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SYNTHETIC STUDIES TOWARDS RISTOCETIN A AND RELATED COMPOUNDS USING ARENE-RUTHENIUM CHEMISTRY

by

KIESEUNG LEE

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

Thesis Advisor: Anthony J. Pearson

Department of Chemistry
Case Western Reserve University
August, 1995
CASE WESTERN RESERVE UNIVERSITY

GRADUATE STUDIES

We hereby approve the thesis of

Kiesung Lee

candidate for the Ph. D.
degree.*

(signed) Lawrence A. Pegg
(chair)

Valerio D. Rossi

Michael D. Zagorski

(date) May 3, 1995

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SYNTHETIC STUDIES TOWARDS RISTOCETIN A AND RELATED COMPOUNDS USING ARENE-RUTHENIUM CHEMISTRY

Abstract

by

KIESEUNG LEE

Chapter I. As part of the overall project directed toward the total synthesis of glycopeptide antibiotics, e.g., Vancomycin and Ristocetin A, a formal total synthesis of K-13 was studied.

![Chemical structures](image)

K-13 (1.1) K-13 Precursor (1.25)

The aryl ether bond was constructed between the dipeptide and the Ru-complex of a p-chlorophenylalanine derivative under very mild conditions (-78 °C, 1 h, then rt, 3.5 h) and subsequent demetallation using a sunlamp (275W) gave the diaryl ether intermediate in good yield. (CH$_3$CN)$_3$Ru$^+$CpPF$_6$ was recovered in high yield from this demetallation. Among the various carboxyl protecting groups examined, the 2-bromoethyl ester was found to be the best behaved during Ru-metallation, condensation and demetallation reactions, but a serious problem during deprotection was observed. This problem was finally solved by conversion of 2-bromoethyl ester...
to the 2-iodoethyl ester followed by its deprotection using SmI₂, but the procedure still needs to be optimized. This synthetic approach based on ruthenium chemistry presents the most convergent route so far for this kind of compound.

Chapter 2. The deprotection of 2-bromoethyl esters using reported methods usually gave 2-hydroxyethyl esters as the major products presumably via neighboring group participation of the carboxyl oxygen. A general study of a new protocol for removing the 2-bromoethyl ester group was studied, by using a two-step sequence, *i.e.* (i) converting 2-bromoethyl esters into their 2-iodoethyl esters via Finkelstein reaction, and (ii) reacting the resulting 2-iodoethyl esters with SmI₂ (6.0 or 7.0 equiv) at 35-40 °C under deoxygenated-Ar. Under these conditions, no racemization can be observed using *N*-Benzyloxy carbonyl-(R)-phenylglycine 2-bromoethyl ester as a model compound. The *N*-Benzyloxy carbonyl group was determined to be very stable, and the *N*-t-Butoxy carbonyl-protecting group is relatively stable under these conditions.

Chapter 3: To evaluate coupling reagents for the problematic 16-membered ring cycloamidation, 16-membered rings mimicking the "northern" parts of Vancomycin and Ristocetin A were designed as 3.9 and 3.28, and various macrocyclization methods were investigated.
The aryl ether bond was formed under very mild conditions (-78 °C, 15 min then rt, 1.5 h) via Ru-mediated $S_N$Ar reaction and the subsequent two steps (Demetallation and Finkelstein reaction) were successfully optimized. SmI$_2$-mediated removal of the 2-iodoethyl ester blocking group was optimized by using SmI$_2$ in the presence of DMPU ($N,N'$-dimethyl-$N,N'$-propylene urea) at room temperature.
Among the four macrocyclization methods examined for 3.42, the pentafluorophenyl ester/Et$_3$N method gave the best overall yield, two cyclization products being obtained. It seems to be clear from $^1$H-NMR data and Chem 3D molecular modelling studies that one of the two cyclization products separated is an atropisomer of the other. Because of limited amounts of cyclization product obtained, no extensive studies for structure determination were made.

For 3.41, three different variations (one-step and two-step sequence) based on the pentafluorophenyl ester intermediate 3.50 were examined but no cyclization products were observed.

Chapter 4. The total syntheses of OF4949-III and IV were examined based on the results obtained in K-13 and BCF-model studies.
t-Butyldimethylsilyl ether protecting group of phenol was well-behaved in hydrogenation and Evans azidation reaction conditions, but deprotection required *anhydrous* TBAF (tetrabutylammonium fluoride). The methoxyethoxymethyl ester protecting group was successfully introduced in the presence of a phenolic group. The dipeptide which has polar groups such as acetamide and amide groups was successfully Ru-metallated to give an important intermediate **4.4** in almost quantitative yield.
Dedication

This work is dedicated to my Father who sacrificed his life for his family
and to my Mother, brothers, my lovely wife Regina and my son Richard

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Acknowledgement

First of all, I would like to express my sincere gratitude to my advisor, Prof. A. J. Pearson. He taught me from English to the Gentlemanship, of course, the science including chemistry. His great personality and gentlemanship is a wonder for me and is a standard that I am going to be and also his broad and deep knowledge of chemistry encourage me to study harder.

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<tr>
<td>Bn</td>
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<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Terahydrofuran</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TMSE</td>
<td>2-Trimethylsilylethyl Ester</td>
</tr>
<tr>
<td>Trisyl</td>
<td>2, 4, 6-Triisopropylbenzenesulfonyl</td>
</tr>
<tr>
<td>TROC</td>
<td>2, 2, 2-Trichloroethyl</td>
</tr>
<tr>
<td>TTN</td>
<td>Thallium trinitrate</td>
</tr>
</tbody>
</table>
CHAPTER 1

A FORMAL TOTAL SYNTHESIS OF THE ACE INHIBITOR K-13. AN APPLICATION OF ARENE-RUTHENIUM CHEMISTRY TO COMPLEX CHEMICAL SYNTHESIS
1.1 INTRODUCTION

K-13 (1.1) is an L,L-isodityrosine-derived cyclic tripeptide, isolated from the culture broth of *Micromonospora halophytica subsp. exilis* K-13,\(^1\) that has been shown to be a novel, noncompetitive inhibitor of angiotensin I converting enzyme (\(I_{50} = 0.17 \ \mu g/mL, \ K_i = 0.35 \ \mu M\)) and weak inhibitor of aminopeptidase B. Its structure was elucidated by spectroscopic and chemical degradation studies.\(^2\) The key structural features of K-13 are the isodityrosine subunit which is connected by diaryl ether linkage of the amino acid residues, and a cyclic peptide bond linkage (Figure 1.1.1).\(^3,4\)

![K-13 (1.1)](image)

**Figure 1.1.1 Structure of K-13 (1.1)**

1.2 SYNTHETIC APPROACHES

1.2.1 Construction of the Diaryl Ether Linkage

The synthesis of isodityrosine subunits is a challenging problem because the
amino acid functionality is heat- and base-sensitive and so not compatible with the harsh reaction conditions usually required for the construction of the diaryl ether linkage. The classical Ullmann reaction\(^5\) has been applied in the synthesis of a isodityrosine derivative, but the yield (1.5%) was disappointingly low (Scheme 1.2.1).\(^2\)

![Chemical structure](image)

**Scheme 1.2.1** Classical Ullmann Reaction in the Synthesis of a Isodityrosine Derivative

More recently, Schmidt's group has reported a modified Ullmann reaction\(^6\) for the preparation of the isodityrosine precursor (Scheme 1.2.2), which was applied in the synthesis of K-13 and OF 4949-III by Evans.\(^4\)

![Chemical structure](image)

**Scheme 1.2.2** Modified Ullmann Reaction in the Synthesis of an Isodityrosine Precursor

Other variations of the Ullmann reaction using different Cu-reagents such as CuBr,\(^3\) CuBr-SMe,\(^7\) and CuCl\(^8\) have also been reported. An alternative method for the synthesis of isodityrosine-derived cyclic peptides is the biomimetic, oxidative
thallium trinitrate (TTN)-promoted two-step phenolic coupling method introduced by Yamamura, which was illustrated in total syntheses of K-13,9 OF 4949-III (Equation 1.2.1)7 and piperazinoacycin.11

This method was modified later by Evans by using CrCl₃ instead of (Zn/AcOH) in an approach to the vancomycin family,12 but the modest yields for macrocyclization detract from the practical utility of these reactions. In another approach, Hamilton adopted a method involving displacement, by phenolate (or phenoxide), of a tosylate from an activated dinitrotyrosine derivative.13 In a related approach, Brown used the reactivity of aryliodonium salts toward the phenoxide of tyrosine to give aryl ether derivatives without racemization,14 while Still prepared similar thioethers by a photochemical SN₁ reaction in ammonia (Scheme 1.2.3).15

Scheme 1.2.3 Photochemical Thioether Synthesis in Ammonia
Most recently, Rao's group\textsuperscript{16a,b} reported new routes to isodityrosine precursor synthesis by using the reactivity of 2-bromobenzoquinone and 2,6-dibromobenzoquinone toward phenoxy nucleophilic addition to give (di)-aryloxybenzoquinone, followed by conversion of the benzoquinone skeleton to the corresponding arylamino acid (Scheme 1.2.4).

\[ \text{Scheme 1.2.4 \ Rao's Route to Isodityrosine Precursor} \]

Another interesting approach for these kinds of compounds was developed by Japanese chemists. Dienone mono-epoxides were reacted with potassium phenoxydes, followed by CH\textsubscript{2}N\textsubscript{2}, Zn/AcOH to give diphenyl ethers having the tyrosine moiety in good yield (33–72\%) (Scheme 1.2.5).\textsuperscript{17}

\[ \text{Scheme 1.2.5 \ Inoue's Route to Tyrosine Derivative} \]

As another novel approach, Pearson's group used transition metal moieties such as Mn,\textsuperscript{18} Fe,\textsuperscript{19} and Ru\textsuperscript{20} (Scheme 1.2.6) to activate arenes toward nucleophilic addition, allowing the use of very mild conditions to effect the construction of diaryl ethers from amino acid derivatives, without any noticeable racemization. Among the above metal-mediated coupling methods, the Ru-method is the only one
suitable for amino acid derivatives because it does not require harsh reaction conditions or very reactive reagents such as AlCl₃ etc., for its complexation and also its metal-complex is sufficiently reactive toward phenoxide anion to allow the use of very mild reaction conditions.

1.2.2 MACROCYCLIZATION REACTION

Together with the diaryl ether formation via Ullmann reaction, intramolecular peptide coupling is one of the key steps for the syntheses of these kinds of molecules. Macrocyclization is achieved via either C₁₁-N₁₀ bonding³ or C₁₄-N₁₃ bonding⁴ (Figure 1.2.1) by reacting the carboxylic acid with amine (or amine salt) in the presence of various coupling reagents such as DCC (or EDC)²¹ or DPPA²² etc. or by reacting an activated ester such as pentafluorophenyl ester²³ with amine (or amine salt) in the presence of base (eg., Et₃N or pyridine or NaHCO₃ solution).
Usually, these intramolecular reactions are conducted either under high dilution conditions (0.3–8 mM) or by slow addition of reactants from syringe pump to avoid dimerization, but in some cases of 15- and 14-membered-ring construction, dimer was obtained as a single product. General yields of macrocyclization reaction via peptide coupling are less than 50% in most cases and the success of the cyclization is dependent on the ring size, orientation of coupling, the nature of the protecting group on the neighboring amine, and the substituent (C4) on the phenyl ring.\textsuperscript{3} For the optimized route to K-13, Boger\textsuperscript{3b} conducted systematic, comparative studies on the method, site, and substrate structural features and found that with the N\textsubscript{15}-Ac group, coupling via ether C\textsubscript{14}-N\textsubscript{13} or C\textsubscript{11}-N\textsubscript{10} was not successful, and a C\textsubscript{4}-alkoxy substituent in the substrate caused a substantial rate decrease for the macrocyclization reaction. The unfavorable effect of N\textsubscript{15}-Ac was rationalized later as due to a 5-membered oxazolidinone ring formation between the N\textsubscript{15}-Ac and activated ester, that is preferred over the peptide cyclization, thus inhibiting the cyclization as shown in Scheme 1.2.7. This was confirmed by the quantitative recovery of the free carboxylic acid from the attempted cyclization of the free ester. The unfavorable C\textsubscript{4}-alkoxy effect for macrocyclization was explained by the
Scheme 1.2.7 The Unfavorable Effect of N$_{15}$-Ac Group in K-13 Synthesis

observation that with C$_4$-alkoxy group on the aryl ring, the unproductive conformations are preferentially populated via H-bonding and lone pair-lone pair repulsion. This unfavorable C$_4$-alkoxy effect was overcome by using activated pentafluorophenyl ester for macrocyclization in Evans' case.

1.2.3 Previous Reports of K-13 Synthesis

After the structure determination of K-13 by Yasuzawa et al. in 1987,2 several groups have reported the synthesis of K-13. Yamamura's group reported a biomimetic synthesis of K-13 from N-acetyl-3,5-dichloro-L-tyrosyl-O-benzyl-L-tyrosyl-3,5-diido-L-tyrosine methyl ester, by using oxidation with thallium trinitrate (TTN) as a key step followed by zinc reduction (Scheme 1.2.8).9

Scheme 1.2.8 Yamamura's Approach to K-13
Boger's group reported the total synthesis of K-13, starting from a selectively protected L-dopa derivative and t-butyl-4-iodobenzoate, via Ullmann condensation reaction, and C_{11}-N_{10} amide bond formation as key steps to afford K-13 (Scheme 1.2.9).³

![Scheme 1.2.9 Boger's Approach to K-13](image)

Evans' group also reported the total synthesis of K-13 by using the Ullmann condensation reaction as a key step for the synthesis of the diaryl ether linkage and then introducing the amino acid functionalities via Evans' de novo amino acid synthesis, and C_{15}-N_{14} bond formation (Scheme 1.2.10).⁴

![Scheme 1.2.10 Evans's Approach to K-13](image)

Most recently, Rao's group used 2-bromobenzoquinone¹⁶a and 3-bromo-4-nitrobenzaldehyde²⁴ to make a diaryl ether linkage in the presence of KF or under...
Ullmann reaction conditions followed by aromatization and functionalization to the requisite amino acids, and then several steps to give K-13 precursors (Scheme 1.2.11).

\[
\begin{align*}
\text{Scheme 1.2.11 Rao's Approach to K-13}
\end{align*}
\]

1.3 EXPERIMENTAL RESULTS AND DISCUSSION

We have previously shown that arene metal-complexes (especially Ru) can be coupled with phenolic derivatives under very mild conditions (e.g., 2,6-di-t-butylphenol+NaH, THF, -78 °C, or -20 °C). With this strategy in mind, we elected to develop an asymmetric formal total synthesis of K-13. Based on the retrosynthetic analysis shown in Scheme 1.3.1, three intermediates (1.3, 1.4 and 1.5) should be prepared.
Scheme 1.3.1 Retrosynthetic Analysis of K-13

We first synthesized 1.3 by using Evans’ chiral auxiliary method (Scheme 1.3.2). By Knoevenagel reaction, the commercially available starting material 1.6 was transformed into 1.7,25 which was further catalytically hydrogenated to give 1.8 in good yield.26 Protection of the phenolic and carboxylic moieties by benzylolation followed by saponification provided 1.10 in quantitative yield. The purified monoacid 1.10 was then treated with pivaloyl chloride and triethylamine to obtain the mixed anhydride, which upon treatment with 1.05 equiv of lithiated (4S)-4-(phenylmethyl)-2-oxazolidinone27 at -78 °C, afforded the carboximide 1.11 as a white crystalline solid in good yield. Complete enolization of the carboximide 1.11 by the rapid addition of 1.50 equiv of KHMD at -78 °C, and then reaction of the resulting enolate with trisylazide followed by the usual acetic acid quench according
Reaction Conditions, Reagents and Yields:

a) Malonic acid, piperidine, pyridine, 3 h (105 °C), 1 h (145 °C), 86%
b) Pd-C (10%), MeOH, 12 h, rt, 88%  c) BnBr (2.1 equiv), K₂CO₃ (3.0 equiv), 20 h, rt, 89%
d) KOH (2.1 equiv), 20 h, rt, 96%  e) Et₂N, pivaloyl chloride then (4S)-4-(phenethyl)-2-oxazolidinone/n-BuLi, 83%  f) KHMDS, trisylazide, 71%
g) LiOOH (2.0 equiv), 0 °C, 1 h
h) PTSA/MeOH, reflux, 8 h, 84%
i) Pd-C (10%), THF, 8 h, rt

Scheme 1.3.2 Synthetic Routes to Intermediate 1.3

to the established procedure gave the crude α-azidocarboximide 1.12. The minor diastereomer from the azidation reaction was separated by successive elution of the crude product loaded on a preparative TLC plate (silica gel, hexanes/EtOAc, 85/15) and the diastereomeric selectivity was determined to be 97:3 by HPLC. The crude product was purified by flash chromatography and then further purified by recrystallization (hexanes/EtOAc, 9/1) to remove any diastereomeric impurity,
which afforded the pure product in 71% yield. Removal of chiral auxiliary from 1.12 with LiOOH at 0 °C,30 followed by protection of carboxylic group as the methyl ester, and subsequent simultaneous catalytic reduction of the azide group into amino and deprotection of benzyl group of the phenolic moiety in 1.13 afforded the desired chiral intermediate 1.3 in good yield.

To prepare the other part 1.4 of the dipeptide, L-tyrosine ethyl ester-HCl (1.14, Sigma chemicals) was used as the starting material (Scheme 1.3.3).

\[
\begin{align*}
1.14 & \xrightarrow{a} 1.15 \\
1.15 & \xrightarrow{b} 1.4
\end{align*}
\]

**Reaction Conditions, Reagents and Yields:**

a) CbzCl (1.08 equiv), Na₂CO₃ (0.5 equiv), 0 °C then rt, 91%

b) Me₂SO₄, NaOH, rt, 92%

**Scheme 1.3.3** Synthetic Routes to Intermediate 1.4

Cbz-protection of 1.14 under slightly basic conditions (Na₂CO₃),31 followed by saponification of ester and simultaneous *in situ* protection of the phenolic group as methyl ether (dimethyl sulfate/excess of NaOH) afforded the desired intermediate 1.4 with [α]D value consistent with the literature.32a

To synthesize the requisite dipeptide 1.2 (Scheme 1.3.4) which has the free phenolic group, 1.3 and 1.4 were reacted in the presence of EDC and HOBT at 0 °C
Reaction Conditions, Reagents and Yields:

a) EDC (1.2 equiv), HOBT (1.5 equiv), THF/DMF, 0 °C, overnight, 82%

Scheme 1.3.4  Synthetic Routes to Dipeptide 1.2

and stirred overnight. After purification by flash chromatography, the dipeptide 1.2 was obtained in 82% yield.

The chiral ruthenium complexes 1.5 having a variety of carboxyl protecting group were prepared by the Evans chiral auxiliary methodology following the similar procedures as for 1.3 (Scheme 1.3.5). Catalytic hydrogenation of commercially available p-chlorocinnamic acid (1.16) with Pd-C (10%)/H₂ (1 atm) gave 1.17 which was further reacted via its mixed anhydride with lithiated (4S)-4-(phenylmethyl)-2-oxazolidinone (1.05 equiv), and subsequent treatment with KHMDS and trisylazide afforded the crude α-azidocarboximide in good yield. The minor diastereomer from the azidation reaction was separated by preparative TLC by multiple elution with (hexanes/EtOAc, 85/15) and the diastereoselectivity was determined as 95:5 by HPLC. The crude product 1.19 was purified by flash chromatography, and recrystallization from (hexanes/EtOAc, 9/1) afforded the diastereomerically pure compound 1.19a in good yield. Then, the chiral auxiliary was removed with LiOH (2.0 equiv) at 0 °C to provide the α-azidoacid 1.20 in 92%
yield. At this point, we had to select the ester-protecting groups carefully which are stable in the condensation, Ru-metallation and demetallation reaction and also

![Chemical Structures](image)

**Reaction Conditions, Reagents and Yields:**

(a) Pd-C (10%)/H₂ (1 atm), THF, 4 h, rt, 88%  
(b) Et₃N, pivaloyl chloride,  
(4S)-4-(phenylmethyl)-2-oxazolidinone/n-BuLi, 86%  
(c) KHMD, trisylazide, 76%  
(d) LiOH (2.0 equiv), 0°C, 1 h, 92%  
(e) MEMCl, (i-Pr)₂NEt, 0°C, 2 h, 75%  
(f) Raney-Ni/H₂ (1 atm), (BOC)₂O, (1.2 equiv), 44%

**Scheme 1.3.5 First Synthetic Routes to Intermediate 1.5**

labile enough to be deprotected easily under neutral conditions. From these points of view, MEM ester protecting group was the first choice for our trial, because this group was reported to be deprotected easily with neutral MgBr₂/Et₂O. The carboxylic group of 1.20 was protected as the MEM ester with MEMCl/Hünig base at 0 °C, then the resulting compound 1.21 was treated with (BOC)₂O/(Pd-C (10%)), H₂ (1 atm) to effect in situ protection of the amino group. The yield of the latter step was poor probably due to the instability of MEM ester group toward Pd-C
(10%)/H₂ (1 atm) conditions, so we turned our attention to another route (Scheme 1.3.6).

![Chemical Structure and Reaction Conditions](image)

**Reaction Conditions, Reagents and Yields:**

(a) Pd-C (10%), HCl (2.0 equiv), H₂ (1 atm) then K₂CO₃ (2.5 equiv), (BOC)₂O (1.5 equiv), 85%  
(b) LiOH (2.0 equiv), 0 °C, 1 h, 77%  
(c) MEMCl (1.2 equiv), (i-Pr)₂NEt (1.1 equiv), 0 °C, 2 h, 96%  
(d) 2-Haloethanol (1.2 equiv), DCC (1.1 equiv), pyridine (2.0 equiv), 0 °C, overnight, 75-92%  
(e) (CH₃CN)₆Ru(CpPF₆) (1.5 equiv), 1,2-dichloroethane, reflux, 5 h, 93-98%

**Scheme 1.3.6 Second Synthetic Route to Intermediate 1.5**

From our unpublished results, (4S)-4-(phenylmethyl)-2-oxazolidinone was known to be stable toward the hydrogenation conditions, so 1.19a was subjected to Pd-C(10%)/H₂ (1 atm), HCl (2.0 equiv) to give the amine-HCl which was further reacted with (BOC)₂O/K₂CO₃, affording the N-BOC protected compound 1.23 in 85% yield. After removal of chiral auxiliary with LiOH (2.0 equiv), the resulting crude acid 1.23' was used without purification for the next reaction i.e., crude acid 1.23' was treated with MEM-Cl/Hünig base at 0 °C, and after purification by flash chromatography, it provided the N-BOC, MEM ester protected amino acid derivative 1.22a in 96% yield. The [α]D values of 1.22a from both procedures were nearly the same, which demonstrated that the basic BOC-protection step did
not lead to any detectable racemization. The Ru-metalation of 1.22a was accomplished by refluxing it with [(CH₃CN)₃Ru⁺Cp]PF₆⁻ for 5 h under N₂, and the resulting crude complex was purified by filtering it through a Celite pad, then a neutral alumina column (1 x 5 cm) to provide the complex that was sufficiently pure for the next condensation. Due to the intrinsic difficulty of purification of these kinds of cationic metal-complexes, we did not try further purification of Ru-Complex 1.5a. The Ru-complexation was confirmed by ¹H-NMR which showed downfield-shift of Cp to ca. 5.45 ppm and upfield-shift of complexed aromatic H's to ca. 6.30 ppm after complexation.

Reaction Conditions, Reagents and Yields:
(a) Na, 2,6-di-i-butyphenoxide (1.1 equiv), 0 °C, N₂, 20-30 min (b) 1.5 (1.0 equiv), -78 °C, 1 h then rt, 3.5 h (c) Sunlamp(275W), CH₂CN, N₂ 20-24 h (d) NaI (5.0 equiv), reflux, 7 h, N₂, 95% (e) Sml₂ (7.0 equiv), THF, 35 °C, 10 h, Ar, 70%

Scheme 1.3.7 Synthetic Route to Target Molecule 1.25
For the condensation reaction (Scheme 1.3.7), 2,6-di-t-butylphenol Na salt was used as a sterically hindered weak base which was prepared from equimolar amounts of NaH and the phenol in dry THF. Experimentally, it was very difficult to take just equimolar amount of NaH in mineral oil, so we normally made a stock solution of NaH/2,6-di-t-butylphenol in THF just before the experiment, and introduced the requisite amount of stock solution into the reaction flask containing the dipeptide to be deprotonated. The dipeptide 1.2 was reacted with 1.10 equiv of hindered base at 0 °C for 30 min, then it was transferred into a precooled (-78 °C) solution of the Ru-complex 1.5a via cannula, and the resulting solution was stirred for 1–2 h at -78 °C, then 3–4 h at rt. When we first tried the condensation reaction of 1.5a, we obtained pure arylated-, Ru-complexed product 1.23a in 29% yield. The condensation reaction was easily confirmed by ¹H-NMR which showed that, after coupling, complexed-aromatic H peaks were shifted upfield to ca. 6.05 ppm and Cp peaks were also shifted upfield slightly to ca. 5.35 ppm owing to the diaryl ether oxygen. The yield was never improved further presumably due to the instabilities of MEM-ester protecting group and/or Ru-complexed compound itself toward the reaction conditions.

The next candidate for successful implementation of this strategy was the Troc ester protecting group. This Troc ester has been widely used in synthesis,36,37 and is easily removed by nonbasic deprotecting reagents such as Zn/HOAc/H₂O36 and Zn-dust/buffer.38,39 But, more importantly, in our preliminary experiment using model compound, Troc ester protecting group was deprotected quantitatively under very mild conditions (Sml₂ (7.0 equiv), rt, 2 h, Ar) (Equation 1.3.1).
This new nonaqueous deprotecting reagent allowed us to circumvent the devastating results of 2-bromoethyl ester protecting group which was tried in our earlier related works, and prompted us to use the Troc ester protected 1.5b for condensation.

The synthesis of 1.2b and subsequent Ru-complexation were achieved by using the standard reaction conditions. However, the attempted condensation of 1.5b with Na,dipeptide-phenoxide 1.2' gave very disappointing yields (< 5%) presumably due to the instability of Troc ester functionality toward the arylation reaction. At this point, we were very frustrated with the above failed attempted trials and also with the earlier failed results of related works. We again turned our attention to the use of a 2-bromoethyl ester as carboxyl blocking group.

In the earlier related works, various deprotecting methods reported such as Zn with or without NaI in boiling aqueous THF(or MeOH), Zn/ZnCl₂, ethanedithiol/NaH/CH₃CN, Na₂CS₃/CH₃CN, vitamin B₁₂/aqueous EtOH(or DMF), Na/liquid NH₃, Ca/liquid NH₃, Pd(PPh₃)₄/CH₃CN all gave the 2-hydroxyethyl ester as a major product. (Equation 1.3.2).
Although no detailed mechanistic study has been made yet, a possible mechanism for 2-hydroxyethyl ester formation via a neighboring group participation from the ester carbonyl oxygen is suggested in Scheme 1.3.8.

Scheme 1.3.8 A Possible Mechanism for the Formation of 2-Hydroxyethyl Ester

Interestingly, a similar result was reported for deprotection of 2-chloroethyl carbamate case by Magnus. Even though there is an apparent, close similarity between the present work and our earlier related works, we did not have any other choice except to re-examine the 2-bromoethyl ester protecting group. Ru-complexed, 2-bromoethyl ester protected chiral intermediate 1.5c was prepared by following the established standard procedure and was subjected to the condensation reaction conditions similar for 1.23a, and after filtering it through a Celite pad and a short neutral alumina column, pure arylated-, Ru-complexed product 1.23c was
obtained in ca. 80% yield. This reaction was very reproducible and the product was characterized by $^1$H-NMR which showed the characteristic proton peaks of arylated-, Ru-complexed arene and Cp (Figure 1.3.1).
Figure 1.3.1 $^1$H-NMR of 1.23c and 1.24a in CDCl$_3$
For the demetallation reaction, the Ru-complexed, diaryl ether 1.23c was irradiated with UV light (Sunlamp, 275W) in a quartz tube (typical size 1.5 x 20 cm, CH₃CN, N₂) for ca. 20 h at rt. After the reaction was complete, the organic product was separated from [(CH₃CN)₃Ru⁺Cp]PF₆⁻ (ether-insoluble) by adding the concentrated CH₃CN solution to diethyl ether. The average recovery of [(CH₃CN)₃Ru⁺Cp]PF₆⁻ was ca. 85%. After purification by flash chromatography, 1.24a was obtained in 65% yield, and the structure was confirmed by ¹H-NMR which showed that the aromatic protons on the demetallated material were shifted to the normal aromatic region, and Cp-peaks had disappeared (Figure 1.3.1).

At this point, we had another challenge to overcome, i.e., how the 2-bromoethyl ester protecting group could be removed. With the hope that the 2-bromoethyl ester group could be deprotected with SmI₂, we conducted a model study again using N-BOC-R-(4-chlorophenyl)alanine 2-bromoethyl ester. Attempted deprotection at rt using SmI₂ (7.0 equiv) did not give any product (no reaction), and under reflux condition, it gave multiple products. Now, the situation was narrowed. In conjunction with the earlier two model studies and the generally known reactivity order of 2-haloethyl ester protecting groups towards bases and nucleophiles along the series (Scheme 1.3 9), we turned our attention to the 2-iodoethyl ester protecting group.

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

**Scheme 1.3.9** Reactivity Order of 2-Haloethyl Ester Protecting Group toward Bases and Nucleophiles
Before trying the real system, N-BOC, R- (4-chlorophenyl)alanine 2-iodoethyl ester was reacted with SmI$_2$ (7.0 equiv) at rt under deoxygenated-Ar for 1 day: 75% of starting material was converted into its acid, and 25% still remained. Prolonged stirring (2 days) with use of excess SmI$_2$ (10.0 equiv) did not lead to further progress. At a slightly elevated temperature (35 °C) with use of 7.0 equiv of SmI$_2$, the reaction was determined to be complete from the $^1$H-NMR of the crude product. From the above promising result, the 2-iodoethyl ester was selected as a possible acid protecting group for our strategy. Now, the situation was simplified as how to convert the 2-bromoethyl ester protecting group into corresponding 2-iodoethyl ester functionality. For this type of halide displacement, various reagents were reported.$^{47}$ Conversion of the 2-bromoethyl ester 1.24a into the 2-iodoethyl ester 1.24b in high yield (~95%) was achieved by refluxing it with NaI in anhydrous acetone ($Finkelstein$ reaction)$^{48}$ for 7 h. The $^1$H-NMR spectrum (Figure 1.3.2) exhibited the expected upfield-shift by 0.2 ppm of methylene (triplet or multiplet) peak of 2-iodoethyl ester (-CO$_2$CH$_2$CH$_2$I) to ca. 3.3 ppm.

The final transformation of the key intermediate 1.24b into its corresponding acid 1.25 was accomplished by using the same reaction conditions (SmI$_2$ (7.0 equiv), 35 °C, 10h, THF, deoxygenated-Ar) acquired from the model study (Scheme 1.3.7). The $^1$H-NMR spectrum of the crude product and TLC-analysis exhibited that the only noticeable by-products were highly nonpolar and polar materials which were always formed even in the simple model study. The [α]$_{Hg,365}$ value (+30.4°, c 0.38, MeOH) of pure product was somewhat higher than the reported value ([α]$_{Hg,365}$ = +27.6°, c 0.54, MeOH).$^{4}$ Methanol-d$_4$ was used as the NMR-solvent in earlier reports, but the broad H$_2$O-peak that appears at ca. 5 ppm masked some important peaks such as methylene of Cbz and also via proton-deuterium
Figure 1.3.2 $^1$H-NMR Spectra of 1.24b in CDCl$_3$ and 1.25 in (CD$_3$CN/CDCl$_3$.)
exchange, the other amide peaks were not seen. To circumvent this problem, CD$_3$CN-CDC$_3$ (ca 7:3 mixture) was used in our case as the NMR solvent and $^1$H-NMR spectrum (Figure 1.3.2) clearly exhibited amide-proton peaks and methylene peaks of Cbz and also demonstrated the disappearance of two methylene peaks of the 2-iodoethyl ester protecting group in the product.

Another crucial problem to be addressed was the possible racemization of the two-step deprotection sequence (i.e., Finkelstein reaction and deprotection by Sml$_2$). For this critical issue, a racemization-prone phenylglycine derivative was used for the model study following the standard reaction condition (Scheme 1.3.10).

![Chemical Reaction Diagram]

**Reaction Conditions, Reagents and Yields:**
(a) 2-Bromoethanol (1.2 equiv), DCC (1.1 equiv), pyridine (2.0 equiv), 0 °C, N$_2$, 16 h, 86%
(b) NaI (5.0 equiv), acetone, reflux, 7 h, 87%
(c) Sml$_2$(6.0 equiv), THF, 40 °C, 8 h, Ar, 89%

**Scheme 1.3.10** Control Experiment of Sml$_2$-Mediated Deprotection using N-Cbz, R-Phenylglycine 2-Bromoethyl Ester as a Model Compound

The optical rotation of starting acid has been compared with that of the recovered acid and it was confirmed unchanged. So, this two-step sequence provided a nice,
racemization-free, breakthrough for deprotection of 2-bromoethyl ester protecting group.

As a last stage, we turned our attention to a possible direct way to prepare the 2-iodoethyl ester-protected condensation product 1.24b. Conversion of 1.23' to 1.22d by treatment with 2-iodoethanol/DCC in methylene chloride at 0 °C, followed by Ru-complexation and condensation, produced the diaryl ether Ru-complex 1.23d in 59% yield. This Ru-complex 1.23d was found to be less stable than its Br-counterpart 1.23c because, after filtering it through a Celite pad, when it was passed through a short neutral alumina column, the yield was decreased appreciably and the purity only marginally improved (confirmed by 1H-NMR). The [α]D value (+34.8°, c 0.69, CHCl₃) of 1.24b from the direct process is nearly the same as that (+34.3°, c 0.58, CHCl₃) acquired from the two-step sequence and this is further supporting evidence for racemization-free two-step sequence. Even though one more step (Finkelstein reaction) was required, the two-step sequence is better than direct sequence in terms of overall yield.

Since the carboxylic acid 1.25 has been previously employed by Evans' group as an advanced intermediate for the total synthesis fo K-13, the present work constitutes a formal total synthesis of this natural product.
1.4 CONCLUSIONS

Several amino acid intermediates were asymmetrically synthesized in practical yields by using Evans' auxiliary, and Ru-complexation of arylamino acid with appropriate protecting groups was accomplished by refluxing with [(CH$_3$CN)$_3$Ru$^+$Cp]PF$_6^-$ in 1,2-dichloroethane under N$_2$. The condensations of aryl Ru-complexes and phenolic-dipeptide by use of a sterically hindered weak base (Na 2,6-di-t-butylphenoxide) were accomplished successfully when 2-bromoethyl ester was used as carboxylic protecting group. Among the various acid protecting groups examined, 2-bromoethyl ester was best in complexation, condensation and demetallation reactions. The two-step sequence of Finkelstein reaction and deprotection by SmI$_2$ provided a versatile, reproducible method for the synthesis of carboxylic acids from these kinds of molecules. We strongly believe that these strategies developed can be directly applicable to our long-term program of total synthesis of ristocetin A and related molecules as discussed in Chapter 3.
1.5 EXPERIMENTAL SECTION

General: All reactions were conducted under dry N₂ except the SmI₂-mediated deprotection reaction (under deoxygenated-, dry-Ar). ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) spectra were recorded in CDCl₃, CD₃CN-CDCl₃ on a Varian Gemini-300 spectrometer. ¹H-NMR was referenced to TMS and ¹³C-NMR was referenced to CHCl₃ (77.0 ppm). IR spectra were recorded on a Perkin-Elmer Series 1600 FT-IR using CHCl₃ or CH₂Cl₂ as solvent. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. Mass spectra were recorded on a Kratos MS-25A instrument and CHN analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed using E. Merck Silicagel 60 F-254 0.25mm plates. Visualization was accomplished with UV, phosphomolybdic acid or ninhydrin solution. Flash chromatography was carried out on E. Merck 320-400 mesh silica gel and solvents are reported as V/V percent mixtures. Analytical HPLC was performed on a Rainin HPLC using Dynamax-60A normal phase analytical column. THF was distilled from the sodium ketyl of benzophenone. CH₂Cl₂, Et₃N and CH₂CN were distilled from calcium hydride. All solvents were distilled under dry nitrogen. n-Butyllithium in hexane was obtained from Aldrich Co. and standardized according to the method of Duhamel and Plagnevant. SmI₂ (0.1 M in THF) was purchased from Aldrich Co. and used directly without titration. All other commercial reagents were purchased from Aldrich Co. and used without further purification.
(3-Hydroxy-4-methoxy)cinnamic acid (1.7). To a stirred solution of the commercially available 3-hydroxy-4-methoxybenzaldehyde (1.6, 10.0 g, 65.7 mmol) in 40 mL of distilled pyridine was added 10.0 g (1.46 equiv) of malonic acid and 1.0 mL of piperidine and the reaction mixture was heated to 105 °C for 3 h and 145 °C for 1 h under N₂. After cooling to rt, the mixture was poured over a mixture of 80 g of ice and 25 mL of conc HCl. The aqueous mixture was filtered and the filter cake was washed well with 100 mL of cold water and dried in vacuo to give 10.55 g (86%) of crude 1.7 as a pale-orange solid, which was used for the next reaction without further purification: mp 229.5-231.5 °C (dec) (lit²⁵ 230 °C, dec); R_f 0.71 (MeOH/EtOAc, 5/5).

3-[(3-Hydroxy-4-methoxy)phenyl]propionic acid (1.8). A solution of 1.7 (5.0 g, 25.8 mmol) in 30 mL of MeOH was added to a stirred, pre-saturated (by H₂) slurry of Pd-C (10%) (500 mg) in MeOH (20 mL) and the resulting slurry was stirred at rt for 12 h under H₂ (1 atm). The mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo to afford 4.42 g (88%) of 1.8 as a white solid, which was used directly in the following reaction: mp 146.5-148.0 °C (lit²⁶ 146.0 °C); R_f 0.32 (hexanes/EtOAc, 2/8); IR (CHCl₃) 3538, 3018, 2939, 1711, 1593, 1513, 1443, 1273, 1220 cm⁻¹; ¹H NMR (CDCl₃) δ 7.89-7.47 (bs, 1H, phenolic H), 6.79-6.67 (m, 3H, aromatic Hs), 3.87 (s, 3H, -OCH₃), 2.87 (t, 3H, J = 7.6 Hz, ArCH₂CH₂⁻), 2.64 (t, 3H, J = 7.6 Hz, ArCH₂CH₂⁻).

3-[(3-Benzylxoxy-4-methoxy)phenyl]propionic acid Benzyl Ester (1.9).
To a stirred suspension of crude 1.8 (4.12 g, 21.0 mmol) and 8.70 g (3.0 equiv) of K$_2$CO$_3$ in 60 mL of dry acetone was added 5.35 mL (2.1 equiv) of benzyl bromide in one portion. The reaction mixture was refluxed for 20 h under N$_2$, cooled to rt, then filtered through a Celite pad. The filter cake was washed well with acetone and the combined organic layers were evaporated to give the crude product. Purification by flash chromatography on silica gel (hexanes/EtOAc, 85/15) provided 8.29 g (89%) of 1.9 as a white solid; mp 60.0-61.5 °C; R$_f$ 0.32 (hexanes/EtOAc, 8/2); IR (CHCl$_3$) 3020, 2954, 1734, 1591, 1515, 1214 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.45-7.26 (m, 10H, aromatic Hs), 6.83-6.75 (m, 3H, aromatic Hs), 5.09 (s, 4H, ArOCH$_2$Ph overlapping with $-$CO$_2$CH$_2$Ph), 3.86 (s, 3H, $-OCH_3$); $^{13}$C NMR (CDCl$_3$) δ 172.7, 148.2, 148.1, 137.1, 135.9, 132.9, 128.5, 128.2, 127.8, 127.3, 120.8, 114.4, 111.9, 71.0, 66.2, 56.0, 36.1, 30.4; HRMS calcd for C$_{24}$H$_{24}$O$_4$ 376.1674, found 376.1666.

3-[(3-Benzylxloxy-4-methoxy)phenyl]propionic acid (1.10). To a stirred solution of 1.9 (5.38 g, 14.3 mmol) in 30 ml of THF, 20 mL of MeOH and 20 mL of water was added a solution of 1.68 g (2.10 equiv) of KOH in 10 mL of water and the mixture was stirred for 2 h at rt. The organic solvent was removed in vacuo and the aqueous layer was acidified to ca. pH 2 with 5N HCl, then extracted with EtOAc (30 mL x 3). The combined organic extracts were washed with brine, dried over MgSO$_4$ and the solvent was removed in vacuo to give the crude product which was purified by recrystallization (EtOAc/hexanes, 6/4) to afford 3.59 g (1st crop) of pure product 1.10. The residue was concentrated and flash-chromatographed on silica gel (hexanes/EtOAc, 2/8) to give the second crop (324 mg).
of 1.10. Total yield: 3.91 g (96%); mp 122.5-124.5 °C; Rf 0.41 (hexanes/EtOAc, 2/8); IR (CHCl₃) 3522, 3017, 2935, 1710, 1591, 1515, 1214 cm⁻¹; ¹H NMR (CDCl₃) δ 7.45-7.26 (m, 5H, aromatic Hs), 6.84-6.74 (m, 3H, aromatic Hs), 5.13 (s, 2H, -OCH₂Ph), 3.86 (s, 3H, -OCH₃), 2.85 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-), 2.60 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-); ¹³C NMR (CDCl₃) δ 179.0, 148.2, 148.0, 1137.1, 132.6, 128.5, 127.8, 127.3, 120.7, 114.5, 111.9, 71.0, 56.0, 35.7, 30.0; HRMS calcd for C₁₇H₁₈O₄ 286.1205, found 286.1210.

(4S)-3-Benzylxoy-4-methoxy-[3-oxo-3-[2-oxo-4-[(phenylmethyl)-3-oxazolidinyl]propyl]benzene (1.11). To a stirred solution of 1.10 (1.57 g, 5.47 mmol) in 50 mL of dry THF at -78 °C was added freshly distilled Et₃N (0.99 mL, 1.30 equiv) and followed by distilled pivaloyl chloride (0.74 mL, 1.10 equiv). The mixture was stirred for 15 min at -78 °C and 50 min at rt to form the mixed anhydride, then cooled again to -78 °C under N₂. In a separate flask, 0.90 g (1.0 equiv) of (4S)-4-(phenylmethyl)-2-oxazolidinone in 30 mL of THF at -78 °C was added 2.33 mL (2.35M, 1.0 equiv) of n-BuLi by syringe and the solution was stirred for 20 min at -78 °C under N₂. The mixture was transferred to the above mixed anhydride solution via cannula and the resulting mixture was stirred for 15 min at -78 °C and 4 h at rt. After quenching the reaction with 30 mL of NaHSO₄ (1.0 N) and removal of THF in vacuo, the product was extracted into CH₂Cl₂ (30 mL x 3). The combined extracts were washed with dilute NaHCO₃, brine, dried over MgSO₄ and concentrated in vacuo to afford the crude product as a yellow residue. The first crop (1.89 g) of pure product was obtained by recrystallization (hexanes/EtOAc, 6/4) and the residue was flash-
chromatographed on silica gel (hexanes/EtOAc, 7/3) gave the second crop (138 mg) of pure product. Total Yield: 2.03 g (83%); mp 122.0-123.5 °C; [α]_{D}^{22} +41.9° (c 0.49, CHCl_{3}); Rf 0.23 (hexanes/EtOAc, 7/3); IR (CHCl_{3}) 3019, 2924, 1781, 1700, 1515, 1255, 1214 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.47-7.16 (m, 10H, aromatic Hs), 6.84 (m, 3H, aromatic Hs), 5.14 (s, 2H, -OCH\(_2\)Ph), 4.68-4.60 (m, 1H, -NCH\(_2\)O-), 4.17-4.13 (m, 2H, -NCH\(_2\)H\(_2\)O-), 3.86 (s, 3H, -OCH\(_3\)), 3.31-3.12 (m, 3H, ArCH\(_2\)CH\(_2\)CO- overlapping with -NCHCH\(_2\)Ph), 2.92 (t, 2H, J = 7.0 Hz, ArCH\(_2\)CH\(_2\)CO-), 2.74 (dd, 1H, J = 13.4, 9.5 Hz, -NCHCH\(_2\)HPh); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 172.4, 153.4, 148.1, 148.0, 137.1, 135.1, 132.9, 129.4, 128.9, 128.5, 127.7, 127.4, 121.1, 114.6, 111.9, 71.0, 66.1, 56.1, 55.1, 37.8, 37.2, 29.8; HRMS calcd for C\(_{27}\)H\(_{27}\)N\(_{1}\)O\(_{5}\) 445.1889, found 445.1890.

\((4S,2S)-3\)-Benzyloxy-4-methoxy-[2-azido-3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (1.12a). To a pre-cooled (-78 °C), stirred solution of 17.2 mL (1.30 equiv) of KHMDS (0.5M in toluene) in 30 mL of dry THF was added 2.95 g (1.0 equiv) of 1.11 in 40 mL of dry THF via cannula and the resulting mixture was stirred for 30 min at -78 °C under N\(_2\). To this mixture was transferred a precooled (-78 °C) solution of trisylazide (2.25 g, 1.10 equiv) in 40 mL of dry THF via cannula and the resulting mixture was stirred for 2 min at -78 °C, then rapidly quenched by the addition of 1.14 mL of glacial acetic acid, followed by immediate warming to 30 °C with a water bath. The white slurry was stirred further for 3 hr at rt., then partitioned between 130 mL of CH\(_2\)Cl\(_2\) and brine (50 mL), and the aqueous layer was washed with CH\(_2\)Cl\(_2\) (30 mL x 2). The combined organic extracts were washed with dilute NaHCO\(_3\), brine, dried over MgSO\(_4\), and evaporated to afford a pale yellow residue
which was purified by flash chromatography on silica gel (hexanes/EtOAc, 8/2). Further purification by recrystallization (hexanes/EtOAc, 9/1) gave 2.28 g (71%) of 1.12a as a diastereomerically pure product. The diastereomeric-minor product 1.12b was separated by successive elutions (>20 times) of the crude product loaded on a prep-TLC (silica, hexanes/EtOAc, 85/15), and the diastereoselectivity was determined to be 97:3 by HPLC (RAININ HPXL, 284 nm, Dynamax-60A normal phase analytical column, hexanes/EtOAc = 8/2, 2 mL/min, rt (1.12a) = 13.3 min, rt (1.12b) = 9.7 min): mp 93.5-94.5 °C; [α]$_{22}^{D}$ +75.5° (c 0.50, CHCl₃); R$_f$ 0.22 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3023, 2936, 2110, 1782, 1707, 1515, 1258, 1219 cm$^{-1}$; $^1$H NMR (CDCl₃) δ 7.47-7.20 (m, 10H, aromatic Hs), 6.85 (m, 3H, aromatic Hs), 5.19 (dd, 1H, J = 9.1, 5.6 Hz, ArCH₂CN₃-), 5.15 (s, 2H, -OCH₂Ph), 4.54 (m, 1H, -NCH CH₂O-), 4.20-4.05 (m, 2H, -NCHCH₂O-), 3.87 (s, 3H, -OCH₃), 3.30 (dd, 1H, J = 13.4, 3.2 Hz, -NCHCHPh), 3.11 (dd, 1H, J = 13.6, 5.5 Hz, ArCHHCN₃-), 2.93 (dd, 1H, J = 13.6 Hz, 9.1 Hz, ArCHCHCN₃-), 2.82 (dd, 1H, J = 13.4, 9.4 Hz, -NCHCHPh); $^{13}$C NMR (CDCl₃) δ 170.5, 152.8, 148.9, 148.1, 136.9, 134.7, 129.4, 129.0, 128.5, 127.9, 127.8, 127.5, 122.0, 114.9, 111.8, 70.9, 66.5, 61.4, 56.0, 55.4, 37.6, 37.2.; HRMS calcd for C$_{27}$H$_{26}$N$_{4}$O$_{5}$ 486.1903, found 486.1900.

(4S,2R)-3-Benzylxy-4-methoxy-[2-azido-3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]propyl]benzene (1.12b). [α]$_{21}^{D}$ +30.0° (c 0.34, CHCl₃); R$_f$ 0.26 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3027, 2935, 2110, 1782, 1708, 1516, 1257, 1210 cm$^{-1}$; $^1$H NMR (CDCl₃) δ 7.45-7.13 (m, 10H, aromatic Hs), 6.96-6.84 (m, 3H, aromatic Hs), 5.15 (s, 2H, -OCH₂Ph), 5.12 (dd, 1H, J = 9.4, 4.9 Hz, ArCH₂CN₃-), 4.77-4.69 (m, 1H, ...
(2S)-[2-Azido-3-[(3-benzyloxy-4-methoxy)phenyl]propionic acid Methyl Ester (1.13). To a pre-cooled (0 °C) solution of 1.12 g (2.42 mmol) of 1.12a in 40 mL of THF and 10 mL of water was added
1.48 mL of H₂O₂ (30 %, 6.0 equiv) followed by 9.7 mL of LiOH solution (0.5M). The mixture was stirred for 1.5 h at 0 °C, quenched by addition of 10.6 mL of Na₂SO₃ (1.5 N, 6.6 equiv) solution and the resulting solution stirred further for 15 min at 0 °C. After the solution was buffered to basic with saturated NaHCO₃ and removal of THF under reduced pressure, the oxazolidinone was recovered with CH₂Cl₂ (10 mL x 3). The aqueous layer was acidified with 5N HCl to ca. pH 2, then extracted with EtOAc (30 mL x 3), dried over MgSO₄, concentrated in vacuo to afford (775.0 mg, 98%) of crude acid 1.12'.

The crude acid 1.12' (719.0 mg, 2.20 mmol) was dissolved in 30 mL of anhydrous MeOH containing 418.0 mg (1.0 equiv) of PTSA and the reaction mixture was heated at reflux for 8 hr under N₂. After cooling to rt, the mixture was treated with saturated NaHCO₃ to basic solution, extracted with EtOAc (30 mL x 2), washed with brine, dried over MgSO₄ and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes/EtOAc, 8/2) gave 6.33 mg (84%) of 1.13 as a colorless oily product which was solidified in a refrigerator: mp 38.0-39.5 °C; [α]ᵢ²°₃ -31.6° (c 0.52, CHCl₃), Rf 0.32 (hexanes/EtOAc, 8/2); IR (CHCl₃) 3024, 2956, 2109, 1744,
1592, 1516, 1260, 1214 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.46-7.26 (m, 5H, aromatic Hs), 6.77 (m, 3H, aromatic Hs), 5.15 (s, 2H, -OCH\(_2\)Ph), 3.97 (dd, 1H, J = 8.7, 5.4 Hz, ArCH\(_2\)CHN\(_3\)-), 3.88 (s, 3H, -OCH\(_3\)), 3.74 (s, 3H, -OCH\(_3\)), 3.06 (dd, 1H, J = 14.1, 5.3 Hz, ArCH\(_2\)CHN\(_3\)-), 2.89 (dd, 1H, J = 14.1, 8.6 Hz, ArC\(_2\)H\(_2\)CHN\(_3\)-);
\(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 170.4, 148.9, 148.1, 137.0, 128.5, 128.2, 127.8, 127.3, 121.9, 115.2, 111.8, 71.0, 63.4, 56.0, 52.6, 37.2; HRMS calcld for C\(_{18}\)H\(_{19}\)N\(_3\)O\(_4\) 341.1375, found 341.1380.

(3-Hydroxy-4-methoxy)-L-phenylalanine Methyl Ester (1.3). A solution of 1.13 (3.30 g, 9.67 mmol) in 20 mL of THF was added to a stirred, presaturated (by H\(_2\)) slurry of Pd-C (10%) (400 mg) in 30 mL of THF and the resulting mixture was stirred for 8 h at rt under H\(_2\) (1 atm). After filtration over a Celite pad, the solution was concentrated under reduced pressure to afford the solid residue which was chromatographed on silica gel (EtOAc/MeOH, 95/5). Further purification by recrystallization from diethyl ether gave 1.86 g (85%) of 1.3 as a white solid: mp 82.5-84.5 °C; [\(\alpha\)]\(_{22}^{D}\) +9.5° (c 0.60, CHCl\(_3\)); R\(_f\) 0.17 (EtOAc/MeOH, 95/5); IR (CHCl\(_3\)) 3542, 3384, 3026, 2955, 1736, 1593, 1513, 1273, 1226 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.78-6.64 (m, 3H, aromatic Hs), 3.87 (s, 3H, -OCH\(_3\)), 3.73 (s, 3H, -OCH\(_3\)), 3.70 (dd, 1H, J = 7.8, 5.1 Hz, ArCH\(_2\)CH -), 3.01 (dd, 1H, J = 13.5, 5.0 Hz, ArC\(_2\)H\(_2\)CH-), 2.77 (dd, 1H, J = 13.5, 7.8 Hz, ArC\(_2\)H\(_2\)CH-); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 175.4, 145.6, 145.6, 130.2, 120.7, 115.4, 110.7, 55.9, 55.8, 52.0, 40.3; HRMS calcld for C\(_{11}\)H\(_{15}\)N\(_1\)O\(_4\) 225.1001, found 225.0980.
N-[(Phenylmethoxy)carbonyl]-L-tyrosine Ethyl Ester (1.15). To a stirred, precooled (0 °C) suspension of commercially available 1.14 (from Sigma Chemicals, 3.69 g, 15.0 mmol) in 40 mL of CH₂Cl₂ and 5 mL of H₂O was added 0.80 g (0.5 equiv) of Na₂CO₃ in one portion and the resulting mixture was vigorously stirred at 0 °C. To this mixture were added 2.42 mL (1.08 equiv) of CbzCl and 1.19 g (0.75 equiv) of Na₂CO₃ in 15 mL of H₂O and the resulting suspension was stirred for 30 min at 0 °C and for 2 h at rt, then diluted with 20 mL of CH₂Cl₂. The aqueous layer was washed with CH₂Cl₂ (10 mL x 2) and the combined organic extracts were washed with brine, dried over MgSO₄ and evaporated to give the crude product. Flash chromatography on silica gel (hexanes/EtOAc, 7/3) and further purification by recrystallization (hexanes/EtOAc, 9/1) afforded 4.66 g (91%) of 1.15 as a white solid: mp 78.5-80.5 °C (lit³¹ 78-80 °C); [α]²²_D  -7.5° (c 1.1, MeOH, lit³¹ ([α]D  -7.4°, c 1.0, MeOH)); Rᶠ 0.33 (CH₂Cl₂/EtOAc, 9/1); IR (CHCl₃) 3598, 3431, 3018, 1718, 1515, 1214 cm⁻¹; ¹H NMR (CDCl₃) δ 7.38-7.31 (m, 5H, aromatic Hs of Cbz), 7.27 (d, 2H, J = 8.5 Hz, aromatic Hs ortho to -OH), 6.95 (d, 2H, J = 8.5 Hz, aromatic Hs meta to -OH), 5.44 (s, 1H, phenolic H), 5.26 (bd, 1H, J = 8.1 Hz, ArCH₂CHNH-), 5.12 (d, 1H, J = 12.4 Hz, PhCHHO-), 5.07 (d, 1H, J = 12.4 Hz, PhCHHO-), 4.63-4.56 (m, 1H, ArCH₂CH-), 4.20-4.13 (m, 2H, -CO₂CH₂CH₃), 3.08-2.96 (m, 2H, ArCH₂CH-), 1.27-1.22 (m, 3H, -CO₂CH₂CH₃); ¹³C NMR (CDCl₃) δ 171.8, 155.8, 155.0, 136.1, 130.4, 128.5, 128.2, 128.0, 127.3, 115.4, 67.0, 61.6, 55.0, 37.5, 14.1.
**N-[(Phenylmethoxy)carbonyl]-O-methyl-L-tyrosine (1.4).** N-Cbz-L-tyrosine ethyl ester (1.15, 4.40 g, 12.8 mmol) was dissolved in 32 mL of NaOH (1.0 N) and the solution was stirred for 15 min at rt, then it was treated alternatively with 1.42 mL of NaOH (5.0N) and 0.70 mL of Me$_2$SO$_4$ with vigorous stirring by four times in all. The resulting mixture was stirred for 2 hr at rt and acidified by the addition of HCl (1.0N) to ca. pH 2, cooled in the refrigerator, then filtered. The crude product was recrystallized from aqueous ethanol to give 3.90 g (92%) of pure product 1.4 as a white needle: mp 110.5-111.5 °C (lit$^{32a}$ 111-112 °C); [α]$_D^{22}$ +12.0° (c 2.02, 95% EtOH) (lit$^{32}$ [α]$_D$ +12.0° (c 2.0, 95% EtOH)); R$_f$ 0.40 (CHCl$_3$/MeOH, 8/2); IR (CHCl$_3$) 3433, 3018, 2956, 1718, 1613, 1514, 1250, 1218 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.34-7.29 (m, 5H, aromatic Hs), 7.06 (d, 2H, J = 8.5 Hz, aromatic Hs, ortho to -OMe), 6.82 (d, 2H, J = 8.5 Hz, aromatic Hs meta to -OMe), 5.15 (bd, 1H, J = 8.4 Hz, ArCH$_2$CHNH$^-$), 5.13 (d 1H, J = 13.0 Hz, PhCHHO$^-$), 5.08 (d, 1H, J = 13.0 Hz, PhCHHO$^-$), 4.69-4.63 (m, 1H, ArCH$_2$CH$^-$), 3.78 (s, 3H, -OCH$_3$), 3.18-3.03 (m, 2H, ArCH$_2$CH$^-$); $^{13}$C NMR (CDCl$_3$) δ 176.3, 158.7, 155.8, 136.0, 130.3, 128.5, 128.2, 128.1, 127.3, 114.1, 67.1, 55.2, 54.7, 36.8.

**N-[N-[(phenylmethoxy)carbonyl]-O-methyl-L-tyrosyl]-L-[(3-hydroxy-4-methoxy)phenyl]alanine Methyl Ester (1.2).** To a stirred, precooled (0 °C) solution of free amine 1.3 (1.71 g, 7.59 mmol) and free acid 1.4 (3.00 g, 1.20 equiv) in 20 mL of THF and 20 mL of DMF were added 1.54 g (1.50 equiv) of HOBT and 1.75g (1.20...
equiv) of EDC. The reaction mixture was stirred for 20 h at 0 °C under N₂, poured over 30 mL of water then it was extracted with EtOAc (50 mL x 3). The combined organic extracts were washed with 10% NaHCO₃, brine and dried over MgSO₄ and concentrated under reduced pressure to give a solid residue. Purification by flash chromatography on silica gel (EtOAc/CH₂Cl₂, 2/8) and further purification by recrystallization from (hexanes/EtOAc, 8/2) afforded 3.33 g (82%) of pure product 1.2 as a white solid: mp 131.5-133.5 °C; [α]^{23}_{D} +45.2° (c 1.1, CHCl₃); R₆ 0.27 (CH₂Cl₂/EtOAc, 8/2); IR (CHCl₃) 3542, 3418, 3015, 2956, 1740, 1718, 1680, 1513 cm⁻¹; ¹H NMR (CDCl₃) δ 7.43-7.13 (m, 5H, aromatic Hs of Cbz), 7.10-6.78 (m, 4H, aromatic Hs of Ar−OMe), 6.69-6.42 (m, 3H, aromatic Hs of Ar−OMe−OH), 6.12 (bd, 1H, J = 7.6 Hz, Ar−OMe−OHCH₂CHNH−), 5.65 (s, 1H, phenolic H of Ar−OMe−OH), 5.29 (bd, 1H, J = 8.4 Hz, PhCH₂CO₂NH−), 5.10 (s, 2H, PhCH₂OCONH−); 4.74-4.68 (m, 1H, Ar−OMe−OHCH₂CHNH−), 4.37-4.30 (m, 1H, Ar−OMeCH₂CHC−), 3.83 (s, 3H, -OCH₃), 3.77 (s, 3H, -OCH₃), 3.70 (s, 3H, -OCH₃), 3.00-2.90 (m, 4H, Ar−OMe−OHCH₂CHNH− overlaapt with Ar−OMeCH₂CHC−); ¹³C NMR (CDCl₃) δ 171.3, 170.4, 158.6, 155.9, 145.8, 145.5, 136.1, 130.3, 128.5, 128.4, 128.2, 128.0, 120.6, 115.5, 114.1, 110.7, 67.1, 56.2, 55.8, 55.2, 53.3, 52.3, 37.5, 37.1; HRMS calcd for C₂₉H₃₂N₂O₈ 536.2159, found 536.2198.

4-Chlorohydrocinnamic acid (1.17). To a stirred, pre-saturated (by H₂) slurry of Pd-C (10%) (30 mg) in 40 mL of THF was added p-chlorohydrocinnamic acid (1.16, 3.00 g, 16.4 mmol) and the resulting mixture was stirred for 4 hr under atmospheric H₂. The Pd-catalyst was filtered off and the solvent was
removed in vacuo to give 2.68 g (88%) of crude product 1.17 which was pure enough for the next reaction. The analytical sample was purified by recrystallization (hexanes/EtOAc, 7/3): mp 120.5-122.0 °C (lit. 122-123 °C); Rf 0.45 (MeOH/CHCl₃, 1/9); IR (CHCl₃) 3019, 2949, 1712, 1493, 1409 cm⁻¹; ¹H NMR (CDCl₃) δ 7.27 (d, 2H, J = 8.5 Hz, aromatic Hs ortho to -Cl), 7.14 (d, 2H, J = 8.5 Hz, aromatic Hs meta to -Cl), 2.93 (t, 2H, J = 7.4 Hz, ArCH₂CH₂⁻), 2.67 (t, 2H, J = 7.4 Hz, ArCH₂CH₂⁻).

(4S)-4-Chloro-[3-oxo-3-[2-oxo-4-(phenylmethyl)-3-oxazolidinyl]-propyl]benzene (1.18). To a stirred solution of 4-chlorohydrocinnamic acid (1.17, 1.44 g, 7.82 mmol) in 40 mL of THF at -78 °C were added 1.42 mL (1.30 equiv) of Et₃N and 1.06 mL (1.10 equiv) of pivaloyl chloride and the resulting mixture was stirred for 15 min at -78 °C, for 45 min at 0 °C and then cooled again to -78 °C. In a separate flask, 1.26 g (1.05 equiv) of (4S)-4-(phenylmethyl)-2-oxazolidinone in 30 mL of THF at -78 °C was added 5.23 mL of n-BuLi (1.05 equiv, 1.57 M) by syringe, then stirred for 20 min at -78 °C. The metallated-oxazolidinone was transferred to the above white slurry via cannula and the resulting slurry was stirred for 15 min at -78 °C, then warmed to rt and stirred for 10 h under N₂. The reaction was quenched with 60 mL of 1N NaHSO₄ solution and THF was removed under reduced pressure. The product was extracted into CH₂Cl₂ (30 mL x 3) and the combined organic layers were washed with dilute NaHCO₃ and brine, then dried over MgSO₄. The solvent was removed in vacuo to provide a pale yellow residue. The first crop (2.14 g) of pure product was obtained by recrystallization (hexanes/EtOAc, 9/1) and second crop (178 mg) of product was obtained by flash chromatography on silica gel (hexanes/EtOAc, 7/3).
from the filtrate. The total yield of pure product 1.18 was 2.31 g (86%): mp 116.5-
118.0 °C; [α]$_{D}^{25}$ +64.2° (c 0.55, CHCl$_3$); R$_f$ 0.35 (hexanes/EtOAc, 7/3); IR (CHCl$_3$
) 3018, 2982, 1781, 1700, 1494, 1385 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.38-7.14, (m, 9H,
_aromatic_ Hs), 4.70-4.62 (m, 1H, -NCH$_2$CH$_2$O-), 4.23-4.14 (m, 2H, -NCH$_2$H$_2$O-),
3.36-3.16 (m, 3H, ArCH$_2$CH$_2$C- overlapped with -CHCHPh), 3.04-2.94 (m, 2H,
ArCH$_2$CH$_2$C-), 2.75 (dd, 1H, J = 13.3, 9.5 Hz, -CHCHPh); $^{13}$C NMR (CDCl$_3$
) δ 172.0, 153.4, 138.9, 135.1, 132.0, 130.0, 129.4, 128.9, 128.5, 127.4, 66.2,
55.1, 37.8, 37.0, 30.0; HRMS calcd for C$_{19}$H$_{18}$N$_1$O$_3$Cl$_1$ 343.0975, found
343.0999.

(4$_S$,2$_S$)-4-Chloro-[2-azido-3-oxo-3-(2-oxo-4-(phenylmethyl)-3-
oxazolidinyl)propyl]benzene (1.19a). A precooled (-78 °C) solution of 1.61
g (4.67 mmol) of 1.18 in 40 mL of dry THF was added
to a precooled (-78 °C) solution of 12.1 mL (0.5M in
toluene, 1.20 equiv) of KHMDS in 30 mL of THF via
cannula and the resulting solution was stirred for 30 min at
-78 °C under N$_2$. To this solution was added a precooled
(-78 °C) solution of 1.59 g (1.10 equiv) of trisylazide in 40 mL of THF via cannula
and the resulting solution was stirred for 2 min at -78 °C under N$_2$, then quenched by
the rapid addition of 0.80 mL (3.0 equiv) of glacial acetic acid, followed by
immediate warming to 30 °C with a water bath. The white slurry was stirred further
for 3h at rt, then partitioned between 150 mL CH$_2$Cl$_2$ and brine and the aqueous layer
was washed again with CH$_2$Cl$_2$ (30 mL x 2). The combined organic layers were
washed with dilute NaHCO$_3$, brine and dried over MgSO$_4$. The solvent was removed
_in vacuo_ to afford a yellow oily product which was purified by flash chromatography
on silica gel (hexanes/EtOAc, 8/2). Recrystallization (hexanes/EtOAc, 9/1) gave 1.36
g (76%) of diastereomerically pure product 1.19a as a white solid. The
diastereomeric minor product 1.19b was separated by multiple elutions (>20 times)
of crude product loaded on a prep-TLC (silica, hexanes/EtOAc, 85/15) and the
diastereoselectivity was determined to be 95: 5 by HPLC (RAININ HPXLC, 254 nm
UV-detector, Dynamax-60A normal phase analytical column, hexanes/EtOAc = 8/2.2
mL/min, rt (1.19a) = 8.7 min, rt (1.19b) = 6.50 min): mp 115.0-117.0 °C; [α]^{22}_D
+84.7° (c 0.55, CHCl₃); R_f 0.33, (hexanes/EtOAc, 7/3); IR (CHCl₃) 3019, 2926,
2112, 1781, 1707, 1494, 1387 cm⁻¹; ¹H NMR (CDCl₃) δ 7.35-7.20, (m, 9H,
aromatic Hs), 5.22 (dd, IH, J = 9.5, 5.1 Hz, ArCH₂CHN₃⁻), 4.66-4.60 (m, 1H,
-NCH₂CH₂O⁻), 4.24-4.14 (m, 2H, -NCHCH₂O⁻), 3.30 (dd, 1H, J = 13.5, 3.2 Hz,
-NCHCH₃HPh), 3.18 (dd, 1H, J = 13.7, 5.2 Hz, ArCHHCH₃⁻), 2.99 (dd, 1H, J
= 13.7, 9.3 Hz, ArCHHCH₃⁻), 2.84 (dd, 1H, J = 13.5, 9.5 Hz, -NCHCH₃HPh),
¹³C NMR (CDCl₃) δ 170.1, 152.8, 134.5, 134.2, 133.2, 130.6, 129.4, 129.1,
128.8, 127.6, 66.6, 61.4, 55.4, 37.5, 36.8; HRMS calcd for C₁₉H₁₇N₂O₃Cl₁ (M-
2N)⁺ 359.0528, found 359.0949.

(4S,2R)-4-Chloro-[2-azido-3-oxo-3-[2-oxo-4-(phenylmethyl)-3-
oxazolidinyl]propyl]benzene (1.19b). The diastereomeric-minor product

was obtained by successive elutions (>20 times) of crude
product loaded on a prep-TLC (silica) with
(hexanes/EtOAc, 85/15) and the diastereoselectivity was
confirmed to be 95: 5 by HPLC: mp 86.0-88.0 °C;
[α]^{22}_D +55.1° (c 0.21, CHCl₃); R_f 0.38
(hexanes/EtOAc, 7/3); IR (CHCl₃) 3026, 2926, 2115, 1782, 1708, 1494, 1387 cm⁻¹
¹H NMR (CDCl₃) δ 7.37-7.15 (m, 9H, aromatic Hs), 5.14 (dd, 1H, J = 9.6, 4.6
Hz, ArCH₂CHN₃⁻), 4.79-4.71 (m, 1H, -NCH₂CH₂O⁻), 4.34-4.23 (m, 2H,
-NCHCH₂O-), 3.29-3.20 (m, 2H, ArCHHCHN₃- overlapped with -NCHCHHPh), 2.98 (dd, 1H, J = 13.7, 9.6 Hz, ArCHHCHN₃-), 2.74 (dd, 1H, J = 13.4, 9.4 Hz, -NCHCHHPh).

(2S)-[2-Azido-3-(4-chlorophenyl)propionic acid (1.20). To a precooled (0 °C) solution of 628 mg (1.63 mmol) of 1.19a in 24 mL of THF and 8 ml of water was added 1.0 mL (6.0 equiv, 30% H₂O₂), followed by 6.53 mL of LiOH (0.5M). The resulting mixture was stirred at 0 °C for 1 h and the excess peroxide was quenched at 0 °C by adding 7.2 mL of Na₂SO₃ solution (1.5N). The solution was buffered to basic with saturated aqueous NaHCO₃ and after the removal of THF in vacuo, the oxazolidinone was recovered by extraction (CH₂Cl₂, 15 mL x 3). The aqueous layer was acidified to ca. pH 2 with HCl (5.0N) and the product was extracted with EtOAc (25 mL x 3). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to afford a solid residue. Purification by flash chromatography (silica gel, hexanes/EtOAc, 1/9) gave 338 mg (92%) of pure product 1.20 as a white solid: [α]²¹_D -55.7° (c 0.52, CHCl₃); Rf 0.16 (EtOAc/MeOH, 85/15); IR (CHCl₃) 3026, 2112, 1722, 1494 cm⁻¹; ¹H NMR (CDCl₃) δ 9.38 (bs, 1H, -CHCO₂H), 7.32 (d, 2H, J = 8.4 Hz, aromatic Hs ortho to -Cl), 7.20 (s, 2H, J = 8.4 Hz, aromatic Hs meta to -Cl), 4.15 (dd, 1H, J = 8.7, 5.0 Hz, ArCH₂CH-), 3.19 (dd, 1H, J = 14.2, 5.0 Hz, ArCHHCH-), 3.00 (dd, 1H, J = 14.2, 8.7 Hz, ArCHHCH-); ¹³C NMR (CDCl₃) δ 175.5, 134.0, 133.4, 130.6, 128.9, 62.8, 36.7; HRMS calcd for C₉H₈N₃O₂Cl₁ 225.0305, found 225.0291.
(2S)-[2-Azido-3-(4-chlorophenyl)]propionic acid 2-Methoxyethoxy-methyl Ester (1.21). To a stirred, pre-cooled (0 °C) solution of 1.20 (0.66 g, 2.92 mmol) in 20 mL of CH₂Cl₂ were added 0.56 mL (1.10 equiv) of (i-Pr)₂NEt and 400 µL (1.20 equiv) of MEMCl and the resulting solution was stirred at 0 °C for 2 h under N₂. The reaction was quenched by adding 3.0 mL (0.1 equiv) of 0.1N HCl. The product was extracted with CH₂Cl₂ (20 mL x 3) and the combined extracts were washed with brine and dried over MgSO₄. After evaporation of solvent in vacuo, the crude product was flash-chromatographed on silica gel (hexanes/EtOAc, 7/3) afforded 691.4 mg (75%) of pure product 1.21 as a colorless liquid: Rf 0.31 (hexanes/EtOAc, 7/3) [α]D₂₁ -43.6° (c 0.69, CHCl₃); IR (CHCl₃) 3016, 2932, 2111, 1747 cm⁻¹; ¹H NMR (CDCl₃) δ 7.30 (d, 2H, J = 8.4 Hz, aromatic Hs ortho to -Cl), 7.18 (d, 2H, J = 8.4 Hz, aromatic Hs meta to -Cl), 5.41 (dd, 2H, J = 8.7, 6.0 Hz, -CO₂CH₂OCH₂-), 4.09 (dd, 1H, J = 8.4, 5.5 Hz, ArCH₂CH-), 3.74-3.71 (m, 2H, -CO₂CH₂CH₂O-), 3.55-3.52 (m, 2H, -CO₂CH₂CH₂O-), 3.16 (dd, 1H, J = 8.4, 5.5 Hz, ArCHHCH-), 3.00 (dd, 1H, J = 14.1, 8.4 Hz, ArCHHCH-); ¹³C NMR (CDCl₃) δ 169.2, 134.3, 133.2, 130.6, 128.8, 90.7, 71.3, 69.9, 63.0, 59.1, 36.7; HRMS calcd for C₁₃H₁₆N₁O₄Cl₁ (M-2N)⁺ 285.0768, found 285.0766.

N-[(1,1-Dimethylethoxy)carbonyl]-L--(4-chlorophenyl)alanine 2-Methoxyethoxymethyl Ester (1.22a). (i) With Pd-C (10%) catalyst: A suspension of 6.30 mg of Pd-C (10%) in 5 mL THF was vigorously stirred under H₂ (1 atm) for 1 h. To this was added a mixture of 27.9 mg of 1.21 and 23.3 mg (1.20 equiv) of (BOC)₂O in 5 mL THF and the resulting slurry
was stirred for 4 h at rt, filtered through a Celite pad and concentrated in vacuo to give an oily product. Purification by flash chromatography on silica gel (hexanes/EtOAc, 7/3) gave 11.4 mg (33%) of pure product 1.22a which was solidified in the refrigerator: mp 39.0-40.5 °C; [α]21D +21.7° (c 0.71, CHCl3); Rf 0.24 (hexanes/EtOAC, 7/3); IR (CHCl3) 3016, 2982, 1746, 1710, 1493 cm⁻¹; ¹H NMR (CDCl3) δ 7.27 (d, 2H, J = 8.5 Hz, aromatic Hs ortho to -Cl), 7.10 (d, 2H, J = 8.5 Hz, aromatic Hs meta to -Cl), 5.40 (d, 1H, J = 6.1 Hz, -CO₂CH₂HO⁻), 5.32 (d, 1H, J = 6.1 Hz, -CO₂CH₂HO⁻), 4.99 (bd, 1H, J = 7.9 Hz, ArCH₂CH₂NH⁻), 4.62-4.55 (m, 1H, ArCH₂CH₂NH⁻), 3.73-3.69 (m, 2H -OCH₂CH₂O⁻), 3.55-3.52 (m, 2H, -OCH₂CH₂O⁻), 3.39 (s, 3 H, -CH₂CH₂OCH₃), 3.17-3.01 (m, 2H, ArCH₂CH₂NH⁻), 1.42 (s, 9H, -BOC); ¹³C NMR (CDCl3) δ 171.2, 155.0, 134.4, 132.9, 130.7, 128.7, 90.3, 80.1, 71.4, 69.8, 59.0, 54.3, 37.5, 28.2; HRMS calced for C₁₈H₂₆N₁O₆Cl₁ 387.1449, found 387.1464. (ii) With Raney-Ni catalyst: To a stirred solution of 264 mg (0.84 mmol) of 1.21 in 20 mL of CH₂Cl₂ was added 20 mg of Raney-nickel (washed successively with water (x3), methanol (x3), and CH₂Cl₂ (x3) previously). The reaction slurry was stirred overnight under H₂ atmosphere, filtered through a Celite pad and concentrated under reduced pressure to provide an oily residue. Purification by flash chromatography on silica gel (hexanes/EtOAc, 7/3) gave 144 mg (44%) of pure product 1.22a as a white solid:

All the physical data (including spectral data) were same as those from procedure (i).

(4S,2S)-4-Chloro-[2-[[1,1-dimethylethoxy]carbonyl]amino]-3-oxo-3-[2-oxo-4-phenylmethyl-3-oxazolidinyl]propyl]benzene (1.23). (i) One-step (in situ) protection with Pd-C (10%) catalyst: To a stirred, pre-saturated (by H₂) slurry of Pd-C (10%) (30 mg) in 20 mL of CH₂Cl₂ was added 291 mg of 1.19a
(0.76 mmol) and 330 mg (2.0 equiv) of (BOC)$_2$O. The resulting mixture was stirred for 30 h at rt under H$_2$ atmosphere, then filtered through a Celite pad. The filter cake was washed with CH$_2$Cl$_2$ (10 mL x 2) and the combined organic layers were concentrated in vacuo to give a solid residue which was purified by flash chromatography on silica gel (hexanes/EtOAc, 8/2), affording 159.0 mg (46%) of pure sample 1.23. (ii) Two-step protection with Pd-C (10%) catalyst: To a stirred, pre-saturated (by H$_2$) slurry of Pd-C (10%) (265 mg) in 40 mL of THF and 10 mL of MeOH was added 2.654 g (6.90 mmol) of 1.19a and 2.76 mL (2.0 equiv) of 5N HCl. The resulting suspension was stirred for 8 h at rt under atmospheric pressure of H$_2$. The reaction mixture was filtered through a Celite pad and the filter cake was washed well with THF/MeOH (1:1, 10 mL x 3). The combined organic layers were evaporated to give amine·HCl salt as a white solid. To this crude amine·HCl salt dissolved in 40 mL of THF and 10 mL of water were added 2.03 g (1.50 equiv) of (BOC)$_2$O and 2.14 g (2.5 equiv) of K$_2$CO$_3$ and the resulting suspension was stirred overnight at rt, then poured over 30 mL of water and extracted with EtOAc (20 mL x 5). The combined organic extracts were washed with saturated brine, dried over MgSO$_4$ and evaporated to give crude product. Flash chromatography of the crude product on silica gel (hexanes/EtOAc, 8/2) afforded 2.69 g (85%) of pure product 1.23 as a white solid. (All the data were same for both methods): mp 150.0-152.0 °C; [α]$^2_2$D +80.1° (c 0.49, CHCl$_3$); R$_f$ 0.25 (hexanes/EtOAc, 7/3); IR (CHCl$_3$) 3440, 3027, 2930, 1784, 1703, 1492, 1385, 1368 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.37-7.18 (m, 9H, aromatic Hs), 5.72-5.65 (m, 1H, ArCH$_2$CH-), 5.15 (bd, 1H, J = 7.0 Hz, ArCH$_2$CHNH-), 4.62-4.57 (m, 1H, -NCH$_2$CH$_2$O-), 4.22-4.11 (m, 2H,
-NCHCH$_2$O-), 3.33 (dd, 1H, J = 13.6, 1.3 Hz, -NCHCHPh), 3.14 (dd, 1H, J = 12.2, 2.0 Hz, ArCHHCH-), 2.81-2.74 (m, 2H, ArCHHCH- overlapped with -NCHCHPh), 1.38 (s, 9H, -BOC); $^{13}$C NMR (CDCl$_3$) δ 172.6, 155.1, 152.7, 135.0, 134.6, 132.9, 130.8, 129.4, 129.0, 128.6, 127.4, 80.1, 66.5, 55.50, 54.1, 38.0, 37.5, 28.2; HRMS calcd for C$_{20}$H$_{18}$N$_2$O$_4$Cl$_1$ (M-O(CH$_3$)$_3$)$^+$ 385.0955, found 385.0953.

$N$-[(1,1-Dimethylethoxy)carbonyl]-L-(4-chlorophenyl)alanine, 2-Methoxyethoxymethyl Ester (1.22a). (ii) To a pre-cooled (0 °C), stirred solution of 2.28 g (5.38 mmol) of 1.23 in 60 mL of THF and 20 mL of methanol was added 21.5 mL of aqueous LiOH (0.5M, 2.0 equiv) and the resulting mixture was stirred at 0 °C for 1 h, then treated with saturated NaHCO$_3$ to make buffer solution. The organic solvent was removed under reduced pressure at rt and the auxiliary was recovered into CH$_2$Cl$_2$ (30 mL x 3). The aqueous layer was acidified with 1H HCl to ca. pH 5, then the product was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine, dried over MgSO$_4$ and the solvent was evaporated to give 1.25 g (77%) of crude acid 1.23' which was used for next reaction without purification. (ii) To a pre-cooled (0 °C), stirred solution of 218.3 mg (0.73 mmol) of crude acid 1.23' in 20 mL of CH$_2$Cl$_2$ were added 139.9 ml (1.10 equiv) of (i-Pr)$_2$NEt and 119.0 mL (1.20 equiv) of MEMCl and the resulting mixture was stirred for 2 h at 0 °C under N$_2$. The reaction was quenched with 0.73 mL of 0.1N HCl and diluted with 30 mL of CH$_2$Cl$_2$. The organic layer was washed with brine, dried over MgSO$_4$ and the solvent was removed under reduced pressure to give the crude product as a oily residue. Flash chromatography on silica gel (hexanes/EtOAc, 7/3) afforded 271.0 mg (96%) of 1.22a as an oily
product which was solidified in a refrigerator: mp 39.0-40.5 °C; \([\alpha]^{22}_D +21.8^\circ\) (c 0.83, CHCl₃); Every other data were same as before.

**N-[(1,1-Dimethylethoxy)carbonyl]-(4-chloro)-L-phenylalanine 2,2,2-Trichloroethyl Ester (1.22b).** To a pre-cooled (0 °C), stirred solution of

\[
\text{Cl} \\
|\text{O}|
\text{SOCH₃} \\
|\text{OCH₂CCl₃}|
\]

501.4 mg (1.68 mmol) of crude acid 1.23' in 20 mL of CH₂Cl₂ were added 271.2 μL (2.0 equiv) of pyridine and 193.0 μL of 2,2,2-trichloroethanol (1.2 equiv) and the mixture was stirred for 10 min at 0 °C under N₂. To this solution was added 380.5 mg (1.1 equiv) of DCC in one portion and the mixture was stirred overnight at 0 °C under N₂. The reaction was quenched with 22.7 mg (0.15 equiv) of oxalic acid in 0.5 mL THF and the resulting mixture was allowed to come to rt and stirred for 30 min. The mixture was filtered and the filter cake was washed well with CH₂Cl₂ (10 mL x 3). The combined organic extracts were washed with brine, dried over MgSO₄ and the solvent was evaporated to give the crude product. Flash chromatography on silica gel (hexanes/EtOAc, 8/2) and further recrystallization from hexanes afforded 658.5 mg (92%) of 1.22b as a white solid: mp 131.0-133.0 °C; \([\alpha]^{21}_D +8.0^\circ\) (c 0.54, CHCl₃); R_f 0.20 (CH₂Cl₂/hexanes, 7/3); IR (CHCl₃) 3441, 3020, 1759, 1712, 1494 cm⁻¹; ¹H NMR (CDCl₃) δ 7.28 (d, 2H, J = 8.2 Hz, aromatic Hs ortho to -Cl), 7.13 (d, 2H, J = 8.2 Hz, aromatic Hs meta to -Cl), 4.92 (bd, 1H, J = 8.2 Hz, ArCH₂CHNH⁻), 4.81 (d, 1H, J = 12.0 Hz, -CHHCCl₃), 4.72-4.68 (m, 2H, -CHHCCl₃ overlapped with ArCH₂CH⁻), 3.21 (dd, 1H, J = 13.9, 5.6 Hz, ArCHHCH⁻), 3.06 (dd, 1H, J = 13.9, 6.9 Hz, ArCHHCH⁻), 1.41 (s, 9 H, -BOC); ¹³C NMR (CDCl₃) δ 170.3,
$N$-[(1,1-Dimethylethoxy)carbonyl]-(4-chloro)-L-phenylalanine, 2-Bromoethyl Ester (1.22c). Reaction procedures were same as 1.22b except the use of 2-bromoethanol instead of 2,2,2-trichloroethanol: Yield (76%); mp 97.5-79.0 °C; $[\alpha]^{22}_D + 22.5^\circ$ (c 0.63, CH$_2$Cl$_2$); R$_f$ 0.45 (hexanes/EtOAc, 7/3); IR (CHCl$_3$) 3020, 1745, 1709, 1493 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.28 (d, 2H, J = 8.4 Hz, aromatic Hs ortho to -Cl), 7.11 (d, 2H, J = 8.4 Hz, aromatic Hs meta to -Cl), 4.94 (bd, IH, J = 8.2 Hz, ArCH$_2$CHNH$^-$), 4.61-4.59 (m, 1H, ArCH$_2$CH$^-$), 4.44-4.40 (m, 2H, -CH$_2$CH$_2$Br), 3.48 (m, 2H, -CH$_2$CH$_2$Br), 3.14 (dd, 1H, J = 13.8, 5.7 Hz, ArCHHCH$^-$), 3.04 (dd, 1H, J = 13.8, 6.4 Hz, ArCHHCH$^-$), 1.42 (s, 9H, -BOC); $^{13}$C NMR (CDCl$_3$) $\delta$ 171.2, 155.0, 134.3, 133.0, 130.7, 128.7, 80.2, 64.6, 54.2, 37.6, 28.3, 28.1; HRMS calcd for C$_{12}$H$_{12}$N$_{10}$O$_3$Br$_1$Cl$_1$ (M-OC(CH$_3$)$_3$)$^+$ 331.9690, found 331.9683.

$N$-(1,1-Dimethylethoxy)carbonyl]-L-(4-chlorophenyl)alanine, 2-Iodoethyl Ester (1.22d). Reaction procedures were same as 1.22b except the use of 2-iodoethanol instead of 2,2,2-trichloroethanol: Yield (81%); mp 78.5-80.0 °C; $[\alpha]^{26}_D + 15.3^\circ$ (c 0.77, CHCl$_3$); R$_f$ 0.37 (hexanes/EtOAc, 7/3); IR (CHCl$_3$) 3437, 3019, 2981, 1745, 1711, 1601, 1493 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.28 (d, 2H, J = 8.3 Hz, aromatic Hs, ortho to -Cl), 7.11 (d, 2H, J = 8.3 Hz, aromatic Hs meta to -Cl), 4.95
(d, 1H, J = 7.2 Hz, ArCH₂CHNH⁻). 4.59-4.57 (m, 1H, ArCH₂CH⁻), 4.39-4.34 (m, 2H, -CH₂CH₂I), 3.28-3.00 (m, 4H, -CH₂CH₂I overlapped with ArCH₂CH⁻), 1.42 (s, 9H, -BOC); ¹³C NMR (CDCl₃) δ 171.1, 155.0, 134.4, 133.0, 130.7, 128.7, 80.2, 65.4, 54.2, 37.7, 28.3, -0.6; HRMS calcd for C₁₆H₂₁N₁O₄Cl₁I₁ 453.0206, found 453.0213.

[η⁶-[((S)-4-Cloro-[[2-[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-methoxyethoxymethoxy)propyl]benzene]]-η⁵-(cyclopentadienyl)-ruthenium Hexafluorophosphate (1.5a). To a stirred suspension of 183.2 mg (0.47 mmol) of the starting amino ester 1.22a in 15 mL of 1.2-dichloroethane was added 308.3 mg (1.50 equiv) of [(CH₃CN)₃Ru⁺Cp]PF₆⁻ in one portion and the resulting mixture was bubbled with N₂ for 20 min, then heated at reflux for 5 h under N₂.

The reaction mixture was cooled to rt, filtered through a Celite pad (1 x 2 cm) and concentrated in vacuo to give a dark brown residue. The crude product was dissolved in 20 mL of CH₃CN and filtered through a neutral alumina column (1 x 5 cm) to afford a dark brown solution. Removal of solvent in vacuo gave a dark brown residue which was dissolved again in CHCl₃, then passed through a Celite pad (1 x 2 cm). The solvent was evaporated to provide 308.3 mg (95%) of 1.5a as a yellowish brown foam. This product was confirmed to be pure enough for the next reaction by ¹H NMR: IR (CHCl₃) 3024, 2932, 1747, 1706, 1602, 1500 cm⁻¹; ¹H NMR (CDCl₃) δ 6.49-6.30 (m, 4H, aromatic HS), 5.51-5.38 (m, 7H, Cp overlapped with -CO₂CH₂O⁻), 4.47-4.46 (m, 1H, ArCH₂CH⁻), 3.87-3.84 (m, 2H, -OCH₂CH₂O⁻), 3.59-3.56 (m, 2H, -OCH₂CH₂O⁻), 3.38, (s, 3 H, -OCH₃), 3.13 (dd, 1H, J = 14.0
Hz, 4.7 Hz, ArCHHCH-), 2.86 (dd, 1H, J = 14.0, 8.5 Hz, ArCHHCH-), 1.39 (s, 9H, -BOC).

[η⁶-{(S)-4-Chloro-[2-[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2,2,2-trichloroethoxy)propyl]benzene}]-η⁶-(cyclopentadienyl)-ruthenium Hexafluorophosphate (1.5b). The reaction procedures were same as 1.5a except the use of 1.22b instead of 1.22a:

Yield (93%); IR (CHCl₃) 3426, 3019, 2984, 1761, 1706, 1502, 1223 cm⁻¹; ¹H NMR (CDCl₃) δ 6.48-6.32 (m, 4H, aromatic Hs), 5.48 (s, 5H, Cp), 4.88 (d, 1H, J = 11.9 Hz, -CHHCCl₃), 4.82 (d, 1H, J = 11.9 Hz, -CHHCCl₃), 4.56-4.52 (m, 1H, ArCH₂CH⁻), 3.16 (dd, 1H, J = 14.2, 4.9 Hz, ArCHHCH⁻), 2.94 (dd, 1H, J = 14.2, 8.7 Hz, ArCHHCH⁻), 1.38 (s, 9H, -BOC).

[η⁶-{(S)-4-Chloro-[2-[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-bromoethoxy)propyl]benzene}]-η⁶-(cyclopentadienyl) ruthenium Hexafluorophosphate (1.5c). Reaction procedures were same as 1.5a except the use of 1.22c instead of 1.22a: Yield (95%); IR (CHCl₃) 3426, 3020, 2982, 1747, 1707, 1501, 1455 cm⁻¹; ¹H NMR (CDCl₃) δ 6.47-6.28 (m, 4H, aromatic Hs), 5.48 (s, 5H, Cp), 4.53-4.44 (m, 3H, -CH₂CH₂Br overlapped with ArCH₂CH⁻), 3.64-3.58 (m, 2H, -CH₂CH₂Br), 3.13 (dd, 1H, J = 14.1, 4.9 Hz, ArCHHCH⁻), 2.87 (dd, 1H, J = 14.1, 8.0 Hz, ArCHHCH⁻), 1.40 (s, 9H, -BOC).
[\eta^6-((S)-4-Chloro-[[2-[[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-idoethoxy)propyl]benzene]]-\eta^5-(cyclopentadienyl)ruthenium

Hexafluorophosphate (1.5d). The reaction procedures were same as 1.5a except the use of 1.22d instead of 1.22a: Yield (98%); IR (CHCl₃) 3427, 3019, 2981, 1745, 1709, 1602, 1499, 1456 cm⁻¹; ¹H NMR (CDCl₃) δ 6.47-6.28 (m, 4H, aromatic Hs), 5.48 (s, 5H, C₅H), 4.48-4.43 (m, 3H, ArCH₂CH₂- overlapped with -CH₂CH₂I), 3.40-3.36 (m, 2H, -CH₂CH₂I), 3.14 (dd, 1H, J = 14.1, 4.9 Hz, ArCHHCH₂-), 2.87 (dd, 1H, J = 14.1, J = 8.2 Hz, ArCHHCH₂-), 1.40 (s, 9H, -BOC).

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[\eta^6-((S,S)-[4-[2-Methoxy-5-[N-[O-methyl-N-[((phenylmethoxy)carbonyl]-L-tyrosyl]]-2-amino-3-oxo-3-methoxy)propyl]phenoxy-1-[2-[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-methoxyethoxy)methoxy]propyl]benzene]]-\eta^5-(cyclopentadienyl)ruthenium Hexafluorophosphate (1.23a). (i) The sterically hindered-, weak basic-stock solution was made first: Into a 50 mL of round bottom flask containing 276.0 mg (1.34 mmol) of 2,6-di-t-butylphenol and NaH (53.5 mg, 1.0 equiv, 60% in mineral oil) was added 20 mL of freshly distilled THF by syringe and the resulting slurry was stirred for 30 min at rt under N₂, then cooled to 0 °C. (ii) To a stirred, pre-cooled (0 °C) solution of 361.9 mg (0.67 mmol) of 1.2 was added 9.60 mL (1.10 equiv) of basic-stock solution by
syringe and the mixture was stirred for 15 min at 0 °C under N₂, then transferred via cannula into a precooled (-78 °C) solution of 1.5a (471.5 mg, 1.0 equiv) in 15 mL of THF. The resulting mixture was stirred for 1 hr at -78 °C, 3.5 h at rt under N₂. the reaction mixture was filtered through a Celite pad, concentrated in vacuo to give a dark brown residue which was dissolved in 15 mL of acetonitrile. The resulting solution was filtered through a neutral alumina column (1 x 5 cm) and the filtrate was concentrated to ca. 1 mL under reduced pressure which was diluted with 40 mL of diethyl ether. The ethereal solution was cooled in a refrigerator, decanted and the brown residue was further washed with cold diethyl ether (10 mL x 3). The residue was dried in vacuo to afford 230.5 mg (29%) of 1.23a as a pale brown solid foam: IR (CHCl₃) 3422, 3016, 2981, 1740, 1711, 1513, 1478 cm⁻¹; ¹H NMR (CDCl₃) δ 7.38-6.78 (m, 12H, aromatic Hs of Ar-O-Me, Cbz, Ar-O-Me-O-), 6.44 (d, 1H, J = 6.3 Hz, Ar-O-Me-O-CH₂CHNH-), 6.15-5.95 (m, 4H, aromatic Hs of ArRu+), 5.52-5.31 (m, 9H, PhCH₂OCONH- overlapped with ArRu+CH₂CHNH-, C₆H₆, -CO₂CH₂O-), 5.07 (s, 2H, PhCH₂OCO-), 4.79-4.75 (m, 1H, Ar-O-Me-O-CH₂CHNH-), 4.42-4.31 (m, 2H, Ar-O-CH₂CHNH- overlapped with Ar-O-MeCH₂CHCO-), 3.87-3.84 (m, 2H, -OCH₂CH₂O-), 3.79 (s, 3H, -OCH₃), 3.77 (s, 3H, -OCH₃), 3.70 (s, 3H, -OCH₃), 3.58-3.55 (m, 2H, -OCH₂CH₂O-), 3.37 (s, 3H, -OCH₂CH₂OCH₃), 3.08-2.82 (m, 6H, benzyl Hs of Ar-O-Me-O-, ArRu+, Ar-O-Me except for Cbz), 1.41 (s, 9H, -BOC).

[η⁶-((S,S)-4-[2-Methoxy-5-[(N-[O-methyl-N-[(phenylmethoxy)-carbonyl]-L-tyrosyl]-(2-amino-3-oxo-3-methoxy)propyl]]phenoxy)-1-[2-[N-(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-bromoethoxy)]]
propyl]benzene]-\eta^5-(cyclopentadienyl)ruthenium Hexafluorophosphate (1.23c). The same scale of basic-stock solution was made again just before doing the experiment (refer to 1.23a). To a stirred, precooled (0 °C) solution of 169.2 mg (0.32 mmol) of 1.2 in 15 mL of THF was added 5.2 mL (1.10 equiv) of basic-stock solution by syringe and the mixture was stirred for 15 min at 0 °C under N₂, then the resulting solution was transferred via cannula into a precooled (-78 °C) solution of 1.5c (226.1 mg, 1.0 equiv) in 10 mL of dry THF. The resulting mixture was stirred for 1 hr at -78 °C and 3.5 h at rt under N₂, and then filtered through a Celite pad (1 x 2 cm) and the solvent was evaporated to provide a dark brown residue. The residue was dissolved again in 10 mL of CH₃CN, filtered through a neutral alumina column (1 x 5 cm). The dark brown eluent was concentrated in vacuo to ca. 1 mL which was diluted with 20 mL of diethyl ether. The ethereal solution was cooled in a refrigerator and the solvent was decanted. The brown residue was further washed with cold diethyl ether (10 mL x 3), dried in vacuo to afford 311.0 mg (81%) of 1.23c as a pale brown solid foam which was confirmed to be basically pure enough for the next reaction by ¹H-NMR: Rf 0.71 (Al₂O₃ IB-F, CH₃CN); IR (CHCl₃) 3418, 3014, 2981, 1741, 1712, 1681, 1613, 1513, 1478 cm⁻¹; ¹NMR (CDCl₃) δ 7.39-6.79 (m, 12H, aromatic Hs of Ar⁺O⁻Me⁻, Cbz, Ar⁺O⁻Me⁻-, O⁻), 6.45 (d, 1H, J = 9.1 Hz, Ar⁺O⁻Me⁻-, O⁻CH₂CHNH⁻), 6.13-5.94 (m, 4H, aromatic Hs of ArRu⁺), 5.49-5.30 (m, 7H, PhCH₂OCONH⁻- overlapped with ArRu⁺CH₂CHNH⁻, C₆H₅), 5.06 (s, 2H, PhCH₂OCO⁻), 4.77-4.75 (m, 1H, Ar⁺O⁻Me⁻-, O⁻CH₂CHNH⁻, Ar⁺Ru⁺CH₂CHNH⁻, C₆H₅), 4.51-4.31 (m, 4H, -CH₂CH₂Br, Ar⁺O⁻-CH₂CHNH⁻, Ar⁺O⁻MeCH₂CHCO⁻), 3.78 (s, 3H, -OCH₃), 3.76 (s, 3H, -OCH₃), 3.69 (s, 3H,
-OCH$_3$), 3.59-3.55 (m, 2H, -CH$_2$CH$_2$Br), 3.13-2.80 (m, 6H, benzyllic Hs except for Cbz), 1.42 (s, 9 H, -BOC).

[η$^6$-((S,S)-[4-2-Methoxy-5-[N-[(O-methyl-N-[(phenylmethoxy)carbonyl]-L-tyrosyl]-(2-amino-3-oxo-3-methoxy)propyl]phenoxy]-1-
[2-[N-(1.1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-iodoethoxy)-
propyl]benzene])-η$^5$-(cyclopentadienyl)ruthenium Hexafluoro-
phosphate (1.24c). The same scale of basic-stock solution was made again just

before doing the experiment: (refer to 1.23a). To a stirred, precooled (-78 °C)
solution of 67.8 mg (0.13 mmol) of 1.2 in 10 mL of THF was added 2.08 mL (1.10
equiv) of basic-stock solution by syringe and the mixture was stirred for 15 min at 0
°C under N$_2$, then the resulting solution was transferred via cannula into a precooled
(-78 °C) solution of 1.5d (96.6 mg, 1.0 equiv) in 5 mL of THF. The resulting
mixture was stirred for 1 h at -78 °C, then 3.5 h at rt under N$_2$ and filtered through a
Celite pad (1 x 2 cm), then concentrated in vacuo to give a dark brown residue. The
residue was dissolved in 5 mL of CHCl$_3$, filtered through Celite pad (1 x 2 cm) and
the solvent was evaporated to afford a dark brown residue. The resulting residue was
dissolved again in 1 mL of CH$_3$CN, then diluted with 20 mL of Et$_2$O. The etheral
solution was cooled in a refrigerator and the solvent was decanted. The solid residue
was washed with cold Et$_2$O (10 mL x 2), dried in vacuo to give 94.5 mg (59%) of
1.23d as a pale brown solid foam which was confirmed to be basically pure enough
for the next reaction by $^1$H-NMR: IR (CHCl$_3$) 3417, 3020, 2956, 1741, 1713, 1681,
1602, 1513, 1443 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.38-6.78 (m, 12H, aromatic Hs of Ar-
OMe, Cbz, ArOMe, O-), 6.43 (d, 1H, J = 8.9 Hz, Ar\textsuperscript{OMe, O-} CH\textsubscript{2}CHNH-), 6.14-
5.97 (m, 4H, aromatic Hs of Ar\textsuperscript{Ru+}), 5.50-5.28 (m, 7H, PhCH\textsubscript{2}OC\textsubscript{ONH-}
overlapped with Ar\textsuperscript{Ru+} CH\textsubscript{2}CHNH-,Cp), 5.07 (s, 2H, PhCH\textsubscript{2}OCO-), 4.78-4.76
(m, 1H, Ar\textsuperscript{OMe, O-} CH\textsubscript{2}CHNH-), 4.49-4.30 (m, 4H, -CH\textsubscript{2}CH\textsubscript{2}I
overlapped with Ar\textsuperscript{OMe, CH\textsubscript{2}CHNH-, ArCH\textsubscript{2}CHCO-}, 3.79 (s, 3H, -OCH\textsubscript{3}),
3.77 (s, 3H, -OCH\textsubscript{3}), 3.70 (s, 3H, -OCH\textsubscript{3}), 3.40-3.33 (m, 2H, -CH\textsubscript{2}CH\textsubscript{2}I),
3.12-2.84 (m, 6H, benzylic Hs except for Cbz), 1.42 (s, 9H, -BOC).

(S)-3-[4-[2-[[[(1,1-Dimethylethoxy)]-carbonyl]amino]-3-oxo-3-(2-
bromoethoxy)propyl]-phenoxy]-O-methyl-N-[O-methyl-N-
[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine Methyl Ester
(1.24a). 298.0 mg (0.25 mmol) of arene Ru-complex 1.23c was dissolved in

![Chemical structure](image)

20 mL of dry CH\textsubscript{3}CN in a quartz cell (1.5
x 20 cm) and the resulting solution was bubbled with N\textsubscript{2} for 20 min. The solution
was irradiated with a sunlamp (UV, 275
W) for 24 h under N\textsubscript{2}, then concentrated \textit{in vacuo} to ca. 2 mL which was diluted with
50 mL of Et\textsubscript{2}O. The ether-insoluble precipitate was filtered off and washed well with
Et\textsubscript{2}O (20 mL x 3). The combined ethereal extracts were evaporated to give a pale
brown residue which was purified by flash chromatography on silica gel
(CH\textsubscript{2}Cl\textsubscript{2}/EtOAc, 85/15) providing 144.1 mg (65%) of 1.24a as a white solid. From
the ether-insoluble, 90.4 mg (85%) of (CH\textsubscript{3}CN)\textsubscript{3}Ru\textsuperscript{+}CpPF\textsubscript{6} was recovered: mp
52.0-53.5 °C; [\(\alpha\)]\textsubscript{26}D + 31.6° (c 0.57, CHCl\textsubscript{3}); Rf 0.26 (hexanes/EtOAc, 6/4);
\textsuperscript{1}H
NMR (CDCl\textsubscript{3}) \(\delta\) 7.37-6.58 (m, 16H, aromatic Hs), 6.25 (bd, 1H, J = 7.3 Hz, Ar-
OMe, O- CH\textsubscript{2}CHNH-), 5.31 (bs, 1H, PhCH\textsubscript{2}OC\textsubscript{ONH-}), 5.13-5.04 (m, 3H,
PhCH₂CO- overlapped with Ar-O₂CO₂CH₂NH-, 4.72-4.66 (m, 1H, Ar-OMe, -OCH₂CH₂NH-), 4.59-4.53 (m, 1H, Ar-OMe, -OCH₂CH₂NH-), 4.44-4.35 (m, 3H, -CH₂CH₂Br overlapped with Ar-OMeCH₂CH₂CO-), 3.77 (s, 3H, -OCH₃), 3.76 (s, 3H, -OCH₃), 3.60 (s, 3H, -OCH₃), 3.47-3.43 (m, 2 H, -CH₂CH₂Br), 3.11-2.85 (m, 6H, benzylid Hs except Cbz), 1.41 (s, 9H, -BOC); ¹³C NMR (CDCl₃) δ 171.5, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.7, 80.0, 67.0, 64.4, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5, 37.3, 37.0, 28.2, 28.1; Anal. calcd for C₄₅H₅₂N₃O₁₂Br₁: C 59.65, H 5.79, found C 59.59, H 5.77.

(S)-3-[4-[2-[[1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-O-methyl-N-[O-methyl-N-[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine Methyl Ester (1.24b). (i)

Synthesis from 1.24a: To a stirred solution of 1.24a (114.7 mg, 0.13 mmol) in 15 mL of dry acetone was added 95.0 mg (5.0 equiv) of NaI (anhydrous 99+% ) and the resulting slurry was heated at reflux for 7 h under N₂. The reaction mixture was cooled to rt, filtered and the filter cake was washed well with acetone (10 mL x 3). The combined organic extracts were evaporated to provide a solid residue which was dissolved in 50 mL of CH₂Cl₂, washed with brine, dried over MgSO₄ and concentrated in vacuo. The crude product was flash-chromatographed on silica gel (hexanes/EtOAc, 65/35) gave 114.7 mg (95%) of 1.24b as a white pure solid: mp 63.5-65.5 °C; [α]D +34.3° (c 0.58, CHCl₃); Rf 0.19 (hexanes/EtOAc, 6/4); IR (CHCl₃) 3427, 3028, 2983, 1742, 1713, 1683,
1612, 1505, 1228 cm⁻¹; ¹H NMR (CDCl₃) δ 7.34-6.59 (m, 16H, aromatic Hs), 6.27 (d, 1H, J = 7.1 Hz, Ar⁻OMe-O⁻CH₂CHNH⁻), 5.33 (bs, 1H PhCH₂OCONH⁻), 5.12-5.04 (m, 3H, PhCH₂OCONH⁻ overlapped with Ar⁻O⁻CH₂CHNH⁻), 4.72-4.68 (m, 1H, Ar⁻OMe-O⁻CH₂CHNH⁻), 4.56-4.54 (m, 1H, Ar⁻O⁻CH₂CHNH⁻), 4.36-4.32 (m, 3H, -CH₂CH₂I overlapped with Ar⁻OMeCH₂CHCO⁻), 3.77 (s, 3H, -OCH₃), 3.76 (s, 3H, -OCH₃), 3.60 (s, 3H, -OCH₃), 3.25-3.20 (m, 2H, -CH₂CH₂I), 3.11-2.85 (m, 6H, benzylic Hs except Cbz), 1.41 (s, 9H, -BOC); ¹³C NMR (CDCl₃) δ 171.3, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.8, 80.0, 67.0, 65.2, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5, 37.3, 37.0, 28.2, -0.4; Anal. calcd for C₄₅H₅₂N₃O₁₂I₁: C 56.65, H 5.50, found C 56.56, H 5.43. (ii) Synthesis from 1.23d: 84.5 mg (0.0668 mmol) of arene Ru-complex 1.23d was dissolved in 10 mL of CH₃CN in a quartz-cell (1.5 x 20 cm) and it was degassed with N₂-bubbling for 10 min. The resulting solution was irradiated with a sunlamp (275 W, UV) for 20 hr under N₂ and concentrated in vacuo to ca. 1 mL. The residual solution was diluted with 30 mL of Et₂O and filtered through a filter paper. The ether-insoluble precipitate was washed well with Et₂O (20 mL x 3) and the combined ethereal extracts were evaporated to give a brown residue. The brown crude product was purified by flash chromatography on silica gel (hexanes/EtOAc, 6/4) afforded 30.2 mg (48%) of 1.24b as a white solid; [α]²²D +34.8° (c 0.69, CHCl₃); All the other physical data (including spectroscopic data) are same as those derived from 1.23d.
(S)-3-[4-[2-Carboxy-2-[(1,1-dimethylethoxy)carbonyl]amino]ethyl]-phenoxy]-O-methyl-N-[O-methyl-N-[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine Methyl Ester (1.25). To a stirred, pre-cooled (0 °C) solution of 1.24b (76.0 mg, 0.080 mmol) in 10 mL of freshly distilled THF was added 5.6 mL (7.0 equiv) of SmI₂ (0.1M in THF) by syringe and the resulting mixture has warmed to 35 °C for 10 h under deoxygenated-Ar. The reaction mixture was cooled to rt, diluted with 20 mL of EtOAc and quanched by the addition of 10 mL of 0.1N HCl. The organic layer was separated and the aqueous layer was washed well with EtOAc (10 mL x 2). The combined organic extracts were washed with 10 mL of aqueous Na₂S₂O₃ (0.2M), brine and dried over MgSO₄ and concentrated in vacuo to give a solid residue. Purification by short column chromatography on silica gel (1 x 15 cm, CH₂Cl₂/MeOH, 95/5 then EtOAc/MeOH, 95/5) gave 44.5 mg (70%) of pure acid 1.25. [α]²³₅H₂₃₆₅ +30.4° (c 0.38, MeOH, lit²⁺H₂₅₆₅ +27.6° (c 0.54, MeOH)); Rf 0.17 (EtOAc/MeOH, 9/1); IR (CHCl₃) 3412, 3054, 2985, 2939, 2865, 1741, 1715, 1684, 1612, 1513, 1262 cm⁻¹; ¹H NMR (CDCl₃) δ 7.34-6.72 (m, 17H, aromatic Hs overlapped with Ar-O⁻Me, -O-CH₂CHN⁻H⁻), 5.70 (bd, 1H, J = 6.3 Hz, PhCH₂OCONH⁻), 5.33 (bd, 1H, -CH₂CHNHBOC ), 5.05 (d, 1H, J = 12.6 Hz, PhCHHOCO⁻), 4.98 (d, 1H, PhCHHOCO⁻), 4.65-4.58 (m, 1H, Ar⁻O⁻Me, -O-CH₂CHNH⁻), 4.40-4.24 (m, 2H, -CH₂CHNHBOC overlapped with Ar⁻O⁻MeCH₂CHCO⁻), 3.75 (s, 3H, -OCH₃), 3.74 (s, 3H, -OCH₃), 3.62 (s, 3H, -OCH₃), 3.08-2.73 (m, 6H, benzylic Hs except Cbz), 1.38 (s, 9H, -BOC).


39. The deprotecting trials of amino acid based N-BOC, 2-bromoethyl ester compounds by various reported methods always gave 2-hydroxyethyl esters as the major compound, and the results were confirmed by 1H-NMR and by conversion of 2-hydroxyethyl esters into their corresponding 2-acetoxyethyl esters. For more information, see reference 26, 40.


   b) Ho, T. L. "Use of Trithiocarbonate Ion for the Cleavage of 2-Haloethyl Esters" *Synthesis* 1974, 715.


CHAPTER 2

SOME STUDIES ON THE USES OF 2-BROMOETHYL AND 2-IODOETHYL ESTER PROTECTING GROUPS IN PEPTIDE SYNTHESIS
2.1 INTRODUCTION

Protection of the carboxylic group is frequently encountered in organic synthesis. For this, there are two different approaches.\(^1\) The first is the use of ester groups which may be removed under non-hydrolytic conditions (\textit{e.g.}, hydrogenolysis, photolysis, oxidation, \textit{etc.}). The alternative modus operandium is to employ the readily available methyl and ethyl ester groups and to devise novel, mild and if possible non-hydrolytic conditions for their removal. But, the deprotection of these kinds of esters employed so far requires basic or acidic conditions.\(^2\) In conjunction with the problems discussed in Chapter 1, some novel ester protecting groups\(^3\) were reported recently which are deprotected under mild conditions and differentiated from other ester groups as well as the other functionalities.

2.2 PRACTICAL APPLICATIONS OF CARBOXYLIC PROTECTING GROUPS IN OUR STUDIES

2.2.1 Previous Experimental Results on the Use of the 2-Bromoethyl Ester Protecting Group

The most widely used protecting groups in peptide chemistry are \(N\)-BOC and \(N\)-Cbz for the amino functional group and alkyl (Me- or Et-), or other novel carboxyl protecting groups for the acid group. The key point to be kept in mind is selectivity \textit{i.e.}, selective, mild removal in the presence of the other groups that remain intact.
The target molecules discussed in this dissertation have chiral centers in their amino acid side chains which are possibly racemizable and also unstable toward harsh reaction conditions (e.g., heat, oxidation or reduction). The other points to be carefully considered, especially for our Ru-mediated strategy, are the stabilities toward the Ru-metallation, coupling, and Ru-demetallation reaction conditions. From these points of view, the 2-bromoethyl ester was chosen as a carboxylic protecting group in a previous model study, because this group was reported to be removed selectively by the use of Zn in aqueous MeOH, or boiling THF with or without NaI etc. But, the attempted deprotection of 2-bromoethyl ester in the real systems by using Zn/NaI in THF afforded decomposed and unidentifiable products. On the other hand, when these procedures were tried in the presence of NaI or ZnCl₂ in DMF as a solvent, 2-hydroxyethyl esters were formed as major products (Equation 2.2.1).

![Chemical Structure](image)

The same phenomenon has also been found in a simple molecule such as N-BOC-R-(4-chlorophenyl)alanine 2-bromoethyl ester. These somewhat unexpected products were confirmed by their ¹H-NMR which showed 2 triplet methylene peaks (-CO₂CH₂CH₂OH) and conversion to their acetate-derivatives by reacting with Ac₂O/DMAP in CH₂Cl₂. Various other reported methods such as ethanedithiol/NaH⁷a, Na₂CS₃⁷b, vitamin B₁₂/Zn/NH₄Cl⁷c were examined using N-Cbz-D-phenylglycine 2-bromoethyl ester as a model compound which is known to be
most racemization-prone. But, only the vitamin B_{12b} method provided somewhat promising results (deprotected acid 45%, SM 23%) without racemization.\textsuperscript{6} This vitamin B_{12b} and other reported\textsuperscript{7a,8} and new methods\textsuperscript{9} were applied to the real systems 2.1, but all the methods that were tried gave decomposed materials or 2-hydroxyethyl ester as a major compound. Another interesting direct deprotecting method using Na_2S in aqueous CH_3CN was reported,\textsuperscript{10} but we believe that this will provide the same results as the other aqueous reagent methodologies. So, even though the 2-bromoethyl ester was a good protecting group for complexation and coupling reactions,\textsuperscript{4} it proved to be problematic in its removal. Interestingly, Magnus reported a similar problem during 2-chloroethyl carbamate deprotection (Scheme 2.2.1).\textsuperscript{11}

![Scheme 2.2.1](image)

**Scheme 2.2.1** 2-Hydroxyethyl Ester Formation in the Case of 2-Chloroethyl Carbamate Deprotection

Although no detailed mechanistic study has been made yet, a plausible mechanism for formation of 2-hydroxyethyl ester via a neighboring group participation from the ester carboxyl oxygen is suggested in Scheme 1.3.10. From the above suggested mechanism, nonaqueous, anhydrous, mild deprotection methods were required to circumvent the formation of 2-hydroxyethyl ester as a major compound.
2.2.2 Experimental Results of Various Carboxylic Acid Protecting Groups Tried for the Formal Total Synthesis of K-13

With the above disappointing results in mind, we have examined the formal total synthesis of K-13 (Chapter 1). The key step is the successful coupling reaction between the Ru-complex of a protected chlorophenylalanine and a dipeptide phenoxide under very mild conditions.\(^4\) The required ester protecting group should be stable toward the Ru-metallation, coupling and Ru-demetallation and also sufficiently labile to be easily deprotected with the appropriate reagent. To this end, we examined the MEM ester,\(^{13}\) Troc ester,\(^{14}\) 2-bromoethyl ester, and finally 2-iodoethyl ester. The reason why we did try the Troc ester\(^{14c}\) and 2-iodoethyl ester protecting groups was that, in our preliminary studies, these two groups were deprotected completely or partially with SmI\(_2\) under very mild conditions. But very disappointingly, 2-bromoethyl ester is best in terms of overall yields (Ru-metallation, coupling and Ru-demetallation reaction) and reproducibility.\(^4,12\) Now, we again encountered the same problem of how to deprotect the 2-bromoethyl ester protecting group successfully. Except the various direct deprotecting methods, indirect deprotecting approaches of using two-step sequence \textit{i.e.}, (i) Converting the 2-bromoethyl ester into a somewhat more reactive intermediate (ii) then, reacting the resulting intermediate with some reagent to get the corresponding acid were reported.\(^{15,16}\) In Ho's work,\(^{15}\) 2-bromoethyl ester was treated with trimethylstannyl lithium in THF, followed by TBAF. Kunz's group\(^{16}\) reported an \textit{in situ} conversion of 2-bromoethyl ester into 2-iodoethyl ester with NaI/acetone, which was eventually deblocked by reductive elimination with Zn/acid. But, these two methodologies have some potentially severe problems, \textit{i.e.}, (i) high possibility of
racerization induced by trimethylstannyllithium and $F^-$ base in Ho's method. (ii) possible formation of 2-hydroxyethyl ester as a major product.

At this stage, we decided to investigate a new deprotecting strategy for 2-bromoethyl ester protecting group by adopting Finkelstein reaction and deprotection of resulting 2-iodoethyl ester with SmI$_2$.

2.3 EXPERIMENTAL RESULTS AND DISCUSSION OF DEPROTECTION STUDY OF 2-BROMOETHYL ESTER VIA FINKELSTEIN REACTION AND SmI$_2$

Since samarium iodide was introduced by Kagan,$^{17}$ it has been widely used in chemical synthesis$^{18}$ in various fields due to its high reducing potential ($\text{Sm}^{2+}/\text{Sm}^{3+} = -1.55 \text{ V in H}_2\text{O}$).

The syntheses of starting 2-bromoethyl esters were achieved in good yields from their corresponding acids by following the standard method using 2-bromoethanol/ (DCC, pyridine) (Table 2.3.1, exceptions are 2.10a, 2.11a).
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<th>Entry</th>
<th>Table 2.3.1</th>
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**Reaction Conditions and Reagents:**

(a) Acid (1.0 equiv), 2-Bromoethanol (1.2 equiv), DCC (1.1 equiv), CH2Cl2 0 °C, overnight, N2  (b) NaI (5.0 equiv), dry acetone, 7 h, N2, flash chromatography  (c) SmI2 (6.0 equiv), 40 °C, THF, Ar, 8 h, short column chromatography  (d) SmI2 (7.0 equiv), 35 °C, THF, Ar, 10 h, short column chromatography  (e) The 2-bromoethyl ester compounds were obtained by irradiating their Ru-complexes with sun lamp (275W) for 24 h (f) (b) 1-21.2v, 0.58, EtOAc, starting acid, (b) 121.0v, 0.48, EtOAc, recovered acid  (g) (b) 226v, 0.4v, c 0.38, MeOH  (h) 226v, 27.6v, c 0.54, MeOH

**Table 2.3.1** Results of Syntheses of 2-Bromoethyl Esters, Finekstein Reaction and Deprotecting Studies with SmI2.
The halide exchange reaction (*Finkelstein* reaction) was performed by refluxing the 2-bromoethyl ester with NaI (5.0 equiv) in dry acetone for 7 h under N₂ to afford 2-iodoethyl ester protected compounds in excellent yields. This halide conversion was easily confirmed by ¹H- and ¹³C NMR *i.e.*, the upfield-shift of methylene (triplet or multiplet) peak of 2-iodoethyl ester (-CO₂CH₂CH₂I) to ca. 3.3 ppm (by 0.2 ppm) and the strong upfield-shift of methylene-¹³C of (-CO₂CH₂CH₂I) to (-0.5 ~ -1.0 ppm region) owing to I-atom effect were detected. To get the broader scope of applicabilities of this methodology, we prepared some 2-iodoethyl esters directly from corresponding acids by following the exactly same procedures as 2-bromoethyl ester synthesis (Table 2.3.2).

**Table 2.3.2**

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<th>R&lt;sup&gt;2&lt;/sup&gt;-CH&lt;sub&gt;2&lt;/sub&gt;Y&lt;sub&gt;2&lt;/sub&gt;</th>
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**Reaction Conditions and Reagents:**

(a) Acid (1.0 equiv), 2-iodoethanol (1.2 equiv), pyridine (2.5 equiv), DCC (1.10 equiv), CH₂Cl₂, 0 °C, overnight, N₂, flash chromatography (b) SmI₂ (8.0 equiv), THF, 40 °C, 8 h, Ar, short column chromatography (c) SmI₂ (7.0 equiv), 35 °C, 10 h, THF, Ar, short column chromatography (d) [(c)₂] (26.7 µL, 6 0.42, EDAC, stirring acid), [(c)₂] (26.7 µL, 6 c 0.20, EDAC, recovered acid)

Table 2.3.2 Results of *Finkelstein* Reaction and Deprotecting Studies with SmI₂.
Before embarking on extensive studies, we carried out a model study using N-BOC-D-p-chlorophenylalanine 2-iodoethyl ester (2.15b) to obtain optimum reaction conditions. The reasons for choosing 2.15b as a model compound are that it has a relatively unstable protecting group (N-BOC) and it is a chiral amino acid which is closely related to our target molecule 2.11a. The model compound 2.15b was reacted with SmI\(_2\) (7.0 equiv) at rt under deoxygenated-Ar for 1 day, 75% of SM was deprotected (25% SM still remained, no significant impurities were detected by \(^1\text{H}-\text{NMR}\)) and prolonged stirring for 2 days with excessive amount of SmI\(_2\) (10.0 equiv) did not lead to further progress. A slightly higher temperature (40 °C) with the use of 6.0 equiv of SmI\(_2\) was tried for the same model compound, and it gave a considerable amount of unidentified impurities presumably due to the instability of N-BOC group. So, somewhat milder conditions (35 °C, 7.0 equiv of SmI\(_2\), 10 h) were applied to 2.15b and the reaction was determined to be complete from \(^1\text{H}-\text{NMR}\) of the crude product with dramatic decrease of levels of impurities. For the comparison of stability between N-Cbz and N-BOC toward SmI\(_2\), we did the same reaction for 2.9c and it showed that N-Cbz is stable enough under this reaction condition (6.0 equiv of SmI\(_2\) at 40 °C). These optimized reaction conditions (i) SmI\(_2\) 6.0 equiv, 40 °C, 8 h or (ii) SmI\(_2\) 7.0 equiv, 35 °C, 10 h) were applied for various compounds, i.e., the reaction conditions (i) are for the simple aromatic-, aliphatic- and N-Cbz protected compounds (Entries No. 1, 2, 3, 4, 9, 12) and the reaction conditions (ii) are for N-BOC amino acid derivatives (Entries No. 6, 7, 8, 11). For the simple aromatic, aliphatic 2-iodoethyl ester derivatives (Entries No. 1, 2, 3, 9, 10, 12), reaction conditions (i) gave pure crude products in nearly quantitative yields. For the N-BOC amino acid derivatives, reaction conditions (ii) gave moderate to good yields (38 - 82%). At this stage, one more crucial factor i.e., possible racemization, should be addressed in our two-step process (Finkelstein
reaction and SmI₂-mediated deprotection). To this end, the racemization-prone phenylglycine derivative was chosen as a model compound as shown in Scheme 1.3.10, and the optical rotations of the corresponding starting acid and recovered acid 2.9c demonstrated that no racemization occurred during our two-step sequence. Theoretically, 2.0 equiv of SmI₂ are sufficient for successful deprotection but in the real experiment, at least 6.0-7.0 equiv of SmI₂ are required for the reaction completion, presumably due to side reactions or decomposition of SmI₂ under the reaction conditions.
2.4 CONCLUSIONS

2-Iodoethyl ester protecting group is removed successfully with SmI$_2$ under mild conditions. The two-step sequence (Finkelstein reaction and deprotection with SmI$_2$) can provide a useful solution for the problem of deprotecting 2-bromoethyl esters which are known to be very stable toward various reaction conditions. This strategy will afford an important breakthrough for our Ru-mediated diaryl ether synthesis of the amino acid based-derivatives. We are continuing to optimize the deprotection reaction conditions in terms of reducing the amounts of SmI$_2$ used and reaction temperature.
General: All reactions were conducted under dry N\textsubscript{2} except the SmI\textsubscript{2}-mediated deprotection reaction (under deoxygenated-, dry-Ar). \textsuperscript{1}H-NMR (300 MHz) and \textsuperscript{13}C-NMR (75 MHz) spectra were recorded in CDCl\textsubscript{3}, CD\textsubscript{3}CN-CDCl\textsubscript{3} on a Varian Gemini-300 spectrometer. \textsuperscript{1}H-NMR was referenced to TMS and \textsuperscript{13}C-NMR was referenced to CHCl\textsubscript{3} (77.0 ppm). IR spectra were recorded on a Perkin-Elmer Series 1600 FT-IR using CHCl\textsubscript{3} or CH\textsubscript{2}Cl\textsubscript{2} as solvent. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. Mass spectra were recorded on a Kratos MS-25A instrument and CHN analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed using E. Merck Silicagel 60 F-254 0.25mm plates. Visualization was accomplished with UV, phosphomolybdic acid or ninhydrin solution. Flash chromatography was carried out on E. Merck 320-400 mesh silica gel and solvents are reported as V/V percent mixtures. THF was distilled from the sodium ketyl of benzophenone. CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{3}N and CH\textsubscript{3}CN were distilled from calcium hydride. All solvents were distilled under dry nitrogen. SmI\textsubscript{2} (0.1 M in THF) was purchased from Aldrich Co. and used directly without titration. All other commercial reagents were purchased from Aldrich Co. and used without further purification.
3-(4-Methoxyphenyl)propionic acid 2-Bromoethyl Ester (2.5a). Yield (72%); Rf 0.56 (hexanes/EtOAc, 6/4); IR (CHCl₃) 3014, 1734, 1514 cm⁻¹; ¹H NMR (CDCl₃) δ 7.11 (d, 2H, J = 8.6 Hz, aromatic Hs ortho to -OMe), 6.82 (d, 2H, J = 8.6 Hz, aromatic Hs meta to -OMe), 4.35 (t, 2H, J = 6.1 Hz, -CH₂CH₂Br), 3.76 (s, 3H, -OCH₃), 3.45 (t, 2H, J = 6.1 Hz, -CH₂CH₂Br), 2.90 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-), 2.63 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-); ¹³C NMR (CDCl₃) δ 172.3, 158.0, 132.1, 129.1, 113.8, 63.6, 55.1, 35.8, 29.9, 28.6; HRMS calcld C₁₂H₁₅O₃Br₁ 286.0205, found 286.0203.

3-(4-Methoxyphenyl)propionic acid 2-Iodoethyl Ester (2.5b). Yield (86%); Rf 0.49 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3020, 1734, 1514 cm⁻¹; ¹H NMR (CDCl₃) δ 7.12 (d, 2H, J = 8.6 Hz, aromatic Hs ortho to -OCH₃), 6.83 (d, 2H, J = 8.6 Hz, aromatic Hs meta to -OCH₃), 4.32(t, 2H, J = 6.9 Hz, -CH₂CH₂I), 3.78 (s, 3H, -OCH₃), 3.25 (t, 2H, J = 6.9 Hz, -CH₂CH₂I), 2.91 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-), 2.63 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-); ¹³NMR (CDCl₃) δ 172.3, 158.1, 132.3, 129.2, 113.9, 64.5, 55.3, 36.0, 30.0, 0.3; HRMS calcld for C₁₂H₁₅O₃I₁ 334,0068, found 334.0067.

3-(4-Methoxyphenyl)propionic acid (2.5c). Yield (93%); mp 102.5-104.0 °C (lit 21 98-100 °C); Rf 0.56 (hexanes/EtOAc, 2/8); IR (CHCl₃) 3011, 2957, 1711, 1612, 1514, 1248 cm⁻¹; ¹H NMR (CDCl₃) δ 10.98 (bs, 1H, -CO₂H), 7.12 (d, 2H, J = 8.0 Hz, aromatic Hs ortho to -OCH₃), 6.83 (d, 2H, J = 8.0 Hz, aromatic Hs meta to -OCH₃), 3.79 (s, 3H, -OCH₃), 2.90 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-), 2.65 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-).
3-[(3-Benzylxy-4-methoxy)phenyl]propionic acid 2-Bromoethyl Ester (2.6a). Yield (83%); mp 44.0-45.5 °C; Rf 0.35 (hexanes/EtOAc, 8/2); IR (CHCl₃) 3016, 1737, 1515 cm⁻¹; ¹H NMR (CDCl₃) δ 7.45-7.27 (m, 5H, aromatic Hs), 6.84-6.74 (m, 3H, aromatic Hs), 5.13 (s, 2H, -OCH₂Ph), 4.34 (t, 2H, J = 6.2 Hz, -CH₂CH₂Br), 3.86 (s, 3H, -OCH₃), 3.45 (t, 2H, J = 6.2 Hz, -CH₂CH₂Br), 2.86 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-), 2.60 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-); ¹³C NMR (CDCl₃) δ 172.4, 148.3, 148.1, 137.1, 132.8, 128.5, 127.8, 127.3, 120.8, 114.5, 111.9, 71.0, 63.7, 56.1, 35.8, 30.3, 28.7; HRMS calcd for C₁₉H₂₁O₄Br₁ 392.0624, found 392.0629.

3-[(3-Benzylxy-4-methoxy)phenyl]propionic acid 2-Iodoethyl Ester (2.6b). Yield (91%); mp 52.5-54.0 °C; Rf 0.55 (hexanes/EtOAc, 8/2); IR (CHCl₃) 3016, 1737, 1515 cm⁻¹; ¹H NMR (CDCl₃) δ 7.46-7.26 (m, 5H, aromatic Hs), 6.84-6.74 (m, 3H, aromatic Hs), 5.13 (s, 2H, -OCH₂Ph), 4.29 (t, 2H, J = 6.8 Hz, -CH₂CH₂I), 3.86 (s, 3H, -OCH₃) 3.23 (t, 2H, J = 6.8 Hz, -CH₂CH₂I), 2.86 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-), 2.59 (t, 2H, J = 7.7 Hz, ArCH₂CH₂-); ¹³C NMR (CDCl₃) δ 172.2, 148.3, 148.1, 137.1, 132.8, 128.5, 127.8, 127.3, 120.8, 114.5, 111.9, 71.0, 64.4, 56.1, 35.9, 30.4, 0.4; HRMS calcd for C₁₉H₂₁O₄I₁ 440.0486, found 440.0487.

3-[(3-Benzylxy-4-methoxy)phenyl]propionic acid (2.6c). Yield (91%); mp 122.5-124.5 °C; Rf 0.41 (hexanes/EtOAc, 2/8); IR (CHCl₃) 3522, 3017, 2935, 1710, 1591, 1515, 1256, 1211 cm⁻¹; ¹H NMR (CDCl₃) δ 7.45-7.26 (m, 5H, aromatic Hs), 6.84-6.74 (m, 3H, aromatic Hs), 5.13 (s, 2H, -OCH₂Ph), 3.86 (s, 3H, -OCH₃), 2.85 (t, 2H, J = 7.7 Hz, -CH₂CH₂C-), 2.60 (t, 2H, J = 7.7 Hz, -CH₂CH₂C-); ¹³C NMR (CDCl₃) δ 179.0, 148.2, 148.0, 137.1, 132.6, 128.5,
127.8, 127.3, 120.7, 114.5, 111.9, 71.0, 56.0, 35.7, 30.0; HRMS calc'd for C_{17}H_{18}O_{4} 286.1205, found 286.1210.

(3-Benzylxy-4-methoxy)phenylacetic acid 2-Bromoethyl Ester (2.7a). Yield (71%); mp 54.0-55.5 °C; R_f 0.32 (hexanes/EtOAc, 8/2); IR (CHCl_3) 3019, 2944, 1736, 1515 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.46-7.25 (m, 5H, aromatic Hs), 6.86-6.82 (m, 3H, aromatic Hs), 5.15 (s, 2H, -OCH\(_2\)Ph), 4.35 (t, 2H, J = 6.2 Hz, -CH\(_2\)CH\(_2\)Br), 3.87 (s, 3H, -OCH\(_3\)), 3.54 (s, 2H, ArCH\(_2\)C-), 3.44 (t, 2H, J = 6.2 Hz, -CH\(_2\)CH\(_2\)Br); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 171.2, 148.9, 148.1, 137.0, 128.5, 127.8, 127.3, 125.9, 122.0, 115.0, 111.8, 70.9, 64.0, 56.0, 40.6, 28.6; HRMS calc'd for C\(_{18}\)H\(_{19}\)O\(_4\)Br\(_1\) 378.0467, found 378.0464.

(3-Benzylxy-4-methoxy)phenylacetic acid 2-Iodoethyl Ester (2.7b). Yield (89%); mp 59.5-61.5 °C; R_f 0.35 (hexanes/EtOAc, 7/3); IR (CHCl\(_3\)) 3019, 2936, 1734, 1515 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.45-7.25 (m, 5H, aromatic Hs), 6.86-6.84 (m, 3H, aromatic Hs), 5.16 (s, 2H, -OCH\(_2\)Ph), 4.28 (t, 2H, J = 6.8 Hz, -CH\(_2\)CH\(_2\)I), 3.86 (s, 2H, -OCH\(_3\)), 3.53 (s, 2H, ArCH\(_2\)CO\(_2\)-), 3.20 (t, 2H, J = 6.8 Hz, -CH\(_2\)CH\(_2\)I); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 171.0, 148.9, 148.1, 137.0, 128.5, 127.8, 127.2, 125.9, 122.0, 115.0, 111.8, 70.9, 64.7, 56.0, 40.6, 0.2; HRMS calc'd for C\(_{18}\)H\(_{19}\)O\(_4\)I\(_1\) 426.0330, found 426.0319.

(3-Benzylxy-4-methoxy)phenylacetic acid (2.7c). Yield (94%); mp 122.0-123.5 °C (lit\(^{20}\) 123.0-125.0 °C); R_f 0.47 (CHCl\(_3\)/MeOH, 10/1); IR (CHCl\(_3\)) 3020, 2936, 1711, 1515, 1443 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.45-7.25 (m, 5H, aromatic Hs), 6.85 (s, 3H, aromatic Hs), 5.13 (s, 2H, -OCH\(_2\)Ph), 3.87 (s, 3H, -OCH\(_3\)), 3.55 (s, 2H, ArCH\(_2\)CO\(_2\)-).
N-[(Phenylmethoxy)carbonyl]glycine 2-Bromoethyl Ester (2.8a). To a stirred, precooled (0 °C) solution of N-Cbz-glycine (1.00 g, 4.78 mmol) in 40 mL of dry CH₂Cl₂ were added 407.0 µl (1.20 equiv) of 2-bromoethanol followed by 773.0 µl (2.0 equiv) of pyridine by syringe. The mixture was stirred for 10 min at 0 °C then 1.09 g (1.1 equiv) of DCC was added in one portion and the resulting mixture was stirred for 16 h at 0 °C under N₂. The reaction was quenched with 143.0 µl (0.15 equiv) of 5M oxalic acid in THF and it was allowed to come to rt, then stirred further for 30 min. The mixture was filtered and the filter cake was washed well with CH₂Cl₂ (10 mL x 3). The combined organic extracts were washed with dil HCl (0.1N, 20 mL), brine and dried over MgSO₄. After removal of solvent in vacuo, the crude product was flash-chromatographed (silica gel, hexanes/EtOAc, 7/3) to give 1.27 g (84%) of pure product 2.8a as a pale yellow solid: mp 59.0-60.0 °C; Rf 0.21 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3452, 3020, 1752, 1724, 1517, 1220 cm⁻¹; ¹H NMR (CDCl₃) δ 7.36-7.29 (m, 5H, aromatic Hs), 5.26 (bs, 1H, CbzNH⁻), 5.14 (s, 2H, PhCH₂OCONH⁻), 4.46 (t, 2H, J = 6.1 Hz, -CH₂CH₂Br), 4.04 (d, 2H, J = 5.6 Hz, -NHCH₂CO₂⁻), 3.51 (t, 2H, J = 6.1 Hz, -CH₂CH₂Br); ¹³C NMR (CDCl₃) δ 169.6, 156.2, 136.1, 128.5, 128.2, 128.1, 67.1, 64.5, 42.6, 28.1; HRMS calcd for C₁₂H₁₄N₁O₄Br₁ 315.0107, found 315.0104.

N-[(Phenylmethoxy)carbonyl]glycine 2-Iodoethyl Ester (2.8b). Yield (86%); mp 85.5-87.0 °C; Rf 0.26 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3447, 3021, 1751, 1724, 1517 cm⁻¹; ¹H NMR (CDCl₃) δ 7.36-7.26 (m, 5H, aromatic Hs), 5.24 (bs, 1H, CbzNH⁻), 5.14 (s, 2H, PhCH₂OCONH⁻), 4.41 (t, 2H, J = 6.8 Hz, -CH₂CH₂I), 4.02 (d, 2H, J = 5.7 Hz, -NHCH₂CO₂⁻), 3.29 (t, 2H, J = 6.8 Hz, -CH₂CH₂I); ¹³C NMR (CDCl₃) δ 169.4, 156.2, 136.1, 128.5, 128.2, 128.1, 67.2, 65.3, 42.7, -0.5; HRMS calcd for C₁₂H₁₄N₁O₄I₁ 362.9969, found 362.9967.
$N\text{-}[(\text{Phenylmethoxy})\text{carbonyl}]\text{glycine (2.8c). Yield (89%); mp 116.5-118.5 °C (lit}$\text{22 118-119 °C); $R_f 0.25 \text{(EtOAc/MeOH, 9/1)}; \text{IR (CHCl}_3) 3451, 3018, 1726, 1517 \text{ cm}^{-1}; \text{^1H NMR (CDCl}_3) \delta 7.37-7.24 \text{ (m, 5H, aromatic Hs), 5.23 \text{ (bs, 1H, -OCONHCH}_2\text{-}), 5.14 \text{ (s, 2H, PhCH}_2\text{OCO-)}, 4.06 \text{ (d, 2H, J = 6.7 Hz, -CH}_2\text{CO}_2\text{H)}.}$

$N\text{-}[(\text{Phenylmethoxy})\text{carbonyl}]\text{-D-phenylglycine 2-Bromoethyl Ester (2.9a). Yield (86%); mp 62-64 °C; [\alpha]_D^{\text{25}} -50.1^\circ \text{ (c 0.74, EtOAc); R}_f 0.30 \text{(hexanes/EtOAc, 7/3); IR (CHCl}_3) 3435, 3036, 2946, 1723, 1500. 1216 \text{ cm}^{-1}; \text{^1H NMR (CDCl}_3) \delta 7.36-7.25 \text{ (m, 10H, aromatic Hs), 5.78 \text{ (d, 1H, J = 7.3 Hz, CbzNHCH}_2\text{-), 5.41 \text{ (d, 1H, J = 7.3 Hz, CbzNHCH}_2\text{-), 5.13 \text{ (d, 1H, J = 12.2 Hz, PhCHHOCO-)}, 5.08 \text{ (d, 1H, J = 12.2 Hz, PhCHHOCO-)}, 4.40 \text{ (m, 2H, -CH}_2\text{CH}_2\text{Br), 3.41 \text{ (m, 2H, -CH}_2\text{CH}_2\text{Br); ^13C NMR (CDCl}_3) \delta 170.4, 155.3, 136.0, 129.0, 128.7, 128.5, 128.2, 127.2, 67.2, 64.8, 58.0, 27.7; HRMS calcd for C}_{18}\text{H}_{18}\text{N}_1\text{O}_4\text{Br}_1, 391.0420, \text{found 391.0408).}$

$N\text{-}[(\text{Phenylmethoxy})\text{carbonyl}]\text{-D-phenylglycine 2-Iodoethyl Ester (2.9b). Yield (87%); mp 68.5-70.5 °C; [\alpha]^{\text{25}}_D -55.3^\circ \text{ (c 0.6, CHCl}_3); R_f 0.36 \text{(hexanes/EtOAc, 7/3); IR (CHCl}_3) 3435, 3014, 2967, 1742, 1723, 1602, 1517 \text{ cm}^{-1}; \text{^1H NMR (CDCl}_3) \delta 7.37-7.26 \text{ (m, 10H, aromatic Hs), 5.78 \text{ (d, 1H, J = 7.1 Hz, PhCHNHCO}_2\text{-), 5.39 \text{ (d, 1H, J = 7.1 Hz, PhCHNHCO}_2\text{-), 5.13 \text{ (d, 1H J = 12.1 Hz, PhCHHOCO-)}, 5.08 \text{ (d, 1H, J = 12.1Hz, PhCHHOCO-)}, 4.40-4.33 \text{ (m, 2H, -CH}_2\text{CH}_2\text{I), 3.49-3.17 \text{ (m, 2H, -CH}_2\text{CH}_2\text{I); ^13C NMR (CDCl}_3) \delta 170.2, 155.3, 136.1, 136.0, 129.0, 128.7, 128.5, 128.2, 127.2, 67.2, 65.6, 58.0, -0.9; HRMS calcd for C}_{18}\text{H}_{18}\text{N}_1\text{O}_4\text{I}_1 439.0282, \text{found 439.0283).}$
N-[(Phenylmethoxy)carbonyl]-D-phenylglycine (2.9c). To a stirred, precooled (0 °C) solution of 2-iodoethyl ester 2.9b, (9.6 mg, 0.18 mmol) in 10 mL THF, 10.9 mL of SmI$_2$ (0.1M in THF) by syringe. The resulting mixture was warmed to 35 °C and stirred for 8 h under deoxygenated-Ar. The mixture was cooled to rt, diluted with 30 mL of EtOAc and quenched by the addition 10 mL of 0.1 N HCl. The organic layer was separated and the aqueous layer was washed with EtOAc (10 mL x 2). The combined organic extracts were washed with 10 mL of Na$_2$S$_2$O$_3$ (0.2M, sodium thiosulfate), brine, dried over MgSO$_4$ and the solvent was removed in vacuo to give a yellow residue. Purification by short column chromatography on silica gel (1 x 15 cm, EtOAc/MeOH, 95/5) afforded 45.7 mg (88%) 2.9c as a white solid: Mp 127.5-129.5 °C; [α]$_{D}^{24}$ -121.0° (c 0.48, EtOAc); R$_f$ 0.21 (EtOAc/MeOH, 9/1); IR (CHC$_3$) 3436, 3026, 1725, 1667, 1497 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 12.86 (bs, 1H, -CO$_2$H), 8.11 (d, 1H, J = 8.1 Hz, CbzNH-), 7.41-7.30 (m, 10H, aromatic Hs), 5.16 (d, 1H, J = 8.1 Hz, PhCHCO$_2$-), 5.04 (s, 2H, PhCH$_2$CO-); $^{13}$C NMR (DMSO-$d_6$) δ 172.0, 155.8, 137.1, 136.9, 128.4, 127.7, 65.6, 58.0; HRMS calc'd for C$_{16}$H$_{15}$N$_1$O$_4$ 285.1001, found 285.1001.

(R)-4-[3-1-[[[(Phenylmethoxy)carbonyl]amino]-2-[[methylcarbonyl]ethyl]phenoxy-N-[(1,1-dimethylethoxy)carbonyl]-D-tyrosine 2-Bromoethyl Ester (2.10a). Oily foam; [α]$_{D}^{24}$ -9.2° (c 0.47, CHCl$_3$); R$_f$ 0.50 (hexanes/EtOAc, 6/4); IR (CHC$_3$) 3434, 3020, 1742, 1718, 1506 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.33-6.88 (m, 13H, aromatic Hs), 5.96 (d, 1H, J = 7.2 Hz, CbzNHCH-), 5.36 (d, 1H, J = 7.2 Hz, CbzNHCH-), 5.14-5.04 (m, 3H, PhCH$_2$CO-overlapped with -NHBoc), 4.61-4.57 (m, 1H, ArCH$_2$CHCO$_2$-), 4.42-4.36 (m, 2H, -CH$_2$CH$_2$Br), 3.71 (s, 3H, -CO$_2$CH$_3$), 3.47-3.43 (m, 2H, -CH$_2$CH$_2$Br), 3.14-3.00 (m, 2H, ArCH$_2$CHCO$_2$-), 1.42 (s, 9H, -NHBOC); $^{13}$C NMR (CDCl$_3$) δ
171.4, 170.9, 157.5, 155.7, 155.3, 155.0, 138.4, 136.0, 131.0, 130.6, 130.1, 128.4, 128.1, 121.7, 119.0, 118.4, 117.5, 80.0, 67.1, 64.5, 57.5, 54.4, 5.28, 37.4, 28.2.

(R)-4-[3-[[((Phenylmethoxy)carbonyl]amino]-2-[[methoxy]-carbonyl]]-ethyl]phenoxy-N-[[1,1-dimethylethoxy]carbonyl]-D-tyrosine 2-Iodomoethyl Ester (2.10b). Yield (83%); Oily foam; \([\alpha]^{D}_{25} -5.5^\circ\) (c 0.55, CHCl\(_3\)); \(R_f \) 0.51 (hexanes/EtOAc, 6/4); IR (CHCl\(_3\)) 3436, 3019, 1743, 1718, 1506 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta \) 7.34-6.89 (m, 13H, aromatic Hs), 5.89 (d, 1H, \(J = 7.4\) Hz, CbzNHCH-), 5.36 (d, 1H, \(J = 7.4\) Hz, CbzNHCH-), 5.11-5.00 (m, 3H, PhCH\(_2\)OCO- overlapped with -NHBoc), 4.63-4.57 (m, 1H, ArCH\(_2\)CH\(_2\)CO-), 4.39-4.34 (m, 2H, -CH\(_2\)CH\(_2\)I), 3.78 (s, 2H, -OCH\(_3\)), 3.27-3.22 (m, 2H, -CH\(_2\)CH\(_2\)I), 3.17-3.01 (m, 2H, ArCH\(_2\)CH\(_2\)CO-), 1.42 (s, 9H, -NHBoc); \(^1\)C NMR (CDCl\(_3\)) \(\delta \) 171.3, 170.9, 157.6, 155.8, 155.2, 155.0, 138.5, 136.0, 131.0, 130.7, 130.2, 128.5, 128.1, 121.8, 119.1, 118.5, 117.6, 80.1, 67.1, 65.3, 57.6, 54.4, 52.9, 37.6, 28.3, -0.4.

(R)-4-[3-[[((Phenylmethoxy)carbonyl]amino]-2-[[methoxy]-carbonyl]]-ethyl]phenoxy-N-[[1,1-dimethylethoxy]carbonyl]-D-tyrosine (2.10c). Yield (76%); \([\alpha]_{Hg,365} -1.8^\circ\) (c 0.5, CH\(_3\)CN); \(R_f \) 0.25 (EtOAc/MeOH, 9/1); IR (CHCl\(_3\)) 3433, 3028, 3012, 2982, 1750, 1716, 1590, 1506, 1223 cm\(^{-1}\); \(^1\)H NMR (CD\(_3\)CN/CDCl\(_3\), 7/3) \(\delta \) 7.36-6.90 (m, 13H, aromatic Hs), 6.39 (d, 1H, \(J = 7.2\) Hz, CbzNHCH-), 5.40 (d, 1H, \(J = 7.2\) Hz, CbzNHCH-), 5.28 (d, 1H, \(J = 7.7\) Hz, -NHBoc), 5.07 (s, 2H, PhCH\(_2\)OCO-), 4.35 (bs, 1H, ArCH\(_2\)CH-), 3.68 (s, 3H, -CO\(_2\)CH\(_3\)), 3.13 (dd, 1H, \(J = 15.8, 4.3\) Hz, Ar\(\text{CH}_2\text{CH}_2\text{CO}_2\)-), 2.91 (dd, 1H, \(J = 13.1, 8.3\) Hz Ar\(\text{CH}_2\text{CH}_2\text{CO}_2\)-).
(S)-3-[4-[[1,1-Dimethylethoxy)carbonyl]amino]-3-oxo-3-(2-bromoethoxy)propyl]phenoxy]-O-methyl-N-[O-methyl-N-[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine Methyl Ester (2.11a). Arene-Ru-complex (298.0 mg, 0.245 mmol) was dissolved in 20 mL of dry CH$_3$CN in a quartz cell (1.5 x 20 cm) and the resulting solution was bubbled with N$_2$ for 20 min. The solution was irradiated with a sunlamp (UV, 275W) for 24 h under N$_2$, then concentrated in vacuo to ca. 2 mL which was diluted with 50 mL of Et$_2$O. The ether-insoluble precipitate was filtered off and washed well with Et$_2$O (20 mL x 3). The combined etheral-extracts were evaporated to give a pale brown residue which was purified by flash chromatography on silica gel (CH$_2$Cl$_2$/EtOAc, 85/15) providing 144.1 mg (65%) of 2.11a as a white solid. From the ether-insoluble, 90.4 mg (85%) of (CH$_3$CN)$_3$Ru*CPF$_6$ was recovered: mp 52.0-53.5 °C; [α]$^{26}_D$ + 31.6° (c 0.57, CHCl$_3$); R$_f$ 0.26 (hexanes/EtOAc, 6/4); $^1$H NMR (CDCl$_3$) δ 7.37-6.58 (m, 17H, aromatic Hs overlapped with ), 6.25 (bd, 1H, J = 7.3 Hz, Ar$^\text{OMe}$-O-CH$_2$CHNH-), 5.31 (bs, 1H, CbzNH-), 5.13-5.04 (m, 3H, PhCH$_2$OCO- overlapped with Ar$^\text{O}$-CH$_2$CHNH-), 4.72-4.66 (m, 1H, Ar$^\text{OMe}$-O-CH$_2$CHNH-), 4.59-4.53 (m, 1H, Ar$^\text{O}$-CH$_2$CHNH-), 4.44-4.35 (m, 3H, -CH$_2$CH$_2$Br overlapped with Ar$^\text{OMe}$CH$_2$CHO-), 3.77 (s, 3H, -OCH$_3$), 3.76 (s, 3H, -OCH$_3$), 3.60 (s, 3H, -OCH$_3$), 3.47-3.43 (m, 2H, -CH$_2$CH$_2$Br), 3.11-2.85 (m, 6H, benzylic Hs except Cbz), 1.41 (s, 9H, -NHBOC); $^{13}$C NMR (CHCl$_3$) δ 171.5, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.7, 80.0, 67.0, 64.4, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5, 37.3, 37.0, 28.2, 28.1; Anal. calcd for C$_{45}$H$_{52}$N$_3$O$_{12}$Br$_1$: C 59.65, H 5.79 found C 59.59, H 5.77.
(S)-3-[4-[2-[[1,1-Dimethylethoxy]carbonyl]amino]-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-O-methyl-N-[O-methyl-N-[(phenylmethoxy)carbonyl]-L-tyrosyl]-L-tyrosine Methyl Ester (2.11b). To a stirred solution of 2.11a (114.7 mg, 0.127 mmol) in 15 mL of dry acetone was added 95.0 mg (5.0 equiv) of NaI (anhydrous 99+%) and the resulting slurry was heated at reflux for 7 h under N₂. The reaction mixture was cooled to rt, filtered and the filter cake was washed well with acetone (10 mL x 3). The combined organic extracts were evaporated to provide a solid residue which was dissolved in 50 mL of CH₂Cl₂, washed with brine, dried over MgSO₄, then concentrated in vacuo.

The crude product was flash-chromatographed on silica gel (hexanes/EtOAc, 65/35) gave 114.7 mg (95%) of 2.11b as a white pure solid: mp 63.5-65.5 °C; [α]₂⁵D +34.3° (c 0.58, CHCl₃); Rₚ 0.19 (hexanes/EtOAc, 6/4); IR (CHCl₃) 3427, 3028, 2983, 1742, 1713, 1683, 1612, 1505, 1228 cm⁻¹; ¹H NMR (CDCl₃) δ 7.34-6.59 (m, 17H, aromatic Hs overlapped with ), 6.27 (d, 1H, J = 7.1 Hz, Ar-OMe-O-CH₂CHNH⁻), 5.33 (bs, 1H, CbzNH⁻), 5.12-5.04 (m, 3H, PhCH₂OCONH⁻ overlapped with Ar-O-CH₂CHNH⁻), 4.72-4.68 (m, 1H, Ar-OMe-O-CH₂CHNH⁻), 4.56-4.54 (m, 1H, Ar-O-CH₂CHNH⁻), 4.36-4.32 (m, 3H, -CH₂CH₂I overlapped with Ar-OMeCH₂CHCO⁻), 3.77 (s, 3H, -OCH₃), 3.76 (s, 3H, -OCH₃), 3.60 (s, 3H, -OCH₃), 3.25-3.20 (m, 2H, -CH₂CH₂I), 3.11-2.85 (m, 6H, benzyllic Hs except Cbz), 1.41 (s, 9H, -BOC); ¹³C NMR (CDCl₃) δ 171.3, 171.1, 170.4, 158.6, 157.1, 155.8, 155.1, 150.6, 144.4, 136.1, 130.4, 130.3, 129.7, 128.5, 128.4, 128.1, 127.9, 125.7, 122.1, 116.9, 114.0, 112.8, 80.0, 67.0, 65.2, 56.1, 55.9, 55.1, 54.4, 53.3, 52.3, 37.5, 37.3, 37.0, 28.2, -0.4; Anal. calcd for C₄₅H₅₂N₃O₁₂I₁: C 56.65, H 5.50, found C 56.56, H 5.43.
To a stirred, precooled (0 °C) solution of 2.11b (76.0 mg, 0.08 mmol) in 10 mL of freshly distilled THF was added 5.6 mL (7.0 equiv) of SmI$_2$ (0.1M in THF) by syringe and the resulting mixture has warmed to 35 °C for 10 h under deoxygenated-Ar. The reaction mixture was cooled to rt, diluted with 20 mL of EtOAc and quenched by addition of 10 mL of 0.1N HCl. The organic layer was separated and the aqueous layer was washed well with EtOAc (10 mL x 2). The combined organic extracts were washed with 10 mL of Na$_2$S$_2$O$_3$ (0.2M, sodium thiosulfate) solution, washed with brine, dried over MgSO$_4$ and concentrated in vacuo to give a solid residue. Purification by short column chromatography on silica gel (1 x 15 cm, CH$_2$Cl$_2$/MeOH, 95/5 then EtOAc/MeOH, 95/5) gave 44.5 mg (70%) of pure acid 2.11c. [α]$_{23}^{20}$Hg$_{365}$ +30.4° (c 0.38, MeOH, lit$_{19}$Hg$_{365}$ +27.6° (c 0.54, MeOH)); Rf 0.17 (EtOAc/MeOH, 9/1); IR (CHCl$_3$) 3412, 3054, 2985, 2939, 2865, 1741, 1715, 1684, 1612, 1513, 1262 cm$^{-1}$; $^1$H NMR (CD$_3$CN/CDCl$_3$=7/3) δ 7.34-6.72 (m, 17H, aromatic Hs overlapped with), 5.70 (bd, 1H, J = 6.3 Hz, CbzNH- ), 5.33 (bd, 1H, ArO-CH$_2$CHNH- ), 5.05 (d, 1H, J = 12.6 Hz, PhCHHOCO-), 4.98 (d, 1H, PhCHHOCO-), 4.65-4.58 (m, 1H, ArOMe,-O-CH$_2$CHNH-), 4.40-4.24 (m, 2H, ArO-CH$_2$CHNH- overlapped with ArOMeCH$_2$CHO-), 3.75 (s, 3H, -OCH$_3$), 3.74 (s, 3H, -OCH$_3$), 3.62 (s, 3H, -OCH$_3$), 3.08-2.73 (m, 6H, benzylic Hs except Cbz), 1.38 (s, 9H, -NHBOC).

(R)-3-[4-[2-[[[1,1-Dimethylethoxy]carbonyl]amino]-2-[[[(2-iodoethyl)oxy]carbonyl]methylamino]carbonyl]ethyl]phenoxy-N-[(phenylmethoxy)carbonyl]-D-phenylglycine Methyl Ester (2.12b). Yield (82%); mp 46.0-48.0 °C; [α]$_{26}^{20}$D -1.8° (c 0.56, CHCl$_3$); Rf 0.28
(hexanes/EtOAc, 6/4); IR (CHCl₃) 3430, 3019, 1734, 1718, 1685, 1507, 1220 cm⁻¹;
¹H NMR (CDCl₃) δ 7.34-6.89 (m, 13H, aromatic Hs), 6.67-6.65 (m, 1H, -CONHCH₂CO₂⁻), 5.97 (bs, 1H, CbzNH⁻), 5.36 (d, 1H, J = 6.1 Hz, CbzNHCH⁻), 5.19 (d, 1H, J = 7.7 Hz, -NHBOC), 5.12 (d, 1H, J = 12.4 Hz, PhCHHOOC⁻), 5.07 (d, 1H, J = 12.4 Hz, PhCHHOOC⁻), 4.42-4.35 (m, 3H, -CH₂NHBOC overlapped with -CH₂CH₂I), 4.02-3.96 (m, 2H, -NHCH₂CO₂⁻), 3.72 (s, 3H, -CO₂CH₃), 3.28-3.24 (m, 2H, -CH₂CH₂I), 3.14-2.98 (m, 2H, ArCH₂CHCONH⁻), 1.40 (s, 9H, -NHBOC); ¹³C NMR (CDCl₃) δ 171.6, 170.9, 168.8, 157.7, 155.4, 155.3, 138.4, 136.0, 131.8, 130.7, 130.1, 128.4, 128.1, 121.6, 119.2, 118.2, 117.3, 80.2, 67.1, 65.2, 57.5, 55.6, 52.9, 41.1, 37.6, 28.2, -0.5.

(R)-3-[(4-[2-(((1,1-Dimethylethoxy)carbonyl)amino]-2-[(carboxy-methyl)amino]-carbonyl)ethyl]phenoxy]-N-[[phenylmethoxy]carbonyl]-D-phenylglycine Methyl Ester (2.12c). Yield (38%); [α]Hg,436 +2.4° (c 0.34, MeOH); IR (CHCl₃) 3426, 3020, 2961, 2927, 1724, 1675, 1507, 1217 cm⁻¹; ¹H NMR (CD₃CN/CDCl₃, 7/3) δ 7.42-6.78 (m, 13H, aromatic Hs), 6.37-6.32 (m, 1H, -CONHCH₂CO₂⁻), 5.42-5.26 (m, 2H, CbzNH⁻ overlapped with CbzNHCH⁻), 5.11 (d, 1H, J = 12.6 Hz, PhCHHOOC⁻), 5.03 (d, 1H, J = 12.6 Hz, PhCHHOOC⁻), 4.38-4.28 (m, 2H, -NHBOC overlapped with -CH₂NHBOC), 3.89-3.75 (m, 2H, -NHCH₂CO₂⁻), 3.69 (s, 3H, -CO₂CH₃), 3.10-2.86 (m, 2H, ArCH₂CHCONH⁻), 1.38 (s, 9H, -NHBOC).

3-(4-Chlorophenyl)propionic acid 2-Iodoethyl Ester (2.13b). Yield (80%); Rf 0.49 (hexanes/EtOAc, 8/2); IR (CHCl₃) 3019, 1735, 1493 cm⁻¹; ¹H NMR (CDCl₃) δ 7.26 (d, 2H, J = 8.3 Hz, aromatic Hs ortho to -Cl), 7.14 (d, 2H, J = 8.3 Hz, aromatic Hs meta to -Cl), 4.32 (t, 2H, J = 6.8 Hz, -CH₂CH₂Br), 3.26 (t, 2H, J = 6.8 Hz, -CH₂CH₂Br), 2.94 (t, 2H, J = 7.6 Hz, ArCH₂CH₂⁻), 2.65 (t, 2H, J =
7.6 Hz, ArCH₂CH₂⁻; \(^{13}\)C NMR (CDCl₃) δ 171.7, 138.6, 132.0, 129.6, 128.5, 64.4, 35.3, 30.0, 0.35; HRMS calc for C₁₁H₁₂O₂Cl₁I₁ 337.9572, found 337.9573.

3-(4-Chlorophenyl)propionic acid (2.13c). Yield (90%); mp 120.5-122.0 °C (lit\(^{23}\) 122-123 °C); Rₕ 0.45 (MeOH/CHCl₃, 1/9); IR (CHCl₃) 3019, 2949, 1712, 1493, 1409 cm\(^{-1}\); \(^{1}\)H NMR (CDCl₃) δ 7.27 (d, 2H, J = 8.5 Hz, aromatic Hs ortho to -Cl), 7.14 (d, 2H, J = 8.5 Hz, aromatic Hs meta to -Cl), 2.93 (t, 2H, J = 7.4 Hz, ArCH₂CH₂⁻), 2.67 (t, 2H, J = 7.4 Hz, ArCH₂CH₂⁻)

n-Octanoic acid 2-Iodoethyl Ester (2.14b). Yield (75%); Rₕ 0.47 (hexanes/CH₂Cl₂, 5/5); IR (CHCl₃) 2955, 2930, 2857, 1734, 1602, 1468, 1220 cm\(^{-1}\); \(^{1}\)H NMR (CDCl₃) δ 4.33 (t, 2H, J = 6.8 Hz, -CH₂CH₂I), 3.30 (t, 2H, J = 6.8 Hz, -CH₂CH₂I), 2.34 (t, 2H, J = 7.5 Hz, -CH₂CH₂CO₂⁻), 1.66-1.62 (m, 2H, CH₃CH₂CH₂⁻), 1.30-1.28 (m, 8H, CH₃CH₂(CH₂)₄CH₂⁻), 0.88 (t, 3H, J = 6.5 Hz, CH₃CH₂-CH₂⁻); \(^{13}\)C NMR (CDCl₃) δ 173.1, 64.2, 34.1, 31.6, 29.0, 28.8, 24.8, 22.5, 14.0, 0.5; HRMS calc for C₁₀H₁₉O₂I₁ 298.0432, found 298.0434.

n-Octanoic acid (2.14c). Yield (93%); IR (CHCl₃) 2958, 2930, 1708 cm\(^{-1}\); \(^{1}\)H NMR (CDCl₃) δ 2.35 (t, 2H, J = 7.5 Hz, -CH₂CO₂⁻), 1.66-1.59 (m, 2H, CH₃CH₂(CH₂)₄CH₂CO₂⁻), 0.88 (t, 3H, J = 6.8 Hz, CH₃CH₂CH₂⁻).

*N-[(1,1-Dimethylethoxy)carbonyl]-D-(4-chlorophenyl)alanine 2-Iodoethyl Ester (2.15b). To a precooled (0 °C), stirred solution of N-BOC-4-chloro-D-phenylalanine (556.6mg, 1.86 mmol) in 20 mL of CH₂Cl₂ were added 174.2 µl (1.20 equiv) of 2-iodoethanol followed by 301.0 µl of pyridine (2.0 equiv) by syringe. The mixture was stirred for 10 min at 0 °C under N₂ and then 422.4 mg of DCC (1.1 equiv) was added in one portion. The resulting mixture was stirred for
16 h at 0 °C under N₂. The reaction was quenched by addition of 25.2 mg (0.15 equiv) of oxalic acid in 0.5 ml of THF, then it was allowed to come to rt, stirred for 30 min. The solid was filtered off and the filter cake was washed well with CH₂Cl₂ (10 mL x 3). The combined organic extracts were washed with 0.1 N HCl, brine, dried over MgSO₄ and the solvent was removed in vacuo to give a solid residue. Purification by flash chromatography (silica gel, hexanes/EtOAc, 7/3) gave 628.6 mg (75%) of 2.15b as a white solid. mp 80.5-81.5 °C; [α]D 0.37 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3438, 3026, 2982, 2934, 1744, 1711, 1493 cm⁻¹; ¹H NMR (CDCl₃) δ 7.28 (d, 2H, J = 8.3 Hz, aromatic Hs ortho to -Cl), 7.11 (d, 2H, J = 8.3 Hz, aromatic Hs meta to -Cl), 4.96 (d, 1H, J = 7.2 Hz, ArCH₂CHNHC(=O)₂⁻), 4.59-4.57 (m, 1H, ArCH₂CHNHCO₂⁻), 4.39-4.34 (m, 2H, -CH₂CH₂I), 3.28-3.00 (m, 4H, -CH₂CH₂I overlapped with ArCHCH⁻, ArCHCH⁻), 1.42 (s, 9H, -NBOC); ¹³C NMR (CDCl₃) δ 171.1, 155.0, 134.4, 133.0, 130.7, 128.7, 80.2, 65.5, 54.2, 37.7, 28.3, -0.6; HRMS calcd for C₁₆H₂₁N₁O₂Cl₁I₁ 453.0206, found 453.0213.

N-[(1,1-Dimethylethoxy)carbonyl]-D-(4-chlorophenyl)alanine (2.15c). Yield (82%); mp 106.5-108.5 °C; [α]D²² 28.7° (c 0.2, EtOAc); R₇ 0.35 (EtOAc/MeOH, 9/1); IR (CHCl₃) 3438, 3026, 2982, 1719, 1653, 1493, 1221 cm⁻¹; ¹H NMR (DMSO-d₆) δ 12.62 (bs, 1H, -CO₂H), 7.32-7 (m, 4H, aromatic Hs), 7.10 (d, 1H, J = 8.8 Hz, ArCH₂CHNH⁻), 4.11-4.04 (m, 1H, ArCH₂CHNH⁻), 3.00 (dd, 1H, J = 13.7, 3.8 Hz, ArCHCH⁻), 2.80 (dd, 1H, J = 13.7, Hz, ArCHCH⁻); ¹³C NMR (DMSO-d₆) δ 173.4, 155.4, 137.1, 131.0, 128.0, 78.1, 55.0, 35.8, 28.1.

(3-Benzylexoy)phenylacetic acid 2-Iodoethyl Ester (2.16b). Yield (73%); R₇ 0.49 (hexanes/EtOAc, 8/2); IR (CHCl₃) 3019, 1737, 1600, 1519 cm⁻¹; ¹H NMR
(CDCl$_3$) $\delta$ 7.45-7.22 (m, 6H, aromatic Hs), 6.93-6.88 (m, 3H, aromatic Hs), 5.06 (s, 2H, -OCH$_2$Ph), 4.33 (t, 2H, J = 6.9 Hz, -CH$_2$CH$_2$I), 3.62 (s, 2H, ArCH$_2$CO$_2$-), 3.26 (t, 2H, J = 6.9 Hz, -CH$_2$CH$_2$I); $^{13}$C NMR (CDCl$_3$) $\delta$ 170.6, 158.8, 136.8, 134.9, 129.5, 128.5, 127.9, 127.4, 121.8, 115.8, 113.6, 69.8, 64.8, 41.1, 0.2; HRMS calc'd for C$_{17}$H$_{17}$O$_3$I$_1$ 396.0224, found 396.0226.

3-(Benzyloxy)phenylacetic acid (2.16c). Yield (88%); mp 123.0-125.0 °C; R$_f$ 0.52 (EtOAc/MeOH, 9/1); IR (CHCl$_3$) 3012, 2917, 1712, 1598 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.42-7.18 (m, 6H, aromatic Hs), 6.89-6.84 (m, 3H, aromatic Hs), 5.02 (s, 2H, ArOCH$_2$Ph), 3.60 (s, 2H, ArCH$_2$-); $^{13}$C NMR (CHCl$_3$) $\delta$ 177.6, 159.0, 136.8, 134.6, 129.7, 128.6, 128.0, 127.5, 122.0, 116.0, 113.7, 90.0, 41.0; HRMS calc'd for C$_{15}$H$_{14}$O$_3$ 242.0943, found 242.0941.
2.6 REFERENCES AND NOTES


9. (a) Na/liq. NH\(_3\) / -78 °C
   (b) Ca/liq NH\(_3\) / -33 °C/10 min
   (c) Pd(CPh\(_3\)\(_2\) / CH\(_3\)CN


14. Various deprotection methods reported:
   (c) Unpublished new deprotecting method for the model compound N-BOC-4-chloro-D-phenylalanine 2,2,2-trichloroethyl ester: SmI\(_2\) (7.0 equiv), rt, 2 h, dry THF, under dry-, deoxygenated-Ar, quantitative yield.


(c) Sturgess, M. A.; Yarberry, D. J. "Rapid Stereoselective Reduction of Thermally Labile 2-Aminonitroalkanes" Tetrahedron lett. 1993, 34, 4743-4746.


CHAPTER 3

MACROCYCLIZATION STUDY OF RISTOCETIN A BCF-RING MODEL
3.1 INTRODUCTION

Vancomycin and ristocetin A are the representative members of a large and growing family of glycopeptide antibiotics, that were isolated from *Amycolatopsis orientalis*\(^1\) and from *Nocardia luria*\(^2\), respectively, in the mid-fifties. The structural features of these kinds of glycopeptide antibiotics are the sugars on the aryl rings and the presence of a heptapeptide backbone that is cross-linked by aryl ether bonds. These antibiotics can be further subdivided into two main families depending upon the identity of units F and G of the "south-eastern" part of the molecules. In the vancomycin family (Figure 3.1.1), F and G are side chains of (S)-Asparagine and (R)-Leucine and these are separated from each other.

\[
\begin{align*}
\text{Name} & \quad n & \quad X & \quad Y & \quad R \\
3.1 & \text{Vancomycin} & 1 & \text{Cl} & \text{Cl} & \text{H} \\
3.2 & \text{Orientin-A} & 1 & \text{H} & \text{Cl} & \text{Sugar} \\
3.3 & \text{Orientin-D} & 2 & \text{Cl} & \text{Cl} & \text{Sugar} \\
3.4 & \text{A82846-A} & 1 & \text{Cl} & \text{H} & \text{Sugar} \\
3.5 & \text{A82846-B} & 1 & \text{Cl} & \text{Cl} & \text{Sugar} \\
\end{align*}
\]

*Figure 3.1.1* Some Glycopeptide Antibiotics of Vancomycin Family
Members of this family include vacomycin, orienticin-A, B, C, D³-A51568⁴ and A82846-A, B, and C.⁵ In the ristocetin family (Figure 3.1.2), F and G are (S)- and (R)-aryl glycine side chains connected via a diaryl ether linkage.

![Diagram of a glycopeptide antibiotic]

<table>
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<th>U</th>
<th>V</th>
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<th>X</th>
<th>Y</th>
<th>Z</th>
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<td>Me</td>
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<td>H</td>
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<td>H</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
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<tr>
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<td>OH</td>
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<td>Cl</td>
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**Figure 3.1.2** Some Glycopeptide Antibiotics of Ristocetin A Family

This family includes ristocetin A,⁶,⁷ aridicin,⁸ teichomycin,⁹ actiplatin,¹⁰ A 40926¹¹ and A35512-B.¹² These kinds of glycopeptide antibiotics have received much attention not only because of their effective antibiotic activities but also due to their structural complexities. For example, vancomycin has been routinely used against *Staphylococcus* infections *i.e.*, gram-positive bacteria which exhibit resistance to β-lactam antibiotics, such as septicemia, pneumonia and wound infections¹³ for the last 20 years.
The mode of action, especially of vancomycin and ristocetin A, has been studied extensively by the use of the NMR techniques such as NOESY and truncated driven pseudo-NOESY. Ristocetin A expresses its antibiotic activity by selectively binding with the carboxyl-terminal of D-ala-D-ala residues of a peptido glycan precursor (Figure 3.1.3), a so-called mucopeptide, and thus inhibits bacterial cell wall biosynthesis and eventually leads to destruction of the bacteria by lysis.

![Figure 3.1.3 Binding Model of Ristocetin A with D-Ala-D-Ala](image)

The sugar unit in vancomycin appears to be unimportant and its removal has no effect on its *in vitro* activity. However, selective removal of the vancosamine does cause a small drop in activity (by a factor 2-4), but the gross structure and precise configurational and conformational arrangement of the heptapeptide proves to be crucial. For example: (1) The removal of the N-terminal N-methylleucine unit by Edmann degradation leads to zero antibacterial activity. (2) Acetylation of this nitrogen terminus substantially reduces its ability to complex with an Ac-D-ala-D-ala
model mucopeptide terminus.\textsuperscript{14c} (3) Deprotonation of the ammonium ion significantly reduces the binding energy with the model compound.\textsuperscript{16}

The first complete structure of vancomycin was proposed by Sheldrick et al.\textsuperscript{17} in 1978 on the basis of chemical degradation studies, high-field NMR studies and X-ray diffraction study of a crystalline degradation product CDP-I which is formed by hydrolytic loss of ammonia. Its structure was revised by Williamson and Williams in 1981\textsuperscript{18} on the basis of further NMR studies (mainly through the use of nuclear Overhauser effect difference spectroscopy). This initially-proposed structure had some incorrect assignments because of a poor understanding of asparagine rearrangements, and was re-revised by Harris' group in 1983\textsuperscript{19} as assigned in Figure 3.1.1, in which aspartate is present as asparagine, rather than isoasparagine. The structure of ristocetin A was first proposed by Williams' group in 1980,\textsuperscript{6} and was revised as Figure 3.1.2 in 1985.\textsuperscript{7}

3.2 STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF VANCOMYCIN AND RISTOCETIN A AGLYCONES

3.2.1 Synthetically Challenging Issues

The structural complexity of these kinds of glycopeptide antibiotics, as well as their effective antibiotic activities, has presented attractive and challenging targets for total synthesis for more than a decade. Although there is a successful model study mimicking the vancomycin aglycon reported recently by Evans et al.\textsuperscript{20} and Yamamura's group,\textsuperscript{21} no total synthesis of any member of these families of
antibiotics has yet been reported. From the synthetic point of view, several challenging issues should be addressed, as follows.

(i) Synthesis of Nonproteinogenic Amino Acids

The Vacomycin aglycone has 3 arylglycines and ristocetin A has 5 arylglycines. These arylglycines are known to be more racemization-prone than alanine by 60 times and are known to be racemized easily by direct α-proton abstraction. There are also two additional nonproteinogenic amino acids that are syn- and anti-β-hydroxy-γ-amino acids in both families of antibiotics. These are generally non-natural amino acids and must be prepared in enantiomerically pure form.

(ii) Atropisomerism

Some compounds that have no stereogenic center can be chiral if there are significant rotation barriers about certain single bonds. Unsymmetrically substituted biaryls with ortho substituents are a good example because the substituents are large enough to hinder the free rotation along the aryl-aryl bond. A similar kind of atropisomerism was observed by Evans' group in their DE-biaryl ring model study. Another kind of atropoisomerism was reported in the 16-membered macrocyclic model rings such as ring-ABE and -BCF which have ortho-chloro substituents. Very recently, Pearson's group reported a very interesting atropisomerism found in the 14-membered ring CFG model study, which shows the existence of two different stable conformations. Since there is one chlorine substituent on each ring A and C of the diaryl ether linkage in the northern bicyclic ring of the vancomycin family aglycone, four atropdiastereomers are possible.
Taking into account other kinds of atropdiastereoisomerisms so far found in rings DE and BCF, any attempt toward the total synthesis of any member of these kinds of glycopeptide aglycone provides formidable challenging work to the synthetic chemist.

(iii) Macrocyclic Ring Formation

As shown above, vancomycin and ristocetin A have very unique structural features, i.e., there are two 16-membered rings that are oxidatively cross-linked through a diaryl ether linkage and one highly strained, 12-membered ring via biaryl C-C bond in both cases. There is one more oxidatively linked 14-membered ring in ristocetin A. Theoretically, two strategies are possible to make these kinds of ring structures: (1) introduction of the diphenyl ether bond first and then an intramolecular macrolactamization reaction for the peptide bond formation; (2) a biomimetic (-type) approach, which requires assembling the peptide bonds first and then intramolecular construction of the diaryl ether bond using, e.g., oxidative coupling. To date, there are three methods reported for intramolecular diaryl ether formation.26,28,29,30

3.2.2 Significant Synthetic Approaches Reported Towards the Total Synthesis of Glycopeptide Aglycone

Since vancomycin and ristocetin A aglycones have been challenging target molecules for synthetic chemists, several groups such as Pearson’s, Evans’, Yamamura’s, Rao’s and recently Beugelmans’ have reported interesting unique results.
(i) Approaches to Ristomycinic Acid (FG Diaryl Ether Subunit)

Pearson and coworkers\textsuperscript{31} developed an elegant approach to make a diaryl ether linkage based on arene-manganese chemistry and applied this methodology to synthesize a fully-protected deoxyristomycinic acid\textsuperscript{32} and ristomycinic acid (Scheme 3.2.1).\textsuperscript{33}

![Chemical reaction diagram]

\textbf{Scheme 3.2.1} Pearson's Approach to Ristomycinic Acid

The metal-complexation was accomplished in over 90\% yield and the subsequent coupling reaction of arene-Mn complexes with phenoxide anions derived from arylglycines proceeded without any detectable racemization. Treatment of the resulting Mn-complexes with Schoellkopf's chiral glycine enolate equivalent\textsuperscript{34} and subsequent demetallation using N-bromosuccinimide furnishes an arylglycine bislactim in 44\% yield (diastereoselectivity, 4:1).
(ii) Approaches to Actinoidinic Acid and Its Ring Analogue (DE-Diaryl Subunit and Its Peptide Ring)

The first synthesis of actinoidinic acid was reported by Rao and coworkers\textsuperscript{35} by using Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} as a catalyst for intramolecular coupling of the phenyl rings. The second phenylglycine moiety was introduced via diastereoselective Strecker reaction\textsuperscript{36} using phenylglycinol as a chiral auxiliary (Scheme 3.2.2). Later, Rao et al.

![Scheme 3.2.2 Rao's Approach to Actinoidinic Acid](image)

reported another alternative approach based on a Pd-complex of the aryl Schiff's base.\textsuperscript{37} More recently, a fairly efficient synthesis of protected actinoidinic acid was reported by Beugelmans' group\textsuperscript{38} utilizing Meyer's oxazoline as a key intermediate for a regioselective cross-coupling reaction. Evans' group recently disclosed very interesting results including atropdiastereoselectivity for the macrocyclic actinoidinic-containing (DE) subunit which were synthesized via a biomimetic approach using VOFy/BF\textsubscript{3}-OEt\textsubscript{2} (Scheme 3.2.3).\textsuperscript{25}
(iii) Approaches to Vancomycinic Acid

Pearson et al.\textsuperscript{38} successfully synthesized a derivative of vancomycinic acid using iron-arene complex under very mild conditions (-78 °C to rt) and found that a protected tyrosine residue was not racemized (Scheme 3.2.4).

Scheme 3.2.4 Pearson's Approach to Vancomycinic Acid

In 1993, Beugelmans and coworkers\textsuperscript{39} developed an efficient procedure for the synthesis of triaryl diether compounds. Along similar lines, Rao's group utilized the reactivity of a 2,6-dibromonitroarene toward phenoxide anion to make a bis-diaryl ether,\textsuperscript{40} and later reported the first synthesis of fully-protected vancomycinic acid by using benzoquinone as an efficient intermediate to form triaryl diether subunits.\textsuperscript{41}
(iv) Approaches to the N-Terminal 14-Membered Ring (CFG-Ring Subunit)

The first successful synthesis of a N-terminal 14-membered ring as a model for the CFG ring system was reported by Chakraborty and coworkers.\textsuperscript{42} In their work, the two α-arylglycines in the ring were prepared in optically pure form by diastereoselective Strecker synthesis using α-phenylglycinol as a chiral auxiliary, and the final macrocyclization was accomplished via the active ester method (pentafluorophenyl ester) under high dilution conditions.

![Chemical structures](image)

**Scheme 3.2.5 Pearson's Approach to CFG-Peptide Ring Model**

Another unique approach for the 14-membered ring model was recently disclosed by Pearson's group (Scheme 3.2.5).\textsuperscript{27} The key aryl ether bonds were constructed by using the reaction of phenoxide from ((3-hydroxy-4-methoxy)phenyl)glycine with an arene-Mn complex and the second arylglycine side
chain was introduced by reaction of the aryl ether manganese complexes with Schoellkopf's bislactim glycine enolate equivalent. Two different cycloamidation methods for two different synthetic pathways were tried and it was clear that regardless of routes taken, two different atropdiastereomers with substantial activation energy barrier to conformational flipping were produced, and their conformations were later proposed based on 2D-NOESY NMR studies and molecular modelling. Attempted interconversion between them failed even at elevated temperature (160 °C, DMSO-d$_6$).

(v) Approaches to a Vancomycin Aglycone Model

Evans'\textsuperscript{20} and Yamamura's group\textsuperscript{21} have reported successful syntheses of a bicyclic hexapeptide model compound, closely resembling the vancomycin aglycone, \textit{via} an intramolecular oxidative cyclization method using TTN, followed by treatment of the ortho- dichloro-/or dibromo-substituted triaryl diethers formed with H$_2$/Pd-black to give reductive dehalogenated product in low yields (\textit{ca.} 20%).

3.3 16-MEMBERED CYCLIC PEPTIDE RING SYNTHESIS (ABE- OR BCF-RING SUBUNIT)

3.3.1 Unsuccessful Results via Conventional Macrolactamization Methods

The 16-membered macrocyclic ring constitutes a very important parent skeleton of the northern bicyclic framework in both vancomycin and ristocetin A families of
glycopeptide antibiotics and its synthesis has been an active research area. Hamilton et al.\textsuperscript{43} and Crimmin et al.\textsuperscript{44} have reported the synthesis of 16-membered macrocyclic rings through amide bond closure using conventional macrolactamization procedure, but the yields in both cases were less than 10%. Interestingly, in related studies, Williams et al.\textsuperscript{47} and Pearson et al.\textsuperscript{38} failed to obtain the cyclized product even using the same strategy (Scheme 3.3.1).

Scheme 3.3.1 Unsuccessful Results Reported for the Synthesis of 16-Membered Cyclic Peptide Rings via Macrolactamization Methods
3.3.2 Alternative Approaches: Biomimetic (-type) Approaches and Their Limitations

More successful results have been obtained through the use of a two-step, thallium trinitrate (TTN) promoted oxidative cyclization of dichloro- (or dibromo-)/dibromo- (diiodo-) intermediates and the yields reported were ca. 40%.\textsuperscript{20,21} But, the product formed in either case has dichloro- (or dibromo-) substituents on both aryl rings (ring A and C) ortho to the aryl ether linkage, so it is practically impossible to remove one chlorine (or bromine) atom selectively from each of the rings A and C.

In another biomimetic-type approach, Boger et al.\textsuperscript{28} have implemented an intramolecular Ullmann cyclization reaction for 16-membered ring models using standard reaction conditions (Cul·SMe\textsubscript{2} (3.0 equiv), MeLi (3.0 equiv), pyridine, 130 °C, 6 h) and found that 5\% of racemization occurred during the process (Equation 3.3.1).\textsuperscript{28b} The possibly major shortcoming in this approach is that the harsh reaction conditions requiring reflux in pyridine will most certainly cause racemization at the most racemization-prone phenylglycine segments. According to a model study from our laboratory, fully protected phenylglycine was completely racemized in 2h in refluxing pyridine.\textsuperscript{32b}
Very recently, Beugelmans' group\textsuperscript{26} developed a new approach for this kind of 16-membered cyclic ring based on the intramolecular S\textsubscript{N}Ar reaction (Scheme 3.3.2) and shortly after Rao's group\textsuperscript{30} reported virtually the same approach to this problem.

Scheme 3.3.2 Beugelmans' Approach to 16-Membered Cyclic Ring

Because of the enhanced reactivity of the o-nitrofluoroarene owing to strong electron withdrawing group (-NO\textsubscript{2}) at the ortho-position, the fluorine anion can be displaced under relatively mild conditions and the reaction proceeds in over 90\% yield by simply stirring the precursors with anhydrous K\textsubscript{2}CO\textsubscript{3} in DMF at rt for ca. 6h. Even though this approach is apparently superior to the earlier two biomimetic (-type) ways in terms of total yield and operational simplicity, its application to compounds with phenylglycine side chains is highly questionable because it is not evident from their experimental results that this is racemization-free methodology.
3.4 NEW 16-MEMBERED RING CYCLIZATION MODEL STUDY
BASED ON RECENTLY DEVELOPED COUPLING REAGENTS

3.4.1 Significance and Objective of Our Study

It is generally known that macrocyclization of peptides depends on the size of the ring to be closed, orientation of coupling, the nature of the protecting groups on the neighboring amine, substituents on the ring and the coupling methods used. Considering the successful implementation of conventional macrocyclization approaches for 14-27,42 and 17-membered45,46 ring cyclization, it is peculiar that 16-membered ring cyclization reactions using similar procedures gave very low yield or failed to provide any cyclized product. In their failed trial, Williams' group47 have attributed the failure for the cyclized product to "the difficulty of macrocyclic lactamization of conformationally restricted systems". But, in a related study, Pearson et al.38 have conducted MM2 calculations and shown that the optimum conformation for the cyclization reaction in which the terminal amino- and carboxyl-groups are placed closest to each other is not sufficiently higher energetically than conformation where they are much further apart and also conformation of the lowest energy still places terminal amine- and carboxyl-group fairly close for cyclization. These MM2 results imply a somewhat promising prospective that the success of cycloamidation in 16-membered ring is quite variable and if the reaction conditions including coupling reagents are carefully chosen, it may provide successful results. And, also considering the somewhat serious drawbacks of biomimetic (-type) approaches as discussed in Section 3.3.2, it is very urgently needed to secure the powerful new peptide coupling reagents for 16-membered ring cyclization.
3.4.2 Promising Coupling Reagents for 16-Membered Ring Cyclization

Among the conventional macrolactamization approaches, the active ester method using pentafluorophenyl ester has been successfully applied for similar size ring cyclizations. So, this methodology for 16-membered ring cyclization should be re-examined. And also, there are some new, effective peptide coupling reagents reported recently for peptide cyclization partly because cyclic peptides, due to their restricted conformational flexibility, are good substrates for a study of structure-activity relationships and elucidation of bioactive conformations. FDPP (pentafluorophenyl diphenylphosphinate) (Figure 3.4.1) was developed in 1991\textsuperscript{48}

\[ \text{FDPP} \quad \text{HOAT} \quad \text{HAPyU} \]

Figure 3.4.1 Structures of FDPP, HOAT and HAPyU

and successfully applied in the total synthesis of cyclic peptides.\textsuperscript{49a,b} Very recently, Carpino has developed a new efficient peptide coupling additive, HOAT (1-hydroxy-7-azabenzotriazole) (Figure 3.4.1). He has reported a series of experiments showing that replacement of HOBT by HOAT during carbodiimide-promoted reactions led to significantly improved coupling efficiencies and racemization supression and its mode of action was believed to be a neighboring group effect (Figure 3.4.1).\textsuperscript{50} In connection with HOAT, Carpino and coworkers\textsuperscript{51} developed a new efficient cyclic peptide coupling reagent, HAPyU (O-(7-azabenzotriazol-1-yl)-1,1,3,3-
tetramethylenuronium hexafluorophosphate) (Figure 3.4.1). This new coupling reagent was very effective in peptide cyclization even for a very cyclization-resistant linear hexapeptide\textsuperscript{52,53} with minimum racemization (0.5\%) at the C-terminal tyrosine residue.

3.5 RESULTS AND DISCUSSION

3.5.1 General Synthetic Strategy

Initially we were planning to synthesize an ABE-ring model system, but we changed our focus to the BCF-ring model because synthetic procedures for this ring system appeared to be somewhat easier, and any information including successful coupling reagents can be directly applied to synthesis of the ABE-ring. The requisite non-natural amino acids can be prepared by Evans' azidation method which has been used in our related studies\textsuperscript{54,55}. The diaryl ether linkage between the dipeptide, made of two fully-protected phenylglycines and fully-protected p-chlorophenylalanine, can be constructed via Ru-mediated reaction under very mild conditions as for our earlier work described in Chapter 1 and summarized in Scheme 3.5.1\textsuperscript{55a}
Scheme 3.5.1 Ru-mediated Construction of Diaryl Ether Linkage between Dipeptide and p-Chlorophenylalanine Derivative

The 2-Bromoethyl ester protecting group will be converted into its 2-ido counterpart, then eventually deprotected by SmI$_2$. Various promising newly developed coupling reagents discussed in Chapter 3.4.3 will be examined for effecting the cycloamide reaction.

3.5.2 First BCF-ring Model Study

The simplified first BCF-ring model was designed as 3.9, and by the following analysis as shown in Scheme 3.5.2, dipeptide 3.10 (BF-component) and Ru-complexed p-chlorophenylalanine 3.11 (C-component) are to be prepared.
Scheme 3.5.2 First BCF-Ring Model 3.9 and Its Retrosynthetic Analysis

(i) Synthesis of B-Component of Dipeptide 3.10

Reaction Conditions, Reagents and Yields:

a) NaHSO₃, KCN, H₂SO₄ quant (b) AcOH, SnCl₂ conc HCl, 34% (c) NaOH (2.01 equiv), BrCl (2.01 equiv), reflux, 71% (d) Et₃N, pivaloyl chloride then (4R)-4-phenylmethyl)-2-oxazolidinone·BuLi, 73% (e) KHMS, triazide, 84% (f) LiOH (2.5 equiv), 0 °C, 1 h then PTSA/MeOH, reflux, 5 h, 78% (g) Pd-C (10%), H₂ (1 atm), (MeOH/THF-1:1), 24 h, rt, 79%

Scheme 3.5.3 Synthetic Route for B-Component of Dipeptide 3.10
The asymmetric synthesis of phenylglycine derivative 3.18 (B-component) began with commercially available isovanillin 1.6, which was treated with aqueous KCN under mild conditions (-5 °C) to give unstable 3-hydroxy-4-methoxymandelonitrile (3.12) as a pale yellow solid (Scheme 3.5.3). This mandelonitrile was immediately transformed into (3-hydroxy-4-methoxy)phenylacetic acid (3.13) via reductive dehydration with SnCl₂/HCl under reflux conditions. Selective protection of the phenolic-\( \text{-H} \) as benzyl ether was accomplished by refluxing it with BnCl/NaOH to give O-Me, O-Bn protected phenylacetic acid 3.14 in excellent yield. To introduce \( R \)-stereochemistry at the chiral center, phenylacetic acid 3.14 was treated first with pivaloyl chloride/Et₃N to form the mixed anhydride which was then treated with lithiated, (4R)-phenylmethyl-2-oxazolidinone at -78 °C to provide acyloxazolidinone 3.15 in 73% yield. The asymmetric azidation reaction was done following the established procedure using KHMDS/trisylazide and the selectivity was determined to be 96:4 by \(^1\)H-NMR of the crude product. Attempted removal of the minor diastereomer by flash chromatography or fractional recrystallization using a variety of solvent systems failed, so the diastereomeric mixture 3.16 was used for the next reaction in anticipation that separation could be accomplished at a later stage. Removal of chiral auxiliary using LiOH (2.0 equiv) at 0 °C and the subsequent esterification using anhydrous MeOH/PTSA (2.0 equiv) at reflux temperature furnished the desired intermediate 3.17 in good yield. This intermediate was prepared by a somewhat different route in our related work\(^{27}\) and based on the [\( \alpha \)]\(_D\) value, the optical purity was determined to be ca. 96:4, which demonstrated that no detectable racemization occurred during removal of the auxiliary and subsequent esterification. Reduction of azide to amine and simultaneous cleavage of the benzyl group by using Pd-C/H₂ (1 atm) in methanol provided the dipeptide precursor 3.18 in excellent yield.
(ii) Synthesis of F-Component of Dipeptide 3.10

\[
\text{CbzCl, Na}_2\text{CO}_3 \quad \xrightarrow{82\%} \quad \text{CbzCl, Na}_2\text{CO}_3
\]

\[
\begin{align*}
\text{(L)-Phenylglycine} & \quad \rightarrow \\
3.19 & \quad \rightarrow \\
3.20 & \quad \text{HO} & \quad \text{NH} & \quad \text{Cbz}
\end{align*}
\]

Scheme 3.5.4  Synthetic Route for F-Component of Dipeptide 3.10

Commercially available L-phenylglycine (3.19) was treated with CbzCl/Na₂CO₃ at 0 °C to give N-Cbz-L-phenylglycine 3.20 as a white powder in good yield.

(iii) Preparation of Dipeptide 3.10

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{NH} & \quad \text{Cbz} \\
3.18 & \quad \rightarrow \\
3.20 & \quad \text{EDC, HOBT} \\
0 \degree \text{C, N}_2, 77\% & \quad \rightarrow \\
\text{MeO} & \quad \text{OMe} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{NH} & \quad \text{Cbz} \\
3.10 & \quad \text{H} \\
\end{align*}
\]

Scheme 3.5.5  Synthesis of Dipeptide 3.10

To prepare the requisite dipeptide 3.10 which has a free phenolic group, the free amine 3.18 and the acid 3.20 were coupled using EDC and HOBT at 0 °C under N₂. After purification by flash chromatography and recrystallization from THF/hexanes, the diastereomerically pure dipeptide was obtained in 77% yield.
The synthetic sequences were the same as described in our previous published result\(^5\) except for the use of (4R)-phenylmethyl-2-oxazolidinone chiral auxiliary in place of (4S)-chiral auxiliary as shown in Scheme 3.5.6.

\[
\begin{align*}
1.17 & \xrightarrow{a} 3.21 \xrightarrow{b} 3.22 \xrightarrow{c} 3.23 \\
 & \xrightarrow{d} 3.24 \xrightarrow{e} \text{(Ru}\text{CpPF}_6) \\
\end{align*}
\]

Reaction Conditions, Reagents and Yields:

(a) Et\(_3\)N, pivaloylchloride; (4R)-4-(phenylmethyl)-2-oxazolidinone/ n-BuLi, 82%  
(b) KHMDS, trisylazide, 77%  
(c) Pd-C (10%), HCl (2.0 equiv), H\(_2\) (1 atm) then K\(_2\)Cr\(_2\)O (2.5 equiv), (BOC)\(_2\)O (1.5 equiv), 83%  
(d) LiOH (2.0 equiv), 0 °C, 1 h then 2-Bromoethanol (1.2 equiv), DCC (1.1 equiv), pyridine (2.0 equiv), 0 °C, overnight, 75 %  
(e) (CH\(_3\)CN)\(_3\)Ru\(^+\)CpPF\(_6\) (1.35 equiv), 1,2-dichloroethane, reflux, 4 h, quant

Scheme 3.5.6 Synthetic Route for C-component  \(\text{3.11}\)

Commerciaally available p-chlorocinnamic acid was hydrogenated over Pd-C(10%) catalyst under atmospheric pressure of H\(_2\) to provide 1.17, which was
coupled with (4R)-4-phenylmethyl-2-oxazolidinone to give carboximide 3.21 in good yield. Diastereoselective azidation using KHMDS/trisylazide at -78 °C and purification of the crude product by flash column chromatography (SiO₂, hexanes/EtOAc = 8/2) followed by recrystallization (hexanes/EtOAc = 9/1) gave diasteromerically pure product 3.22 as fine, needle-type crystals. Reduction of azide into amine-HCl was accomplished by using Pd-C(10%)/H₂(1 atm), (THF/MeOH = 4/1, HCl (2.0 equiv)). Surprisingly, if the reaction was carried out in methanol alone under the same conditions, it afforded considerable amounts of reductively dechlorinated compound as a side product. Saponification of N-BOC protected, carboximide 3.23 using LiOH (2.0 equiv) at 0 °C gave the α-azido acid in excellent yield. Among the various acid protecting groups, 2-bromoethyl ester has been shown to be well-behaved during the complexation, coupling and demetallation reactions in our related studies, so it was adopted as an acid-protecting group. The Ru-complexation reaction was optimized to the current reaction conditions (i.e, (CH₃CN)₃Ru⁺CpPF₆⁻(1.35 equiv), reflux, 4.0 h) and immediate work-up of product by filtering through a Celite pad and chromatography through an alumina column normally afforded the product 3.11 in an apparent 108 - 110% yield, which was shown to contain a considerable amounts of (CH₃CN)₃Ru⁺CpPF₆⁻ by ¹H-NMR. On the other hand, after the reaction was finished, if the reaction mixture was kept overnight at rt, most of the excess (CH₃CN)₃Ru⁺CpPF₆⁻ was precipitated out. After filtering through a Celite pad and a alumina column, pure Ru-complex 3.11 was obtained quantitatively and this material was sufficiently pure for the next coupling reaction.
(iv) Coupling, Demetalation and *Finkelstein* Reaction

![Chemical diagrams](image)

**Reaction Conditions, Reagents and Yields:**

(a) Na, 2,6-di-t-butylphenoxide (1.0 equiv), 0 °C, N₂, 15 min
(b) 3.3 (1.0 equiv), 15 min (-78 °C) then 1.5 h (rt), 87% (c) Suzuki (275W), CH₂CN, N₂, 20-24 h, three times, 58% (d) NaI (5.0 equiv), reflux, 5 h, N₂, 66%

**Scheme 3.5.7** Coupling, Demetalation and *Finkelstein* Reaction

The coupling reaction was done on ca. 100 mg scale of p-chlorophenylalanine derivative 3.24 and for operational convenience, a stock solution (ca. 50 mmol scale) of the sterically hindered base, sodium 2,6-di-t-butylphenoxide, was prepared and used immediately (Scheme 3.5.7). To avoid any possible racemization at the chiral center of the arylglycines, 1.0 equiv of base was added into the dipeptide solution and stirred for 15 min at 0 °C under N₂, then transferred into a precooled (-78 °C), stirred solution of Ru-complexed p-chlorophenylalanine derivative 3.11 in THF. After the reaction was complete, THF was removed and the residue was dissolved in CH₃CN and passed through a neutral alumina column to remove any polar material such as (CH₃CN)₃Ru⁺CpPF₆. Additional purification was done by washing with cold Et₂O to remove any unreacted dipeptide 3.10. The coupling
reaction was easily confirmed by $^1$H-NMR of 3.25 which showed that the Ru-complexed, aromatic $H$ peaks were shifted upfield to ca. 6 ppm owing to the electron-donating diaryl ether oxygen. The other proton peaks appeared at the expected places with appropriate integral values. But, surprisingly, there were 4 methyl peaks that appeared ca. 3.85-3.70 ppm (3/2H x 4). Purification of this kind of cationic-complex is limited to a few methods such as filtration or washing with cold Et$_2$O, etc.. Consequently, we proceeded to the photochemical ligand exchange reaction, using sunlamp (275W) in CH$_3$CN solvent, but the reaction was not completed even after 24 h (slight heating, yield = ca. 45 %). Repeating the same procedure three times gave a total yield of ca. 55% and (CH$_3$CN)$_3$Ru$^+$CpPF$_6$ was recovered in ca. 80% yield. When the reaction mixture was heated by locating the sunlamp closer to the quartz cell, the yield of demetallation reaction decreased severely presumably due to the heat-instability of the product. Therefore, the other alternative demetallation procedure by using high temperature in DMSO reported$^{56}$ was not tried because the reaction conditions apparently decompose the product. The $^1$H-NMR spectrum of the resulting diaryl ether 3.26 clearly showed that the two methyl groups appeared as two sets of peaks (3/2H x 4) and also the proton-peak of chiral center of F-component showed up as two doublets with equal intensity (1/2H x 2) in CDCl$_3$. To clarify the situation and to get information regarding the C-H connectivity of this complicated molecule, we took the $^1$H-$^1$H COSY spectrum (Figure 3.5.1), which showed that there were two other sets of doublets corresponding to the proton of chiral center and amide of B-component.
Figure 3.5.1 $^1$H-NMR spectrum and $^1$H-$^1$H COSY Experiment of Compound 3.26 in CDCl$_3$ at rt
There are possibly two explanations for this phenomenon: (i) conformational effect due to amide resonance, inter- or intramolecular H-bonding interaction and (ii) complete (100%) racemization occurring at one of the two arylglycine chiral centers. At this point we were confident from our earlier result\textsuperscript{54} that this was not a case of total racemization. In our related study for 14-membered ring cyclization,\textsuperscript{27} we observed one case of a similar phenomenon for a pentafluorophenyl ester intermediate and the split methyl peaks coalesced at elevated temperature (50 °C) in CDCl\textsubscript{3}. So, we tried D-NMR study in CDCl\textsubscript{3} at 55 °C (Figure 3.5.2), but the methyl peaks for compound 3.26 did not coalesce. To check for any solvent-effects, CD\textsubscript{3}CN was next used as a NMR-solvent, but the results were the same as CDCl\textsubscript{3} in terms of the splitting pattern for the methyl peaks. Finally, we tried DMSO-\textit{d}_6 as a NMR-solvent (Figure 3.5.2). The reasons we chose DMSO-\textit{d}_6 as a NMR-solvent are that the amide protons could be readily observed and the line-widths are smaller in this solvent.\textsuperscript{7} Interestingly, the \textsuperscript{1}H-NMR spectrum recorded at rt clearly showed two sets of proton peaks for each chiral center and amide proton and also two sets of two methyl peaks, which suggested that there are possibly two different conformers or in the worst case, that there are two different diastereomers present in the mixture. This DMSO-\textit{d}_6 NMR data also suggested that this strange \textsuperscript{1}H-NMR phenomenon is not due to inter- or intramolecular H-bonding interaction. We also tried D-NMR study in DMSO-\textit{d}_6 from rt to 140 °C, but the methyl peaks never collapsed into one set of peaks and the compound began to decompose at higher temperature.
Figure 3.5.2 $^1$H-NMR Spectra of 3.26 at 55 °C (a) in CDCl$_3$ and at rt (b) in DMSO-$d_6$. 
We did not attempt to separate the two "differrent" substances by HPLC since, by TLC analysis using different solvent systems, it appeared absolutely as one spot. The conversion of Br- into I- of 2-bromoethyl ester protecting group was accomplished in a usual way (NaI (5.0 equiv), acetone, reflux, 6 h) and the reaction was easily confirmed by $^1$H-NMR, which showed that the methylene-peak (m, apparently t) adjacent to halide was shifted upfield from 3.44 to 3.22 ppm. Unfortunately, this iodo compound 3.27 exhibited the same problem in its $^1$H-NMR spectrum. At this point, we were very disappointed with the situation and we decided to re-evaluate the first BCF-model itself. Assuming this is the case of two different diastereomers being formed, the site of total racemization should be only one of the two phenylglycines (B or F-component) of the dipeptide. From our earlier related study, the chiral center of F-phenylglycine segment is more prone to racemization because the B-component has another methoxy group at the para-position in the phenyl ring compared to the model compound in our earlier related study. So, it is far less racemization-prone under basic conditions than the model compound in the earlier related study. This analysis suggests that if the F-component of the dipeptide has an electron-donating group such as p-methoxy in the phenyl ring, it should suppress any possible racemization at the chiral center of the phenylglycine moiety. Furthermore ristocetin A itself has 3 electron-donating groups in the phenyl ring of the F-component, so a better model system would have at least one electron-donating group in the phenyl ring of the F-segment. So, we decided to change our model system.
The modified, second BCF-ring model was designed as 3.28, and the following retrosynthetic analysis as shown in Scheme 3.5.8, new dipeptide 3.29 was to be prepared (Scheme 3.5.8).

![Chemical structures](image)

**Scheme 3.5.8 Modified, Second BCF-Ring Model 3.28 and Its Retrosynthetic Analysis**

(i) **Synthesis of B-Component of Dipeptide 3.29**

The synthesis again began with phenylacetic acid 3.14 (Scheme 3.5.9), but this time (4R, 5S)-4-methyl-5-phenyl-2-oxazolidinone was adopted as a chiral auxiliary because, in our related study, it gave the diastereomerically pure α-azido chiral auxiliary-adduct 3.30 in good yield. This diastereomerically pure α-azido,
carboximide 3.30 was treated with LiOH (2.0 equiv) at 0 °C to remove the chiral auxiliary, then the resulting acid was protected as the ethyl ester in 3.31. Catalytic hydrogenation of azide into amine and simultaneous removal of the benzyl group by using Pd-C/H₂(l atm) in methanol/THF furnished 3.32 in good yield.

(ii) Synthesis of F-Component of Dipeptide 3.29

Commercially available p-methoxyphenylacetic acid 3.33 was coupled with (4S)-phenylmethyl-2-oxazolidinone in a usual way and the purified carboximide 3.34 was subjected to asymmetric azidation to give α-azido compund 3.35 (Scheme 3.5 10). The diastereoselectivity was determined to be ca. 95:5 by ¹H-
Reaction Conditions, Reagents and Yields:

(a) Et3N, pivaloyl chloride, (4S)-4-(phenylmethyl)-2-oxazolidinone
(b) KH, DMF, trityl azide, 68%  (c) Pd/C(10%), H2 (1 atm), HCl (2.0 equiv) 8 h, rt then CbzCl (1.5 equiv), NaHCO3, 0 °C, 4 h, 80% (d) LiOH (2.0 equiv), 0 °C, 1 h, quant

Scheme 3.5.10 Synthetic Route for F-Component of Dipeptide 3.29

NMR of the crude product, which was then purified by flash chromatography and subsequent recrystallization to afford the diastereomerically pure α-azido carboximide in 68% yield. Conversion to 3.36 was accomplished by the following two steps: (i) reduction of azido group into amine-HCl by using Pd-C(10%)/(H2, 1 atm), HCl (2.0 equiv)) in methanol/THF; (ii) treatment of resulting amine-HCl with CbzCl/satd NaHCO3. Removal of the chiral auxiliary from 3.36 by treatment with LiOH (2.0 equiv) at 0 °C provided the crude acid 3.37 in excellent yield.
(iii) Synthesis of Dipeptide 3.29

\[
\begin{align*}
\text{Scheme 3.5.11 Synthesis of Dipeptide 3.29} \\
\text{The synthesis of 3.29 was carried out by using the same coupling reagents (EDC/HOBT) under the same reaction conditions as in Scheme 3.5.5. After purifying the crude product by flash chromatography and recrystallization from (hexanes/THF = 7/3), it gave the diastereomerically pure product 3.29 as white needle-type crystals in 71\% yield.}
\end{align*}
\]

(iv) Coupling, Demetallation and Finkelstein Reaction

The coupling reaction was conducted in exactly the same way as the first model-system using sodium 2,6-di-t-butylphenoxide as the sterically-hindered base (Scheme 3.5 12)
Reaction Conditions, Reagents and Yields:
(a) Na, 2,6-di-t-butylphenoxide (1.0 equiv), 0 °C, N₂, 15 min (b) 3.11 (1.0 equiv), 15 min (-78 °C) then 1.5 h (rt), 84% (c) Sunlamp (275W), CH₂CN, N₂, 20–24 h, three times, 55% (d) NaI (5.0 equiv), reflux, 5 h, N₂, 89%

Scheme 3.5.12 Coupling, Demetalation and Finkelstein Reaction

But, unfortunately, the product 3.38 gave similar results in terms of ¹H-NMR behavior. i.e., two methoxy-groups on the phenyl ring of B and F-Phenylglycine side chains appeared as four singlets. Attempted modification of coupling reaction conditions, by using 0.98 equiv of base for the deprotonation of dipeptide or by cooling the basic-stock solution to -78 °C before using it or by reducing the reaction time of hindered base with dipeptide to 5 min to avoid any possible racemization at one of the phenylglycine chiral centers, gave the same result. Once again, it was very difficult to purify this cationic-complex 3.38, and so we proceeded to the demetallation reaction using 275W sunlamp under the same conditions as for 3.39. The results were very similar in terms of incompleteness of reaction and total yield (ca. 55%) when repeating the photochemical reaction three times. The ¹H-NMR spectrum of demetallated product 3.39 was very similar to its counterpart 3.26 and
clearly showed 4 methyl peaks with same integrals (3/2H x 4) and also two doublets
(1/2H x 2) for the chiral center of F-phenylglycine moiety. This very disappointing
result, however, strongly implies that this is a the case of total racemization because
according to our earlier related study, a p-methoxy group that is attached to the F-
phenylglycine segment should completely suppress any racemization at the
corresponding chiral center. Next, we decided to run a D-NMR study using
CD$_3$NO$_2$ as a NMR-solvent. The reasons for this choice as follows: (i) CD$_3$NO$_2$ is
polar enough to break down any intra- and/or intermolecular H-bonding interactions.
(ii) Its boiling point (101 °C) is high enough for the D-NMR experiment. (iii) It is far
less viscous than DMF-d$_7$ or DMSO-d$_6$, so it can provide better resolution. Figure
3.5.5 shows the D-NMR study of compound 3.39. At 45 °C, one set of two
singlets began to merge and completely collapsed into one sharp peak at 70 °C. The
other set of two singlet methyl-peaks coalesced at 90 °C. Upon cooling to rt, the
collapsed peaks split again into their original patterns. The chiral center at the F-
component was beginning to overlap but did not completely collapse into one peak,
which means that the temperature is not high enough for complete rapid equilibrium
between the two conformers.
Figure 3.5.3  D-NMR Study of Compound 3.39 in CD$_3$NO$_2$ at Different Temperatures (a: rt; b: 45 °C; c: 70 °C; d: 90 °C; e: rt)
It is clear from our earlier related studies\textsuperscript{54} that this ruthenium-mediated coupling reaction generally proceeds without any racemization, but to confirm any possible racemization during this process, we also conducted a series of control experiments. In control experiment-1 (Equation 3.5.1), \textsuperscript{1}H-, \textsuperscript{13}C-NMR spectra of recovered, crude dipeptide from the \textit{Et}_2\text{O}-layer by extraction clearly showed that there was no racemized product in the mixture and the $[\alpha]_D$ value of the recovered dipeptide exactly matched that of the authentic sample. This experiment implies that the sterically hindered base used, or the sodium phenoxide formed from the dipeptide, do not cause any racemization at the chiral centers. In control experiment-2 (Equation 3.5.2), two equivalents of dipeptide were introduced into the same coupling reaction mixture and the recovered starting dipeptide from \textit{Et}_2\text{O}-layer also showed that there was no racemized product in the mixture (by \textsuperscript{1}H-, \textsuperscript{13}C-NMR spectra of the crude product). This experiment signifies that the counter-anion (PF$_6^-$) in the system does not cause any racemization at the phenylglycine chiral centers.
The Finkelstein reaction was carried out under exactly the same reaction conditions as for 3.27 and easily confirmed by $^1$H-NMR which showed that the methylene-peak next to the halide was shifted upfield from 3.44 to 3.21 ppm region.

(V) Optimization of SmI$_2$-Mediated Deprotection of 2-Iodoethyl Ester Protecting Group

In our earlier published results related to K-13 in Chapter 1, 2-iodoethyl ester protecting group was deprotected with SmI$_2$ at slightly elevated temperatures (35 °C or 40 °C) under deoxygenated-Ar. In that study, the $N$-Cbz protecting group was known to be very stable even at 40 °C, but $N$-BOC protecting group was determined to be relatively stable at 35 °C and also excess amounts (6.0 or 7.0 equiv) of SmI$_2$ used was believed to cause side reactions. So, the reaction conditions should be optimized in terms of reducing the amount of SmI$_2$ used and lowering the reaction temperature. Careful literature searches revealed that HMPA,$^{57}$ DMPU$^{58}$ and inorganic bases$^{59}$ such as KOH and NaOH have been used to stabilize and increase the reducing potential of SmI$_2$ by reacting as a strong electron donor ligand toward samarium (II). Although Curran et al.$^{55c}$ reported that DMPU was not as effective an additive as HMPA in THF solvent for the reduction of an aryl iodide, HMPA is known to be a very strong carcinogen. So, we decided to try DMPU first. For a simple comparison, $N$-BOC-R-(4-chlorophenyl)alanine 2-iidoethyl ester was used again as a model compound. Without additive, the reaction was never complete even for prolonged reaction time (2 days) or with the use of excess amounts of SmI$_2$ (10.0 equiv) at rt. In a series of experiments varying the amounts of SmI$_2$ and DMPU, it is clear that there is a critical relationship between SmI$_2$ and DMPU used and the
reaction was determined to be complete with the use of 5.5 equiv of SmI\textsubscript{2} and 33 equiv of DMPU (ratio of SmI\textsubscript{2}/DMPU, 1/6) (Figure 3.5.4).
Figure 3.5.4 Effect of DMPU on the Deprotection of N-BOC-R-(4-Chlorophenyl)alanine 2-Iodoethyl Ester with SmI₂ at rt. ((a): SmI₂ (4.0 equiv), DMPU (20.0 equiv), 3 h; (b): SmI₂ (4.0 equiv), DMPU (24.0 equiv), 3 h; (c): SmI₂ (5.5 equiv), DMPU (16.5 equiv), 3 h; (d): SmI₂ (5.5 equiv), DMPU (33.0 equiv), 3 h; (e): SmI₂ (5.5 equiv), DMPU (33.0 equiv), 10°C, 5 h)
These optimized reaction conditions were applied to the real molecule 3.27, but the reaction did not proceed to completion. By using a greater excess of SmI₂ (7.0 equiv) and same ratio (x 6) of DMPU (42 equiv), the deprotection was confirmed to be complete in 2.5 h at rt and the ¹H-NMR spectrum of the crude product 3.41 indicated that the product was very pure and that the N-BOC group is very stable under these reaction conditions (Scheme 3.5.13).

Scheme 3.5.13 SmI₂-Mediated Deprotection of 2-Iodoethyl Ester Protecting Group of 3.27 and 3.40 in the Presence of DMPU at rt

Purification by flash chromatography (silica gel, hexanes/EtOAc/AcOH = 35/65/1%, then CH₂Cl₂/EtOAc/1%) of the crude product gave pure acid 3.41 in 81% yield (Figure 3.5.5). Under similar reaction conditions (SmI₂ (6.5 equiv), DMPU (39 equiv), 2.5 h, rt), 3.40 was deprotected into 3.42 in 79% yield (Figure 3.5.6).
Figure 3.5.5 $^1$H-NMR Spectra of 3.27 in CDCl$_3$ and 3.41 in (CD$_3$CN/CDCl$_3$).
Figure 3.5.6  $^1$H-NMR Spectra of 3.40 in CDCl$_3$ and 3.42 in (CD$_3$CN/CDCl$_3$, 7/3)
(VI) Macrocyclization Reaction Using Various Coupling Reagents

After solving all the problems encountered during the above synthetic scheme, finally we had the requisite acids (3.41, and 3.42) in hand for the final cyclization reaction. It is well known that dimerization and/or oligomerization is often a major problem for macrocyclization. Therefore high dilution (0.3 mM - 0.8 mM) and/or slow addition techniques are normally adopted to minimize these side reactions. In our case, the combined method of high dilution and slow addition techniques was utilized in most cases except when using HAPyU. The most promising coupling reagents such as HAPyU and FDPP were prepared according to the reported (for FDPP)\(^4\), and our modified procedures (for HAPyU) (Scheme 3.5.14).

\[
\begin{align*}
\text{Ph-P-Cl} & \quad \xrightarrow{a} \quad \text{Ph-O-Ph} \\
3.43 & \quad \text{3.44 (FDPP)} \\
\end{align*}
\]

Reaction Conditions, Reagents and Yields:
(a) Diphenylphosphinic chloride, pentafluorophenol (1.0 equiv), 93 %
(b) triphosgene (1/6 equiv), 10 °C, 73 % (c) triphosgene (1/3 equiv), 10 °C, 76 %
(d) HOAT (1.0 equiv), Et3N (1.0 equiv), overnight, 29 %

**Scheme 3.5.14 Synthetic Routes for FDPP and HAPyU**

It is worth noting that "triphosgene" was successfully utilized during this synthesis of HAPyU, as a safe substitute for highly toxic phosgene. HOAT was purchased from Waters Inc. Among the various promising cyclization methods, we decided to
try the pentafluorophenyl ester method first, because Charkaborty et al.\textsuperscript{42} reported a successful cyclization (yield, 50\%) without racemization for a substrate with phenylglycine subunits.

\[
\begin{align*}
\text{3.42 (X=Cbz, } Y=\text{OH)} & \quad \text{3.49 (X=Cbz, } Y=\text{OC}_6\text{F}_5) \quad \text{b} \\
\text{3.49' (X=NH.HCl, } Y=\text{OC}_6\text{F}_5) & \quad \text{c} \\
\text{3.28-F}_{1}, \text{ F}_{2} &
\end{align*}
\]

**Reaction Conditions, Reagents and Yields:**

(a) pentafluorophenol (3.0 equiv), DCC (1.5 equiv), Dichloromethane, 64 \% (b) Pd-C(10\%), H\textsubscript{2} (1 atm) (c) Et\textsubscript{3}N (5.0 equiv), 1,4-dioxane, 90 °C, 4 h, 14\%

**Scheme 3.5.15** Macrocyclization of 3.42 via Pentafluorophenyl Ester/Et\textsubscript{3}N Method

As a prerequisite to the cyclization (Scheme 3.5.15), 3.42 was converted to its pentafluorophenyl ester using pentafluorophenol (3.0 equiv)/DCC (1.5 equiv) to give 3.49 in 64\% yield. The N-Cbz group of 3.49 was then to be deprotected into amine, so 3.49 was treated with Pd-C(10\%)/H\textsubscript{2} (1 atm), HCl (2.0 equiv) using THF as a solvent, but most of the starting material still remained even after stirring.
for 4 h under H₂ (1 atm). By using 30% EtOH in THF as a solvent, the reaction progress was greatly improved and was complete in 3 h. The resulting pentafluorophenyl ester, amine·HCl salt 3.49’ was dried under high vacuum, then subjected to the cyclization reaction immediately without characterization, i.e., the pentafluorophenyl ester, amine·HCl salt 3.49 dissolved in dry 1.4-dioxane was slowly added into a preheated (90 °C) solution of Et₃N (5.0 equiv) in 1,4-dioxane (150 mL, 0.3 mM) using syringe pump over 3 h under Ar. After addition was finished, the reaction mixture was heated at 90 °C for an additional one hour, then cooled to rt. After work-up as usual, TLC-analysis was performed using silica gel (hexane/EtOAc, 5/5) and showed that there were 6-7 UV-active substances (or 7-8 PMA-active substances). By the careful HPLC-analysis using normal phase column (Whatman Partisil M20 10/25; CH₂Cl₂/EtOAc = 75/25; flow rate = 6 mL/min), six seemingly important fractions were collected and ¹H-NMR studies showed that the overlapped fractions with rt = 32.2. 33.4 min appeared to be the cyclized product. By another round of HPLC-analysis using different normal phase column (Whatman Magnum 9; hexanes/EtOAc = 5/5, flow rate = 5 mL/min), the overlapped fractions were cleanly separated and analyzed. ¹H-NMR of fraction-1 (3.28-F₁) and fraction-2 (3.28-F₂) were very similar in terms of peak positions and integrals and both spectra matched well with the monomeric cyclic structure (Figure 3.5.7).
Figure 3.5.7 $^1$H-NMR Spectra of Cyclization Products 3.28-F$_1$ and 3.28-F$_2$ in (CD$_3$CN/CDC$_3$, 7/3)
Thus, strongly upfield-shifted aromatic proton signals for B-\(H^2\) of the central phenylglycine subunit (B-component) were observed at 6.11 ppm (bs) in 3.28-F\(_1\) and 6.26 ppm (bs or d) in 3.28-F\(_2\), respectively. These are the key structural markers confirming both compounds to be cyclization products. This large shielding effect on aromatic B-\(H^2\) can be explained by considering that aromatic B-\(H^2\) of B-Component is located under the plane of the aromatic ring of C-Component. In a similar case reported by Beugelmans et al.\(^{26b}\) B-\(H^2\)s of cyclization products appeared at 5.85-6.18 ppm region and the equivalent protons in vancomycin and ristocentin A were found at 5.65 ppm\(^7\) and 5.85 ppm\(^6\), respectively. For further characterization, mass spectrometry was carried out using EI and FAB modes. In our earlier related study,\(^{27}\) high energy (70 eV) in EI mode produced M\(^+\) ion peak together with many fragments heavier than M\(^+\) ion even for a monomeric cyclization product. This problem was eventually solved by using the lowest possible ionizing energy (18 eV for Kratos MS 25A) along with stepwise increase of probe temperature. Because of close similarities between the current cyclic monomers and our earlier results, the very same technique was employed for EI mass spectrometry. Electron impact ionization was begun at the lowest possible energy (18 eV for Kratos MS 25A) and increased stepwise with raising temperature slowly. At 22 eV and 380-390 °C, molecular ion peaks appeared (M\(^+\) = 633.2660 for 3.28-F\(_1\) and 633.2701 for 3.28-F\(_2\), calc'd = 633.2686) together with expected fragments of lower mass than M\(^+\), but the fragmentation patterns in both cases were different (Figure 3.5.8).
Figure 3.5.8 EI-Mass Spectra of Cyclization Products 3.28-F₁ and 3.28-F₂.
To verify the existence of any molecular ions at higher mass than \( M^+ \), FAB mass spectrometry was tried and showed that no significant higher mass ions were observed. At this point, we decided to put aside this somewhat surprising result for the time being and turned to the other three promising coupling reagents (Scheme 3.5.16).

\[
\begin{align*}
3.42 \quad (X=\text{Cbz}) & \quad \xrightarrow{a} \quad 3.42' \quad (X=\text{H}) & \quad \xrightarrow{b} \quad 3.28-\text{F1} \quad \text{a} - \text{F2} \\
\end{align*}
\]

Reaction Conditions, Reagents and Yields:
(a) Pd-C(10%), \( H_2 \) atm, 30% EtOH in THF, quant. (b) DCC/HOAT, 2%; HAPyU, 5%; FDPP, 2%

Scheme 3.5.16 Macrocyclization of 3.42 via DCC/HOAT, HAPyU and FDPP

The reactions were carried out in \( ca. \) 0.05 mmol scale based on 3.42. In these cases, the free acid can be used directly, so the \( N\)-Cbz protecting group was removed by using our earlier reaction conditions (Pd-C(10%), \( H_2 \) (1 atm), 30% EtOH in THF, 4 h). After work-up as usual, the thoroughly dried crude amine-acid precursor 3.42' was dissolved in an appropriate solvent (CH\(_2\)Cl\(_2\) for DCC/HOAT, DMF for HAPyU and FDPP) and slowly added to an appropriate solution of the coupling reagent under Ar at 0 °C or rt over 4-10 h using syringe pump. The product distributions from HAPyU and FDPP promoted reactions were very similar to pentafluorophenyl ester/Et\(_3\)N system based on TLC-analysis, but the DCC/HOAT
reaction showed a somewhat simpler pattern (fewer impurities). By HPLC-analysis using (Whatman Partisil M20 10/25, CH₂Cl₂/EtOAc = 75/25, flow rate = 6 mL/min), the three different systems gave the same overlapped-fraction of 3.28-F₁ and 3.28-F₂ but in different ratios. The results are summarized in Table 3.5.1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>Conc. (mM)</th>
<th>Reagent Used</th>
<th>Base Used (equiv)</th>
<th>Reaction Conditions</th>
<th>Combined Yield (%)</th>
<th>Ratio&lt;sup&gt;d&lt;/sup&gt; (F₁/F₂)</th>
</tr>
</thead>
</table>
| 1     | 3.49' | 0.3        | C₄F₇OH      | Et₄N (5)          | (a) 90°C, 1,4-dioxane, 3h 
(b) 90°C, 1h          | 14 %              | 70:30                    |
| 2     | 3.42' | 0.3        | DCC/HOAT     | no                | (a) 0°C, CH₂Cl₂, 10h 
(b) rt, 14h            | 2 %               | 20:80                    |
| 3     | 3.42' | 1.5        | HAPγU        | (i-Pr<sub>2</sub>NEt (3.0)<sup>c</sup>) | (a) rt, DMF, 4.5h 
(b) rt, 20h           | 5 %               | 40:60                    |
| 4     | 3.42' | 0.3        | FDPP         | (i-Pr<sub>2</sub>NEt (2.0)<sup>c</sup>) | (a) 0°C, DMF, 4h 
(b) rt, 20h           | 2 %               | 40:60                    |

(a) Conditions for addition of starting material to the solution of coupling reagent. (b) Reaction time and temperature after addition. (c) Combined yield refers to the yield of overlapped fraction of (3.28-F₁ and 3.28-F₂) separated by first HPLC-analysis. (d) Ratio was determined by <sup>1</sup>H-NMR spectrum of the overlapped fraction of (3.28-F₁ and 3.28-F₂) based on the integral of H<sub>2</sub>²

**Table 3.5.1** Results of Macrocyclization Reaction of 3.42 via Various Coupling Reagents

At this point, we were very surprised with the results. Regardless of the coupling reagents used, two different cyclization products were obtained and the ratio of (3.28-F₁/3.28-F₂) appears to be dependent on the amounts of base used and the reaction conditions. There are probably two possibilities to account for these results. One possibility is that epimerization occurred at one of the three chiral centers, most likely at one of the two phenylglycine chiral centers. This being the case, 3.28-F₂ may be the initial cyclization product because this is the major product in the least basic conditions (DCC/HOAT) and the ratio of (3.28-F₁/3.28-F₂) was shifted in favor
of 3.28-F₁ depending on the basicity of the system and vigor of the reaction conditions. To determine if any epimerization occurred during the cyclization-step, a control experiment (control experiment-3) was conducted using 3.28-F₂ as a model i.e., 3.28-F₂ (ca. 0.8 mg) was heated at 90 °C for 12 h in the presence of excess amounts of Et₃N (30 µL, 170 equiv) in dry 1,4-dioxane (30 mL) under Ar. But, ¹H-NMR of the recovered, crude product showed that no epimerization had occurred. This result may be explained by reasoning that, once cyclization took place, the structure of the product is relatively nonflexible and also sterically restricted for base to approach to the chiral centers. So, if 3.28-F₁ is an epimer of 3.28-F₂, epimerization would have to occur before and/or during the cyclization.

Another possibility is atropisomerism. This kind of interesting observation had been reported recently, mostly in studies related to vancomycin and ristocetin A glycopeptides. For the 16-membered cyclic system mimicking the upper ring of vancomycin and ristocetin A, two atropisomers were reported due to the presence of the bulky o-substituent (Cl or NO₂ or NH₂) in the A- or C-aromatic ring.²⁶ A similar type of atropisomerism was also reported in the case of a 16-membered cyclic lactone⁶⁰ and 17-membered ring systems such as CDP-I-M and CDP-I-M¹⁹ which are degradation products of vancomycin because of bulky o-Cl substituents. From the earlier reported results regarding atropisomerism of 16-membered cyclic systems, it has been assumed that the bulky o-substituent on the C-aromatic ring is prerequisite for atropisomerism to occur. Since there is no bulky substituent at o-position of C-aromatic ring in our model compound, we conclude that this kind of atropisomers by rotation of the C-ring are not formed in our case.

For other size of ring systems such as a 12-membered vancomycin ADE-ring subunit²⁵ and 14-membered ristocetin CFG-ring subunit,²⁷ two distinct atropisomers
were separated in each case as discussed in Section 3.2.1. In those cases, atropisomers were formed partially due to amide resonance structure (cis & trans interconversion) and partially because of the difference of three-dimensional orientations of the aromatic rings.\textsuperscript{24} Interestingly, Boger et al.\textsuperscript{61} reported that 14-membered ring of RA-VII underwent a conformational change from E to less-stable Z-amide when the 18-membered ring next to it was built.

For this crucial problem whether one of the two cyclization products is an epimer or an atropisomer of the other, we have done Chem 3D molecular modelling studies (Figure 3.5 9 & 3.5.10) together with a careful analysis of $^1$H-NMR data of 3.28-F\textsubscript{1} and 3.28-F\textsubscript{2} (Figure 3.5.7). The most important difference between the two $^1$H-NMR spectra besides the peak-positions of B-$H^2$ is the vicinal coupling constants of $H_a$ and $H_a'$ with $H_{x1}$ of the phenylalanine subunit. The vicinal coupling constants of $H_a$ and $H_a'$ with $H_{x1}$ in 3.28-F\textsubscript{2} are 5.2 and 2.9 Hz which signifies that one of the two dihedral angles between $H_a$ (or $H_a'$) and $H_{x1}$ is near 90°. On the other hand, the similar vicinal coupling constants in the case of 3.28-F\textsubscript{1} are 5.2 and 12.1 Hz, respectively. This means that the dihedral angle corresponding to $J = 12.1$ Hz is almost 180°.
Figure 3.5.9 Chem 3D Molecular Modelling of 3.28-F2 and Its Epimers.
In the Chem 3D molecular modelling study (Figure 3.5.9), cyclization product 3.28-F₂ was assumed to have all the three chiral centers retained (structure A) because 3.28-F₂ was the major product under the most mild reaction conditions (DCC/HOAT). In this structure (A), the calculated dihedral angles (43°, 73°) between H_a (and H_a') and H_x₁ are clearly matched with the observed vicinal coupling constants (5.2, 2.9 Hz). Under these conditions, X₂-epimer in which inversion was made at X₂, the chiral center of F-phenylglycine subunit, the calculated dihedral angles (45°, 71°) remained almost the same as structure A. This means that the observed vicinal coupling constants (5.2, 12.1 Hz) of 3.28-F₁ are not matched with the calculated dihedral angles. Similarly, in X₃-epimer in which epimerization is assumed at the B-phenylglycine chiral center, the calculated dihedral angles (44°, 72°), once again, remain almost the same as A. On the other hand, in X₁ epimer in which the phenylalanine chiral center is inverted, the calculated dihedral angles (61°, 179°) are well matched with the observed vicinal coupling constants. But, the big energy difference (ΔG° = 3.68 Kcal/mole) (16.82 Kcal/mole for structure A vs 20.50 Kcal/mole for structure D) suggests that it is practically impossible to obtain the observed equilibrium ratio (80 : 20) at 0 °C. Furthermore, the reported degree of racemization during the dipeptide formation reaction between phenylglycine acid and valine amine under similar reaction conditions (HOAT, EDC, DMF, 24h) was less than 1-2%. In light of these results, 20% racemization is highly questionable to occur in our case (coupling of phenylalanine acid with phenylglycine amine).
Figure 3.5.9 Chem 3D Molecular Modelling of 3.28-F1 and Its Epimers.
The alternative possibility that 3.28-F2 and 3.28-F1 are atropisomers, was next considered (Figure 3.5.10). The standard structure A' (3.28-F1) in which the stereochemistry at all three chiral centers were retained was obtained as an energy (G = 18.66 Kcal/mole) minimized form by changing the three-dimensional orientations of aryl rings and amide bonds. In this case, the calculated dihedral angles are 58°, 175° which appears to be well matched with the observed vicinal coupling constants (5.2, 12.1 Hz). The same operation (inversion) were made at chiral centers Hx2, Hx3. But, the calculated dihedral angles in each case remained almost the same as A', which means that those structures do not correspond to 3.28-F2 (assuming A' is 3.28-F1) not the real cases. On the other hand, X1-epimer (D') of A' gave the calculated dihedral angles (43°, 73°) which seems to be matched well with the observed vicinal coupling constants (5.2, 2.9 Hz) of 3.28-F2. But, as discussed above, it is highly questionable that 20% racemization at the phenylalanine chiral center could occur under this mild coupling conditions (DCC/HOAT, 0 °C). We also have calculated the dihedral angles between Hx2 and Hw2, Hx3 and Hw3, but both dihedral angles did not provide any consistent and valuable informations.

So, at this point, we believe that the only possible explanation remaining for two cyclization products is atropisomerism. i.e., the major cyclization product 3.28-F2 formed under the most mild coupling conditions (DCC/HOAT, 0 °C) appears to adopt structure A, whose calculated dihedral angles (43°, 73°) are well matched with the observed vicinal coupling constants (5.2, 2.9 Hz) and also energetically resonable because it is the more stable than the other structure (A'). In this structure, B-H2 is located in the shielding region of aromatic C-ring because the distances between B-H2 and C-H3, C-H5 are 3.27 Å, 2.60 Å, so it is observed at 6.26 ppm. The other atropisomer 3.28-F1 which is the major cyclization product under the most harsh reaction conditions (pentafluorophenyl ester/Et3N, 90 °C) is less stable than its
counterpart and seems to adopt structure A', because its calculated dihedral angles (58°, 175°) are well matched with the observed vicinal coupling constants (5.2, 12.1 Hz). In this structure, the distances between B-H² and C-H³, C-H⁵ are 3.37 Å, 2.72 Å, which means that B-H² is still located under the aromatic C-ring shielding region, so B-H² appeared at 6.11 ppm.
Figure 3.5.11 Chem 3D Molecular Modellings of Cyclization Products 3.28-F₂ and 3.28-F₁
Figure 3.5.12 Space-Filling Models of Cyclization Products 3.28-F₂ and 3.28-F₁
When Chem 3D molecular modelling structures and their corresponding space-filling CPK-models were compared with the structure of ristocetin A proposed by Williams, the lower energy structure (3.28-F2) is similar to ristocetin A structure in terms of the direction of amide protons of H,w1, H,w2 and H,w3, i.e., all the amide protons of H,w1, H,w2 and H,w3 are directed outside for the H-bonding interaction.

To investigate if any interconversion could occur between the two cyclization products, 3.28-F2 was heated at 95 °C in CD3NO2 for 12 h, but no change was observed. We also tried high temperature (120 °C) using DMSO, but 3.28-F2 began to decompose probably due to lability of a N-BOC protecting group.

From the above four methods tried for 3.42, the pentafluorophenyl ester method appears to be the best in terms of overall yield. Although a two-step (deprotection of N-Cbz into amine-HCl, then cyclization) sequence was employed for 3.42, one-step (in situ deprotection of N-Cbz and simultaneous cyclization) method may provide better yields by minimizing possible degradation or side reactions, because pentafluorophenyl ester derivatives are generally known to be unstable. So, we decided to try a one-step approach for cyclization of the methyl ester/acid 3.41 (Scheme 3.5 17)
Scheme 3.5.17 Macrocyclization of 3.41 Using One-step and Two-step Sequence through Pentafluorophenyl Ester Intermediate 3.50

Careful literature survey reveals that there are two successful preceded cases reported for one-step cyclization using N-methylmorpholine\textsuperscript{45} and 4-pyrrolidinopyridine\textsuperscript{60} as base. The methyl ester/acid 3.41 was converted to its pentafluorophenyl ester using standard conditions (C\textsubscript{6}F\textsubscript{5}OH (3.0 equiv)/DCC (1.5 equiv), THF, 71% yield) and the resulting pentafluorophenyl ester 3.50 was subjected to the one-step cyclization conditions using slow addition/high dilution technique with bubbling H\textsubscript{2} over 6 h (Table 3.5.2).
<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M. (mM)</th>
<th>Conc. (mM)</th>
<th>Reagent Used</th>
<th>Base Used (equiv)</th>
<th>Reaction Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3.50</td>
<td>0.8</td>
<td>CuF₂OH</td>
<td>4-methylmorpholine</td>
<td>(a) 95°C, 1,4-dioxane, 6h (b) 95°C, 1h</td>
<td>Recovered 3.50 (57%) No cyclization products</td>
</tr>
<tr>
<td>6</td>
<td>3.50</td>
<td>0.4</td>
<td>CuF₂OH</td>
<td>4-pyrrolidinopyridine</td>
<td>(a) 95°C, 1,4-dioxane, 6h (b) 95°C, 1h</td>
<td>Recovered 3.50 (9%) No cyclization products</td>
</tr>
<tr>
<td>7</td>
<td>3.50'</td>
<td>0.3</td>
<td>CuF₂OH</td>
<td>(i-Pr)₂NET (2.0)</td>
<td>(a) 40°C, DMF (b) 40°C, 24h</td>
<td>Dimer (?) No cyclization products</td>
</tr>
</tbody>
</table>

(a) Conditions for addition of starting material to Pd-C(10%) in dry 1,4-dioxane (containing 2% of EtOH) with H₂-bubbling  (b) Reaction time and temperature after addition

Table 3.5.2 Results of Macrocyclization Reaction of 3.41 under Various Reaction Conditions.

After work-up as usual, the crude mixtures in each case were separated by HPLC and each fraction was characterized by ¹H-NMR. For entry-5 in which 4-methylmorpholine was used as a base, starting material (3.50) was recovered in 57% yield, and no cyclization products were obtained. For entry-6 in which 4-pyrrolidinopyridine was used as an additive, 3.50 was recovered in 9% yield, but no cyclization products were detected. It is worth noting that 4-pyrrolidinopyridine is normally utilized as a nucleophilic catalyst, but in this case it is not clear whether it is acting as a weak base or a nucleophilic catalyst. As a final trial (entry-7), we turned back to the earlier two-step sequence, but this time, employing milder reaction conditions (HOBT (2.0 equiv), (i-Pr)₂NET (2.0 equiv), DMF, rt and 40 °C) because it appears that the pentafluorophenyl ester is normally very reactive toward amine nucleophiles, so it may cyclize at rt or lower temperatures. In the event, the N-Cbz group of 3.50 was deprotected under the usual conditions to afford amine-HCl salt 3.50', which was dried under high vacuum, then subjected to the cyclization reaction conditions. After stirring for 24 h at rt under high dilution (0.3 mM), the reaction progress was monitored by TLC and ¹H-NMR, but most of the starting
material still remained, even though there were some spots observed which are probably cyclization products. So the reaction temperature was raised to 40 °C and stirred for 24 h at that temperature. After removal of DMF under high vacuum with slight heating (45 °C), the residue was worked-up as usual and then analyzed by TLC, and HPLC, but once again no cyclization products were obtained even though one fraction separated seems to be a dimeric product.
Sixteen-membered peptidic rings are important subunits of the "northern" part of Vancomycin and Ristocetin A glycopeptide antibiotics. Even though our first study\textsuperscript{54} for ABE (16-membered) ring cyclization failed partly because of a problem with deprotection of a 2-bromoethyl ester, more extensive study was undertaken.

All the subunits were successfully prepared by using Evans’ azidation method or direct conversion from amino acids, and arylation via Ruthenium-mediated chemistry was achieved under very mild conditions in good yields. Photochemical demetallation (sunlamp, 275W) and Finkelstein reaction were optimized to give reasonable yields. Deprotection of the resulting 2-iodoethyl ester was accomplished in good yields at rt by using SmI\(_2\) in the presence of DMPU as an additive. The final cyclization was extensively investigated by using various macrocyclization reagents and reaction conditions.

For 3.42, four different cyclization methods were examined including pentafluorophenyl ester/Et\(_3\)N, DCC/HOAT, HAPyU and FDPP. Among them pentafluorophenyl ester/Et\(_3\)N gave the best overall yield but provided two cyclization products (3.28-F\(_1\) and 3.28-F\(_2\)). It seems to be clear from \(^1\)H-NMR data and Chem 3D molecular modelling studies that one (3.28-F\(_1\)) of two cyclization products is an atropisomer of the other. Because of limited amounts of cyclization products obtained, no extensive studies for structure determination were made.

For 3.41, three different methods based on pentafluorophenyl ester intermediate 3.50 were tried, but no methods provided any cyclization products.
3.7. FUTURE PLANS

The "northern" part of vancomycin and ristocetin A is a very unique and important subunit which can be prepared by using Ru-chemistry under very mild conditions. One of the key requirements for this strategy is that successful macrocyclization reagents (or method) to be secured. Among the seven different macrocyclization methods (four methods for 3.42 and three methods for 3.41) tried, pentafluorophenyl ester/Et$_3$N methods appeared to be best in terms of overall yield but gave two cyclization products (3.28-F$_1$ and 3.28-F$_2$). In any case, this pentafluorophenyl ester method (including one-step or two-step sequence) should be thoroughly studied again using different reaction conditions.
General: All reactions were conducted under dry N₂ except the SmI₂-mediated deprotection reaction (under deoxygenated-, dry-Ar). ¹H-NMR (300 MHz) and ¹³C-NMR (75 MHz) spectra were recorded in CDCl₃, CD₃CN-CDCl₃ on a Varian Gemini-300 spectrometer. ¹H-NMR was referenced to TMS and ¹³C-NMR was referenced to CHCl₃ (77.0 ppm). IR spectra were recorded on Nicolet Impact 400 using CHCl₃ or CH₂Cl₂ as solvent. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. EI, HR and LRFAB mass spectra were recorded on a Kratos MS-25A instrument and HRFAB mass analysis was performed by Washington University Resource for Biomedical and Bio-organic Mass Spectroscopy, Washington University, St. Louis, Mo. CHN analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed using E. Merck Silicagel 60 F-254 0.25mm plates. Visualization was accomplished with UV, phosphormolybdic acid or ninhydrin solution. Flash chromatography was carried out on E. Merck 320-400 mesh silica gel and solvents are reported as V/V percent mixtures. Preparative HPLC was performed on a Gilson HPLC using Dynamax-60A normal phase preparative and semi-preparative columns. THF was distilled from the sodium ketyl of benzophenone. CH₂Cl₂, Et₃N and CH₃CN, DMPU were distilled from calcium hydride. All solvents were distilled under dry nitrogen. n-Butyllithium in hexane was obtained from Aldrich Co. and standardized according to the method of Duhamel and Plangnevant.⁴⁹ SmI₂ (0.1 M in THF) was purchased from Aldrich Co. and used directly without titration. HOAT was purchased from Waters inc. All other commercial reagents were purchased from Aldrich Co. and used without further purification.
(3-Hydroxy-4-methoxy)mandelonitrile (3.12). To a pre-heated (50 °C) solution of 9.6 g of NaHSO₃ in H₂O (60 mL) was added isovanillin 1.6 (12.16 g, 79.9 mmol) in one portion and the resulting mixture was stirred at 50 °C until all the starting material was completely dissolved. The solution was cooled to -5 °C (dry ice/MeOH) and a solution of KCN (10.4 g) in 16 mL of H₂O was added dropwise over 30 min. The resulting mixture was stirred for 30 min and made slightly acidic using 5 N H₂SO₄ (32 mL), then extracted with Et₂O (100 mL, 20 mL x 5). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. Since the product is known to be unstable at rt, the pale yellow crude product was immediately used for the next reaction without further purification and an analytical sample was recrystallized from CHCl₃. Yield: 13.5 g (94%); mp 96.5-98.0 °C (lit64 100 °C); Rᶠ 0.44 (hexanes/EtOAc/AcOH, 5/5/1%); IR (CHCl₃) 3432, 3346 (br), 3029, 2980, 2943, 2846, 2260, 1625, 1595, 1522, 1436, 1363, 1284, 1229 cm⁻¹; ¹H NMR (CDCl₃) δ 7.10 (d, 1H, J = 2.2 Hz, aromatic-H²), 7.05 (dd, 1H, J = 8.3, 2.2 Hz, aromatic-H⁶), 6.89 (d, 1H, J = 8.3 Hz, aromatic-H⁵), 5.72 (s, 1H, phenolic-H), 5.45 (d, 1H, J = 7.1 Hz, ArCHOH), 3.93 (s, 3H, -OCH₃), 2.40 (d, 1H, J = 7.1 Hz, ArCHCN).

(3-Hydroxy-4-methoxy)phenylacetic Acid (3.13). A slurry of SnCl₂·2H₂O (27.3 g) in conc HCl (24.2 mL) was added to a stirred, warm (50 °C) solution of crude mandelonitrile 3.12 (14.5 g, 80.7 mmol) in 20.0 mL of glacial acetic acid and the resulting mixture was heated at 110 °C for 4 h, then cooled to rt and filtered. The filtrate was diluted with 20 mL of water, then extracted with CHCl₃ (50 mL x 5). The filter cake was washed with 50 mL of
CHCl₃. The combined CHCl₃ layers were washed with brine, dried over MgSO₄ and the solvent was evaporated. The crude product was purified by recrystallization (CHCl₃) to afford a pale-brown solid. Yield: 4.61 g (34%); mp 126.5-128.0 °C (lit 65 127-128 °C); R_f 0.67 (EtOAc/1% AcOH); IR (CHCl₃) 3389, 3032, 2980, 2957, 1704, 1595, 1520, 1451, 1411, 1278, 1221 cm⁻¹; ¹H NMR (CDCl₃) δ 6.87-6.74 (m, 3H, aromatic-H), 5.59 (d, 1H, phenolic-H), 3.88 (s, 3H, -OCH₃), 3.56 (s, 2H, ArCH₂CO₂H).

(3-Benzyloxy-4-methoxy)phenylacetic Acid (3.14). A mixture of phenylacetic acid 3.13 (4.61 g, 27.7 mmol), NaOH (2.23 g, 2.01 equiv) and benzyl chloride (6.41 mL, 2.01 equiv) in 15 mL of dry MeOH was heated at reflux for 2.5 h under Ar and then cooled to rt. To this slurry was added a solution of NaOH (1.12 g) in H₂O (2.5 mL) and the resulting mixture was refluxed for 4 h. The organic solvent was removed under reduced pressure to provide a brown residue which was dissolved in 30 mL of water, then washed with chloroform (20 mL x 3). The aqueous layer was acidified with 10% HCl to ca. pH 2 and the product was extracted with EtOAc (50 mL x 3), dried over MgSO₄, concentrated in vacuo. Recrystallization from benzene afforded 5.31 g (71%) of the pure product as pale-yellow needles: mp 115-117 °C (lit 66 115-120 °C); R_f 0.46 (hexanes/EtOAc/AcOH, 5/5/1%); IR (CHCl₃) 3014, 1710, 1514, 1442, 1428 cm⁻¹; ¹H NMR (CDCl₃) δ 11.21 (bs, 1H, -CO₂H), 7.45-7.25 (m, 5H, -OCH₂C₆H₅), 6.84 (s, 3H, aromatic-H of ArOMe), 5.13 (s, 2H, -OCH₂Ph), 3.86 (s, 3H, -OCH₃), 3.54 (s, 2H, -CH₂CO₂H).
(4R)-3-[2-(3-Benzylxoy-4-methoxy)phenyl]-1-oxoethyl-4-phenylmethyl-2-oxazolidinone (3.15). To a stirred solution of phenylacetic acid 3.14 (3.77 g, 13.8 mmol) in 100 mL of THF at -78 °C was added freshly distilled Et₃N (2.51 mL, 1.30 equiv) and pivaloyl chloride (1.87 mL, 1.10 equiv) and the mixture was stirred for 15 min at -78 °C, then for 1h at 0 °C to form the mixed anhydride and then cooled again to -78 °C under N₂. Into a separate flask containing (4R)-4-(phenylmethyl)-2-oxazolidinone (2.51 g, 1.10 equiv) dissolved in 60 mL of THF at -78 °C was introduced n-BuLi (12.7 mL, 1.10 equiv, 1.20 M in hexanes) rapidly by syringe and this mixture was stirred for 20 min under N₂. This metallated oxazolidinone solution was transferred to the mixed anhydride solution via cannula and stirred for 30 min at -78 °C, then for 12 h at rt under N₂. After quenching the reaction with NaHSO₄ (100 mL, 1.0 N) and evaporating the solvent in vacuo, the residue was extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were washed with dil NaHCO₃, brine, dried over MgSO₄, filtered and concentrated under reduced pressure to afford a yellow oily residue. Flash column chromatography (silica gel, hexanes/EtOAc, 7/3) and recrystallization (hexanes/EtOAc, 9/1) gave 4.38 g (73%) of the pure product as pale-yellow crystals. mp 100.5-102.0 °C; [α]²³ D -50.7° (c 0.53, CHCl₃); Rf 0.37 (hexanes/EtOAc, 6/4); IR (CHCl₃) 3019, 1781, 1700, 1515 cm⁻¹; ¹H NMR (CDCl₃) δ 7.46-6.86 (m, 13H, aromatic Hs), 5.15 (s, 2H, -OCH₂Ph), 4.63 (m, 1H, -NCHCH₂-), 4.27-4.11 (m, 4H, ArCH₂CO- overlapped with -NCHCH₂O-), 3.88 (s, 3H, -OCH₃), 3.20 (dd, 1H, J = 13.4, 3.3 Hz, -NCHCH₂Ph), 2.69 (dd, 1H, J = 13.4, 9.5 Hz, -NCHCH₂Ph); ¹³C NMR (CDCl₃) δ 171.4, 153.3, 148.9, 148.1, 137.1, 135.1, 129.4, 128.9, 128.5, 127.8, 127.4, 127.3, 125.8, 122.6, 115.4,
(2R,4R)-3-[2-Azido-2-(3-benzyl-4-methoxyphenyl-1-oxo)ethyl-4-phenylmethyl-2-oxazolidinone (3.16). To a stirred solution of imide 3.15 (2.52 g, 5.83 mmol) in 50 mL of THF at -78 °C was added KHMDS (12.3 mL, 1.05 equiv, 0.5 M in toluene) by syringe in one portion and the resulting solution was stirred for 25 min at -78 °C under N₂. Into this was transferred a pre-cooled (-78 °C) solution of trisyl azide (2.26 g, 1.25 equiv) in 40 mL of THF via cannula rapidly, then stirred further for 2 min at -78 °C. The reaction was quenched with acetic acid (1.17 mL, 3.5 equiv) and warmed immediately to 35 °C with a water bath, then stirred for 3 h at rt under N₂. The reaction mixture was partitioned between brine and CH₂Cl₂ (150 mL), shaken and separated. The aqueous layer was washed again with CH₂Cl₂ (20 mL x 2) and the combined organic layers were washed with dil NaHCO₃, brine, dried over MgSO₄, evaporated in vacuo to afford the crude product as a yellow oil. Flash column chromatography (hexanes/EtOAc, 8/2 then 7/3) gave the purified product which contained minor diastereomer (diastereomeric ratio = 96 : 4, determined by ¹H-NMR) as an impurity. Recrystallization using various solvent systems failed and the diastereomeric mixture was used for the next reaction. Yield: 2.30 g (84%); mp 42.0-43.5 °C; [α]²²D -187.4° (c 0.5, CHCl₃); Rf 0.43 (hexanes/EtOAc, 6/4); IR (CHCl₃) 3019, 2109, 1784, 1710, 1515, 1385, 1222 cm⁻¹; ¹H NMR (CDCl₃) δ 7.49-6.88 (m, 13H, aromatic Hs), 6.06 (s, 1H, ArCH=N₃-), 5.23 (d, 1H, J = 12.3 Hz, -OCH₂Ph), 5.13 (d, 1H, J = 12.3 Hz, -OCH₂Ph), 4.45 (m, 1H, -NCH₂CH₂O-), 4.15-3.90 (m, 5H, -NCH₂CH₂O- overlapped with -OCH₃), 3.38 (dd, 1H, J = 13.3,
3.2 Hz, -NCHCH2Ph), 2.80 (dd, 1H, J = 13.3, 9.8 Hz, -NCHCH2Ph); 13C NMR (CDCl3) δ 169.3, 152.2, 150.5, 148.2, 136.7, 134.8, 129.3, 129.0, 128.4, 127.8, 127.44, 127.38, 124.8, 122.1, 113.5, 111.7, 70.8, 66.3, 63.3, 55.9, 55.6, 37.6; HRMS calcd for C26H24N2O5 (M-N2)+ 444.1685, found 444.1714.

(2R)-2-Azido-2-[(3-benzyloxy-4-methoxy)phenyl]acetic Acid Methyl Ester (3.17). To a pre-cooled (0 °C), stirred solution of α-azido imidate

![Image](image_url)

3.16 (752.8 mg, 1.59 mmol) in 30 mL of THF was added 6.38 mL of aqueous LiOH solution (0.5 M, 2.0 equiv) and the resulting mixture was stirred for 1 h at 0 °C. It was acidified with 10% HCl solution to ca. pH 2, then extracted with Et2O (30 mL x 3). The combined organic layers were dried over MgSO4 and the solvent was removed in vacuo to give an off-white solid, which was dried further under high vacuum. The crude product was dissolved in 20 mL of dry MeOH containing 607 mg (2.0 equiv) of PTSA and the mixture was heated at reflux for 5h under Ar, then cooled to rt. The solvent was removed under reduced pressure and the product was taken up in CH2Cl2 (50 mL), washed with dil NaHCO3, then dried over MgSO4 and concentrated. Purification by flash chromatography on silica gel (hexanes/EtOAc, 8/2) gave 407.8 mg (78%) of α-azido methyl ester as a colorless liquid. The optical purity based on [α]D value reported was (96 : 4) which showed no significant racemization occurred during the esterification process. [α]24D -102.3° (c 0.44, CHCl3) (lit33 -110.6° (c 2.84, CHCl3)); Rf 0.33 (hexanes/EtOAc, 7/3); IR (CHCl3) 3024, 2956, 2838, 2117, 1750, 1595, 1520, 1215 cm⁻¹; 1H NMR (CDCl3) δ 7.45-7.26 (m, 5H, -OCH2C6H5), 6.96-6.88 (m, 3H, aromatic Hs of Ar-OME)
(2R)-2-Amino-2-[(3-hydroxy-4-methoxy)phenyl]acetic acid Methyl Ester (3.18). 40 mg (10 wt %) of Pd-C(10%) was pre-activated by stirring it in 40 mL of mixed solvent (MeOH/THF, 1/1) for 1 h under H₂ (1 atm). To this slurry was added 394.8 mg (1.21 mmol) of α-azido methyl ester 3.17 and the resulting mixture was stirred for 24 h at rt under H₂ (1 atm). The mixture was filtered through a Celite pad (1 x 2 cm) and the filter cake was washed well with MeOH. The combined organic layers were concentrated in vacuo to afford the crude product as a pale-brown solid which was purified by flash column chromatography on silica gel (EtOAc then EtOAc/MeOH, 95/5). Yield: 202.2 mg (79%); mp 151.5-153.5 °C; [α]²⁴_D -106.6° (c 0.56, CHCl₃); Rᵣ 0.27 (hexanes/EtOAc, 5/5); IR (CHCl₃) 3697, 3542, 3029, 2963, 1736, 1598, 1515, 1223 cm⁻¹; ¹H NMR (CDCl₃) δ 6.94 (d, 1H, J = 1.8 Hz, aromatic-H²), 6.86 (dd, 1H, J = 7.8, 1.8 Hz, aromatic-H⁶), 6.82 (d, 1H, J = 7.8 Hz, aromatic-H⁵), 4.52 (s, 1H, ArCHCO₂⁻), 3.88 (s, 3H, -OCH₃), 3.70 (s, 3H, -OCH₃); ¹³C NMR (CDCl₃) δ 174.5, 146.4, 145.8, 133.5, 118.4, 113.1, 110.7, 58.2, 55.9, 52.3; HRMS calcd for C₁₀H₁₃NO₄ 211.0845, found 211.0849.

N-(Phenylmethoxy)carbonyl-L-phenylglycine (3.20). To a stirred solution of Na₂CO₃ (1.31 g, 12.4 mmol) in 38 mL of H₂O was added L-phenylglycine 3.19 (0.75 g, 4.96 mmol) in one portion and the resulting mixture was stirred vigorously until
all the starting material was completely dissolved, then cooled to 0 °C with an ice bath. To this solution was added 0.90 mL (1.27 equiv) of CbzCl by syringe and the resulting mixture was stirred vigorously for 2h at 0 °C, then for 22 h at rt. The solution was washed with Et₂O (10 mL x 3) and the aqueous layer was acidified to pH 2 with 10 % HCl. The white solid that formed was filtered and washed well with cold H₂O, then dissolved in 50 mL of EtOAc. The organic layer was washed with H₂O, then dried over MgSO₄ and evaporated. Recrystallization of the crude product (hexanes/EtOAc, 5/5) gave 1.16g (82%) of pure product as a white power. mp 130.5-132.5 °C; [α]²³_D +120.7° (c 0.65, EtOAc); Rf 0.21 (EtOAc/MeOH, 9/1); IR (CHCl₃) 3436, 3026, 1725, 1667, 1497 cm⁻¹; ¹H NMR (CDCl₃) δ 12.87 (bs, 1H, -CO₂H), 8.12 (d, 1H, J = 8.1 Hz, -NH), 7.42-7.29 (m, 10H, aromatic Hs), 5.18 (d, 1H, J = 8.1 Hz, -CHCO₂H), 5.05 (s, 2H, -OCH₂Ph); ¹³C NMR (CDCl₃) δ 172.1, 155.9, 137.1, 136.9, 128.4, 128.3, 127.9, 127.7, 65.6, 58.1; HRMS calcd for C₁₆H₁₅NO₄ 285.1001, found 285.1001.

\[ N-\{N-(\text{Phenylmethoxy})\text{carbonyl-L-phenylglycyl}\}-\text{D-[(3-hydroxy-4-methoxy)phenyl]glycine Methyl Ester (3.10).} \] A mixture of crude α-amino methyl ester 3.18 (186.0 mg, 0.88 mmol), crude acid 3.20 (276.3 mg, 1.10 equiv) and HOBT (142.9 mg, 1.20 equiv) was dissolved in 10 mL of mixed solvent (THF/DMF, 1/1) and the resulting solution was cooled to 0 °C under N₂. To this was added EDC (185.8 mg, 1.10 equiv) in one portion and the resulting mixture was stirred for 2h at 0 °C, then 20 h at rt under N₂. The solvent was evaporated in vacuo and the residue was extracted with CH₂Cl₂ (20 mL x 3). The combined organic layers were washed with NaHSO₃ (10 mL, 1N), brine, then dried over MgSO₄ and concentrated. Flash column chromatography on silica gel
(hexanes/EtOAc, 5/5) and subsequent recrystallization from (hexanes/THF, 6/4) gave 325.1 mg (77%) of diastereomERICALLY pure product as a white powder. mp 187.5-189.5 °C; [α]$_{23}^{D}$ -7.1° (c 0.42, CHCl$_3$); R$_f$ 0.41 (hexanes/EtOAc, 4/6); IR (CHCl$_3$) 3545, 3415, 3033, 2970, 1738, 1689, 1684, 1512, 1220 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.33-7.22 (m, 10H, aromatic Hs of C$_6$H$_5$CHNH- and Cbz), 6.71-6.58 (m, 4H, aromatic Hs of Ar$^{O}$Me overlapped with -NHCBz), 6.00 (bs, 1H, Ar$^{O}$MeCHNH-), 5.58 (s, 1H, Phenolic -H), 5.40 (d, 1H, J = 6.8 Hz, -CHNHCBz), 5.29 (bs, 1H, Ar$^{O}$MeCHNH-), 5.10 (d, 1H, J = 12.3 Hz, -OCHHPPh), 5.02 (d, 1H, J = 12.3 Hz, -OCHHPPh), 3.84 (s, 3H, -OCH$_3$), 3.70 (s, 3H, -OCH$_3$); $^{13}$C NMR (CDCl$_3$) δ 170.9, 168.9, 155.6, 146.8, 145.9, 137.7, 136.1, 129.1, 128.6, 128.5, 128.1, 127.4, 118.8, 113.0, 110.6, 67.0, 58.7, 56.2, 55.9, 52.9; HRMS calcd for C$_{24}$H$_{26}$N$_2$O$_7$ 478.1740, found 478.1751.

(4R)-3-[3-(4-Chlorophenyl)-1-oxo]propyl-4-phenylmethyl-2-oxazolidinone (3.21). Reaction procedures were the same as 1.18 except for the use of (4R)-4-(phenylmethyl)-2-oxazolidinone instead of (4S)-auxiliary. Yield: (82%); [α]$_{22}^{D}$ -64.4° (c 1.22, CHCl$_3$); $^1$H NMR (CDCl$_3$) δ 7.35-7.15 (m, 9H, aromatic Hs), 4.70-4.62 (m, 1H, -NCHCH$_2$O-), 4.22-4.15 (m, 2H, -NCHCH$_2$O-), 3.35-3.16 (m, 3H, ArCH$_2$CH$_2$- overlapping with -CHCHHPPh), 3.02-2.96 (m, 2H, ArCH$_2$CH$_2$-), 2.75 (dd, 1H, J = 13.4, 9.5 Hz, -CHCHHPPh).

(2R,4R)-3-[2-Azido-3-(4-chlorophenyl)-1-oxo]propyl-4-phenylmethyl-2-oxazolidinone (3.22). Reaction procedures were the same as 1.19a except for the use of (R)-auxiliary adduct. Yield: (77%); [α]$_{22}^{D}$ -84.3° (c 0.51, CHCl$_3$); $^1$H
NMR (CDCl$_3$) $\delta$ 7.38-7.21 (m, 9H, aromatic Hs), 5.22 (dd, 1H, $J = 9.3$, 5.2 Hz, ArCH$_2$CH$-$), 4.66-4.61 (m, 1H, -NCHCH$_2$Ph), 4.25-4.14 (m, 2H, -NCHCH$_2$CO$-$), 3.33 (dd, 1H, $J = 13.5$, 3.2 Hz, -NCHCHHPH), 3.19 (dd, 1H, $J = 13.7$, 5.2 Hz, ArCHHCH$-$), 3.00 (dd, H, $J = 13.7$, 9.3 Hz, ArCHHCH$-$), 2.84 (dd, 1H, $J = 13.5$, 9.5 Hz, -NCHCHHPH).

$(2R,4R)$-3-[3-(4-chlorophenyl)2-[(1,1-dimethylethoxy)carbonyl]-amino-1-oxo]propyl-4-phenylmethyl-2-oxazolidinone (3.23). Reaction procedures were the same as 1.23 except for the use of its enantiomer. Yield: (83%); $[\alpha]^{23}_{D} = 80.6^o$ (c 0.49, CHCl$_3$; 1H NMR $\delta$ 7.37-7.19 (m, 9H, aromatic Hs), 5.72-5.65 (m, 1H, ArCH$_2$CH$-$), 5.13 (d, 1H, $J = 6.8$ Hz, -CH$_2$CHNH$-$), 4.62-4.56 (m, 1H, -NCHCH$_2$Ph), 4.22-4.10 (m, 2H, -NCHCH$_2$O$-$), 3.33 (bd, 1H, $J = 12.1$ Hz, -NCHCHHPH), 3.14 (dd, 1H, $J = 11.6$, 2.3 Hz, ArCHHCH$-$), 2.31-2.74 (m, 2H, ArCHHCH$-$ overlapped with -NCHCHHPH), 1.38 (s, 9H, -BOC).

$N$-(1,1-Dimethylethoxy)carbonyl-D-(4-chlorophenyl)alanine 2-Bromoethyl Ester (3.24). Reaction procedure was the same as 1.22c except for the use of (R)-amino acid. Yield: (75%); $[\alpha]^{25}_{D} = -21.4^o$ (c 0.42, CHCl$_3$; 1H NMR (CDCl$_3$) $\delta$ 7.27 (d, 1H, $J = 8.3$ Hz, aromatic Hs ortho to -Cl), 7.16 (d, 1H, $J = 8.3$ Hz, aromatic Hs meta to -Cl), 4.95 (bd, 1H, $J = 7.6$ Hz, -CH$_2$CHNH$-$), 4.65-4.58 (m, 1H, ArCH$_2$CH$-$), 4.43-4.36 (m, 2H, -CH$_2$CH$_2$Br),
3.50-3.42 (m, 2H, -CH$_2$CH$_2$Br), 3.14 (dd, 1H, J = 13.7, 5.9 Hz, ArCH/HCH-),
3.04 (dd, 1H, J = 13.7, 6.5 Hz, ArCH/HCH-).

$[\eta^6-\{(2R)-[4-Chloro-\{2-\{(1,1-dimethylethoxy)carbonyl\}amino-3-oxo-3-(2-bromoethoxy)propyl\}]benzene\}\eta^5$-cyclopentadienyl]ruthenium

Hexafluorophosphate (3.11). Reaction procedures were the same as 1.5c

except for the use of (R)-amino acid derivate. Yield: (quant); $^1$H NMR (CDCl$_3$) δ 6.46-6.27 (m, 4H, aromatic Hs), 5.47 (s, 5H, CP), 4.54-4.44 (m, 3H,
-CH$_2$CH$_2$Br overlapped with ArCH$_2$CH-), 3.65-3.59 (m, 2H, -CH$_2$CH$_2$Br), 3.14 (dd, 1H, J = 14.2, 5.2 Hz, ArCHHCH-), 2.88 (dd, 1H, J = 14.2, 5.2 Hz, ArCHHCH-). 1.40 (s, 9 H, -BOC).

$[\eta^6-\{(2R,2'R)-4-\{(2-Methoxy-5-[1-[\text{N-(phenylmethoxy)carbonyl-L-phenylglycyl}amino-2-methoxy-2-oxoethyl]}phenoxyl]-1-\{(1,1-dimethylethoxy)carbonyl\}amino-3-oxo-3-(2-bromoethoxy)propyl\}]$-
benzene$\eta^5$-cyclopentadienyl]ruthenium Hexafluorophosphate (3.25).

(i) A stock basic-solution of sodium 2,6-di-t-butylphenoxide was made as follows: Into a 50 mL round bottom flask containing 395.6 mg (1.92 mmol) of 2,6-di-t-tert-butylphenol and NaH (76.6 mg, 1.0 equiv, 60 % in mineral oil) was added 30 mL of freshly distilled THF by syringe and the resulting slurry was stirred for 30 min at rt, then cooled to 0 °C with an ice bath under N$_2$. (ii) To a stirred, precooled (0 °C) solution of dipeptide 3.10 (162.5 mg, 1.0 equiv) in 10 mL of THF was added 5.3 mL (1.0 equiv) of pre-made basic stock solution by syringe and the resulting mixture was stirred for 15 min at 0
°C under N₂. This cooled (0 °C) solution was then trasferred via cannula into a precooled (-78 °C) solution of arene-Ru complex 3.3 (241.9 mg, 1.0 equiv) in 10 mL of THF and the resulting mixture was stirred for 30 min at -78 °C and 1.5 h at rt under N₂, then evaporated in vacuo to afford a dark brown residue which was dissolved in 10 mL of CH₃CN. The CH₃CN solution was then filtered through a neutral alumina column (1 x 5 cm) and the column was washed further with 15 mL of CH₃CN. The combined filtrate was concentrated to ca. 1 mL, then diluted with 40 mL of Et₂O. The ethereal mixture was cooled in a refrigerator for 1 h and decanted carefully. The pale-brown residue was washed further with cold Et₂O (10 mL x 2), then dried under high vacuum to provide diaryl-Ru complex 3.25 (341 mg, 87 %) as a pale-brown solid foam, which was judged to be pure enough for the next reaction by ¹H-NMR. IR (CHCl₃) 3684, 3421, 3019, 2987, 1741, 1707, 1602, 1511, 1500, 1216 cm⁻¹; ¹H NMR (CDCl₃) δ 7.42-6.80 (m, 14H, aromatic Hs of Ar OMe, Ar, Cbz, overlapped with -NHCbz), 6.46-5.82 (m, 5H, aromatic Hs ArRu+ overlapped with Ar OMeCHNH-), 5.54-5.00 (m, 9H, Ar OMeCHNH-, -CHNHCbz, Cp, -OCH₂Ph, -NHBOC), 4.53-4.41 (m, 3H, -CH₂CH₂Br overlapped with -CHNHBOC), 3.84 (s, 3/2H, -OCH₃), 3.82(s, 3/2H, -OCH₃), 3.77 (s, 3/2H, -OCH₃), 3.70 (s, 3/2H, -OCH₃), 3.11-2.80 (m, 2H, ArRu+CH₂-), 1.42 (s, 9H, -BOC).

(2R)-[3-[4-[2-[(1,1-Dimethylethoxy)carbonyl]amino-3-oxo-3-(2-bromoethoxy)propyl]phenoxy-4-methoxy-N-[N-(phenylmethoxy)carbonyl-L-phenylglycinyl]]-D-phenylglycine Methyl Ester (3.26). The arene-Ru complex 3.25 (283.0 mg, 0.24 mmol) was dissolved in 25 mL of dry CH₃CN in a quartz cell (1.5 x 20 cm) and was degassed by bubbling
with N₂ for 20-30 min. The resulting dark-brown solution was irradiated with a sunlamp (275 W) for 20-24 h under N₂ (caution: no refluxing, slightly heated), then cooled to rt and concentrated in vacuo to ca. 1 mL, which was diluted with 40 mL of Et₂O. The etheral suspension was put aside for 2 h at rt to allow the dark Ru-complex sedimented, then filtered. The ether-insoluble filter cake was washed well with additional 30 mL of Et₂O. The combined ether extracts were concentrated under reduced pressure to give a pale-brown residue which was purified by flash column chromatography (SiO₂, hexanes/EtOAc, 6/4) providing 85.2 mg of product 3.26 as an off-white solid. The filter cake and dark-brown sticky deposits inside the flask were recovered in 25 mL of CH₃CN and the resulting solution was bubbled with N₂, then subjected to the same photochemical reaction conditions. Repeating the whole procedure twice provided additional 40.6 mg of pure product. 85.0 mg (80%) of crude (CH₃CN)₃ Ru⁺CpPF₆ was recovered. Total yield: 115.4 mg (56%); [α]²³D
+34.9° (c 0.45, CHCl₃); Rf 0.30 (hexanes/EtOAc, 5/5); IR (CHCl₃) 3440 (br), 3020, 2986, 1744, 1710, 1693, 1512, 1223, 1177 cm⁻¹; ¹H NMR (CDCl₃) δ 7.34-6.72 (m 18H, aromatic Hs overlapped with -NHCbz), 6.09 (bs, 1H, Ar-OMeCHNH-), 5.46-5.32 (m, 2H, two doublets (2 x 1/2H) of -CHNHCBz overlapped with Ar-OMeCH-: 5.44 (d, 1/2H, J = 6.8 Hz, -CHNHCBz), 5.39 (d, 1/2H, J = 6.8 Hz, -CHNHCBz), 5.15-4.99 (m, 3H, two doublets (2 x 1H) of -OCH₂Ph overlapped with -NHBOC: 5.07 (d, 1H, J = 12.2 Hz, -OCH₂Ph), 5.01 (d, 1H, J = 12.2 Hz, -OCH₂Ph), 4.60-4.56 (m, 1H, -CHNHBOC), 4.43-4.36 (m, 2H, -CH₂CH₂Br), 3.79 (s, 3/2H, -OCH₃), 3.76 (s, 3/2H, -OCH₃), 3.68 (s, 3/2H, -OCH₃), 3.62 (s, 3/2H, -OCH₃), 3.46-3.41 (m, 2H, -CH₂CH₂Br), 3.07 (bs, 2H, -CH₂CH₂Br), 1.41 (s, 9H, -BOC); ¹H NMR (DMSO-d₆) 9.08 (d, 1/2H, J = 7.7 Hz), 9.01 (d, 1/2, J = 7.7 Hz), 7.96 (d, 1H, J = 8.8 Hz), 7.43-6.95 (m, 16H), 6.73 (d, 1H, J = 8.4 Hz), 6.68 (d, 1H, J = 8.4 Hz), 5.46 (d, 1/2H, J = 9.2 Hz), 5.42 (d, 1/2H, J = 9.1 Hz), 5.35 (d,
1/2H, J = 3.4 Hz), 5.33 (d, 1/2H, J = 3.2 Hz), 5.02 (s, 2/2H, -OCH<sub>2</sub>Ph), 5.01 (s, 2/2H, -OCH<sub>2</sub>Ph), 4.41-4.29 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>Br), 4.18-4.11 (m, 1H, -CHNHBOC), 3.72 (s, 3/2H, -OCH<sub>3</sub>), 3.70 (s, 3/2H, -OCH<sub>3</sub>), 3.61 (s, 3H, -OCH<sub>3</sub>), 3.52 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>Br), 2.97 (dd, 1H, J = 14.0, 4.7 Hz, -CHHCHNHBOC), 2.83 (dd, 1H, J = 14.0, 10.0 Hz, -CHHCHNHBOC), 1.32 (s, 9H, -BOC); HRMS FAB (m-NBA) calcd for (MH)<sup>+</sup> (Br<sup>79</sup>, Br<sup>81</sup>) 848.2394, 850.2373, found (MH)<sup>+</sup> (Br<sup>79</sup>, Br<sup>81</sup>) 848.2349, 850.2358; Anal. calcd for C<sub>42</sub>H<sub>46</sub>N<sub>3</sub>O<sub>11</sub>Br<sub>1</sub> : C, 59.44; H, 5.46; N, 4.95. Found: C, 59.80; H, 5.70; N, 4.80.

(2R)-[3-4-[2-[(1,1-Dimethylethoxy)carbonyl]amino-3-oxo-3-(2-iodoethoxy)propyl]phenoxy]-N-[N-(phenylmethoxy)carbonyl-L-phenylglycyl]l-D-phenylglycine Methyl Ester (3.27). To a stirred solution of bromoethyl ester 3.26 (134 mg, 0.16 mmol) in 10 mL of dry acetone was added 119.0 mg (5.0 equiv) of anhydrous NaI (99+ %) in one portion and the resulting slurry was refluxed for 6 h under N<sub>2</sub>. The reaction mixture was cooled to rt, then filtered and the filter cake was washed well with acetone (10 mL x 2). Solvent was removed in vacuo to afford a solid residue which was taken up in 30 mL of CH<sub>2</sub>Cl<sub>2</sub>, washed with brine and dried over MgSO<sub>4</sub>, filtered and then evaporated. The crude product was purified by flash chromatography (SiO<sub>2</sub>, hexanes/EtOAc = 5/5) to give 122 mg (86%) of pure 3.27 as an off-white solid form. [α]<sup>26</sup><sub>D</sub> +34.3° (c 0.65, CHCl<sub>3</sub>); R<sub>f</sub> 0.35 (hexanes/EtOAc, 5/5); IR (CHCl<sub>3</sub>) 3431 (br), 3018, 2989, 1744, 1716, 1507, 1218, 1173 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.35-6.72 (m, 18H, aromatic Hs overlapped with -NHCbz), 6.15 (bs, 1H, Ar-OMeCH=), 5.49-5.39 (m, 2H, two doublets (2 x 1/2H) of -CHNHCbz overlapped with Ar-OMeCH-, 5.45 (d, 1/2H, J = 7.0 Hz,
\(-\text{CHNHCbz}\), 5.40 (d, 1/2H, J = 6.9 Hz, -\text{CHNHCbz}\)), 5.14-4.97 (m, 3H, Two doublets (2 x 1H) of -\text{CO}_2\text{CH}_2\text{Ph} overlapped with -\text{CHNHBOC}, 5.08 (d, 1H, J = 4.7 Hz, -\text{OCH}_2\text{HPh}), 5.02 (d, 1H, J = 4.7 Hz, -\text{OCH}_2\text{HPh}), 4.57 (m, 1H, -\text{CHNHBOC}, 4.35-4.30 (m, 2H, -\text{CH}_2\text{CH}_2\text{I}), 3.77 (s, 3/2H, -\text{OCH}_3), 3.75 (s, 3/2H, -\text{OCH}_3), 3.67(s, 3/2H, -\text{OCH}_3), 3.61 (s, 3/2H, -\text{OCH}_3), 3.23-3.21 (m, 2H, -\text{CH}_2\text{CH}_2\text{I}), 3.19-3.06 (m, 2H, -\text{CH}_2\text{CH}_2\text{NHBOC}), 1.41 (s, 9H, -\text{BOC}); HRMS FAB (m-NBA) calcd for (MH)\(^+\) 896.2257, found 896.2291; Anal. calcd for C\(_{42}\)H\(_{46}\)N\(_3\)O\(_{11}\): C, 56.32; H, 5.18; N, 4.69. Found: C, 56.61; H, 5.36; N, 4.56.

(**R)**-2-Azido-2-[(3-benzylxy-4-methoxy)phenyl]acetic Acid Ethyl Ester (3.31). (i) To a pre-cooled (0 °C) solution of \(\alpha\)-azido imidate 3.30 (2.78 g, 5.88 mmol) in 45 mL of THF was added 11.8 mL (1.0 M in H\(_2\)O, 2.0 equiv) of LiOH and it was stirred for 1 h at 0 °C, then acidified to ca. pH 2 with 5 N HCl. The product was taken up into Et\(_2\)O (150 mL) and the aqueous layer was washed with Et\(_2\)O (50 mL x 2). The combined organic layers were washed with brine, dried over MgSO\(_4\), concentrated in vacuo to give an off-white solid which was further dried under high vacuum. This crude acid was used for the next reaction without purification. (ii) The crude acid thus obtained above dissolved in 30 mL of dry EtOH, followed by addition of PTSA (2.24 g, 2.0 equiv) and the resulting mixture was refluxed overnight under N\(_2\). The solvent was removed in vacuo and the residue was dissolved in CH\(_2\)Cl\(_2\) (80 mL). The organic layer was washed successively with dil NaHCO\(_3\), brine and dried over Na\(_2\)SO\(_4\) and the solvent was removed in vacuo. Flash chromatography of the crude product on silica gel (hexanes/EtOAc, 8/2) provided 1.42 g (71%) of the pure product 3.31 as a white solid. mp 43.0-45.0 °C; [\(\alpha\)]\(^{22}\)_D -93.5° (c 0.49, CHCl\(_3\))；R\(_f\) 0.37
(hexanes/EtOAc, 7/3); IR (CHCl₃) 3019, 2996, 2935, 2117, 1741, 1601, 1523, 1265 cm⁻¹; ¹H NMR (CDCl₃) δ 7.45-7.26 (m, 5H, -OCH₂C₆H₅), 6.97-6.88 (m, 3H, aromatic Hs of Ar²OMe), 5.15 (s, 2H, -OCH₂Ph), 4.82 (s, 1H, ArCHCO₂-), 4.24-4.11 (m, 2H, -OCH₂CH₃), 3.89 (s, 3H, -OCH₃), 1.20 (dd, 3H, J = 7.1, 7.1 Hz, -OCH₂CH₃); ¹³C NMR (CDCl₃) δ 169.2, 150.4, 148.4, 136.6, 128.5, 127.9, 127.4, 126.1, 121.0, 113.0, 111.7, 71.0, 65.0, 62.0, 56.0, 14.0; HRMS calcd for C₁₈H₁₉N₃O₄ 341.1375, found 341.1369.

D-[(3-Hydroxy-4-methoxy)phenyl]glycine Ethyl Ester (3.32). To a slurry of pre-activated (with H₂, 30 min) Pd-C (10%, 140.0 mg) in 40 mL of mixed solvent (THF/MeOH, 1/1) was added α-azido ethyl ester 3.31 (1.36 g, 3.98 mmol) and the resulting mixture was stirred for 24 h at rt under H₂ (1 atm). The solid Pd-C catalyst was filtered off through a Celite pad (1 x 2 cm) and the filter cake was washed well with MeOH (30 mL). The combined organic layers were concentrated in vacuo and dried under high vacuum to furnish α-amino ethyl ester 3.32 as an off-white solid. The crude product was pure enough to be used for the next reaction without purification. Yield: 887.0 mg (99%); mp 114.5-116.5 °C; [α]²³D -97.6° (c 0.50, CHCl₃); Rf 0.36 (EtOAc/MeOH, 9/1); IR (CHCl₃) 3546, 3018, 2981, 1731, 1595, 1514, 1215 cm⁻¹; ¹H NMR (CDCl₃) δ 6.94 (d, 1H, J = 2.0 Hz, aromatic-H²), 6.84 (dd, 1H, J = 8.3, 2.0 Hz, aromatic-H⁶), 6.78 (d, 1H, J = 8.3 Hz, aromatic-H⁵), 4.54 (s, 1H, ArCHC-), 4.27-4.08 (m, 4H, ArCHNH₂-overlapped with -OCH₂CH₃), 3.84 (s, 3H, -OCH₃), 1.20 (dd, 3H, J = 7.1, 7.1 Hz, -OCH₂CH₃); ¹³C NMR (CDCl₃) δ 173.5, 164.7, 145.9, 132.5, 118.5, 113.4, 110.9, 61.4, 58.0, 55.9, 14.0; HRMS calcd for C₁₁H₁₅NO₄ 225.1001, found 225.0999.
(4S)-3-[[2-(4-Methoxyphenyl)-1-oxo]ethyl]-4-phenylmethyl-2-oxazolidinone (3.34). Freshly distilled Et₃N (2.25 mL, 1.30 equiv) and pivaloyl chloride (2.06 mL, 1.10 equiv) was added sequentially to a pre-cooled (-78 °C), stirred solution of p-methoxyphenylacetic acid (3.33, 2.53 g, 15.2 mmol) in 70 mL of THF under N₂. The mixture was stirred for 20 min at -78 °C then 50 min at rt and cooled again to -78 °C. Into a separate flask containing 2.64 g (1.05 equiv) of (4S)-4-benzyl-2-oxazolidinone in 60 mL of THF at -78 °C was added n-BuLi (10.6 mL, 1.05 equiv, 1.51 M in hexanes) and the mixture was stirred for 30 min at -78 °C under N₂. The metallated solution was then transferred to the above mixed anhydride mixture via cannula and the resulting mixture was stirred for 30 min at -78 °C and for 20 h at rt under N₂. The reaction was quenched with NaHSO₄ (100 mL, 1.0 N) and THF was removed in vacuo to give a pale-brown oily residue which was extracted with CH₂Cl₂ (50 mL x 3). The combined organic layers were washed with dil NaHCO₃, brine, dried over MgSO₄, then filtered and concentrated. Flash column chromatography (SiO₂, hexanes/EtOAc, 7/3) provided a pale-yellow oil, which solidified in the refrigerator. Yield: 3.88 g (79%); mp 81.0-83.0 °C; [α]²³D +64.6° (c 0.68, CHCl₃); Rf 0.28 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3024, 2981, 1781 1700, 1619, 1514, 1222 cm⁻¹; ¹H NMR (CDCl₃) δ 7.32-7.20 (m, 5H, -CHCH₂-C₅H₅), 7.14 (d, 2H, J = 7.7 Hz, aromatic Hs ortho to -OMe), 6.89 (d, 2H, J = 7.7 Hz, aromatic Hs meta to -OMe), 4.69-4.64 (m, 1H, -NCHCH₂Ph), 4.31-4.13 (m, 4H, Ar-OMeCH₂C- overlapped with -NCHCH₂O-), 3.80 (s, 3H, -OCH₃), 3.26 (dd, 1H, J = 13.3, 3.3 Hz, -NCHCH₃Ph), 2.75 (dd, 1H, J = 13.3, 9.4 Hz, -NCHCH₃Ph); ¹³C NMR (CDCl₃) δ 171.4, 158.8, 153.4, 135.1, 130.8, 129.4, 128.9, 127.3, 125.4, 114.0, 69.5, 68.2, 55.5, 55.3, 50.9, 45.4, 42.4, 42.2, 36.0, 21.0, 15.0.
[2S,4S]-3-[2-Azido-2-(4-methoxyphenyl)-1-oxoethyl]-4-phenyl-methyl-2-oxazolidinone (3.35). KHMDS (14.3 mL, 0.5 M in toluene, 1.10 equiv) was added to a stirred, pre-cooled (-78 °C) solution of imide 3.34 (2.11 g, 6.48 mmol) in 80 mL of THF by syringe and the resulting solution was stirred for 30 min at -78 °C under N₂. Into this was transferred a pre-cooled (-78 °C) solution of trisyl azide (2.51 g, 1.25 equiv) in 40 mL of THF via cannula and the resulting mixture was stirred for 2 min at -78 °C, then rapidly quenched by 1.30 mL (3.5 equiv) of glacial acetic acid and warmed up immediately to ca. 35 °C with a water bath. The mixture was stirred for an additional 5 h at rt, diluted with 150 mL of Et₂O, then washed with brine. The aqueous layer was extracted with Et₂O (10 mL x 2) and the combined organic layers were washed successively with dil NaHCO₃, brine, dried over MgSO₄, filtered and concentrated in vacuo to afford a pale-brown residue. The diastereoselectivity of the crude product was determined to be 95 : 5 by ¹H-NMR. Flash column chromatography on silica gel (hexanes/EtOAc, 8/2) and subsequent recrystallization from (hexanes/Et₂O) gave 1.62 g (68%) of α-azido imidate 3.35 in a diastereomerically pure form. mp 120.0-121.5 °C; [α]²²D +289.8° (c 0.51, CHCl₃); Rf 0.31 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3689, 3627, 3030, 2981, 2110, 1787, 1706, 1613, 1514, 1222, 1035 cm⁻¹; ¹H NMR (CDCl₃) δ 7.40-7.22 (m, 7H, -CHCH₂C₆H₅ overlapped with aromatic Hs ortho to -OMe), 6.93 (d, 2H, J = 8.8 Hz, aromatic Hs meta to -OMe), 6.11 (s, 1H, Ar-OMeCHN₃-), 4.67-4.61 (m, 1H, -NCH₂CH₂Ph), 4.19-4.07 (m, 2H, -NCHCH₂O-), 3.81 (s, 3H, -OCH₃), 3.41 (dd, 1H, J = 13.4, 3.1 Hz, -NCHCH₂Ph), 2.85 (dd, 1H, J = 13.4,
9.7 Hz, -NCHCH/Ph); 13C NMR (CDCl₃) δ 169.5, 160.4, 152.3, 134.8, 130.0, 129.4, 129.0, 127.5, 124.7, 114.5, 66.4, 63.2, 55.7, 55.3, 37.7; HRMS calcd for C₁₉H₁₈N₂O₄ (M-N₂)+ 338.1266, found 338.1279.

[2S,4S]-3-[2-[(Phenylmethoxy)carbonyl]amino-2-(4-methoxyphenyl)-1-oxo]ethyl]-4-phenylimethyl-2-oxazolidinone (3.36). (i) To a pre-

![Chemical Structure Image]

activated (with H₂, 30 min) Pd-C (10%, 73.0 mg) in 40 mL of organic solvent (THF/MeOH, 1/1) were added 702.5 mg (1.92 mmol) of α-azido imidate 3.35 and 767 μL (2.0 equiv) of 5 N HCl and the resulting slurry was stirred for 8 h at rt under H₂ (1 atm). The mixture was filtered through a Celite pad (1 x 5 cm) and the filter cake was washed well with MeOH (20 mL x 2). The combined organic layers were concentrated in vacuo and dried under high vacuum to give the amine-HCl salt as an off-white solid, which was used for the next reaction without purification. (ii) The crude amine-HCl salt obtained above was dissolved in 25 mL of CH₂Cl₂ and the solution was cooled down to 0 °C with an ice bath. To this was added 410.9 μL (1.50 equiv) of benzyl chloroformate followed by 25 mL of satd NaHCO₃ and the resulting mixture was stirred for 4 h at 0 °C, then diluted with 20 mL of CH₂Cl₂. The organic layer was separated and the aqueous layer was extracted further with CH₂Cl₂ (10 mL x 2). The combined organic layers were washed with brine, dried over MgSO₄ and concentrated in vacuo. Flash column chromatography of the crude product on silica gel (hexanes/EtOAc, 7/3) afforded 723.2 mg (80%) of the pure product 3.37 as a white solid. mp 143.0-144.5 °C; [α]²²D + 166.2° (c 0.69, CHCl₃); Rf 0.56 (hexanes/EtOAc, 5/5); IR (CHCl₃) 3441, 3019, 2956, 2919, 1789, 1703, 1611, 1514, 1394, 1215 cm⁻¹; ¹H NMR (DMSO-d₆) δ 8.13 (d, 1H, J = 7.5
Hz, CbzNH-), 7.38-7.26 (m, 12H, aromatic Hs of auxiliary, Cbz and ortho to -OME), 6.90 (d, 1H, J = 8.6 Hz, aromatic Hs meta to -OME), 6.39 (d, 1H, J = 7.5 Hz, ArCHN=H-), 5.10 (s, 2H, -OCH2Ph), 4.69 (bs, 1H, -NCH2CH2Ph), 4.29-4.16 (m, 2H, -NCHCH2O-), 3.73 (s, 3H, -OCH3), 3.00 (bs, 2H, -NCHCH2Ph); 13C NMR (DMSO-d6) δ 171.1, 159.9, 155.2, 152.2, 136.2, 135.1, 129.6, 129.4, 129.0, 128.5, 128.1, 127.6, 127.3, 114.3, 67.0, 66.2, 56.3, 55.7, 55.2, 37.6; HRMS calcd for C27H25N2O6 473.1712, found 473.1684.

N-[N-(Phenylmethoxy)carbonyl-L-(4-methoxyphenyl)glycynyl]-D-[(3-hydroxy-4-methoxy)phenyl]glycine Ethyl Ester (3.29). (i) To a stirred, pre-cooled (0 °C) solution of N-Cbz imidate 3.36 (1.71g, 3.61 mmol) dissolved in 45 mL of THF was added LiOH (14.4 mL, 0.5 M in H2O, 2.0 equiv) dropwise and the resulting suspension was stirred for 1 h at 0 °C. The mixture was diluted with 50 mL of Et2O and separated. The aqueous layer was washed further with Et2O (20 mL x 2), then acidified with 10% HCl to ca. pH 2 and extracted with CH2Cl2 (30 mL x 3). The combined organic layers were dried over MgSO4, evaporated and dried further under high vacuum to give a white solid 3.37 (983.5 mg, 87%) which was used for the next coupling reaction without purification. (ii) A solution of crude amine 3.32 (702.6 mg, 3.12 mmol), crude acid (983.5 mg, 1.0 equiv) prepared above and HOBT·H2O (506.1 mg, 1.20 equiv) in 30 mL of THF was cooled to 0 °C with an ice bath. To this solution was added EDC (598.3 mg, 1.0 equiv) in one portion and the resulting mixture was stirred for 4 h at 0 °C and for 15 h at rt under Ar. The solvent was removed in vacuo at rt and the residue was dissolved again in 50 mL of CH2Cl2. The organic layer was washed with water (20 mL), NaHSO4 (20 mL, 1.0 N), brine
and dried over MgSO₄, then evaporated in vacuo to furnish a pale-brown residue. Flash column chromatography on silica gel (hexanes/THF, 6/4) and subsequent recrystallization from (hexanes/THF, 8/2) afforded the pure product 3.29 as white needles. Yield: 1.14 g (71%); mp 163.0-165.0 °C; [α]²⁳D +21.2° (c 0.68, CHCl₃); Rf 0.35 (hexanes/THF, 5/5); IR (CHCl₃) 3549, 3410, 3025, 2984, 1736, 1689, 1607, 1515, 1223, 1039 cm⁻¹; ¹H NMR (CDCl₃) δ 7.30 (m, 5H, aromatic Hs of Cbz), 7.24 (d, 2H, J = 8.5 Hz, aromatic Hs ortho to -OMe), 6.85-6.62 (m, 6H, aromatic Hs of meta to -OMe, Ar-ΟH overlapped with -NHCbz), 6.04 (d, 1H, J = 5.1 Hz, Ar-ΟHCHNΗ-), 5.78 (s, 1H, phenolic-H), 5.37 (d, 1H, J = 6.7 Hz, -CHNHCbz), 5.30 (d, 1H, J = 5.1 Hz, Ar-ΟHCH-), 5.04 (d, 1H, J = 12.3 Hz, -CH2PH), 4.98 (d, 1H, J = 12.3 Hz, -OCH2Ph), 4.20 (dq, 1H, J = 10.7, 7.1 Hz, -OCHHCH3), 4.09 (dq, 1H, J = 10.7, 7.1 Hz, -OCHHCH3), 3.82 (s, 3H, -OCH3), 3.78 (s, 3H, -OCH3), 1.19 (dd, 3H, J = 7.1, 7.1 Hz, -CH2CH3); ¹³C NMR (CDCl₃) δ 170.5, 169.4, 159.6, 155.6, 146.7, 145.8, 136.1, 129.8, 128.8, 128.6, 128.4, 128.0, 118.8, 114.4, 113.1, 110.6, 66.9, 62.0, 58.0, 56.3, 55.8, 55.2, 13.9; HRMS calcd for C₂₈H₃₀N₂O₈ 522.2002, found 522.2035

[η⁶-(2R,2'R)-4-[[2-Methoxy-5-[1-[N-(phenylmethoxy)carbonyl-L-(4-methoxyphenyl)glycyl]amino-2-ethoxy-2-oxo]ethyl]phenoxy]-1-[2-[(1,1-dimethylethoxy)carbonyl]amino-3-oxo-3-(2-bromoethoxy)propyl]benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (3.38). Reaction procedures were the same as 3.25 except the use of dipeptide 3.29 instead of 3.10. Yield 84%; Pale-brown solid foam; IR (CHCl₃) 3640, 3422, 3024, 2981, 1744, 1713(br), 1514, 1220, 1035, 849 cm⁻¹; ¹H NMR (CDCl₃) δ 7.37-6.73 (m, 14H, aromatic Hs
of Ar$^{\text{OMe}}$-O-, Ar$^{\text{OMe}}$, Cbz overlapped with -NHCbz, 6.46-5.79 (m, 5H, aromatic Hs of Ar$^{\text{Ru+}}$ overlapped with Ar$^{\text{OMe}}$-O-CHNH-), 5.46-5.00 (m, 9H, Ar$^{\text{OMe}}$-O-CHNH-, -CHNHCBz, Cp, -OCH$_2$Ph, -NHBOC), 4.53-4.41 (m, 3H, -CH$_2$CH$_2$Br overlapped with -CHNHBOC), 4.30-4.10 (m, 2H, -OCH$_2$CH$_3$), 3.85 (s, 3/2H, -OCH$_3$), 3.84 (s, 3/2H, -OCH$_3$), 3.83 (s, 3/2H, -OCH$_3$), 3.79 (s, 3/2H, -OCH$_3$), 3.63-3.56 (m, 2H, -CH$_2$CH$_2$Br ), 3.12-2.82 (m, 2H, Ar$^{\text{Ru+}}$CH$_2$CH-), 1.43 (s, 9H, -BOC), 1.27-1.17 (m, 3H, -OCH$_2$CH$_3$)

(2R)-3-[4-[2-[(1,1-Dimethylethoxy)carbonyl]amino-3-oxo-3-(2-bromoethoxy)]propyl]phenoxy-4-methoxy-N-[N-(phenylmethoxy)-carbonyl-L-(4-methoxyphenyl)glycinyl]-D-Phenylglycine Ethyl Ester (3.39). Reaction procedures were the same as 3.26 except the use of 3.38 instead of 3.25. Yield 55%; Off-white solid foam; $[\alpha]^{22}_D$ +47.9° (c 0.56, CHCl$_3$); R$_f$ 0.39 (hexanes/EtOAc, 5/5); IR (CHCl$_3$) 3432(br), 3027, 2985, 1733, 1716, 1683, 1609, 1509, 1221, 1171, 1032 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$

7.30-6.73 (m, 17H, aromatic Hs overlapped with -NHCbz), 6.05 (bs, 1H, Ar$^{\text{OMe}}$-O-CHNH-), 5.42 (d, 1/2H, J = 6.9 Hz, -CHNHCBz), 5.37 (d, 1/2H, J = 6.7 Hz, -CHNHCBz), 5.27 (d, 1H, J = 4.5 Hz, Ar$^{\text{OMe}}$-O-CHNH-), 5.09-4.98 (m, 3H, two doublets of -OCH$_2$Ph overlapped with -NHBOC: 5.08 (d, 1H, J = 12.4 Hz, -OCHHPh), 5.00 (d, 1H, J = 12.4 Hz, -OCHHPh), 4.58 (bs, 1H, -CHNHBOC), 4.41-4.35 (m, 2H, -CH$_2$CH$_2$Br), 4.19-4.05 (m, 2H, -OCH$_2$CH$_3$), 3.79 (s, 3/2H, -OCH$_3$), 3.774 (s, 3/2H, -OCH$_3$), 3.768 (s, 3/2H, -OCH$_3$), 3.75 (s, 3/2H, -OCH$_3$), 3.46-3.4 (m, 2H, -CH$_2$CH$_2$Br), 3.06 (bs, 2H, -CH$_2$CHNH-), 1.41 (s, 9H, -BOC),
1.19-1.10 (m, 3H, -OCH₂CH₃); ¹H NMR (CD₃NO₂, 90 °C) 7.36-6.77 (m, 17H, aromatic Hs overlapped with -NH-Cbz), 6.07 (d, 1H, J = 4.9 Hz), 5.44-5.40 (m, 1H), 5.27-5.23 (m, 2H), 5.07 (s, 2H, -OCH₂Ph), 4.49-4.42 (m, 3H, -CH₂CH₂Br overlapped with -NH/BOC), 4.21-4.08 (m, 2H, -OCH₂CH₃), 3.81 (s, 3H, -OCH₃), 3.79 (s, 3H, -OCH₃), 3.60-3.56 (m, 2H, -CH₂CH₂Br), 3.16 (dd, 1H, J = 14.2, 5.9 Hz, -CHHCHNH-), 3.00 (dd, 1H, J = 14.2, 8.2 Hz, -CHHCHNH-), 1.38 (s, 9H, -BOC); HRMS FAB (m-NBA) calcd for C₄₄H₅₁N₃O₁₂Br (MH)+ (Br⁺), 892.2656, 894.2635 found (MH)+ (Br⁺) 892.2612, 894.2592; Anal. calcd for C₄₄H₅₀N₃O₁₂Br: C, 59.19; H, 5.64; N, 4.71, found C, 59.40; H, 5.85; N, 4.48.

Control Experiment-1. To a stirred, precooled (0 °C) solution of dipeptide 3.29 (42.0 mg, 0.0804 mmol) in 10 mL of THF was added 1.0 equiv of Na, 2,6-di-t-butylphenoxide in THF by syringe. The resulting solution was stirred for 15 min at 0 °C, for 15 min at -78 °C then for 1.5 h at rt under N₂. The mixture was diluted with 30 mL of Et₂O, then the resulting mixture was washed with brine, dried over MgSO₄, filtered and the solvent was evaporated in vacuo. The ¹H-, and ¹³C-NMR of the crude product showed that no racemized-dipeptide was observed. Purification by flash chromatography (SiO₂, hexanes/EtOAc = 6/4) gave 32.1 mg (76%) of pure recovered dipeptide which has exactly same [α]D value as that of starting dipeptide.

Control experiment-2. The reaction procedures were exactly same as 3.38 except the use of 2.0 equiv of dipeptide 3.29 was used. From Et₂O layer, 56.8 mg (52%) of crude dipeptide was recovered. ¹H-, ¹³C-NMR of the crude product did not show any racemized-dipeptide formed. From the dark-deposit after washing
with Et₂O, 10.1 mg of dipeptide was recovered. Total recovery yield of dipeptide was 66.9 mg (61%).

\((2R)-3-[4-[2-[[1,1-Dimethylethoxy]carbonyl]amino-3-oxo-3-(2-iodoethoxy)]propyl]phenoxy-4-methoxy-N-[N-(phenylmethoxy)carbonyl-L-(4-methoxyphenyl)glycinyl]-D-phenylglycine Ethyl Ester (3.40).\) Reaction procedures were the same as 3.27 except the use of 3.39 instead of 3.26. Yield 89%; White solid foam; \(R_f\) 0.37 (hexanes/EtOAc, 5/5); \([\alpha]^D_{22}\) +41.2\(^\circ\) (c 0.5, CHCl₃); IR (CHCl₃) 3422(br), 3024, 2962, 1734, 1712, 1685, 1612, 1508, 1222, 1171, 1029 cm\(^{-1}\);

\(^1\)H NMR (CDCl₃) \(\delta\) 7.31-6.66 (m, 17H, aromatic Hs overlapped with -NHCbz), 6.01 (bs, 1H, Ar-OMe,-O-CHNH-), 5.42 (d, 1/2H, J = 7.0 Hz, -CHNHCbz), 5.37 (d, 1/2H, J = 6.6 Hz, -CHNHCbz), 5.23 (bs, 1H, Ar-OMe,-O-CHNH-), 5.10-4.99 (m, 3H, two doublets of -OCH₂Ph overlapped with -NHBOC), 5.08 (d, 1H, J = 12.5 Hz, -OCHHPh), 5.01 (d, 1H, J = 12.5 Hz, -OCHHPh), 4.57 (bs, 1H, -CHNHBOC), 4.36-4.31 (m, 2H, -CH₂CH₂I), 4.17-4.06 (m, 2H, -OCH₂CH₃), 3.81 (s, 3/2H, -OCH₃), 3.79 (s, 3H, -OCH₃), 3.76 (s, 3/2H, -OCH₃), 3.25-3.19 (m, 2H, -CH₂CH₂I), 3.11-3.07 (m, 2H, -CH₂CHNH-), 1.42 (s, 9H, -BOC), 1.25-1.11 (m, 3H, -OCH₂CH₃); LRMS FAB (m-NBA) calcd for C₄₄H₅₁N₃O₁₂I (MH)\(^+\) 940, found (MH)\(^+\) 940; Anal. calcd for C₄₄H₅₀N₃O₁₂I: C, 56.23; H, 5.36; N, 4.47, found C, 56.52; H, 5.57; N, 4.30.

\((R)-4-[2-Methoxy-5-[[1-N-(Phenylmethoxy)carbonyl-L-(4-methoxy phenyl)glycinyl]amino]-2-ethoxy-2-oxo]ethyl]phenoxy-N-(1,1-dimethylethoxy)carbonyl-D-phenylalanine (3.42).\) To a stirred solution of
3.40 (77.7 mg, 0.083 mmol) in 8 mL of THF was added DMPU (390.0 µl, 39.0 equiv) by syringe and the resulting solution was cooled to 10 °C with an ice bath under deoxygenated-Ar. To this was added 5.38 mL (6.5 equiv, 0.1M in THF) of SmI₂ by syringe. The solution was immediately changed into a dark-purple suspension and it was stirred for 5 min at 10 °C, then rt under deoxygenated-Ar. After stirring for 1h at rt, the color of the suspension slowly changed to pale-yellow and it was stirred further for one hour at rt. The reaction mixture was diluted with 50 mL of CH₂Cl₂, then treated with 10 mL of 0.1N HCl. The organic layer was separated and the aqueous layer was extracted further with 10 mL of CH₂Cl₂ (x 3). The combined organic layers were washed with 10 mL of Na₂S₂O₃ (0.2 M), brine and dried over MgSO₄. The solvent was evaporated in vacuo to give a pale-yellow oil. Purification by flash chromatography on silica gel (hexanes/EtOAc/AcOH, 35/65/1% then CH₂Cl₂/EtOAc/AcOH, 75/25/1%) gave 51.2 mg (79%) of pure acid 3.42 as a white powder. The fractions containing product were diluted with heptane (30 mL) and concentrated under reduced pressure while maintaining the bath-temperature below 10 °C. The concentrated solution was diluted again with heptane (10 mL) and evaporated in vacuo under 10 °C. Rf 0.48 (EtOAc/hexanes/AcOH, 8/2/1%); [α]²⁴D +36.9° (c 0.51, CHCl₃); IR (CHCl₃) 3683, 3615, 3434(br), 3018, 2981, 1730, 1709(br), 1684, 1613, 1514, 1427, 1222, 1041, 936 cm⁻¹ ¹H NMR (CD₃CN/CDCl₃, 7/3) δ 7.32-6.70 (m, 17H, aromatic Hs overlapped with -NHCbz), 6.28 (d, 1H, J = 1.5 Hz, Ar-OMe,-O-CHNH-), 5.39 (bs, 1H, Ar-OMe,-O-CHNH-), 5.33 (d, 1H, J = 7.0 Hz, -CHNHCbz), 5.22 (d, 1H, J = 7.3 Hz, -NHBoc), 5.07 (d, 1H, J = 12.6 Hz, -OCH₂Ph), 5.01 (d, 1H, J = 12.6 Hz, -OCH₂Ph), 4.33-4.29 (m, 1H, -CHNHBOc), 4.16-4.02 (m, 2H, -OCH₂CH₃), 3.78 (s, 3/2H, -OCH₃), 3.77 (s,
3/2H, -OCH₃), 3.752 (s, 3/2H, -OCH₃), 3.746 (s, 3/2H, -OCH₃), 3.08 (dd, 1H, J = 13.8, 5.2 Hz, ArCHHCHCO₂H), 2.89 (dd, 1H, J = 13.8, 8.3 Hz, ArCHHCH-), 1.37 (s, 9H, -BOC), 1.15 (t, 3/2H, J = 7.2 Hz, -OCH₂CH₃), 1.09 (t, 3/2H, J = 7.2 Hz, -OCH₂CH₃); HRMS FAB (m-NBA) calcd for C₄₂H₄₈N₃O₁₂ (MH)+ 786.3238, found 786.3241; Anal. calcd for C₄₂H₄₇N₃O₁₂: C, 64.19; H, 6.03; N, 5.35, found C, 63.75; H, 6.37; N, 5.03.

(R)-4-[[1-[N-(Phenylmethoxy)carbonyl-L-(4-methoxyphenyl)glycyl]amino]-2-(ethoxycarbonyl)ethyl]-4-methoxy]phenoxy]-N-(1,1-dimethyletheroxy)carbonyl-D-phenylalanine Pentafluorophenyl Ester (3.49). To a stirred, precooled (0 °C) solution of 3.42 (57.1 mg, 0.0727 mmol) in 10 mL of CH₂Cl₂ and pentafluorophenol (40.1 mg, 3.0 equiv) was added DCC (22.5 mg, 1.5 equiv) and the resulting mixture was stirred for 3 h at 0 °C, then for 12 h at rt under Ar. The reaction mixture was diluted with 40 mL of CH₂Cl₂, then washed with dil NaHCO₃, dried over MgSO₄ and filtered. Removal of the solvent under reduced pressure afforded a pale-yellow residue, which was purified by flash chromatography on silica gel (hexanes/EtOAc) to give 44.1 mg (64%) of pure product 3.49. After taking ¹H-NMR, the product was subjected to the next reaction immediately without further identification. ¹H NMR (CDCl₃) δ 7.36-6. (m, 17H, aromatic Hs overlapped with -NHCbz), 6.81 (bs, 1H, Ar-O⁻Me⁻²⁻O⁻CHNH⁻), 5.94 (d, 1H, J = 5.2 Hz, Ar-O⁻Me⁻²⁻O⁻CHNH⁻), 5.42 (d, 1/2H, J = 6.8 Hz, -CHNHCbz), 5.36 (d, 1/2H, J = 6.6 Hz, -CHNHCbz), 5.18 (bs, 1H, -NHBOC), 5.09 (d, 1H, J = 12.3 Hz, -OCHHPh), 5.02 (d, 1H, J = 12.3 Hz, -OCHHPh), 4.97-4.84 (m, 1H, -CHNHBOC), 4.16-4.02 (m, 2H, -OCH₂CH₃), 3.81 (s, 3/2H, -OCH₃), 3.79 (s,
3/2H, -OCH$_3$), 3.78 (s, 3/2H, -OCH$_3$), 3.76 (s, 3/2H, -OCH$_3$), 3.29-3.13 (m, 2H, -CH$_2$CHNH-), 1.43 (s, 9H, -BOC), .120-1.07 (m, 3H, -CO$_2$CH$_2$CH$_3$)

(1$R$,2$R$)-[1-[[3-[[4-[[2-[[1,1-Dimethylethoxy]carbonyl]amino-3-oxo-3-(pentafluorophenoxy)propyl]phenoxy]-4-methoxy]phenyl]-2-ethoxy-2-oxoethyl]amino]-(S)-(4-methoxyphenyl)glycine Hydrochloride (3.49'). To a stirred slurry of Pd-C(10%, 44.0 mg) in 10 mL of (30% EtOH in THF) were added 3.49 (44.1 mg, 0.0464 mmol) and 18.5 µL of HCl (5.0N, 2.0 equiv). The resulting slurry was stirred for 3 h under H$_2$ atmosphere (1 atm). The mixture was filtered through a Celite pad (1 x 2 cm) and the filter cake was washed well with 20 mL of THF. The organic solvent was removed in vacuo to afford a pale-yellow residue which was dissolved in 20 mL of CH$_2$Cl$_2$. Removal of the solvent gave a solid residue which was dried under high vacuum for 30 min, then subjected to the cyclization reaction without characterization.

(1$R$,2$R$)-[1-[[3-[[4-[[2-[[1,1-Dimethylethoxy]carbonyl]amino-3-hydroxy-3-oxo]propyl]phenoxy]-4-methoxy]phenyl]-2-ethoxy-2-oxo]ethyl]amino]-(S)-(4-methoxyphenyl)glycine (3.42'). To a stirred slurry of Pd-C(10%, 38.6 mg) in 10 mL of organic solvent (30% EtOH in THF) was added 3.42 (38.6 mg, 0.0492 mmol) and the resulting slurry was stirred for 4 h under H$_2$ (1 atm). The reaction mixture was filtered and the filter cake was washed with 20 mL of THF. The solvent was evaporated to give a solid residue which was dissolved again
in 20 mL of CH₂Cl₂. Removal of the solvent afforded a pale-yellow residue which was dried under vacuum for 3 h, then subjected to the cyclization reaction without characterization.

1,1'-Carbonylbispyrrolidinidine (3.45). A solution of triphosgene (5.02 g, 16.9 mmol) in 20 mL of THF was added dropwise to a pre-cooled (10 °C), stirred solution of pyrrolidinidine (8.5 mL, 6.0 equiv) and Et₃N (15.6 mL, 6.6 equiv) in 100 mL of THF over 30 min. The white solid began to form immediately. The resulting mixture was refluxed for 2 h, then stirred for an additional 2 h at rt under N₂, filtered and the filter cake was washed well with THF. The THF layers were combined, and concentrated in vacuo. The residue was subjected to vacuum distillation to afford 6.22 g (73%) of colorless liquid. bp 175-180 °C/20 torr (lit⑥7 148-150 °C/12 torr); IR (CHCl₃) 3410, 2979, 2880, 1603, 1493, 1433, 1345, 1219 cm⁻¹; ¹H NMR (CDCl₃) δ 3.39-3.35 (m, 8H, -CH₂CH₂N-), 1.85-1.80 (m, 8H, -CH₂CH₂N-)

(1,1,3,3)-Tetramethylene chlorouronium hexafluorophosphate (3.46).

To a stirred, pre-cooled (10 °C) solution of 1,1'-carbonylbispyrrrolidinidine 3.45 (1.25 g, 6.96 mmol) in 60 mL of mixed solvent (Et₂O/THF, 2/1) was added a solution of triphosgene (688.5 mg, 0.33 equiv) in 30 mL of Et₂O dropwise over 30 min under Ar. The white precipitate began to form in 10 min and the resulting mixture was stirred overnight at rt under Ar. The precipitate was filtered, washed well with dry Et₂O, then immediately dissolved in CH₂Cl₂ (30 mL). The organic solution was treated with NH₄PF₆ (1.36 g, 1.20 equiv) dissolved in 10 mL of water. The organic layer was separated and washed well with water, dried over
MgSO$_4$ and the solvent was removed in vacuo. The white salt formed was washed further with dry Et$_2$O and dried under high vacuum with P$_2$O$_5$ to furnish 1.75 g (76%) of a highly hygroscopic white solid. mp 148.5-150.5 °C (lit. $^{68}$ 148.5-150.5 °C); $^1$H NMR (CDCl$_3$) δ 3.80-3.75 (m, 8H, -CH$_2$CH$_2$N-), 2.02-1.98 (m, 4H, -CHHCH$_2$N-), 1.96-1.92 (m, 4H, -CHHCH$_2$N-)

O-(&-Azabenzoazol-1-yl)-1,1:3,3-bis(trimethylene) uronium hexafluorophosphate (HAPyU) (3.47). To a stirred solution of chloro

![Uronium hexafluorophosphate](image)

uronium hexafluorophosphate 3.46 (1.40 g, 4.2 mmol) in 35 mL of CH$_2$Cl$_2$ was added HOAT (1.0 equiv, 574.0 mg) followed by Et$_3$N (1.0 equiv, 587.0 µL) and the resulting solution was stirred overnight at rt under N$_2$.

The mixture was filtered to remove the precipitate which was washed with CH$_2$Cl$_2$ (15 mL x 3). The combined organic layers were washed with H$_2$O (35 mL x 3), then dried over MgSO$_4$, filtered and evaporated in vacuo to give a solid residue which was washed again with H$_2$O (35 mL x 3), ether (20 mL x 3) and then dried. Recrystallization from acetone-ether afforded 534.0 mg (29%) of white needle-type crystals. mp 155 - 157 °C dec (lit. $^{69}$ 148 - 150°C dec); $^1$H NMR (DMSO-$_d_6$) δ 8.86 (d, 1H, J = 4.4 Hz, aromatic α-H), 8.38 (d, 1H, J = 9.3 Hz, aromatic γ-H), 8.01 (dd, 1H, J = 9.3, 4.4 Hz, aromatic β-H), 3.8-4.1 (m, 8H, -CH$_2$NCH$_2$-), 2.0-2.3 (m, 8H, -CH$_2$CH$_2$CH$_2$CH$_2$-).

Pentafluorophenyl diphenylphosphinate (FDPP) (3.44). To a stirred

![Pentafluorophenyl diphenylphosphinate](image)

solution of diphenylphosphinic chloride (1.97g, 8.34 mmol) and pentafluorophenol (1.0 equiv, 1.54 g) in 20 mL of anhydrous CH$_2$Cl$_2$ was added imidazole (1.0
equiv, 0.57 g) dissolved in 10 mL of CH₂Cl₂ dropwise over 30 min at rt under Ar. The white solid was formed slowly and the reaction mixture was stirred further for 1 h after the addition was complete. The imidazole-HCl salt was filtered off and the filtrate was concentrated in vacuo to give a pale-yellow residue, which was purified by flash chromatography (silica gel, hexanes/EtOAc, 8/2) to afford 2.98 g (93%) of an off-white solid. The compound appeared to be unstable on TLC: mp 49.5-51.5 °C (lit70 46-49 °C); Rf 0.44 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3012, 1595, 1520, 1476, 1445, 1240, 1135, 998 cm⁻¹; ¹H-NMR (CDCl₃) δ 7.94-7.87 (m, 4H, aromatic Hs), 7.66-7.49 (m, 6H, aromatic Hs)

Cycloamidation Reactions of 3.42 using Various Coupling Reagents to give Cyclization Products (3.28-F₁, 3.28-F₂). (i) Pentafluorophenyl ester/Et₃N method: pentafluorophenyl ester, amine-HCl salt 3.49 (0.0404 mmol) dissolved in 15 mL of dry 1,4-dioxane was added slowly to a stirred, warmed (90 °C) solution of Et₃N (32.3 μL, 5.0 equiv) in 150 mL of 1,4-dioxane by syringe pump over 3 h under Ar atmosphere. After stirring for an additional 1 h at 90 °C, the mixture was cooled to rt, then the solvent was removed in vacuo to give a brown residue, which was dissolved again in 30 mL of CH₂Cl₂. The solution was washed with 10 mL of HCl (1.0N), brine, dried over MgSO₄, filtered and evaporated. By the TLC-analysis (silica gel, hexanes/EtOAc, 5/5), 6-7 UV-active substances were observed. By the first HPLC analysis (column: Whatman Partisil M20 10/25; eluent: CH₂Cl₂/EtOAc, 75/25; flow rate: 6 mL/min), the overlapped fraction (4.2 mg, 14%) of 3.28-F₁ (rt = 32.2 min) and 3.28-F₂ (rt = 33.4 min) were separated and ¹H-NMR was taken to show that this was a mixture of two cyclization products with a ratio of (70 : 30). By
the second HPLC analysis (column: Whatman Magnum 9; eluent: hexanes/EtOAc, 5/5; flow rate: 5 mL/min), the overlapped fraction was separated into two fractions 3.28-F₁ (1.5 mg, τt = 14.9 min) and 3.28-F₂ (0.8 mg, τt = 20.8 min). The still overlapped fraction was discarded: 3.28-F₁: Rf 0.50 (EtOAc/hexanes, 6/4); [α]$_{D}^{22}$ +31.1° (c 0.15, MeOH); IR (CHCl₃) 3687, 3622, 3413 (br), 3019, 2979, 2939, 1735, 1708, 1667, 1603, 1512, 1425, 1227, 929 cm$^{-1}$; $^1$H NMR (CD$_3$CN/CDCl$_3$, 7/3) $\delta$ 7.40-6.81 (m, 12H, *aromatic* Hs except B-H$^2$ overlapped with $H_{w2}$ and $H_{w3}$), 6.13 (s, 1H, B-H$^2$), 5.41-5.38 (m, 2H: $H_x$ (5.40, d, 1H, J = 8.2 Hz) overlapped with $H_{w1}$), 5.25 (d, 1H, J = 7.1 Hz, $H_x$), 4.31-4.18 (m, 3H, $H_{x1}$ overlapped with -OCH$_2$CH$_3$), 3.93 (s, 3H, -OCH$_3$), 3.75 (s, 3H, -OCH$_3$), 3.17 (dd, 1H, J = 12.2, 5.2 Hz, ArCHHCH-), 2.74 (dd, 1H, J = 12.2, 12.1 Hz, ArCHHCH-), 1.41 (s, 9H, -BOC), 1.30-1.26 (m, 3H, -OCH$_2$CH$_3$ overlapped with residual solvent peaks); HRMS calc'd for C$_{34}$H$_{39}$N$_3$O$_9$ 633.2686, found 633.2660. MS: m/e 634 (9), 633 (29), 577 (56), 560 (25), 533 (67), 516 (33), 490 (100), 443 (18), 415 (20), 401 (15). 3.28-F$_2$: Rf 0.38 (EtOAc/hexanes, 6/4); [α]$_{D}^{22}$ +12.3° (c 0.08, CHCl₃); IR (CHCl₃) 3689, 3615, 3018, 2981, 1776, 1714, 1670, 1602, 1526, 1421, 1215, 929 cm$^{-1}$; $^1$H NMR (CD$_3$CN/CDCl$_3$, 7/3) $\delta$ 7.45-6.77 (m, 12H, *aromatic* Hs except B-H$^2$ overlapped with $H_{w2}$ and $H_{w3}$), 6.23 (s, 1H, B-H$^2$), 5.50-5.40 (m, 2H: $H_x$ (5.48, d, 1H, J = 9.2 Hz) overlapped with $H_{w1}$), 5.24 (d, 1H, J = 7.0 Hz, $H_x$), 4.34-4.29 (m, 1H, $H_{x1}$), 4.28-4.16 (m, 2H, -OCH$_2$CH$_3$), 3.93 (s, 3H, -OCH$_3$), 3.76 (s, 3H, -OCH$_3$), 3.35 (dd, 1H, J = 14.0, 5.2 Hz, ArCHHCH-), 2.90 (dd, 1H, J = 14.0, 2.9 Hz, ArCHHCH-), 1.47 (s, 9H, -BOC), 1.31-1.26 (m, 3H, -OCH$_2$CH$_3$ overlapped with residual solvent peaks); HRMS calc'd for C$_{34}$H$_{39}$N$_3$O$_9$ 633.2686, found 633.2701. MS: m/e 633 (2), 577 (6), 533 (100), 516 (12), 505 (26), 490 (96), 475 (7), 460 (9), 432 (10), 415 (14). (ii) (DCC/HOAT) method: The acid, amine salt 3.42' (0.0492 mmol) dissolved in 20
mL of CH₂Cl₂ was slowly added to a stirred, pre-cooled (0 °C) solution of DCC (22.2 mg, 2.2 equiv) and HOAT (19.9 mg, 3.0 equiv) in 160 mL of CH₂Cl₂ by syringe pump over 10 h. The resulting solution was stirred further for 14 h at rt under Ar and then washed with 20 mL of HCl (1.0N), brine, dried over MgSO₄, filtered and concentrated. By using the same first HPLC analysis conditions as (pentafluorophenyl ester/Et₃N) method. The overlapped fraction of 3.28-F₁ and 3.28-F₂ was collected and the ratio was determined to be (20 : 80) by ¹H-NMR based on the integrals of B-H²s. (iii) HAPyU method: To a stirred solution of the acid, amine salt 3.42' (0.0490 mmol) in 35 mL of dry DMF were added HAPyU (923.4 mg, 1.10 equiv) and (i-Pr)₂NEt (25.7 µL, 3.0 equiv) and the resulting solution was stirred for 4.5 h at rt under Ar. The solvent was removed under high vacuum with slight heating (40 °C) and the resulting brown residue was dissolved again in 30 mL of CH₂Cl₂. The CH₂Cl₂ layer was washed with 10 mL of HCl (1.0N), brine, dried over MgSO₄, filtered and concentrated. By using the same first HPLC-analysis conditions as (pentafluorophenyl ester/Et₃N) method, the overlapped fraction of 3.28-F₁ and 3.28-F₂ was collected and the ratio was determined to be (40 : 60) by ¹H-NMR based on the integral of B-H²s. (iv) FDPP method: The acid, amine salt 3.42' (0.0545 mmol) dissolved in 20 mL of dry DMF was added slowly to a solution of FDPP (25.1 mg, 1.20 equiv) and (i-Pr)₂NEt (1.90 µL, 2.0 equiv) by syringe over 4 h under Ar. After the addition was finished, the resulting solution was stirred further for 20 h at rt. The solvent was removed under high vacuum with slight heating (40 °C) and the residue was worked-up as HAPyU method. The ratio of 3.28-F₁ and 3.28-F₂ was determined to be (40 : 60) by ¹H-NMR based on the integrals of B-H²s.
Control Experiment-3. The cyclization product (0.8 mg, 3.28-F<sub>2</sub>) was dissolved in 30 mL of dry 1,4-dioxane and the resulting solution was heated to 90 °C in the presence of excess Et<sub>3</sub>N (30 µl, 170 equiv) for 12 h under Ar. The solvent was removed under high vacuum with slight heating (40-45 °C) to give a pale-yellow residue, which was dried under high vacuum. <sup>1</sup>H-NMR of the crude product showed that no interconversion took place. (based on the integral of B-H²)

(R)-4-[2-Methoxy-5-[(1-[N-(phenylmethoxy)carbonyl-L-phenylglycanyl]amino]-2-methoxy-2-oxoethyl]phenoxy]-N-(1,1-dimethylmethoxy)carbonyl-D-tyrosine (3.41). To a stirred, pre-cooled (10 °C) solution of 2-idoethyl ester 3.27 (86.6 mg, 0.098 mmol) in 7 mL of THF was added DMPU (491.3 µl, 42.0 equiv) by syringe and the resulting solution was stirred for 5 min under deoxygenated-Ar. To this was added SmI<sub>2</sub> (6.77 mL, 7.0 equiv, 0.1 M in THF) by syringe. The reaction mixture was immediately turned into a deep-purple suspension which was stirred for 10 min at 10 °C, then at rt under deoxygenated-Ar. After 1.5 h, the color of reaction mixture had changed into pale-yellow. The reaction mixture was stirred further for 1h, then diluted with 50 mL of CH<sub>2</sub>Cl<sub>2</sub> and washed with 10 mL of 0.1 N HCl. The organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (10 mL x 2). The combined organic layers were washed with 10 mL of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (0.2 M, sodium thiosulfate), brine, then dried over MgSO<sub>4</sub> and evaporated. Purification of the pale-yellow residue by flash chromatography on silica gel (hexanes/EtOAc/AcOH, 35/65/1%, then CH<sub>2</sub>Cl<sub>2</sub>/EtOAc/AcOH, 7/3/1%) afforded 58.4 mg (81%) of pure acid 3.41 as a white solid powder. The fractions containing product were diluted with heptane (30 mL) and concentrated under reduced pressure while maintaining the
temperature below 10 °C. The concentrated solution was diluted again with heptane (10 mL) and evaporated in vacuo below 10 °C. Rf 0.42 (hexanes/EtOAc/AcOH, 2/8/1%); [α]$_D^{22}$ +24.1° (c 0.53, CHCl$_3$); IR (CHCl$_3$) 3683, 3627, 3428(br), 3020, 2981, 1737, 1704(br), 1686, 1509, 1429, 1222, 1048, 929 cm$^{-1}$; 1H NMR (CDCl$_3$) δ 7.38-6.69 (m, 18H, aromatic Hs overlapped with -NHCbz), 6.36 (d, 1H, J = 2.5 Hz, Ar$^{OMe}CHNH$-), 5.41 (bs, 1H, Ar$^{OMe}CHNH$-), 5.36 (d, 1H, J = 7.0 Hz, -CH(NH)Cbz), 5.33 (d, 1H, J = 7.3 Hz, -NHBOC), 5.05 (s, 2H, -OCH$_2$Ph), 4.33-4.28 (m, 1H, -CHNHBOC), 3.77 (s, 3/2H, -OCH$_3$), 3.74 (s, 3/2H, -OCH$_3$), 3.66 (s, 3/2H, -OCH$_3$), 3.59 (s, 3/2H, -OCH$_3$), 3.08 (dd, 1H, J = 13.7, 5.0 Hz, ArCH/HCHCO$_2$H), 2.92-2.83 (m, 1H, ArCH/HCH-), 1.36 (s, 9H, -BOC); HRMS FAB (m-NBA) calcd for C$_{40}$H$_{44}$N$_3$O$_{11}$ (MH)$^+$ 742.2976, found 742.3000; Anal. calcd for C$_{40}$H$_{44}$N$_3$O$_{11}$: C, 64.77; H, 5.84; N, 5.66, found C, 64.66; H, 6.26; N, 5.51.

(R)-4-[[3-[[1-[N-[N-(Phenylmethoxy)carbonyl-L-(4-methoxyphenyl)-
glycyl]amino]-2-(methoxycarbonyl)ethyl]-4-methoxy]phenoxy]-N-
(1,1-dimethylethoxy)carbonyl-D-tyrosine Pentafluorophenyl Ester (3.50). To a stirred, pre-cooled (0 °C) solution of 3.41 (88.0 mg, 0.119 mmol)

and pentafluorophenol (65.6 mg, 3.0 equiv) in 20 mL of THF was added DCC (34.7 mg, 1.5 equiv) in one portion. The resulting solution was stirred for 3 h at 0 °C, then for 12 h at rt under N$_2$. THF was evaporated in vacuo and the residue was dissolved again in 30 mL of CH$_2$Cl$_2$, washed with dil NaHCO$_3$, brine and dried over MgSO$_4$. Removal of the solvent under reduced pressure gave an oily residue, which was purified by flash chromatography on silica gel (hexanes/EtOAc, 6/4) to provide 76.5 mg (71%) of pure
product 3.50. After taking $^1$H-NMR, the product was subjected to the next reaction immediately without further identification. Rf 0.41 (hexanes/EtOAc, 5/5), $^1$H NMR (CDCl$_3$) δ 7.35-6.78 (m, 18H, aromatic Hs overlapped with -NHCbz), 6.73 (Ar-OMe-O·CHNH·), 6.02 (bs, 1H, Ar-OMeCHNH·), 5.44 (d, 1/2H, J = 6.7 Hz, -CHNHCbz), 5.38 (d, 1/2H, J = 6.6 Hz, -CHNHCbz), 5.28 (bs, 1H, -NHBOC), 5.08 (d, 1H, J = 12.2 Hz, -OCHHPh), 5.02 (d, 1H, J = 12.2 Hz, -OCHHPh), 4.89-4.87 (m, 1H, -CHNHBOC), 3.80 (s, 3/2H, -OCH$_3$), 3.77 (s, 3/2H, -OCH$_3$), 3.70 (s, 3/2H, -CO$_2$CH$_3$), 3.64 (s, 3/2H, -CO$_2$CH$_3$), 3.26 (dd, 1H, J = 14.5, 5.5 Hz, -CHHCHNHBOC), 3.16 (dd, 1H, J = 14.5, 5.0 Hz, -CHHCHNHBOC), 1.43 (s, 9H, -BOC).

(1R,2R)-[1-[1-[3-[[2-((1,1-Dimethylethoxy)carbonyl]amino)-3-oxo-3-(pentafluorophenoxy)]propyl]phenoxy]-4-methoxy]phenyl]-2-methoxy-2-oxoethyl]amino]-(S)-phenylglycine.Hydrochloride

(3.50'). To a stirred slurry of Pd-C(10%, 464.4 mg) in 10 mL of solvent (30% EtOH in THF) was added 3.50 (23.2 mg, 0.0256 mmol) and the resulting slurry was stirred for 4 h under H$_2$ atmosphere (1 atm). The reaction mixture was filtered and the filter cake was washed with 20 mL of THF. Removal of the solvent afforded a pale-yellow residue which was dried under high vacuum for 3 h, then subjected to the cyclization reaction without characterization.
Cycloamidation Reaction of 3.41 under Various Reaction Conditions.

(i) (Pentafluorophenyl ester/4-methylmorpholine) method: The pentafluorophenyl ester, N-Cbz protected precursor 3.50 (0.0434 mmol) dissolved in 15 mL of dry 1,4-dioxane was added slowly by syringe pump over 6 h to a stirred, warmed (95 °C) slurry of Pd-C (10%, 50.0 mg) and 4-methylmorpholine (4.8 μL, 1.0 equiv) in 100 mL of 1,4-dioxane and 2 mL of EtOH with bubbling of H2 gas. Stirring was continued further for one hour after addition was complete. The mixture was cooled to rt, filtered and the filter cake was washed with 30 mL of (CH2Cl2/MeOH, 5/5). The solvent was removed in vacuo to give a brown residue which was dissolved again in 30 mL of CH2Cl2. The CH2Cl2 layer was washed with 20 mL of HCl (0.5 N), brine, dried over MgSO4 and filtered. After removal of the solvent, the residue was analyzed by TLC (silica gel, hexanes/EtOA, 5/5) and HPLC (column : Whatman Magnum 9; eluent : hexanes/EtOAc, 6/4); flow rate : 6 mL/min). 21.0 mg (57%) of starting material 3.50 was recovered and no cyclization products were observed.

(ii) (Pentafluorophenyl ester/4-pyrrolidinopyridine) method: The reaction procedure was the same as before except the use of 4-pyrrolidinopyridine (1.0 equiv) instead of 4-methylmorpholine. 3.5 mg (9%) of starting material 3.50 was recovered together with 6.5 mg (16%) of the epimerized starting material 3.51. (iii) (Pentafluorophenyl ester/(i-Pr)2NEt) method: To a stirred solution of pentafluorophenyl ester, amine-HCl salt 3.50' (0.0256 mmol) in 90 mL of dry DMF were added HOBT 6.9 mg, 2.0 equiv) and (i-Pr)2NEt (8.9 μL, 2.0 equiv) and the resulting solution was stirred at 45 °C for 24 h under Ar. After removal of the solvent, the residue was worked-up as usual and analyzed by TLC and HPLC as before.
The following compounds were prepared for ABE-ring study of Ristocetin A

\((2R,4R)-3\text{-}[2\text{-}(\text{Benzyloxycarbonyl})\text{amino}-2\text{-}(3\text{-hydroxy-4\text{-methoxy}}\text{-phenyl)-1\text{-oxo}ethyl-4\text{-phenylmethyl-2\text{-oxazolidinone}} (3.53).\)  

(i) To a stirred solution of 3.16 (1.35 g, 2.86 mmol) in 50 mL of organic solvent (THF/MeOH, 4/1) was added Pd-C(10\%, 140 mg) and 1.14 mL of HCl (5.0N, equiv) and the resulting slurry was stirred for 24 h at rt under atmospheric pressure of H\(_2\). The solid catalyst was filtered off and the filter cake was washed well with 20 mL of methanol. The solvent was removed in vacuo to afford a pale-yellow solid, which was dried under high vacuum for 3 h at rt.  

(ii) The solid amine-HCl salt was dissolved in 50 mL of CH\(_2\)Cl\(_2\) and the solution was cooled to 0 °C with an ice bath. To this was added 40 mL of saturated NaHCO\(_3\) and 490.5 μL of CbzCl and the resulting suspension was stirred for 1 h at 0 °C, then for 3 h at rt. The organic layer was separated and the aqueous layer was washed further with CH\(_2\)Cl\(_2\) (100 mL x 2). The combined CH\(_2\)Cl\(_2\) layers were washed with brine, dried over MgSO\(_4\) and evaporated to dryness. Flash chromatography of the crude product on silica gel (hexanes/EtOAc, 7/3) gave 0.85 g (62\%) of pure sample as a white solid. mp 66.5-68.5 °C; [α]\text{D}\text{22} -150.7° (c 0.76, CHCl\(_3\)); R\(_f\) 0.23 (hexanes/EtOAc, 5/5); IR (CHCl\(_3\)) 3683, 3541, 3442, 3019, 1787, 1720, 1703, 1595, 1511, 1385, 1219 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) δ 7.42-6.97(m, 12H, aromatic Hs except C\(_5\)-H of Ar-OMe), 6.80 (d, 1H, J = 9.2 Hz, C\(_5\)-H of Ar-OMe), 6.54 (d, 1H, J = 7.3 Hz, Ar-OMeCHNH-), 5.75 (d, 1H, J = 7.3Hz, Ar-OMeCHNH-), 5.62 (s, 1H, phenolic -H), 5.11 (s, 2H, -CO\(_2\)CH\(_2\)Ph), 4.60-4.57 (m, 1H, -NCH\(_2\)H\(_2\)O), 4.13-4.00 (m, 2H, -NCH\(_2\)CH\(_2\)O-), 3.87 (s, 3H, -OCH\(_3\)), 3.36 (bd, 1H, -CHCH\(_2\)Ph), 2.83 (dd, 1H, J = 13.2, 9.5 Hz, -CHCH\(_2\)Ph); \(^13\)C NMR (CDCl\(_3\)) δ 171.0, 155.3, 152.2, 147.0, 145.8, 136.1, 135.0, 129.4, 128.9, 128.4, 128.0, 127.3, 121.0, 113.7, 110.8.
(2R,4R)-3-[2-(Benzyloxy carbonyl)amino-2-(3-hydroxy-4-methoxy)phenyl-1-oxo]ethyl-4-phenylmethyl-2-oxazolidinone (3.54).

This compound was obtained as a minor product in 19% yield in the synthesis of 3.53: Rf 0.34 (hexanes/EtOAc, 5/5); 1H NMR (CDCl3) δ 7.43-7.12 (m, 17H, aromatic Hs except C5-H of Ar-OMe), 6.91 (d, 1H, J = 8.7 Hz, C5-H of Ar-OMe), 6.59 (d, 1H, J = 7.3 Hz, Ar-OMeCHNH-), 5.81 (d, 1H, J = 7.3 Hz, Ar-OMeCHNH-), 5.25 (s, 2H, -OCH2Ph), 5.11 (s, 1H, PhCHHCO2-), 5.10 (s, 1H, PhCHHCO2-), 4.58-4.55 (m, 1H, -NCH2CH2O-), 4.12-4.02 (m, 2H, -NCHCH2O-), 3.78 (s, 3H, -OCH3), 3.81 (Appt t, 1H, -NCHCHHPH), 2.82 (dd, 1H, J = 13.2, 9.5 Hz, -NCHCHHPH); 13C NMR (CDCl3) δ 170.7, 155.2, 152.9, 152.2, 151.5, 140.1, 136.1, 135.0, 134.8, 129.4, 128.9, 128.6, 128.5, 128.3, 128.1, 127.9, 127.3, 121.7, 112.7, 70.4, 67.1, 66.2, 55.9, 55.7, 37.5

(2S)-2-Azido-3-(4-chlorophenyl)propionic Acid Methyl Ester (3.55).

(i) To a stirred, pre-cooled (0 °C) solution of (2S,4S)-α-azido, chiral auxiliary-adduct 1.19a (4.76 g, 12.4 mmol) in 100 mL of THF was added 24.7 mL of aqueous LiOH (1.0M) dropwise and the resulting solution was stirred for 1 h at 0 °C. The reaction was treated with 10 mL of saturated NaHCO3 and the solvent was removed in vacuo. The product was extracted with EtOAc (30 mL x 3) and the combined organic layers were washed with brine, dried over MgSO4 and evaporated. The crude acid was dried under high vacuum, then used for the next reaction without further purification. (ii) The acid was added into the flask containing PTSA (2.35 g, 2.0 equiv) in 25 mL of dry MeOH and the resulting mixture was heated at reflux.
overnight under Ar. After cooling to rt, the solvent was evaporated and the residue was dissolved again in 50 mL of CH₂Cl₂. The organic layer was washed with dil NaHCO₃, brine, dried over MgSO₄ and evaporated. Purification by flash chromatography on silica gel (hexanes/EtOAc, 8/2) gave 2.33 g (79%) of pure product as a colorless liquid. [α]₂¹D -50.7° (c 0.76, CHCl₃); Rf 0.41 (hexanes/EtOAc, 8/2); IR (CHCl₃) 3020, 2956, 1740, 1493, 1211 cm⁻¹; ¹H NMR (CDCl₃) δ 7.29 (d, 2H, aromatic Hs ortho to -Cl), 7.16 (d, 2H, aromatic Hs meta to -Cl), 4.06 (dd, 1H, J = 8.6, 5.3 Hz, ArCH₂CH-). 3.78 (s, 3H, -CO₂CH₃), 3.78-3.75 (m, 2H, -OCH₂CH₂O-), 3.57-3.54 (m, 2H, -OCH₂CH₂O-), 3.14 (dd, 1H, J = 1.40, 5.3 Hz, ArCHHCH-), 2.97 (dd, 1H, J = 14.0, 8.6 Hz, ArCHHCH-); ¹³C NMR (CDCl₃) δ 170.1, 134.3, 133.2, 130.5, 128.8, 63.0, 59.1, 52.7, 36.9; HRMS calcld for C₁₀H₁₀N₃O₂Cl₁ 239.0461, found 239.0461.

N-[(1,1-Dimethylethoxy)carbonyl]-L-(4-chlorophenyl)alanine Methyl Ester (3.56). To a stirred solution of α-azido, methyl ester 3.55 (1.78 g, 7.44 mmol) and (BOC)₂O (1.95 g, 1.20 equiv) in 60 mL of THF was added 180 mg of Pd-C(10%) and the resulting slurry was stirred for 7 h at rt under H₂ (1 atm). The mixture was filtered and the filter cake was washed well with 20 mL of THF. The combined filtrate was concentrated to give a yellow residue, which was purified by flash chromatography on silica gel (hexanes/EtOAc, 8/2) followed by recrystallization (hexanes) to give 1.72 g (74%) of pure product as needle-type crystals. mp 65.5-67.5 °C; [α]²⁳D +53.6° (c 0.8, CHCl₃); Rf 0.38 (hexanes/EtOAc, 7/3); IR (CHCl₃) 3434, 3051, 2985, 1744, 1713, 1493, 1368, 1266, 1166 cm⁻¹; ¹H NMR (CDCl₃) δ 7.26 (d, 2H, J = 8.4 Hz, aromatic Hs ortho to -Cl), 7.06 (d, 2H, J = 8.4 Hz, aromatic Hs meta to -Cl), 5.00 (bd, 1H, J = 7.6 Hz, -CHNHBOC), 4.60-4.54 (m, 1H, ArCH₂CH-), 3.72 (s, 3H, -CO₂CH₃), 3.13 (dd, 1H, J = 13.7, 5.6 Hz,
ArCH/HCH-), 3.00 (dd, 1H, J = 13.7, 6.0 Hz, ArCH/HCH-), 1.42 (s, 9H, -BOC);
$^{13}$C NMR (CDCl$_3$) δ 172.1, 155.0, 134.6, 132.9, 130.6, 128.7, 80.1, 54.3, 52.3,
37.8, 28.3; HRMS calc'd for C$_{15}$H$_{20}$NO$_4$Cl$_1$ 313.1081, found 313.1052.

[η6-[(2S)-4-Chloro-[[2-[[1,1-dimethylethoxy]carbonyl]amino-3-oxo-3-methoxy]propyl]benzene]](η5-cyclopentadienyl)ruthenium Hexa-
fluorophosphate (3.57). A combined mixture of 3.56 (121.6 mg, 0.388
mmol) and (CH$_3$CN)$_3$Ru$^+$CpPF$_6^-$ (236.1 mg, 1.40 equiv) in 15 mL of dry 1.2-
dichloroethane was degassed by bubbling with N$_2$ over 20 min, then the resulting
slurry was heated at reflux for 4 h under N$_2$. The mixture was cooled to rt and put
aside for 3-4 h at rt. The brown solid was removed by filtration through a Celite pad
(1 x 2 cm) and the solvent was removed in vacuo to give a brown residue, which was
dissolved again in 10 mL of CH$_3$CN. The resulting solution was passed through a
neutral alumina column (1 x 5 cm) and the column was washed with additional 5 mL
of CH$_3$CN. The solvent was evaporated to give 242.8 mg (100%) of pale-brown
solid foam. IR (CHC$l_3$) 3420, 3100, 3040, 2980, 1740, 1705, 845 cm$^{-1}$; $^1$H NMR
(CDCl$_3$) δ 6.48-6.24 (m, 4H, aromatic Hs of Ar$^+Ru$), 5.47 (s, 5H, Cp), 4.45-4.43
(m, 1H, ArCH$_2$CH-), 3.83 (s, 3H, -CO$_2$CH$_3$), 3.10 (dd, 1H, J = 14.1, 3.1 Hz,
Ar$^+Ru$CH/HCH-), 2.85 (dd, 1H, J = 14.1, 7.8 Hz, Ar$^+Ru$CH/HCH-)
3.5 REFERENCES AND NOTES


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CHAPTER 4

APPROACHES TOWARDS THE TOTAL SYNTHESSES OF OF4949-III AND -IV
4.1 INTRODUCTION

OF4949-III, and IV are isodityrosine-derived cyclic tripeptides isolated in 1986 from the culture filtrate of the fungus *Penicillium rugulosum* OF4949\(^1\), and their structures were determined based on spectroscopic and chemical degradative studies\(^2\) (Figure 4.1.1).

![Chemical Structure](image)

**Figure 4.1.1** Structures of OF4949-III, IV

These compounds exhibit potential aminopeptidase B inhibitory activity, immunopotentiating activity and confirmed antitumor activity without appreciable cytotoxic activity.\(^3a,b,c\) Thus, these agents may constitute a new class of potentially useful antitumor agents that can act as toxicity-free immunopotentiators. The first total synthesis of OF4949-III was reported by Yamamura's group.\(^4\) The synthesis was based on the so called "biomimetic" approach by utilizing thallium (III) nitrate to effect the oxidative cyclization of a di-bromotyrosylasparaginyl dichlorotyrosine derivative as a key step (25%). Later, Schmidt et al.\(^5\) disclosed a successful total synthesis of OF4949-III and the key steps are two preparations of didehydroamino acid residues by condensation of requisite aldehydes and phosphorylglycine esters followed by two homogeneous hydrogenations with more than 98% ee and de by
using Rh(DIPAMP)*. Bober et al.⁶a,b have also reported total syntheses of OF4949-III and IV. The basic strategy of their approach is the formation of the diaryl ether between a selectively-protected L-dopa derivative and sodium p-iodobenzoate under Ullmann reaction conditions and subsequent introduction of the second amino acid functionality by reacting the derived bromo-compounds with Schoellkopf's reagent. The final cycloamidation was accomplished via the DPPA method in 58% yield. Evans group⁷ reported an elegant approach to OF4949-III based on the expedient bidirectional synthesis of a fully differentiated isodityrosine which was obtained by employing the Evans de novo amino acid synthesis on a functionalized diaryl ether. The final cyclization was accomplished in 71% yield by employing the pentafluorophenyl ester method.⁸

### 4.2 SYNTHETIC PLAN

In designing the optimum synthetic route for the ring system of OF4949-III, IV from the fully developed isodityrosine derivative, two different approaches for the cycloamidation reaction are possible (Scheme 4.2.1). From the extensive studies of Bober et al.⁶b and from the fact that the activated carboxyl ester of asparagine residues readily cyclize to make both succinimide and β-cyanoalanine derivatives,⁹ option (B) appears to be the more favorable, even though Schmidt's group⁵ adopted option (A) for the total synthesis of OF4949-III. Based on our earlier results⁴a,b utilizing the reactivity of chloroarene-ruthenium complexes toward nucleophiles
under very mild conditions, fully protected (3-hydroxy-4-methoxy)tyrosine derivative 4.3 and ruthenium complex 4.4 of the dipeptide prepared from L-chlorophenylalanine and N-BOC-asparagine are to be synthesized. These important intermediates are eventually to be synthesized asymmetrically from commercially available 3-hydroxy-4-methoxybenzaldehyde and p-chlorocinnamic acid by using Evans' asymmetric azidation methodology. This route exemplifies the most convergent synthesis so far for this kind of compound. One of the key points to be addressed for this kind of peptide synthesis is the careful choice of appropriate protecting groups for the carboxyl and amine functionalities. Among the various amine protecting groups, azide group was successfully employed in Evans' case as a
latent amine. By careful consideration of the reaction conditions of each step in our synthetic approach, the azide group can be successfully employable as an amine surrogate. In the case of carboxyl group, MEM ester protecting group is our first choice over others such as TMSE because it can be removed under neutral conditions with MgBr₂·OEt₂. After condensation of the chloroarene-ruthenium complex with the phenolic derivative under very mild conditions and subsequent demetallation using sunlamp (275W) at rt, the MEM ester of the arylated product will be deprotected and eventually cyclized using various cycloamidation reagents such as pentafluorophenyl ester, especially HAPyU and FDPP. The remaining seemingly easy steps will afford OF4949-III and -IV.

4.3 RESULTS AND DISCUSSION

The synthesis of an important intermediate 4.3 was begun with the commercially available 3-hydroxy-4-methoxybenzaldehyde 1.6 (Scheme 4.3.1). To synthesize the intermediate 4.3, we first tested the selective debenzylation from 1.12.a, that was an important intermediate in the formal synthesis of K-13, by using TMSCl/NaI, but the yields were not satisfactory. So, we decided to adopt TBDMS- as a phenolic-protecting group which is easily removable with TBAF. The carboxylic acid was selectively protected as a benzyl ester in the presence of the phenolic group with BnBr/DBU and subsequent protection of the phenolic group with TBDMScI was accomplished employing the known procedure. Selective removal of benzyl group from benzyl ester 4.5 under catalytic hydrogenolysis conditions was accomplished by Pd-C(10%)/H₂ (1 atm). This TBDMS-protected
phenylpropionic acid 4.7 was treated with lithiated (4S)-4-phenylmethyl-2-oxazolidinone as usual, then with trisylazide under Evans' azidation conditions to

![Chemical structures](image)

**Reaction Conditions, Reagents and Yields:**

(a) BnBr (1.0 equiv), DBU (1.0 equiv), reflux, 7 h, 62%  
(b) TBDMS (1.2 equiv), DMAP (0.08 equiv), Et$_3$N (1.30 equiv), rt, 17 h, 86%  
(c) Pd-C (10%) (10 wt%), H$_2$ (1 atm), 99%  
(d) Et$_3$N (1.30 equiv), Pivaloyl chloride (1.10 equiv), Lithiated (4S)-4-Phenylmethyl-2-oxazolidinone, 73%  
(e) KHMS (1.30 equiv), Trisyl azide (1.10 equiv), 71%  
(f) TBAF (1.0 equiv), 0 ºC, 40%  
(g) LIOH (2.0 equiv), 0 ºC  
(h) MEMCl (1.20 equiv), (i-Pr)$_2$NEt (1.10 equiv), 0 ºC, 59%

**Scheme 4.3.1** Synthetic Routes for the Intermediate 4.3
afford α-azido auxiliary-adduct 4.9 in good yield (71%). Deprotection of TBDMS with TBAF appeared to be straightforward, but surprisingly, it suffered from low yield. This problem could be solved by using anhydrous TBAF/THF reagent. At this point, the possible racemization at the newly introduced-chiral center may not be a problem because TBAF was successfully utilized for the deprotection of TMSE ester protecting group of the similar compound. After removal of the chiral auxiliary from 4.10 with LiOH (3.0 equiv, 0 °C, 1 h), the resulting acid 4.10' was protected with MEMCl/Hunig base to give the important intermediate 4.3 in good yield.

Reaction Conditions, Reagents and Yields:
(a) LiOH (2.0 equiv), 0 °C, 1 h then PTSA (2.0 equiv)/MeOH, reflux, overnight, 79% (b) Pd-C (10%), H₂ (1 atm) (c) NBOC-Asparagine (1.20 equiv), HOBt (1.50 equiv), EDC (1.20 equiv), 0 °C, then rt, 78% (d) (CH₂CN)₂Ru*CPF₆⁻ (1.35 equiv), reflux, 4 h, quantitative.

Scheme 4.3.2 Synthetic Route for the Intermediate 4.4
The other important intermediate of dipeptide 4.4 was synthesized from commercially available p-chlorocinnamic acid via α-azido, chiral auxiliary-adduct 1.19.a which was prepared in the formal synthesis of K-13 (Scheme 4.3.2). Removal of chiral auxiliary from 1.19.a under the usual conditions, then subsequent esterification under reflux conditions gave α-azido-methyl ester 4.11 in good yield. Reduction of azido into amino group under atmospheric pressure of hydrogen with Pd-C(10%) provided 4.11', which was then coupled with N-BOC-asparagine using EDC/HOBt to afford the requisite dipeptide 4.12 in good yield. At this point, selective Ru-complexation is of question because multiple polar functionalities such acetamide, amide groups may interfere with the arene-complexation. But, in the event, selective Ru-complexation was accomplished in quantitative yield and 1H-NMR of 4.4 clearly showed that Ru-complexed aromatic-Hs are shifted by ca. 1 ppm to ca. 6.2 ppm region and also the overlapped amide-proton peak of -CHNHCO- appeared (Figure 4.3.1). This very important finding paves the way for a convergent synthesis of the target molecule.
Figure 4.3.1 $^1$H-NMR Spectra of 4.12 in CDCl$_3$ and 4.4. in CD$_3$CN
Having the two important intermediates 4.3, 4.4 in hand, the next steps appear to be straightforward as in our earlier published results (Scheme 4.4.1).

![Chemical Structures]

**Reaction Conditions, Reagents and Yields:**

(a) Na, 2,6-di-t-Butylphenoxide (1.0 equiv), 0 °C, 15 min (b) 4.4 (1.0 equiv), -78 °C, 30 min then rt, 1-2 h (c) Sunlamp (275W), rt, 24 h (d) MgBr₂OEt₂ (5 equiv), rt, 2 d (e) TFA, 0 °C (f) Various Coupling Reagents (g) C₆F₅OH, DCC, rt (h) TFA, 0 °C (i) Pd-C(10%), Base, 90 °C, N₂

Scheme 4.4.1 Future Synthetic Plan for the Cyclic Ring System 4.18 of OF4949-III and -IV

4.3 will be treated with 2,6-di-t-butylphenoxide (1.0 equiv) at 0 °C for 10-15 min, then reacted with chloroareneruthenium complex 4.4 under very mild
conditions (-78 °C, 30 min, then rt, 1-2 h, N₂). The separated arylated ruthenium complex 4.13 will be irradiated with sunlamp (275W) at rt for 20-24 h to afford the demetallated product 4.14. At this stage, we believe that azide group may be sufficiently stable for coupling and demetallation reaction conditions. But, if it is not stable enough especially for demetallation conditions, the azide group should be converted into N-Cbz in the earlier stage of 4.10 and in this case, 2-bromo(or 2-iodo)ethyl ester seems to be plausible as an alternative for MEM ester protecting group. The MEM ester of 4.14 will be deprotected under neutral conditions (MgBr₂·OEt₂, Et₂O, rt, 2 days, N₂) to provide acid 4.15. At this point, we will have two routes to obtain the cyclic peptide system for OF4949-III and IV. The one is the deprotection of N-BOC of L-asparagine subunit with TFA/thioanisole and then direct intramolecular cycloamidation between the free acid and Amine-TFA of 4.16 using HaPyU and FDPP under slightly basic conditions. Even though HAPyU and FDPP failed to give successful results for 16-membered ristocetin A BCF-ring model study, they are very promising cycloamidation reagents and well exemplified in the recent reports.¹³ The other approach is the well-known activated ester method utilizing pentafluorophenyl ester. The acid 4.15 will be treated with pentafluorophenol/DCC to give 4.17 which, in turn, will be subjected to hydrogenation and in situ cycloamidation reaction conditions. Once the ring system of 4.18 is obtained (Scheme 4.4.2), the synthesis of OF4949-III appears to be very simple.
Scheme 4.4.2 Future Synthetic Plan for OF4949-III and -IV

Hydrolysis of 4.18 with LiOH (2.0 equiv, rt, 2-3 h) and subsequent reduction under hydrogenation conditions will give OF4949-III. For OF4949-IV, methyl groups of methylphenylether and methyl ester of 4.18 are to be deprotected. This can be done in one step with AlBr₃/EtSH.⁷ At this stage, we believe that the azide group of 4.18 can be reduced into amino group simultaneously under these reaction conditions. But, in the event of difficulty, the azide group will be protected as N-BOC with (BOC)$_2$O/Pd-C(10%). It is reported that N-BOC is deprotected into amine with (AlCl₃/PhOCH$_3$, 0-25 °C, 3-5 h).¹⁸ So, we believe that AlBr₃/EtSH (or AlCl₃/PhOCH$_3$) will afford OF4949-IV from 4.19 in one step.
Reaction Conditions, Reagents and Yields:

(a) Na, 2,6-di-t-Butylphenoxide (1.0 equiv), 0 °C, 15 min (b) 4.4 (1.0 equiv), -78 °C, 30 min than rt, 1-2 h, N₂ (c) Sunlamp (275W), 1 h; 24 h (d) LiOOH (2.0 equiv), 0 °C, 1 h

Scheme 4.4.3 Another Possible Shorter Synthetic Route for the Intermediate 4.15

Another possible interesting shorter route is to use 4.10 as a precursor for condensation (Scheme 4.4.3). In this case, the chiral auxiliary of 4.10 can act as a director for azidation and also as a carboxylic protecting group. We believe that this chiral auxiliary can survive the very mild condensation reaction and demetallation reaction conditions to provide 4.21, which then will be reacted with LiOOH to give the same intermediate 4.15 because the auxiliary used can be selectively removed in the presence of the methyl ester group.¹⁹ This sequence avoids the use of carboxylic-protection and -deprotection steps and ultimately presents the most convergent and also shortest synthetic routes for OF4949-III and IV.
4.5 CONCLUSIONS

TBDMS-ether protecting group of phenolic moiety has shown good behavior under hydrogenation and Evans' azidation reaction conditions as a phenolic protecting group and MEM ester protecting group can be introduced in the presence of phenolic functionality in good yield. The dipeptide with polar substituent such as acetamide can be metallated selectively under the usual conditions in excellent yield.
General: All reactions were conducted under dry N\textsubscript{2} or Ar unless stated otherwise. \textsuperscript{1}H-NMR (300 MHz) and \textsuperscript{13}C-NMR (75 MHz) spectra were recorded in CD\textsubscript{2}Cl\textsubscript{2}, CDCl\textsubscript{3}, DMSO-d\textsubscript{6} on a Varian Gemini-300 spectrometer. \textsuperscript{1}H-NMR was referenced to TMS and \textsuperscript{13}C-NMR was referenced to CHCl\textsubscript{3} (77.0 ppm). IR spectra were recorded on Nicolet Impact 400 using CHCl\textsubscript{3} or KBr. Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. Mass spectra were recorded on a Kratos MS-25A instrument and CHN analyses were performed by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed using E. Merck silica gel 60 F-254 0.25mm plates. Visualization was accomplished with UV, phosphomolybdic acid or ninhydrin solution. Flash chromatography was carried out on E. Merck 320-400 mesh silica gel and solvents are reported as V/V percent mixtures. Analytical HPLC was performed on a Gilson HPLC using Dynamax-60A normal phase analytical column. THF was distilled from sodium benzophenone ketyl. CH\textsubscript{2}Cl\textsubscript{2}, Et\textsubscript{3}N and CH\textsubscript{3}CN were distilled from calcium hydride. All solvents were distilled under dry nitrogen. n-Butyllithium in hexane was obtained from Aldrich Co and standardized according to the method of Duhamel and Plangnevant.\textsuperscript{19} TBDMSCl, MEMCl and DBU were purchased from Aldrich Co and used without further purification. All other chemicals were purchased from Aldrich Co and used without further purification.
b3-[(3-Hydroxy-4-methoxy)phenyl]propionic Acid Benzyl Ester (4.5).

To a stirred solution of 3-[(3-hydroxy-4-methoxy)phenyl]propionic acid 1.8 (4.90 g, 25.0 mmol) in 50 mL of dry benzene were added DBU (3.73 mL, 1.0 equiv) and benzyl bromide (3.56 mL, 1.0 equiv) and the resulting mixture was heated to reflux for 7 h under Ar. The reaction mixture was cooled to rt, washed with water, saturated NaHCO₃, brine and dried over MgSO₄. Removal of solvent under reduced pressure gave a pale yellow residue, which was purified by flash chromatography (SiO₂, hexanes/EtOAc, 65/35) to afford 4.44 g (62%) of 4.5 as a pale yellow solid. mp 52.5-54.0 °C; Rf 0.47 (hexanes/EtOAc 6/4); IR (KBr) 3415, 3034, 2968, 1723, 1590, 1519, 1447, 1269, 1237 cm⁻¹; ¹H NMR (CDCl₃) δ 7.36-7.25 (m, 5H, -OCH₂Ph), 6.77-6.64 m, 3H, aromatic Hs of Ar-OMe, 5.58 (s, 1H, Phenolic-H), 5.11 (s, 2H, -OCH₂Ph), 3.85 (s, 3H, ArOCH₃), 2.88 (t, 2H, J = 7.8 Hz, ArCH₂CH₂C-), 2.64 (t, 2H, J = 7.8 Hz, ArCH₂CH₂C-): ¹³C NMR (CDCl₃) δ 172.7, 145.5, 145.0, 135.0, 133.7, 128.5, 128.2, 119.6, 114.5, 110.6, 66.2, 55.9, 36.0, 30.3; HRMS calc'd for C₁₇H₁₈O₄ 286.1205, found 286.1210

3-[[4-Methoxy-3-(t-butyldimethylsilyloxy)]phenyl]propionic acid Benzyl Ester (4.6). To a stirred solution of the benzyl ester 4.5 (4.36 g, 15.3 mmol) and TBDMSCl (2.75 g, 1.20 equiv) in 50 mL of CH₂Cl₂ were added DMAP (0.149 g, 0.08 equiv) and Et₃N (2.76 mL, 1.30 equiv) and the resulting mixture was stirred for 17 h at rt under Ar. The mixture was washed with water, saturated NH₄Cl (50 mL), brine and dried over MgSO₄. The solvent was evaporated to give crude product, which was flash-chromatographed on silica gel
(hexanes/EtOAc, 75/25) to provide 5.22 g (86%) of 4.6 as a colorless liquid. Rf 0.49 (hexanes/EtOAc, 7/3); 1H NMR (CD2Cl2) δ 7.36-7.32 (m, 5H, -OCH2Ph), 6.78 (d, 1H, J = 8.2 Hz, C5-H), 6.75 (d, 1H, J = 2.0 Hz, C2-H), 6.71 (dd, 1H, J = 2.0, 8.2 Hz, C6-H), 5.09 (s, 2H, -OCH2Ph), 3.77 (s, 3H, -OCH3), 2.85 (t, 2H, J = 7.7 Hz, ArCH2CH2C-), 2.63 (t, 2H, J = 7.7 Hz, ArOMeCH2CH2C-), 1.00 (s, 9H, -OSi(t-Bu)), 0.14 (s, 6H, -OSi(Me)2); 13C NMR (CDCl3) δ 172.8, 149.4, 144.9, 135.9, 133.0, 128.5, 128.2, 121.2, 121.0, 112.2, 66.2, 55.5, 36.1, 30.2, 25.7, 18.4, -4.6; HRMS calcd for C23H32O4Si1 400.2070, found 400.2074

3-[[4-Methoxy-3-(t-butyldimethylsilyloxy)]phenyl]propionic Acid (4.7). TBDMS-protected phenylpropionic acid benzyl ester 4.6 (5.19 g, 13.0 mmol) was combined with Pd-C(10%) (ca. 530 mg) in 60 mL of THF and the slurry was stirred for 3.5 h at rt under hydrogen atmosphere (1 atm). The solid catalyst was filtered off and the filter cake was washed with 20 mL of THF. The solvent was removed in vacuo to give a white solid, which was dried further under high vacuum to provide pure product 4.7 (3.95 g, 99%) as a white solid. mp 75.5-77.5 °C; 1H NMR (CD2Cl2) δ 6.79 (d, 1H, J = 8.2 Hz, C5-H), 6.76 (d, 1H, J = 2.0 Hz, C2-H), 6.71 (dd, 1H, J = 2.0, 8.2 Hz, C6-H), 3.76 (s, 3H, -OCH3), 2.83 (t, 2H, J = 7.7 Hz, PhCH2CH2C-), 2.62 (t, 2H, J = 7.7 Hz, PhCH2CH2C-), 0.98 (s, 9H, -OSi(t-Bu)), 0.14 (s, 6H, -OSi(Me)2); 13C NMR (CD2Cl2) δ 179.3, 149.9, 145.2, 133.3, 121.5, 121.3, 112.5, 55.8, 36.1, 30.1, 25.8, 18.7, -4.6; HRMS calcd for C16H26O4Si1 310.1600, found 310.1600.

(4S)-3-[[3-[4-Methoxy-3-(t-butyldimethylsilyloxy)]phenyl-1-oxo]pro- pionyl]-4-phenylmethyl-2-oxazolidinone (4.8). To a stirred, pre-cooled (-
78 °C) solution of TBDMS-protected phenylpropionic acid 4.7 (1.99 g, 6.49 mmol) in 60 mL of THF under N2 were added by syringe 1.18 mL (1.30 equiv) of freshly distilled Et3N followed by 0.88 mL (1.10 equiv) of distilled pivaloyl chloride. The resulting slurry was stirred at -78 °C for 25 min and 0 °C for 50 min, then cooled again to -78 °C under N2. In a separate flask, 1.07 g (1.0 equiv) of (4S)-4-(phenylmethyl)-2-oxazolidinone was dissolved in 40 mL of THF and cooled to -78 °C, then to this solution was added by syringe 4.06 mL of n-BuLi (1.60 M in hexanes) and the resulting solution was stirred at -78 °C for 25 min under N2. This metalated oxazolidinone solution was transferred to the above slurry via cannula and the resulting mixture was stirred for 30 min at -78 °C, then stirred overnight at rt under N2. The reaction was quenched by addition of 40 mL of aqueous NaHSO4 (1.0 N) and the solvent was removed in vacuo. The product in aqueous mixture was extracted with CH2Cl2 (50 mL x 3) and the combined organic layers were washed with brine, dried over MgSO4 and concentrated to give a pale-yellow oily residue. Purification of the crude product by flash chromatography (SiO2, hexanes/EtOAc, 75/25) provided 4.8 (2.10 g, 73%) as a colorless oil. [α]23D +38.6° (c 0.49, CHCl3); Rf 0.32 (hexanes/EtOAc, 7/3); IR (CHCl3) 3695, 3610, 3026, 2963, 2934, 1786, 1706, 1611, 1517, 1390, 1224 cm⁻¹; 1H NMR (CD2Cl2) δ 7.35-7.16 (m, 5H, aromatic Hs of Araux), 6.83-6.78 (m, 3H, aromatic Hs of ArOMe), 4.69-4.62 (m, 1H, -NCHCH2O-), 4.21-4.11 (m, 2H, -NCHCH2O-), 3.76 (s, 3H, -OCH3), 3.29-3.09 (m, 3H, ArOMeCH2CH2- overlapped with -NCHCHPh), 2.92-2.77 (m, 3H, ArOMeCH2CH2- overlapped with -NCHCHPh), 1.00 (s, 9H, -OSi(t-Bu)), 0.15 (s, 6H, -OSi(Me)2); 13C NMR (CD2Cl2) δ 172.6, 153.8, 149.8, 145.2, 135.9, 133.7, 129.8, 129.2, 127.2, 121.8, 121.6, 112.5, 66.6, 55.8, 55.3, 38.0, 37.7, 29.8, 25.9, 18.7, -4.6; HRMS calcd C26O35NO5Si 469.2284, found 469.2296.
(4S,2S)-3-[[2-Azido-3-[4-methoxy-3-(t-butyldimethylsilyloxy)]phenyl-1-oxo]propionyl]-4-phenylmethyl-2-oxazolidinone (4.9). To a stirred solution of chiral auxiliary-adduct 4.8 (474.6 mg, 1.04 mmol) in 20 mL of THF at -78 °C was added rapidly by syringe 2.71 mL (0.5 M in toluene, 1.30 equiv) of KHMDS and the resulting solution was stirred for 20 min at -78 °C under N₂. To this solution was transferred via cannula over 30 seconds a precooled (-78 °C) solution of 354.5 mg (1.10 equiv) of trisylazide in 10 mL of THF. The resulting solution was stirred for 2 min at -78 °C and quenched by rapid addition of 149.0 µL (2.50 equiv) of glacial acetic acid followed by immediate warming to 35 °C with a water bath. The white slurry was stirred further for 3 h at rt, diluted with 50 mL of CH₂Cl₂ and separated. The organic layer was washed with brine, dilute NaHCO₃, dried over MgSO₄ and concentrated in vacuo to give an oily residue. Flash chromatography of the crude product on silica gel (CH₂Cl₂/hexanes, 7/3) gave 378.0 mg (71%) of 4.9 as a colorless oil. [α]²³D +70.4° (c 0.50, CHCl₃); Rₚ 0.36 (CH₂Cl₂); IR (CHCl₃) 3024, 2963, 2932, 2859, 2110, 1785, 1711, 1515, 1233 cm⁻¹; ¹H NMR (CD₂Cl₂) δ 7.39-7.22 (m, 5H, aromatic Hs of Araux), 6.89-6.81 (m, 3H, aromatic Hs of Ar⁻OMe)), 5.17 (dd, 1H, J = 9.2, 5.2 Hz, Ar⁻OMeCH₂CH⁻), 4.67-4.61 (m, 1H, -NCH₂CH₂O⁻), 4.23-4.14 (m, 2H, -NCH₂CH₂O⁻), 3.78 (s, 3H, -OCH₃), 3.28 (dd, 1H, J = 13.5, 3.2 Hz, -NCHCH₂Ph), 3.12 (dd, 1H, J = 13.8, 5.2 Hz, Ar⁻OMeCH₂CH⁻), 2.96-2.85 (m, 2H, Ar⁻OMeCH₂CH⁻, overlapped with -NCHCH₂Ph), 1.00 (s, 9H, -OSi(t-Bu)), 0.166 (s, 3H, -OSi(Me)(Me)), 0.161 (s, 3H, -OSi(Me)(Me)) ¹³C NMR (CD₂Cl₂) δ 170.8, 153.2, 150.7, 145.3, 135.4, 129.8, 128.7, 127.7, 122.7, 122.2, 112.5, 67.1, 62.1, 55.8, 37.8, 37.1, 25.8,
18.7, -4.59, -4.63; HRMS calcd for C_{25}H_{34}N_{2}O_{5}Si (M-N\textsubscript{2})\textsuperscript{+} 482.2237, found 482.2256.

(4S,2S)-3-[[2-Azido-3-(3-hydroxy-4-methoxy)phenyl-1-oxo]propionyl]-4-phenylmethyl-2-oxazolidnone (4.10). α-Azido, auxiliary-adduct 4.9 (815.6 mg, 1.60 mmol) was dissolved in 20 mL of THF and the resulting solution was cooled to 0°C with an ice bath. To this was added 1.60 mL (1.0 equiv) of TBAF (1.0 M in THF) by syringe and the solution was stirred for 1 h at 0°C, then diluted with 50 mL of CH\textsubscript{2}Cl\textsubscript{2}. The solution was washed with brine and the aqueous layer was extracted again with 10 mL of CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layers were dried over MgSO\textsubscript{4} and concentrated in vacuo. Purification by flash chromatography (SiO\textsubscript{2}, hexanes/EtOAc, 713) gave 4.10 (250.0 mg, 40%) as a pale yellow solid. mp 153.0-155.0°C; [α]\textsuperscript{23}_{D} +79.3° (c 0.60, CHCl\textsubscript{3}); R\textsubscript{f} 0.34 (hexanes/EtOAc 5/5); IR (CHCl\textsubscript{3}) 3546, 3018, 2981, 2117, 1787, 1713, 1595, 1514, 1396, 1278, 1116, 1035 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) δ 7.36-7.20 (m, 5H, aromatic Hs of Ar\textsuperscript{aux}), 6.88-6.80 (m, 3H, aromatic Hs of Ar\textsuperscript{OMe}), 5.63 (s, 1H, phenolic-H), 5.22 (dd, 1H, J = 9.0, 5.4 Hz, Ar\textsuperscript{OMe}CH\textsubscript{2}CH\textsubscript{-}), 4.65-4.60 (m, 1H, -NCHCH\textsubscript{2}O-), 4.21-4.10 (m, 2H, -NCHCH\textsubscript{2}O-), 3.85 (s, 3H, -OCH\textsubscript{3}), 3.32 (dd, 1H, J = 13.4, 3.1 Hz, -NCHCH\textsubscript{2}PPh), 3.13 (dd, 1H, J = 13.7, 5.4 Hz, Ar\textsuperscript{OMe}CH\textsubscript{2}CH\textsubscript{-}), 2.95 (dd, 1H, J = 13.7, 9.0 Hz, Ar\textsuperscript{OMe}CH\textsubscript{2}CH\textsubscript{-}), 2.82 (dd, 1H, J = 13.4, 9.5 Hz, -NCHCH\textsubscript{2}PPh); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) δ 170.5, 152.7, 145.8, 145.6, 134.7, 129.4, 129.0, 128.7, 127.5, 120.9, 115.3, 110.7, 66.5, 61.4, 55.9, 55.4, 37.5, 37.0; HRMS calcd for C\textsubscript{20}H\textsubscript{20}N\textsubscript{4}O\textsubscript{5} 396.1434, found 396.1424.
(2S)-[2-Azido-3-(3-hydroxy-4-methoxy)phenyl]propionic acid Methoxyethoxymethyl Ester (4.3). (i) To a stirred, pre-cooled (0 °C) solution
of 4.10 (228.4 mg, 0.58 mmol) in 30 mL of THF was
added 3.46 mL (3.0 equiv) of aqueous LiOH (0.5 M) and
the slurry was stirred for 1 h at 0 °C. To this was added
10% HCl solution to ca. pH 2 and the mixture was extracted
with Et₂O (20 mL x 3). The combined organic layers were dried over MgSO₄ and
evaporated in vacuo to give a white solid which was further dried under high
vacuum. (ii) The dried acid was dissolved in 20 mL of dry CH₂Cl₂ and the solution
was cooled to 0 °C with an ice bath. To this was added 79.0 µL (1.20 equiv) of
MEMCl, followed by 110.5 µL (1.10 equiv) of (i-Pr)₂NEt by syringe and the
resulting solution was stirred for 2 h at 0 °C under N₂. The reaction was quenched
by addition of 10 mL of HCl (1.0 N) and the organic layer was separated, washed
with brine, dried over MgSO₄ and concentrated. Flash chromatography of the oily
residue gave 110.0 mg (59%) of 4.3 as a colorless oil. [α]²⁴D -32.0° (c 0.51,
CHCl₃); Rf 0.29 (hexanes/EtOAc, 5/5); IR (CHCl₃) 3546, 3030, 3012, 2943, 2844,
2117, 1756, 1595, 1514, 1445, 1278, 1141, 1035 cm⁻¹; ¹H NMR (CDCl₃) δ 6.81-
6.71 (m, 3H, aromatic Hs), 5.73 (s, 1H, phenolic-H), 5.43 (d, 1H, J = 6.0 Hz,
-CO₂CH₂OH-), 5.40 (d, 1H, J = 6.0 Hz, -CO₂CH₂OH-), 4.05 (dd, 1H, J = 8.3, 5.6
Hz, ArCH₂CH₂-). 3.88 (s, 3H, -OCH₃), 3.78-3.75 (m, 2H, -OCH₂CH₂O-), 3.57-
3.54 (m, 2H, -OCH₂CH₂O-), 3.39 (s, 3H, -OCH₃), 3.11 (dd, 1H, J = 1.40, 5.6
Hz, ArCHHCH-), 2.95 (dd, 1H, J = 14.0, 8.3 Hz, ArCHHCH-); ¹³C NMR
(CDCl₃) δ 169.6, 145.9, 145.7, 128.8, 120.8, 115.3, 110.7, 90.6, 71.4, 69.9,
63.3, 59.1, 55.9, 36.9; HRMS calcd for C₁₄H₁₉N₃O₆ 325.1274, found 325.1267.

L-(p-Chlorophenyl)alanine Methyl Ester (4.11). To a slurry of Pd-C
(10%, 110 mg) in 20 mL of THF was added 3.53 (924.8 mg, 3.88 mmol) and the resulting mixture was stirred 7 h under hydrogen atmosphere (1 atm). The mixture was filtered through a Celite pad and the filter cake was washed well with 20 mL of methanol. The solvent was removed under reduced pressure to provide a pale yellow residue. Recrystallization of the crude product from (THF/hexanes) gave 666.2 mg (81%) of pure product. mp 148.5-150.5 °C; Rf 0.34 (EtOAc/MeOH, 9/1); $^1$H NMR (CDCl$_3$) δ 8.74-8.72 (bs, 2H, -NH$_2$), 7.29-7.27 (m, 4H, aromatic Hs), 4.43-4.39 (m, 1H, ArCH$_2$CH-), 3.67 (s, 3H, -CO$_2$CH$_3$), 3.48-3.32 (m, 2H, ArCH$_2$CH-); $^{13}$C NMR (CDCl$_3$) δ 169.1, 133.8, 129.6, 129.0, 127.7, 54.3, 53.0, 36.3.

$N$-[$N$-(1,1-Dimethylethoxy)carbonyl-L-asparaginyl]-L-(p-chlorophenyl)alanine Methyl Ester (4.12). To a stirred mixture of crude amine 4.11 (631.5 mg, 2.81 mmol), $N$-BOC-asparagine (781.9 mg, 1.20 equiv) and HOBT (644.6 mg, 1.50 equiv) in 25 mL of THF and 5 mL of DMF at 0 °C was added EDC (645.5 mg, 1.20 equiv) in one portion. The resulting mixture was stirred for 2 h at 0 °C and overnight at rt under N$_2$. The mixture was diluted with 100 mL of CH$_2$Cl$_2$, then the resulting organic layer was washed with 20 mL of HCl (1.0 N), saturated NaHCO$_3$, brine and dried over MgSO$_4$. Removal of solvent in vacuo afforded an off-white residue, which was purified by flash chromatography (silica gel, THF/EtOAc, 5/5) to give 4.12 (724.8 mg, 78%) as a white amorphous solid. mp 196.5-198.5 °C; Rf 0.42 (EtOAc/MeOH, 9/1); IR (CHCl$_3$) 3532, 3415, 3024, 2987, 1744, 1688 (br), 1595, 1501, 1375, 1228, 1172 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 7.33-7.08 (m, 5H, aromatic Hs overlapped
with -CH_2CHNHCO-, 6.02 (d, 1H, J = 6.6 Hz, -NHBOC), 5.83 (s, 1H, -CO_2CONH), 5.41 (s, 1H, -CH_2CONH), 4.80 (dd, 1H, J = 13.6, 6.1 Hz, ArCH_2CHNH-), 4.46 (bd, 1H, J = 1.5 Hz, -CHNHBOC), 3.69 (s, 3H, -CO_2CH_3), 3.13 (dd, 1H, J = 14.0, 5.7 Hz, ArCHHCH-), 3.06 (dd, 1H, J = 14.0, 6.3 Hz, ArCHHCH-), 2.91 (dd, 1H, J = 15.5, 5.3 Hz, -CHCHHCO-), 2.55 (dd, 1H, J = 15.5, 6.1 Hz, -CHCHHCO-), 1.42 (s, 9H, -BOC); ^13C NMR (CDCl_3) δ 173.3, 171.5, 170.9, 135.9, 130.7, 129.3, 128.6, 127.1, 80.4, 53.6, 52.2, 51.1, 38.0, 36.9, 28.2; HRMS calcd for C_{19}H_{26}N_3O_5Cl 427.1510, found 427.1526.

[η₆-(2S)-[4-Chloro-[2-[N-(1,1-dimethylethoxy)carbonyl-L-asparaginyl]amino-2-methoxycarbonyl]ethyl]benzene][η₅-cyclopenta-
dienyl]ruthenium Hexafluorophosphate (4.4). To a stirred solution of (CH_3CH)₃Ru+CPF₆⁻ (179.5 mg, 1.35 eqv) in 10 mL of dry 1,2-dichloroethane was added dipeptide 4.12 (132.2 mg, 0.31 mmol). The resulting mixture was degassed with N₂-bubbling over 20 min at rt (dipeptide is insoluble in 1,2-dichloroethane), then refluxed for 4 h under Ar. The brown solution was cooled to rt and filtered through a Celite column (1 x 2 cm). The solvent was evaporated in vacuo to afford a dark brown residue, which was dissolved again in 10 mL of CH_3CN, then passed through a neutral alumina column (1 x 5 cm). Removal of solvent in vacuo gave 238.7 mg (105%) of product as a brown solid which was confirmed to be sufficiently pure for the next reaction (by ^1H-NMR, The main impurity is (CH_3CN)₃Ru+CPF₆⁻). ^1H NMR (CD_3CN) δ 7.36 (bs, 1H, -CH_2CHNHC-), 6.43-5.96 (m, 6H, aromatic Hs of ArRu⁺ overlapped with -NHBOC and -CH_2CONH), 5.74 (bs, 1H, -CH_2CONH), 5.25 (s, 5H, Cp), 4.62 (dd, 1H, J = 8.0, 4.7 Hz, ArCH_2CHNH-), 4.34-4.25 (m, 1H,
-C\textsubscript{H}NHBOC), 3.70 (s, 3H, -CO\textsubscript{2}CH\textsubscript{3}), 3.03 (dd, 1H, J = 14.1, 4.7 Hz, ArCH/HCH-), 2.81 (dd, 1H, J = 14.1, 8.4 Hz, ArCH/HCH-), 2.67-2.46 (m, 2H, -CHCH\textsubscript{2}CO-), 1.42 (s, 9H, -BOC).
4.7. REFERENCES AND NOTES


CHAPTER 5

BIBLIOGRAPHY


39. The deprotecting trials of amino acid based N-BOC, 2-bromoethyl ester compounds by various reported methods always gave 2-hydroxyethyl esters as the major compound, and the results were confirmed by 1H-NMR and by conversion of 2-hydroxyethyl esters into their corresponding 2-acetoxyethyl esters. For more information, see reference 26, 40.


9. (a) Na/liq. NH₃ / -78 °C
   (b) Ca/liq NH₃ / -33 °C/10 min
   (c) Pd(CPh₃)₄ / CH₃CN


14. Various deprotection methods reported:
   (c) Unpublished new deprotection method for the model compound N-BOC-4-chloro-D-phenylalanine 2,2,2-trichloroethyl ester: Sml₂ (7.0 equiv), rt, 2 h, dry THF, under dry-, deoxygenated-Ar, quantitative yield.


Chapter 3


d) Waltho, J. P.; Cavanagh, J.; Williams, D. H. "Aspects of Molecular Recognition: Use of a Truncated Driven Pseudo-NOESY Experiment to ..."


22. Advanced organic Chemistry edited by Jerry March, 3rd Ed. pp89


