30 min) r.t. (30 min)</td>
<td>97.9</td>
</tr>
</tbody>
</table>

The two chlorines in the benzene ring can be replaced by two different nucleophiles by reacting 1 equivalent of nucleophile at each time. Thus, one of the two chlorines in m-dichlorobenzeneCpFe⁺ complex was replaced by 4-methoxyphenol and optically active (D)- and (L)-N-Cbz-tyrosine methyl ester to give aryloxychlorobenzeneCpFe⁺ complexes (2.20a-c) in excellent yield (eq 2.7).
The remaining chlorine was replaced by other nucleophiles in the subsequent step (eq 2.8). The results are summarized in Table 2.3. First of all several enolates were reacted with the complex (2.20) in an effort to introduce a chiral glycine enolate equivalent in the later step. In many cases the carbanions did not give clean substitution products. Their isolation and purification were extremely difficult because of their easy decomposition. NMR spectra of the crude mixture always showed different chemical shifts from those of starting materials (entries 1, 4, 6, 7, 10, 13, 14). Subsequent uv irradiation (sunlamp, 275W) without purification resulted in total decomposition except for dimethyl malonate cases (entries 1, 2, 7, and 16).

Such an easy decomposition can be rationalized by decomposition of the initial addition intermediates (e.g., 2.21, Scheme 2.7), possibly due to the easy removal of the H α to the carbonyl carbon. Generally carbanions add predominantly ortho to Cl, and meta to O to give neutral (η^5^-cyclohexadienyl)CpFe complexes as an unstable intermediate, causing rapid decomposition in this step.
Table 2.3. Nucleophilic substitution and photolytic demetallation.

<table>
<thead>
<tr>
<th>Nucleophile 1</th>
<th>Nucleophile 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Substitution</td>
</tr>
<tr>
<td>1 4-Methoxy-phenoxo</td>
<td>CH(CO₂Me)₂</td>
<td>--</td>
</tr>
<tr>
<td>(2.20a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 *</td>
<td>CH(SO₂Ph)(CO₂Me)</td>
<td>2.22a, 76.4%</td>
</tr>
<tr>
<td>3 *</td>
<td>CN</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4 *</td>
<td>CH(CO₂Me)(CN)</td>
<td>--</td>
</tr>
<tr>
<td>5 *</td>
<td>CH(N=CHPh)(CO₂Et)³</td>
<td>No Reaction</td>
</tr>
<tr>
<td>6 *</td>
<td>Schöllkopf anion</td>
<td>--</td>
</tr>
<tr>
<td>7 (L)-Tyrosyl (2.20b)</td>
<td>CH(CO₂Me)₂</td>
<td>--</td>
</tr>
<tr>
<td>8 *</td>
<td>4-Methoxyphenoxy</td>
<td>2.22b, 85%</td>
</tr>
<tr>
<td>9 *</td>
<td>CH(SO₂Ph)(CO₂Me)</td>
<td>2.22c, 72-76%</td>
</tr>
<tr>
<td>10 *</td>
<td>CH(CO₂Me)(CN)</td>
<td>--</td>
</tr>
<tr>
<td>11 *</td>
<td>CH(N=CHPh)(CO₂Et)³</td>
<td>--</td>
</tr>
<tr>
<td>12 *</td>
<td>CN</td>
<td>--</td>
</tr>
<tr>
<td>13 *</td>
<td>Evans' enolate</td>
<td>Decomposition</td>
</tr>
<tr>
<td>14 *</td>
<td>Schöllkopf anion</td>
<td>--</td>
</tr>
<tr>
<td>15 *</td>
<td>(L)-N-Cbz-Tyrosine Me ester Na salt</td>
<td>2.22d, 87%</td>
</tr>
<tr>
<td>16 (D)-Tyrosyl (2.20c)</td>
<td>CH(CO₂Me)₂</td>
<td>--</td>
</tr>
</tbody>
</table>

² Irradiation without isolation of the precursor. ³ Purification and isolation were extremely difficult. ⁴ Ref 43.
Scheme 2.7. Formation of unstable neutral cyclohexadienyl FeCp complexes.

Also, when the carbanions were added into the solution of the (chloroarene)-CpFe⁺ complexes (2.20a-c), characteristic color changes were observed from yellowish brown to deep red; this type of color change is unique for hydride²⁵ and other alkyl anions (eq 2.9).⁶,²⁶,³⁹

Sutherland et al.¹⁰⁷ have described addition of cyanide ion to nitrobenzeneFe⁺Cp complex, but in our case it did not replace the Cl presumably due to the electron donating group in the benzene ring (entries 3 and 12). However, Cl was replaced by aryloxy nucleophiles without decomposition problems (entries 8 and 15).

Table 2.4 shows the photochemical decomplexation for compounds 2.20b and c. When complex 2.20b was treated with only silica gel¹⁰⁸ the yield was less than 1%
(entry 1), whereas an attempt of 30 min irradiation gave 26% of demetallated product (entry 2). In the presence of a two-electron donor ligand such as P(OEt)₃, the yield increased as much as 76% (unoptimized) under the same conditions (entry 3).

![Chemical structure diagram](image)

Table 2.4. Photolytic demetallation of 2.20b and c.

<table>
<thead>
<tr>
<th>R</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (L)-Tyrosyl (2.20b)</td>
<td>Silica gel/CH₂Cl₂</td>
<td>2.24a, &lt;1%</td>
</tr>
<tr>
<td>2 &quot;</td>
<td>hv/CH₂Cl₂/30 min</td>
<td>&quot;</td>
</tr>
<tr>
<td>3 &quot;</td>
<td>hv/P(OEt)₃/30 min</td>
<td>&quot;</td>
</tr>
<tr>
<td>4 (R)-Tyrosyl (2.20c)</td>
<td>hv/CH₂Cl₂/1 hr</td>
<td>2.24b, 46.1%</td>
</tr>
</tbody>
</table>

3. Nucleophilic addition and rearomatization

As described above, carbanions can add meta to oxy- or alkyl substituents in benzene ring to give a neutral cyclohexadienyl CpFe complex (2.26, eq 2.11).

Selective removal of the endo hydrogen from the neutral complexes can afford a new way to introduce alkyl onto a benzene ring. For such an oxidation, trityl cation,
NBS\textsuperscript{93,110} and DDQ\textsuperscript{107} have been reported. This methodology was attempted using our 1,3-diarylxybenzeneCpFe\textsuperscript{+} complex in an effort to introduce glycine enolate equivalents. By this method the "upper half" skeleton of vancomycin can be provided.

First, simple (benzene)CpFe\textsuperscript{+} complex was chosen as a model for this purpose (eq 2.12 and Table 2.5). Generally, the yield of alkyl adducts was higher at lower temperature (entries 9, 10), which indicates that the adduct may be unstable at higher temperature. The only productive nucleophiles were Me, Vinyl and t-Butyl anion, and none of the enolate adduct was obtained (entries 1, 4-6). Although the Schöllkopf anion was added into the solution of the complex, and the characteristic color change was observed, due to the instability of the product, clean isolation was not possible. Subsequent trityl oxidation of the crude adduct resulted in alkyl abstraction (entry 7). The vinyl adduct was identified only by NMR spectrum of crude sample. The use of NBS led to decomposition for t-butyl adduct (entry 12). Treatment of t-Bu adduct with trityl resulted in quantitative alkyl abstraction (entry 13), while other oxidants caused decomposition of the complex (entries 14-22).
The same trend was found for diaryloxy substituted complexes (entries 23-39); thus, no enolate adduct was obtained. The methyl adduct was very unstable, and so all the oxidants were added directly to the deep red reaction mixture.

![Chemical structures](image)

**Table 2.5.** Nucleophilic addition and rearomatization.

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;, R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R</th>
<th>Nucleophilic Addition</th>
<th>Rearomatization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conditions</td>
<td>Results&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 R&lt;sub&gt;1&lt;/sub&gt; = R&lt;sub&gt;2&lt;/sub&gt; = H</td>
<td>Li cyclohexenolate</td>
<td>THF/0 °C</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>MeLi</td>
<td>THF/r.t., 2.28a, 59%&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>THF/r.t.</td>
<td>D</td>
</tr>
<tr>
<td>4</td>
<td>Cyclohexanone</td>
<td>NaH/THF/r.t., 16 hr</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>t-Butyl acetate</td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>LDA/THF/0 °C</td>
<td>Trityl&lt;sup&gt;d&lt;/sup&gt;</td>
<td>R, 73.4%</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi/THF/0 °C</td>
<td>2.28b, 42%&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Vinyllithium</td>
<td>THF/0 °C</td>
<td>2.28c, 50%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>t-BuLi</td>
<td></td>
<td>2.28d, 41%</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>THF/-78 °C</td>
<td>88.1%</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>SiO&lt;sub&gt;2&lt;/sub&gt;/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>NBS&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>Trityl</td>
<td>R, 100%</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>DDQ&lt;sup&gt;g&lt;/sup&gt;/CH&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>NBS/NH&lt;sub&gt;4&lt;/sub&gt;PF&lt;sub&gt;6&lt;/sub&gt;</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>NBS/MeOH</td>
<td>D</td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>I&lt;sub&gt;2&lt;/sub&gt;/CCl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>D</td>
</tr>
</tbody>
</table>

<sup>a</sup> Results are given as reaction yields or reactivity. Oxidants are used to facilitate the rearomatization step.
<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;, R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R</th>
<th>Nucleophilic Addition</th>
<th>Rearomatization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conditions</td>
<td>Results&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>-</td>
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</tr>
<tr>
<td>20</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>23</td>
<td>R₁ = R₂ = Li cyclohexenolate</td>
<td>CH₂Cl₂/0 °C</td>
<td>N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-Methoxy-phenoxo(2.19)</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>-</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>25</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>26</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>27</td>
<td>-</td>
<td>Methyl acetate</td>
<td>LDA/THF/-78 °C</td>
</tr>
<tr>
<td>28</td>
<td>-</td>
<td>MeLi</td>
<td>THF/0 °C</td>
</tr>
<tr>
<td>29</td>
<td>-</td>
<td>t-BuLi</td>
<td>*</td>
</tr>
<tr>
<td>30</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>31</td>
<td>-</td>
<td>Schöllkopf anion</td>
<td>THF/0 °C</td>
</tr>
<tr>
<td>32</td>
<td>-</td>
<td>Vinylithium</td>
<td>THF/-78 °C</td>
</tr>
<tr>
<td>33</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>34</td>
<td>-</td>
<td>MeLi</td>
<td>*</td>
</tr>
<tr>
<td>35</td>
<td>-</td>
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<td>39</td>
<td>R₁ = 4-Methoxy-phenoxo, R₂ = (L)-Tyrosyl(2.26b)</td>
<td>CH₃CN</td>
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<sup>a</sup> N = No Reaction; D = Decomposition; R = Alkyl abstraction.  
<sup>b</sup> Ref 25, 26.  
<sup>c</sup> Crude yield.  
<sup>dp</sup> Ph₃CPF₆.  
<sup>ε</sup> Ceric ammonium nitrate.  
<sup>f</sup> N-Bromosuccinimide.  
<sup>g</sup> 2,3,5,6-Dichloro-1,4-benzoquinone.  
<sup>i</sup> Ref 42.  
<sup>j</sup> TBQ = o-Chloranil = 2,3,5,6-Tetrachloro-p-benzoquinone.

The NBS and KMnO₄ oxidation of complex 2.28 obtained from 2.19 resulted in trace amounts of alkyl abstraction with decomposition of the complex (entries 35, 37). For amino acid side chain substituted aryl compound (entry 39), attempted TBQ oxidation gave alkyl abstraction in 32% yield.

Although the Schöllkopf anion gave the deep red product-like material, oxidation was not attempted due to its instability (entry 30).
In conclusion, the construction of symmetric and non-symmetric di- and triaryl ethers utilizing the nucleophilic substitution reaction between aryloxides and (m-dichlorobenzene)CpFe⁺ complex have been shown to be a potentially efficient approach to the “upper half” skeleton of the vancomycin class. Although the direct introduction of glycine enolate equivalent onto the complexed benzene ring seems to be fascinating, it is still in need of effective oxidation method. The difficulties encountered in this approach led us to investigate an alternative strategy based on the chemistry of arene-ruthenium systems.
Experimental

Analytical Instrumentation

NMR (proton or $^{13}$C) spectra were recorded on a Varian XL 200 (200 MHz) or Varian Gemini-300 (300 MHz) using CDCl$_3$, acetone-d$_6$, CD$_3$CN or DMSO-d$_6$ as solvent with internal TMS standard. Infrared spectra were recorded on a Perkin-Elmer 1420 or Perkin-Elmer 1600 series FTIR. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Mass spectral analyses were performed by the Chemistry Department of Case Western Reserve University using a Kratos MS25A, elemental analyses were obtained from Galbraith Laboratories, Knoxville, Tennessee. Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

Apparatus and Materials

All reactions were conducted under an inert atmosphere of dry, oxygen free argon or nitrogen unless otherwise noted. Organic solvents were purified prior to use as follows: ether and THF were freshly distilled from Na/benzophenone; CH$_3$CN and CH$_2$Cl$_2$ were distilled from CaH$_2$; DMF was vacuum distilled after stirring over 4 Å molecular sieves then stored over 4 Å molecular sieves under nitrogen.

General procedure for the synthesis of (chloroarene)CpFe$^+$ complexes (2.16, Table 2.1).

Method A (from ferrocene)
1 equivalent of Al powder was added into a stirred solution of ferrocene and arene (at room temperature, or in the cases of solid arenes, at their melting point) followed by AlCl₃ then heated to reflux (~130 °C for solid) overnight. The reaction mixture was cooled to room temperature then small portions of ice were added slowly with external cooling using an ice-water bath. The resultant mixture was filtered, the aqueous layer was collected, and washed with ether (or petroleum ether) to remove unreacted ferrocene. A concentrated aqueous solution of NH₄PF₆ was added to the aqueous layer until the maximum cloudiness was obtained. The yellow precipitate was filtered and dried in air. The crude complex may be further purified by repeated recrystallization by adding a concentrated CH₂Cl₂ solution of the complex to ether or by eluting through neutral alumina column (CH₃CN). Unreacted ferrocene can be purified by recrystallization from appropriate solvent, and arenes were recovered by treating with 10% HNO₃ (to oxidize remaining ferrocene to water soluble ferricinium ion) and vacuum distillation (or recrystallization).

Method B (ligand exchange)
Equimolar amounts of (chloroarene)CpFe⁺ complexes and CpFe⁺Ln [Ln = (CO) (CH₃CN)(PPh₃) or (P(OEt)₃)₃] were dissolved in an appropriate solvent followed by the addition of AlCl₃ then heated to reflux. Work up procedure was same as method A.

Method C (Photolytic ligand exchange, Table 2.1, entry 31)
Equimolar amounts of (m-dichlorobenzene)CpFe⁺ complex and 3,5-dichloroanisole were dissolved in CH₂Cl₂ and irradiated with uv light (sunlamp, 275W). A normal pyrex flask was used as the reaction vessel.
\[ \eta^6-[1,3\text{-bis-(4-Methoxyphenoxy)benzene}] - \eta^5\text{-cyclopentadienyliron hexafluorophosphate (2.19)} \]

To a stirred suspension of 4.13 g (10 mmol) m-dichlorobenzeneCpFe⁺ complex (2.16) in 10 mL THF was added a solution of 4-methoxyphenol Na salt [from 1.06 g (22 mmol, 2.2 equiv) 50% NaH in oil and 3.10 g (25 mmol) of 4-methoxyphenol] in 10 mL of THF at 0 °C over 30 min. The mixture was stirred for an additional 30 min at 0 °C, then quenched with 2 mL of water. After THF was evaporated on a rotary evaporator, the residue was redissolved in CH₂Cl₂, washed with 1 N NaOH (2 × 50 mL) to remove unreacted phenol, then with water until neutral. The organic phase was dried over MgSO₄ then concentrated to give 5.76 g (97.9%) of yellow powder. This was pure enough for characterization. IR (ClICl₃) 3100, 2940, 1590, 835 cm⁻¹; \(^1\)H NMR (200 MHz) in CD₃CN: \( \delta \) 7.17 and 7.05 (4 H each, d, J = 9.2 Hz, uncomplexed aromatic Hs), 6.10 and 5.87 (2 H each, m, complexed aromatic Hs), 5.03 (5 H, s, Cp), 3.83 (6 H, s, OCH₃); in CDCl₃: \( \delta \) 7.00 (8 H, br s, uncomplexed aromatic Hs), 6.27 (1 H, t, J = 6 Hz, complexed aromatic 5-H), 5.96 (1 H, s, complexed aromatic 2-H), 5.86 (2 H, d J = 6 Hz, complexed aromatic 4- and 6-H), 4.99 (5 H, s, Cp), 3.82 (6 H, s, OCH₃); \(^13\)C NMR (75 MHz, CDCl₃) \( \delta \) 158.0, 145.8, 133.7, 121.5, 115.9, 84.0, 77.1, 72.2, 65.9, 55.7.

\[ \eta^6\text{-3-Chloro-1-(4-methoxy)phenoxybenzene}-\eta^5\text{-cyclopentadienyliron hexafluorophosphate (2.20a)} \]
4-Methoxyphenol Na salt (12.11 mmol, from 4-methoxyphenol and NaH) in 15 mL THF was added dropwise into a stirred suspension of (1,3-dichlorobenzene)CpFePF$_6$ 2.16a in 15 mL THF at -78 °C. After the addition, the reaction was allowed to reach to room temperature then quenched with 5 mL of water. THF was removed in vacuo, and the residue was taken up into CH$_2$Cl$_2$. The organic layer was washed with water then dried over MgSO$_4$. CH$_2$Cl$_2$ was evaporated in vacuo to give 5.97 g (98.5% yield) of very thick, dark brown oil. IR (CHCl$_3$) 3100, 3050, 2990, 1500, 1260, 850 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.06 (4 H, s, uncomplexed aromatic Hs), 6.50–6.43 (2 H, m, 4- and 5-H), 6.24 (1 H, s, 2-H), 6.16 (1 H, d, J = 6.3 Hz, 6-H), 5.15 (5 H, s, Cp), 3.86 (3 H, s, OCH$_3$); MS m/z 129.1 (76%), 234.0 (100%), [M]$^+$ not found.

$\eta^6$-3-Chloro-1-[[4-(L)-[2-(N-benzyloxy carbonyl)amino-3-methoxy-3-oxopropyl]phenoxy]benzene-$\eta^5$-cyclopentadienyliniron hexafluorophosphate (2.20b)

N-Benzylxoxycarbonyl-L-tyrosine methyl ester (500 mg, 1.52 mmol) in 5 mL dry THF was added dropwise to a stirred slurry of NaH (50% in oil, 70.7 mg, 1.47
mmol, 0.97 equiv) in dry THF (5 mL) at 0 °C. The resulting clear solution was transferred with a cannula to a stirred solution of (1,3-dichlorobenzene)CpFePF₆ (2.16a, 626.8 mg, 1.52 mmol) in 10 mL dry THF at -78 °C. After the addition of the aryloxide solution, the dry ice-acetone bath was removed to allow the reaction to come to room temperature. The color of the solution turned to cloudy yellow upon warming. Stirring was continued for additional 30 min at room temperature. The reaction was quenched by adding 0.5 mL of water. Solvent was removed in vacuo, and the residue was taken up into CH₂Cl₂, washed with water until neutral then dried over MgSO₄. The solution was filtered and evaporated to 5 mL on a rotary evaporator. The concentrated solution was added to 200 mL of ether. The product was obtained as a yellow solid (916.3 mg, 85.5% yield). Because the product is sensitive to light, it should be stored in the dark: mp 83-5 °C; IR (CHCl₃) 3420, 3100, 2950, 1740, 1720, 1500, 850 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.34 (5 H, s, CO₂CH₂Ph), 7.26 (2 H, d, J = 8.3 Hz, uncomplexed aromatic Hs, meta to O), 7.04 (2 H, d, J = 8.3 Hz, uncomplexed aromatic Hs, ortho to O), 6.45 (2 H, br s, 2-H and 4-H), 6.28 (1 H, d, J = 5.9 Hz, 6-H), 6.17 (1 H, t, J = 6.4 Hz, 5-H), 5.43 (1 H, d, J = 7.6 Hz, N-H), 5.14 (5 H, s, Cp), 5.10 (2 H, s, OCH₂Ph), 4.62 (1 H, apparently br q with J = 7 Hz) 3.76 (3 H, s, CO₂Me), 3.20 (1 H, dd, J = 9.6 and 4.8 Hz, ArCH₂HCHNH), 3.08 (1 H, dd, J = 15 and 9.6 Hz, ArCHNH); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 155.6, 151.6, 136.2, 135.4, 133.2, 131.9, 131.8, 128.5, 128.2, 128.0, 120.4, 106.2, 86.4, 85.4, 79.4, 75.7, 66.9, 54.8, 52.6, 37.4; MS m/z (rel. int.) [M]⁺ not found, 129.1 (100%), 239.2 (48%), 368.3 (65%).
$\eta^6$-3-Chloro-1-[(4-(D)-[2-(N-benzylxycarbonyl)amino-3-methoxy-3-oxo]propyl]phenoxy]benzene-$\eta^5$-cyclopentadienyliiron hexafluorophosphate (2.20c)

\[ \text{Image of chemical structure} \]

The title compound was synthesized following as same procedure as 2.20b using 828.2 mg, 2.52 mmol of protected (D)-tyrosine, 117.1 mg, 0.97 equiv of 50% NaH, and 1.04 g, 2.52 mmol of m-dichlorobenzeneCpFe⁺ (2.16) to afford 1.37 g (77.4 %) of yellow powder. IR (CHCl₃) 3426, 3030, 2950, 1724, 844 cm⁻¹; $^1$H NMR (200 MHz, CDCl₃) δ 7.33 (5 H, br s, CH₂Ph), 7.08–6.94 (4 H, m, uncomplexed aromatic Hs), 6.5–6.2 (4 H, m, complexed aromatic Hs), 5.40 (1 H, br, N-H), 5.17 (2 H, CH₂Ph), 5.12 (5 H, s, Cp), 4.64 (1 H, br, chiral center H), 3.75 (3 H, s, CO₂CH₃), 3.17 (2 H, br m, ArCH₂CHNHBz); $^{13}$C NMR spectrum was same as that of compound 2.20b.

$\eta^6$-1-(4-Methoxyphenoxy)-3-(1-phenylsulfonyl-2-methoxy-2-oxo)ethyl-benzene-$\eta^5$-cyclopentadienyliiron hexafluorophosphate (2.22a)

\[ \text{Image of chemical structure} \]
To a stirred solution of 0.50 g (3-chloroarene)CpFePF₆ 2.20a (1 mmol) in THF (at -30 °C) was added dropwise a solution of methyl phenylsulfonylsodioacetate (1 mmol, from methyl phenylsulfonylacetate and NaH) in THF. After the addition the reaction was allowed to come to room temperature. Stirring was continued for additional 30 min then the reaction was quenched with 0.5 mL of water. Solvent was removed in vacuo and the residue was taken up into 5 mL of CH₂Cl₂ then dried over MgSO₄ (deep red solution). The product was isolated as a deep red oil (493 mg, 76.4% yield) by dropping a concentrated CH₂Cl₂ solution of the reaction mixture into 150 mL of ether. IR (neat) 3100, 2950, 1740, 1300, 850 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.06 (9 H, SO₂Ph and uncomplexed aromatic Hs), 6.58 (1 H, t, J = 6.4 Hz, 5-H), 6.45 (1 H, d, J = 6.4 Hz, 4-H), 6.24 (1 H, s, 2-H), 6.17 (1 H, dd, J = 6.4 and 1.1 Hz, 6-H), 5.16 (5 H, s, C₆p), 5.04 (1H, s, CHSO₂), 3.87 (3 H, s, ArOCH₃), 3.86 (3 H, s, CO₂CH₃).

η⁶-1-(4-Methoxy)phenoxy-3-[4-(L)-[2-(N-benzyloxycarbonyl)amino-3-methoxy-3-oxo]propyl]phenoxybenzene-η⁵-cyclopentadienyl hexafluorophosphate (2.22b)

To a stirred solution of 500 mg (0.71 mmol) of the starting (3-chloroarene)CpFePF₆ 2.20b in 10 mL of THF at -78 °C was added dropwise a solution of 4-methoxyphenol Na salt in 5 mL THF. The reaction was allowed to come to room temperature then stirred for additional 1 hr. The reaction was quenched with 1
mL of water then THF was evaporated in vacuo. The residue was dissolved in 5 mL of CH$_2$Cl$_2$ then dried (MgSO$_4$). The solution was concentrated to 2 mL, and added dropwise to 100 mL of ether. The yellow-brown precipitate was collected and dried to give 478 mg (85%) of powder. mp 85-7 °C; IR (CHCl$_3$) 3677, 3425, 3033, 2950, 1716, 1500, 848 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) δ 7.35 (5 H, s, CH$_2$Ph), 7.24-7.0 (8 H, m, uncomplexed aromatic Hs ), 6.34 (1 H, td, J = 8 and 1.4 Hz, 5-H), 6.0 (3 H, m, 2-, 4-, and 6-H), 5.40 (1 H, br d, J = 8 Hz, N-H), 5.11 (2 H, s, CH$_2$Ph), 5.03 (5 H, s, Cp), 4.68 (1 H, m, CHNHZ), 3.85 (3 H, s, ArOCH$_3$), 3.76 (3 H, s, CO$_2$CH$_3$), 3.23 (1 H, dd, J = 14 and 5.5 Hz, ArCHHCHNHCbz), 3.08 (1 H, dd, J = 14 and 6 Hz, ArCHHCHNHCbz); Anal. Calcd for C$_{36}$H$_{34}$O$_7$NF$_6$PFe: C, 54.44; H, 4.28; N, 1.76. Found: C, 54.44; H, 4.37; N, 1.79.

$\eta^6$-1,3-bis-[4-(L)-[[2-(N-benzyloxycarbonyl)amino-3-oxo-3-methoxy]-propyl]phenoxy]benzene-$\eta^5$-cyclopentadienyliron hexafluorophosphate (2.22d)

![Structure of 2.22d](image)

N-Cbz-Tyrosine methyl ester Na salt (from N-Cbz-Tyrosine methyl ester and NaH) in 5 mL of dry THF (0.71 mmol) was added dropwise to a stirred solution of the (chloroarene)Fe$^+$CP complex 2.20b (500 mg, 0.71 mmol) in 5 mL THF at -78 °C. The reaction mixture was allowed to come to room temperature by removing the dry ice-acetone bath (40 min). The reaction was quenched with 2 mL of water, the product was extracted with CH$_2$Cl$_2$, and the combined extracts were washed with water, dried.
over MgSO₄, and concentrated to 5 mL then slowly added to 200 mL of ether to give 614.9 mg (86.9%) of yellow powder. mp 92-95 °C; IR (CHCl₃) 3400, 3060, 2920, 1720, 1700, 1485, 830 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.34 (10 H, s, CH₂Ph), 7.23-6.99 (8 H, m, uncomplexed aromatic Hs), 6.35 (1 H, t, J = 6 Hz, 5-H), 6.03 (1 H, s, 2-H), 5.96 (2 H, apparently t, 4- and 6-H), 5.40 (2 H, d, J = 12.8 Hz, N-H), 5.10 (4 H, s, CH₂Ph), 5.04 (5 H, s, Cp), 4.64 (2 H, br q, J = 7 Hz, CHNHZ), 3.76 (6 H, s, CO₂Me), 3.20 (1 H, dd, J = 14 and 6 Hz, ArCHHCH), 3.08 (1 H, dd, J = 14 and 6 Hz, ArCHHCH); ¹³C NMR (75 MHz, CDCl₃) δ 171.2, 155.2, 151.5, 135.7, 134.6, 132.3, 131.4, 128.1, 127.8, 127.6, 119.8, 84.3, 77.3, 73.1, 66.7, 66.6, 54.4, 52.1, 37.0; Anal. Calcd for C₄₇H₆₅F₆FeN₂O₁₉P: C, 56.47; H, 4.51; N, 2.80. Found: C, 55.13; H, 4.50; N, 2.62.

1-(4-Methoxyphenoxy)-3-(2,2′-dimethoxy-2,2′-dioxo)propylbenzene (2.23a)

Dimethyl sodiomalonate (1.21 mmol, from dimethyl malonate and NaH) in 5 mL THF was added dropwise to a stirred solution of (3-chloro-1-(4-methoxy)-phenoxybenzene)CpFe⁺ complex 2.20a in 5 mL THF at -78 °C. After the addition of the aryl oxide the reaction was allowed to come to room temperature (solution turned to cloudy dark red). Stirring was continued for additional 30 min at room temperature, then the mixture was cooled to -78 °C. The reaction mixture was irradiated with uv light (sunlamp, 275 W) for 90 min. Solvent was removed in vacuo then the residue
was dissolved into 10 mL of CH₂Cl₂ and filtered through silica gel to remove polar by-products. Flash chromatography on silica gel (25% EtOAc-Hexs) gave 75.9 mg (20% yield, unoptimized) of pale yellow oil: \( R_f \) 0.21 (25% EtOAc-Hexs); IR (neat) 3000, 2950, 1750, 1730, 1600, 1500 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃) \( \delta \) 7.23 (1 H, t, \( J = 8.0 \) Hz, 5-H), 7.06–6.88 (7 H, m, aromatic Hs), 4.60 (1 H, s, \( CH(CO₂Me)_2 \)), 3.81 (3 H, s, OCH₃), 3.75 (6 H, s, CO₂CH₃); MS m/z (rel. int.) 330.111 (76.6%, [M]+). C₁₈H₁₈O₆ requires 330.1103, 112 (31%), 129.1 (100%), 331.1 (11.7%, [M + 1]+); Anal. Calcd for C₁₈H₁₈O₆: C, 65.39; H, 5.45. Found: C, 65.52; H, 5.34.

**1-(4-Methoxy)phenoxy-3-(1-phenylsulfonyl-2-methoxy-2-oxo)ethylbenzene (2.23b)**

![Chemical Structure](image)

493 mg of the starting (arene)Cp Fe⁺ complex (2.22a, 0.73 mmol) in CH₂Cl₂ was cooled to -78 °C then irradiated with uv light for 1 hr (dark brown). Solvent was removed in vacuo and the product was isolated by preparative TLC (5% EtOAc-Benzene) to give 99.4 mg (33%) of pale yellow oil: \( R_f \) 0.22 (25% EtOAc-Hexs), 0.37 (5% EtOAc-benzene); IR (neat) 3060, 2950, 1740, 1585, 1500, 1330 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃) \( \delta \) 7.67–6.86 (8 H, m, aromatic Hs), 5.05 (CHSO₂Ph), 3.81 (3 H, s, ArOMe), 3.76 (3 H, s, CO₂Me); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 165.0, 158.4, 156.0, 149.2, 136.2, 130.1, 129.8, 129.7, 129.2, 128.6, 124.1, 120.8, 119.2, 118.6, 114.8, 74.9, 55.6, 53.2; MS m/z 412.0998 ([M]+), C₂₂H₂₀O₆S requires 412.0980);
(L)-(−)-N-Benzoxycarbonyl-4-[3-(1,3-dimethoxy-1,3-dioxo-)-2-propyl]phenoxyphenylalanine methyl ester (2.23c)

To a stirred solution of dimethyl sodiomalonate (from 34 mg, 0.71 mmol of NaH and 93.6 mg, 81 μL of dimethylmalonate) in 5 mL THF was added 500 mg (0.71 mmol) of Arene-Fe⁺Cp complex 2.20b in one portion. The mixture was stirred for 30 min at room temperature. The resulting solution was irradiated with uv light (sunlamp, 275 W) for 40 min at room temperature. The color changed from deep red to very dark brown. Flash chromatography on silica gel (50% EtOAc-Hexs) gave 22.2 mg of (L)-(−)-N-Benzoxycarbonyl-4-(3-chlorophenoxy)phenylalanine methyl ester (2.28) and 171 mg of product [45.1% yield based on the unreacted demetallated product (2.28)].

RF 0.43 (50% EtOAc-Hex); [α]D -8.5° (c 1.03, EtOH); IR (CHCl₃) 3360, 3020, 2950, 1750, 1700 cm⁻¹; ¹H NMR (CDCl₃) δ 7.34 (5 H, s, CH₂Ph), 7.29–6.90 (8 H, m, aromatic Hs), 5.24 (1 H, d, J = 8.3 Hz, N-H), 5.11 (2 H, s, CH₂Ph), 4.67 (1 H, m, CHNHCbz), 4.61 (1 H, s, CH(CO₂Me)₂), 3.75 (6 H, s, CH(CO₂Me)₂), 3.73 (3 H, s, CO₂Me), 3.10 (1 H, dd, J = 10.6 and 5.3 Hz, ArCHHCH); 13C NMR (75 MHz, CDCl₃) δ 171.9, 168.2, 157.2, 155.9, 155.6, 136.1, 134.2, 130.6, 129.8, 128.5, 128.2, 128.0, 124.0, 119.8, 119.0, 118.4, 66.9, 57.3, 54.8, 52.9, 52.3, 37.4; MS m/z (rel. int.) 207.1 (61.8%), 313.1 (96.5%), 402.1 (57.6%, [M - CO₂Bn]⁺), 462.2 (35.4%, [M - (C₃H₆O₂)]⁺), 492.2 (51%, [M-(CO₂)]⁺), 536.2 (100%, [M + 1]⁺).
(L)-(+-)(N-Benzyl oxycarbonyl)-4-[3-(4-methoxyphenoxy)phenoxy]phenylalanine methyl ester (2.23d)

200 mg (0.25mmol) of the starting diaryloxy CpFePF₆ 2.22a in 10 mL CH₂Cl₂ was irradiated with uv light at 0 °C for 2 hr. The reaction mixture was filtered through silica gel then the solvent was evaporated in vacuo. Purification by preparative TLC (10% EtOAc-Hexs) gave 108 mg (81.4%) of thick pale yellow oil: Rf 0.42; [α]D +4.73° (c 0.47, THF); IR (CHCl₃) 3420, 3020, 2950, 1720 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.34 (5 H, s, CH₂Ph), 7.0~6.6 (12 H, m, aromatic Hs), 5.24 (1 H, br d, J = 8 Hz, N-H), 5.10 (2 H, s, CH₂Ph), 4.66 (1 H, m, CHNHCbz), 3.80 (3 H, s, ArOCH₃), 3.71 (3 H, s, CO₂CH₃), 3.15 (1 H, dd, J = 14 and 5.5 Hz, ArCHHCHNHCBz), 3.05 (1H, dd, J = 14 and 6 Hz, ArCHHCHNHCBz); ¹²C NMR (75 MHz, CDCl₃) δ 171.9, 158.1, 155.5, 136.1, 135.0, 131.3, 131.0, 130.7, 130.5, 128.5, 128.2, 128.1, 127.8, 123.3, 119.4, 118.9, 116.7, 67.0, 54.8, 52.4, 38.1, 37.5; MS m/z 527.1943 ([M]+, C₃₁H₂₉O₇N requires 527.1944), 108.1 (71.1%), 322.1 (100%), 395.1 (23.8%); Anal. Calcd for C₃₁H₂₉O₇N: C, 70.51; H, 5.50; N, 2.65. Found: C, 69.25; H, 5.49; N, 2.75.

(L)-(+-)-N-(Benzyl oxycarbonyl)-4-[3-(2-phenylsulfonyl-2-oxo-2-methoxy)phenoxy]phenylalanine methyl ester (2.23e)
To a stirred solution of 300 mg (0.43 mmol) of the starting 3-ChloroareneCpFe⁺ complex 2.20b in 5 mL THF was added a solution of methyl phenylsulfonylsodioacetate (from methyl phenylsulfonylacetate and NaH, 0.43 mmol) in 5 mL THF at room temperature. The solution turned to cloudy red-brown. Stirring was continued for 1 hr. The reaction was quenched with 1 mL of water. Solvent was evaporated in vacuo then the residue was dissolved into 5 mL of CH₂Cl₂ and dried over MgSO₄. The solution was filtered using a disposable pipette with cotton plug and the filtrate was directly introduced into 50 mL of ether to give 269 mg of yellow powder. 100 mg of the crude product was dissolved into 15 mL of CH₂Cl₂ then irradiated with uv light (sunlamp, 275W) at -78 °C for 1 hr. The demetallated compound was isolated by preparative TLC (10% EtOAc-benzene) to give 23.4 mg (33% based on crude intermediate complex) of pale yellow oil. Rf 0.43 (50% EtOAc-Hexs), 0.207 (10% EtOAc-benzene); [α]D +3.10° (c 0.58, THF); IR (CHCl₃) 3420, 3020, 2950, 1720, 1500, 1320 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.7–6.8 (18 H, m, aromatic Hs), 5.26 (1 H, br d, J = 8 Hz, N-H), 5.14 (2 H, s, CH₂Ph), 5.10 (1 H, s, CHSO₂), 4.68 (1 H, m CHNH), 3.80 (3 H, s, SO₂CH₂CO₂CH₃), 3.78 (3 H, s, CO₂CH₃), 3.12 (2 H, m, ArCH₂); 13C NMR (75 MHz, CDCl₃) δ 171.8, 159.9, 158.3, 156.0, 155.9, 155.5, 149.4, 136.1, 130.5, 130.1, 128.4, 128.1, 128.0, 121.0, 119.0, 114.8, 112.0, 112.0, 108.2, 66.9, 55.5, 54.8, 52.3, 37.4; Anal. Calcld for C₃₃H₃₁O₉NS: C, 64.11; H, 5.02; N, 2.27. Found: C, 64.33; H, 5.48; N, 2.15.
(L,L)-(+) -1,3 -bis-[4-[2-(N -benzyloxy carbonyl) amino -3-methoxy -3-oxo]propyl] phenoxy benzene (2.23f)

Dityrosylbenzene-Fe+Cp complex 2.22d was dissolved in a mixed solvent of 5 mL CH₂Cl₂ and 5 mL CH₃CN then irradiated with uv light (sunlamp 275W) at room temperature for 30 min. The color changed from brown to black. The solvent was removed in vacuo then the black residue was redissolved in CH₂Cl₂ (in the presence of polar solvent, colored by-product can not be removed). The solution was filtered through silica gel to give a pale yellow solution. The product was further purified by flash chromatography on silica gel (50% EtOAc-Hexs) and preparative TLC (50% EtOAc-Hexs) to give 172.6 mg (45.3% yield) of pale yellow oil. Rf 0.49 (50% EtOAc-Hexs), [α]D +41.8° (c 0.51, CH₂Cl₂); IR (neat) 3420, 3020, 2950, 1740, 1715, 1500 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.33 (10 H, s, CH₂Ph), 7.24 (1 H, t, J = 8.4 Hz, 5-H), 7.05 (4 H, d, J = 8.6 Hz, phenoxy ring H, meta to O), 6.92 (4 H, d, J = 8.6 Hz, phenoxy ring H, ortho to O), 6.75-6.63 (3 H, m, 2-, 4- and 6-H), 5.25 (2H, d, J = 8 Hz, N-H), 5.10 (4 H, m, CH₂Ph), 4.64 (2 H, br q, J = 6 Hz, CHNH), 3.71 (6 H, s, CO₂Me), 3.12 (2 H, dd, J = 14 and 6 Hz, ArCH/HCH), 3.04 (2 H, dd, J = 14 and 6 Hz, ArCHHCH); ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 158.5, 155.7, 155.6, 136.2, 131.0, 130.6, 130.4, 128.5, 128.2, 128.1, 119.1, 113.2, 109.4, 66.9, 54.9, 52.3, 37.4; MS m/z [M]+ not found, 129.1 (100%), 236.2 (60%), 368.3 (68%);
Anal. Calcd for \( \text{C}_{42}\text{H}_{40}\text{N}_2\text{O}_{10} \): C, 68.78; H, 5.46; N, 3.82. Found: C, 68.40; H, 5.37; N, 3.61.

\text{(D)}\text{-N-Benzyl}oxycarbonyl-4-[\text{3-(1,3-dimethoxy-1,3-dioxo)propyl}]\text{phenoxyp}henylalanine \text{ methyl ester (2.23g)}

500 mg (0.71 mmol) of the starting complex \textbf{2.20c} was reacted with 0.85 mmol (1.1 equiv) of dimethyl sodiomalonate (from 37.4 mg 50% \text{NaH} (1.1 equiv) and 112.3 mg (97.2 \text{\mu L}, 1.2 equiv) of dimethyl malonate) in total volume 10 \text{mL} of \text{THF} at room temperature for 30 min. The reaction mixture was irradiated with uv light for 90 min at room temperature. \text{THF} was evaporated, then the residue was filtered through silica gel (\text{CH}_2\text{Cl}_2). Flash chromatography on silica gel (50% \text{EtOAc-Hex}) afforded 211.8 mg (55.8%, unoptimized) of pale yellow oil. \( R_f \) 0.57 (50% \text{EtOAc-Hexs}). \text{IR (neat) 3360, 3030, 2950, 1730, 1585 cm}^{-1; \text{1H NMR} (200 MHz, \text{CDCl}_3) \delta 7.32 (5 \text{H, br s, CH}_2\text{Ph}), 7.14-6.88 (8 \text{H, m, aromatic Hs}), 5.22 (1 \text{H, br d, J = 8 Hz, N-H}), 5.08 (2 \text{H, s, CH}_2\text{Ph}), 4.60 (1 \text{H, br m, chiral center H}), 4.58 (1 \text{H, s, CH(CO}_2\text{CH}_3)_2), 3.75 (6 \text{H, s, CH(CO}_2\text{CH}_3)_2), 3.70 (3 \text{H, s, CO}_2\text{CH}_3), 3.06 (2 \text{H, m, CH}_2\text{CHNHCbz}).

\text{(L)-( )-N-Benzyl}oxycarbonyl-4-(\text{3-Chlorophenoxy})\text{phenylalanine \text{ methyl ester (2.24a)}}
400 mg (5.67 × 10⁻⁴ mol) of the starting Fe⁺Cp complex 2.20b in a mixed solvent of 10 mL CH₃CN and 10 mL CH₂Cl₂ was irradiated with uv light (sunlamp, 275 W) for 40 min at room temperature. The color changed from brown to black. Solvent was removed in vacuo then the product was isolated by flash chromatography on silica gel (10% AcOEt-Hexs) to give 250 mg (100% yield) of pale yellow, thick oil. Part of the product was further purified by preparative TLC for further characterization. \( R_f \) 0.44 (10% EtOAc-Hex) [α]D⁻14.4° (c 0.59, EtOH); IR (CHCl₃) 3432, 3030, 2950, 1722 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃) δ 7.34 (5 H, s, OCH₂Ph), 7.24–6.85 (8 H, m, aromatic Hs), 5.25 (1 H, d, J = 7.8 Hz, N-H), 5.10 (2 H, s, OCH₂Ph), 4.68 (1 H, br dd, J = 14 and 5.7 Hz, CH₂CHNHBz), 3.74 (3 H, s, CO₂CH₃), 3.14 (1 H, dd, J = 14 and 5.5 Hz, CH₂CHNHBz), 3.07 (1 H, dd, J = 14 and 6 Hz, CH₂CHNHBz); \(^13\)C NMR (75 MHz, CDCl₃) δ 171.9, 158.1, 155.6, 155.4, 136.2, 135.0, 131.5, 130.8, 130.5, 128.5, 128.2, 123.2, 119.3, 119.2, 118.8, 116.7, 66.9, 54.9, 52.3, 37.5; MS m/z [M]+ not found, 135 (37%), 217 (100%), 288 (155%); Anal. Calcd for C₂₄H₂₂ClNO₅: C, 65.47; H, 5.00; N, 3.18. Found: C, 65.39; H, 4.93; N, 3.09.

\((D)-(+)\)-N-Benzyloxycarbonyl-4-(3-chlorophenoxy)phenylalanine methyl ester (2.24b)
A solution of 506.4 mg (0.72 mmol) of the starting complex (2.20c) in 10 mL of CH$_2$Cl$_2$ was irradiated with uv light for 1 hr in the presence of 3 g of silica gel. The mixture was filtered, then the silica gel was washed thoroughly with ether to give 145.5 mg (46.1%, unoptimized) of clear oil after flash chromatography on silica gel (10% EtOAc-Hex). Silica gel was used only to remove iron containing polar by-products. 

$R_f$ 0.44 (10% EtOAc-Hex); [$\alpha$]$_D$ +14.7° (c 0.79, EtOH); IR (CHCl$_3$) 3432, 3030, 2950, 1722 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.32 (5 H, s, CH$_2$Ph), 7.26–6.82 (8 H, aromatic Hs), 5.08 (2 H, s, CH$_2$Ph), 4.64 (1 H, br dd, $J = 14$ and 5.7 Hz, CH$_2$CHNHCbz), 3.71 (3 H, s, CO$_2$CH$_3$), 3.13 (1 H, dd, $J = 13.7$ and 5.5 Hz, ArCHHCHNHCbz), 3.03 (1 H, dd, $J = 13.7$ and 6 Hz, ArCHHCHNHCbz).
CHAPTER III

$\eta^6$-(Arene)$\cdot \eta^5$-Cyclopentadienylruthenium

Hexafluorophosphate Complexes
1. Introduction

Since the synthesis of $\pi$-C$_6$H$_6$RuCl$_2$ by Winkhaus and Singer$^{111}$ in 1967, it has been shown that the ($\pi$-C$_6$H$_6$)Ru$^{\text{II}}$ moiety forms a variety of stable complexes in which the ruthenium generally coordinates three other ligands.$^{112}$ In 1972, Zelonka and Baird$^{113}$ have described the first synthesis of (C$_6$H$_6$)CpRuCl (3.3) from the reaction between (C$_6$H$_6$)RuCl$_2$)$_x$$^{111}$ and thallium cyclopentadienide$^{114}$ using acetonitrile as solvent (eq 3.1).

\[
[(\text{benzene})\text{RuCl}_2]_x + \text{TiCp} + \text{CH$_3$CN} \xrightarrow{r.t.} [(\text{benzene})\text{Ru}^{\text{Cp}}\text{Cl}]^+ \quad (\text{eq } 3.1)
\]

This method has been modified by Robertson et al.$^{115}$ in an effort to obtain the substituted [(arene)RuCl$_2$] complexes, and, eventually, [(arene)Ru$^+$Cp] complexes. Thus, the starting materials, methyl or methoxy substituted 1,4- and/or 1,3-cyclohexadienes (obtained by the Birch reduction$^{116}$ of the corresponding arenes) were treated with RuCl$_3$.3H$_2$O to give the (arene)RuCl which was converted to the (arene)Ru$^+$Cp complexes in the subsequent step (eq 3.2). A flaw of this method is that a halogenated arene cannot be subjected to the Birch reduction, and the Birch reduction is an extra step.

\[
\text{R} \quad \text{and/or} \quad \text{R} \quad + \quad \text{RuCl}_3.3\text{H}_2\text{O} \quad \rightarrow \quad \text{R} \quad \text{Ru}^{\text{Cp}} \quad (\text{eq } 3.2)
\]

\[
\text{R} = \text{H, OMe, Me}_6
\]
The importance of the Zelonka and Baird's method was not fully recognized until the report of Gill and Mann\cite{117} on the synthetically useful intermediate \((\text{CH}_3\text{CN})_3\text{Ru}^+\text{Cp}\) (3.6) obtained from \((\text{C}_6\text{H}_5)\text{CpRuPF}_6\) (3.3). They described photochemical ligand exchange between (benzene)Ru\(^+\)Cp complex and the two-electron donor ligand, CH\(_3\)CN, resulting in the \((\text{CH}_3\text{CN})_3\text{Ru}^+\text{Cp}\) complex (eq 3.3). They also showed that the labile ligand, CH\(_3\)CN, can be easily replaced by any other aromatic compound under mild thermal reaction conditions. For example, p-dichlorobenzene was treated with \((\text{CH}_3\text{CN})_3\text{Ru}^+\text{Cp}\) to give \((\text{p-Cl}_2\text{C}_6\text{H}_4)\text{Ru}^+\text{Cp}\) in 66% yield (eq 3.4).

\[
\begin{align*}
\text{[}(\text{benzene})\text{Ru}^+\text{Cp}]\text{ PF}_6^- & \xrightarrow{\text{hv}} (\text{CH}_3\text{CN})_3\text{Ru}^+\text{Cp PF}_6^- \quad \text{(eq 3.3)} \\
\text{3.3} & \quad \text{3.6} \\
(\text{CH}_3\text{CN})_3\text{Ru}^+\text{Cp PF}_6^- & + \text{3.7} \xrightarrow{1,2\text{-dichloroethane \text{reflux, 15 hr}}} \text{3.8, 66%} \\
\text{3.6} & \quad \text{3.7} & \quad \text{3.8} \\
\end{align*}
\]

At the same time, Nesmeyanov et al\cite{118,119} and Astruc et al\cite{120} have reported on the ability of ruthenocene (3.9) and substituted ruthenocenes to exchange one cyclopentadienyl ligand with various arenes to form (arene)Ru\(^+\)Cp complexes (eq 3.5).

\[
\begin{align*}
\text{Cp}_2\text{Ru} & + \text{arene} \xrightarrow{\text{AlCl}_3} (\text{arene})\text{Ru}^+\text{Cp PF}_6^- \quad \text{(eq 3.5)} \\
\text{3.9} & \quad \text{arene} & \quad \text{3.9} \\
\end{align*}
\]
Unfortunately, the Nesperyanov route requires a long reaction time, high temperature and only low yields are obtained (3–7%).\textsuperscript{118,119} These yields can be increased to 30\% for 1,3,5-Me\textsubscript{3}C\textsubscript{6}H\textsubscript{6} by addition of water to the reaction mixture,\textsuperscript{120} but with C\textsubscript{6}Me\textsubscript{6} this also results in extensive demethylation and disproportionation of the aromatic ligand. Although the Nesperyanov method has been modified by Vol’kenau et al.,\textsuperscript{121} it still requires high pressure (autoclave), and high temperature (105-140 °C).

Gill and Mann’s method requires the use of toxic cyclopentadienylthallium, but owing to the attractive mild conditions and readily available arenes, this is accepted as a general method for the synthesis of (arene)Ru\textsuperscript{+}Cp complexes.\textsuperscript{122}

The chemical shifts (in DMSO-d\textsubscript{6}) of C\textsubscript{5}H\textsubscript{5} in (benzene)CpM\textsuperscript{+} complexes are δ 5.23 for M = Fe,\textsuperscript{118} 5.43 for M = Ru,\textsuperscript{115} 5.67 ppm for M = Os.\textsuperscript{115} Conversely, benzene proton shifts to higher field, e.g., for M = Fe, δ 6.44;\textsuperscript{118} M = Ru, 6.20;\textsuperscript{115} M = Os, 6.14 ppm.\textsuperscript{115} As Nesperyanov suggested,\textsuperscript{118} this might indicate that the positive charge of the cations is delocalized onto the arene ligand in the order of Fe > Ru > Os.

The reactivity of (arene)Ru\textsuperscript{+}Cp complexes is similar to that of (arene)Fe\textsuperscript{+}Cp complexes. Thus, halogen (Cl, F) and nitro group in the arene ring can be substituted by various nucleophiles (Table 3.1).\textsuperscript{123}

\[
\begin{align*}
\text{Ru}^+\text{Cp} & \quad \text{X} \quad \text{R} \\
+ \quad \text{Nu} & \quad \rightarrow \quad \text{Nu} \quad \text{R} \\
\text{R} & = \text{various alkyl or part of cyclohexane ring}
\end{align*}
\]
Table 3.1. Nucleophilic substitution reactions of (arene)Ru\(^{+}\)Cp complexes.

<table>
<thead>
<tr>
<th>X</th>
<th>Nu</th>
<th>yield (%)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>· OH</td>
<td>56.5</td>
<td>123a, 123c</td>
</tr>
<tr>
<td>&quot;</td>
<td>· SPh</td>
<td>72</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>· CN</td>
<td>76</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>· CH(CO(_2)Me(_2))</td>
<td>80-90</td>
<td>122b, 123c</td>
</tr>
<tr>
<td>&quot;</td>
<td>· OBn</td>
<td>73</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>NH(_2)CH(_3)</td>
<td>60</td>
<td>123c</td>
</tr>
<tr>
<td>&quot;</td>
<td>· OPh</td>
<td>-</td>
<td>123d</td>
</tr>
<tr>
<td>F</td>
<td>CH(_3)OH</td>
<td>-</td>
<td>123a</td>
</tr>
<tr>
<td>NO(_2)</td>
<td>· CH(CO(_2)Me(_2))</td>
<td>76-88</td>
<td>123b</td>
</tr>
<tr>
<td>&quot;</td>
<td>· OMe</td>
<td>83-89</td>
<td>&quot;</td>
</tr>
<tr>
<td>&quot;</td>
<td>N-pyrrolidinyl</td>
<td>70-76</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Also, (arene)Ru\(^{+}\)Cp complexes can undergo nucleophilic addition by hydride (NaBH\(_4\))\(^{115,123a}\) or phenyllithium (eq 3.7).\(^{123a}\)

\[
\text{Ru}^{+}\text{Cp} + R^- \rightarrow \text{Ru}^{+}\text{Cp}R \quad \text{(eq 3.7)}
\]

The oxidation of 3.11 with NBS resulted in a mixture of exo-alkyl and endo-H abstraction products (eq 3.8).\(^{123a}\)
Robertson et al.\textsuperscript{115} also have described nucleophilic addition reactions of (arene)CpM+ complexes with various nucleophiles. The results were either no reaction (for M = Ru, Nu = various PR\textsubscript{3}, for M = Os, Nu = PR\textsubscript{3}, H\textsuperscript{-}, CN\textsuperscript{-}, OH\textsuperscript{-}) or extensive decomposition (for M = Ru, Nu = CN\textsuperscript{-}, OH\textsuperscript{-}). This behavior is to be contrasted with that of the (arene)CpFe\textsuperscript{+} complexes which readily react with various nucleophiles to give exo-substituted \(\eta^5\)-cyclohexadienyl complexes. The suggested explanation for such a different reactivity was the greater \(\pi\)-back-bonding ability of Ru and Os compared to Fe.\textsuperscript{124}

2. **Nucleophilic Substitution Reactions**

As described in Chapter 2, in an effort to construct the "upper half" or triaryl diether moiety of the vancomycin class, several (chloroarene)Ru\textsuperscript{+}Cp complexes were prepared, and their reactivity toward various nucleophiles has been studied. The (chloroarene)Ru\textsuperscript{+}Cp complexes include those of m-dichlorobenzene, 3,5-dichloroanisole, and 1,3,5-trichlorobenzene, prepared according to Gill and Mann's method (eq 3.9).\textsuperscript{117} In this way, complexes 3.14a (X = OMe) and b (X = Cl) were prepared. It is noteworthy that the corresponding Fe complexes could not be made (Chapter 2.1 ).
The complexes 3.14a-c were allowed to react with various nucleophiles including protected tyrosine. Results are summarized in eq 3.10 and Table 3.2.

Table 3.2. Nucleophilic substitution of polyhaloarene Ru⁺Cp complexes 3.14a-c.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4-Methoxyphenoxy NaH/THF/-78 °C → r.t.</td>
<td>81% 3.15a, 8% 3.15b</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>2equiv of &quot; -30 °C → r.t.</td>
<td>74.4% 3.15b</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>(L)-N-Cbz-tyrosine Me ester &quot;</td>
<td>total 86.4% yield, S.M.: 3.15c: di-sub. = 1:14:1</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;CH(CO₂Me)₂ &quot;</td>
<td>Decomp + S.M.</td>
</tr>
<tr>
<td>5</td>
<td>OMe</td>
<td>Evans' enolate† NaH/THF/0 °C</td>
<td>No Reaction</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>(R)-Schöllkopf§ n-BuLi/THF/-78 °C → 0°C</td>
<td>Decomp + S.M. (3.2%)</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>&quot; /-20 °C</td>
<td>Decomp + S.M.</td>
</tr>
</tbody>
</table>

† Evans' enolate
§ Schöllkopf reagent
Although all the aryloxy nucleophiles underwent substitution reaction with high yield (entries 1-3), the reactions with carbanions (entries 4-7) were unsuccessful, in contrast with the (chloroarene)Fe\(^+\)Cp complexes. The reaction of (1,3-dichlorobenzene)CpRu\(^+\) and 1 equivalent of aryloxy anion resulted in mono substituted complexes 3.15a and c along with a small amount (8%) of disubstituted product in high total yield (entries 1 and 3). This disubstitution was almost unavoidable, and the difficult separation was not attempted because the disubstituted product does not interfere with the second substitution. The separation is much easier after demetallation. Two equivalents of aryloxy anion (entry 2) showed a clean conversion to 3.15b in 74% yield.

The replacement of the remaining Cl in the benzene ring with nucleophiles was attempted in an effort to introduce a glycine moiety into the aryl ring (eq 3.11).

![Chemical Reaction Diagram]

3.15 a, X = 4-methoxyphenoxy
3.16 X = 4-methoxyphenoxy
   c, X = protected tyrosyl
   Y = protected tyrosyl
Table 3.3 The second nucleophilic substitution of (chboroarene)RuCp complexes 3.15.

<table>
<thead>
<tr>
<th>X</th>
<th>Nu</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4-Methoxyphenoxy</td>
<td>(R)-Schöllkopf reagent</td>
<td>n-BuLi/THF/-78 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2 &quot;</td>
<td>Evans' enolate</td>
<td>NaH/THF/r. t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>3 &quot;</td>
<td>&quot;</td>
<td>/reflux</td>
<td>&quot;</td>
</tr>
<tr>
<td>4 &quot;</td>
<td>Dimethyl malonate</td>
<td>NaH/THF/reflux</td>
<td>&quot;</td>
</tr>
<tr>
<td>5 &quot;</td>
<td>(L)-N-Cbz-Tyrosine Me ester</td>
<td>NaH/THF/0 °C</td>
<td>3.16, 25%</td>
</tr>
<tr>
<td>6 protected Tyrosyl</td>
<td>Dimethyl malonate</td>
<td>K₂CO₃/THF/0 °C</td>
<td>Decomp + S.M.</td>
</tr>
<tr>
<td>7 &quot;</td>
<td>&quot;</td>
<td>/DMF/r.t.</td>
<td>&quot;</td>
</tr>
<tr>
<td>8 &quot;</td>
<td>&quot;</td>
<td>/50 °C</td>
<td>&quot;</td>
</tr>
<tr>
<td>9 &quot;</td>
<td>&quot;</td>
<td>/HMPA/r.t.</td>
<td>&quot;</td>
</tr>
<tr>
<td>10 &quot;</td>
<td>&quot;</td>
<td>/DMSO/r.t.</td>
<td>+ demetal.</td>
</tr>
<tr>
<td>11 &quot;</td>
<td>&quot;</td>
<td>/THF/HMPA</td>
<td>+ S.M.</td>
</tr>
<tr>
<td>12 &quot;</td>
<td>&quot;</td>
<td>KH/THF/r.t.</td>
<td>&quot;</td>
</tr>
<tr>
<td>13 &quot;</td>
<td>&quot;</td>
<td>NaH/THF/AgBF₄/r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>14 &quot;</td>
<td>PhSO₂CH₂CO₂Me</td>
<td>K₂CO₃/DMF/r.t.</td>
<td>No reaction</td>
</tr>
<tr>
<td>15 &quot;</td>
<td>(R)-Schöllkopf reagent</td>
<td>n-BuLi/THF/r.t.</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

As experienced with the (arene)FeCp complexes, reactions with many carbanions resulted in either decomposition or no reaction. When DMSO was used as the solvent (entry 10), demetallation occurred along with extensive decomposition. Usually thermal demetallation\textsuperscript{123a} is conducted in DMSO at high temperature (~200 °C). In this case, because both reagent (dimethyl malonate) and DMSO can behave as an active ligand, such low temperature demetallation might be facilitated. Early in 1969, Pavlicheva et al.\textsuperscript{125} described the mechanism of ligand exchange between (benzene)FeCp and β-diketone (Scheme 3.1) suggesting two possible ligation models of β-diketone to the complex (Scheme 3.1).\textsuperscript{125}
Scheme 3.1 Mechanism of ligand exchange by β-diketone.

Because all the attempted halogen replacements by dimethyl malonate anion resulted in failure, we made a direct comparison of the reactivity of Ru and Fe complexes. Thus, an equimolar mixture of 3-chloro-1-(4-methoxy)phenoxybenzeneCpFe⁺ (2.20a) and Ru⁺ (3.15a) was reacted with 0.5 equivalents of 4-methoxyphenol Na salt under the usual conditions (Scheme 3.2). ¹H NMR spectral analysis of the reaction mixture showed 4 C₅H₅ peaks at δ 5.66 (starting Ru⁺Cp), 5.57 (product Ru⁺Cp), 5.35 (starting Fe⁺Cp), 5.25 (product Fe⁺Cp) at the ratio of 1.9 : 1.1 : 1.8 : 1 ≡ 2 : 1 : 2 : 1; indicating the same reactivity toward the aryloxy nucleophile.

When the same comparison was attempted using 3-chloro-1-tyrosylbenzene-CpFe⁺ (2.20c) and CpRu⁺ (3.15c), precise analysis was not possible because the benzylic CH₂ peaks from the Cbz group overlapped with the most important Cp peaks. When dimethyl malonate was used instead of 4-methoxyphenol, serious decomposition prevented the analysis.
Scheme 3.2 The reactivity comparison between CpFe\textsuperscript{+} and CpRu\textsuperscript{+} complexes

3. Nucleophilic Addition Reactions

An attempted nucleophilic addition of methyl anion to 1,3-diaryloxybenzene-
Ru\textsuperscript{+}Cp complex 3.15b resulted in either decomposition (at 0 °C) or no reaction (at -78 °C, eq 3.12).

Up to the present the only known example of alkyl addition to (arene)Ru\textsuperscript{+}Cp is
the addition of phenyllithium to (benzene)Ru\textsuperscript{+}Cp by Nesmeyanov et al.\textsuperscript{123a} As
Robertson et al.\textsuperscript{115} have described, general alkyl addition seems to be difficult. For
that reason, no further attempt was made.
4. Model Studies for Ristocetin A

As discussed so far, introduction of a glycine equivalent into benzene ring of the (arene)Ru\textsuperscript{+}Cp complex was not successful (Scheme 3.3, Model I). Instead, direct introduction of phenylglycine moiety via double O-Cl displacement using two equivalents of (chlorophenylalanine)Ru\textsuperscript{+}Cp complexes (Model II) appears more promising.

Scheme 3.3 Two models for the construction of the "upper half" of vancomycin

Model I

Model II

As a preliminary study, we have reported\textsuperscript{126} the synthesis of dityrosine derivatives using arene-Ru\textsuperscript{+}Cp. Thus, treatment of (±)-N-acetyl-4-chlorophenylalanine methyl ester with (CH\textsubscript{3}CN\textsubscript{)}\textsubscript{3}Ru\textsuperscript{+}Cp in 1,2-dichloroethane at 40-45 °C for 72 hr furnished the complex 3.18 in 65% yield. Preparation of (arene)Fe\textsuperscript{+}Cp complex was
not attempted because of the harsher reaction conditions that are necessary. Treatment of 3.18 with the phenoxide 3.19 gave complex 3.20, which was difficult to purify and which was therefore submitted to photochemical demetallation to afford the dityrosine derivative 3.21 in 66% overall yield from 3.18. This establishes that aromatic amino acids can be directly coupled under mild conditions providing methodology that is suitable for the preparation of subunits found in OF4949,127 bouvardin,128 and K-13.129

Scheme 3.4 Ruthenium-mediated synthesis of dityrosine derivatives

Our first plan was to synthesise the 16-membered cyclic compound (3.22) as a model for the "upper-right" portion of Ristocetin A.
Compound 3.22 consists of 3-hydroxyphenylglycine, phenylalanine, and glycine. The peptide macro cyclization can be achieved through a peptide bond formation between glycine and either phenylalanine or 3-hydroxyphenylglycine (Scheme 3.5, disconnections and b). In this manner the optimum site and method of cyclization will be studied. The aryl ethers (3.23 and 3.26) can be obtained by nucleophilic substitution reaction between (chloroarene)-Ru+\textit{Cp} (3.25 and 3.28) and aryloxide (3.24 and 3.27).

In the following sections, (1) synthesis of amino acid starting materials, (2) complexation, coupling, demetallation, (3) deprotection, and (4) attempted macro-peptide cyclization will be described.
Scheme 3.5 Retrosynthetic analysis of the simplified target molecule.
4.1. Synthesis of amino acid starting materials

4.1.1. Synthesis of (D)-4-chlorophenylalanine derivatives

The "right-half" of the target molecule, (D)-4-chlorophenylalanine was synthesized starting from commercially available 4-chlorocinnamic acid (3.29). Catalytic hydrogenation afforded 4-chlorohydrocinnamic acid in 90% yield, which was converted to an amide via the mixed anhydride method. To this amide (3.31), an azide group was introduced asymmetrically following the method which has been first developed by Evans.130

Scheme 3.6 Synthesis of (D)-N-Boc-4-Chlorophenylalanine methyl ester. a

\[ \text{Cl} \text{CH} = \text{CH} \text{COOH} \quad \xrightarrow{a} \quad \text{Cl} \text{CH} = \text{CH} \text{CO}R \]
\[ \xrightarrow{b} \quad \text{R} = \text{OH}, 90\% \quad \text{R} = \text{X}, 91\% \]
\[ \text{Cl} \text{CH} \text{N} \text{Me} \text{Ph} \]
\[ \text{Cl} \text{CH} \text{CO} \]
\[ \xrightarrow{c} \quad \text{Cl} \text{CH} \text{NHBOC} \text{OMe} \]
\[ \text{3.35} \ 60\% \text{from 3.32} \]

(a) H\textsubscript{2}/Pd-C; (b) pivaloyl chloride, Et\textsubscript{3}N, 0 °C, lithiated oxazolidinone; (c) KHMDS, -78 °C, trisyl azide; (d) LiOH, H\textsubscript{2}O\textsubscript{2}, 0 °C; (e) CH\textsubscript{3}N\textsubscript{2}, 0 °C; (f) H\textsubscript{2}/Pd-C, (Boc)\textsubscript{2}O.
The diastereomeric excess in this step could not be calculated because the diastereomer peaks were very difficult to resolve in the NMR spectrum of the crude sample. Evans has shown that the diastereoselectivity during similar reactions is more than 98\%.\textsuperscript{130} The purified azido amide 3.32 was subjected to hydrolysis by LiOH to give an azido acid 3.33, which was further transformed to an azido ester 3.34 without extensive purification. The azido ester was then converted to the N-Boc-amino ester via a one-pot transformation,\textsuperscript{131} giving 3.35 in 60\% yield from 3.32.

Several other esters and amides (3.38) were prepared using optically active (3.36) or racemic N-Boc-4-chlorophenylalanine (3.37, eq 3.13).

![Chemical structures]

**Table 3.4. Preparation of various acids and amides from N-Boc-4-chlorophenylalanine.**

<table>
<thead>
<tr>
<th>Alcohols or amine</th>
<th>Conditions</th>
<th>Product, yield</th>
<th>mp (°C)</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO(CH(_2)(_2)TMS</td>
<td>DCC/CH(_3)CN/0 °C</td>
<td>3.38a(±), 87%</td>
<td>91-92.5</td>
<td>132</td>
</tr>
<tr>
<td>HO(CH(_2)(_2)Br</td>
<td>&quot;</td>
<td>3.38b(±), 82.3%</td>
<td>64-65</td>
<td>&quot;</td>
</tr>
<tr>
<td>HO(CH(_2)(_2)Br</td>
<td>&quot;</td>
<td>3.38c(R), 67%</td>
<td>70-71</td>
<td>&quot;</td>
</tr>
<tr>
<td>HOC(_6)F(_5)</td>
<td>DCC/py/CH(_2)Cl(_2)</td>
<td>3.38d(±), 92.4%</td>
<td>118.5-119</td>
<td>133</td>
</tr>
<tr>
<td>H(_2)NCH(_2)CO(_2)(CH(_2)(_2)Br</td>
<td>DCC/HOBT CH(_2)Cl(_2)/0 °C</td>
<td>3.38e(R), 68%</td>
<td>121-122</td>
<td></td>
</tr>
</tbody>
</table>
4.1.2. Synthesis of (D)-3-hydroxyphenylglycine derivatives

(D)-3-Hydroxyphenylglycine had been commercially available from Aldrich Co., but during the development of this project, that supply was discontinued. Therefore, it had to be synthesized de novo, from 3-hydroxyphenylacetic acid (3.39, Scheme 3.7).

Scheme 3.7 Synthesis of (D)-3-hydroxyphenylglycine derivatives. a

\[ \text{3.39} \xrightarrow{\text{a}} \text{3.40} \xrightarrow{\text{b}} \text{3.41} \xrightarrow{\text{c}} \text{3.42} \xrightarrow{\text{d}} \text{Xc} = \begin{array}{c} N \hline \text{O} \end{array} \]

\[ \text{3.40} \quad R = \text{OBn} \quad 100\% \]

\[ \text{3.41} \quad R = \text{OH} \quad 88\% \]

\[ \text{3.42} \quad R = \text{Xc} \quad 73-89\% \]

\[ \text{3.43} \quad R = \text{Xc} \quad 49.7\% \]

\[ \text{3.44} \quad R = \text{OH} \]

\[ \text{3.45} \quad R = \text{OMe} \quad 83\% \text{ from 3.43} \]

\[ \text{3.46} \quad R = \text{H} \]

\[ \text{3.47} \quad R = \text{COCH}_2\text{NHCbz} \quad 91\% \]

\[ \text{3.48} \quad R = \text{Cbz} \quad 95\% \]

\( ^{a} (\text{a}) \) 2.5 equiv BnBr/K_2CO_3; (b) KOH; (c) pivaloyl chloride, Et_3N, 0°C, lithiated oxazolidinone; (d) KHMDS, -78 °C, trisyl azide; (e) LiOH; (f) p-toluenesulfonic acid/MeOH; (g) H_2/Pd-C; (h) CbzNHCH_2CO_2H/DCC/HOBT; (i) ClCO_2Br/NaHCO_3.
3-Hydroxyphenylacetic acid was reacted with 2 equivalents of benzyl bromide to give dibenzylc compound 3.40 in quantitative yield, which was hydrolyzed with dilute aqueous solution of KOH in a mixed solvent of THF, water and MeOH. MeOH was added to make the mixture homogeneous; without addition of MeOH, the reaction was not clean, resulting in a low yield. The resulting acid (3.41) was subjected to the Evans' asymmetric azidation procedure. Thus, 3.41 was converted to 3.42 via the mixed anhydride, which was very difficult to purify, so that it could not be fully characterized.

Scheme 3.8 Mechanism of asymmetric azidation.

To this crude amide was introduced an azide group following the established procedure to afford 3.43 in 40% yield. Unlike other reported compounds, 3.42 afforded the azidation product usually in about 30% yield, and the highest yield was only 49.7%. This low yield might have resulted from extensive decomposition during
the reaction. According to Evans, azide group is introduced through the decomposition of the sulfonyl triazene intermediate (Scheme 3.8, 3.50). Depending on the quench reagent, it gives either 3.51 or 3.52 as the major product.

This process can easily be detected by TLC; the polar intermediate appears at $R_f \equiv 0.1$ (25% EtOAc-Hexs), and the intensity of the new spot at $R_f \equiv 0.3$ slowly increased compensating the spot corresponding to the intermediate. In the case of 3.42, several deep pink, polar by-products were observed which do not move on TLC. In most cases this decomposition is very fast (~2 hr at room temperature), but in the case of 3.42, it required 17 hr for the complete decomposition of the intermediate. Although the addition of tetramethylammonium acetate accelerated the decomposition rate, the overall yield remained unchanged.

The azide 3.43 was hydrolyzed by LiOH, the resulting the acid 3.44 was converted to the ester 3.45 under an acidic (p-toluensulfonic acid) conditions in 83% yield over two steps. Both the benzyl and azide groups in 3.45 were converted to OH and NH$_2$ (3.46) in a one-step catalytic hydrogenolysis. 3.47 and 3.48 were prepared by reacting 3.46 with N-Cbz-glycine and benzyl chloroformate, respectively. The ethyl ester analogue 3.55 was prepared using commercially available 3.53 (which was purchased before the supply disconnection) following the same sequence (eq 3.14).
Preparation of (D)-3-hydroxyphenylglycine was also attempted via classical resolution of the racemic mixture produced by the Strecker amino acid synthesis. Thus, 3.58 and 3.60 were prepared from 3-methoxy (3.56) and 3-hydroxybenzaldehyde (3.59) respectively, following the known procedures (Scheme 3.9).  

Scheme 3.9 An attempted classical resolution of 3-hydroxyphenylglycine.

\[
\begin{align*}
\text{MeO} & \text{-C\(=\)H} & \xrightarrow{1) \text{KCN, } \text{NH}_4\text{Cl, 2) 6N HCl}} & \text{MeO} & \text{-C\(=\)H}
\end{align*}
\]

\[
\begin{align*}
3.56 & \quad & 3.57 & \quad & 3.58
\end{align*}
\]

\[
\begin{align*}
\text{24\%} & \quad & \text{45\%}
\end{align*}
\]

\[
\begin{align*}
\text{(D)-tartaric acid} & \quad & \text{(D)-\(\alpha\)-methylbenzylamine}
\end{align*}
\]

\[
\begin{align*}
\text{No Resolution} & \quad & \text{No Resolution}
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \text{-C\(=\)H} & \xrightarrow{1) \text{NaCN, } \text{NH}_4\text{Cl, 2) 20\% HCl}} & \text{HO} & \text{-C\(=\)H}
\end{align*}
\]

\[
\begin{align*}
3.59 & \quad & 3.60
\end{align*}
\]

\[
\begin{align*}
55\% & \quad & +10.8^\circ (c = 1.0, 1\text{N HCl})
\end{align*}
\]

\[
\begin{align*}
lit. -145^\circ (c = 1.0, 1\text{N HCl})
\end{align*}
\]

Attempted resolutions were totally unsuccessful, e.g., resolution of 3.57 using (D)-\(\alpha\)-phenylethylamine\(^{136}\) resulted in no optical rotation, and resolution of 3.60 with (L)-tartaric acid\(^{138}\) resulted in small degrees of opposite rotation (lit.\(^{28}\) = -145\(^\circ\),...
observed = +10° c = 1.0, 1N HCl in both measurement). Also Eizember and Ammons\textsuperscript{137} have described that they were unable to resolve 3-methoxyphenylglycine (3.57) using (D)-tartaric acid.

Classical resolution has no merits because it requires as many steps as the Evans method to get the same product even if the resolution was successful, and yields are limited to a maximum of 50% in the resolution step.

4.2. Complexation, Coupling, and Demetallation

4.2.1. Complexation

All the 4-chlorophenylalanine derivatives as well as N-acetylphenylglycine methyl ester (3.61) were reacted with (CH$_3$CN)$_3$Ru$^+$Cp. Racemic N-acetylphenylglycine methyl ester was used for model study to test the complexation of arylglycine derivatives. The results are summarized in eq 3.15 and Table 3.5

![Chemical Reaction Image]

\[3.61, X = H, Y = CH(CO_2Me)(NHAc)\]
\[3.37, X = Cl, Y = CH_2CH(NHBoc)CO_2H\]
\[3.35, X = Cl, Y = CH_2CH(NHBoc)CO_2Me\]
\[3.38 \text{a}, X = Cl, Y = CH_2CH(NHBoc)CO_2(CH_2)_2TMS\]
\[b, X = Cl, Y = CH_2CH(NHBoc)CO_2(CH_2)_2Br\]
\[c, X = Cl, Y = CH_2CH(NHBoc)CO_2CH_2F_5\]
\[d, X = Cl, Y = CH_2CH(NHBoc)CONHCH_2CO_2\]
\[\text{eq} 3.15\]
\[3.62 \text{a}, X = H, Y = CH(CO_2Me)(NHAc)\]
\[b, X = Cl, Y = CH_2CH(NHBoc)CO_2H\]
\[c, X = Cl, Y = CH_2CH(NHBoc)CO_2Me\]
\[d, X = Cl, Y = CH_2CH(NHBoc)CO_2(CH_2)_2Br\]
\[e, X = Cl, Y = CH_2CH(NHBoc)CONHCH_2CO_2\]
Table 3.5. Complexation of various esters and amides.

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>CH$_3$(CO$_2$)Me(NHAc)</td>
<td>CH$_3$CN/reflux/16hr</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>THF/reflux/16hr</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>CH$_2$CH(NHBoc)CO$_2$H</td>
<td>THF/r.t./2 hr</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>1,2-dichloroethane/reflux/5 hr</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>Cl(CH$_2$)$_2$Cl/reflux/16hr</td>
<td>3.62c, 27%</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>Cl(CH$_2$)$_2$Cl/reflux/5 hr</td>
<td>3.62c, 87-89%</td>
</tr>
<tr>
<td>7</td>
<td>&quot;</td>
<td>CH$_2$CH(NHBoc)CO$_2$(CH$_2$)$_2$ TMS</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>CH$_2$CH(NHBoc)CO$_2$(CH$_2$)$_2$Br</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>CH$_2$CH(NHBoc)CO$_2$C$_6$F$_5$</td>
<td>&quot; /1 hr</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>CH$_2$CH(NHBoc)CONHCH$_2$CO$_2$(CH$_2$)$_2$Br</td>
<td>&quot; /5 hr</td>
</tr>
</tbody>
</table>

§ Many side reactions occurred when scaled up.

When phenylglycine derivative (3.61) was reacted with (CH$_3$CN)$_3$Ru+Cp in CH$_3$CN it resulted in a mixture at the ratio of starting complex : product = 1 : 2 (entry 1). The same result was obtained using THF (entry 2). Although the acid (3.37) was completely decomposed at THF (entry 3), it was cleanly converted to the complex 3.57b in 1,2-dichloroethane (entry 4).

For the ester 3.35, the use of CH$_3$CN as the solvent gave no reaction even after 48 hr (entry 5), but 3.62c was obtained in 29% yield in 1,2-dichloroethane (entry 6). The yield was increased to as high as 89% by reducing the reaction time to 5 hr (entry 7). Although the trimethylsilyl ester 3.38 afforded the complex in 97% yield in a small scale reaction, this was never reproduced in larger scale reaction (several by-
products were obtained). Presumably the F\textsuperscript{-} from the counter ion (PF\textsubscript{6}\textsuperscript{-}) promotes decomposition of the trimethylsilylethyl group. Also, the pentafluorophenyl ester decomposed very easily (entry 10).

2-Bromoethyl ester was well-behaved during the complexation, giving almost quantitative yield in each case (entries 9 and 10) with good reproducibility.

4.2.2. Coupling

Various complexed aryl ethers (3.63a-e) were prepared in high yield via nucleophilic substitution reaction between the (chloroarene)Ru\textsuperscript{+}Cp complexes and 3-hydroxyphenylglycine derivatives. The results are summarized in eq 3.16 and Table 3.6.

To prevent possible racemization at the chiral center of phenylglycine, 2,6-di-\textit{t}-butylphenol Na salt was used as a sterically hindered weak base\textsuperscript{134} which was produced from equimolar amounts of NaH and the phenol in anhydrous THF.
Table 3.6 Formation of complexed diaryl ethers.

<table>
<thead>
<tr>
<th>3-Hydroxyphenylglycine</th>
<th>(Chloroarene)Ru⁺Cp</th>
<th>Products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>P</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td>Me</td>
<td>COCH₂NHCbz (3.47)</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>Cbz (3.48)</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>COCH₂NHCbz (3.55)</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

When the complexed acid (3.62b) was reacted with the aryloxide 3.47, the NMR spectrum showed different peaks from those of both the starting materials (3.47b and 3.62b), but they were all broad (entry 1) and after irradiation with uv light, it was completely decomposed. All other complexes afforded the complexed aryl ethers in very high yields (entries 2-6).

4.2.3. Demetallation

All the complexed aryl ethers were irradiated with uv light (sunlamp, 275W) in a quartz tube (typical size, 1.5 × 10 cm) overnight at room temperature (eq 3.17). The typical solvent was CH₃CN, and N₂ was bubbled through to remove oxygen before use. After the reaction was complete (followed by NMR spectroscopy), the organic product (ether soluble) was separated from (CH₃CN)₃Ru⁺Cp PF₆⁻ (ether insoluble) by adding the concentrated reaction mixture to ether. The ether insoluble (CH₃CN)₃Ru⁺Cp complex was purified by eluting through a neutral alumina column (CH₃CN). The average recovery was 85% based on the complexed ethers. Thus,
although ruthenium is rather expensive to use as a stoichiometric reagent it may be recovered and recycled.

\[
\begin{align*}
3.63a, b, d, e & \quad \text{(eq 3.17)} \\
\text{hv} & \\
(\text{CH}_3\text{CN})_2\text{Ru}^*\text{Cp} & \\
85\% & \\
3.64 & \\
\end{align*}
\]

\[
\begin{align*}
a, R = \text{Me}, & P = \text{COCH}_2\text{NH}C\text{bz}, X = \text{O(\text{CH}_2)_2Br} \\
b, R = \text{Me}, & P = \text{C}\text{bz}, X = \text{NHCH}_2\text{CO}_2(\text{CH}_2)_2\text{Br} \\
c, R = \text{Et}, & P = \text{COCH}_2\text{NH}C\text{bz}, X = \text{OMe} \\
d, R = \text{Et}, & P = \text{COCH}_2\text{NH}C\text{bz}, X = \text{O(\text{CH}_2)_2Br}
\end{align*}
\]

To address the possibility of racemization if any during the complexation and the photolytic demetallation, the optical rotation of compound 3.35 has been compared before and after the two steps. The optical purity remained unchanged during those reactions. Although the optical purity was not measured for the reactions in eq 3.17, it is known that no racemization was detected for the similar reactions of Mn(CO)3 complexes.\textsuperscript{170} Thus, in conclusion, such an operation can provide useful methodology for activation of carbon-halogen bond in aryl amino acid derivatives and subsequently, for the formation of diaryl ethers with amino acid side chains.
4.3. Deprotection of amino acid side chain

After demetallation, the protecting groups in the amino acid had to be removed for the cyclization. The demetallated products have four different protecting groups in one molecule which should be selectively removed.

Our protecting groups consist of N-Boc and 2-bromoethyl ester on the phenylalanine side, and N-Cbz and methyl ester in the phenylglycine side. The deprotections under consideration are 2-bromoethyl ester in the phenylalanine side and N-Cbz in the phenylglycine side. Because the phenylglycine chiral center is very prone to racemize under basic conditions, deprotection of those two groups must use acidic or neutral conditions. Since the N-Boc group is routinely removed by acid, the choice is limited to neutral conditions. The 2-bromoethyl ester was chosen because it can be removed by the use of Zn in aqueous MeOH, and N-Cbz can be removed by catalytic hydrogenolysis. Both these methods are known to be very efficient and mild enough not to affect other functionalities in the molecule.
4.3.1. Deprotection of 2-bromoethyl ester

The first target is 2-bromoethyl ester. The choice was Zn in boiling aqueous \( \text{THF}^{139b} \) with or without \( \text{NaI} \). The first attempt using this method for compound \( \text{3.64d} \) afforded the corresponding acid in about 75% yield in the presence of \( \text{NaI} \) (eq 3.18).

The product was easily distinguished by TLC and NMR spectroscopy; the polar product did not move in EtOAc-Hexs solvent systems, and the disappearance of the two methylene triplets at \( \delta \) 4.2 and 3.5 ppm was observed. The crude acid (3.65), which was difficult to purify, was subjected to hydrogenolysis, and the free amino acid 3.66 was obtained as a pale yellow powder. An attempted purification by ether trituration resulted in deterioration of the compound. Consequently, this material was used in the cyclization reactions without purification.
Unexpectedly, however, the above result has never been reproduced when the Zn/NaI method was applied to the compound 3.64a, which differs only in the nature of the ester group on the arylglycine. This gave a yellow polar material which consisted of at least three components. Attempted HPLC analysis showed three broad peaks without clear separation. Also the NMR spectrum showed all broad peaks indicating decomposition (eq 3.20).

\[
\begin{align*}
\text{3.64a} & \quad \xrightarrow{\text{Zn/NaI, THF}} \quad \text{Unidentifiable mixture} \\
\end{align*}
\]

On the other hand, in DMF as the solvent,\textsuperscript{142} this procedure led to 2-hydroxyethyl ester (3.67) in 70% yield in the presence of NaI\textsuperscript{142} or ZnCl\textsubscript{2}\textsuperscript{139} (eq 3.21).

\[
\begin{align*}
\text{3.64} & \quad \xrightarrow{\text{Zn/NaI or ZnCl}_2, \text{DMF, } 80 \, ^\circ\text{C, 16 hr}} \quad \text{5.67} \\
\text{a, } P &= \text{COCH}_2\text{NHCbz, } R = \text{O(CH}_2)_2\text{Br} \\
\text{b, } P &= \text{Cbz, } R = \text{NHCH}_2\text{CO}_2\text{(CH}_2)_2\text{Br} \\
\end{align*}
\]
Because the result of the elemental analysis was far off from the calculated values for the carboxylic acid, and mass spectrometry did not give a parent ion peak, the structure was tentatively assigned by $^1$H NMR spectroscopy. For instance, in the compound 3.64b, the two methylene protons adjacent to O and to Br resonate at $\delta$ 4.4 and 3.5 ppm respectively. In the product 3.67b, the chemical shifts change to $\delta$ 4.3 and 3.8 ppm, respectively. The structure 3.67b was confirmed by acylating the OH group with acetic anhydride. The chemical shifts of the two adjacent methylenes in the acylated compound 3.68 are expected to be significantly different from those of 3.67b because they are now in similar magnetic environments. As expected, the two methylenes merged to give a multiplet at $\delta$ 4.3 ppm in the compound 3.68. The NMR spectra are collected in Figures 3.1-3.
Figure 3.1. $^1$H NMR (200 MHz) spectrum of 3.64b (RCO$_2$CH$_2$CH$_2$Br).
Figure 3.2. $^1$H NMR (200 MHz) spectrum of 3.67b (RCO$_2$CH$_2$CH$_2$OH).
Figure 3.3. $^1$H NMR (200 MHz) spectrum of 3.68 (RCO$_2$CH$_2$CH$_2$OAc).
Although no detailed mechanistic study has been made, a possible mechanism is suggested in Scheme 3.10. The key step seems to be the neighboring group effect exerted by the carbonyl oxygen.

Scheme 3.10. A possible mechanism for the formation of 2-hydroxyethyl ester during attempted deprotection.

The same phenomenon also has been found in a simpler molecule. For instance, attempted hydrolysis of 3.38b resulted in the hydroxy compound, 3.69 under the same conditions (eq 3.23). A literature survey revealed that no such a transformation has yet been documented. The bromoethyl ester has been employed as a protecting group in peptide synthesis quite successfully.
Conversion of the hydroxyethyl ester (3.67a, b) to the desired acids was attempted (Scheme 3.11). An attempted acidic hydrolysis resulted in recovery of the starting material along with decomposition (Table 3.7, entry 1). If 3.67a can be converted to an aldehyde 3.70, which is an α-acyloxy carbonyl compound, this can be reductively cleaved to an acid (3.71) by reaction with CrCl₂, Fe(CO)₅, or Ca/liq NH₃. Consequently, various oxidation methods have been applied in an effort to obtain the aldehyde 3.70. However, no method gave clean conversion to the desired aldehyde. The results are summarized in eq 3.24 and Table 3.7.

Scheme 3.11 A possible transformation from a 2-hydroxyethyl ester to an acid.
Table 3.7  Attempted hydrolysis and oxidation of 2-hydroxyethyl ester.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 0.25N HCl/r.t./168 hr</td>
<td>Decomp + S. M. (36%)</td>
<td>147</td>
</tr>
<tr>
<td>2 DMSO/(COCl)₂/NEt₃/CH₂Cl₂/-78 °C</td>
<td>Decomp</td>
<td></td>
</tr>
<tr>
<td>3 PCC⁴/NaOAc/CH₂Cl₂/r.t. or reflux</td>
<td>mixture at the ratio of aldehyde : unknown = 1 : 4 in total 8.2% yield + 16% S.M.</td>
<td>148</td>
</tr>
<tr>
<td>4 DMSO/Ac₂O</td>
<td>3.68a, 36%</td>
<td>149</td>
</tr>
<tr>
<td>5 PCC/NaOAc/Mol. Sieves/CH₂Cl₂</td>
<td>Decomposition</td>
<td>150</td>
</tr>
<tr>
<td>6 TPAP⁵/NMO⁶/CH₂Cl₂</td>
<td>“</td>
<td>151</td>
</tr>
</tbody>
</table>

⁴ Pyridinium chlorochromate. ⁵ Tetra-n-propylammonium per ruthenate. ⁶ N-Methyl morpholine N-oxide.

Swern oxidation,¹⁴⁷ the PCC method¹⁴⁸,¹⁵⁰ and the TPAP method¹⁵¹ led to decomposition (entries 2, 5 and 6). Although a small amount of aldehyde was obtained by the PCC method (entry 3), it was found only in an inseparable mixture in very low yield. The Albright and Goldman method¹⁴⁹ led to the formation of acetate, 3.67b.

Thus, without any further attempts of oxidation, a search for alternative methods for removal of 2-bromoethyl esters was begun. This includes hydrolysis under basic conditions which would clearly lead to epimerization of the arylglycine. To this end, (D)-N-Cbz-phenylglycine 2-bromoethyl ester was chosen as a model (eq
3.25, Table 3.8), in order to concurrently determine the overall success of the deprotection method as well as its compatibility with the sensitive arylglycine moiety.

![Chemical Structure](image)

(eq 3.25)

<table>
<thead>
<tr>
<th>Method used</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Ethanediithiol/NaH/CH₃CN</td>
<td>Decomp + 3.73 (18.7%), [α]D = 0'</td>
<td>152</td>
</tr>
<tr>
<td>2 Na₂CS₃/CH₃CN</td>
<td>S.M.(92.5%) + 3.73 (3.3%) -16% of racemization on both S.M. and 3.73</td>
<td>153</td>
</tr>
<tr>
<td>3 Vitamin B₁₂/Zn/NH₄Cl</td>
<td>S.M. (22.7%) + 3.73 (44.7%) No racemization detected.</td>
<td>154</td>
</tr>
</tbody>
</table>

Although the reaction with ethanediithiolate, which has been developed by Ho,¹⁵² afforded the acid (3.73), total racemization occurred during the reaction (entry 1). The principle of the cleavage is stepwise expulsion of the halide and the carboxylate; the crucial second step being intramolecular in nature (Scheme 3.12).

\[
\begin{align*}
&\text{RCO}_2\text{CH}_2\text{CH}_2^-\text{X} + \text{SS}^- + 2\text{Na}^+ & \rightarrow & \left[\begin{array}{c}
\text{SS}^-
\end{array}\right]
\rightarrow \text{ROO}_2^- + \text{Na}^+ + \text{SS}
\end{align*}
\]

The disodium thiosulfocarbonate method which has been introduced also by Ho\textsuperscript{153} resulted in \(\sim 16\%\) of racemization on both the recovered starting material and the product (3.73, entry 2). The concept of this method is the same as that of the ethanedithiolate reaction which involves a double ejection of the halogen and the carboxylate ion through attack by a nucleophile (Scheme 3.13).

Scheme 3.13. Mechanism of the sodium thiosulfocarbonate method.

\[
\begin{align*}
&\text{RCO}_2\text{CH}_2\text{CH}_2^-\text{X} + \text{SS}^+ + 2\text{Na}^+ & \rightarrow & \left[\begin{array}{c}
\text{SS}^-
\end{array}\right]
\rightarrow \text{ROO}_2^- + \text{SS}
\end{align*}
\]

The vitamin B\textsubscript{12b} method\textsuperscript{151} seems to be the most promising over other methods because no racemization was detected during the conversion (entry 3). The mode of action of the catalyst is shown in Scheme 3.14.
In step A, the octahedral Co\textsuperscript{III} complex vitamin B\textsubscript{12b} (3.74) is reduced to the catalytically active square-planar green Co\textsuperscript{I} complex 3.75. This reacts in step B as a nucleophile with 3.72 to form the octahedral red Co\textsuperscript{III}-alkyl complex 3.76.\textsuperscript{151} In the presence of Zn, the complex undergoes two-electron reduction according to step C, and decomposes to 3.73, ethylene, and the Co\textsuperscript{I} complex (3.75). If the reduction of 3.76 is maintained by Zn, the reaction continues until the substrate is completely consumed.

The vitamin B\textsubscript{12b} and other neutral and basic methods have been applied to (D)-N-Boc-4-chlorophenylalanine derivatives (3.38c and e) as a closer model to the real molecule (eq 3.26 and Table 3.9).
Table 3.9 Hydrolysis of (D)-N-Boc-4-chlorophenylalanine derivatives.

<table>
<thead>
<tr>
<th>R</th>
<th>Methods Used</th>
<th>Solvents</th>
<th>Results</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(CH$_2$)$_2$Br</td>
<td>Vitamin B$_{12b}$/Zn</td>
<td>EtOH : H$_2$O = 3 : 1</td>
<td>Unidentified mixture</td>
<td>154</td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>DMF/tr.l.</td>
<td>3.77†</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>THF : H$_2$O = 3 : 1</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>CH$_3$CN : H$_2$O = 3 : 1</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>DMSO : H$_2$O = 5 : 2</td>
<td>3.77†</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>acetone</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>/Mg</td>
<td>DMF</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>/Zn</td>
<td>DMF/NaOAc</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>ethanedithiolate</td>
<td>CH$_3$CN</td>
<td>3.77, 20% 16% racemization</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>CH$_2$Cl$_2$</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Et$_2$O</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>Zn only</td>
<td>MeOH/reflux</td>
<td>&quot;</td>
<td>155</td>
</tr>
<tr>
<td>&quot;</td>
<td>Zn/AcOH/NEt$_3$</td>
<td>&quot;</td>
<td>&quot;</td>
<td>155</td>
</tr>
<tr>
<td>&quot;</td>
<td>Zn/ZnCl$_2$</td>
<td>DMF</td>
<td>3.69, 47%</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>Mg’</td>
<td>Et$_2$O</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>&quot;</td>
<td>&quot;</td>
<td>Et$_2$O/I$_2$</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>NHCH$_2$CO$_2$(CH$_2$)$_2$Br</td>
<td>CrCl$_2$</td>
<td>dioxane</td>
<td>&quot;</td>
<td>156a</td>
</tr>
</tbody>
</table>

† Due to the difficulties in purification, % yield could not be calculated.

Although the vitamin B$_{12b}$ method gave the acid (3.77), purification of the product was extremely difficult (entries 2 and 5). Also, this method gave no reaction (entries 3, 4, and 6), or extensive side reaction (entry 1), in solvents other than DMF or DMSO.
When magnesium metal was used instead of Zn, no reaction occurred (entry 7). An attempted reaction under buffered conditions also gave the same result (entry 8).

While the ethanedithiolate method gave the acid, 16% racemization had occurred (entry 9). In methylene chloride or in ether the reaction did not take place (entries 10 and 11).

The use of Zn only, or Zn/HOAc/Et$_3$N$^{155}$ also led to no reaction, whereas in the presence of ZnCl$_2$ (as mentioned before), this resulted in the formation of the 2-hydroxyethyl ester 3.69 in 47% yield. Treatment with Mg (entries 15, 16) or chromous chloride$^{155}$ (entry 17) also was unsuccessful. Therefore, despite the difficulties in purification, the vitamin B$_{12b}$ method is preferred over other methods.

For a closer model to the real compounds, a mixture of 3-hydroxyphenylglycine derivative 3.47 and 4-chlorophenylalanine 2-bromoethyl ester was treated with vitamin B$_{12b}$ and CrCl$_2$ with subtle variations in the conditions (eq 3.27 and Table 3.10).
Table 3.10. Attempted hydrolysis of N-Boc-4-chlorophenylalanine in the presence of 3-hydroxyphenylglycine derivative.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Vitamin B$_{12b}$/Zn/NH$_4$Cl Ultrasound</td>
<td>3.77, 16.3% No racemization in both the S, M and the product</td>
<td>154</td>
</tr>
<tr>
<td>2 CrCl$_2$/Ethylenediamine/DMF</td>
<td>No reaction</td>
<td>156b</td>
</tr>
</tbody>
</table>

The use of ultrasound instead of heating gave the acid 3.77 in 16.3% yield (unoptimized) with no detectable racemization in both starting material and the product entry 1). And at this point, it is evident that the phenylglycine moiety in the real molecule will not be affected under these conditions. When the mixture was treated with chromous chloride in the presence of ethylenediamine, following the known procedure, no reaction occurred (entry 2).

The deprotection method which was selected based on the preceding studies was the vitamin B$_{12b}$ method. This method was applied to the real molecule, 3.64b, and the results are summarized in Table 3.11. For the compound 3.64a, some other methods were also used which were not studied using the model compound.
Table 3.11 Hydrolysis of the diaryl ethers with amino acid side chains.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Methods used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 3.64b</td>
<td>NaI/Zn/acetone</td>
<td>intractable material</td>
</tr>
<tr>
<td>2</td>
<td>Vitamin B12/ EtOH/H2O</td>
<td>“</td>
</tr>
<tr>
<td>3</td>
<td>“/DMF</td>
<td>“</td>
</tr>
<tr>
<td>4</td>
<td>Ethanedithiolate/CH3CN</td>
<td>“</td>
</tr>
<tr>
<td>5 3.64a</td>
<td>Na/liq. NH3/-78 °C</td>
<td>“+ over reduction</td>
</tr>
<tr>
<td>6</td>
<td>Ca/liq. NH3/-33 °C/10 min</td>
<td>18% [diastereomeric mix(?)]</td>
</tr>
<tr>
<td>7</td>
<td>Pd/(PPh3)4/CH3CN</td>
<td>3.67a, 41%</td>
</tr>
</tbody>
</table>

First, 3.64b was treated with NaI in acetone (entry 1). The underlying idea is that substitution of Br by I would give higher reactivity toward reduction by Zn. But this resulted in a yellow polar material which did not move on TLC plate, indicating decomposition. Also, both the vitamin B12 and the ethanedithiolate methods led to intractable material (entries 2-4). This is an unexpected result because they were the most productive methods for the model compounds.

Reaction with sodium in liquid ammonia at -78 °C gave a compound that showed no 2-bromoethyl ester or methyl ester peak in the NMR spectrum of the crude reaction mixture, indicating an over-reduction by the metal along with extensive side reactions (entry 5). On the other hand, the use of calcium instead of sodium resulted in
a small amount of oily product: The NMR spectrum showed loss of the bromoethyl ester, but also two methyl esters and two Boc peaks—presumably a diastereomeric mixture of carboxylic acids, which were obtained in 18% yield. Therefore, deprotection is successful, but racemization occurs.

For the last attempt, Pd(PPh₃)$_4$ was employed in the hope of obtaining the desired acid via oxidative addition followed by β-elimination of ethylene, however, this again gave the 2-hydroxyethyl ester, 3.67b in 41% yield (eq 3.29).

![Chemical reaction diagram]

In conclusion, even though the 2-bromoethyl ester was a good protecting group for the complexation and nucleophilic substitution reaction, it proved to be problematic in its removal. Therefore, the use of other protecting groups which are stable enough for complexation and labile enough for deprotection are desirable. Some of them are suggested at the end of this chapter. It should be remembered that aromatic-containing protecting groups, e.g., benzyl ester and Cbz, cannot be used on the phenylalanine residue because of potential problems of non-selective complexation.
4.3.2. Deprotection of N-Cbz group

Deprotection of the N-Cbz group can be accomplished quite easily by catalytic hydrogen transfer using 1,3-cyclohexadiene\textsuperscript{141} in the presence of Pd-C. 1,3-Cyclohexadiene can be replaced by cyclohexene. For instance, the Cbz group was removed from compounds 3.67a and b by cyclohexene/Pd-C in boiling ethanol to furnish 3.78a and b, respectively. The use of hydrogen gas often leads to decomposition.

\[
\begin{array}{c}
\text{MeO} & \begin{array}{c}
\text{O} \\
\text{NHP}
\end{array} & \begin{array}{c}
\text{O} \\
\text{NH}_{\text{Boc}}
\end{array} & \begin{array}{c}
\text{R} \\
\text{O}
\end{array} \\
\text{MeO} & \begin{array}{c}
\text{O} \\
\text{NHP}
\end{array} & \begin{array}{c}
\text{O} \\
\text{NH}_{\text{Boc}}
\end{array} & \begin{array}{c}
\text{R} \\
\text{O}
\end{array} \\
\end{array}
\]

(eq 3.30)

3.67a, P = COCH\text{2}NH\text{Cbz}, R = O(CH\text{2})\text{2}OH
b, P = Cbz, R = NHCH\text{2}CO\text{2}(CH\text{2})\text{2}OH

3.78a, P = COCH\text{2}NH\text{2}, R = O(CH\text{2})\text{2}OH
b, P = H, R = NHCH\text{2}CO\text{2}(CH\text{2})\text{2}OH

4.4. Attempted macropeptide cyclizations

Several cyclization attempts have been made for the compounds 3.64c, 3.65, and 3.66. The methods include the standard Curtius method, the active ester method, the DPPA method and some other coupling methods, that are known to promote cyclization of o-amino acids and peptides.

4.4.1. The standard Curtius method

If the two different esters in compound 3.64c could be differentiated than a standard Curtius coupling\textsuperscript{157a} would be a useful approach. It is known that ethyl esters are hydrazinolated more slowly than methyl esters.\textsuperscript{157b}
Thus, when a 1 : 1 molar ratio mixture of N-acetyl-3-hydroxyphenylglycine ethyl ester and N-Cbz-tyrosine methyl ester was treated with hydrazine a mixture of compounds was obtained. Assignment of the NMR spectrum showed a chemoselectivity of 15 : 1 in the desired direction (Scheme 3.15). 

**Scheme 3.15 Selective hydrazinolysis**

![Scheme 3.15](image)
With this result in hand, 3.64c was treated with hydrazine using exactly the same conditions as above, and the NMR spectrum of the product was carefully examined. After separation of hydrazide and unreacted starting material, it was found that there was no methyl ester as well as no ethyl ester peak in the product NMR spectrum, indicating no selectivity and formation of the bis hydrazide (Scheme 3.16). This reaction was duplicated, but the results were consistent. The reason for this result is not obvious at the present time.

Scheme 3.16 Nonselective hydrazinolysis of 3.64c.
4.4.2. Attempted active ester cyclization

The compound 3.65 was converted to the pentafluorophenyl ester (3.85, Scheme 3.12) in the hope of obtaining the cyclized product via the active ester method which has been used by Boger et al.\textsuperscript{158} and Evans et al.\textsuperscript{159} for the syntheses of K-13, OF4949, and related compounds.

When 3.85 was treated with 1,3-cyclohexadiene in the presence of palladium catalyst and N-methyl morpholine, decomposition resulted. The same result was obtained with the use of hydrogen\textsuperscript{159} (eq 3.31).

\[ \text{N-methylmorpholine} \searrow \text{Unidentifiable mixture} \]
\[ \text{H}_2\text{Pd-C} \searrow \text{Unidentifiable mixture} \]

4.4.3. Attempted DPPA and some other coupling methods.

Although it was not very pure, the free amino acid, 3.66 has been treated with various coupling reagents which include DPPA,\textsuperscript{160,161} DCC,\textsuperscript{162} Morpho CDI,\textsuperscript{163} and BOP.\textsuperscript{164,165} The results are summarized in eq 3.32 and Table 3.12.
Table 3.12 Attempted cyclization with various coupling reagents.

<table>
<thead>
<tr>
<th>reagents</th>
<th>conditions</th>
<th>results (TLC)</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 DPPA(^a)</td>
<td>NaHCO(_3)/DMF/0 °C/3 days</td>
<td>1 major spot (R_f 0.63) (20% MeOH-CHCl(_3))</td>
<td>160, 161</td>
</tr>
<tr>
<td>2 DCC(^b)</td>
<td>CuCl(_2)/CH(_3)CN/DMF</td>
<td>3 major spots (R_f 0.08, 0.10, 0.45) (7% MeOH-CHCl(_3))</td>
<td>162</td>
</tr>
<tr>
<td>3 Morpho CDI(^c)</td>
<td>DMF/t.t./2 days</td>
<td>1 major spot (R_f 0.44) (20% MeOH-CHCl(_3))</td>
<td>163</td>
</tr>
<tr>
<td>4 DCC</td>
<td>HOBT/DMF/0 °C</td>
<td>no major spot</td>
<td></td>
</tr>
<tr>
<td>5 BOP(^d)</td>
<td>DMF/iPr(_2)NEt/0 °C</td>
<td>“</td>
<td>164, 165</td>
</tr>
</tbody>
</table>

\(^a\) DPPA = Diphenylphosphoryl azide  \(^b\) DCC = Dicyclohexylcarbodiimide  \(^c\) Morpho CDI = 1-Cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate  \(^d\) BOP = Benzotriazolyl-N-oxytris(dimethylamino)phosphonium hexafluorophosphate

To minimize dimerization or polymerization, all the reactions were conducted under high dilution (0.008 M) conditions. In all cases, the starting material was consumed completely, but the products were different depending on the reagents used. The major products were carefully separated by preparative TLC using appropriate solvent systems, and characterized by FAB-MS (fast atom bombardment MS) and FD-MS (field desorption data MS).\(^{166}\) Unfortunately, none of the products had a molecular ion peak which corresponding to the desired cyclic compound, dimer, or cyclic dimer. During the preparation of this dissertation, results were reported by Williams’ group citing difficulties in an almost identical peptide cyclization.\(^{167}\)
Summary

1. Many Ru complexes of arylamino acids were synthesized without racemization. Similar complexation attempts with other cationic methods have failed during previous studies in our laboratory.

2. Chloroarene-Ru\textsuperscript{+}Cp complexes underwent nucleophilic substitution reaction by weak nucleophiles such as aryloxyde under very mild conditions.

3. Direct coupling of arylamino acids, which is not possible by other methods, gave highly functionalized diaryl ethers.

4. Selective nucleophilic substitution resulted in symmetric and non-symmetric triaryl diethers which cannot be prepared directly using other methods.

5. Future work

Recently, Kim et al.\textsuperscript{16} have described the deprotection of various functional alkyl esters under mild conditions. The groups include methoxymethyl (MOM), methyliothiomethyl (MTM), methoxyethoxymethyl (MEM), and β-(trimethylsilyl)-ethoxymethyl (SEM) ester. These esters are removed by treatment with MgBr\textsubscript{2} in ether at room temperature. Because the conditions are mild, this protecting method can be applied to our molecule.
Early in 1966, Woodward et al. described the use of \( \beta,\beta,\beta \)-trichloroethyl (removed by Zn/HOAc) as a carboxylic acid protecting group. Although it is known that removal of this \( \beta,\beta,\beta \)-trichloroethyl is much faster than that of the monohaloethyl ester, still there is possibility of generation of 2-hydroxyethyl ester. The reactivity is as following:

\[
\text{Br}_3\text{CCH}_2\text{O}^- > \text{Cl}_3\text{CCH}_2\text{O}^- > \text{ICH}_2\text{CH}_2\text{O}^- > \text{BrCH}_2\text{CH}_2\text{O}^- \gg \text{ClCH}_2\text{CH}_2\text{O}^-.
\]

Also, Evans has shown the use of the allyl ether group for the protection of OH in tyrosine derivative, and its selective removal by treatment with Bu\(_3\)SnH and Pd(PPh\(_3\))\(_2\)Cl\(_2\). An allyl ester would therefore be a suitable carboxyl blocking group.

Along the same lines as Kim’s deprotection of ester, \( \beta,\beta,\beta \)-trichloroethoxy-methyl (TCEM) group is another possibility. This group is removed by Zn/MeOH or Zn/HOAc/NEt\(_3\)/MeOH.
Experimental

$\eta^6$-1,3-Dichlorobenzene-$\eta^5$-cyclopentadienylruthenium hexafluorophosphate (3.14a)

![Chemical Structure](3.14a)

To a stirred solution of 1.2 mL (10 equiv) 1,3-dichlorobenzene in 1,2-dichloroethane (degassed, 10 mL) was added 434.3 mg (1.0 mmol) of (CH$_3$CN)$_3$Ru-CpPF$_6$ and the mixture was then refluxed under Ar for 17 hrs. Solvent was removed in vacuo. The residue was diluted with ether. The precipitate was collected, washed with ether, then dried. The crude product was eluted through columns of neutral alumina (acetone) then silica gel (acetone) to give a colorless solution. Further purification by recrystallization from 95% ethanol gave 360.5 mg (78.7%) of pale brown-grey solid. mp 265-70 °C (decomp); IR (Nujol) 3100, 1130, 1065, 850 cm$^{-1}$; $^1$H NMR (200 MHz, acetone-d$_6$) $\delta$ 7.35 (1 H, t, $J = 1.1$ Hz, 2-H), 6.80 (2 H, dd, $J = 6.4$ and 1.1 Hz, 4- and 6-H), 6.61 (1 H, dd, $J = 6.4$ and 6.4 Hz, 5-H), 5.73 (5 H, s, Cp). Anal. calcd for C$_{11}$H$_9$Cl$_2$F$_6$PRu: C, 28.84; H, 1.98. Found: C, 28.95; H, 1.91.

$\eta^6$-1-Methoxy-3,5-dichlorobenzene-$\eta^5$-cyclopentadienylruthenium hexafluorophosphate (3.14b)

![Chemical Structure](3.14b)
The title compound was prepared by heating 434.3 mg (1 mmol) of \((\text{CH}_3\text{CN})_3\text{Ru-CpPF}_6\) in 10 g of 3,5-dichloroanisole at 110 °C for 20 min. Dichloroanisole was washed out with ether and the residue was eluted through a column of neutral alumina and a column of silica gel with acetone. Recrystallization from acetone-ether afforded 390.8 mg (80.1%) of pale brown needles. mp 262-4 °C (decomp); IR (Nujol) 3100, 1520, 1270, 1100, 1015, 835 cm\(^{-1}\); \(^1\)H NMR (200 MHz, acetone-\text{d}_6) \(\delta\) 7.12 (1 H, s, 4-H), 6.95 (2 H, s, 2- and 6-H), 5.71 (5 H, s, \(\text{Cp}\)), 3.99 (3 H, s, OCH\(_3\)). Anal. calcd for \(\text{C}_{12}\text{H}_{11}\text{Cl}_2\text{OF}_6\text{PRu}\): \(\text{C}\), 29.53, \(\text{H}\), 2.27. Found: \(\text{C}\), 29.60; \(\text{H}\), 2.18.

\(\eta^6\)-1,3,5-Trichlorobenzene-\(\eta^5\)-cyclopentadienylruthenium hexafluorophosphate (3.14c)

\[
\begin{align*}
\text{Cl} & \quad \text{Ru}^+\text{Cp} \\
\text{Cl} & \quad \text{PF}_6^- \\
\text{Cl} & \quad \text{Cl}
\end{align*}
\]

1.84 g (4.25 mmol) of \((\text{CH}_3\text{CN})_3\text{Ru-CpPF}_6\) and 7.71 g of 1,3,5-trichlorobenzene were refluxed in 30 mL of 1,2-dichloroethane (degassed) overnight. Solvent was removed in vacuo and the residue was washed with ether then eluted through a column of neutral alumina (acetone). The crude product was recrystallized from acetone-EtOH-ether to give 626.1 mg (30%) of a white solid. mp 250-3 °C; IR (Nujol) 3090, 1160, 1080, 840 cm\(^{-1}\); \(^1\)H NMR (200 MHz, acetone-\text{d}_6) \(\delta\) 7.39 (3 H, s, complexed aromatic Hs), 5.84 (5 H, s, \(\text{Cp}\)); Anal. calcd for \(\text{C}_{11}\text{H}_8\text{Cl}_3\text{F}_6\text{PRu}\): \(\text{C}\), 26.82; \(\text{H}\), 1.64. Found: \(\text{C}\), 26.79; \(\text{H}\), 1.53.
$\eta^6$-[1-Chloro-3-(4-methoxy)phenoxy]benzene-$\eta^5$-cyclopentadienyl-ruthenium hexafluorophosphate (3.15a)

![Chemical Structure](image)

To a stirred solution of 200 mg (0.44 mmol) of 3.14a in 5 mL THF was added dropwise a solution of 4-methoxyphenol Na salt [from 65 mg of 4-methoxyphenol and 21 mg NaH (50% in oil)] in 5 mL THF at -78 °C. The mixture was stirred for 2 hr at -78 °C and 2 hr at room temperature. The reaction mixture was filtered through a celite pad (THF) then the solvent was removed in vacuo. The residue was dissolved in 2 mL of acetone and the solution was added to 30 mL of ether to give 212.5 mg of pale yellow oil. NMR spectrum showed 15 : 1 mixture of mono : di-substituted products. Total yield = 89%. $^1$H NMR (200 MHz, acetone-d$_6$) δ 7.31 and 7.11 (2 H each, d, $J = 9.1$ Hz, uncomplexed aromatic Hs), 6.80 (1 H, t, $J = 1.2$ Hz, complexed aromatic 2-H), 6.66 (1 H, dd, $J = 1.1$ and 5.5 Hz, complexed aromatic 6-H), 6.48 (1 H, t, $J = 6$ Hz, complexed aromatic 5-H), 6.30 (1 H, dd, $J = 1.5$ and 6 Hz, complexed aromatic 4-H), 5.70 (5 H, s, Cp), 3.86 (3 H, s, OCH$_3$).

$\eta^6$-1,3-bis-(4-Methoxy)phenoxybenzene-$\eta^5$-cyclopentadienylruthenium hexafluorophosphate (3.15b)

![Chemical Structure](image)
To a stirred solution of 4-methoxyphenol Na salt (from 81.3 mg, 0.66 mmol of 4-methoxyphenol and 36.7 mg of 50% NaH in oil) in 10 mL of THF was added 100 mg (0.22 mmol) of (1,3-dichlorobenzene)FeCpPF₆ as a solid in one portion at -30 °C. The mixture was stirred for 30 min at -30 °C and 2 hrs at room temperature. The reaction was quenched with 1 drop of water, filtered through a celite pad, then THF was removed in vacuo. The residue was dissolved in CH₂Cl₂ and dried over MgSO₄. Solvent was evaporated and the residue was eluted through a neutral alumina column with acetone then the product was isolated by dropping the concentrated solution into 100 mL of ether to give 102.9 mg (74.4%) of white foam after drying in vacuo. IR (CHCl₃) 3020,1500, 1210, 750 cm⁻¹; ¹H NMR (200 MHz, acetone-d₆) δ 7.24 and 7.06 (4 H each, d, J = 9.1 Hz, uncomplexed aromatic Hs), 6.32 (1 H, t, J = 1.4 Hz, 5-H), 6.25 (1 H, dd, J = 6.5 and 5.5 Hz, 2-H), 6.04 (2 H, dd, J = 5.9 and 1.4 Hz, 4- and 6-H), 5.59 (5 H, s, Cp), 3.83 (6 H, s, OCH₃); ¹³C NMR (75 MHz, CDCl₃) δ 150.03, 145.37, 133.42, 121.56, 115.68, 81.70, 80.56, 72.60, 67.01, 55.65; Anal. calcd for C₂₅H₂₃F₆O₄PRu: C, 47.40; H, 3.66. Found: C, 47.51; H, 3.96.

η⁶-1-(S)-[4-[2-(N-Benzoylcarbonyl)amino-3-methoxy-3-oxo]propyl]-phenoxy-3-(4-methoxy)phenoxybenzene-η⁵-cyclopentadienylruthenium hexafluorophosphate (3.16)

![Structure of 3.16](image)

To a stirred solution of (L)-N-Cbz-tyrosine methyl ester Na salt [from 22.2 mg (67.4 × 10⁻⁶ mmol, 2 equivalent) of (L)-N-Cbz-tyrosine and 3.2 mg of NaH (50% in
oil) in 5 mL THF] was added 18.4 mg (33.7 × 10⁻⁶ mmol) of 1-chloro-3-aryloxy benzene RuCp complex (3.15a) as a solid in one portion at room temperature, then the mixture was stirred for 30 min. Solvent was removed in vacuo then the residue was dissolved in acetone and filtered through celite and neutral alumina (acetone). Attempted crystallization from acetone-ether resulted in a gum (7.1 mg, 25% yield) which turned into white foam during drying under vacuum. IR (CHCl₃) 3420, 3200, 2950, 1720, 1500, 750 cm⁻¹; ¹H NMR (200 MHz, acetone-d₆) δ 7.49–7.06 (13 H, m, uncomplexed aromatic Hs), 6.76 (1 H, br d, J = 8.4 Hz, N-H), 6.39–6.04 (4 H, m, complexed aromatic Hs), 5.59 (5 H, s, Cp), 5.04 (2 H, s, CH₂Ph), 4.50 (1 H, m, CHNH), 3.84 (3 H, s, ArOCH₃), 3.70 (3 H, s, CO₂CH₃), 3.24 (1 H, dd, J = 14 and 5.3 Hz, ArCHH), 3.05 (1 H, dd, J = 14 and 9.2 Hz, ArCHH).

(4R,5S)-4-Chloro-[3-oxo-3-(2-oxo-4-methyl-5-phenyl-3-oxazolidinyl)]propylbenzene (3.31)

To a stirred solution of 4-chlorohydrocinnamic acid (312.0 mg, 1.69 mmol) and 282.7 µL (1.2 equiv) of triethylamine in 20 mL of THF was added 218.6 µL (1.05 equiv) of pivaloyl chloride at -78 °C and the mixture was stirred for 10 min at -78 °C and 30 min at 0 °C. The resulting white slurry was cooled to -78 °C then a solution of lithiated oxazolidinone [from 300.0 mg (1.69 mmol) of oxazolidinone in 20 mL of THF and 735 µL (1.69 mmol) of 2.3 M n-BuLi in hexane at -78 °C] was added via a teflon cannula. The mixture was stirred for 15 min at -78 °C then the reaction was
warmed to room temperature (45 min). The reaction was quenched with 10 mL 1N NaHSO₄ aqueous solution. THF was evaporated on a rotatory evaporator and the product was extracted with CH₂Cl₂, washed with dilute NaHCO₃ and with brine then dried over MgSO₄. Flash chromatography on silica gel (30% EtOAc-Hexs) afforded 528.0 mg (90.9%) of white crystalline solid. The product was further purified by crystallization from EtOAc-Hexs. mp 94.5-95 °C; Rf 0.28; (30% EtOAc-Hexs); IR (CHCl₃) 3540, 3020, 2920, 1780, 1700, 1350 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.43 (9 H, m, aromatic), 5.65 (1 H, d, J = 7.3 Hz, C₆H₅CH), 4.75 (1 H, quintet, J = 7.0 Hz, CH₃CH), 3.28 (2 H, m, CH₂CO), 2.98 (2 H, t, J = 7.3 Hz, ArCH₂), 0.88 (3 H, d, J = 6.5 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 171.81, 152.97, 138.89, 133.13, 131.95, 129.92, 128.69, 128.51, 125.58, 79.03, 54.73, 37.07, 29.55, 14.51; [α]D +32.9° (c 0.51, CHCl₃); MS m/z 343.0954 ([M⁺], C₁₉H₁₈ClNO₃ requires 343.0975).

(4R,5S,2R)-4-Chloro-[2-azido-3-oxo-3-(2-oxo-4-methyl-5-phenyl-3-oxazolidinyl)]propylbenzene (3.32)

![Chemical structure](image)

To a stirred solution of 5.0 g (14.54 mmol) of 3.31 in 50 mL THF at -78 °C was added via a cannula 13.57 mL (1.05 equiv) of 1.125 M KHMDS in THF (purchased from Alfa Products). The mixture was stirred for 30 min at -78 °C. To this solution was added a precooled (-78 °C) solution of 5.40 g (17.45 mmol, 1.2 equiv) of trisyl azide in 50 mL of THF with a cannula. The solution was stirred for 2 min at -78
*C then quenched by rapid addition of 4.16 mL (72.7 mmol, 5 equiv) of glacial acetic acid with immediate warming to 30 °C with a water bath. After stirring the yellow to white slurry at room temperature for 1.5 hr, it was diluted with CH₂Cl₂, washed with brine and with dil. NaHCO₃ then dried over MgSO₄. Flash chromatography on silica gel (10% EtOAc-pet. ether then EtOAc) afforded 3.82 g (68.3%) of yellow oil. Rf 0.41 (30% EtOAc-Hexs); IR (neat) 3100, 2920, 2110, 1780, 1700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.42–7.22 (9 H, m, aromatic Hs), 5.56 (1 H, d, J = 7.2 Hz, PhCH), 5.22 (1 H, dd, J = 9.2 and 5.3 Hz, CHN₃), 4.67 (1 H, quintet, J = 7 Hz, CH₃CH), 3.18 (1 H, dd, J = 13.7 and 5.3 Hz, ArCHH), 2.97 (1 H, dd, J = 13.7 and 9.2 Hz, ArCHH), 0.92 (3 H, d, J = 4.8 Hz, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 170.16, 152.85, 134.68, 133.64, 132.92, 131.06, 129.43, 129.21, 125.98, 79.84, 61.99, 55.63, 37.35, 14.80; [α]D -12.97° (c 0.37, CHCl₃); MS m/z [M]+ not found, 356.0914 ([M-N₂]+, C₁₉H₁₇ClN₂O₃ (M-N₂) requires 356.0928).

(D)-(-)-N-tert-Butyloxycarbonyl-4-chlorophenylalanine methyl ester (3.35)

![3.35](image)

To a precooled (0 °C) solution of 941.8 mg (2.45 mmol) of 3.32 in 50 mL of THF was added dropwise an aqueous LiOOH solution (prepared from 107.9 mg, 1.05 equiv of LiOH and 1.25 mL of 30% H₂O₂ in 17 mL of H₂O). The mixture was stirred for 1 hr at 0 °C, then the reaction was quenched by dropwise addition of a solution of 2.55 g NaHSO₃ in 30 mL of H₂O then the mixture was stirred for an additional 15 min at 0 °C. The organic solvent was removed in vacuo. The aqueous residue was diluted
with 1 N NaHSO₄ then extracted with CH₂Cl₂. The combined organic phase was
dried over MgSO₄, then concentrated. The unpurified acid (3.33) was diluted with 50
mL of ethyl ether and treated with excess (3 equiv) of diazomethane in ether (the
reaction was monitored by TLC). The excess diazomethane was removed by bubbling
N₂ through the solution. Flash chromatography on silica gel gave 527.2 mg (crude
yield, 89.8%) of pale yellow oil. Rf 0.38 (30% EtOAc-Hexs). This ester (3.34) was
always contaminated with inseparable impurities. Consequently, the crude ester was
converted to the compound 3.35: A suspension of 40 mg 10% Pd-C in 5 mL of ethyl
acetate was vigorously stirred under H₂ (1 atm) until the uptake of hydrogen ceased. To
this was added a mixture of 401.9 mg (1.68 mmol) of azido ester (3.34) and 439.2 mg
(2.02 mmol, 1.2 equiv) of (Boc)₂O in 2 mL ethyl acetate. The resulting solution was
stirred under H₂ at room temperature for 3 hrs. Flash chromatography on silica gel
(10% EtOAc/benzene) afforded 354.6 mg (67% yield) of white solid. It was further
purified by recrystallization from Hexanes (white needles). mp 78-80 °C; Rf 0.39
(10% EtOAc/benzene); IR (CHCl₃) 3430, 3000, 2980, 1740, 1705, 1490 cm⁻¹; ¹H
NMR (200 MHz, CDCl₃) δ 7.23 (2 H, d, J = 8.4 Hz, aromatic Hs, ortho to Cl), 7.02
(2 H, d, J = 8.4 Hz, aromatic Hs, meta to Cl), 4.92 (1 H, br d, N-H, J = ~7 Hz), 4.53
(1 H, br q, J = ~5 Hz, NHCHCO₂), 3.68 (3 H, s, CO₂CH₃), 3.07 (1 H, dd, J = 14
and 5.5 Hz, ArCHH), 2.96 (1 H, dd, J = 14 and 8 Hz, ArCHH), 1.38 (9 H, s,
C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ 172.01, 154.93, 134.52, 132.86, 130.58,
128.59, 79.98, 54.22, 52.24, 37.68, 28.21; [α]D = -44.8° (c 0.5, CH₂Cl₂); MS m/z
313.1840 ([M]+, C₁₅H₂₀ClNO₄ requires 313.1081).

(d,l)-N-(1,1-Dimethylethoxy)carbonyl-4-chlorophenylalanine 2-trimethylsilyl
ethylethyl ester (3.38a)
129.2 mg (4.31 × 10⁻⁴ mol) of (±)-N-Boc-4-chlorophenylalanine (prepared from (±)-4-chlorophenylalanine purchased from Aldrich) was covered with 0.4 mL of acetonitrile. To this stirred slurry was added 0.1 mL of DMF (or sufficient to produce a homogeneous solution), 69.7 μL (2 equiv) of pyridine and 74.0 μL (1.2 equiv) of 2-trimethylsilyl ethanol. The mixture was cooled to 0 °C then 97.5 mg (1.1 equiv) of DCC was added. After stirring overnight at 0 °C, 12.9 mL of 5M oxalic acid in DMF was added, then the reaction was allowed to come to room temperature. The white precipitate (DCU) was filtered off and discarded. Flash chromatography on silica gel (30% EtOAc/Hexs) afforded 192.7 mg of clear oil. The product was further purified by flash chromatography on silica gel (20% EtOAc/pet. ether) and preparative TLC (30% EtOAc/Hexs) to give 149.9 mg (86.9% yield) of white solid. mp 91-92.5 °C; \( R_f \) 0.46 (30% EtOAc/Hexs), 0.49 (20% EtOAc/pet. ether); IR (CHCl₃) 3440, 3020, 2940, 1730, 1710, 1495 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃) \( \delta \) 7.24 (2 H, d, J = 8.4 Hz, aromatic Hs, ortho to Cl), 7.05 (2 H, d, J = 8.4 Hz, aromatic Hs, meta to Cl), 4.96 (1 H, br d, N-H), 4.50 (1 H, br m, ArCH₂CH), 4.16 (2 H, m, CO₂CH₂CH₂), 3.08 (1 H, dd, J = 14 and 5.9 Hz ArCHH), 2.98 (1 H, dd J = 14 and 6.5 Hz, ArCHH), 1.40 (9 H, s, OC(CH₃)₃), 0.93 (2 H, dd, J = 10 and 7 Hz, CH₂SiMe₃), 0.02 (9 H, s, Si(CH₃)₃); \(^1\)C NMR (75 MHz, CDCl₃) \( \delta \) 171.65, 154.93, 134.65, 132.79, 130.67, 128.53, 79.88, 63.82, 54.34, 37.75, 28.23, 17.30, -1.60.

(D)-(−)-N-(1,1-Dimethylethoxy)carbonyl-4-chlorophenylalanine 2-bromoethyl ester (3.38c)
To a stirred suspension of 244.2 mg (8.15 × 10⁻⁴ mol) of (D)-(−)-N-Boc-4-chlorophenylalanine in 0.8 mL of acetonitrile was added the minimum amount of DMF need to make a clear solution, followed by 69 μL (1.2 equiv) of 2-bromoethanol and 131.8 μL (2 equiv) of pyridine. This solution was cooled to 0 °C and 185.0 mg (8.97 × 10⁻⁴ mol, 1.1 equiv) of DCC was added. The mixture was stirred for 16 hrs at 0 °C. The reaction was quenched with 24.5 μL of 5M oxalic acid in DMF then allowed to come to room temperature. The mixture was filtered then solvent was evaporated. The residue was dissolved in CH₂Cl₂, washed with water, and dried over MgSO₄. Flash chromatography on silica gel (30% EtOAc/Hexs) afforded white solid which was further purified by recrystallization from hexanes to give 220.8 mg of white needles (66.6% yield after recrystallization). mp 70-71 °C; \( R_f \) 0.46 (30% EtOAc/Hexs); IR (CHCl₃) 3460, 2960, 2920, 1740, 1710, 1490, 1110 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.25 (2 H, d, J = 7 Hz, aromatic Hs, ortho to Cl), 7.07 (2 H, d J = 7 Hz, aromatic Hs, meta to Cl), 4.93 (1 H, br, N-H), 4.55 (1 H, br, CHNH), 4.39 (2 H, t, J = 6 Hz, OCH₂CH₂), 3.45 (2 H, t, J = 6 Hz, CH₂Br), 3.11 (1 H, dd J = 14 and 6 Hz, ArCHH), 3.00 (1 H, dd, J = 14 and 7 Hz, ArCHH); ¹³C NMR (75 MHz, CDCl₃) δ 171.21, 154.93, 134.32, 132.96, 130.63, 128.66, 80.11, 64.57, 54.19, 37.56, 28.21, 28.11; [α]D -20.5° (c 0.60, CH₂Cl₂). The racemic compound (3.38b) was also prepared following the same procedure as above in 92% yield. mp 64-65 °C.

(d,l)-N-(1,1-Dimethylethoxy)carbonyl-4-Chlorophenylalanine pentafluorophenyl ester (3.38d)
To a stirred solution of 106.4 mg (0.36 mmol) of (±)-N-Boc-4-chlorophenylalanine in 2 mL of THF was added 196 mg (116 mL, 3 equiv) of pentafluorophenol. The mixture was cooled to 0 °C, DCC (109.9 mg, 1.5 equiv) was added, then the mixture was stirred for 2 hr at 0 °C. The reaction was allowed to reach to room temperature then stirred overnight. The resulting reaction mixture was filtered and concentrated in vacuo, and the residue was diluted with CH₂Cl₂, washed with 1N K₂CO₃ (twice) and with brine, then dried over MgSO₄. Purification by flash chromatography on silica gel (50% EtOAc/Hexs) afforded 152.8 mg (92.4% yield) of white solid. mp 118.5-119 °C; Rf 0.57 (50% EtOAc/Hexs); IR (CHCl₃) 3430, 2980, 1770, 1710, 1520 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.30 (2 H, d, J = 8.5 Hz, aromatic Hs, ortho to Cl), 7.15 (2 H, d, J = 8.5 Hz, aromatic Hs, meta to Cl), 4.89 (1 H, br s, CH₂CH), 3.24 (2 H, br m, ArCH₂), 1.41 (9H, s, OC(CH₃)₃).

(D)-(+-)[N-(1,1-Dimethylethoxy)carbonyl]-4-chlorophenylalanylglycine 2-bromoethyl ester (3.38e)

To a stirred solution of 1.27 g (4.83 mmol) glycine 2-bromoethyl ester HBr salt in 5 mL DMF were added 674 μL (4.83 mmol) of Et₃N and a solution of 1.09 g (4.83 mmol) of the crude 2-azido acid (3.33) in 5 mL of DMF, followed by addition of 0.81
g (1.1 equiv) of HOBT. The mixture was cooled to 0 °C, 1.20 g (1.2 equiv) of DCC was added, then the mixture was stirred for 2 hr at 0 °C and for 17 hr at room temperature. DMF was removed in vacuo (0.05 mm Hg, 25 °C), the residue was taken up into 15 mL of ethyl acetate and the resulting solution was filtered. The filtrate was washed with water and NaHCO₃ solution, and dried over MgSO₄. Flash chromatography on silica gel (50% EtOAc-Hexs) afforded 2.00 g of oil. This crude product was added to a H₂-saturated suspension of 200 mg of 10% Pd-C in 20 mL of ethyl acetate then followed by addition of 1.27 g (1.2 equiv) of (Boc)₂O. H₂ was bubbled through the suspension for 1.5 hr at room temperature. The catalyst was filtered off, and solvent was removed in vacuo to give solid residue. The crude product was purified by recrystallization from EtOAc-Hexs to furnish 1.76 g (78.5% over two steps) of white needles. mp 121-2 °C; Rf 0.37 (50% EtOAc-Hexs); IR (CHCl₃) 3430, 2985, 1754, 1680, 1492 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.25 (2 H, d, J = 8.5 Hz, aromatic ring, ortho to Cl), 7.13 (2 H, d J = 8.5 Hz, aromatic ring, meta to Cl), 6.44 (1 H, br, CONH₂CH₂), 4.92 (1 H, br, NHBoc), 4.43 (2 H, t, J = 6 Hz, CO₂CH₂CH₂Br), 4.37 (1 H, m, chiral center), 4.02 (2 H, m, NHCH₂CO₂), 3.48 (2 H, t, J = 6 Hz, CH₂Br), 3.09 (1 H, dd, J = 14.5 and 7 Hz, ArCHH), 2.99 (1 H, dd, J = 14.5 and 8 Hz, ArCHH), 1.38 (9 H, s, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ 171.44, 168.93, 155.38, 134.98, 132.68, 130, 60, 128.59, 80.32, 64.45, 55.23, 41.00, 37.54, 28.11; [α]D +3.01° (c 1.03, CH₂Cl₂); Anal. calcd for C₁₈H₂₄BrClN₂O₅: C, 46.62; H, 5.22; N, 6.04. Found: C, 46.33; H, 5.24; N, 5.92.
3-Benzylxoylphenylacetic acid benzyl ester (3.40)

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{CHO} \\
&\text{Ph} \\
&\text{Ph}
\end{align*}
\]

3.40

A suspension of 2.05 g (13.48 mmol) of 3-hydroxyphenylacetic acid and 5.59 g (40.44 mmol, 3 equiv) of K₂CO₃ in 40 mL of acetone was refluxed for 30 min, followed by addition of 3.36 mL (4.83 g, 26.96 mmol, 2.1 equiv) of benzyl bromide through a dropping funnel to the hot solution. Reflux was continued until the reaction was completed (monitored by TLC, 20 hr was required). The reaction mixture was cooled to room temperature then filtered and the filter cake was washed well with acetone. Acetone was evaporated in vacuo then the crude product was purified by flash chromatography on silica gel (20% EtOAc-Hexs) to give 4.72 g (100%) of clear oil. \(R_f\) 0.41 (20% EtOAc-Hexs); IR (neat) 3030, 2918, 1732, 1584 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl₃) \(\delta\) 7.35–6.77 (14 H, m, Aromatic Hs), 5.04 (2 H, s, benzyl ether \(\text{CH}_2\)), 4.94 (2 H, s, benzyl ester \(\text{CH}_2\)), 3.55 (2 H, s, \(\text{ArCH}_2\text{CO}_2\text{Bn}\)); MS m/z 332.1411 ([M]+, \(\text{C}_{22}\text{H}_{20}\text{O}_3\) requires 332.1423); Anal. calcd for \(\text{C}_{22}\text{H}_{20}\text{O}_3\): C, 79.48; H, 6.07. Found: C, 79.68; H, 6.19.

3-Benzylxoylphenylacetic acid (3.41)

\[
\begin{align*}
&\text{O} \\
&\text{Bn} \\
&\text{OH} \\
&\text{C}
\end{align*}
\]

3.41
To a stirred solution of 4.55 g (13.68 mmol) of the benzyl ester (3.40) in 45 ml of THF, 15 ml of water and 10 ml of MeOH was added 3 ml of 30% aqueous KOH solution then the mixture was stirred for 1.5 hr at room temperature. All volatiles were removed in vacuo then the aqueous residue was washed with ethyl acetate then acidified with 10% HCl to pH = 3. The product was extracted with CH₂Cl₂ then dried over MgSO₄. Solvent was removed to give 2.91 g (87.7%) of off-white plates recrystallized from EtOAc-Hexs. mp 123-5 °C; IR (CHCl₃) 3012, 2917, 1712, 1598 cm⁻¹; ¹H NMR (200 MHz,CDCl₃) δ 7.42-7.18 (6 H, m, aromatic Hs), 6.89-6.84 (3 H, m, aromatic Hs), 5.02 (2 H, s, ArOCH₂Ph), 3.60 (2 H, s, CH₂CO₂H); MS m/z 242.0941 ([M]+, C₁₅H₁₄O₃ requires 242.0943); Anal. cald for C₁₅H₁₄O₃: C, 74.35; H, 5.83. Found: C, 74.10; H, 5.88.

(4R,5S,2R)-3-Benzyloxy-2-azido-2-oxo-2-(2-oxo-4-methyl-5-phenyl-3-oxazolidinyl)]ethylbenzene (3.43)

![Image of chemical structure](image)

To a stirred solution of 4.2 g (17.0 mmol) of 3-benzyloxyphenylacetic acid (3.41) in 70 ml of dry THF was added 2.8 ml of Et₃N, followed by the addition of 2.2 ml (1.05 equiv) of pivaloyl chloride at -78 °C. The mixture was stirred for 10 min at -78 °C and 30 min at 0 °C then cooled to -78 °C. To the resulting white slurry was added via cannula lithiated oxazolidinone (from 3.00 g, 1.0 equiv of oxazolidinone and 10.6 ml, 1.0 equiv of n-BuLi (1.6 M in Hexs) in 25 ml THF at -78 °C) then the mixture was stirred for 15 min at -78 °C. The reaction was allowed to reach to room
temperature (45 min) then quenched with 1 N NaHSO₄ (190 mL). THF was removed in vacuo then the residue was taken up into CH₂Cl₂, washed with brine, and dried over MgSO₄. The solution was filtered and purified by flash chromatography on silica gel (20% EtOAc-Hexs) to give 4.94 g (~73%) of clear oil. Due to difficulties in purification, the crude material was used for the next step. Rf 0.18 (20% EtOAc-Hexs); IR (neat) 3065, 2933, 1772, 1586 cm⁻¹; ¹H NMR (CDCl₃) δ 7.45−7.20 and 6.96−6.85 (14 H, m, aromatic Hs), 5.63 (1 H, d J = 7.3 Hz, oxazolidinone ring 5-H), 5.04 (2 H, s, PhCH₂Ar), 4.74 (1 H, quint, J = 6.8 Hz, oxazolidinone ring 4-H), 4.27 (2 H, AB system, J = 15.5 Hz, ArCH₂), 0.87 (3 H, d J = 6.6 Hz). To a stirred solution of 4.91 g (12.22 mmol, crude) of this compound (3.42) in 60 mL of THF at -78 °C was added 9.3 mL (1.05 equiv) of KHMDS (1.4 M in THF, Alfa products). The mixture was stirred for 15 min at -78 °C and a pre-cooled (-78°C) solution of 4.54 g (1.2 equiv) of trisyl azide in 10 mL of THF was added via cannula. After 2 min of stirring the reaction was quenched by rapid addition of 3.51 mL (5 equiv) of glacial acetic acid followed by immediate warming to 30 °C with a water bath. Then 3.27 g (2 equiv) of tetramethylammonium acetate was added in one portion and the mixture was stirred for 3 hr at room temperature. THF was removed in vacuo, then the residue was taken up into CH₂Cl₂, washed with brine and sat. NaHCO₃ solution, then dried over MgSO₄. The solution was filtered and CH₂Cl₂ was removed in vacuo. The residue (oil + solid) was triturated with hexanes. The crude product was further purified by flash chromatography on silica gel (20% EtOAc-Hexs) and recrystallization from EtOAc-Hexs to give 1.25 g of white needles. From the mother liquor of the trituration, an additional 1.44 g of product was obtained by the same purification method. Combined yield = 2.69 g (49.7%). mp 128-130 °C; Rf 0.22 (20% EtOAc-Hexs); IR (CHCl₃) 3012, 2936, 2100, 1784, 1708, 1599 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ
7.47–6.99 (14 H, m, aromatic Hs), 6.14 (s, 1 H, ArCHN₃), 5.49 (1 H, d, J = 7.2 Hz, oxazolidinone ring 5-H), 5.08 (2 H, s, PhCH₂Ar), 4.66 (1 H, quint, J = 6.8 Hz, oxazolidinone ring 4-H), 0.96 (3 H, d, J = 6.6 Hz, CH₃); [α]D -154.8° (c 0.52, CHCl₃); MS m/z 442.1655 ([M]+, C₂₅H₂₂N₄O₄ requires 442.1641); Anal. cald for C₂₅H₂₂N₄O₄: C, 67.85; H, 5.01, N, 12.67. Found: C, 67.99; H, 5.09; N, 12.69.

(D)-(−)-3-Benzyl oxy-(1-azido-2-methoxy-2-oxo)ethylbenzene (3.45)

4.53 g (10.25 mmol) of the starting azide (3.43) was dissolved in 100 mL of THF and diluted with 30 mL of water then the mixture was cooled to 0 °C. To this solution was added 859.9 mg (2 equiv) of LiOH in one portion. Stirring was continued for 30 min at 0 °C. THF was removed in vacuo. The aqueous residue was washed with EtOAc (twice) then acidified with 10% HCl to pH = 3. The product was extracted with CH₂Cl₂, and the organic layer was dried over MgSO₄. The solution was filtered and CH₂Cl₂ was evaporated. The residue was dissolved in 30 mL of MeOH, followed by addition of 1.95 g (1 equiv) of p-toluenesulfonic acid. The solution was refluxed overnight. MeOH was evaporated, then the crude product was purified by flash chromatography on silica gel (20% EtOAc-Hex) to give 2.52 g (83%) of white solid. mp 50.5-52 °C; Rf 0.30 (20% EtOAc-Hex); IR (CHCl₃) 3012, 2956, 2110, 1747, 1599 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.43–7.23 and 7.01–6.93 (9 H, m, aromatic Hs), 5.05 (2 H, s, PhCH₂), 4.92 (1 H, s, ArCHN₃), 3.74 (3 H, s, CO₂CH₃); [α]D -105.4° (c 0.57, CHCl₃); MS m/z 297.1100 ([M]+, C₁₆H₁₅N₃O₃

(D)-(−)-N-(N′-Benzylxycarbonyl)aminoacetyl-3-hydroxyphenylglycine methyl ester (3.47)

Hydrogen gas was bubbled through a solution of the azido ester (3.45, 1.49 g, 5.03 mmol) and 100 mg of 10% Pd-C in 20 mL MeOH at room temperature overnight. The catalyst was separated by centrifuging the mixture. MeOH was removed in vacuo to give 587.1 mg (crude, 64%) of grey powder (3.46). To a stirred solution of 122.3 mg (0.68 mmol) of the crude 3.46 in 4 mL of DMF were added 136.8 mg (1.5 equiv) of HOBT and 169.4 mg (1.2 equiv) of N-Cbz-glycine. The solution was cooled to 0 °C then followed by addition of 155.3 mg (1.2 equiv) of EDC. The mixture was stirred for 2 hr at 0 °C then the reaction was allowed to warm to room temperature, and stirring was continued for 16 hr. DMF was distilled off in vacuo (0.1 mm Hg, 25 °C), the residue (oil) was dissolved in 50 mL of CH_2Cl_2, washed with 1 N NaHSO_4, NaHCO_3 solution, and brine, then dried over MgSO_4. Flash chromatography on silica gel (60% EtOAc-Hexs) afforded 226.3 mg (92%) of clear oil. R_f 0.23 (60% EtOAc-Hexs); IR (CHCl_3) 3415, 3030, 3013, 2956, 1740, 1681, 1511 cm⁻¹; ¹H NMR (200 MHz, CDCl_3) δ 7.54 (1 H, br d, J = ~6 Hz, ArCHNH), 7.28 (5 H, br s, CH_2Ph), 7.15 (1 H, t, J = 8 Hz, aromatic 5-H), 6.79 (3 H, m, aromatic Hs), 5.64 (1 H, br t, J = 5.8 Hz, COCH_2NH), 5.43 (1 H, d J = 6.8 Hz, chiral center H), 5.00 (2 H, s,
CH$_2$Ph), 3.93 (2 H, m, COCH$_2$NH), 3.67 (3 H, s, CO$_2$Me); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 171.31, 169.58, 157.08, 156.99, 136.64, 135.87, 130.18, 128.46, 128.16, 128.01, 119.10, 116.18, 113.95, 67.29, 56.56, 52.88, 43.98; [α]$_D$ -91.3° (c 0.52, CHCl$_3$); MS m/z 372.1319 ([M]$^+$, C$_{19}$H$_{20}$NO$_6$ requires 372.1321).

(D)-3-Hydroxyphenylglycine ethyl ester (3.54)

![Chemical structure](image)

3.54

To a stirred solution of (D)-3-hydroxyphenylglycine (1.33g, 7.97 mmol) in 50 mL of absolute ethanol was added 3.03g (2 equiv) of p-toluene sulfonic acid hydrate then the mixture was refluxed for 16 hr. The reaction the mixture was cooled to room temperature, and the solvent was removed in vacuo. The white residue was triturated with 500 mL of ether, filtered then dried. The powder was dissolved in 60 mL of cold water then treated with 669.6 mg (1 equiv) of NaHCO$_3$ at 0 °C, and the product was extracted with ethyl acetate (3 × 100 mL). Recrystallization from ethanol gave 919.0 mg (59.1% yield) of pale yellow needles. mp 147-8 °C; IR (KBr) 3470, 3400, 3350, 3120, 3100, 2940, 1740 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) δ 7.18 (1 H, t, J = 8 Hz, aromatic ring 5-H), 6.89 (1 H, d, J = 8 Hz, aromatic ring 6-H), 6.82 (1 H, t, J = 2 Hz, aromatic ring 2-H), 6.72 (1 H, dd, J = 8 and 2 Hz, aromatic ring 4-H), 4.50 (1 H, s, ArCHNH), 4.13 (2 H, m, OCH$_2$CH$_3$), 1.18 (3 H, t, J = 7 Hz, CH$_3$); MS m/z 195.0901 ([M]$^+$, C$_{10}$H$_{13}$NO$_3$ requires 195.0895).

(D)-(-)-2-[N-(N'-Benzyloxy carbonyl)aminoacetyl]amino-2-(3-hydroxyphenyl)acetic acid ethyl ester (3.55)
To a stirred solution of the starting amino ester (900mg, 4.61 mmol) in 20 mL of CH$_2$Cl$_2$ were added 964.0 mg (4.61 mmol) of N-Cbz-glycine and 998.7 mg (4.84 mmol, 1.05 equiv) of DCC. The mixture was stirred for 16 hr at room temperature, the white precipitate was filtered off and the filter cake was washed with CH$_2$Cl$_2$. The filtrate was evaporated in vacuo. Flash chromatography of the residue on silica gel (80% EtOAc/Hex) afforded 1.60 g (89.8% yield) of white foam which melted at 42-44 °C; $R_f$ 0.35 (80% EtOAc/Hex); IR (CHCl$_3$) 3580, 3400, 3330, 3000, 1750, 1670 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.53 (1 H, br d, $J = \sim$7 Hz, ArCHNH), 7.38 (1 H, br s, O-H), 7.25 (5 H, s, OCH$_2$Ph), 7.11 (1 H, t, $J = 8.5$ Hz, aromatic ring 5-H), 6.75 (3 H, m, aromatic Hs), 5.65 (1 H, t, $J = 5.8$ Hz, NHCBz), 5.39 (1 H, d, $J = 7.1$ Hz, ArCHNH), 4.97 (2 H, s, CH$_2$Ph), 4.11 (2 H, m, OCH$_2$CH$_3$), 3.90 (2 H, m, COCH$_2$NHCBz), 1.14 (3 H, t, $J = 7$ Hz, OCH$_2$CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.28, 170.09, 157.49, 137.26, 136.35, 130.48, 128.85, 128.52, 128.37, 119.35, 116.44, 114.45, 67.63, 62.52, 57.07, 44.40, 14.23; [$\alpha$]$_D$ -75.8° (c 0.79, CH$_2$Cl$_2$); MS m/z 386.1484 ([M]$^+$, C$_{20}$H$_{22}$N$_2$O$_6$ requires 386.1478).

$\eta^6$-{(D)-4-Chloro-1-[2-[N-(1,1-dimethyloxy)carbonyl]amino-3-hydroxy-3-oxo]propyl}benzene-$\eta^5$-cyclopentadienylruthenium hexafluorophosphate (3.62b)
To a heated (60 °C) and stirred solution of 100.0 mg (0.33 mmol) N-Boc-4-chlorophenylalalnine (3.36) in 1.2-dichloroethane was added 144.9 mg (0.33 mmol) of (CH₃CN)₃Ru⁺Cp in one portion. The mixture refluxed for 45 min, during which time the color changed from dark brown to brown-yellow. The reaction mixture was cooled to room temperature and solvent was removed \textit{in vacuo}. The residue was dissolved in 0.5 mL of CH₂Cl₂ then added to 30 mL of ether to precipitate 180.3 mg (88.4%) of product, obtained as brown powder. IR (CH₂Cl₂) 3599, 3420, 3084, 2933, 1709, 843 cm⁻¹;¹H NMR (200 MHz, CD₃CN) δ 6.53 (2 H, d J = 6 Hz, aromatic ring, ortho to Cl), 6.26 (1 H, d J = 6 Hz, aromatic ring, meta to Cl), 6.15 (1 H, d J = 6 Hz, aromatic ring, meta to Cl), 5.70 (1 H, br, N-H), 5.43 (5 H, s, Cp), 4.30 (1 H, br, chiral center), 3.05 (1 H, dd, J = 14 and 4.6 Hz, ArCHH), 2.74 (1 H, dd, J = 14 and 9.7 Hz, ArCHH), 1.37 (9 H, s, C(CH₃)₃). Due to the inherent instability and difficulties in purification, other analyses were not satisfactory.

\( \eta^6-\{(D)-4\text{-Chloro-1-[2-[N-(1,1\text{-dimethylethoxycarbonyl})]amino-3-oxo-3\text{-methoxy}propylbenzene]-\eta^5\text{-cyclopentadienyl}\text{ruthenium}} \)

hexafluorophosphate (3.62c)
144.5 mg (0.461 mmol) of the starting amino ester (3.35) was dissolved in 10 mL of N₂-purged 1,2-dichloroethane, followed by addition of 200 mg (0.461 mmol) of (CH₃CN)₃RuCpPF₆ at room temperature. The color immediately changed from yellow to dark brown. The mixture was heated to reflux for 5 hrs under N₂ (monitored by NMR). The reaction mixture was filtered through celite (CH₂Cl₂), concentrated to ~2 mL, and the solution was added to 100 mL of ether to remove unreacted ester. The ether insoluble dark brown residue was dissolved in CH₂CN and filtered through a neutral alumina column (CH₂CN) to afford 192.8 mg (88.8% yield, 99.9% based on the recovered pure starting material) of brown foam. From ether layer, 35.5 mg of unreacted ester was recovered. IR (CHCl₃) 3420, 3100, 3040, 2980, 1740, 1705, 845 cm⁻¹;¹H NMR (200 MHz, CDCl₃) δ 6.46–6.1 (4 H, m, aromatic Hs), 5.45 (5 H, s, Cp), 4.42 (1 H, m, CH₂CHNH), 3.80 (3 H, s, CO₂CH₃), 3.07 (1 H, dd, J = 14 and 5 Hz, ArCHH), 2.82 (1 H, dd J = 14 and 7.7 Hz, ArCHH), 1.37 (9 H, s, C(CH₃)₃);¹³C NMR (75 MHz, CDCl₃) δ 170.71, 155.14, 104.97, 100.91, 86.94, 86.74, 82.89, 80.35, 54.13, 52.81, 36.64, 28.02; MS m/z 625.0133 ([M]+, C₂₀H₂₅ClF₆NO₄PRu requires 625.0151).

η⁶-{4-chloro-1-[(D)-2-[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-bromo)ethoxy]ethylbenzene}·η⁵-cyclopentadienylruthenium hexafluoro-phosphate (3.62d)
To a stirred, heated (75 °C) solution of 100 mg (2.46 × 10⁻⁴ mol) of N-Boc-4-chlorophenylalanine 2-bromoethyl ester (3.38a) in 8 mL of N₂-purged 1,2-dichloroethane was added 160.2 mg (1.5 equiv, 3.69 × 10⁻⁴ mol) of (CH₃CN)₃CpRu⁺ complex as a solid in one portion. The mixture was refluxed for 5 hrs under N₂ cooled to room temperature and insolubles were filtered off on a celite pad. The filtrate was evaporated *in vacuo*, and the black residue dissolved in CH₃CN was eluted through a neutral alumina column (CH₃CN). The acetonitrile solution was concentrated to ~2 mL then added to 50 mL of ether to remove the organic starting material. The ether insoluble precipitate was further washed with ether. The residue was dissolved in 3 mL of chloroform then the precipitate was removed by filtering through a celite column (0.5 × 2 cm). The chloroform solution was evaporated *in vacuo* to afford 167.0 mg of dark brown solid residue (94.6% yield). IR (CHCl₃) 3427, 3088, 2933, 1746, 1707, 1454, 1214, 846 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 6.44–6.26 (4 H, m, aromatic Hs), 5.45 (5 H, s, Cp), 4.49 (2 H, t, J = 6 Hz, OCH₂CH₂Br overlapping with 1 H, br, CHNH), 3.58 (2 H, t, J = 6 Hz, CH₂Br), 3.11 (1 H, dd, J = 14.2 and 5 Hz, ArCHH), 2.85 (1 H, 1′.2 and 8 Hz, ArCHH), 1.38 (9 H, s, OC(CH₃)₃).

48.0 mg of NaH (50% in oil) was stirred with 206.3 mg (1.0 mmol, 1 equiv) of 2,6-di-t-butylphenol in 20 mL dry THF. After H₂ evolution ceased (30 min), the resulting yellow solution was cooled to 0 °C then 372.4 mg (1.0 mmol) of 3.47 was added. The resulting solution was stirred for 5 min at 0 °C then transferred via cannula to a pre-cooled (-78 °C) solution of 719.7 mg (1.0 mmol) 3.62d in 25 mL of dry THF. The mixture was stirred for 15 min at -78 °C and 1 hr at room temperature. The reaction mixture was filtered through a celite pad (CH₂Cl₂), concentrated to ~5 mL then added to 150 mL of ether. The precipitate was filtered, washed well with ether, then dried to give 1.00 g (5.3%) of dark brown powder. Rf 0.58 (5% MeOH-1,2-dichloroethane, aluminum oxide plate); IR (CHCl₃) 3436, 3030, 2950, 1741, 1506 850 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.47 (1 H, t, J = 8 Hz, uncomplexed aromatic ring 5-H), 7.34 (5 H, br s, CH₂Ph), 7.12 and 7.01 (3 H, m, uncomplexed aromatic 2-, 4-, and 6-H), 6.06 (4 H, m, complexed aromatic Hs), 5.35 (5 H, s, Cp), 5.12 (2 H, s, CH₂Ph), 4.49 (2 H, t, J = 6 Hz, CO₂CH₂CH₂Br), 4.48 (1 H, m, phenylalanine chiral center), 3.95 (2 H, m, NHCOCH₂NH), 3.77 (3 H, s, CO₂Me), 3.58 (2 H, t, J = 6 Hz, CH₂Br), 2.94 (2 H, m, Ar CH₂CHNHBoc), 1.41 (9 H, s, C(CH₃)₃).
The title complex was prepared following the same procedure as 3.63a. Yield = 80-87%. IR (CHCl₃) 3425, 3034, 2984, 1749, 1718, 1685, 1497, 847 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.48 (1 H, t, J = 8 Hz, uncomplexed aromatic 5-H), 7.31 (5 H, s, CH₂Ph), 7.06-6.99 (4 H, m, uncomplexed aromatic Hs), 6.19 (1 H, d, J = 5.2 Hz, phenylglycine chiral center), 6.01-5.88 (4 H, m, complexed aromatic Hs), 5.58 (1 H, br, NH), 5.32 (5 H, s, Cp), 5.08 (2 H, m, CH₂Ph), 4.50 (1 H, br, phenylalanine chiral center), 4.41 (2 H, t, J = 6.2 Hz, CO₂CH₂CH₂Br), 4.05 (2 H, m, CONHCH₂CO), 3.76 (3 H, s, CO₂Me), 3.49 (2 H, t, J = 6.2 Hz, CH₂Br), 2.95 (2 H, m, ArCH₂CHNHBoc), 1.38 (9 H, s, C(CH₃)₃).

The title complex was prepared following the same procedure as 3.63a. Yield = 80-87%. IR (CHCl₃) 3425, 3034, 2984, 1749, 1718, 1685, 1497, 847 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.48 (1 H, t, J = 8 Hz, uncomplexed aromatic 5-H), 7.31 (5 H, s, CH₂Ph), 7.06-6.99 (4 H, m, uncomplexed aromatic Hs), 6.19 (1 H, d, J = 5.2 Hz, phenylglycine chiral center), 6.01-5.88 (4 H, m, complexed aromatic Hs), 5.58 (1 H, br, NH), 5.32 (5 H, s, Cp), 5.08 (2 H, m, CH₂Ph), 4.50 (1 H, br, phenylalanine chiral center), 4.41 (2 H, t, J = 6.2 Hz, CO₂CH₂CH₂Br), 4.05 (2 H, m, CONHCH₂CO), 3.76 (3 H, s, CO₂Me), 3.49 (2 H, t, J = 6.2 Hz, CH₂Br), 2.95 (2 H, m, ArCH₂CHNHBoc), 1.38 (9 H, s, C(CH₃)₃).
The title complex was prepared following the general procedure. Yield = 84%.

IR (CHCl₃) 3425, 3034, 2956, 1717, 1642, 1528, 847 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.85 (1 H, t, J = 8 Hz, uncomplexed aromatic 5-H), 7.32 (5 H, br s, CH₂Ph), 7.06-6.99 (3 H, m, uncomplexed aromatic Hs), 6.12 (1 H, br, NH), 6.03-5.94 (4 H, m, complexed aromatic Hs), 5.34 (5 H, s, Cp), 5.08 (2 H, m, CH₂Ph), 4.49 (2 H, t, J = 6 Hz, CO₂CH₂CH₂Br), 4.42 (1 H, m, phenylalanine chiral center), 3.77 (3 H, s, CO₂Me), 3.58 (2 H, t, J = 6 Hz, CH₂Br), 3.08 (1 H, dd J = 14 and 5 Hz, ArCHH), 2.88 (1 H, dd J = 14 and 8 Hz, ArCHH), 1.40 (9 H, s, C(CH₃)₃).

η⁶-[1-(R)-[3-[1-[N-(N¹-Benzoyloxycarbonyl)aminoacetyl]amino-2-oxo-2-ethoxy]ethyl]phenoxy-4-[(R)-2-[N-(1,1-dimethylethoxy)carbonyl]-amino-3-oxo-3-methoxy]propylbenzene]-η⁵-cyclopentadienylruthenium hexafluorophosphate (3.63d)
17.3 mg (8.4 × 10⁻⁵ mol, 1.05 equiv) of 2,6-di-t-butylphenol was stirred with 4.2 mg (8.8 × 10⁻⁵ mol, 1.1 equiv) of NaH (50% in oil) in dry THF at room temperature for 15 min (yellow). The resulting solution was cooled to 0 °C, the 3-hydroxyphenylglycine derivative 3.55 (32.5 mg, 1.05 equiv) in 1 mL THF was added, then the mixture was stirred for 5 min at 0 °C. The mixture was transferred via canula to a pre-cooled (-78 °C), stirred solution of (Arene)CpRu⁺ complex 3.62c (50 mg, 8.0 × 10⁻⁵ mol) in 3 mL dry THF. Stirring was continued for an additional 15 min at -78 °C then the reaction was allowed to come to room temperature. After 4.5 hr at room temperature, solvent was removed in vacuo, the residue was dissolved in CH₃CN and then filtered through a neutral alumina column (3 × 0.5 cm, CH₂CN). The filtrate was concentrated to ~1 mL, and this solution was slowly added to 50 mL of ether to remove all organic materials. The dark brown precipitate was collected, and dissolved in CHCl₃ and filtered through celite. Evaporation of solvent afforded 77.8 mg (99.8% yield) of brown foam. IR (CHCl₃) 3400, 3100, 2950, 1730, 1700, 1500, 850 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.4 (1 H, t, J = 8 Hz, uncomplexed aromatic ring, 5-H), 7.31 (5 H, br s, CH₂Ph), 7.10 (1 H, br m, uncomplexed aromatic ring, 6-H), 6.94 (2 H, m, uncomplexed aromatic ring, 2- and 4-H), 6.15–5.89 (4 H, m, complexed aromatic Hs), 5.54 (1 H, br, CHNHC(OCH₂), 5.39 (1 H, overlaps with Cp, ArCHNH), 5.33 (5 H, s, Cp), 5.10 (2 H, s, CH₂Ph), 4.37 (1 H, br m, MeCO₂CHNH), 4.22 (2 H, m, CO₂CH₂CH₃), 3.91 (2 H, br m, COCH₂NH), 3.79 (3 H, s, CO₂CH₃), 2.97 (1 H, dd, J = 14 and 4 Hz, ArCHH), 2.75 (1 H, dd, J = 14 and 7 Hz, ArCHH), 1.39 (9 H, s, OC(CH₃)₂), 1.23 (3 H, t, J = 7 Hz, CO₂CH₂CH₃).
\( \eta^6\{1-(R)\}[3-[1-N-(N'-Benzyloxy carbonyl) aminoacetyl]-amino-2-oxo-2-ethoxy]ethyl]\)phenoxy-4-(R)-[2-[N-(1,1-dimethylethoxy)carbonyl]-amino-3-oxo-3-(2-bromoethoxy)propyl benzene]-\( \eta^5\) cyclopentadienyl-ruthenium hexafluorophosphate (3.63e)

227.7 mg (1.103 mmol, 1.05 equiv) of 2,6-di-t-butylphenol was stirred with 55.5 mg (1.1 equiv) of NaH (50% in oil) in 25 mL of dry THF at 0 °C. 426.5 mg (1.10 mmol, 1.05 equiv) of 3-hydroxyphenylglycine derivative (3.55) was added to above solution in one portion then stirred for 5 min at 0 °C. The resulting solution was cooled to -20 °C then transferred to a pre-cooled (-20 °C), stirred solution of 754.6 mg phenylalanine Ru^+Cp complex (3.62d) in 50 mL of dry THF via teflon cannula. The mixture was stirred for an additional 2 hrs at -20 °C then the reaction was allowed to come to room temperature. The precipitate was filtered off (celite), and the filtrate was evaporated in vacuo. The dark residue was dissolved in CH₃CN, eluted through a neutral alumina column (CH₃CN), and concentrated to ~3 mL. This solution was added dropwise to ~50 mL of ether to remove the organic starting material and the phenol. The precipitate was collected, washed with ether, and dried. The crude product was dissolved in 10 mL of CHCl₃ then insoluble material was filtered off (celite) to give 717.5 mg (64% yield); IR (CHCl₃) 3412, 3019, 2893, 1737, 1710, 1502, 1210, 847 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.38 (1 H, t, J = 8 Hz,
uncomplexed aromatic 5-H), 7.29 (5 H, br s, CH$_2$Ph), 7.01–6.90 (3 H, m, uncomplexed aromatic Hs), 6.08–5.91 (4 H, m, complexed aromatic Hs), 5.55–5.42 (3 H, m, difficult to assign due to overlapping), 5.31 (5 H, s, Cp), 5.09 (2 H, s, CH$_2$Ph), 4.45 (overlap of OCH$_2$CH$_2$Br (2 H, t, J = 6 Hz) and tyrosine chiral center), 4.28 (2 H, m, OCH$_2$CH$_3$), 3.91 (2 H, d, J = 5.7 Hz, COCH$_2$NHCbz), 3.54 (2 H, t, J = 6 Hz, CH$_2$Br), 3.05–2.74 (2 H, two dd, difficult to assign J due to broad lines), 1.38 (9 H, s, OC(CH$_3$)$_3$), 1.21 (3 H, t, J = 7 Hz, CO$_2$CH$_2$CH$_3$).

{(R)-2-[N-(N’-benzyloxy carbonyl) amino acetyl] amino-2-(3-oxyphenyl)-1-oxo-1-methoxyethyl]-O-(R)-N-[(dim ethylethoxy) carbonyl] tyrosine 2-bromoethyl ester (3.64a)

161.4 mg (1.53 10-4 mol) of the starting complex (3.63a) was dissolved in 16 mL of N$_2$-purged CH$_3$CN, then the solution was irradiated with uv light (sunlamp, 275 W) for 16 hr at room temperature. The resulting mixture was concentrated to ~5 mL then added dropwise to 50 mL of ether. The ether insoluble precipitate was collected, and washed well with ether. The filtrate was concentrated in vacuo, and the yellow residue was purified by flash chromatography on silica gel (50% EtOAc-Hexs) to give 74.0 mg (65.1%) of pale yellow oil. $R_f$ 0.21 (50% EtOAc-Hexs); IR (CHCl$_3$) 3436, 3030, 2955, 1741, 1711, 1506 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.34 (5 H, br s, CH$_2$Ph), 7.0 (8 H, m, aromatic Hs), 5.38 (1 H, d, J = 7.3 Hz, phenylglycine chiral
center), 5.5 (1 H, br, CH$_2$NHCO$_2$), 5.13 (2 H, s, CH$_2$Ph), 5.03 (1 H, br NHBoc), 4.59 (1 H, br m, phenylalanine chiral center), 4.42 (2 H, t, J = 6 Hz, CO$_2$CH$_2$CH$_2$Br), 3.93 (2 H, d J = 5.5 Hz, NHCOCH$_2$NH), 3.74 (3 H, s, CO$_2$Me), 3.48 (2 H, t, J = 6 Hz, CH$_2$Br), 3.12 (1 H, dd, J = 14 and 5.5 Hz, ArCHH), 3.08 (1 H, dd, J = 14 and 6 Hz, ArCHH), 1.42 (9 H, s, C(CH$_3$)$_3$). The optical rotation was not taken because of minor impurities found in both $^1$H and $^{13}$C NMR spectra, which were not removed by usual purification methods. Also attempted MS analysis did not give the molecular ion peak.

[(D)-2-N-(Benzyloxy carbonyl) amino]-2-(3-oxyphenyl)-1-oxo-1-methoxyethyl]-O-[(D)-N-[(1,1-dimethylethoxy) carbonyl]tyrosyl-glycine 2-bromoethyl ester (3.64b)

![Image of the molecular structure](image)

400 mg (3.8 × 10^{-4} mol) of starting Ru complex (3.63b) was irradiated with a sunlamp (275 W) in 35 mL of CH$_3$CN for 24 hrs at room temperature. The reaction was monitored by NMR. The reaction mixture was concentrated to ~1 mL and the resulting residue was introduced into ~75 mL of ether. Ether insoluble precipitate was filtered off. The filtrate and washings were combined, solvent was removed, and product was purified by flash chromatography on silica gel (EtOAc:Hexs = 8 : 2) to give 36.6 mg (57% yield) of white foam. $R_f$ 0.42 (EtOAc : Hexs = 8 : 2); IR (CHCl$_3$)
3430.3, 3028, 2956.4, 1746, 1718.8, 1684.6, 1505.6, 1247.8 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 7.32 (5 H, s, CO\(_2\)CH\(_2\)Ph), 7.3–6.9 (8 H, m, Ar-H), 6.38 (1 H, m, NHCbz), 5.83 (1 H, m, CONHCH\(_2\)CO\(_2\)), 5.32 (1 H, d, J = 7.7 Hz, CHNHCbz), 5.08 (2 H, dd, J = 12 and 14 Hz, NHCO\(_2\)CH\(_2\)Ph), 4.98 (1 H, br, NHBoc), 4.42 (2 H, t, J = 6 Hz, CH\(_2\)CH\(_2\)Br), 4.38 (1 H, m, (Ar)CH\(_2\)CH (NHBoc)), 4.02 (2 H, m, CONHCH\(_2\)CO\(_2\)), 3.71 (3 H, s, CO\(_2\)Me), 3.47 (2 H, t, J = 6 Hz, CH\(_2\)Br), 3.05 (2 H, d, J = 6.8 Hz, (Ar)CH\(_2\)CH(NHBoc)), 1.40 (9 H, s, NHBoc); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.88, 170.98, 169.13, 157.66, 155.33, 138.31, 135.96, 131.96, 130.66, 130.07, 128.41, 128.03, 127.58, 121.62, 119.11, 118.92, 118.14, 117.32, 80.05, 67.03, 64.42, 57.55, 55.44, 52.81, 40.99, 37.68, 28.16; [\(\alpha\)]\(_D\) +4.6° (c = 0.8, EtOAc).

(D)-(D)-N-(1,1-Dimethylethoxy)carbonyl]-4-[[3-[1-[N-(N'-benzylloxycarbonyl)aminoacetyl]amino-2-oxo-2-ethoxy]ethyl]phenoxyphenylalanine methyl ester (3.64c)

![](image)

189 mg (1.94 \(\times\) 10\(^{-4}\) mol) of (arene)CpRu\(^+\) complex (3.63d) was dissolved in 19 mL of CH\(_3\)CN then N\(_2\) was bubbled for 10 min through the solution. The solution was irradiated with a sunlamp (uv, 275 W) under N\(_2\) for 16 hr. The resulting dark brown solution was concentrated \textit{in vacuo} to 1 mL then added to 50 mL of ether to isolate the demetallated organic product from the mixture. Preparative TLC on silica gel
(80% EtOAc/Hexs) gave 125.7 mg of thick, clear, pale yellow oil (97% yield) along with 10.9 mg of deep yellow by product (not characterized). From ether insoluble residue, 89.3 mg (85%) of crude \((\text{CH}_3\text{CN})_3\text{CpRuPF}_6\) was isolated. \(R_f 0.55\) (5\% MeOH/1,2-dichloroethane, alumina); IR (CHCl_3) 3430, 3000, 1730, 1710, 1500 cm\(^{-1}\); \(^1\text{H}\) NMR (200 MHz, CDCl_3) \(\delta\) 7.30 (5 H, br s, CH_2Ph), 7.06–6.85 (8 H, m, aromatic Hs), 5.48 (1 H, d, J = 7 Hz, phenylglycine chiral center), 5.40 (1 H, br, COCH_2NH), 5.09 (2 H, s, CH_2Ph), 5.00 (1 H, br d, NHBoc), 4.86 (1 H, br, tyrosine chiral center H), 4.15 (2 H, m, CO_2CH_2CH_3), 3.89 (2 H, d, J = 5.8 Hz, COCH_2NH), 3.69 (3 H, s, CO_2CH_3), 3.03 (2 H, m, ArCH_2CH), 1.38 (9 H, s, OC(CH_3)_3), 1.18 (3 H, t, J = 7.2 Hz); [\(\alpha\)]\text{D} -16º (c 0.47, CH_2Cl_2).

(D)-N-(1,1-Dimethylethoxy)carbonyl]-4-(D)-[3-[N-(N'-benzyl-oxycarbonyl)aminoacetyl]amino-2-oxo-2-ethoxy]ethyl]phenoxyphenyl-alanine 2-bromoethyl ester (3.64d)

717.5 mg \((6.72 \times 10^{-4} \text{ mol})\) of \((\text{Ar})\text{CpRu}^+\) complex (3.63e) in 15 mL of N_2-purged CH_3CN was irradiated for 24 hr at room temperature. The reaction was monitored by the NMR spectroscopy. The resulting mixture was concentrated to ~5 mL, then added dropwise to 100 mL of ether. The yellow precipitate was filtered and washed well with ether, then dried to give 257.1 mg (88.1\%) of \((\text{CH}_3\text{CN})_3\text{Ru}^+\text{Cp}\). The filtrate and washings were concentrated in vacuo, and the residue was purified by
flash chromatography on silica gel (50% EtOAc-Hexs) to give 369.2 mg (72.6%) of clear oil. \( R_f \) 0.61 (80% EtOAc-Hexs); 0.13 (50% EtOAc-Hexs); IR (CHCl₃) 3435, 3032, 2984, 1736, 1711, 1505 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃) \( \delta \) 7.30 (5 H, br s, CH₂Ph), 7.11–6.86 (8 H, m, aromatic Hs), 5.84 (1 H, d, \( J = 7.2 \) Hz, phenylglycine chiral center), 5.40 (1 H, br, NH), 5.09 (2 H, s, CH₂Ph), 5.00 (1 H, br, NHBoc), 4.60 (1 H, br m, phenylalanine chiral center), 4.35 (2 H, t, \( J = 6 \) Hz, CO₂CH₂CH₂Br), 4.15 (2 H, m, CO₂CH₂CH₃), 3.89 (2 H, d, \( J = \) NHCOCH₂CO₂), 3.44 (2 H, t, \( J = 6 \) Hz, CH₂Br), 3.10 (1 H, dd, \( J = 14 \) and 5.5 Hz, ArCHH), 2.97 (1 H, dd, \( J = 14 \) and 7 Hz, ArCHH), 1.39 (9 H, s, C(CH₃)₃), 1.18 (2 H, t, \( J = 7 \) Hz, CO₂CH₂CH₃). The optical rotation was not taken because of minor impurities found in both \(^1\)H and \(^13\)C NMR spectra, which were not removed by usual purification methods. Also attempted MS analysis did not give the molecular ion peak.

(D)-N-[(1,1-Dimethylethoxy)carbonyl]-O-[(D)-2-[N-N'-benzyl oxy-carbonyl]aminoacetyl]amino-2-(3-oxophenyl)-1-oxo-1-ethoxyethyl]-tyrosine (3.65)

![Chemical Structure Image]

To a stirred solution of 97.8 mg (0.13 mmol) of the starting ester (3.64d) in 8 mL of THF and 7 mL of water were added 84.5 mg (1.29 mmol, 10 equiv) of zinc dust and 96.9 mg (0.65 mmol, 5 equiv) of NaI. The mixture was refluxed overnight, the white precipitate was filtered, and the filter cake was washed with well with THF. The
filtrate was concentrated *in vacuo,* and the residue was taken up into CH$_2$Cl$_2$, then
dried over MgSO$_4$. The solution was filtered, evaporated, and the residue was purified
by flash chromatography on silica gel (10% MeOH-CHCl$_3$) to give 63.3 mg (75.4%,
crude) of oil. *R*$_f$ 0.23 (10% MeOH-CHCl$_3$); IR (CHCl$_3$) 3425, 3343, 2912, 1737,
1727, 1710, 1691, 1502 cm$^{-1}$; $^1$H NMR (200 MHz, CD$_3$CN) $\delta$ 7.36 (5 H, s, CH$_2$Ph),
7.3-6.9 (8 H, m, aromatic Hs), 6.02 (1 H, br, NHCOCH$_2$NH), 5.50 (1 H, br,
NHCOCH$_2$NH), 5.44 (1 H, d $J = 7.2$ Hz, phenylglycine chiral center), 5.09 (2 H, s,
CH$_2$Ph), 5.09 (1 H, br, NH Boc, overlapping with CH$_2$Ph), 4.35 (1 H, br,
phenylalanine chiral center), 4.16 (2 H, m, CO$_2$CH$_2$CH$_3$), 3.79 (2 H, d, $J = 6$ Hz,
NHCOCH$_2$NH), 3.16 (1 H, dd, $J = 14$ and 4 Hz, ArCHH), 2.94 (1 H, dd, $J = 14$ and
6 Hz, ArCHH), 1.37 (9 H, s, C(CH$_3$)$_3$), 1.17 (3 H, t, $J = 7$ Hz, CO$_2$CH$_2$CH$_3$). The
optical rotation was not taken because of minor impurities found in both $^1$H and $^{13}$C
NMR spectra, which were not removed by usual purification methods. Also attempted
MS analysis did not give the molecular ion peak.

(D)-N-[(1,1-Dimethylethoxy)carbonyl]-O-[(D)-2-[N-(2-aminoacetyl)]-
amino-2-(3-oxyphenyl)-1-oxo-1-ethoxyethyl]-tyrosine (3.66)

![Chemical Structure](image)

To a stirred solution of 116.8 mg (0.18 mmol) of 3.65 in 2 mL absolute
alcohol were added 170.1 $\mu$L (1.8 mmol, 10 equiv) of 1,3-cyclohexadiene and 100 mg
of 10% Pd-C. The mixture was refluxed overnight. The removal of the catalyst and
solvent gave 68.5 mg of yellow powder. Attempted purification by ether trituration resulted in deterioration of the compound. $^1$H NMR spectrum of the crude sample showed clear disappearance of the Cbz peak. $R_f$ 0.09 (10% MeOH-CHCl₃); 1H NMR (DMSO-d₆) δ 8.63 (1 H, br, NH), 8.17 (1 H, br, NH), 7.4–6.7 (8 H, m, aromatic Hs), 5.46 (1 H, br s, phenylglycine chiral center), 4.95 (1 H, br s, phenylalanine chiral center), 4.1–3.8 (4 H, m, NHCOCH₂NH₂ and CO₂CH₂CH₃), 1.3 (9 H, s, C(CH₃)₃), 1.2 (3 H, overlapping with impurities, CO₂CH₂CH₃).

**Attempted cyclization of 3.66**

**The DPPA method**

To a cooled (0–5 °C), stirred solution of 12.3 mg ($2.39 \times 10^{-5}$ mol) in 3 mL freshly distilled DMF were added 3.0 mg ($3.89 \times 10^{-5}$ mol, 1.5 equiv) of NaHCO₃ and 7.7 μL ($3.89 \times 10^{-5}$ mol, 1.5 equiv) of DPPA. The mixture was stirred for 3 days in a cold room. The TLC analysis showed all starting material was consumed, and the major band was separated by preparative TLC (20% MeOH-CHCl₃) to give 0.8 mg of white powder. Both FD and FAB MS show a probable MH⁺ or MNa⁺ at m/z 1018 (expected MS is 515.2267).

**The DCC method**

To a stirred solution of 10 mg ($1.94 \times 10^{-5}$ mol) 3.66 in 3 mL of DMF were added 2.6 mg ($1.94 \times 10^{-5}$ mol mol, 1 equiv) of CuCl₂ and 1.6 mg ($1.94 \times 10^{-5}$ mol) of NaHCO₃ at 0 °C, and followed by addition of 6.0 mg of ($3.88 \times 10^{-5}$ mol, 2 equiv) DCC, then the mixture was stirred for 2 hr at 0 °C and overnight at room temperature. The TLC analysis showed three major spots at $R_f$ ~0.08 (0.7 mg, Band C) 0.10 (0.4 mg, band B) and 0.45 (0.9 mg, band A). Band A: Both FAB and FD MS showed a
probable \( MH^+ \) at \( m/z \) 856 and \( MNa^+ \) 878. This separation of two ions by 22 amu almost always indicates a \( MH^+/MNa^+ \) combination. Band B: FAB shows a probable \( MH^+ \) 676 and \( MNa^+ \) 698. FD is less clear. Band C: FAB showed the same ions as above (\( MH^+ \) 676 and \( MNa^+ \) 698).

**The Morpho CDI method**

To a stirred solution of 5 mg \( (9.7 \times 10^{-6} \text{ mol}) \) in 1.5 mL of DMF was added 4.1 mg \( (9.7 \times 10^{-6} \text{ mol}) \) of morpho CDI at room temperature, then the mixture was stirred for 2 days at room temperature. Solvent was removed *in vacuo*, and the product was separated by preparative TLC (20% MeOH-CHCl\(_3\)) to give two major bands at \( R_f \) 0.6 (band B, 1.0 mg) and 0.7 band A, 1.3 mg). Band A: FAB showed a probable \( MH^+ \) 498 and \( MNa^+ \) 520. FD was less clear. Characterization was not attempted for Band B because it was more overlapped with other bands.

\[
[(\text{D})-2-[(\text{N}-(\text{N'}-\text{Benzylloxycarbonyl})\text{aminoacetyl})\text{amino}-2-(3-\text{oxyphenyl})-1-\text{oxo}-1-\text{methoxyethyl}]-\text{O-}[(\text{D})-\text{N-}[(1,1-\text{dimethylethoxy})\text{carbonyl}]]-\text{tyrosine 2-hydroxyethyl ester (3.67a)}
\]

![Image of chemical structure](image)

To a stirred solution of 351.1 mg \( (4.73 \times 10^{-4} \text{ mol}) \) of the starting bromoethyl ester (3.64a) in 15 mL of DMF (freshly distilled) were added 37.1 mg (1.2 equiv, \( 5.68 \times 10^{-4} \text{ mol} \)) of Zn dust and 97 mg (1.5 eqv., \( 7.10 \times 10^{-4} \text{ mol} \)) of \( \text{ZnCl}_2 \) at room
temperature, then the mixture was warmed to 80-90 °C for 24 hrs. DMF was removed by vacuum distillation and the product was isolated by flash chromatography on silica gel (8 : 2 EtOAc-Hexs) to give 266.2 mg (82.8% yield) of white foam: Rf 0.34 (8 : 2 EtOAc-Hex); IR (CHCl₃) 3437, 3027, 2956, 1739, 1710, 1506 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.32 (5 H, s, CO₂CH₂Ph), 7.20-6.9 (8 H, m, aromatic Hs), 5.55* (1 H, d, J = 8 Hz, MeO₂C(Ar)CHNH), 5.42* (1 H, br, m, COCH₃NHCO₂), 5.13* (2 H, s, CO₂CH₂Ph), 5.05* (1 H, br, NH2Boc), 4.54 (1 H, br, q, J = 6 Hz, CHNH2Boc), 4.20 (2 H, m, CO₂CH₂CH₂OH), 3.92 (2 H, d, J = 6 Hz, NHCOC₂NH), 3.72 (5 H, s, CO₂Me + CH₂OH), 3.06* (2 H, m, (Ar)CHNH2Boc), 1.44 (9 H, s, NH2Boc) (*data at 55 °C to overcome multiple peaks due to amide resonance); [α]D -2.46° (c 0.61, EtOAc).

[(D)-2-[N-(Benzyloxycarbonyl)amino]-2-(3-oxophenyl)-1-oxo-1-methoxy-ethyl]-O-[(D)-N-[(1,1-dimethylethoxy)carbonyl]]tyrosyl-glycine 2-hydroxy-ethyl ester (3.67b)

![3.67b](image)

To a stirred solution of starting bromoethyl ester (3.64b, 464.0 mg, 6.25 x 10⁻⁴ mol) in 20 mL of DMF were added 49.0 mg (1.2 equiv, 7.50 x 10⁻⁴ mol) of zinc dust and 120 mg (1.4 equiv, 8.75 x 10⁻⁴ mol) of ZnCl₂ then the flask was warmed to 80-90 °C for 17-24 hrs. DMF was distilled off under reduced pressure and the residue
was eluted through silica gel with 20% hexanes in ethyl acetate to give 319.5 mg of foamy product (75.2% yield): *R*₂ 0.23 (EtOAc : Hexs = 8 : 2); IR (CHCl₃) 3431, 2956, 1743, 1720, 1505, 1249 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.32 (5 H, s, CH₂Ph), 7.28–6.89 (8 H, m, Ar-H), 6.50 (1 H, m, NHCbz), 5.83 (1 H, m, CONHCH₂CO₂), 5.30 (1 H, d, J = 6.7 Hz, CHNHCbz), 5.07 (2 H, s, CO₂CH₂Ph), 5.07 (1 H, m, NHBoc), 4.34 (1 H, q, J = 7 Hz, CH₂CH(NHBoc)), 4.24 (2 H, t, J = 4.5 Hz, CH₂CH₂OH), 3.98 (2 H, m, CONHCH₂CO₂), 3.78 (2 H, t, J = 4.5 Hz, CH₂OH), 3.71 (3 H, s, CO₂Me), 3.04 (2 H, m, (Ar)CH₂CHNH), 1.398 (9 H, s, NHBoc).

\[
[(D)-2-[N-(Benzyloxy carbonyl) amino]-2-(3-oxyphenyl)-1-oxo-1-\]

methoxyethyl]-O-[(D)-N-[1,1-dimethylethoxy) carbonyl]] tyrosyl-
glycine 2-acetoxy-ethyl ester (3.68)

\[\text{3.68}\]

The starting 2-hydroxyethyl ester (20 mg, 2.94 × 10⁻⁵ mol) was stirred with 11 µL (3.9 equiv, 11.7 × 10⁻⁵ mol) in the presence of 16.9 mg (4.7 equiv, 13.82 × 10⁻⁵ mol) of DMAP in 0.15 mL of CH₂Cl₂ at room temperature for 25 min. Flash chromatography on silica gel 60% EtOAc-Hexs) gave 20.1 mg of clear oil (99.9% yield): *R*₂ 0.47 (EtOAc : Hex = 8 : 2); IR (CHCl₃) 3430, 3026, 2957, 1742, 1722, 1686, 1589, 1506 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.32 (5 H, s, CH₂Ph),
7.27–6.87 (8 H, m, Ar-H), 6.40 (1 H, br, m, NHCbz), 5.85 (1H, br, d, CONHCH₂),
5.32 (1 H, d, J = 7.7 Hz, MeO₂CH(Ar)), 5.07 (2H, ABq, J = 12 Hz, CH₂Ph), 5.0 (1
H, m, NHBoc), 4.38–4.24 (5 H, m, 4 Hs from (CH₂)₂OAc and 1 H from tyrosyl
chiral H), 4.0 (2 H, m, CONHCH₂CO₂), 3.71 (3 H, s, CO₂Me), 3.05 (2 H, m,
CH₂NHBoc), 2.06 (3 H, s, OAc), 1.399 (9 H, s, NHBoc).

(R)-(-)-N-(1,1-Dimethylethoxy)carbonyl-4-chlorophenylalanine

2-hydroxyethyl ester (3.69)

![Chemical Structure](image)

To a stirred solution of N-Boc-4-chlorophenylalanine 2-bromoethyl ester
(3.38b, 100 mg, 2.46 × 10⁻⁴ mol) in 5 mL of DMF were added 19.3 mg (1.2equiv,
2.95 × 10⁻⁴ mol) of Zn dust and 50.3 mg (1.5equiv, 3.69 × 10⁻⁴ mol) of ZnCl₂ at room
temperature. Then the reaction mixture was warmed to ~90 °C for 18 hrs. DMF was
distilled off then product was isolated by flash chromatography on silica gel (2% HOAc
in 1:1 mixture of EtOAc-Hex) to give 39.5 mg of clear oil (46.7% yield): Rf 0.32 (2%
HOAc in 50% EtOAc-Hex); IR (CHCl₃) 3690, 3628, 3439, 3019, 2981, 1741, 1709,
1493, 1216 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.26 (2 H, d, J = 8.4 Hz, aromatic H
ortho to Cl), 7.09 (2 H, d, J = 8.4 Hz, aromatic H meta to Cl), 4.95 (1 H, br d, J =
6.8 Hz, J = 7 Hz, NHBoc), 4.48 (1 H, q, J = 6.8 Hz, CH₂NHBoc), 4.24 (2 H, m,
OCH₂CH₂OH), 3.75 (2 H, m, CH₂OH), 3.09 (1 H, dd, J = 13.5 and 6Hz,
ArCH₂HCHNBoc), 3.01 (1 H, dd, J = 13.5 and 5.5 Hz, ArCH₂HCHNBoc), 1.40
(9 H, s, NHBoc); [α]D -6.86° (c 0.35, EtOAc). Satisfactory MS and elemental
analyses were not obtained.
(R)-(−)-N-Benzylxocarbonylphenylglycine 2-bromoethyl ester (3.72)

To a stirred, cooled (0 °C) solution of (R)-(−)-N-Cbz-Phenylglycine (2.0 g, 7.01 mmol) in 18 mL CH₂Cl₂ and 3.5 mL DMF were added 2-bromoethanol (497.0 mL, 7.01 mmol), HOBT (1.29 g, 1.2 equiv, 8.41 mmol) and DCC (1.74 g, 1.2 equiv, 8.41 mmol). The mixture was stirred for 2 hr at 0 °C and 17 hr at room temperature. The white solid was filtered off, the filtrate was concentrated, and flash chromatographed on silica gel (30% EtOAc-Hex) to give 1.18 g (85.6% yield) of pale yellow solid. mp 62-64 °C; Rf 0.30 (30% EtOAc-Hex); IR (CHCl₃) 3435, 3036, 2946, 1723, 1500, 1216 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.35-7.33 (10 H, m, aromatic Hs), 5.73 (1 H, br d, NH-Cbz), 5.39 (1 H, d, J = 7.4 Hz, ArCHNHCbz), 5.09 (2 H, ABXq, J = 12 and 14Hz, OCH₂Ph), 4.40 (2 H, m, OCH₂CH₂Br), 3.40 (2 H, t, J = 6.4 Hz, CH₂Br); ¹³C NMR (75 MHz, CDCl₃) δ 170.34, 155.31, 136.00, 128.92, 128.66, 128.45, 128.11, 127.84, 127.13, 67.09, 64.74, 57.93, 27.78; [α]D -50.1° (c 0.74, EtOAc);

[(R)-2-[N-(2-Aminoacetyl)]amino-2-(3-oxyphenyl)-1-oxo-1-methoxy-ethyl]-O-[(R)-N-[(1,1-dimethylethoxy)carbonyl]]tyrosine 2-hydroxy-ethyl ester (3.78a)
To a stirred solution of 121.9 mg (1.79 × 10^{-4} mol) of starting material in 10 mL of EtOH were added 100 mg of 10% Pd-C and 1 mL of cyclohexene. The reaction mixture was heated to reflux for 13 hr. The catalyst was recovered by centrifuge. Flash chromatography on silica gel (10% MeOH-CHCl₃) gave 62.3 mg (63.7% yield) of white foam: \( R_f 0.30 \) (15% MeOH in CHCl₃); IR (CHCl₃) 3436, 3346, 2956, 1742, 1708, 1590, 1506 cm⁻¹; \(^1\)H NMR (200 MHz, CDCl₃) \( \delta \) 8.15 (1 H, d, \( J = 6.7 \) Hz, CHNHOCH₂), 7.33~6.91 (8 H, m, aromatic Hs), 5.56 (1 H, d, \( J = 7.7 \) Hz, MeO₂CCH(Ar)), 5.02 (1 H, br d, NHBoc), 4.48 (1 H, br m, CHNHBoc), 4.20 (2 H, t, \( J = 4.5 \) Hz, OCH₂CH₂OH), 3.72 (5 H, s, CO₂Me + CH₂OH), 3.37 (2 H, s, CH₂NH₂), 3.06 (2 H, m, (Ar)CH₂), 1.42 (9 H, s, NHBoc); \([\alpha]_D -3.55^\circ \) (c 0.31, EtOAc).

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\text{[(D)-2-Amino-2-(3-oxyphenyl)-1-oxo-1-methoxyethyl]-O-[(D)-N-[(1,1-dimethylethoxy)carbonyl]]tyrosylglycine 2-hydroxyethyl ester (3.78b)}
\]
To a stirred solution of 106.6 mg (1.57 \times 10^{-4} \text{ mol}) starting compound in 10 mL of ethanol were added 100 mg of 10\% Pd-C and 1 mL of cyclohexene and the mixture was heated to reflux for 17 hrs. At the end of this period TLC showed no starting material. The catalyst was recycled by centrifuging the reaction mixture. Flash chromatography on silica gel (10\% MeOH-CHCl_3) gave 41.3 mg of pale yellow foam (48.2\% yield): \( R_f \) 0.568; \( ; \) IR (CHCl_3) 3620.9, 3431.6, 2981.5, 1739.7, 1682.8, 1588, 1506, 1249.2 cm\(^{-1}\); \(^1\)H NMR (200 MHz, CDCl_3) \( \delta \) 7.32~6.87 (8 H, m, aromatic Hs), 6.47 (1 H, br, CONHCO_2), 5.01 (1 H, br, NHBOc), 4.56 (1 H, s, MeO_2CCHNH_2), 4.30 (1 H, q, J = 6.7 Hz, CHNHBOc), 4.24 (2 H, t, J = 4.5 Hz, OCH_2CH_2OH), 4.00 (2 H, m, NHCOCH_2CO_2), 3.78 (2 H, t, J = 4.5 Hz, CH_2OH), 3.68 (3 H, s, CO_2Me), 3.04 (2 H, m, (Ar)CH_2), 1.40 (9 H, s, NHBOc); \(^{13}\)C NMR (75 MHz, CDCl_3) \( \delta \) 171.02, 171.97, 169.59, 157.62, 155.67, 155.55, 141.80, 131.71, 130.67, 130.07, 121.43, 119.15, 118.13, 116.99, 80.37, 66.84, 60.33, 58.28, 55.66, 52.50, 41.36, 37.65, 28.22; [\alpha]_D^{+3.41^\circ} (c 0.41, EtOAc).
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166. Both instrumental analyses were done in The BFGoodrich Company, Brecksville, OH by Dr. R. P. Lattimer.


