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Part I. Studies towards a synthesis of ristocetin A. Part II. Asymmetric synthesis of an aryglycinol

Shin, Hunwoo, Ph.D.

Case Western Reserve University, 1994
PART I. STUDIES TOWARDS A SYNTHESIS OF RISTOCETIN A
PART II. ASYMMETRIC SYNTHESIS OF AN ARYLGLYCINOL

By
HUNWOO SHIN

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

Thesis Advisor: Prof. Anthony J. Pearson

Department of Chemistry
CASE WESTERN RESERVE UNIVERSITY
January, 1994
CASE WESTERN RESERVE UNIVERSITY

GRADUATE STUDIES

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PART I. STUDIES TOWARDS A SYNTHESIS OF RISTOCETIN A  
PART II. ASYMMETRIC SYNTHESIS OF AN ARYLGLYCINOL

Abstract
by
HUNWOO SHIN

Part I. In order to probe the applicability of arene-manganese complexes to the synthesis of ristocetin A, the synthesis of a protected ristomycinic acid was studied.

The aryl ether bond was made under very mild conditions (0 °C, 1 h) and racemization of the arylglycine chiral center of the G-ring unit was not observed during phenoxide ion generation using sodium hydride. The glycine side chain was built using the Schöllkopf bislactim anion. Racemization of the chiral center (G-ring unit) by this anion did not occur. However, the yield and diastereoselectivity of this reaction was low (8–25 %, 30 – 60% d.e.). It was found that the use of an "aged" lithiated
anion improves the yield, but this was also dependent on the method used for rearomatization of the dienyl manganese complexes. Dealkylation is a major reaction pathway with almost all oxidizing agents. With NBS in acetonitrile, the ratio of rearomatization: dealkylation was \( \sim 9:1 \). Demetallation of the arene-manganese complex during the bislactim addition reaction was \( \sim 10\% \) (NMR). Following this analysis, yields of the bislactim addition/aromatization sequence were improved to 50%.

The CFG ring moiety of ristocetin A was made using two different pathways and two different peptide cyclo-coupling methods. From both pathways, two atropisomers were obtained. Cyclic dimer was not found in the reaction mixture and the structure of the two isomers were deduced from NMR NOESY experiments. None of the isomers exactly match to the structure of the CFG ring moiety of ristocetin A, but isomer 1.3.22a (minor product) is closely related to the desired conformation except for the orientation of the amide bond between C- and F-ring units. The yield of cyclization was better with the pathway A (19 and 22\% for 1.3.22a and 1.3.22b, respectively).
which forms the amide bond between the C- and F-ring units, and coupling by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was better than by using active ester methods. Equilibration between the two atropisomers could not be effected at high temperature (160 °C, in DMSO d_6).

**Part II.** Asymmetric synthesis of amino alcohol 2.1.5 was attempted using different strategies. Using asymmetric aminonitrile synthesis (Strecker synthesis), the desired amino alcohol was obtained in 9% yield (e.e. = 73%) but this method was not useful for the preparation of large quantities of amino alcohol. An approach using Sharpless epoxidation was not successful either because of the electron donating ability of the substrate. Eventually the desired amino alcohol was prepared using Evans' electrophilic azidation method. The overall yield was 31% and the enantiomeric excess was greater than 99%.

![Amino alcohol 2.1.5.](image)

Amino alcohol 2.1.5.
Dedication

This work is dedicated to my Parents who love their son
and to my lovely wife, who shared difficult times together.
Acknowledgements

I wish to express my deep thanks to Prof. A. J. Pearson. Not only did he give me his merciful hand when I was at my most difficult points, he also encouraged me patiently through the whole research period especially when progress was slow. His broad and deep knowledge of chemistry is one of my wonders and also a standard that I am aiming at. I also would like to thank Prof. P. Garner for his advise for Part II. The financial support by NIH for the ristocetin A project is greatly appreciated. I thank Ray Shively for his help in sampling for NMR NOESY experiments, for his attempts at X-ray and for proofreading post-doctorate applications. Ann Gelormini helped me already with the proofreading and I owe her a big debt. Alvise Perosa also helped me a lot with my thesis. I thank Kieseung Lee for helpful research discussions and Dr. Jewn-Giew Park for his help for the research and for his compassion. Dr. Seung Han Lee's excellent previous work in this area was a big help to me, also. I also thank my other colleagues, Ping Yeh Zhu and Srinivasan for their friendship and Kieyoung for the moments we had. I thank Jim for his excellent mass spectrometric analysis which enabled me to successfully conclude my research and Dr. Ron in Midwest Center for tandem mass spectrometry.

Finally, I would like to thank to my parents who love their son and who sacrificed greatly for a better life for their son. I thank my brothers, my cousin Dongwoo Shin and my Uncle and Aunt who love me more than I deserve. I wish to express my special thanks to my lovely wife who shared all the difficult times I had.
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LIST OF ABBREVIATIONS USED

Ac     Acetyl
Apt    Attached Proton Test
Boc    tert-Butoxycarbonyl
Cbz    Carbobenzyloxy
Cp     Cyclopentadienyl
m-CPBA m-Chloroperoxybenzoic Acid
DDQ    2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H Diisobutylaluminium Hydride
DIPT   Diisopropyltartate
DMAP   N,N-dimethylaminopyridine
DMSO   Dimethylsulfoxide
DNA    Deoxyribonucleic Acid
E⁺     Electrophile
EDC    1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
FT-IR  Fourier Transform Infrared Spectroscopy
g     grams
h     Hours
HOBT   1-Hydroxybenzotriazole Hydrate
HPLC   High Performance Liquid Chromatography
HRMS   High Resolution Mass Spectroscopy
KHMDS  Potassium Bis(trimethylsilyl)amide
Me     Methyl
MEM    Methoxyethoxymethyl
MHz    Megahertz
min Minutes
mp Melting Point
(R)-MTPA (R)-(+)–α-Methoxy-α-(trifluoromethyl)phenylacetic Acid
(S)-MTPA (S)(-)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid
NBS N-Bromosuccinimide
NCS N-Chlorosuccinimide
NIS N-Iodosuccinimide
NMR Nuclear Magnetic Resonance
NOESY Nuclear Overhauser Enhancement Spectroscopy
Nu Nucleophile
OMe Methoxy
Piv Pivaloyl
RNA Ribonucleic Acid
rt Room Temperature
TFAA Trifluoroacetic Anhydride
THF Tetrahydrofuran
TLC Thin Layer Chromatography
TMS Trimethylsilyl or Tetramethylsilane
t_{ret} Retention Time
Trisyl 2,4,6-Triisopropylbenzenesulfonyl
Triton B N-Benzyltrimethylammonium Hydroxide
TTN Thallium Trinitrate
Preface

Part I. Studies towards a Synthesis of Ristocetin A.
Part II. Asymmetric Synthesis of an Arylglycinol.

Part I. Part I describes studies towards a synthesis of ristocetin A. For a synthesis of ristocetin A, very mild aryl ether bond formation reaction conditions are required because of the base sensitivity of arylglycine chiral centers. Arene-manganese complexes were used for the formation of aryl ether under mild conditions and this method was further utilized in the synthesis of the CFG ring moiety of a ristocetin A model.

In Chapter 1, the general properties of ristocetin A are described, and methods that have been used for the synthesis of related compounds are introduced.

In Chapter 2, synthesis of a protected ristomycinic acid derivative is described. The protected ristomycinic acid has two arylglycine units that are connected via an aryl ether bond, thus representing the potential problems that might occur in a synthesis of ristocetin A. Using the arene-manganese chemistry, however, we successfully synthesized a protected ristomycinic acid, thus demonstrating the feasibility of this method to the synthesis of ristocetin A.

In Chapter 3, we further extended our research to the synthesis of the CFG ring moiety of ristocetin A cyclic peptide model. Aryl ether bond was made following the protocol, and the cyclization was tested by two different connections and two different methods. From each method, we obtained two atropisomers of the cyclic monomer and the structures of these isomers were deduced using mass spectrometry, molecular modeling and NMR NOESY experiments.

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Part II. For the synthesis of quinocarcin, it is necessary to prepare a chiral amino alcohol precursor. The synthesis of the requisite amino alcohol was attempted using three different methods.

Chapter 1 gives a general introduction to the target natural product and synthetic approaches to the amino acids.

In chapter 2, the results of this investigation are discussed. Asymmetric Strecker synthesis using pentapivaloylalactose as an sugar auxiliary did not provide a product in good yield and the product was obtained in low optical purity. Manipulation of the intermediates was difficult. Attempts to use Sharpless epoxidation failed because of the electron donating effect of methyl and methoxy substituent, but the desired amino alcohol was finally made using the Evans asymmetric azidation method. The enantiomeric excess of the product was greater than 99% as determined by NMR.
Part I

Studies Towards a Synthesis of Ristocetin A
Chapter 1

Ristocetin A and its Synthetic Approaches.
1.1 General

The objectives of the work outlined in this chapter are to introduce the general properties of ristocetin A and synthetic approaches to ristocetin A and related compounds.

Following the isolation of the glycopeptide antibiotic vancomycin\(^1\) in 1956 from *Amycolatopsis orientalis*, many compounds which have similar structures were found, including ristocetin A.\(^2\) Not only do these compounds have synthetically challenging structures, they are also clinically useful. Vancomycin is active against gram-positive bacteria which have developed resistance to \(\beta\)-lactam antibiotics, and has been used clinically for 20 years in the treatment of severe staphylococcal infections such as

![Vancomycin](image)

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*Figure 1.1.1 Examples of Vancomycin Type Glycopeptides*
septicemia, pneumonia and wound infections.³

Members of this family include vancomycin, orienticin-A, ⁴ B, C, D; A82846-A, B, and C; ristocetin A,¹⁰¹¹ aricidin,⁵ teicoplanin,⁶ A35512B⁷. Most of these compounds can be divided into two types according to the structure of the "south-east" part of the molecules as shown in figure 1.1.1 and 1.1.2.

![Ristocetin A](image)

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<th>Z</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.4 Ristocetin A</td>
<td>0</td>
<td>OH</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>1.1.5 Teicoplanin</td>
<td>&quot;</td>
<td>H</td>
<td>&quot;</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>&quot;</td>
<td>Cl</td>
</tr>
<tr>
<td>1.1.6 Aricidin</td>
<td>1</td>
<td>OH</td>
<td>H</td>
<td>&quot;</td>
<td>Cl</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Figure 1.1.2 Some Family Members of Ristocetin

The full structure of vancomycin was proposed in 1978 by D. H. Williams and G. M. Sheldrick⁸ based on the X-ray crystallography of its degradation product, CDP-I, NMR (mainly nOe difference experiments), and mass spectrometry. The initial structure had some incorrect assignments because of ill-understood asparagine rearrangements, and was revised by Harris' group in 1983, as depicted in figure 1.1.1, based on chemical transformations.⁹ The structure of ristocetin A was elucidated in
1980\textsuperscript{10} by D. H. Williams' group, mainly based on NMR spectroscopic studies and information obtained from the study of vancomycin. The stereochemistry of the chiral center of the G ring unit was revised in 1985.

According to extensive NMR studies,\textsuperscript{11} these antibiotics bind selectively to the -D-Ala-D-Ala terminus of the mucopeptide precursor for bacterial cell wall biosynthesis, thereby inhibiting cell wall growth which eventually leads to death of the bacteria.

![Figure 1.1.3 Binding Mode of Ristocetin A with D-Ala-D-Ala\textsuperscript{11}](image)

In the case of ristocetin A, the binding energy with the cell wall analogue Ac-D-Ala-D-Ala was estimated\textsuperscript{12} as 7.5 kcal mol\textsuperscript{-1} and it was largely attributed to:

1) hydrogen bonding between the carboxylate (and amide proton) of the substrate and the amide proton and carbonyl of the antibiotic which is strengthened in a hydrophobic environment (also low dielectric constant).

2) compensation of the unfavorable entropy due to restriction of freedom of motion by dehydration of the highly ordered water molecules from the substrate and antibiotics after its binding. Dehydration of the water molecules is also a controlling
factor of the "on-rate" of antibiotics and although the binding energy of ristocetin A is 1.3 kcal mol\(^{-1}\) more favorable than for vancomycin, its rate of binding is 100 times slower\(^{12}\). This is because the rigid ristocetin requires dehydration of the molecule all at once thereby making the activation energy higher than that of vancomycin. Also it is reported\(^{12}\) that the terminal -NH\(_3^+\) group plays an important role at the initial stage of the binding by interacting with -CO\(_2^-\) electrostatically, thus making two molecules approach each other for the next step of hydrophobic binding of -CO\(_2^-\) to the amides in the binding pocket. Vancomycin forms a salt bridge between the leucine methyl ammonium ion and carboxylate which directly leads the substrate into the binding pocket. In the case of ristocetin A, it is not well understood how the dipeptide creeps into the binding pocket after initial coordination between the ammonium ion and carboxylate. The ammonium ion is located outside of the binding pocket and this moiety can not undergo a conformational change because of its rigid structure, in contrast to the case of vancomycin. Still, when this ammonium ion was neutralized or acetylated, it showed significant reduction in the binding rate and energy.

### 1.2 Synthetic Approaches

The construction of synthetic analogues of vancomycin and ristocetin A is a significant challenge. Its key synthetic steps are:

1. Construction of the aryl ether linkage in the presence of temperature- and base sensitive protected aryl glycine units

2. Macrocyclic ring formation.

3. Synthesis of non-proteinogenic amino acid units and their manipulation.
1.2.1 Construction of Aryl Ether Linkage.

Aryl Ether Formation: Low Yield & Racemization  Typically aryl ether bonds are made by the Ullman reaction and this is conducted in refluxing pyridine or nitrobenzene (90 ~ 130 °C) for several hours in the presence of one of various copper reagents.\(^{13}\) Though diaryl ether bond formation reactions are necessary in the synthesis of ristocetin A and other vancomycin family members, the yields of reactions are often affected by the substituents on the ring\(^{14}\) and by the side chains of the starting materials. Yields are generally low (0 ~ 50%). For example, the amino acid side chains of iodophenyglycine seem to decompose during the reaction and no product is obtained (Table 1.1.1, Entry 4). Also racemization of the amino acid chain was observed to a great extent, even in case of phenylalanine.\(^{15}\)

![Chemical structure](image)

\(^{(1)}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>(R^1)</th>
<th>(R^2)</th>
<th>Solvent (°C)</th>
<th>Yield (D:L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>(\text{CO}_2\text{^1Bu})</td>
<td>nitrobenzene (130)</td>
<td>46 (94:6)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CH}_3)</td>
<td>&quot;</td>
<td>&quot;</td>
<td>45 (94:6)</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>&quot;</td>
<td>pyridine (125)</td>
<td>36 (55:45)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>(\text{CH}_2\text{CH(NH\text{^1Boc})CO}_2\text{Bn})</td>
<td>&quot;</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 1.1.1** Examples of Ullman Reaction

However, for simple molecules with appropriate protecting groups, very high yields are obtained under similar conditions as shown in equation 2. Using this
modification, several groups have constructed the aryl ether bond first, and later manipulated the resulting aryl ether to give the requisite amino acids.\(^\text{16}\)

\[
\begin{align*}
\text{O}^\text{Me} & + \text{Br} & \overset{\text{CuO, K}_2\text{CO}_3}{\text{Pyridine}} & \overset{145 \degree \text{C}}{\text{91 \%}} & \overset{}{\text{R} = 4\text{-hydroxyphenyl(methyl)}} & \text{K-13}
\end{align*}
\]

On several occasions, the aryl ether bond has been formed under milder conditions (typically \(0 \degree \text{C} - \text{rt, overnight in MeOH}\)) by thallium trinitrate (TTN)

\[
\begin{align*}
\text{Cl} & + \text{OH} & \overset{1}{}{\text{TTN, 0 \degree \text{C} - \text{rt}}} & \overset{\text{MeOH}}{\text{AcOH}} & \overset{2}{}{\text{Zn, AcOH}} & \text{desired pd 15 \%} & \text{side pd 5 \%}
\end{align*}
\]

\[
\begin{align*}
\text{Br} & + \text{Cl} & \overset{\text{TTN, 0 \degree \text{C} - \text{rt}}}{} & \overset{}{\text{MeOH}} & \overset{43\% \text{Zn, ACOH}}{\text{9 \%}} & \text{16 \%}
\end{align*}
\]

\textbf{Scheme 1.1.1.} Examples of Side Reactions of Aryl Ether Formation Reaction by the TTN Method.
oxidation\textsuperscript{17} of the dibromophenols followed by reduction with Zn or CrCl\textsubscript{2}.

This method seems feasible for synthesis of strained cyclic aryl ethers but yields are generally low. For example, precursors of K-13, OF4949 III and RA-VII were obtained in 15, 18 and 5\% yield though it was improved up to 40 \% by Evans, using CrCl\textsubscript{2} instead of Zn/HOAc in the synthesis of a vancomycin moiety. This reaction often affords reverse addition reaction products (eq. 3),\textsuperscript{17b} and in some cases, a methoxy substituted product was obtained (eq 4).\textsuperscript{17d} Aryl ether synthesis by this method usually require a large excess of TTN, which is often difficult to remove. Yields from the dehalogenation of the reaction product range between 20 \~ 90 \% but for the synthesis of vancomycin and teicoplanin, each of which bear a single chlorine on the aromatic ring, it would be a Herculean task to achieve selective dechlorination.

In several cases, aryl ether bonds were made using the benzoquinone derivatives followed by reduction of the resulting ether to the aromatic ring or by employing a highly activated aromatic ring.

Rama Rao's group used benzoquinones such as 2-bromobenzoquinone\textsuperscript{18} and 2,6-dibromobenzoquinone\textsuperscript{19} to make an ether bond in the presence of KF in DMF (90 °C) and the product was then aromatized and manipulated to the requisite (aryl) amino acid (eq. 5).
In the case of the highly activated 3-bromo-4-nitrobenzaldehyde or 3,5-dibromo-4-nitrobenzaldehyde, the nitro group served also as a surrogate for the o-hydroxy group and using this methodology, K-13 was successfully synthesized.

In Hamilton's ether formation reaction, a highly activated dinitrophenyl tosylate was coupled with an arylxide in pyridine (90 °C) and the product was obtained in 24% yield. Brown et al. have reported an Ullman condensation reaction between aryl iodonium salts and the phenoxide ions. The yields of this reaction were 30-70%, without noticeable racemization.

Concerning preservation of the optical purity of the chiral center of the amino acid side chain, the aforementioned methods were generally useful for the synthesis of K-13 and OF-4949-III owing to the relative stability of the tyrosine moiety to basic conditions (less than 5% racemization but in some cases, complete racemization occurred: see Table 1.1.1, entry 3). However, it is not at all possible to apply these strategies to the synthesis of ristocetin A because of the base sensitivity of the arylglycine moieties. In a study from our laboratory, phenyl glycine unit 1.1.7 was completely racemized in 2h in refluxing pyridine. (For this matter, see Table 1.2.3. in Chapter 2 and Scheme 1.3.7 in Chapter 3). Because of this problem, very mild aryl ether forming reaction conditions are required for the synthesis of ristocetin A.
1.2.2 Macrocyclization Reaction

**Macro Peptide Cyclization** Together with the intramolecular Ullman cyclization, peptide cyclization is an important method in the synthesis of these kinds of molecules. Peptide cyclization is achieved by formation of a good leaving group from the carboxylic acid using one of various activating agents such as DCC (EDC),$^{24}$ C$_6$F$_5$OH$^{25}$ or DPPA.$^{26}$ This is then coupled with free amine. Usually these reactions are performed under high dilution (0.3–8 mM) to prevent dimerization but in some cases of 15- and 14-membered ring construction, dimer was obtained as the sole product irrespective of concentration (see later).

Generally yields of macrocyclization via peptide coupling are not good (in most cases, less than 50 %) and the success of the cyclization depends on ring size, orientation of coupling, the nature of the protecting group on the neighboring amine, substituents on the ring and the coupling method.

For example, in the case of K-13 (17 membered ring),$^{14}$ coupling depended on the protecting group of N$^{15}$ and the substituent on the aromatic ring, both of which were not suspected at first.

![Diagram](image)

**Figure 1.1.4.** Cyclization leading to K-13.
With the N\textsuperscript{15}-Ac group, coupling between C\textsuperscript{14}-N\textsuperscript{13} and C\textsuperscript{11}-N\textsuperscript{10} was not successful but with N\textsuperscript{15}-Boc (= CO\textsubscript{2}Bu), K-13 was obtained in 51 ~ 61% yield via C\textsuperscript{11}-N\textsuperscript{10} coupling. Using C\textsuperscript{14}-N\textsuperscript{13} coupling,\textsuperscript{5} K-13 was also obtained in 57% yield. This was later rationalized by the fact that a 5-membered oxazolidinone ring formation reaction between N\textsuperscript{15}-Ac and activated ester is preferred over the peptide cyclization, thus inhibiting the peptide cyclization as shown in the Scheme 1.1.2. However, in the case of C\textsuperscript{11}-N\textsuperscript{10}, it was not understood why reaction did not occur with the N\textsuperscript{15}-Ac protecting group. Similarly, OF4949-III and IV were prepared through C\textsuperscript{10}-N\textsuperscript{11} amide bond formation to avoid the competing succinimide formation reaction from C\textsuperscript{13}-N\textsuperscript{14} coupling,\textsuperscript{27} or the terminal asparaginyl amine was introduced after cyclization.

Scheme 1.1.2. Attempted 17-Membered Ring Cyclization Reaction.

When there is an electron donating substituent on the aryl ring, "two arms" of the starting material are splayed in opposite directions and the cyclization becomes slow, thus increasing the probability of side reactions.

Macro ring cyclization also depends on the ring size. As opposed to the 17-membered ring, the 16-membered ring formation reaction suffered from very low yields without certain reason as shown in Figure 1.1.5.\textsuperscript{31}
Figure 1.1.5. Several 16-Membered Cyclic Compounds and Cyclization Yield.

This is particularly important because ristocetin A has a 16-membered ring (ABE and BCF ring) and attempted cyclization of the model compound 1.1.8 in our laboratory was not successful.\textsuperscript{28}

In the case of the 14-membered ring, while we were working on this project, Chakraborty's group\textsuperscript{29} reported successful cyclization of the CFG ring moiety of a teicoplanin model using the activated ester method (Scheme 1.1.3). The yield of this

Scheme 1.1.3. Example of a 14-Membered Ring Cyclization Reaction.
reaction was 50% and, curiously, no racemization during the cyclization reaction was reported. The formation of the cyclic dimer was also not observed.

However, in a study on the total synthesis of combretastatin D-2 (15 membered ring)\textsuperscript{13} and bouvardin (14 membered ring included),\textsuperscript{16d} various peptide cyclization methods under high dilution were not successful for the cyclization of 1.1.12 and 1.1.14. In both cases, cyclic dimers were obtained as a major product instead of cyclic monomer.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {Combretastatin D-2};
  \node at (2,0) {\textbf{x}};
  \node at (4,0) {CO$_2$H};
  \node at (3.5,0) {OH};
  \node at (4,1) {\textbf{x}};
  \node at (6,0) {Cyclic Diolide};
  \draw[->] (0.5,0.5) -- (1.5,0.5);
  \draw[->] (2.5,0.5) -- (3.5,0.5);
  \draw[->] (4.5,0.5) -- (5.5,0.5);
\end{tikzpicture}
\end{center}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {1.1.13};
  \node at (2,0) {\textbf{x}};
  \node at (4,0) {NH$_2$};
  \node at (3.5,0) {C$_2$H$_5$O$_2$C$_{14}$};
  \node at (4,1) {\textbf{x}};
  \node at (6,0) {Dimer \ 14 - 56\%};
  \draw[->] (0.5,0.5) -- (1.5,0.5);
  \draw[->] (2.5,0.5) -- (3.5,0.5);
  \draw[->] (4.5,0.5) -- (5.5,0.5);
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.1.4. Attempted Cyclization of a 14- and 15-Membered Ring.}

**Intramolecular Aryl Ether Cyclization.** An intramolecular aryl ether formation reaction is useful as an alternative to the peptide cyclization. In Scheme 1.1.4 shown above, peptide and ester cyclization reactions were not successful for the macrocyclization. Instead, the desired compounds cambrestatin D-2 and 1.1.13 were obtained through intramolecular aryl ether cyclization reactions in 50 and 37% yield, respectively. While applications of this method are made for simple molecules,\textsuperscript{30} oxidative coupling by TTN was successfully done for some complicated molecules under mild conditions. Using this method, the 17-membered ring precursor of K-13
(42%)\textsuperscript{16b} and OF4949-III (18\%) as well as those of the strained 14-membered macrocycle such as bouvardin (5 ~ 9\%)\textsuperscript{16d} and piperazinomycin (5 ~ 19\%)\textsuperscript{16a} were obtained. The problematic 16-membered ring system\textsuperscript{16e} of vancomycin was also obtained in 40~48\% yield using the TTN method followed by reduction with CrCl\textsubscript{2}.

### 1.2.3 Amino Acid Synthesis.

Syntheses of chiral amino acids are well known, and some of the very important amino acids are commercially available at reasonable prices. However, in the construction of glycopeptides, it is often necessary to build one chiral amino acid moiety in the presence of another (in case the Ullman reaction is performed at the first stage) which may be prone to racemization. Evans' group successfully managed this problem in their synthesis of K-13. They built chiral centers consecutively using the electrophilic azidation method. Though the reaction employs KHMDS at -78 °C, less than 1\% racemization was reported (Scheme 1.1.5).

![Scheme 1.1.5. Example of Amino Acid Synthesis by Evans.](image-url)
In another approach to OF-4949-III,\textsuperscript{31} optically pure (d.e > 98\%) amino ester was also obtained from the aldehyde moiety (Scheme 1.1.6). The glycine equivalent was introduced using protected dimethoxyphosphoryl glycinate and subsequent hydrogenation with the chiral catalyst [Rh(DIPAMP)]\textsuperscript{+} afforded the protected diamino acid in quantitative yield in the presence of a benzylxycarbonyl protecting group. Interestingly, when a similar compound 1.1.18 was subjected to hydrogenation with Pd/C (10\%), diastereomers were obtained in 7:3 ratio and they were separated at a later stage (Scheme 1.1.6).

![Diagram](image1)

Scheme 1.1.6. Protected Amino Acid Synthesis by Asymmetric Hydrogenation.

In an approach to L,L-isodityrosine,\textsuperscript{32} Boger converted the resulting tert-butyl ester to its alkyl halide which was reacted with Na bislactim anion at 0 °C to afford the bis-lactim adduct in 90 \% d.e. The resulting adduct was then hydrolyzed into its methyl ester under acidic conditions (Scheme 1.1.7).
Scheme 1.1.7. Amino Acid Acid Synthesis via a Bislactim Addition Reaction.

In cases when a bromoquinone was used to construct the aryl ether bond, the unusually high yield (78-80%) is offset by tedious multistep sequences and further, by a meager diastereomeric excess (62%) in a subsequent Sharpless asymmetric dihydroxylation. The resulting diol was then substituted with azide to afford the amino acid equivalent (Scheme 1.1.8).

Scheme 1.1.8. Protected Amino Acid Synthesis by Dihydroxylation.
Finally, in the synthesis of the 14-membered ring of teicoplanin, Chakraborty and associates built the amino ester starting from the aldehyde using an asymmetric Strecker synthesis.\textsuperscript{10} Diastereoselectivity of the cyanide introduction reaction was 46-78\%. The resulting amino nitrile was converted to an ethyl ester and the auxiliary was oxidatively cleaved to provide the amino ester (Scheme 1.1.9).

![Scheme 1.1.9. Protected Amino Acid Synthesis by Asymmetric Strecker Synthesis.](image)

1.3 Conclusions.

Ristocetin is a molecule that belongs to a vancomycin family which has clinical use. This molecule is very difficult to make using conventional reactions because of the harsh (basic) conditions required for aryl ether bond synthesis and base sensitivity of the aryglycine moiety. To overcome these problems, in some cases, TTN was used for milder aryl ether bond formation. However, this method suffered a low yield and side reactions. In other approach, aryl ether bonds are made first in the absence of amino acid moieties and the glycine moiety was introduced later. These syntheses,
however, suffered tedious multistep sequences for the amino acid moiety construction and often, low diastereomeric selectivities during the construction of the amino acid moieties.

For an efficient synthesis of this type of molecules, it is essential to develop a methodology to build the aryl ether bond in the presence of amino acid moieties without affecting the optical purity. We approached this problem using our arene-manganese chemistry as described in the next two chapters.
1.4 References and Notes


Chapter 2

Synthesis of a Protected Ristomycinic Acid
2.1 General.

The objective of the work outlined in this chapter is to effect the synthesis of a protected ristomycinic acid derivative in optically pure form (1.2.21, p. 57).

It is widely known that transition metals can activate coordinated arenes and make it possible for the arene to undergo various useful reactions under mild conditions. One of the useful reactions is the displacement of halide by various phenoxide nucleophiles which can provide aryl ether bonds. The reactivity of the coordinated arene largely depends on the metal (e.g. existence or not of a positive charge) and its ancillary ligands. For example,¹ charged arene-manganese complexes are more reactive than neutral arene-chromium complexes. Arene-manganese complexes are also more reactive than the 2,4-dinitrochlorobenzene (eq. 1).

\[
\text{Mn}^*(\text{CO})_3 \quad \text{Fe}^*\text{Cp} \quad \text{O}_2\text{N} \quad \text{Cl} \quad \text{Cr}^*(\text{CO})_3
\]  

Using this advantage, Pearson et al. successfully made aryl ether bonds under very mild conditions.² Using the protected trihydroxy benzyl alcohol 1.2.1, the unsymmetrical triaryl diether 1.2.2 could be made successfully, as would be required in a synthesis of ristocetin A.

\[
\text{HO} \quad \text{O}_2\text{N} \quad \text{Cl} \quad \text{CH}_2\text{OH} \quad \text{OBn}
\]  

1.2.1

1. P., H₂C\text{OCl}, CH₃CN, rt, 18 h

\[
\text{A} \quad \text{B} \quad \text{C} \quad \text{Me}
\]  

1.2.2

2. P., H₂C\text{OCl}, CH₃CN, rt, 18 h
The scheme 1.2.1 shown below is a retrosynthetic analysis of a model compound structure of ristocetin A. Unsymmetrical diaryl ethers could be constructed using the same protocol shown in equation 2 and peptide cyclization could provide the desired 16-membered ring. However, under no circumstances was it possible to introduce the

Scheme 1.2.1. Retrosynthetic Analysis of a Model Compound of Ristocetin A.
manganese tricarbonyl onto a protected aryl amino acid to make an arene-manganese complex such as 1.2.4 and 1.2.5. Although it was possible to prepare the chromium complex 1.2.7, this was insufficiently reactive to allow the formation of the aryl ether bonds. (Unpublished results of F. Gouzuoles, this laboratory)

Scheme 1.2.2 Synthesis of a Chromium Complex 1.2.7 and Attempted Aryl Ether Bond Synthesis.

Scheme 1.2.3 Retrosynthetic Analysis of a Model Compound of Ristocetin A.
Another strategy to construct the aryl ether bonds is shown in Scheme 1.2.3. The aryl ether bond could be made using dihaloarene-manganese complex 1.2.8 and construction of the glycine side chain could be made using the chiral glycine enolate equivalent such as Schöllkopf's bislactim anion. The addition of this anion is expected to be highly regioselective, because of the presence of two meta directing groups. It is not possible, however, to make a dihaloarene-manganese complex such as 1.2.8.\textsuperscript{18}

In contrast to the case of 1.2.8, the dichloroarene-FeCp complex 1.2.10 could be prepared easily in large quantity (Scheme 1.2.4).\textsuperscript{4} The arene-FeCp complex afforded di- and triaryl ether intermediates by reaction with aryloxides but further manipulation of this product to form the "upper half" was not easy because of difficulties in the rearomatization step from 1.2.12 to 1.2.13.

\begin{center}
\includegraphics[width=0.7\textwidth]{Scheme_1.2.4.png}
\end{center}

\textbf{Scheme 1.2.4.} Application of Fe-Cp Complex in the Synthesis of Ristocetin A\textsuperscript{4}

Eventually, it was found possible to make a diaryl ether amino acid by the reaction of the haloarene-manganese complex such as 1.2.14 with the phenoxide, 1.2.15, followed by construction of the asymmetric glycine side chain. Using this methodology, a deoxyristomycinic acid derivative 1.2.16 which possesses a structure representative of ristocetin A, was successfully made.\textsuperscript{5}
Scheme 1.2.5 Utilization of Chloroarene-Manganese Complex in the Synthesis of a Deoxyristomycinic Derivative.

Later, it was also found to be possible to introduce Ru\(^{+}\)Cp onto a protected chlorophenylalanine and the complex (1.2.17) afforded the aryl ether 1.2.19 successfully when reacted with the phenoxide of 1.2.18. Unfortunately, macrocyclization of 1.2.19 which resembles the ABE ring of ristocetin A failed under various conditions.

Scheme 1.2.6. Application of Arene-Ru(+) Complex in the Synthesis of Aryl Ether and Attempted 16-Membered Ring Macrocyclization.
Given that failure, we approached the construction of molecules related to ristocetin A beginning with the synthesis of the 14-membered CFG ring moiety in the hope that we might control the entropy (or conformation) of the bicyclic precursor for the synthesis of the BCFG ring system by a preorganization.

To probe the applicability of our approach to the synthesis of the CFG ring moiety, the synthesis of a protected ristomycinic acid was attempted first, to identify potential difficulties in a synthesis of ristocetin A.

![Scheme 1.2.7. Ristocetin A and Ristomycinic Acid.](image)

For the synthesis of the ristomycinic acid, phenol 1.2.24 was coupled to the manganese complex 1.2.23 and the chiral glycine enolate equivalent was introduced onto the diaryl manganese complex 1.2.22.

The main goals of the synthesis are: (1) preservation of the optical purity of the phenol 1.2.20 and optimization of yield during the aryl ether bond formation; (2) assessment of the diastereoselectivity of the chiral glycine side chain introduction reaction; (3) preservation of the optical purity of the G ring chiral center, and (4) rearomatization of the resulting dienyl-manganese complex with an oxidizing agent such as NBS.
Scheme 1.2.8. Retrosynthetic analysis of a protected restomycinic acid.

2.2 Synthesis of Protected Ristomycinic Acid

2.2.1 Improved Synthesis of Arene-Mn(+) Complex 1.2.23. Previously, preparation of manganese complex 1.2.23, which represents an F-ring precursor for ristomycinic acid, was accomplished in 47% yield using Mn$_2$(CO)$_8$Cl$_2$. An attempted synthesis with Mn(CO)$_5$Br-AlCl$_3$-heat resulted in no yield and only 8% yield was obtained with Mn(CO)$_5$Br-AgBF$_4$. It was, however, found that the requisite complex could be obtained in 76% yield using Mn$_2$(CO)$_{10}$ and tetrafluoroboric acid in trifluoroacetic anhydride (reflux, 16 h) with two condensers in tandem. Although complexation with Mn$_2$(CO)$_8$Cl$_2$ afforded better yield in shorter time (HBF$_4$, TFA anhydride, reflux, 3 h, 90%, see later for the improved yield) than the reaction with Mn$_2$(CO)$_{10}$, this was made in turn from Mn$_2$(CO)$_{10}$ using toxic chlorine gas and CS$_2$. The net yield of the two methods were 77 and 76% respectively and the method which used Mn$_2$(CO)$_{10}$ was mainly used for the complexation. It should be noted that the yields using this method are related to the amount of material which escapes the reaction pot during the reflux. Most importantly when two condensers were used in tandem, the yield was increased from 12% to 86% (Table 1.2.1, entry 2 vs 3).
Scheme 1.2.9. Arene-Manganese Complex Formation Reaction.

Limiting amounts of HBF$_4$ and trifluoroacetic anhydride reduced the yields (entry 3 vs 4 and 5 vs 6). Also, it was unnecessary to use a large excess of arene and 2.2 equivalents of the arene 1.2.25 was sufficient.

Table 1.2.1. Arene-Manganese Complex Formation Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>Arene (equiv)</th>
<th>Mn-Carboxyls</th>
<th>TFAA</th>
<th>HBF$_4$</th>
<th>Time (h)$^a$</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzene (22)</td>
<td>Mn(CO)$_5$Cl</td>
<td>140</td>
<td>15</td>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>1.2.25 (2.9)</td>
<td>Mn$_2$(CO)$_8$Cl$_2$</td>
<td>140</td>
<td>17</td>
<td>3</td>
<td>12$^b$</td>
</tr>
<tr>
<td>3</td>
<td>&quot; (2.9) &quot;</td>
<td>&quot;</td>
<td>140</td>
<td>30</td>
<td>3</td>
<td>86$^c$</td>
</tr>
<tr>
<td>4</td>
<td>&quot; (2.2) &quot;</td>
<td>&quot;</td>
<td>58</td>
<td>14</td>
<td>3</td>
<td>52$^c$</td>
</tr>
<tr>
<td>5</td>
<td>&quot; (2.2) &quot;</td>
<td>Mn$<em>2$(CO)$</em>{10}$</td>
<td>140</td>
<td>30</td>
<td>16</td>
<td>76$^c$</td>
</tr>
<tr>
<td>6</td>
<td>&quot; (2.2) &quot;</td>
<td>&quot;</td>
<td>141</td>
<td>7</td>
<td>16</td>
<td>0$^c$</td>
</tr>
</tbody>
</table>

$^a$ all reactions were done under reflux. $^b$ single condenser was used. $^c$ Two condensers were used in tandem.
2.2.2 Preparation of 3-Hydroxy-4-methoxyphenylglycine Derivatives (1.2.24).

The requisite arylglycine 1.2.24 was prepared as shown in Scheme 1.2.10 (p.34), using the Evans asymmetric azidation procedure\(^9\) to introduce the amino group.

Isovanillin 1.2.26 was protected as its benzyl ether 1.2.27, and this was homologated to the arylacetic acid 1.2.29 via the methylsulfinyl sulfide derivative 1.2.28. Ethanolysis of the sulfinyl complex is normally performed under acidic conditions to provide an ethyl ester, but in the case of 1.2.29, acidic hydrolysis gave mixtures of arylacetic acid 1.2.29 and ethyl/thiomethyl aryl acetates. Subsequent hydrolysis of the mixture in refluxing aqueous KOH afforded the aryl acetic acid 1.2.29 in 48\% yield. This approach, however, is better than the classical Arndt-Eistert homologation which yielded the same product in 24 \% yield over 4 steps (eq. 3).

![Chemical Reaction Diagram](image)

Conversion of 1.2.29 to the imide 1.2.30, using the mixed anhydride method, proceeded without problem and azidation of the imide gave 1.2.31 in 90\% yield. The diastereomeric excess was 92\% based on the integration of the H-2 resonance (ArCHN3) in the \(^1\)H NMR spectrum of the crude product and pure diastereomer was obtained in 71\% yield by crystallization from ether. In this reaction, transformation of the triazine adduct 1.2.35 to the azidoimidate\(^10\) 1.2.31 (eq. 4, p. 35) was sensitive to the amount of acid. The best yield was obtained using 1.3 eq of AcOH (Table 1.2.2).
Scheme 1.2.10. Preparation of 3-Hydroxy-4-Methoxyphenylglycine Derivatives and Determination of its Enantiomeric Purity.
With 6 eq. of AcOH, the triazine intermediate 1.2.35 was obtained in 8% yield along with 1.2.31 (61%) and with 10 eq. of AcOH, triazine decomposed into intractable compounds. Treatment of a 1:1 mixture of triazine 1.2.35 and azidoimidate 1.2.31 with 8 eq of AcOH at rt (4~5 h), however, did not cause any changes. With Me₄NOAc a mixture of intractable compounds was obtained. The diazo compound 1.2.36 was not observed in our reaction product mixture.

![Chemical structure](image)

Table 1.2.2. Influence of AcOH on the Decomposition of Triazine 1.2.35

<table>
<thead>
<tr>
<th>Entry</th>
<th>AcOH (eq)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.0</td>
<td>27</td>
<td>61</td>
<td>+ 8% 1.2.35</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>48</td>
<td>0</td>
<td>intractable materials</td>
</tr>
<tr>
<td>3</td>
<td>1.3</td>
<td>3</td>
<td>90</td>
<td>92% d.e.</td>
</tr>
</tbody>
</table>

Hydrolysis of 1.2.31 was accomplished with 88% e.e. using lithium hydroxide at 0 °C and the resulting mixture of acid and chiral auxiliary was subjected to Fischer esterification. The yield of the methyl ester 1.2.32 was 92% and the chiral auxiliary was recovered intact. On one occasion, methylation of the hydrolyzed carboxylic acid with diazomethane (~ 12 eq) was tried but afforded the methyl ester (34 %) along with a side product (14%) which lacks the methine proton at C₂. The IR
spectrum did not show any sign of azide functionality but instead showed an imine signal (1675 cm\(^{-1}\)). It was tentatively assigned as the α-imino methyl ester \(\text{I.2.38}\).

\[
\begin{array}{c}
\text{MeO} \quad \text{N}_3 \\
\text{I.2.37} \\
\text{CH}_3\text{N}_2(12 \text{ eq}) \quad \text{ether} \\
\text{MeO} \quad \text{N}_3 \\
\text{I.2.32} \quad \text{34\%} \\
\text{MeO} \quad \text{CO}_2\text{Me} \\
\text{I.2.38} \quad \text{14\%} \\
\end{array}
\]

(5)

Treatment of \(\text{I.2.32}\) with hydrogen over 10% palladium on carbon, in the presence of Boc anhydride, gave \(\text{I.2.24}\), resulting from hydrogenolysis of the benzyl ether, reduction of azide, and \textit{in situ} protection of the so formed amine.

![Figure 1.2.1. \(\text{\textsuperscript{19}}\text{F}\)-NMR Spectra of Compounds I.2.34a and I.2.34b (p.p.m. vs CFC 13)](image)

To determine the optical purity of azido methyl ester \(\text{I.2.32}\), the azide group was selectively reduced to the amino ester \(\text{I.2.33}\) using triphenylphosphine and water, and
it was converted to the MTPA amide derivatives\textsuperscript{11} \textbf{1.2.34a} and \textbf{b}, by treatment of the amino ester with (R) and (S)-MTPA, respectively in the presence of carbodiimide coupling reagents. The \textsuperscript{19}F NMR spectra of the diastereomeric amides \textbf{1.2.34a} and \textbf{b} indicated a ratio of \textit{ca} 13:1, corresponding to an enantiomeric excess of \textit{ca} 85\% for \textbf{1.2.32}. Thus, there is a small amount of racemization during the steps leading from \textbf{1.2.31} to \textbf{1.2.32}, which most likely occurs during the hydrolysis of the oxazolidinone. The use of the more nucleophilic, less basic lithium hydroperoxide in this step did not lead to any significant improvement (93\% yield, 89\% e.e.).

\begin{center}
\textbf{Scheme 1.2.11. At tempted Synthesis of 1.2.39 from 1.2.31.}
\end{center}
To overcome the racemization, a synthesis of the Boc protected amine 1.2.39 of which the chiral center is relatively stable to the basic conditions\(^\text{15}\) was attempted. Unexpectedly, reduction of 1.2.31 with hydrogen over 10% Pd/C afforded 1.2.41 which resulted from the reductive cleavage at the benzylic position of oxazolidinone ring, with subsequent decarboxylation. With 5% Pd/C, the desired product 1.2.39 was obtained along with 1.2.42 but because of low yield (39%), it was not pursued further (Scheme 1.2.11)

2.2.3 Diaryl Ether Formation Reaction.

a) Racemization of the Chiral Center. The problem of racemization during the diaryl ether synthesis is one of the most important issues for the synthesis of macrocyclic compounds with structures similar to ristocetin A and other members of vancomycin family. Because of the necessity for generating the phenoxide ion with minimal racemization, mild and bulky sodium 2,6-di-tert-butylphenoxide, which was generated from 2,6-di-tert-butylphenol and NaH, was employed in a previous study for the deprotonation of 1.2.44 instead of employing a stronger base\(^\text{12}\).

\[
\begin{align*}
\text{MeO} & \quad \text{N}^\text{H} & \quad \text{Bu}^\text{t-4} & \quad \text{Na} \\
\text{R} & \quad \text{H} & \quad \text{Na} & \quad \text{R} \\
1.2.24 & \quad R = \text{OMe} & \quad 1.2.44 & \quad R = \text{H} \\
1.2.44 & \quad P = \text{Boc} & \quad 1.2.44 & \quad P = \text{Cbz} \\
\end{align*}
\]

\[\text{Sodium 2,6-di-4-Butylphenoxide} \quad \text{Bu}^\text{t-4} \quad \text{Bu}^\text{t-4} + \quad \text{Na} \quad \text{Bu}^\text{t-4} \quad \text{Bu}^\text{t-4}
\]

(6)

However, it was not basic enough to deprotonate hydroxyphenylglycine 1.2.24, presumably, because of hydroxyphenylglycine’s reduced acidity due to the electron
donating substituent (eq. 6). Therefore, the phenoxide was generated using NaH and racemization of the chiral center of phenylglycine 1.2.20 was investigated as shown in Table 1.2.3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Base</th>
<th>Temp</th>
<th>Optical Rotation ([α]D)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>([α]D)</td>
<td>(eq)</td>
<td>(°C)</td>
<td>min ([α]D, %)</td>
</tr>
<tr>
<td>1 b,c</td>
<td>1.2.45a (-155°)</td>
<td>pyridine (solv.)</td>
<td>reflux</td>
<td>120 (-0.1°, 50%)</td>
</tr>
<tr>
<td>2 b,c</td>
<td>&quot;</td>
<td>NaH (0.8)</td>
<td>rt</td>
<td>30 (-113°, 14%)</td>
</tr>
<tr>
<td>3 b,c</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
<td>30 (-154°, 0%)</td>
</tr>
<tr>
<td>4 b,c</td>
<td>1.2.45b (-104°)</td>
<td>&quot;</td>
<td>rt</td>
<td>30 (-0.3°, 50%)</td>
</tr>
<tr>
<td>5 b,c</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
<td>30 (-86°, 8.7%)</td>
</tr>
<tr>
<td>6 d</td>
<td>1.2.24 (-124°)</td>
<td>NaH (1.1)</td>
<td>rt</td>
<td>32 (-95°, 5.1%) 60 (-76.4°, 17.0%)</td>
</tr>
<tr>
<td>7 d</td>
<td>&quot;</td>
<td>&quot;</td>
<td>0</td>
<td>30 (-117°, 2.9%) 60 (-108.8°, 6.2%)</td>
</tr>
<tr>
<td>8 d</td>
<td>&quot;</td>
<td>&quot;</td>
<td>-18°</td>
<td>30 (-123.9°, 0 %) 60 (-118.3°, 2.3%)</td>
</tr>
<tr>
<td>9 d</td>
<td>Bu4NF</td>
<td>0</td>
<td></td>
<td>30 (-102.6°, 8.7%) 60 (-96.5°, 11.2%)</td>
</tr>
</tbody>
</table>

a) Percentage of epimerization. Calculation was based on the optical rotation. b) Performed by Dr. Seung-Han Lee. c) Performed in THF. d) Performed in CH2Cl2 by Hunwoo Shin. e) at this temperature, solubility of the starting material was not good.

Racemization of 1.2.45a in a refluxing pyridine, the usual conditions for the Ullman reaction, was complete in 2 h thus demonstrating the base sensitivity of an
arylglycine substrate and therefore the need for a mild coupling procedures. Boc protected material was found to undergo far less racemization than the acetyl derivative under basic conditions. Moreover, the electron donating methoxy substituent of the G-ring (ristocetin A lettering) seems to reduce the tendency toward racemization, presumably by destabilization of the intermediate enolate anion (entry 2 vs 6). Racemization was dependent on the temperature and simply by lowering the temperature from rt to 0 °C, the degree of racemization was halved (entry 6 vs 7). However, reaction at lower temperatures (-18 °C) was not desirable because of the poor solubility of the arylglycine. Thus, deprotonation of the phenol at 0 °C was chosen as optimum. It should be noted that fluoride ion is quite basic and caused 9% racemization at 0 °C. Thus although there are many useful silicon based protecting reagents, we could not employ them for the protection of the amine or carboxylic moieties. During the synthesis of the CFG moiety of teicoplanin which is very close to the CFG moiety of ristocetin A, Chakraborty’s group\textsuperscript{13} employed a trimethylsilyl ethyl ester as a carboxylic acid protecting group and deprotected this protecting group using fluoride [Bu\textsubscript{4}NF (1.2 eq), rt, 0.5 h]. Curiously, no racemization was reported in this case.

b) Formation of Diaryl Ether Linkage. The phenoxide of 1.2.24, generated by reaction with 0.95 - 0.98 equivalents of sodium hydride to avoid the presence of excess base, was reacted with 1.2.23 in ice cold methylene chloride in the presence of silver tetrafluoroborate in the dark to afford the diaryl ether complex 1.2.46. Silver tetrafluoroborate was used to remove chloride which can accelerate competing decomplexation of the arene-Mn(CO)\textsubscript{3} system and the presence of the AgBF\textsubscript{4} does not appear to accelerate the coupling reaction. To minimize the possibility of solvent acting as a ligand, the reaction was performed in the dark. Tetrafluoroborate salts of
diaryl manganese complexes are known to be difficult to crystallize, so the product was converted to its PF$_6^-$ salt by treatment with aqueous NH$_4$PF$_6$. It was precipitated from pentane to afford a microcrystalline product **1.2.46** in 79% yield from **1.2.24**.

![Chemical reaction diagram]

**Scheme 1.2.12.** Diaryl Ether Formation Reaction and Determination of Enantiomeric Purity.

In order to check for racemization during the coupling reaction, the diastereomeric mixture of complex **1.2.46** was demetalated in acetonitrile to give the diaryl ether **1.2.47**. This was converted to its MTPA amides **1.2.48a** and **1.2.48b** by removal of the Boc group followed by coupling of the amino ester with (R) and (S)-MTPA, respectively. The $^{19}$F NMR spectra of the diastereomeric amides (Figure 1.2.2.) reveals that enantiomer ratio for **1.2.48a** and **b** is ca 22:1. This is somewhat better than the enantiomeric excess recorded for **1.2.32** (ca 13:1), and it was tentatively attributed to partial fractionation during the isolation of **1.2.46**. The results are strongly indicative, however, that no racemization occurs during the aryl ether-
forming step. Demetallated product 1.2.47 is also obtained in the next step during the introduction of glycine side chain and its optical purity was measured using the same protocol (see later).

![Figure 1.2.2. 19F NMR Spectra of Compounds 1.2.48a and b (p.p.m. vs CFCl3).](image)

c) **Solvent Effect in the Synthesis of the Diaryl Ether Linkage.** During the coupling reaction, it was often observed that the diaryl ether product was demetalated by the interference of solvent. Initially, coupling between 1.2.49a/b and 1.2.50 was
performed in acetone. Though acetone is known to decomplex arene-metal complexes, its use was necessary due to the low solubility of the 1.2.50 in other solvents. The short reaction time and low temperature that is required (5 min, 0 °C) alleviated the decomplexation problem to a large extent. However, arene-manganese complexes with electron donating substituents such as 1.2.51, react much more slowly and decomplexation is a serious problem. Though this problem was nicely solved by employing AgBF₄ to trap the chloride ion (entry 2 vs 3), the reaction was very poor with 1.2.23. In our case, acetone and THF seemed to cause demetalation (NMR and

**Table 1.2.4. Solvents Effect on Aryl Ether Formation Reaction**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenol</th>
<th>ArMn⁺(CO)₃</th>
<th>Phenoxide generation</th>
<th>Reaction conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1.2.49a</td>
<td>1.2.50</td>
<td>NaH, 0.5 h, rt, THF</td>
<td>10 min, acetone, 0 °C-rt</td>
<td>91</td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>1.2.51</td>
<td>NaH, 0.5 h, 0 °C, THF</td>
<td>&quot;</td>
<td>0b</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>&quot;</td>
<td>5 min, acetone, 0 °C, AgBF₄, dark</td>
<td>78</td>
</tr>
<tr>
<td>4c</td>
<td>1.2.49b</td>
<td>1.2.23</td>
<td>NaH, 0.3 h, 0 °C, THF</td>
<td>&quot;</td>
<td>82</td>
</tr>
<tr>
<td>5.</td>
<td>1.2.24</td>
<td></td>
<td>&quot;</td>
<td>&quot;</td>
<td>0d</td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td>NaH, 0.5 h, 0 °C, CH₂Cl₂ CH₂Cl₂, 0 °C, 1 h, AgBF₄/dark</td>
<td>93</td>
<td></td>
</tr>
</tbody>
</table>

a) Performed by Dr. F. Gouzoules. b) Demetallated diaryl ether was obtained. c) Performed by Dr. Seung-Han Lee. d) 1.2.23 was recovered in 30% yield.

![Chemical Structures](image)
TLC) but dichloromethane caused no demetallation and the arene-Mn(CO)₃ was quite soluble at 0 °C in this solvent. Using this solvent, the aryl ether complex was obtained in 93% yield.

2.2.4. Addition of the Chiral Glycine Enolate Equivalent.

a) Problems of the Chiral Enolate Addition Reactions. Introduction of the glycine side chain onto 1.2.46 was accomplished using Schöllkopf's chiral glycine enolate equivalent 1.2.53.³ This nucleophile gave a mixture of diastereomeric dienyl-Mn(0) complexes 1.2.54 which was oxidatively demetalated to produce the rearomatized compound 1.2.55.

Scheme 1.2.13 Introduction of Bislactim Side Chain and Rearomatization.
In a previous study, this coupling reaction was somewhat capricious, often giving low yield (35%\textsuperscript{25} - 65%\textsuperscript{14} over 2 steps) of the desired product. In the present case, the yield was worse and the product was repeatedly obtained in unacceptable 3 ~ 18% yield. In this reaction, demetalation, which presumably occurs by attack of the nucleophile at a carbonyl ligand followed by disengagement of the arene with concomitant CO deinsertion, was considered as a main side reaction. In fact, demetalated product 1.2.47 was obtained as the major product.

Careful inspection of the TLC of the reaction mixture prior to NBS treatment showed only traces of the demetalated product at this stage along with much starting material, suggesting incomplete reaction. Completion of the nucleophile addition reaction seemed to be related to the protonation of the bislactim anion by amide protons but it was still not successful with excess of bis-lactim anion (4 eq, entry 6 of Table 1.2.5) or by stirring at higher temperature (-78 °C, entry 5). Also, the use of different solvents or tetramethylethlenediamine or CuI (to form a softer cuprate reagent) did not improve the yield.

Eventually, it was found that the protocol used for generating the lihtiated bislactim anion was critical for the success of this reaction. Due to the low solubility of the complex in cold (-100 °C) THF, it was helpful to chill a solution of the complex in THF to the requisite temperature, and add this to the solution of the bislactim, rather than to add the complex as solid. Treatment of 1.2.53 with BuLi in THF at -78 °C for 2.8 h prior to the reaction with 1.2.46 in THF solution gave best yields (44%).

Later, however, it was also found that the reverse reaction (dealkylation) occurs during the oxidation reaction using NBS, as is also the case for dienyl-FeCp complexes (Scheme 1.2.14).\textsuperscript{15} According to NMR analysis, demetallation of
Table 1.2.5. Reaction Condition for Bis lactim Addition Reaction and Yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArMn⁺</th>
<th>Bislactim anion&lt;sup&gt;a&lt;/sup&gt; (eq, stirring time)</th>
<th>Reaction Condition</th>
<th>Yield&lt;sup&gt;b&lt;/sup&gt; 1.2.55:1.2.47</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2.46</td>
<td>2.1, 25 min</td>
<td>-78 °C, 30 min</td>
<td>1:3</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>2.0, 2.8 h</td>
<td>-100 °C, 1 h</td>
<td>1(44%)&lt;sup&gt;c&lt;/sup&gt;:1</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>2.0, CH₂Cl₂, 45 min</td>
<td>-90 °C, 4.5 h</td>
<td>s.m. only (82%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>2.0, 20 min, TMEDA (1.8 eq)</td>
<td>-100 ~ -90 °C, 1 h</td>
<td>1.2.47 only&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>3.0, 1 h.</td>
<td>-95 °C, 1 h ~ -78 °C, 1 h</td>
<td>1:4</td>
</tr>
<tr>
<td>6</td>
<td>&quot;</td>
<td>3.9, 3 h</td>
<td>-120 ~ -100 °C, 1 h</td>
<td>1:3</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&quot;</td>
<td>2.2, 3.8 h</td>
<td>-100 ~ -95 °C, 30 min</td>
<td>~2(25%)&lt;sup&gt;c&lt;/sup&gt;:1</td>
</tr>
<tr>
<td>8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&quot;</td>
<td>2.8, 4.5 h</td>
<td>&quot;</td>
<td>&gt;1(35%)&lt;sup&gt;c&lt;/sup&gt;:1</td>
</tr>
<tr>
<td>9</td>
<td>1.2.56&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.0, 3 h</td>
<td>&quot;</td>
<td>1.2.58&lt;sup&gt;a&lt;/sup&gt;:1.2.59&lt;sup&gt;a&lt;/sup&gt;:1.2.60 &lt;br&gt; a:1.2.61&lt;sup&gt;a&lt;/sup&gt; = 11:18:9:0</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>2.0, 70 min, then Cul (1.9 eq), 70 min</td>
<td>&quot;</td>
<td>2:2:1:0</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td>2.0, 3 h</td>
<td>&quot;</td>
<td>1.5:1:0:1.2</td>
</tr>
</tbody>
</table>

<sup>a</sup> all reaction was done at -78 °C.  
<sup>b</sup> ratio was determined by NMR (300MHz) based on the integration of methyl group on F-ring (Ristocetin A lettering).  
<sup>c</sup> isolated yield.  
<sup>d</sup> 1.2.47 was obtained before oxidation.  
<sup>e</sup> Arene manganese complex (30 ~ 120 mg) was dissolved in cold THF (2~5 mL) before addition and immediately cooled to -100 °C. Otherwise, solid was added to the lithiated bis lactim solution (vice versa).
the complex was negligible (~10%) which is consistent with TLC observation and a large amount (~35%) of arene-manganese complex 1.2.56a/b remained unreacted. Unreacted starting material was completely recovered in 38–46% yield by precipitation from pentane. With various oxidizing agents, dealkylation of 1.2.57a to

![Chemical Structures](image)


return 1.2.56a was the exclusive pathway as shown in the Figure 1.2.3. The best result was obtained with NBS/CH₃CN at rt. At 0 °C, similar results were obtained. A CH₃CN/10% DMSO mixture did not make any difference at rt. Employment of 0.5–0.7 equivalents of NBS did not complete the reaction. At rt, 1.2 equivalents of
Figure 1.2.3. Oxidation of Dienyl-Manganese Complex 1.2.57a by Various Methods. 1H-NMR Spectra of the Product Mixtures.
NBS did not cause side reactions (only traces are seen in the NMR spectrum) but aromatization at 45 °C with 1.2 equivalents of NBS showed an unknown peak (see figure 1.2.3) which is, presumably, a brominated product on the F-ring unit (ristocetin lettering) which is activated by two electron donating groups. During the CFG-ring model study to be discussed in Chapter 3, 1.2 equivalents of NBS, 0 °C was chosen as a standard reaction protocol.

Table 1.2.6. Oxidation of Dienyl-Manganese Complex 1.2.57a/b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>s.m.</th>
<th>Oxidation method</th>
<th>Results a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2.57a</td>
<td>KMnO₄, acetone, rt, 30 min.</td>
<td>1.2.57a: 1.2.58a: 1.2.59a: 1.2.60a = 3:0:0:1:0</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Ce(NH₄)₂(NO₃)₆, acetone, CH₃CO₂Na, rt, 2 h</td>
<td>0.2:0:0:1:0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>DDQ, CH₃CN, rt, 1 h</td>
<td>0:trace:0:1:0</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>NCS, Et₂O:THF = 3:1, rt, 1 h</td>
<td>1.7:0:0:1:0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>NBS, Et₂O:THF = 3:1, rt, 1 h</td>
<td>0.13:0.88:0.5:8:trace</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>NBS, CH₃CN, 0 °C, 40 min</td>
<td>trace:2.6:1.3:1:trace</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>NBS, CH₃CN, rt, 25 min</td>
<td>0:3:3:2:1:1:0.13</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>NBS, CH₃CN, 45 °C, 25 min</td>
<td>0:trace:2.6:1.6:1:0.6 b</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>NBS, CH₃CN/DMSO (10%), 25 min</td>
<td>same as entry 7</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>NIS, Et₂O:THF = 3:1, rt, 1 h</td>
<td>0.29:0:0:1:0</td>
</tr>
<tr>
<td>11c</td>
<td>1.2.57b</td>
<td>NBS, CH₃CN, 0 °C, 25 min</td>
<td>1.2.58b: 1.2.59b: 1.2.60b = 56%:16%:23%</td>
</tr>
</tbody>
</table>

a) Except entry 11, all ratios are based on the NMR integration of the methyl peaks on the G-ring unit (ristocetin lettering). 1.2.60a was set as 1 for comparison. b) ratio of unknown product. c) 34% of starting material was recovered.

For the rearomatization, considering the already existing demetalated product, the ratio of aromatization: reverse reaction was more than 9:1. Using this
rearomatization condition, bislactim adduct 1.2.58b could be obtained in 56% yield, along with demetallated starting material 1.2.60b (23%) and diastereomeric adduct 1.2.59b (16%).

The diastereomeric ratio of the crude product by $^1$H NMR was ca. 2:1–4:1 based on the integration of the methyl group on the F-ring unit (ristocetin A lettering). Usually the bislactim anion, on reaction with alkyl halide or aldehyde, gives diastereomeric excess over 90% due to coordination of the lithium, which is positioned on the side opposite to the isopropyl group due to steric hindrance between the lithium and isopropyl group (Scheme 1.2.15). In the absence of a coordination site, however (such as in our case), the steric control of the isopropyl group seems insufficient to give good diastereoselectivities. It is known that titanium bislactim complexes give better diastereoselectivities than the lithiated bislactims owing to a "tighter transition state". Exploration of this, however, was not made because of the difficulties in the synthesis of ClTi(NEt)$_3$ and the base sensitivity of the arylglycine.

![Preferred Nucleophilic Attack Direction](image)

<table>
<thead>
<tr>
<th>M</th>
<th>(3R, 1'R):(3R, 1'S):(3S, 1'R):(3S, 1'S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>15.3 : 2.0 : 0.9 : 1.2</td>
</tr>
<tr>
<td>Ti</td>
<td>64.0 : 0.5 : 0.3 : 0.5</td>
</tr>
</tbody>
</table>

**Scheme 1.2.15.** Example of the Coordination Effect in the Bislactim Addition Reaction.
One of the concerns of this reaction is racemization at the chiral center of the G-ring unit by the basic bislactim anion. To avoid racemization by residual n-BuLi during the generation of bislactim anion, 2.0 equivalents of n-BuLi was used with 2.2 equivalents of bislactim 1.2.53. Using the isolated side product 1.2.47, racemization of the G-ring arylglycine under these reaction conditions was tested by conversion of recovered 1.2.47 to the (R)-MTPA amide 1.2.48b as outlined earlier. $^{19}$F NMR spectroscopy of the amide indicated a diastereomer ratio of ca 25:1, virtually identical to that obtained after the initial formation of 1.2.46, indicating that no racemization occurs during the nucleophile addition (see Figure 1.2.2).

It is known that 1,4-dihydropyrazine undergoes oxidation to give a pyrazine.\textsuperscript{17} Similarly, during the oxidative demetalation, it was found that the bislactim adduct 1.2.58 underwent overoxidation to afford the pyrazine 1.2.61 and trace amount of deoxypyrazine 1.2.62, presumably, from catalytic oxidation by NBS (or oxygen) in ether solution. The overoxidation products are usually obtained in very small quantities ($< 3\%$) immediately after the reaction, but approximately 50\% of the product is transformed into the pyrazine derivative after standing in air for 2 days. Consequently, it is essential to purify 1.2.58 immediately and take it to the next step as quickly as possible.
b) Attempted Synthesis of Arene-Dicarbonyl(trialkylphosphine)-manganese Complexes. Replacement of a metal carbonyl ligand of a metal carbonyl complex with a trialkylphosphine ligand would be expected to decrease the electrophilicity of the remaining metal carbonyls, through a combination of steric and electronic effects. Thus, to encourage the attack by the lithiated bis lactim on the arene ring, and discourage the unwanted decomplexation, attempts were made to substitute a metal carbonyl with either tributyl- or triphenylphosphine, in the presence of sunlight.\textsuperscript{18}

![Scheme 1.2.16](image)

**Scheme 1.2.16.** Example of CO Substitution and Expected Reduced Nu Attack at Carbonyl.

In the case of the model compound \textbf{1.2.56a}, the ligand substitution product was not obtained at all and instead the demetallation product was obtained as the major compound (Table 1.2.7). In the case of \textbf{1.2.23}, the PBu\textsubscript{3} adduct \textbf{1.2.63a/b} was obtained cleanly. However, substitution of the carbonyl in the case of chloroarene-manganese complex was not clean.\textsuperscript{17} While control experiments in the dark definitely give the dienyl-manganese complex \textbf{1.2.64} (IR: 2034, 1946 cm\textsuperscript{-1}), the structure of the product obtained in the presence of sunlight (IR: 2019, 1942 cm\textsuperscript{-1}) was not obvious when compared with other standard materials.
Table 1.2.7. Carbonyl Substitution Reaction with PPh₃ and PBu₃.

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArMn⁺(CO)₃</th>
<th>PR₃ (eq)</th>
<th>Reaction Conditions</th>
<th>Resultsᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2.56a</td>
<td>PPh₃ (1.0)</td>
<td>acetone, N₂, hv, rt</td>
<td>(1.2.56a:1.2.60a:1.2.63a) = 1:3:0</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>CH₂Cl₂, &quot;</td>
<td>(1.2.56a:1.2.60a:1.2.63b) = 1:3:0</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>PBu₃ (1.0)</td>
<td>acetone, &quot;</td>
<td>&quot; = 1:1:0</td>
</tr>
<tr>
<td>4</td>
<td>1.2.23</td>
<td>PPh₃ (1.1)</td>
<td>&quot;</td>
<td>(1.2.49a:1.2.65:1.2.63a) = 1:6:3</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>PBu₃ (3.0)</td>
<td>&quot;</td>
<td>(1.2.49a:1.2.65:1.2.63b) = 0:0:1</td>
</tr>
</tbody>
</table>

ᵃ) ratio was determined from the crude product based on the integration of Me peaks

![Chemical Structures](image)

Figure 1.2.4. Several Manganese Complex and Their Characteristic CO Stretching Frequencies
Moreover, $^{31}$P NMR showed multiple peaks. The aryl ether formation reaction and bislactim addition reaction to the trialkyphosphine substituted arene-manganese complex were expected to be difficult because of the reduced electrophilicity of the arene ring. Because of the problem in the structure determination and expected difficulties in the next step of diaryl ether formation and the bis-lactim addition reaction, further research to develop and utilize this methodology was not undertaken.

c) Reaction of Arene-Manganese Complex with Evans' type Chiral Enolate Equivalents. It is known that various types of chiral enolate afford a dienyl-manganese complex when reacted with arenemanganese complexes.$^{19,20}$

![Scheme 1.2.17](image)

**Scheme 1.2.17.** Examples of Different Type Nucleophilic Addition Reaction.

To introduce the arene diastereoselectively, several Evans type chiral glycine equivalents such as 1.2.71-73 were made by using literature procedures.$^{21}$ However, in general, enolate anion generation was not easy with these substrates and was often
accompanied by decomposition of the starting material (see Table 1.2.8). In the case of 1.2.71, when anion generation was attempted with NaH, n-BuLi, LiHMDS and KHMDS, starting material was recovered in good yield. Tertiary butyllithium was basic enough for the deprotonation. However, reaction of the anion with benzyl chloride or arene manganese complex 1.2.56a did not afford the desired product. Instead, the dimer (1.2.74) and the oxazolidinone (1.2.75) were often obtained along with recovered starting material.

Table 1.2.8. Nucleophilic Addition Reaction of Evans Type Chiral Glycine Enolate Equivalents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nu.</th>
<th>Anion generation</th>
<th>E⁺</th>
<th>Rxn condition</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2.71</td>
<td>NaH, -78 °C, 1.5 h</td>
<td>BnCl</td>
<td>-78 °C, 0.5 h-rt, 0.5 h</td>
<td>s.m. recovered (quant)</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>LiHMDS, THF, -78 °C, 20 min</td>
<td>1.2.56a</td>
<td>-78 °C, 1 h</td>
<td>&quot;</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>KHMDS, THF, -78 °C, 1 h</td>
<td>BnCl</td>
<td>-78 °C, 1 h-rt, 0.5 h</td>
<td>Unknown: s.m: 1.2.74 = 1.5:11:1³</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>t-BuLi, -78 °C, 15 min</td>
<td>BnCl</td>
<td>-78 °C, 0.5 h-rt, 1 h</td>
<td>s.m.: 1.2.74:1.2.75 = 4:1:2</td>
</tr>
<tr>
<td>5</td>
<td>&quot;</td>
<td>t-BuLi, -100 °C, 1 h</td>
<td>1.2.56a</td>
<td>-100 °C, 1 h -78 °C, 1 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>1.2.72</td>
<td>KHMDS, THF, -78 °C, 5 min</td>
<td>D₂O</td>
<td>-78 °C, 20 min</td>
<td>1.2.75: unknown product = 55:28</td>
</tr>
<tr>
<td>7</td>
<td>1.2.73</td>
<td>LDA, THF, -78 °C, 20 min</td>
<td>1.2.56a</td>
<td>-78 °C, 45 min</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

a) ratio was measured by 200 MHz NMR.
Deprotonation of 1.2.72 was not clean and afforded the oxazolidinone 1.2.75. Transformation of 1.2.72 into its amino analogue 1.2.73 by reduction of azide to amine with Raney-Ni under hydrogen, was not clean and with Ph₃P/H₂O, the oxazolidinone and the desired amine were obtained in a 2:1 ratio. In situ reduction of 1.2.72 with Ph₃P in the presence of benzaldehyde gave ~ 80% yield of 1.2.73 (NMR) but reaction of the desired enolate with manganese complex 1.2.56a did not yield the desired product. Further attempts to use this strategy were not pursued.

2.2.5 Hydrolysis and Protection of Bislactim Adduct 1.2.58a.

Selective hydrolysis of the bislactim group of 1.2.58a was accomplished using 0.25 N HCl. Prolonged reaction time severely reduced the yield but 62–69% yield was obtained after 1.5 h stirring.

Table 1.2.9. Conditions and Yield for Hydrolysis of Bis-lactim Adduct 1.2.58a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Reaction time (h)</th>
<th>Base for Cbz Protection</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25N HCl</td>
<td>3.5</td>
<td>NH₄OH</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>2</td>
<td>&quot;</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>1.5</td>
<td>&quot;</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>1.5</td>
<td>NaHCO₃</td>
<td>62</td>
</tr>
</tbody>
</table>

No loss of Boc group was observed during this reaction, but the resulting amino ester was unstable and gave several products if not carried forward
immediately, apparently resulting from dimerization and oligomerization. NMR of a separated product showed the loss of a methyl ester group and mass spectrometry showed peaks much higher than the expected M+. Consequently, the combined ether extracts from the hydrolysis reaction were treated directly with benzyl chloroformate in the presence of ammonium hydroxide (reaction medium pH = 9) to afford the fully protected ristomycinic acid derivative 1.2.21 in 62% yield from 1.2.58a, without any racemization.

![Scheme 1.2.18 Hydrolysis of Bis-lactim Adduct and Protection.](image)

2.3. Conclusion.

A protected ristomycinic acid, which models several potential difficulties anticipated in the synthesis of ristocetin A, was successfully prepared using an arenemanganese complex without losing the enantiomeric purity of the F and G ring unit arylglycines. Difficulties during the bislactim addition reaction were largely attributed to dealkylation during the oxidation reaction and incompleteness of the nucleophilic addition reaction. The selectivity of the improved aromatization reaction was greater than 9>1 and demetalation of the arene-manganese complex 1.2.56a/b was negligible (~10%). It will be necessary, however, to improve the diastereo-
selectivity (2:1 ~ 4:1) of the bislactim addition reaction. Attempts to improve this diastereoselectivity have not been successful so far.
2.4 Experimental Section

General All reactions were conducted under a dry N₂ or Ar atmosphere, unless otherwise noted. N₂ or Ar was passed through anhydrous CaSO₄. THF, ether, benzene and toluene were dried using Na/benzophenone and CH₂Cl₂ was distilled from CaH₂. For chromatography, distilled hexanes and EtOAc were used and ether was distilled over LiAlH₄. Acetonitrile was used as purchased.

¹H, ¹³C, ¹⁹F, ³¹P NMR spectra were recorded using either Varian Gemini-300 (300 MHz) or Varian XL 200 (200 MHz) spectrometers using CDCl₃, benzene-d₆, D₂O, DMSO-d₆, CD₃CN and CD₂Cl₂ solvents. ¹H NMR was referenced to TMS or CHCl₃ (7.26 p.p.m.). ¹³C was referenced to CHCl₃ (77.0 p.p.m.) and the results of attached proton test (APT) are recorded as (+) or (-), and multiplicity of the carbon is denoted as (s), (d), (t) and (q). ¹⁹F NMR was referenced to CFCl₃ as a external standard. Mass spectra were recorded, in house, on a Kratos MS 25A instrument or performed by the Midwest Center for Mass Spectrometry, NE. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN.

Infrared spectra were recorded on a Perkin-Elmer Series 1600 FT-IR using a CHCl₃ in NaCl chamber. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Melting points were measured on a Thomas-Hoover melting apparatus without correction.

Preparative HPLC was performed on a Gilson HPLC using a M20 10/25 silica gel column.
Tricarbonyl(3-chloro-2-methylanisole)manganese tetrafluoroborate (1.2.23).
To a stirred mixture of Mn$_2$(CO)$_{10}$ (394.4 mg, 1.0 mmol, 1.0 eq) and 3-chloro-2-methylanisole (1.2.25) suspended in trifluoroacetic anhydride (20 mL) at 0 °C, was slowly added aqueous HBF$_4$ (48%, 3.9 mL, 29.5 mmol), and the mixture was stirred for 5 min. then refluxed for 16 h. After evaporation of the solvent in vacuo, the residue was dissolved in a mixture of dichloromethane (5 mL) and acetone (2 mL) and the product was precipitated with Et$_2$O (40 mL). After filtration the solid was washed with Et$_2$O (2 x 20 mL) and dried in vacuo to afford the known complex 1.2.23 (591.7 mg, 77 %) as a yellow solid. Mp 133 °C (dec); IR (CHCl$_3$) 2081, 2014 cm$^{-1}$; $^1$H NMR (200 MHz, D$_2$O) $\delta$ 6.65 (t, J = 7.0, 1H), 6.23 (d, J = 7.0, 1H), 5.93 (d, J = 7.0, 1H), 3.91 (s, 3H), 2.31 (s, 3H).

1-Methylsulfinyl-1-methylthio-2-(3-benzyloxy-4-methoxyphenylethylene (1.2.28).
To a solution of the aldehyde 1.2.27 (4.99 g, 20.6 mmol, 1.0 eq) in benzene (100 mL), in a 250 mL flask equipped with Dean-Stark trap, was added methyl methylsulfinylmethyl sulfide (2.5 mL, 24.0 mmol, 1.2 eq) and Triton B (6.5 mL, 14.35 mmol, 0.7 eq) and the reaction mixture was refluxed for 45 min until no more water was collected. After cooling to room temperature, the mixture was acidified to pH = 1 with 1 N HCl, diluted with H$_2$O (30 mL), shaken, extracted with CH$_2$Cl$_2$ (3 x 50 mL) and dried over MgSO$_4$. Evaporation of the solvent followed by purification by column chromatography (SiO$_2$, eluted with 1:1 hexanes/ethyl acetate) afforded the title compound 1.2.28 (4.60 g, 64.3 %) as a colorless liquid which crystallized in the refrigerator: mp 82-84 °C; $R_f$ 0.38 (3:1 hexanes/ethyl acetate); IR (CHCl$_3$) 3007, 1745, 1598, 1511, 1463, 1454, 1442, 1430 cm$^{-1}$; $^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.83
(d, J = 2.0 Hz, 1H), 7.49-7.27 (m, 7H); 5.23 (s, 2H, -OCH₂Ph); 3.95 (s, 3H, -SOCH₃); 2.09 (s, 3H, SCH₃). ¹³C NMR (75 MHz, CDCl₃) δ 150.9 (+, s); 147.7 (+, s); 136.9 (+, s); 136.8 (+, s); 136.10 (d, -); 128.5 (d, -); 127.8 (d, -); 127.0 (d, -); 126.3 (s, +); 125.1 (d, -); 114.1 (d, -); 111.1 (d, -); 70.7 (t, +, -OCH₂Ph); 55.9 (q, -, -OCH₃); 40.1 (q, -, -SOCH₃); 18.1 (q, -, -CH₃). HRMS: found (M⁺-O) 332.0912, calcd for C₁₈H₂₀S₂O₃: 332.0905. MS: m/e 333 (9), 332 (35), 285 (100), 284 (17), 270 (33), 242 (8), 241(17).

2-(3-Benzoyloxy-4-methoxyphenyl)acetic Acid (1.2.29).

Into a solution of the sulfanyl derivative 1.2.28 (8.28 g, 23.8 mmol, 1.0 eq) in CH₂Cl₂ (160 mL) at -78 °C was bubbled HCl gas for 10 min. (which was generated by the addition of 16.5 mL of H₂SO₄ to 50 mL conc. HCl). The EtOH (95 %, 12.6 mL, 1.2 eq) was added to the reaction mixture in one portion. After bubbling HCl for an additional 10 min at -78 °C, the resulting dark brown solution was stirred at rt for 1h. To the mixture was slowly added 50 % KOH solution (24.5 mL, 604.1 mmol, 25 eq) followed by ca 100 mL EtOH as a co-solvent, and the reaction mixture was refluxed for 3 h after removal of CH₂Cl₂ using Dean-Stark apparatus. After cooling, the reaction mixture was extracted with EtOAc (4 x 250 mL) and the aqueous layer was acidified to pH = 2 with 1N HCl, extracted (CH₂Cl₂, 4 x 250 mL), dried (MgSO₄), concentrated to afford a brownish yellow solid. Recrystallization from Et₂O afforded 4.0g of the title compound 1.2.29 as a white solid (60 %): mp 123-125 °C; Rf 0.47 (10:1 CHCl₃:MeOH ); IR (CHCl₃) 3014, 1710, 1514, 1442, 1428, 1364 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.35-7.27 (m, 5H); 6.85 (s, 3H); 5.14 (s, 2H, -OCH₂Ph); 3.87 (s, 3H, -OCH₃); 3.55 (s, 2H, -CH₂CO₂H).
(4R,5S)-3-[2-(3-Benzylxy-4-methoxyphenyl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (1.2.30).

To a stirred solution of the phenylacetic acid 1.2.29 (8.0 g, 29.4 mmol., 1.0 eq) in THF (300 mL) at -78 °C was added freshly distilled pivaloyl chloride (4.0 mL, 322.4 mmol, 1.1 eq) followed by Et\textsubscript{3}N (5.3 mL, 380 mmol, 1.80 eq). The mixture was stirred for 15 min at -78 °C and 1 h at 0 °C to form the mixed anhydride and then cooled to -78 °C. In a separate flask, 45 mL of a THF solution of (4R)-methyl-(5S)-phenyl-2-oxazolidinone was prepared and n-BuLi (2.5 M, 18.8 mL, 47.0 mmol, 1.60 eq) was added to the solution at -78 °C and stirred for 20 min. The mixture was then transferred to the mixed anhydride via cannula and stirred for 25 min at -78 °C and 20 h at rt. After quenching of the reaction with 0.5 M KH\textsubscript{2}SO\textsubscript{4} (100 mL) and evaporation of volatiles in vacuo, the residue was extracted with dichloromethane (3 x 10 mL), dried (MgSO\textsubscript{4}), filtered and concentrated. The resulting yellow oil was flash column chromatographed (SiO\textsubscript{2}, hexanes:EtOAc = 5:1) and crystallized in Et\textsubscript{2}O/hexanes mixture to afford the product (7.7 g, 61 %) as a white solid. A second crop of the product (2.41 g, 20 %) was obtained after repetition of the column chromatography on the liquors and crystallization. \textit{Rf} 0.60 (1:2 hexanes:EtOAc); IR (CHCl\textsubscript{3}) 3023, 3013, 1781, 1699, 1591, 1514, 1456, 1442, 1428, 1351, 1313 cm\textsuperscript{-1}; \textit{1}H NMR (200 MHz, CDCl\textsubscript{3}) \( \delta \) 7.47-7.26 (m, 10H), 6.92-6.83 (m, 3H), 5.60 (d, \textit{J} = 7.3 Hz, 1H), 5.15 (s, 2H, -\textit{CH}_{2}Ph), 4.70 (dt, \textit{J}=7.3, 6.6 Hz, 1H), 4.24 (d, \textit{J} = 5.2 Hz, 1H), 4.15 (d, \textit{J} =5.2 Hz, 1H), 3.87 (s, 3H, -OCH\textsubscript{3}), 0.85 (d, \textit{J} = 6.6 Hz,3H, -\textit{CH}\textsubscript{3}); \textit{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 171.1 (s, +), 152.9 (s, +), 148.9 (s, +), 148.0 (s, +), 137.1 (s, +), 133.2 (s, +), 128.8 (d, -), 128.7 (d, -), 128.5 (d, -), 127.8 (d, -), 127.4 (d, -), 125.9 (s, +), 125.6 (d, -), 122.5 (d, -), 115.3 (d, -), 111.8 (d, -), 78.9 (d, -), 70.9 (t, +), 56.0 (q, -), 55.0 (d, -), 41.1 (t, +), 14.4 (q, -); [\alpha]_{D} + 5.2° (c
2.33, CHCl₃); HRMS: found (M⁺) 431.1724; calcd for C₂₆H₂₅NO₅: 431.1733. MS: m/e 431 (17), 332 (20), 267 (17), 243 (21), 239(14), 221 (25), 218 (18), 217 (16).

[3(2R),4R,5S]-3-[2-azido-2(3-benzyloxy-4-methoxyphenyl)-1-oxoethyl]-4-methyl-5-phenyl-2-oxazolidinone (1.2.31).

To a stirred solution of imide 1.2.30 (1.01 g, 2.32 mmol, 1.0 eq) in THF (50 mL) at -78 °C was added 0.5 M potassium bistrimethylsilylamide (4.86 mL, 2.43 mmol, 1.05 eq) via cannula and the mixture was stirred for 2 min. at -78 °C to form the enolate. In a separate flask at -78 °C, a solution of 2,4,6-triisopropylbenzenesulfonyl azide (896 mg, 2.90 mmol, 1.25 eq) in THF (13 mL) was prepared and was transferred to the enolate solution via cannula. After 2 min stirring at -78 °C, the reaction was rapidly quenched by 170 mL of glacial acetic acid and heated up to rt in 55 °C water bath. After 3 h stirring, the reaction mixture was partitioned between brine (100 mL) and Et₂O (150 mL), shaken and separated. The aqueous layer was extracted with Et₂O (100 mL x 3) and the combined organic layer was dried over Na₂SO₄. Concentration and purification (SiO₂, hexanes:EtOAc = 5:1) afforded the product as a yellow oil (90 % yield, 92 % d.e.). Crystallization from Et₂O afforded the single diastereomer (71 %) as a white solid. Mp 116-118 °C; Rf 0.36 (3:1 hexanes:EtOAc ); IR (CHCl₃) 2110 (-N₃), 1783, 108, 1515, 1368 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.48-7.23 (m, 10H), 7.04 (d, J = 8.3 Hz, 1H), 7.02 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.11 (s, 1H), 5.39 (d, J = 7.1 Hz, 1H), 5.18 (dd, J = 18.4, 12.5 Hz, 2 H, -CH₂Ph), 4.56 (dt, J = 7.1, 6.4 Hz, 1H), 3.90 (s, 3H, -OCH₃), 0.96 (d, J = 6.4 Hz, 3H, -CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 169.10 (s, +), 151.94 (s, +), 150.62 (s, +), 148.22 (s, +), 136.81 (s, +),
132.60 (s, +), 128.92 (d, -), 128.77 (d, -), 128.54 (d, -), 127.83 (d, -), 127.49 (d, -),
125.50 (d, -), 125.05 (s, +), 122.20 (d, -), 113.53 (d, -), 111.82 (d, -), 79.19 (d, -,
-CHN₃), 70.85 (t, +, -OCH₂Ph), 63.61 (d, -), 55.97 (q, +), 55.42 d, -), 14.43 (q, +);
[α]D -130.6° (c 1.85, CHCl₃); HRMS: found 444.1678; calcd for C₂₆H₂₄N₂O₅:

Methyl (2R)-azido-2-(3-benzxyloxy-4-methoxyphenyl)acetate (1.2.32).

To a solution of azidomidate 1.2.31 (731.5 mg, 1.55 mmol, 1.0 eq) in THF:H₂O (3:1, 36 mL), cooled in an ice bath, was added LiOH·H₂O (122.9 mg, 2.93 mmol, 1.89 eq) and the mixture was stirred for 35 min. until the starting material had disappeared (TLC). After evaporation of volatiles in vacuo, the residue was acidified to pH = 1 with 1 N HCl, extracted with CH₂Cl₂ (3 x 20 mL) and dried (MgSO₄). After evaporation of solvent the crude product was dissolved in MeOH (4 mL) containing p-toluenesulfonic acid (588.7 mg, 3.09 mmol, 2.0 eq), and the solution was refluxed for 5 h until all the starting material had disappeared (TLC). After cooling, brine (5 mL) was added and the mixture was extracted with EtOAc (3 x 10 mL), dried (Na₂SO₄) and concentrated in vacuo. Purification of the crude product by column chromatography (SiO₂, eluted with 5:1 ethyl acetate/hexanes) afforded 1.2.32 (467.4 mg, 92.2 %) as a colorless liquid. Rf 0.69 (2:3 hexanes:EtOAc); IR (CHCl₃)
3031, 2109, 1747, 1604, 1593, 1515, 1464, 1456, 1442, 1429 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.43-7.34 (m, 5H), 6.93-6.92 (m, 3H), 5.16 (s, 2H, -CH₂Ph), 4.86 (s, 1H, N₃CH), 3.90 (s, 3H, -OCH₃), 3.71 (s, 3H, -CO₂CH₃); ¹³C NMR (75 MHz,
CDCl₃) δ 169.6 (s, +), 150.5 (s, +), 148.4 (s, +), 136.6 (s, +), 128.5 (d, -), 127.9 (d, -),
127.4 (d, -), 125.9 (s, +), 121 (d, -), 113.0 (d, -), 111.7 (d, -), 71.0 (t, +, CH₂Ph), 65.0
(d, -), -N₃CH), 56.0 (q, - OCH₃), 52.8 (q, - CO₂CH₃); [α]D -110.6° (c 2.84, CHCl₃);
HRMS: found (M⁺) 327.1216; calcld for C₁₇H₁₇N₃O₄ 327.1219. MS: m/e 328 (7), 327 (26.8), 299 (10), 285 (11), 266 (10), 241 (15), 240 (22), 239 (24), 208 (22).

**Procedure for the conversion of 1.2.32 into 1.2.34a and b.**

The azidoester 1.2.32 (15.7 mg, 0.048 mmol) was stirred in THF (1.5 mL) with triphenylphosphine (18.9 mg, 1.5 eq) for 15 h at rt until all starting material was consumed according to TLC. Water (18 μL, 21 eq) was added and the mixture was stirred for 42 h. After evaporation of the volatiles, purification by TLC (SiO₂, EtOAc) afforded the amino ester 1.2.33 (7.9 mg, 55%). The product (2.9 mg) was dissolved in methylene chloride (2.5 mL) and treated with HOBT (2.8 mg, 1.8 eq) and 1-[(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.8 mg, 1.8 eq) followed by (S)-MTPA (3.8 mg, 2.0 eq) and the mixture was stirred for several hours at rt. Volatiles were evaporated in vacuo and the diastereomer ratio was estimated by ¹⁹F NMR spectroscopy (Figure 1.2.1) of the product 1.2.34b. An identical procedure employing (+)-MTPA was used to prepare 1.2.34a. Further purification by TLC did not lead to significant fractionation of diastereomers.

**Methyl 2-imino-2-(3-benzyloxy-4-methoxyphenyl)acetate (1.2.38).**

Ethereal diazomethane solution (8 mL) prepared from N-methyl-N-nitrosourea (124 mg, 1.2 mmol, 6 eq) was added to the 2(R) azido-2-(3-benzyloxy-4-methoxyphenyl)acetic acid (1.2.37) and stirred for 30 min. Reaction was not complete.

Another portion of diazomethane solution (8 mL, 6 eq) was added and the mixture
was stirred for 30 min. The reaction was quenched with glacial AcOH to pH = 1, extracted with EtOAc (3 x 5 mL) and dried (MgSO₄). Product was separated by TLC (hexanes:EtOAc = 3:1) to afford the desired azido methyl ester 1.2.32 along with side product 1.2.38. Compound 1.2.38: Rf 0.41 (3:1 hexanes:EtOAc); IR (CH₂Cl₂) 3674, 2977, 2934, 2872, 2810, 1734, 1675, 1594, 1583, 1524, 1491, 1456, 1444, 1430, 1414 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.70-7.60 (m, 2H), 7.50-7.32 (m, 6H), 7.26 (d, J = 0.8 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 5.19 (s, 2H), 3.97 (s, 3H), 3.95 (s, 3H).

(2R)-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-[[3-hydroxy-4-methoxyphenyl] acetyl]-R-benzylethylamine (1.2.41).

Azidoimidate 1.2.31 (500 mg, 1.0 eq) in EtOAc (6 mL) was combined with Boc₂O (283 mg, 1.2 eq) and stirred with 10% Pd/C (173 mg) for 19 h under hydrogen atmosphere. Reaction mixture was concentrated and purified by column-chromatography (hexanes:EtOAc = 1:1) to afford the side product 1.2.41 (257 mg, 48%). Rf 0.29 (1:1 hexanes:EtOAc); IR (CHCl₃) 3770, 3684, 3620, 3420, 3021, 2977, 2896, 2434, 2400, 1707, 1676, 1648, 1636, 1600, 1518, 1477, 1424 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 6.85-6.77 (m, 5H), 5.85 (s, H), 5.84 (s, 1H), 5.52 (d, J = 8.4 Hz, 1H), 4.92 (d, J = 4.7 Hz, 1H), 4.24 (dtq, J = 8.4, 6.7, 6.0 Hz, 1H), 3.81 (s, 3H), 2.62 (d, J = 6.0 Hz, 2H), 1.76 (s, 1H), 1.39 (s, 9H), 1.08 (d, J = 6.7Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 169.2, 155.1, 146.6, 146.0, 137.1, 131.9, 129.4, 128.2, 126.3, 118.9, 113.3, 110.9, 79.8, 58.1, 55.9, 46.1, 41.9, 28.3, 19.8; [α]D⁻52° (c 0.5, CHCl₃).

Methyl(2R)-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-(3-hydroxy-4-methoxyphenyl) acetate (1.2.24).
A solution of di-tert-butyl dicarbonate (281.3 mg, 1.29 mmol, 1.24 eq) in EtOAc (5.5 mL) was combined with 10% palladium on activated carbon (104.7 mg) and hydrogen was bubbled for 2 h 20 min for presaturation. The azido methyl ester 1.2.32 (347.7 mg, 1.06 mmol, 1.0 eq) was added to the solution and stirring was continued for 24 h while bubbling the H₂ until all starting material had disappeared (TLC). After filtration over Celite, the solution was concentrated and the product was purified by column chromatography (SiO₂, eluted with 3:1 ethyl acetate/hexanes) to afford 1.2.24 (311.6 mg, 94.2%) as a pale yellow liquid which solidified in the refrigerator. Mp 113.5-114.5 °C; Rf 0.70 (1:1 hexanes:EtOAc); IR (CHCl₃) 3543, 3439, 3029, 1742, 1711, 1596, 1510, 1497, 1458, 1438, 1393, 1368, 1331 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 6.93-6.79 (m, 3H), 5.66 (s, 1H, -OHR), 5.51 (bs, 1H, -NHBOc), 5.23 (bd, J = 6.4 Hz, 1H, BocNHCHR), 3.88 (s, 3H, -OCHR), 3.72 (s, 3H, -CO₂CHR), 1.43 (s, 9 H, -CMe₃); ¹³C NMR (75 MHz, CDCl₃) δ 154.8 (s, +), 146.6 (s, +), 145.9 (s, +), 130.0 (s, +), 119.1 (s, +), 118.9 (d, -), 113.2 (d, -), 110.7 (d, -), 80.1 (s, +), 57.1 (d, -), 55.9 (q, -), 52.6 (q, -), 28.3 (q, -); [α]D -126.5° (c 1.25, CHCl₃); HRMS: found (M⁺) 311.1352, calcd for C₁₅H₂₁NO₆: 311.1369. MS: m/e 311 (1), 255 (4), 223 (9), 197 (3), 196 (18).

3-[(Tricarbonyl)(η⁶-2-methyl-3-methoxyphenyloxy)manganese][N-t-butoxycarbonyl-(R)-4-methoxyphenylglycine methyl ester] hexafluorophosphate (1.2.46).

To a stirred suspension of 60% NaH (11.6 mg, 0.29 mmol, 0.98 eq) in dichloromethane (2.5 mL) at 0 °C was added via cannula an ice cold solution of the phenol 1.2.24 (92.2 mg, 0.30 mmol, 1.0 eq) in dichloromethane.
(3 mL). The mixture was stirred for 30 min at 0 °C and the resulting yellow solution was then transferred to a mixture of arene-manganese complex 1.2.23 (125.6 mg, 0.33 mmol, 1.10 eq) and AgBF₄ (307.3 mg, 2.8 mmol, 9.5 eq) suspended in dichloromethane (23 mL) at 0 °C. After 40 min stirring at 0 °C, the reaction was quenched by addition of 0.5 M NH₄PF₆ solution (15 mL) and the mixture was vigorously stirred for 25 min, separated, and extracted with dichloromethane (2 x 15 mL). The combined organic layer was washed with 0.5 M NH₄PF₆ (2 x 15 mL) and dried over Na₂SO₄. After filtration, the solution was concentrated to 1-2 mL and the product was precipitated with ~ 60 mL pentane, filtered, and washed (pentane, 30 mL) to afford the complex 1.2.46 (166.5 mg, 79%) as a yellow solid. IR (CHCl₃) 3023, 2071, 2003, 1744, 1712, 1534, 1512, 1496, 1472, 1428 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.39 (d, J = 8.6 Hz, 1H), 7.26 (s, 1H), 7.10 (d, J = 8.6 Hz, 1H), 6.68 (t, J = 7.3 Hz, 1H), 6.08 (d, J = 7.0 Hz, 1H), 5.71 (bs, 1H), 5.43 (d, J = 7.0 Hz, 1H), 5.29 (bd, J = 6.9 Hz, 1H), 4.15 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 2.40 (s, 3H), 1.43 (s, 9H). Anal. calcd: C 43.65, H 4.09, N 1.96. Found: C 43.31, H 4.31, N 1.85 %.

3-{2-Methyl-3-methoxy-5-[(4R)-isopropyl-3,6-dimethoxypyrazinyl]phenyloxy} [N-t-Butoxy-carbonyl-(R)-4-methoxy-phenylglycine methyl ester] (1.2.55).

To a solution of (6R)-isopropyl-2,5-dimethoxypyrazine (1.2.53) (15.7 mg, 0.085 mmol, 2.0 eq) dissolved in THF (850 mL) at -78 °C was added dropwise n-BuLi (32 mL, 2.71 M, 2.0 eq), and the mixture was stirred for 2 h 45 min at -78 °C. This reaction mixture was quickly added to the diarene-Mn complex 1.2.46 (30.0 mg, 0.042 mmol, 1.0 eq) at -100 °C. The reaction mixture was then stirred for 1 h between -95 and -100 °C (liq. N₂/ pentane bath) and the reaction was quenched with sat. NH₄Cl (1.5
mL) at -100 °C. After warming, the mixture was extracted with Et₂O (5 mL x 3) and the combined organic layer was washed with brine (5 mL) and dried (Na₂SO₄). After filtration, N-bromosuccinimide (7.8 mg, 0.044 mmol, 1.04 eq) was added and the mixture was stirred for 20 min at rt. The reaction was quenched with 3 mL sat. sodium bisulfite and the mixture was extracted with Et₂O (5 mL x 3), washed with brine (1 x 5 mL), dried (MgSO₄) and concentrated to afford a yellow oil. Purification by preparative TLC (SiO₂, hexanes:EtOAc=3.5:1, 6 times developed) afforded compound **1.2.55** (11.4 mg, 44.3 %) as a white solid along with the demetalation side product **1.2.47** (3.7 mg, 20 %) as a colorless oil. Compound **1.2.55**: mp 60-62 °C; Rf 0.50 (2:1 hexanes:EtOAc ); IR (CHCl₃) 3025, 3015, 2972, 1745, 1696, 1512, 1494, 1464, 1437, 1418 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.04 (d, J = 8.3 Hz, 1H), 6.93, (d, J = 8.4 Hz, 1H), 6.70 (d, J = 2.0 Hz, 1H), 6.56 (s, 1H), 6.34 (s, 1H), 5.37 (bs, 1H), 5.14 (bd, 1H, -HNCH₂CO₂Me), 4.96 (d, J = 3.5 Hz, 1H), 4.00 (t, J = 3.5 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 2.33 (m, 1H), 2.07 (s, 3H, PhCH₃), 1.41 (s, 9H), 1.07 (d, J = 6.90 Hz, 3H), 0.72 (d, J = 6.83 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6 (s, +), 162.3 (s, +), 158.7 (s, +), 154.7 (s, +), 150.3 (s, +), 146.6 (s, +), 138.9 (s, +), 129.3 (s, +), 121.9 (d, -), 116.9 (s, +), 116.8 (d, -), 112.6 (d, -), 110.7 (d, -), 105.6 (d, -), 80.1 (s, +), 60.6 (d, -), 59.8 (d, -), 57.0 (d, -), 56.1 (q, -), 55.7 (q, -), 53.0 (q, -), 52.5 (q, -), 31.6 (d, -), 28.3 (q, -), 19.1 (q, -), 16.5 (q, -), 8.8 (q, -); [α]D +1.67° (c 0.78, CHCl₃); HRMS: found (M⁺): 613.2994; calcd for C₃₂H₄₃N₃O₉ 613.2999. MS: m/z 614 (3), 613 (26), 513 (13), 498 (20), 488 (20), 455 (28), 454 (100), 452 (19).

**1-Phenoxy-2-methyl-3-methoxy-5-[(1S,4R)-4-isopropyl-3,6-dimethoxy-1,4-dihydropyrazinyl]benzene (1.2.58a).** Reaction was performed similar to the case of **1.2.55**. ¹H NMR (200 MHz, CDCl₃) δ 7.29 (t, J = 8.8 Hz, 2H), 7.01 (t, J = 7.3 Hz,
1H, 6.89 (d, J = 8.7 Hz, 2H), 6.60 (s, 1H), 6.47 (d, J = 1.6 Hz, 1H), 5.30 (s, 1H), 4.99 (d, J = 3.6 Hz, 1H), 4.03 (t, J = 3.4, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 2.34 (m, 1H), 2.06 (s, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H).

1-Phenoxy-2-methyl-3-methoxy-5-[(1R,4R)-4-isopropyl-3,6-dimethoxy-1,4-dihydropyrazinyl]benzene (1.2.59a).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.03 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 7.7 Hz, 1H), 6.71 (s, 1H), 6.51 (s, 1H), 5.12 (d, J = 4.6 Hz, 1H), 3.93 (t, J = 4.7 Hz, 1H), 3.84 (s, 3H), 3.69 (s, 3H), 3.63 (s, 3H), 2.09 (s, 3H), 2.15-2.05 (m, 1H), 1.00 (d, J = 6.96 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H).

1-Phenoxy-2-methyl-3-methoxybenzene (1.2.60a).

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.31-7.26 (t, J = 7.7 Hz, 2H), 7.12 (t, J = 8.2 Hz, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.90 (d, J = 7.8 Hz, 2H), 6.68 (d, J = 8.10, 1H), 6.57 (d, J = 8.2, 1H), 3.86 (s, 3H), 2.11 (s, 3H).

1-Phenoxy-2-methyl-3-methoxy-5-(4-isopropyl-3,6-dimethoxypyrazinyl)benzene (1.2.61a)

$^1$H NMR (200 MHz, CDCl$_3$) $\delta$ 7.62 (s, 1H), 7.50 (s, 1H), 7.29 (t, J = 8.4 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 6.95 (d, J = 7.8 Hz, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.29 (m, 1H), 2.13 (s, 3H), 1.24 (d, J = 7.0 Hz, 6H).
3-(2-Methyl-3-methoxyphenyloxy)[N-t-Butoxycarbonyl-(R)-4-methoxy-phenylglycine] methyl ester (1.2.47).

This compound was isolated from the reaction of 1.2.46 with 1.2.53, and was also prepared by decomplexation of 1.2.46 using acetonitrile as previously described. Rf 0.58 (2:1 hexanes:EtOAc); IR (CHCl₃) 1712, 1583, 1512, 1496, 1470, 1438, cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.04 (t, J = 8.1 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 6.71 (d, J = 2.1 Hz, 1H), 6.62 (d, J = 8.2, 0.6 Hz, 1H), 5.40 (bs, 1H), 5.13 (bd, 1H), 3.84 (s, 6H, -OCH₃), 3.65 (s, 3H, -CO₂CH₃), 2.11 (s, 3H, -CH₃), 1.38 (s, 9H, -(CH₃)₃), ¹³C NMR (75 MHz, CDCl₃) δ 158.8, 155.3, 150.5, 146.6, 129.5, 126.4, 122.1, 117.3, 112.7, 110.8, 105.7, 80.1, 56.9, 56.1, 55.7, 52.4, 28.1, 8.8; [α]D - 93.8° (c 0.42, CHCl₃); HRMS. Found: 431.1937; calc'd for C₂₃H₂₉NO₇: 431.1944. MS: m/e 431(2), 376(4), 358(4), 357(8), 342(5), 331(3), 330(8), 214(32). For the assessment of optical purity of complex 1.2.46, the following procedure was followed for the preparation of the MTPA derivatives 1.2.48. The N-Boc protected diarylamine-manganese complex 1.2.46 (10 mg) was stirred overnight in CH₃CN (1.5 mL). The resulting brown sludge was filtered over Celite and the crude product was purified by TLC in the usual way (hexanes:EtOAc = 2:1) to afford the protected diaryl ether (5.9 mg, 98 %) as a colorless oil. This compound (2.9 mg, 7.0x10⁻⁶ mol, 1.0 eq) dissolved in MeOH (250 mL) was combined with 6N HCl (250 µL) and stirred for 45 min until all the starting material disappeared. Volatiles were pumped out in vacuo for an hour, residual water was removed by co-evaporation with benzene (1.5 mL x 2) and the residue was dried in vacuo for 1h. The resulting amino acid salt was combined with HOBT (2.9 mg, 2.5 eq) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.9 mg, 2.2 eq) followed by (+)-MTPA (3.4 mg, 2.1 eq) dissolved in CH₂Cl₂ (2 mL) and the
mixture was stirred for 2.8 h under N$_2$ atmosphere until all the starting material was consumed (TLC, NMR). Volatiles were evaporated \textit{in vacuo} and the diastereomeric ratio was determined by $^{19}$F-NMR. (Fig. 1.2. 2).

[N-t-Butoxycarbonyl-(R)-3-hydroxy-4-methoxyphenylglycine methyl ester]-O-[N-benzyloxycarbonyl-(S)-2-methyl-3-methoxyphenylglycine methyl ester] (1.2.21).

The bislactim adduct \textbf{1.2.55} (13.8 mg) was dissolved in THF (1.2 mL), combined with 0.25 N HCl (270 $\mu$L) and was stirred for 1.5 h at rt until all the starting material was consumed (TLC). After evaporation of the volatiles \textit{in vacuo}, the residue was partitioned between Et$_2$O (1 mL) and sat. NaHCO$_3$ solution (1 mL), and benzyl chloroformate (6.5 $\mu$L) was added to the solution. After 1 h 10 min. stirring, the mixture was extracted with Et$_2$O (3 x 3 mL), dried (Na$_2$SO$_4$), and the solvent was removed \textit{in vacuo}. Purification by preparative TLC (SiO$_2$, hexanes:EtoAc = 4:3) afforded the protected ristomycinic acid \textbf{1.2.21} (8.9 mg, 62.1 %) as a colorless oil. \textit{Rf} 0.41 (2:1 hexanes:EtoAc); IR (CHCl$_3$) 3436, 3007, 2955, 1743, 1714, 1582, 1492, 1450, 1439, 1420 cm$^{-1}$; $^1$H NMR (300 MHz, 58 $^\circ$C, CDCl$_3$ + 1 drop C$_6$D$_5$) $\delta$ 7.30 (s, 5H), 7.05 (dd, $J = 8.4$ Hz, 1.8 Hz, 1H); 6.94 (d, $J = 8.4$ Hz, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 6.39 (s, 1H), 5.64 (br. s, 1H), 5.37 (br. s, 1H), 5.19 (br. s, 1H), 5.13 (br. s, 1H), 5.08 (br. s, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.67 (s, 3H), 3.66 (s, 3H), 2.12 (s, 3H), 1.43 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.7 (s, +), 171.2 (s, +), 159.1 (s, +), 155.4 (s, +), 154.8 (s, +), 150.5 (s, +), 146.1 (s, +), 136.1 (s, +), 134.9 (s, +), 129.4 (d, -), 128.5 (d, -), 128.2 (d, -), 122.7 (d, -), 118.1 (s, +), 117.4 (d, -), 112.8 (d, -), 109.5 (d, -), 104.6 (d, -), 80.1 (s, +), 67.1 (t, +), 57.9 (d, -), 56.9 (d, -), 56.1 (q, -), 55.8 (q, -), 52.8
(q, -), 52.6 (q, -), 28.3 (q, -), 8.8 (q, -). $[\alpha]_D^{-} -4.2^\circ$ (c = 0.66, CHCl$_3$). HRMS. Found: 551.2028; calcd for C$_{29}$H$_{31}$N$_{2}$O$_9$ (M$^+$-Boc): 551.2029. A molecular ion could not be obtained for this compound. m/z 593(1), 578(2), 553(3), 552(5), 551(3), 496 (4), 495(18), 494(53).
2.5. References and Notes


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Chapter 3

Ristocetin CFG Ring Cyclization Model Study
3.1 General

The objective of this chapter is to make a CFG ring moiety of a model compound of ristocetin A using the arene-manganese chemistry to probe potential problems anticipated during the synthesis of ristocetin A.

With a successful synthesis of a ristomycinic acid derivative which represents the characteristic structure and some of the difficulties in the synthesis of ristocetin A, we turned our attention to the macrocyclization.

In a previous study, macrocyclization of a model compound which resembled the ABE ring of the ristocetin A failed\(^1\) and similar difficulties were reported in a recent paper.\(^2\) Therefore in the present study, cyclization of a model compound which represents the CFG ring moiety of the ristocetin A is addressed. The hydroxy functional group on the C-ring unit is known\(^3\) not to be important for binding of the D-ala-D-ala terminus to the bacterial cell wall mucoprotein and it was omitted at this time for convenience.

![Chemical structures](image)

**Figure 1.3.1.** Relationship Between CFG Model 1.3.1 and Ristocetin A.

For the synthesis of model compound 1.3.1, it is possible to approach from two pathways as shown in Scheme 1.3.1. Pathway A was chosen first because our
Scheme 1.3.1. Two Pathways for the Synthesis of CFG Model 1.3.1.
3.2 Macrocyclization of CFG Model Compound via Pathway A

Protection of Phenylalanine. The synthesis of the CFG model 1.3.1 started from the synthesis of the protected phenylalanine 1.3.3 which constitutes the C ring moiety.

![Chemical Reaction Diagram]

**Scheme 1.3.2.** Protection of Phenylalanine.

Protection of the amino group with benzylchloroformate (CbzCl) was quantitative in the presence of sat. sodium carbonate. Reaction in the presence of sat. NaHCO₃ solution was poor (38%).

Because of the base sensitivity of the F and G ring arylglycine units and the presence of an acid sensitive Boc protecting group on the G ring amino group, it was necessary to employ a carboxyl protecting group which can be cleaved under neutral conditions. It is known that the methoxylethoxymethyl (MEM) ester is deprotected under neutral conditions with MgBr₂-Et₂O in ether.⁵ Thus, MEMCl was employed in the protection of the carboxylic group and it afforded the MEM ester 1.3.3. in 87% yield in the presence of Bu₄NI.⁶

Synthesis of the C/G Ring Unit Dipeptide. For the synthesis of 1.3.6, 1.3.3 was deprotected using Pd/C (10%) under H₂ atmosphere. However, amine 1.3.4 was very unstable and 4 h stirring in EtOAc led to its complete destruction (no spot on TLC).
This instability of amines was also seen in the protected ristomycinic acid synthesis (see Chapter 2). Fortunately, hydrogenolysis was complete in 15 minutes in ethanol. The ethanol was removed in vacuo at room temperature by co-evaporation with dichloromethane, followed by pumping (3 min) and the reaction mixture was immediately dissolved in dry dichloromethane. Coupling of this amine with the azidoarylacetic acid \textbf{1.3.5} afforded the dipeptide \textbf{1.3.6} in 90% yield (Table 1.3.1, entry 1 vs 3).

\[
\begin{align*}
&\text{MEMO}_2\text{C}_\text{H}_2\text{NHBz,} \quad \text{MEMO}_2\text{C}_\text{H}_2\text{NH}_2, \\
&\begin{array}{c}
\text{Condition 1:} \\
\text{Condition 2:} \\
\text{1.3.5, EDC, HOBT} \\
\end{array}
\end{align*}
\]

\textbf{Scheme 1.3.3. Synthesis of Dipeptide 1.3.6.}

Generally the diastereomeric ratio obtained from this reaction was \(\sim 87\%\) (14:1) based on \(^1\text{H}\) NMR, and the ratio is almost the same as the enantiomeric ratio (13:1) of \textbf{1.3.5}. This suggested that no racemization occurred during the peptide coupling through the well known oxazoline intermediate.\(^7\) However, we found that addition of the coupling agent EDC to a cooled (0 °C) mixture of amine (\textbf{1.3.4})/ carboxylic acid (\textbf{1.3.5}) and HOBT improved the ratio to 30:1 \(\sim 58:1\). This ratio was obtained reproducibly. Previously, amine was added to the mixture of carboxylic acid/ EDC and HOBT at 0 °C or rt. The origin of this high diastereomer ratio was not clear, and it is not likely that accidental fractionation of
the diastereomer occurred during the purification. It is possible that some racemization occurs during the coupling of 1.2.29 with (R) or (S)-MTPA, leading to the MTPA amide 1.2.30a/b that was used to determine the enantiomeric ratio (see Chapter 2). Another possibility is that some kinetic resolution occurs during the peptide coupling. However, further investigation was not made.

**Table 1.3.1 Yields and Diastereomeric Excess of the Dipeptide.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deprotection Conditions(^a)</th>
<th>Reaction Conditions(^b)</th>
<th>Yield (d.e.)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc, 4 h</td>
<td>rt, 0.5 h</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>EtOH, 1 h</td>
<td>rt, 4 h</td>
<td>85% (&gt;14:1)</td>
</tr>
<tr>
<td>3</td>
<td>EtOH, 15 min.</td>
<td>rt, 2 h</td>
<td>90% (&gt;14:1)</td>
</tr>
<tr>
<td>4</td>
<td>&quot;</td>
<td>0 °C, 1 h - rt, 10 min</td>
<td>86% (14:1) --&gt;58% (24:1)(^d)</td>
</tr>
<tr>
<td>5(^b)</td>
<td>&quot;</td>
<td>0 °C, 1.3 h - rt, 20 min</td>
<td>89% (58:1)</td>
</tr>
</tbody>
</table>

\(^a\) deprotection was performed under H\(_2\) atmosphere in the presence of Pd/C. \(^b\) Coupling was done with EDC (1.5 eq), HOBT (2.0 eq) in the dichloromethane solution. \(^c\) determined by \(^1\)H NMR. \(^d\) recrystallization yield from hexanes/Et\(_2\)O mixture.

**Transformation of Pipeptide 1.3.6 to Phenol 1.3.7.** Following similar precedents of transformation from 1.2.26 to 1.2.27 (86% yield), reduction of azide, *in situ* protection of the resulting amine, and deprotection of the benzyl ether was attempted with hydrogen over 10% palladium on carbon in EtOAc solution. However, the reduction or the deprotection of the benzyl group did not occur at all even at 52 psi. The starting material was quite soluble in EtOAc and the different behavior of dipeptide 1.3.6 compared with the similar compound 1.2.26 could not be rationalized.
Table 1.3.2. Transformation of Azido Dipeptide to Phenolic Dipeptide 1.3.7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>Products (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOAc, Pd/C (10%), Boc₂O</td>
<td>1 atm, 7 h, 2 atm, 17 h</td>
</tr>
<tr>
<td>2</td>
<td>EtOH, Pd/C (10%), Boc₂O</td>
<td>1 atm, 15 h</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>1 atm, 2 h then sat. NaHCO₃, 15 min</td>
</tr>
<tr>
<td>4</td>
<td>EtOH, Pd/C (10%, Degussa type)</td>
<td>1 atm, 1 h then Boc₂O in DMF, 4.5 h</td>
</tr>
<tr>
<td>5</td>
<td>CH₂Cl₂, Raney-Ni, Boc₂O</td>
<td>1 atm, overnight</td>
</tr>
<tr>
<td>6</td>
<td>Ph₃P, THF, Δ, 0.5 h then H₂O, Δ, 4.5 h</td>
<td>Boc₂O·CH₂Cl₂, 6.5 h</td>
</tr>
<tr>
<td>7</td>
<td>THF, Pd/C (5%), Boc₂O</td>
<td>18 h</td>
</tr>
</tbody>
</table>

Scheme 1.3.4. Deprotection/In situ Protection of Azidodipeptide 1.3.6.

When EtOH was employed, overnight reaction (s.m. is consumed in 15 min) under H₂ atmosphere (1 atm) provided the phenolic dipeptide 1.3.7. in 15% yield. During this process, TLC showed Boc protected benzyl ether 1.3.8 as a major intermediate, suggesting that azide reduction is faster than the debenzylisation
reaction. Debenzylation prior to azide reduction was not observed. Thin layer chromatography also showed the appearance of a highly polar material at the origin, presumably 1.3.10, as a major product and it seems that 1.3.10. does not react with the Boc₂O at neutral pH, for unknown reasons.

Scheme 1.3.5. Transformation of 1.3.6. to 1.3.7.

Based on this observation, selective reduction of azide and selective deprotection of the benzyl ether was attempted. Differentiation of the debenzylazation and azide reduction reaction by Degussa type 10% palladium on charcoal was poor (22%). Attempts to reduce the azide to the amine in the presence of the benzyl ether using Ph₃P to generate 1.3.9 were also unsuccessful. Reaction between starting material and triphenyl phosphine was very fast but
hydrolysis of the resulting iminophosphorane to the amine 1.3.9 in refluxing THF was not successful and only moderate yield was obtained.

Eventually, satisfactory results were obtained by employing 5% Pd/C, THF and Boc2O conditions (entry 7). Using 5% Pd/C, azide and benzyl ether reducing rates seems to be differentiated and the resulting amine 1.3.9 seems to react rapidly with Boc2O in THF solution before it is reduced further to amino phenol 1.3.10. During this reaction, a large spot corresponding to 1.3.8 was observed on TLC and this is debenzylated to give the desired compound 1.3.7 during the overnight reaction. The yield of this reaction was 78% on a 150 mg scale but with increased scale, the yield decreased.

**Aryl Ether Formation and Schöllkopf Nucleophile Addition Reaction.** The aryl ether formation reaction was performed following the protocol as described in the synthesis of the protected ristomycinic acid (Chapter 2).

![Chemical Structure](image)

The yield of this reaction is 70-80%, but separation of the arene manganese complex 1.3.12 from the starting material by precipitation was not successful. Solvents such as pentane, pentane/CHCl3 mixture (3:1), ether, benzene and carbon tetrachloride were not successful for this purpose but partial separation
was obtained by precipitation in cyclohexane. The product contained 5–10% of the starting material 1.3.7 according to NMR.

Reaction of the slightly contaminated arene manganese complex 1.3.12 with bislactim anion, followed by rearomatization with concomitant demetalation, afforded the desired product along with its diastereomer and demetalated starting material.

Scheme 1.3.6. Bislactim Addition Reaction to the Arene-manganese Complex 1.3.11.

Separation of the product 1.3.13a from the diastereomer 1.3.13b could be achieved using HPLC (M20 10/25 silica gel column) but side product 1.3.14 could not be separated from the desired product. The ratio between 1.3.13a:1.3.13b: 1.3.14 was ~15:4:11 (i.e., d.e. = 58%) by NMR based on integration of the F-ring methyl resonance. After HPLC separation, the calculated yield of 1.3.13a was 28%.
The mixture of the 1.3.13a and 1.3.14 (54, 46% respectively) was hydrolyzed to the corresponding amine which was protected as its benzylxycarbonyl (Cbz) urethane. In contrast to the case of compound 1.2.49a, the resulting amine required strong base to be protected as its benzylxycarbonyl urethane. Following the protocol for the ristomycinic acid synthesis, only moderate yield was obtained.

Table 1.3.3. Hydrolysis and Protection of the Bislactim Adduct 1.3.3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrolysis Condition</th>
<th>Cbz Protection Conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25 N HCl, rt, 1.5 h</td>
<td>NaHCO₃, rt, 3.5 h</td>
<td>18.4%</td>
</tr>
<tr>
<td>2</td>
<td>0.25 N HCl, rt, 2.5 h</td>
<td>NaHCO₃, rt, 3 h</td>
<td>7.4%</td>
</tr>
<tr>
<td>3</td>
<td>0.15 N HCl, rt, 1.5 h</td>
<td>NaHCO₃, rt, 4.5 h</td>
<td>not found</td>
</tr>
<tr>
<td>4⁺</td>
<td>0.25 N HCl, rt, 1.5 h</td>
<td>Pyridine, rt, 15 h</td>
<td>&quot;</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>&quot;</td>
<td>Na₂CO₃, 0 °C, 10 min</td>
<td>36%</td>
</tr>
</tbody>
</table>

a) Pyridine was premixed with CbzCl (2.6:3.0 eq. respectively) to avoid racemization of the amine and to the mixture was added the amine. b) Including the racemized products. Isolated yield of 1.3.15 was 67%.

Weaker base and prolonged reaction time resulted in lower yield. The best yield was obtained, however, by using partially saturated Na₂CO₃ (50%) at 0 °C. Based on HPLC analysis, although pure diastereomer 1.3.15 could be obtained using HPLC (tᵣₑₓ = 94 min, M20 10/25 silica gel column), it was accompanied with two side products, presumably diastereomers, in 1.6% and 3.5% yield (tᵣₑₓ = 90 min, 110 min respectively). The demetalated side product 1.3.14 was recovered in 46% yield, suggesting that Boc and MEM protecting groups are stable under the hydrolysis condition. However, this compound was also
accompanied by a side product, presumably the epimer, in 0.9% yield \((t_{ret} = 58 \text{ min and } 55 \text{ min, respectively})\). Based upon HPLC analysis, it was presumed that 7.5% racemization occurred at the F-ring unit chiral center and 3.5% at the G-ring unit chiral center.

Scheme 1.3.7. Hydrolysis and Protection of the Bislactim Adduct.

Deprotection of MEM Ester and Cyclization. The MEM ester of the pure diastereomer 1.3.15 was deprotected in ether solution in the presence of excess (5 ~ 7 eq) magnesium bromide etherate. The yield was over 80% but this compound is very labile and could not be purified by column chromatography or base extraction. As is known\(^5\), reaction in THF did not provide the product at all. It should be noted that the reaction mixture in ether solution does not show any spot on TLC until the product is hydrolyzed for 30 min with water or dilute acid.
Scheme 1.3.8. Removal of Protecting Groups.

Macrocyclization was performed using either a coupling reagent such as EDC or an active ester such as a pentafluorophenyl ester. For macrocyclization, dimerization and oligomerization is often a major problem (i.e., internal vs external peptide formation reaction) and to minimize this side reaction, the amino acid was cyclized in a highly dilute solution in dichloromethane at 0 °C. As a prerequisite to the EDC coupling, the Cbz protecting group of the 1.3.19 was deprotected using 10% Pd/C in EtOH, and EtOH was removed in vacuo. The resulting amino acid was dissolved in dichloromethane and added at 0 °C dichloromethane solution of EDC and HOBT over 6-10 h. For the active ester method, the protected amino acid was coupled with pentafluorophenol using EDC, and the Cbz group was removed to allow cyclization. However, in our case, the yield of the pentafluorophenyl ester was poor (10-25%). From both reactions, a cyclized product was obtained as shown in Table 1.3.4. Macrocyclization by the imide coupling agent (EDC) furnished the product 1.3.22a (trace ~ 19% yield) and 1.3.22b (14 ~ 29% yield) whose HPLC retention times were t_{ret} = 25 min and 36 min respectively (M20 10/25 silica gel column, hexanes:EtOAc = 2:3, 5 mL/min).
Scheme 1.3.9. Macrocyclization to give Tripeptides

In the case of the cyclization by using the active ester, 1.3.22a was not detected. The compound 1.3.22b was obtained as a mixture with an unknown side product. The side product, presumably arising by macrocyclization of a diastereomer that occurred due to the basic conditions (sat. NaHCO₃/CHCl₃/0 °C), showed a very similar structure (NMR) and it was inseparable from 1.3.22b by HPLC. The ratio of 1.3.22b:side product was ~3:2 and the combined yield was ~30%. Because of the low yield of the active ester and side product formation during the macrocyclization, this method was not studied further.
### Table 1.3.4. Conditions and Yields of Macrocyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>s.m.</th>
<th>Conc. (mM)</th>
<th>Rxn Conditions</th>
<th>1.3.22a</th>
<th>1.3.22b</th>
</tr>
</thead>
</table>
| 1     | 1.3.20 | 0.2        | 1) a 0 °C, CH₂Cl₂, 3 h  
       |        |            | 2) b 0 °C-rt, 3.8 h | 11      | 14      |
| 2     | "      | 1.0        | 1) 0 °C, CH₂Cl₂, 5 h  
       |        |            | 2) 0 °C-rt, 3.8 h | trace   | 29      |
| 3     | "      | 0.8        | 1) 0 °C, CH₂Cl₂, 5 h  
       |        |            | 2) 0 °C-rt, 16 h | 19      | 22      |
| 4c    | 1.3.21 | 0.5        | CHCl₃/ sat. NaHCO₃,(1:1), rt, 4 h  
       |        |            | not found | ~ 20d   |

a) Conditions for addition of starting material to EDC, HOBT solution.  b) Reaction time after addition.  c) all starting material was added at once.  d) product contained other side product which is inseparable from 1.3.22.  The side product showed a spectrum similar to 1.3.22 and the ratio is ~3:2.

### Structure Determination of Cyclization Products.

One of the problems of macrocyclization is the occurrence of undesired intermolecular peptide couplings including dimeric or oligomeric cyclization. To minimize this possibility, reactions are performed under high dilution (typically 8 mM) and in the case of cyclization of 1.3.20, the concentration was 0.2 ~ 0.8 mM. However, it is known that dimer formation reaction is the exclusive processes, in some cases, even under high dilution. For example, during the model study for the synthesis of bouvardin, Boger's group found that compound 1.3.23 produced only cyclic dimer under various conditions. Moreover, proton NMR is deceptively simple because of molecular symmetry and also fits with the monomer structure. The dimer structure was proven using mass spectrometry which shows the parent peak for the dimer (5% intensity) along with that of the monomer (base peak).
Scheme 1.3.10. An Example of a Cyclic Dimer Formation Reaction

Along with this problem, it was recently shown that small cyclic peptides can be obtained as stable atropisomers\(^9\) as shown in the Scheme 1.3.11. In the case of the 12-membered ring which represents a vancomycin ADE ring unit, oxidative cyclization afforded two atropisomers in a ratio of 78:22. The structure that resembles the natural conformation was not necessarily preferred thermodynamically over the unnatural structure. Similar observations of the

Scheme 1.3.11. An Example of Cyclic Conformer Formation during Macrocyclization.

formation of atropisomers during the synthesis of a 15-membered ring has been reported.\(^{10}\) In the case of CDP-I-M and CDP-I-m (17-membered rings) which are degradation products of vancomycin, slow equilibration \((t_{1/2} = 4 \sim 8\) h depending on pH) was established at rt and was complete after 24 h.\(^{11}\)
In our case, proton NMR of both products 1.3.22a and 1.3.22b (Figure 1.3.2) were very similar. Both spectra matched well with the monomer structure and no other unexplained peaks were observed. It was not possible, however, to tell whether both compounds are atropisomeric monomers or a monomer and a dimer.

To determine if any dimer was indeed formed, mass spectrometry was used to determine the molecular weight. High resolution mass spectrometry (HRMS) of 1.3.22b by electron impact ionization at 70 eV showed the M$^+$ ion peak at 633.2698 (calculated mass = 633.2686), however, there were many fragments heavier than the molecular mass. The FAB mass spectrum also showed similar high molecular weight peaks. With field-desorption mass spectroscopy, which usually shows only molecular ion peaks, monomer (M$^+$Na), dimer (2M$^+$Na or associated monomer) and trimer (3M$^+$Na) peaks were obtained along with fragmentations (Figure 1.3.3). Because association of molecules with H$^+$ or Na$^+$ during vaporization is quite often observed in mass spectrometry, it could not be concluded with certainty whether the 2M$^+$ and 3M$^+$ originated from cyclic dimers and trimers or from association of two or three monomers.

Eventually, we obtained the mass spectra for 1.3.22a and 1.3.22b which showed no sign of high molecular weight fragmentation. Electron Impact ionization (EI) was used to ionize the molecule at the lowest possible energy (18eV for Kratos MS25A), along with stepwise increase of temperature. Molecular peaks appeared from 220 – 250 °C for both compounds and showed only the monomer (M$^+$ = 633.2684 for 1.3.22a and 633.2702 for 1.3.22b, calc'd molecular mass = 633.2686) and fragments of lower mass than the molecular ion in both cases.
Thus, it is likely that the high molecular weight fragmentations observed in the earlier spectra originated from sodium (or hydrogen) bound dimer and trimer (Figure 1.3.4). This is further reinforced by tandem mass spectrometry analysis performed at the Midwst Center for Mass Spectrometry. Tandem mass spectrometry with collisional activation of the dimeric fragments (2MH\(^+\), observed mass = 1267.5) produced predominantly the monomer ions (MH\(^+\), observed mass = 634) as well as fragments with masses lower than the monomer (see Figure 1.3.5) along with small amount of the fragment which lacks Boc group from the dimer. This suggests that almost all the dimers decompose to cyclic monomer prior to the loss of the Boc group during the collisional activation, which in turn suggests that the observed dimeric (and trimeric) peak is
Figure 1.3.4. Mass Spectrum of 1.3.22a and 1.3.22b at 18 eV Ionization Energy.
Figure 1.3.5. Tandem Mass Spectrum of 1.3.22b.
the weakly associated cyclic monomer. Also in view of the observation of a single compound in the $^1$H NMR spectra of 1.3.22a and b, these experiments establish that these compounds are atropisomeric cyclic monomers.

Knowing that 1.3.22a and 1.3.22b are atropisomers, their conformations were deduced, as shown in Figure 1.3.6 and 1.3.7, using NOESY and molecular modeling (Biograf). There are some minor discrepancies between simulated structures and NOESY observations. As an example, in the structure 1.3.22a $H_{X3}$ is almost parallel to $H_{3b}$ (ristocetin numbering is used). However, NOE between $X_3$ and 3f was observed, albeit small, suggesting that $H_{X3}$ is not parallel. Overall, however, they match each other quite well.

When the simulated structures are compared with published results, only compound 1.3.22a is similar to the structure of teicoplanin, a molecule that is closely related to ristocetin A, that was proposed by Williams except for the conformation of the amide group between the C and F-ring units.

In our case (for easy comparison, ristocetin A numberings are used), no NOE was observed between proton $W_3$ and 3f and instead, a large NOE was observed between $X_2$ and $W_3$. In the case of Charkraborty's work, in which they made a CFG ring unit of teicoplanin which is very similar to our molecule, a large NOE was observed between $W_3$ and $X_2$ (11%) along with 9 and 3% NOE between $W_3$ and 3f and, between $W_3$ and $X_3$ respectively. This may suggest that proton $W_3$ is pointing away from the F-ring unit, as is the case with ours, or at least lies between 3f and $X_2$. $W_3$ is reported to point in the direction of 3f. In ristocetin A, a large NOE was observed between proton $X_3$ and 3b but not with proton 3f. The calculated distance between proton $X_3$ and 3b was 2.4 Å (by NMR).
Figure 1.3.6. Stereoview of Energy Minimized Structure of 1.3.22a.
Figure 1.3.7. Stereoview of Energy Minimized Structure of 1.3.22b.
Figure 1.3.8. NOESY Spectrum (300 MHz) for 1.3.22a.
Figure 1.3.9. NOESY Spectrum (300 MHz) for 1.3.22b.
Figure 1.3.10. Suggested Structure of 1.3.22a and 1.3.22b and Similar Compounds.
a: Teicoplanin. Taken from reference 15. b: CFG ring moiety of teicoplanin. Taken from reference 14. c: Ristocetin A. Taken from reference 13.
small NOE were observed between X₁/1f and X₁/1b, because of oscillation of the G-ring unit. In the case of 1.3.22a, a strong NOE between X₃ and 3b was observed but with small NOE between X₃ and 3f. The calculated distance (by Biograft) between proton X₃ and 3b was 2.34 Å.

The NOE between X₁ and 1b and X₁ and 1f was small in this case, suggesting a strong similarity between 1.3.22a and ristocetin A. In the case of Charkraborty's work, which is very close to our model compound, X₃ showed a NOE both with 3b (8%) and 3f (2%) similar to our case. However, X₁ showed NOE only with proton 1b (7%) but not with 1f, suggesting that proton X₁ is almost parallel to 1b.

Table 1.3.5. Summary of Observed nOe’s for Compounds 1.3.22a and b, Compared with Ristocetin A.

<table>
<thead>
<tr>
<th>Protons</th>
<th>1.3.22a distance</th>
<th>nOe</th>
<th>1.3.22b distance</th>
<th>nOe</th>
<th>Ristocetin A距离</th>
<th>nOe</th>
</tr>
</thead>
<tbody>
<tr>
<td>X₁, 1f</td>
<td>3.53</td>
<td>+c</td>
<td>2.38</td>
<td>++</td>
<td>2.5</td>
<td>na</td>
</tr>
<tr>
<td>X₁, 1b</td>
<td>2.63</td>
<td>+</td>
<td>3.76</td>
<td>none</td>
<td>3.7</td>
<td>“</td>
</tr>
<tr>
<td>X₁, W₂</td>
<td>2.21</td>
<td>+</td>
<td>2.64</td>
<td>++</td>
<td>“</td>
<td>“</td>
</tr>
<tr>
<td>X₂, W₂</td>
<td>2.94</td>
<td>none</td>
<td>2.88</td>
<td>+</td>
<td>“</td>
<td>“</td>
</tr>
<tr>
<td>X₂, W₃</td>
<td>2.18</td>
<td>++c</td>
<td>3.62</td>
<td>+</td>
<td>“</td>
<td>“</td>
</tr>
<tr>
<td>X₃, 3f</td>
<td>3.78</td>
<td>+</td>
<td>3.75</td>
<td>none</td>
<td>3.5</td>
<td>“</td>
</tr>
<tr>
<td>X₃, 3b</td>
<td>2.34</td>
<td>++</td>
<td>2.38</td>
<td>++</td>
<td>ca 2.5-3.1</td>
<td>“</td>
</tr>
<tr>
<td>X₃, W₃</td>
<td>2.19</td>
<td>+</td>
<td>2.91</td>
<td>none</td>
<td>“</td>
<td>“</td>
</tr>
<tr>
<td>W₁, 1b</td>
<td>4.52</td>
<td>none</td>
<td>2.43</td>
<td>+</td>
<td>“</td>
<td>“</td>
</tr>
<tr>
<td>W₁, 1f</td>
<td>2.22</td>
<td>+</td>
<td>4.39</td>
<td>none</td>
<td>“</td>
<td>“</td>
</tr>
<tr>
<td>W₃, 3f</td>
<td>3.62</td>
<td>none</td>
<td>2.48</td>
<td>++</td>
<td>ca 2.6</td>
<td>“</td>
</tr>
<tr>
<td>3f, 1b</td>
<td>2.32</td>
<td>++</td>
<td>3.38</td>
<td>++</td>
<td>2.7</td>
<td>“</td>
</tr>
</tbody>
</table>

a) In angstroms, from Biograft structures. b) From reference 15; some data corresponds to the ristocetin pseudoaglycone-Ac2-Lys-D-Ala-D-Ala complex. c) +: weak – medium, ++: strong intensity. d) not available.
The revised structure of ristocetin A, suggested by Harris does not match with our structure at the diaryl ether and proton W3. The suggested orientation of the amide proton (W2) between the C- and G-ring units does not match the observed NOE between W2 and X1. The earlier unrevised structure is in better agreement with our NOE data.

The structure 1.3.22b is unprecedented in this type of molecule. It does not match other structures so far reported. In contrast to the structure 1.3.22a, a large NOE was observed, this time between W3 and 3f, thus indicating that W3 is pointing toward proton 3f as was suggested in Chakraborty's work14. Also, a large NOE between X1 and 1f and no NOE between X1 and 1b suggest that X1 is almost parallel with proton 1f.

In a molecular dynamics simulation using Biograf, structure 1.3.22b seems to be the most stable and the structure suggested by Williams15 provided 1.3.22b as an energy minimized structure. In simulations starting from several different structures, 1.3.22b was obtained as a minimum energy. When 1.3.22a and 1.3.22b were simulated, their own structures were observed as minima.

3.3. Macrocyclization of CFG Model Compound via Pathway B.

Though it was possible to obtain a cyclized product using pathway A, this strategy has some limitations. It was difficult to make large amounts of the phenolic dipeptide 1.3.7 and purification of the triarene-manganese complex 1.3.11 was very difficult. The requirement of using HPLC for the separation of the diastereomers 1.3.15-18 was another difficulty. To avoid these difficulties, and to test a new cyclization route, pathway B was tested as shown in Scheme
1.3.1. It started from the synthesis of MEM ester 1.3.25 from the azido acetic acid 1.2.27 using methoxyethoxymethyl (MEM) chloride in the presence of Bu₄NI. The diastereomeric excess was measured as its (R)-MTPA amide by ¹⁹F NMR, as described before, and the ratio was 11.5:1. Hydrogenation of 1.3.25 and in situ protection of the resulting amine with Boc anhydride in THF afforded the arylglycine derivatives 1.3.26 in 80% yield. Scaling up did not decrease the yield.


Coupling of 1.3.26 with the arene-manganese complex 1.2.23 afforded the diarene-manganese complex 1.3.28. Precipitation of the crude product from pentane afforded almost pure material. The bis-lactim addition to this compound was performed following the usual protocol. After the reaction was quenched with NH₄Cl, and extracted with dichloromethane, unreacted manganese complex was recovered in 34% yield by precipitation from pentane. At this time, it was found that dealkylation of the resulting dienyil manganese complex, which occurs
during the rearomatization reaction by NBS, is minimized in CH$_3$CN (see chapter 2) and the product was obtained in 44 ~ 56% yield (see later) after aromatization using these conditions.

![Chemical structure](image)

Scheme 1.3.13. Bislactim Addition Reaction to the Manganese Complex 1.3.28.

The diastereoselectivity of the bis-lactim addition reaction/rearomatization was 3:1 to 4:1 and the side product 1.3.31 was obtained in 9 ~ 16% yield. Diastereomer 1.3.30 could be separated using column chromatography. However, it was not possible to separate the product 1.3.29 from the side product even with HPLC. The separated mixture was hydrolyzed using 0.25N HCl and the resulting amine was coupled with the protected phenylalanine 1.3.32 in ~ 93% yield using EDC and HOBT. However, in this case, product was obtained with ~ 10 % side product, presumably the diastereomer, which is inseparable from the desired product even by HPLC.
Scheme 1.3.14. Cyclization of Tripeptides 1.3.34 and 1.3.35.

The MEM ester of the tripeptide was deprotected following the earlier protocol to afford 1.3.34, the Cbz protecting group was removed, and the product was cyclized following the reaction conditions used in pathway A.

Cyclization via the active ester was also tested as shown in the Scheme 1.3.14. Pentafluorophenyl ester 1.3.35 was obtained in 60% yield using DCC (without HOBT). It was observed that use of EDC instead of DCC gives a poor yield of the pentafluorophenyl ester. Use of HOBT also leads to a poor yield (see
Scheme 1.3.9.). Interestingly, 1.3.35 exists as a 1:1 mixture of two conformers (NMR) at rt at 50 °C, the signals coalesced.

The cyclized products 1.3.22a and 1.3.22b were obtained by both methods as shown above. Yields of 1.3.22a and 1.3.22b were 5 and 12 ~ 53%, respectively, when cyclized using EDC. With the active ester method, they were obtained in 10 and 32 % yield, respectively.

Table 1.3.6. Conditions and Yields of Macrocyclization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>s. m.</th>
<th>Conc. (mM)</th>
<th>Rxn Conditions</th>
<th>Results (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.3.34</td>
<td>0.7</td>
<td>1) a) 0 °C, CH₂Cl₂, 5h 2) b) 0 °C-rt, 3h</td>
<td>4.5 53</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1.0</td>
<td>1) a) 0 °C, CH₂Cl₂, 8h 2) b) 0 °C-rt, 7h</td>
<td>5.5 12</td>
</tr>
<tr>
<td>2</td>
<td>1.3.35</td>
<td>1.0</td>
<td>1) dioxane, Et₃N (5.0 eq), 90 °C, 2) 90 °C, 1 h</td>
<td>10 32</td>
</tr>
</tbody>
</table>

a) Conditions for addition of starting material to EDC, HOBT solution. b) Reaction time after addition.

When pathway B is compared with pathway A, though pathway B is more accommodating for large amount of materials, it afforded decreased yield of 1.3.22a (which has the conformation closest to the CFG ring unit of ristocetin A) and increased yield of 1.3.22b (undesired conformer). By pathway B, the cyclization reaction was not as clean as pathway A (HPLC).

Interconversion of 1.3.22a and 1.3.22b was tested in hot DMSO-d₆ in the hope of transforming 1.3.22b to 1.3.22a. Conformer 1.3.22b did not show any
change after 2 h at 115 °C but after 2 h at 160 °C, it was completely destroyed, giving 4 ~ 5 products. These products were treated with excess amount of Boc₂O and, after a few days, compared with 1.3.22a. However, no matching products were found from the reaction.

3.4 Conclusions.

After failure of the attempted cyclization of a model compound corresponding to the ABE ring system in ristocetin A, cyclization of the CFG ring moiety was tested using a model compound which lacks the side chain hydroxyl group on the C-ring unit. Cycloamidation was tested using two different methods and two different bond dissections. From pathway A (Scheme 1.3.2), two cyclic monomers 1.3.22a and 1.3.22b was obtained in 19 and 22% yield. According to NOESY and molecular modeling, 1.3.22a is closer to the CFG ring moiety of ristocetin A, except for the conformation of proton W₃. Compound 1.3.22b was totally different from 1.3.22a in conformation and is apparently unprecedented.

Pathway B also afforded both 1.3.22a and 1.3.22b. This method was more effective than pathway A for the preparation of large amounts of material. However, 1.3.22a was obtained ~5% yield and 1.3.22b was obtained in 50% yield. Conversion between 1.3.22a and 1.3.22b did not occur in 160 °C DMSO d-6. The active ester method tested so far did not lead to useful results. It suffered a low yields during the ester formation reaction and the cyclization itself provided similar yield. The requirement for base during the cyclization made this a less attractive route owing to the potential for racemization of the glycine moieties.
3.5 Future Work

Although the above synthesis of heterodetic cyclic peptides was successful, it is necessary to search for a better method to make a desired monomeric conformer. Because of limited experiments, it is unknown whether the EDC/HOBt coupling method is the best one for this purpose. Recently, Ehrlich reported efficient new cyclic peptide coupling agents such as HAPyU and TAPiPu (Figure 1.3.12), which may be excellent for our system. Also, a method which can control the relative yields of the two conformers (1.3.22a and 1.3.22b) has to be developed.

![Figure 1.3.11. New Cyclic Peptide Coupling Agents.](image)

So far, we obtained only conformers of the desired structure. Interestingly, Boger reported that the 14-membered ring of RA-VII underwent a conformational change from E to unstable Z-amide (natural form in RA-VII) when the 18-membered ring next to it was built (natural from in RA-VII). In our case and possibly in the Charkraborty's case, amide proton W3 seems to adopt the orientation shown in the structure 1.3.22a. It is not certain whether compound 1.3.22a will undergo conformational change when the BCF ring is built.
A big challenge will be the hydrolysis of the ester group of the cyclic monomer. However, this material may not be as base sensitive as the substrate used in the synthesis of protected ristomycinic acid because of a necessary conformational change. However, it would still be difficult to apply commonly used basic hydrolysis methods to the cyclic compound.

**Figure 1.3.12. Hydrolysis of the Cyclic Monomer.**

Enzymatic hydrolysis by subtilisin will not be possible\(^{19}\) because of the (S)-stereochemistry of the C-ring unit in our case and, hydrolysis by the TMSI\(^{20}\) or TMSCl/NaI methods\(^{21}\) may be very difficult because of the Boc group and aryl
methyl ethers which undergo a cleavage prior to the cleavage of a methyl ester. Careful planning will be necessary to accommodate these difficulties, during the attachment of the F-ring glycine side chain.
3.5 Experimental Section

**General**  All reactions were conducted under a dry N₂ or Ar atmosphere, unless otherwise noted. N₂ or Ar was passed through anhydrous CaSO₄. THF, ether, benzene and toluene were dried using Na/benzophenone and CH₂Cl₂ was distilled from CaH₂. For chromatography, distilled hexanes and EtOAc were used and ether was distilled over LiAlH₄. Acetonitrile was used as purchased.

¹H, ¹³C, ¹⁹F, ³¹P NMR spectra were recorded using either Varian Gemini-300 (300 MHz) or Varian XL 200 (200 MHz) spectrometers using CDCl₃, benzene-d₆, D₂O, DMSO-d₆, CD₃CN and CD₂Cl₂ solvents. ¹H NMR was referenced to TMS or CHCl₃ (7.26 p.p.m.). ¹³C was referenced to CHCl₃ (77.0 p.p.m.) and the results of attached proton test (APT) are recorded as (+) or (-), and multiplicity of the carbon is denoted as (s), (d), (t) and (q). ¹⁹F NMR was referenced to CFCl₃ as a external standard. Mass spectra were recorded, in house, on a Kratos MS 25A instrument or performed by the Midwest Center for Mass Spectrometry, NE. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN.

Infrared spectra were recorded on a Perkin-Elmer Series 1600 FT-IR using a CHCl₃ in NaCl chamber. Optical rotations were recorded on a Perkin-Elmer 141 polarimeter. Melting points were measured on a Thomas-Hoover melting apparatus without correction.

Preparative HPLC was performed on a Gilson HPLC using a M20 10/25 silica gel column.
N-[(2R)-Azido-2-(3-benzyloxy-4-methoxyphenyl)acetyl]-D-phenylalanyl

Methoxyethoxymethyl Ester (1.3.6)

A solution of Cbz protected (D)-phenylalanyl ester 1.3.3 (742 mg, 1.92 mmol, 1.0 eq) dissolved in EtOH (45 mL) was stirred with Pd/C (10 %, 742 mg) for 15 min under H₂ atmosphere until the starting material was consumed. The EtOH was evaporated in vacuo and the residue was co-evaporated with CH₂Cl₂ (3 x 45 mL) and placed under high vacuum for 3 min. The resulting amine was dissolved in CH₂Cl₂ (45 mL), dried with Na₂SO₄ and then added in one portion, via cannula, to an ice cooled solution of the azidoacetic acid 1.3.5 (599.5 mg, 1.91 mmol, 1.0 eq) and HOBT(517.5 mg, 3.83 mmol, 2.0 eq) in CH₂Cl₂ (36 mL). EDC (550.7 mg, 2.87 mmol, 1.50 eq) was added to the mixture, which was then stirred for 1.3 h at 0 °C and 20 min at rt. The reaction mixture was washed with brine (2 x 25 mL), dried (MgSO₄) and filtered through SiO₂ (hexanes:EtOAc = 3:2) to afford 832.5 mg (79.4 %) of a pale yellow solid which showed a 30:1 ratio (93.5 %) of diastereomers by NMR (300 MHz). An analytical sample was prepared using HPLC (Partisil M20 10/25, hexanes:EtOAc = 1:1, 5 mL/min, 254 nm, tᵣ = 59 min); mp 93.5-94.5 °C; Rf 0.66 (EtOAc); IR (CHCl₃) 3401, 3021, 3019, 3016, 2933, 2116 (-N₃), 1741, 1682, 1593, 1513, 1455, 1443, 1428 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.45-7.21 (m, 7H), 7.06-7.03 (m, 2H), 6.8 -6.75 (m, 4H), 5.41(d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 5.37 (d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 5.08 (s, 2H, -OCH₂Ph), 4.94 (s, 1H, N₃CH.CO₂-), 4.85 (ddd, J₁ = 8.1Hz, J₂ = 6.5 Hz, J₃ = 5.8 Hz -HNCH₂CH₂Ph.CO₂-), 3.89 (s, 3H, CH₃OAr), 3.74-3.71 (m, 2H), 3.54-3.51 (m, 2H), 3.38 (s, 3H, CH₃OCH₂CH₂O-) 3.17 (dd, J₁ = 14.0 Hz, J₂ = 5.8 Hz, 1H, 1/2 ArCH₂CH(NH)CO₂-), 3.07 (dd, J₁ = 14.1 Hz, J₂ = 6.5 Hz, 1H, 1/2 ArCH₂CH(NH)CO₂-); ¹³C NMR (75 MHz, CDCl₃) δ 170.66 (s, +), 167.80
(s, +), 150.33 (s, +), 148.44 (s, +), 136.58 (s, +), 135.33 (s, +), 129.19 (d, -), 128.59 (d, -), 128.52 (d, -), 127.94 (d, -), 127.45 (d, -), 127.15 (d, -), 126.78 (s, +), 120.77 (d, -), 113.06 (d, -), 111.79 (d, -), 90.47 (t, +), 71.33 (t, +), 71.06 (t, +), 69.80 (t, +), 66.85 (d, -), 59.03 (q, -), 55.96 (q, -), 53.07 (d, -), 37.43 (t, +); [α]D -123.0° (c 1.17, CHCl3); HRMS: found 548.2216; calcd for C29H32N4O7: 548.2216. MS: m/e 548 (0.4), 520 (1.3), 368 (1), 354 (0.4), 295 (0.6), 284 (1.3), 283 (0.6), 270 (0.6), 257 (1.1).

(2R)-[[((1,1)-Dimethylethoxy]carbonyl]amino]-2-[[3-hydroxy-4-methoxyphenyl]acetyl]-D-penylalanyl Methoxymethoxymethyl Ester (1.3.7)

A mixture of azidodipeptide 1.3.6 (155.6 mg, 0.28 mmol, 1.0 eq), Pd/C (5 %, 160.1 mg) and Boc2O (221.9 mg, 1.0 mmol, 2.6 eq) in THF (34 mL) was stirred under H2 atmosphere for 48 h until all the starting material was consumed. After evaporation of the solvent in vacuo, the crude product was column chromatographed over SiO2 (hexanes: EtOAc = 1:1) to afford 125.3 mg (81.2 %) of the product 1.3.7 as a yellow liquid. Diastereomeric excess of the product was 96% by 1H NMR. An analytical sample was prepared using HPLC (Partisil M20 10/25, hexanes:EtOAc = 1:4, 5 mL/min, 254 nm UV detector, tR = 27 min); Rf 0.57 (EtOAc ); IR (CHCl3) 3539, 3420, 3020, 2933, 1743, 1710, 1684,1507, 1456, 1443 cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.33 - 7.23 (m, 3H), 7.10 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 7.7 Hz, 1H), 6.84 (s, 2H), 6.78 (s, 2H), 6.18 (d, J = 7.4 Hz, 1H, ArCH2CH(NH)CO2−), 5.78 (s, 1H, PhOH), 5.64 (bs, 1H, BocNH−), 5.30 (d, J = 6.0 Hz, 1H, CO2CH2OCH2−), 5.26 (d, J = 6.0 Hz, 1H, CO2CH2OCH2−), 5.00 (bd, J = 5.5 Hz, 1H, BocNHCH(Ar)CONH−), 4.81 (ddd, J1 = 7.7 Hz, J2 = 5.9 Hz, J3 = 5.8 Hz,
ArCH₂CH(NH)CO₂⁻, 3.86 (s, 3H, CH₃OAr), 3.64 - 3.61 (m, 2H), 3.51-3.48 (m, 2H), 3.36 (s, 3H, CH₃OCH₂CH₂O⁻), 3.17 (dd, J₁ = 14.0 Hz, J₂ = 5.8 Hz, 1H, 1/2 ArCH₂CH(NH)CO₂⁻), 3.09 (dd, J₁ = 14.0 H, J₂ = 5.9 Hz, 1H, 1/2 ArCH₂CH(NH)CO₂⁻), 1.41 (s, 9H, (CH₃)₂O₂⁻); ¹³C NMR (75 MHz, CDCl₃) δ 170.87 (s, +), 170.39 (s, +), 155.44 (s, +), 147.16 (s, +), 146.39 (s, +), 135.87 (s, +), 131.12 (s, +), 129.68 (d, -), 128.98 (d, -), 127.50 (d, -), 119.52 (d, -), 113.68(d, -), 111.28 (d, -), 90.66 (t, +), 80.43 (s, +), 71.71 (t, +), 69.96 (t, +), 59.37 (q, -), 58.58(d, -), 56.25 (q, -), 53.88 (d, -), 37.80 (t, +), 28.64 (q,-) [α]D -57.4° (c 0.74, CHCl₃); HRMS: found 532.2414; calcd for C₂₇H₃₆N₂O₉: 532.2421. MS: m/e 532 (0.7), 459 (0.9), 368 (1.0), 326 (0.8), 313 (0.9), 264 (0.9), 255 (1.9).

3-[(Tricarbonyl)(η⁶ 2-methyl-3-methoxyphenylxoy)manganese][N-t-butoxy carbonyl-(R)-4-methoxyphenylglycinyl]-D-[phenylalanyl Methoxyethoxymethyl Ester] hexafluorophosphate (1.3.12)

To an ice cold solution of phenolic dipeptide 1.3.7 (743.6 mg, 1.37 mmol, 1.0 eq) dissolved in dichloromethane (53 mL) was added NaH (54.4 mg, 1.36 mmol, 0.99 eq) at one portion and the mixture was stirred for 30 min at 0 °C. The resulting phenoxyde solution was transferred via cannula to the suspension of arene-manganese complex 1.2.23 and AgBF₄ (1.07 g, 9.74 mmol, 7.0 eq) in dichloromethane (97 mL), and the mixture was stirred 1 h at 0 °C. Reaction was quenched with 0.5 M NH₄PF₆ solution and the reaction mixture was stirred vigorously for 30 min at rt. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (3 x 70 mL) and the combined organic layer was washed with NH₄PF₆ solution (50 mL) and dried (MgSO₄). After filtration and
evaporation of the solvent, concentrated solution was added dropwise to the cyclohexane (200 mL) to afford 900 mg (88%) of a yellow solid. The product contained ~5% of the starting material 1.3.7. IR (CHCl$_3$) 3411, 3016, 2980, 2932, 2070, 2004, 1746, 1709, 1683, 1601, 1511, 1486, 1472, 1427 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.37-6.97 (m, 7H), 6.61 (bs, 1H, (CO)$_3$MnArH), 6.13 (m, 1H, (CO)$_3$MnArH), 5.98 (d, $J = 8.6$ Hz, 1H, ArCH$_2$-CH(NH)CO$_2$-), 5.90 (bs, 1H, (CO)$_3$MnArH), 5.50-5.14 (m, 4H), 5.06 (m, 1H, BocNHCH$^-$), 4.80 (bs, 1H, ArCH$_2$CH(NH)CO$_2$-), 4.12 (s, 3H, (CO)$_3$MnArOMe), 3.80 (s, 3H, CH$_3$OAr), 3.71 (s, 2H), 3.53 (s, 2H), 3.37 (s, 3/2H, CH$_3$OCH$_2$CH$_2$O-$^-$, from the minor diastereomer), 3.35 (s, 3/2H, CH$_3$OCH$_2$CH$_2$O-$^-$, from the major diastereomer), 3.15 (bs, 2H, ArCH$_2$CH(NH)CO$_2$-), 2.40 (s, 3/2H, (CO)$_3$MnArMe, from the minor diastereomer), 2.39 (s, 3/2H, (CO)$_3$MnArMe, from the major diastereomer), 1.41 (s, 9H, (CH$_3$)$_3$O$_2$C-$^-$)

3-{2-Methyl-3-methoxy-5-{[(4R)-isopropyl-3,6-dimethoxy-1,4-dihydropyrazinyl]phenyloxy}{N-t-Butoxycarbonyl-(R)-4-methoxyphenylglycinyl}-D-[phenylalanyl Methoxyethoxymethyl ester]

To a cooled solution (-78 °C) of bislactim 1.2.53 (428 mg, 2.3 mmol, 7.0 eq) dissolved in THF (21 mL) was added n-BuLi (2.5 M, 900 μL) dropwise and the mixture was stirred for 3 h at -78 °C. Each of a third portion of the resulting solution was added every 6 min via cannula to a solution of arene-manganese complex 1.3.12 dissolved in -100 °C THF (7.5 mL). The reaction mixture was stirred for 18 min at -100 °C and quenched with sat. NH$_4$Cl (140 mL). After warming, the mixture was extracted with
ether (3 x 25 mL), dried (Na₂SO₄), filtered and concetrated to \( \sim 40 \) mL. To this solution, NBS (45 mg, 0.76 eq) was added and the mixture was stirred for 20 min at rt and reaction was quenched with NaHSO₃ (40 mL), washed with brine (2 x 30 mL) and dried(MgSO₄). This product was purified with HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 2:3, \( t_r = 40 \) min) to provide a mixture of the desired bislactim adduct 1.3.13a and the demetallated starting material 1.3.14 in a ratio of 1.3:1. The calculated yield of 1.3.13a was 28%. For 1.3.13a; \( R_f \) 0.63 (hex:EtOAc = 1:2); \(^1\)H NMR (300 MHz, CDCl₃, obtained by subtraction of spectrum 1.3.14 from the spectrum of the mixture of 1.3.13a and 1.3.14 ) \( \delta \) 7.29-7.20 (m, 3H), 7.07-6.88 (m, 4H), 6.68 (s, 1H, ArH), 6.51 (s, 1H, ArH), 6.36 (s, 1H, ArH), 6.17 (d, \( J = 7.4 \) Hz, 1H, ArCH₂CH(NH)CO₂⁻), 5.45 (bs, 1H, BocNH⁻), 5.30 (d, \( J = 6.0 \) Hz, 1H, 1/2 CO₂CH₂OCH₂⁻), 5.26 (d, \( J = 6.0 \) Hz, 1H, 1/2 CO₂CH₂OCH₂⁻), 4.93 (d, \( J = 3.4 \) Hz, 1H, NCHArC(OMe)N), 4.76 (m, 1H, ArCH₂CH(NH)CO₂⁻), 4.02 (t, \( J = 3.2 \) Hz, 1H, NCH(iPr)C(OMe)N), 3.86 (s, 3H, CH₃OAr), 3.82 (s, 3H, CH₃OAr), 3.67 (s, 3H, CH₃OC(C)N), 3.65-3.62 (m, 2H), 3.60 (s, 3H, CH₃OC(C)N), 3.52-3.47(m, 2H), 3.36 (s, 3H, CH₃OCH₂CH₂O⁻), 3.14 (dd, \( J = 14.0, 6.0 \) Hz, 1H, 1/2 ArCH₂CH(NH)CO₂⁻), 3.06 (dd, \( J = 14.1, 66.0 \) Hz, 1H, 1/2 ArCH₂CH(NH)CO₂⁻), 2.32 (m, 1H, CHMe₂), 2.06 (s, 3H, CH₃Ar), 1.39 (s, 9H, (CH₃)₃O₂⁻C⁻), 1.07 (d, \( J = 6.8 \) Hz, 3H, CHCH(CH₃)(CH₃)), 0.72 (d, \( J = 6.8 \) Hz, 3H, CHCH(CH₃)(CH₃))

[[N-t-Butoxy carbonyl-(R)-3-hydroxy-4-methoxyphenyl glycine methyl ester]-O-[N-benzyloxy carbonyl-(S)-2-methyl-3-methoxy phenyl glycine Methyl ester] (1.3.15) A mixture of the bislactim adduct 1.3.13a (64 mg, 0.076 mmol, 1.0 eq) and the side product 1.3.14 (58 mg) dissolved in THF (3.7 mL) was combined with of 0.25 N HCl (920 μL) and the mixture was stirred for
1.5 h at rt. Water (2.5 mL) was added to the mixture and after evaporation of THF in vacuo, ether (3.2 mL) was added to the mixture which was then cooled to 0 °C. The mixture was basified to pH = 8–9 with few drops of saturated Na₂CO₃ and benzyl chloroformate (38 mL, 0.27 mmol, 3.5 eq) was added in one portion. After 12 min stirring at 0 °C, the reaction was quenched with 0.25 N HCl (reaction mixture pH = 2) and it was extracted with ether (3 x 20 mL) and dried over MgSO₄. The desired product 1.3.15 was obtained (45 mg, 67%) after purification using HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 1:1, 5 mL/min, tᵣ (1.3.15) = 104 min, tᵣ (side products) = 96, 114 min), along with 2 side products (2.7, 5.7%, respectively). Side product 1.3.14 was also recovered (tᵣ = 62 min, 48.8 mg, 85%) along with its enantiomer (0.8 mg, 1.4%). For 1.3.15: Rf 0.63 (hex:EtOAc = 1:2); IR (CHCl₃) 3683, 3425, 3067, 3020, 1741, 1718, 1684, 1579, 1510, 1476, 1421 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 50 °C) δ 7.29-7.16 (m, 9H), 7.08-7.02 (m, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 2.1 Hz, 1H), 6.93 (s, 1H), 6.90 (s, 1H), 6.71 (d, J = 1.8 Hz, 1H), 5.75 (s, 1H), 6.42 (s, 1H), 6.35 (bs, 1H), 3.59 (s, 1H), 5.57 (s, 1H), 5.26 (d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 5.24 (d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 5.14 (d, J = 7.2 Hz, 1H), 5.08 (d, J = 12.4 Hz, 1H, 1/2 ArCH₂O₂CNH), 5.03 (d, J = 12.6 Hz, 1H, 1/2 ArCH₂O₂CNH), 4.90 (d, J = 6.5 Hz, 1H), 4.71 (m, 1H, ArCH₂CHNH-), 3.82 (s, 3H, ArOCH₃), 3.81 (s, 3H, ArOCH₃), 3.66 (s, 3H, -CO₂CH₃), 3.62-3.57 (m, 2H), 3.47-3.43 (m, 2H), 3.33 (s, 3H, CH₃OCH₂CH₂O-), 3.12 (dd, J₁ = 14.0, 5.8 Hz, 1H, 1/2 ArCH₂CHNH), 3.02 (dd, J₁ = 14.1, 6.7 Hz, 1H, 1/2 ArCH₂CHNH), 2.12 (s, 3H, ArCH₃), 1.37 (s, 9H, (CH₃)₃CO₂C-). ¹³C NMR (75 MHz, CDCl₃) δ 171.24 (s, +), 170.61 (s, +), 169.80 (s, +), 159.19 (s, +), 155.34 (s, +), 154.99 (s, +), 150.26 (s, +), 146.15 (s, +), 136.05 (s, +), 135.95 (s,
+, 134.81 (s, +), 130.71 (d, -), 129.24 (d, -), 128.50 (d, -), 128.14 (d, -), 128.04 (d, -), 126.98 (d, -), 122.07 (d, -), 118.20 (s, +), 117.51 (d, -), 112.95 (d, -), 110.40 (d, -), 104.03 (d, -), 90.38 (t, +), 79.96 (s, +), 71.33 (t, +), 69.60 (t, +), 67.07 (t, +), 59.00 (q, -), 57.89 (d, -), 56.09 (q, -), 55.74 (q, -), 53.75 (d, -), 52.78 (q, -), 37.11 (t, +), 28.24 (q, -), 8.75 (q, -); [α]D +9.2° (c =1.32, CHCl3); HRMS: found 896.3594; calcd for C46H55O14N3Na (M+Na): 896.3582.

3-(2-Methyl-3-methoxyphenyloxy)[N-t-butoxycarbonyl-(R)-4-methoxyphenylglycyl]-D-[phenylalanine] Methoxyethoxymethyl Ester (1.3.14); Obtained as a byproduct during the formation of compound 1.3.15.

Rf 0.63 (hex:EtOAc = 1:2); IR (CHCl3) 3419, 3025, 3018, 2981, 2935, 2839, 1745, 1711, 1684, 1582.2, 1506, 1489, 1473 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.29-7.22 (m, 3H, ArH), 7.08-6.90 (m, 5H, ArH, ArH), 6.70 (d, J =1.9 Hz, 1H, ArH), 6.61 (d, J = 7.6 Hz, 1H, ArH), 6.37 (dd, J1 = 8.3 Hz, J2 = 1.0 Hz, 1H, ArH), 6.14 (d, J = 7.7 Hz, 1H, ArCH₂CHNH-), 5.50 (bs, 1H, BocNH-), 5.31 (d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 5.27 (d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 4.93 (bs, 1H, BocNHCH-), 4.78 (m, 1H, ArCH₂CH-), 3.85 (s, 3H, ArOMe), 3.84 (s, 3H, ArOMe), 3.65-3.61 (m, 2H), 3.50-3.48 (m, 2H), 3.36 (s, 3H, CH₃OCH₂CH₂O-), 3.14 (dd, J₁ = 13.8 Hz, J₂ = 6.0 Hz, 1H, 1/2 ArCH₂CHNH-), 3.06 (dd, J₁ = 14.0 Hz, J₂ = 5.8 Hz, 1H, 1/2 ArCH₂CHNH-), 2.13 (s, 3H, ArCH₃), 1.39 (s, 9H, (CH₃)₃CO₂C-); ¹³C NMR (75 MHz, CDCl3) δ 170.4 (s, +), 169.6 (s, +), 158.7 (s, +), 155.4 (s, +), 154.9 (s, +), 150.6 (s, +), 146.6 (s, +), 135.4 (s, +), 130.4 (s, +), 129.3 (d, -), 128.6 (d, -), 127.2 (d, -), 126.4 (d, -), 122.4 (d, -), 117.5 (d, -), 117.4 (s, +), 112.8 (d, -), 110.6 (d, -), 105.5 (d, -), 90.3 (t, +), 80.1 (s, +), 71.3 (t, +), 69.7 (t, +), 59.0 (q, -), 58.1 (d, -), 56.1 (q, -),
55.6 (q, -), 53.4 (d, -), 37.5 (t, +), 28.2 (q, -), 8.7 (q, -); [α]D -38.8° (c = 0.97, CHCl₃);
HRMS: found 652.3037; calcd 652.2996. MS: m/e 652 (1), 578 (5), 503 (1), 502 (4),
489 (2), 472 (2), 460 (3), 447 (2), 446 (10), 374 (3), 373 (7).

[[N-t-Butoxycarbonyl-(R)-3-hydroxy-4-methoxyphenylglycinyl]-D-
phenylalanine]-O-[N-benzyloxy carbonyl-(S)-2-methyl-3-methoxy phenyl glycine
Methyl ester] (1.3.19)

A solution of the MEM ester 1.3.15 dissolved in ether (25 mL) was combined with MgBr₂Et₂O (57 mg, 5.0 eq) and the mixture was stirred for 26 h at rt. Water (14 mL) was added to the reaction mixture and it was stirred for 30 min. After separation of the organic layer, the aqueous layer was extracted with dichloromethane (2 x 10 mL), and the combined organic layer was dried (MgSO₄) and evaporated to afford the desired product 1.3.19 in 82% yield. This product decomposed during column chromatography. Thus, it was used without purification in the next step. For 1.3.19; ¹H NMR (300 MHz,
CDCl₃) δ 8.00 (d, J = 8.0 Hz, 1H), 7.40-7.20 (m, 9H), 7.09 (d, J = 8.0 Hz, 2H), 6.91
(d, J = 8.8 Hz, 1H), 6.58 (S, 1H), 6.48 (d, J = 2.1 Hz, 1H, Ar(F)H), 6.36 (s, 1H, ArH),
5.77 (bs, 1H, BocNH-), 5.45 (d, J = 8.0, 1H), 5.21 (d, J = 12.0 Hz, 1H, 1/2
-CO₂CH₂Ar), 5.14 (d, J = 12.0 Hz, 1H, 1/2 -CO₂CH₂Ar), 5.05 (d, J = 8.0 Hz, 1H),
4.93 (bs, 1H, BocNHCH-), 4.52 (m, 1H, ArCH₂CHNH-), 3.84 (s, 6H, Ar(F)OCH₃,
Ar(G)OCH₃), 3.58 (s, 3H, -CO₂CH₃), 3.12 (dd, J = 14.4, 5.6 Hz, 1H, 1/2
-CHCH₂Ar), 3.00 (dd, J = 14.4, 8.0 Hz, 1H, 1/2 -CHCH₂Ar), 2.02 (s, 3H, CH₃Ar),
1.35 (s, 9H, -CO₂C(CH₃)₃).
Cyclic monomer (1.3.22a)/(1.3.22b)

A solution of the carboxylic acid 1.3.19 (18.6 mg, 0.025 mmol, 1.0 eq) in EtOH (7.5 mL) was combined with Pd/C (10%, 42 mg) and stirred for 1 h under hydrogen atmosphere until all the starting material was consumed (TLC). The reaction mixture was filtered through Celite, and the EtOH was removed in vacuo. To remove the EtOH completely, the resulting product was co-evaporated with dichloromethane (2 x 20 mL) and placed under high vacuum for 30 min. The product was then dissolved in dichloromethane (6 mL) and this solution was slowly injected, over 5 h, to an ice cooled solution of EDC (10.4 mg, 0.054 mmol, 2.2 eq) and HOBT (7.7 mg, 0.057 mmol, 2.3 eq) in dichloromethane (27 mL). The reaction mixture was stirred for an additional 4 h at 0 °C and 12 h at rt. The solvent was removed in vacuo and the residue was purified using HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 2:3, 5 mL/ min). Two products 1.3.22a (t_r = 26 min) and 1.3.22b (t_r = 35 min) were obtained in 19 and 22% yield respectively.

For 1.3.22a: (ristocetin numbering is used for assignment of proton)

IR (CHCl3) 3019, 1734, 1718, 1701, 1696, 1676, 1653, 1601, 1583, 1560, 1517, 1437, 1420 cm⁻¹; ¹H NMR (300 MHz, CDCl3) δ 7.31-7.17 (m, 5H, H₂b-d), 7.09 (dd, J = 8.4 Hz, 2.3 Hz, 1H, H₁f), 6.97 (d, J = 8.4 Hz, 1H, H₁e), 6.75 (d, J = 7.6 Hz, 1H, H₃), 6.67 (d, J = 2.2 Hz, 1H, H₁b), 6.48 (s, 1H, H₃b), 6.27 (s, 1H, H₃f), 5.90 (bd, J = 8.9 Hz, 1H, H₂w), 5.74 (bd, J = 7.0 Hz, 1H, H₃w₁), 5.42 (d, J = 7.6 Hz, 1H, H₃x3), 4.97 (d, J = 7.0 Hz, 1H, H₃x₁), 4.60 (ddd, J = 9.2, 8.9, 5.9 Hz, 1H, Hx2), 3.88 (s, 3H, H₁d), 3.85 (s, 3H, H₃e), 3.70 (s, 3H, -CO₂CH₃), 3.10 (dd, J = 13.6, 9.2 Hz, 1H, Hz or Hz'), 2.90 (dd, J = 13.6, 5.9 Hz, 1H, Hz' or Hz),...
2.18 (s, 3H, H₃d), 1.41 (s, 9H, -CO₂C(CH₃)₃); [α]D -12.9° (c 0.21, CHCl₃); HRMS: found 633.2684; calcd for C₃₄H₃₉N₃O₉: 633.2686 :MS: m/e 633 (8), 577 (20), 533 (52), 529 (27), 527 (30), 490 (64), 471 (28), 374 (74).

For 1.3.22b: (ristocetin numbering is used for assignment of proton)

IR (CHCl₃) 3684, 3589, 3419, 3027, 3013, 2959, 2933, 2854, 1884, 1735, 1690, 1599, 1581, 1516, 1478, 1420 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.25 (m, 3H, H₂c-2d), 7.19 (d, J = 8.3 Hz, 2H, H₂b), 7.11 (bd, J = 1H, H₁f), 6.98 (d, J = 8.3 Hz, 1H, H₁e), 6.65 (d, J = 2.2 Hz, 1H, H₁f), 6.56 (d, J = 1.3 Hz, 1H, H₁b), 6.46 (d, J = 6.9 Hz, 1H, H₁c), 5.62 (s, 1H, H₃b), 5.61 (d, J = 7.0 Hz, 1H, H₃c), 5.55 (bd, J = 6.7 Hz, 1H, H₃f), 5.19 (d, J = 6.9 Hz, 1H, H₃c), 4.91 (bd, J = 6.7 Hz, 1H, H₃f), 4.65 (ddd, J = 8.5, 7.0, 5.9, 1H, H₂d), 3.91 (s, 3H, H₁d), 3.87 (s, 3H, H₂c), 3.68 (s, 3H, CO₂CH₃), 3.24 (dd, J = 14.3, 5.9, 1H, Hz or z'), 3.03 (dd, J = 14.3, 8.5 Hz, 1H, H₂d or z), 2.19 (s, 3H, H₃d), 1.35 (s, 9H, -CO₂C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ 170.9, 170.1, 169.2, 159.0, 157.4, 151.4, 135.5, 135.0, 129.8, 129.0, 128.9, 127.4, 125.1, 118.1, 117.7, 113.3, 107.7, 105.5, 80.1, 57.5, 56.2, 55.9, 55.7, 52.8, 36.7, 28.2, 8.5; [α]D -82.4° (c 0.29, CHCl₃); HRMS: found 633.2702; calcd for C₃₄H₃₉N₃O₉: 633.2686 :MS: m/e 634 (1), 633 (2), 560 (2). 559 (4), 533 (17), 526 (7), 497 (3), 491 (8), 490 (25).

Methoxyethoxymethyl (2R)-azido-2-(3-benzyl-4-methoxyphenyl)acetate (1.3.25) A solution of azidoacetic acid 1.2.27 (506.4 mg, 1.0 eq) dissolved in dichloromethane (16 mL) was combined with Bu₄NI dissolved in water (16 mL) and the mixture was cooled to 0 °C, then basified with saturated NaHCO₃ to pH = 8.
Methoxyethoxymethyl chloride (220 μL, 1.2 eq) was added to the mixture and the reaction mixture was stirred for 30 min. Reaction was quenched with 2.5 N HCl to pH = 1, extracted with dichloromethane (2 x 20 mL) and dried over MgSO4. After column chromatography (SiO2, hexanes:EtOAc = 3:1), desired product 1.3.25 was obtained as a yellow liquid (576 mg, 89 %). Rf 0.45 (1:1 hexanes:EtOAc ); IR (CHCl3) 2934, 2838, 2106, 1749, 1604, 1592, 1515, 1455, 1443, 1428 cm⁻¹; ^1H NMR (300 MHz, CDCl3) δ 7.46-7.29 (m, 5H, ArH), 6.98-6.88 (m, 3H, ArH), 5.34 (d, J = 6.0 Hz, 1H, 1/2 ArCH2O-), 5.32 (d, J = 6.0 Hz, 1H, 1/2 ArCH2O-), 5.17 (d, J = 12.7 Hz, 1H, 1/2 -CO₂CH₂OCH₂-), 5.13 (d, J = 12.7 Hz, 1H, 1/2 -CO₂CH₂OCH₂), 4.87 (s, 1H, N₃CH-), 3.89 (s, 3H, CH₃OAr), 3.65-3.63 (m, 2H), 3.47-3.44 (m, 2H), 3.33 (s, 3H, CH₃OCH₂CH₂O-); ^13C NMR (75 MHz, CDCl₃) δ 168.7 (s, +), 150.5 (s, +), 148.44 (s, +), 136.5 (s, +), 128.5 (d, -), 127.9 (d, -), 127.4 (d, -), 125.7 (s, +), 121.0 (d, -), 113.0 (d, -), 111.7 (d, -), 90.5 (t, +), 71.2 (t, +), 71.0 (t, +), 69.7 (t, +), 64.9 (d, -), 59.0 (q, -), 56.0 (q, -); [α]D -76.6° (c 0.74, CHCl₃); HRMS. Found: 401.1590; calc’d for C₂₀H₂₃N₃O₆: 401.1586. MS: m/e 401 (4), 373 (2), 297 (1), 270 (1).

Methoxyethoxymethyl (2R)-[(1,1-Dimethylethoxy)carbonyl]amino]-2-(3-hydroxy-4-methoxy phenyl)acetate (1.3.26)

A solution of azido methoxyethoxymethyl ester 1.3.25 (370 mg, 0.92 mmol, 1.0 eq) dissolved in THF was combined with Boc₂O (300 mg, 1.4 mmol, 1.5 eq) and 10% Pd/C (105 mg). The mixture was then stirred for 38 h under hydrogen atmosphere and was column-chromatographed (SiO₂, hexanes:EtOAc = 2:1) to afford the desired product 1.3.26. Analytical sample was purified using HPLC to
afford a white solid. Mp 91-92 °C; Rf 0.51 (2:1 hexanes:EtOAc); IR (CHCl₃) 3542, 3439, 3016, 2981, 2937, 2844, 1747, 1711, 1596, 1511, 1496, 1456, 1444 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.93 (d, J = 2.1 Hz, 1 H), 6.89 (dd, J = 8.2, 2.1 Hz, 1 H), 5.74 (s, 1 H, ArOH), 5.49 (bd, J = 7.2 Hz, 1 H, BocNHCH), 5.40 (d, J = 6.0 Hz, 1 H, 1/2 CO₂CH₂OCH₂-), 5.28 (d, J = 6.0 Hz, 1 H, 1/2 CO₂CH₂OCH₂-), 5.23 (d, J = 7.3 Hz, 1 H, NHCHCO₂-), 3.88 (s, 3 H, CH₃OAr), 3.66-3.63 (m, 2 H), 3.47-3.44 (m, 2 H), 3.34 (s, 3 H, CH₃OCH₂CH₂O-), 1.43 (s, 9 H, (CH₃)₃C-); ¹³C NMR (75 MHz, CDCl₃) δ 170.8 (s, +), 154.77 (s, +), 146.76 (s, +), 145.9 (s, +), 129.7 (s, +), 119.2 (d, -), 113.3 (d, -), 110.8 (d, -), 90.1 (t, +), 80. (s, +), 71.3 (t, +), 69.4 (t, +), 58.9 (q, -), 57.2 (d, -), 55.9 (q, -), 28.2 (q, -); [α]D = 80.3° (c 1.22, CHCl₃); HRMS. Found: 385.1739; calc'd for C₁₈H₂₇NO₈: 385.1737. MS: m/e 385 (1), 299 (1.1), 254 (1), 253 (9), 252 (16), 223 (7), 209 (9), 208 (1).

3-[(Tricarbonyl)(η⁶-2-methyl-3-methoxyphenyloxy)manganese][N-t-butoxy carbonyl-(R)-4-methoxyphenylglycine methoxycethoxymethyl ester] hexafluorophosphate (1.3.28)

To an ice-cold solution of the phenol 1.3.26 dissolved in dichloromethane (25 mL) was added NaH (60%, 51.7 mg, 0.99 eq) and the mixture was stirred at 0 °C for 30 min. The mixture was then transferred to a stirred mixture of arene-manganese complex 1.2.23 (546 mg, 1.1 eq) and AgBF₄ (800 mg, 5.6 eq) suspended in ice-cold dichloromethane (80 mL) and stirring was continued for 1 h at 0 °C, 5 min at rt. Reaction was quenched with 0.5 M NH₄PF₆ (65 mL) and the mixture was stirred vigorously for 1 h. The resulting dark solution was filtered through Celite and extracted with CH₂Cl₂ (2
x 50 mL), dried over MgSO₄. The crude product was dissolved in ~ 3 mL CHCl₃ and the solution was filtered through Celite to remove residual arene-manganese complex 1.2.23. The desired product (805 mg, 78.3%) was obtained as a yellow solid from treatment with pentane (75 mL). Mp 205 °C (decompose); IR (CHCl₃) 3691, 3433, 3118, 3046, 3012, 2985, 2937, 2846, 2070, 2004, 1748, 1711, 1618, 1602, 1558, 1534, 1513, 1497, 1471, 1444, 1428 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40* (dd, J = 8.7, 2.2 Hz, 1/2H), 7.39* (dd, J = 8.6, 2.3 Hz, 1/2H), 7.28* (d, J = 2.0 Hz, 1/2H), 7.24* (d, J = 2.1 Hz, 1/2H), 7.07 (d, J = 8.6 Hz, 1H), 6.65 (t, J = 7.0 Hz, 1H), 6.06 (d, J = 7.1 Hz, 1H), 5.73* (bd, J = 6.6 Hz, 1/2H), 5.69* (bd, J = 7.0 Hz, 1/2H, BocNH-), 5.46* (d, J = 7.0 Hz, 1H, BocNH-), 5.38–5.33 (m, 2H, -CO₂CH₂O-), 5.29 (d, J = 6.6 Hz, 1H, -CH₂NHBOc), 4.13 (s, 3H, CH₃OAr-Mn(+)), 3.82 (s, 3 H, CH₃OAr), 3.69–3.65 (m, 2H), 3.50–3.46 (m, 2H), 3.34* (s, 3/2H, -OCH₂CH₂OCH₃), 3.33* (s, 3/2H, -OCH₂CH₂OCH₃), 2.39 (s, 3H, ArCH₃), 1.42 (s, 9H, (CH₃)₃CO₂C-) * --- peaks due to one diastereomer or the other one. non asterisked peaks are common for both diastereomers.; ¹³C NMR (75 MHz, CDCl₃) δ 215.34 (s, +, Mn⁺(CO)₃), 170.04 (s, +), 154.81 (s, +), 150.19* (s, +), 150.12* (s, +), 148.91* (s, +), 148.82* (s, +), 147.11 (s, +), 130.71* (s, +), 130.56* (s, +), 127.67* (d, -), 127.46* (d, -), 121.07* (d, -), 120.77* (d, -), 120.98 (d, -), 113.62 (d, -), 100.69 (d, -), 90.69 (s, +), 88.41 (s, +), 80.41 (s, +), 75.78* (q, -, Mn(+-)ArOCH₃), 75.68* (q, -, Mn(+-)ArOCH₃), 73.36 (d, -), 71.31 (t, +), 69.72 (t, +), 58.97* (d, -), 58.91* (d, -), 56.74 (q, -, CH₃OAr), 55.97 (d, -), 28.58 (q, -, -CO₂C(CH₃)₃), 9.47 (q, -, Mn(+-)ArCH₃) * --- peaks due to one diastereomer or the other one. non asterisked peaks are common for both diastereomers. Anal. Calcd for C₂₉H₃₅NO₁₂MnPF₆: C 44.12, H 4.47, N 1.77. Found: C 42.01, H 4.54, N 2.06.
3-[2-Methyl-3-methoxy-5-[(1R,4R)-isopropyl-3,6-dimethoxy-1,4-dihydroxy pyrazinyl] phenyloxy]N-t-Butoxycarbonyl-(R)-4-methoxyphenylglycine methoxyethoxymethyl ester] (1.3.29)

To a cold (-78 °C) stirred solution of (6R)-isopropyl-2,5-dimethoxy-3,6-dihydropyrazine 1.2.53 in THF (14 mL) was added n-BuLi (2.4 M, 526 µL) in hexanes. After 3 h stirring, the resulting lithiated bislactim was transferred to a cold solution (-100 °C) of arene-manganese complex 1.3.28 in THF (14 mL), which was prepared just before the addition of lithiated bislactim to minimize the demetallation by THF, and the mixture was stirred in the dark for 30 min at -100 ~ -95 °C. The reaction was quenched with NH₄Cl (50 mL) at -95 °C and after warming up, the mixture was separated and the aqueous layer was extracted with dichloromethane (4 x 25 mL), and the combined layers were dried over MgSO₄. After filtration and concentration of the solvent, the crude product was dissolved in CHCl₃ (5 mL) and was added portionwise to pentane (50 mL), centrifuged and decanted to remove the unreacted arene-manganese complex 1.3.28 (170.2 mg, 34%) as a yellow precipitate. The supernatant was evaporated and the resulting product was dissolved in ice-cold CH₃CN (20 mL) and reacted with NBS (107 mg, 1.5 eq) for 45 min at 0 °C. The reaction was quenched with NaHSO₃ (10% w/w, 20 mL) and, after separation of the organic layer, the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extract was washed with brine (2 x 20 mL) and dried over MgSO₄. Column chromatography (SiO₂, hexanes:EtOAc = 2.5:1) afforded the product 1.3.29 (56%) as a 2.5:1 mixture with side product 1.3.31(23%). Pure diastereomer 1.3.30 (8.5%) was also obtained from the chromatography. For 1.3.29: Rf 0.60 (hexanes:EtOAc =1:1); ¹H NMR (300 MHz, CDCl₃, obtained by subtraction
of spectrum 1.3.31 from the spectrum of the mixture of 1.3.29 and 1.3.31) δ 6.94 (d, J = 8.1 Hz, 1H, ArH), 6.73 (d, J = 2.6 Hz, 1H, ArH), 6.55 (s, 1H, ArH), 6.34 (s, 1H, ArH), 5.45-5.30 (m, 2H), 5.27 (d, J = 6.0 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 5.13 (d, J = 7.1 Hz, 1H, 1/2 CO₂CH₂OCH₂-), 4.95 (d, J = 3.2 Hz, 1H, ArCH(N)C(N)OMe), 4.00 (t, J = 3.5 Hz, 1H, (CH₃)₂CHCH(N)COMe), 3.87 (s, 6H, two CH₃OAr)), 3.67 (s, 3H, CH₃OC(N)CH), 3.63 (s, 3H, CH₃OC(N)CH), 3.63-3.55 (m, 2H), 3.44-3.40 (m, 2H), 3.33 (s, 3H, CH₃OCH₂CH₂O-), 2.33 (m, 1H, (CH₃)₂CH-), 2.07 (s, 3H, ArCH₃), 1.41 (s, 9H, (CH₃)₃CO₂C-), 1.08 (d, 7.9 Hz, 3H, (CH₃)CH(CH₃)), 0.72 (d, 7.9 Hz, 3H, (CH₃)CH(CH₃)).

For 1.3.30:

Rf 0.52 (1:1 hexanes:EtOAc ); IR (CHCl₃) 3683, 3438, 3032, 3026, 3016, 2964, 2945, 2872, 2840, 2400, 1746, 1710, 1694, 1650, 1642, 1613, 1581, 1511, 1498, 1464, 1442, 1417 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 60 °C )

δ 7.08 (dd, J = 8.4, 2.1 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 6.66 (s, 1H), 6.39 (s, 1H), 5.33 (d, J = 6.0 Hz, 1H), 5.29 (d, J = 6.0 Hz, 1H), 5.26 (bd, 1H), 5.16 (bd, J = 8.7 Hz, 1H), 5.06 (d, J = 5.0 Hz, 1H), 3.92 (t, J = 4.8 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.64-3.61 (m, 5H), 3.45-3.42 (m, 2H), 3.33 (s, 3H), 2.12 (s, 3H), 2.16-2.02 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.7 (s, +), 164.5 (s, +), 161.6 (s, +), 158.4 (s, +), 155.1 (s, +), 154.7 (s, +), 150.8 (s, +), 146.3 (s, +), 138.6 (s, +), 129.1 (s, +), 122.6 (d, -), 118.1 (d, -), 116.0 (s, +), 112.6 (d, -), 109.9 (d, -), 105.2 (d, -), 90.2 (t, +), 80.1 (s, +), 71.2 (t, +), 69.4 (t, +), 60.9 (d, -), 59.4 (d, -), 59.0 (q, -), 57.1 (d, -), 56.1 (q, -), 55.6 (q, -), 52.6 (q, -), 31.8 (d, -), 28.2 (q, -), 19.7 (q, -), 17.9 (q, -), 8.7 (q, -); [α]D
-95.0° (c 1.25, CHCl₃); HRMS. Found: 687.3366; calcd for C₃₅H₄₉N₃O₁₁: 687.3367.
MS: m/e 688 (8), 687 (32), 466 (10), 455 (19), 454 (100), 452 (16), 450 (18).

3-(2-Methyl-3-methoxy-5-[(1R,4R)-4-isopropyl-3,6-dimethoxy-1,4-dihydropyrazinyl]phenyloxy)[N-t-Butoxycarbonyl-(R)-4-methoxyphenylglycine methoxy ethoxy methyl ester] (1.3.31)

$R_f$ 0.60 (1:1 hexanes:EtOAc); IR (CHCl₃) 3683, 3438, 3032, 3026, 3016, 2964, 2945, 2872, 2840, 2400, 1746, 1710, 1694, 1650, 1642, 1613, 1581, 1511, 1498, 1464, 1442, 1417 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 60 °C) δ 7.08 (dd, $J = 8.4$, 2.1 Hz, 1H), 6.94 (d, $J = 8.4$ Hz, 1H), 6.84 (d, $J = 2.1$ Hz, 1H), 6.66 (s, 1H), 6.39 (s, 1H), 5.33 (d, $J = 6.0$ Hz, 1H), 5.29 (d, $J = 6.0$ Hz, 1H), 5.26 (bd, 1H), 5.16 (bd, $J = 8.7$ Hz, 1H), 5.06 (d, $J = 5.0$ Hz, 1H), 3.92 (t, $J = 4.8$ Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.68 (s, 3H), 3.64-3.61 (m, 5H), 3.45-3.42 (m, 2H), 3.33 (s, 3H), 2.12 (s, 3H), 2.16-2.02 (m, 1H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.68 (d, $J = 6.8$ Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.7 (s, +), 164.5 (s, +), 161.6 (s, +), 158.4 (s, +), 155.1 (s, +), 154.7 (s, +), 150.8 (s, +), 146.3 (s, +), 138.6 (s, +), 129.1 (s, +), 122.6 (d, -), 118.1 (d, -), 116.0 (s, +), 112.6 (d, -), 109.9 (d, -), 105.2 (d, -), 90.2 (t, +), 80.1 (s, +), 71.2 (t, +), 69.4 (t, +), 60.9 (d, -), 59.4 (d, -), 59.0 (q, -), 57.1 (d, -), 56.1 (q, -), 55.6 (q, -), 52.6 (q, -), 31.8 (d, -), 28.2 (q, -), 19.7 (q, -), 17.9 (q, -), 8.7 (q, -); [α]D -57° (c 0.7, CHCl₃); HRMS. Found: 505.2316; calcd for C₂₆H₃₅NO₉: 505.2312. MS: m/e 505 (2), 404 (1.3), 385 (1.1), 374 (2.2), 373 (10.7), 372 (9.5), 330 (3.3), 328 (6.6), 327 (2.5), 318 92.8), 317 (18.2).

Compound 1.3.33.
To a solution of the mixture of the bislactim adduct 1.3.29 and side product 1.3.31 dissolved in THF (13 mL) was added 0.25 N HCl (3.4 mL) and the mixture was stirred for 1.5 h at rt. The reaction mixture was then basified to pH = 8-9 with NaHCO₃, extracted with CH₂Cl₂ (3 x 10 mL), dried over MgSO₄ and filtered. This solution was added via cannula to an ice-cold solution of N-benzyloxy carbonyl-D-phenylalanine (186 mg, 2.2 eq) and HOBT followed by EDC. The mixture was stirred for 1 h at 0 °C and 15 min at rt. After concentration, the resulting product was column-chromatographed to afford the desired product 1.3.33 (205 mg, 93%) as a white solid. This compound contains ~10% of side product which could not be separated by HPLC. Further purification was not attempted. For 1.3.33: Rf 0.42 (1:2 hexanes:EtOAc); IR (CHCl₃) 3423, 3013, 2957, 2936, 1742, 1711, 1582, 1497, 1464, 1456, 1442, 1420 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 55 °C) δ 7.29-7.23 (m, 3H), 7.13-7.10 (m, 3H), 7.08 (d, J = 2.1 Hz, 1H), 7.05 (d, J = 2.2 Hz, 1H), 7.03-6.99 (m, 2H), 6.94 (s, 1H), 6.91 (s, 1H), 6.80 (d, J = 1.9 Hz, 1H), 6.66 (d, J = 6.9 Hz, 1H), 6.43 (bs, 1H), 6.32 (s, 1H), 5.60 (bs, 1H), 5.33 (s, 1H), 5.31 (d, J = 6.0, 1H, 1/2 CO₂CH₂OCH₂-), 5.24 (d, J = 6.0, 1H, 1/2 CO₂CH₂OCH₂-), 5.13 (d, J = 6.0 Hz, 1H), 5.03 (s, 2H, ArCH₂OCO-), 4.39 (m, 1H, ArCH₂C/NHCbz), 3.80 (s, 3H, ArOCH₃), 3.78 (s, 3H, ArOCH₃), 3.63 (s, 3H, -CO₂CH₃), 3.60-3.56 (m, 2H), 3.40-3.36 (m, 2H), 3.27 (s, 3H, CH₃OCH₂CH₂O-), 3.01-2.97 (m, 2H, ArCH₂C/NHCbz), 2.13 (s, 3H, ArCH₃), 1.38 (s, 9H, (CH₃)₃CO₂C-); HRMS. Found: 896.3601; calcd for C₄₆H₅₅N₃O₁₄Na (M⁺Na): 896.3582.

**Compound 1.3.34.**
To a solution of compound 1.3.33 (60.5 mg, 0.07 mmol, 1.0 eq) dissolved in methylene chloride (18 mL) was added MgBr₂·Et₂O and it was stirred for 36 h at rt. To the reaction mixture was added water (9 mL) and stirred for 30 min. The reaction mixture was acidified (pH = 2) with 2.5N HCl and was extracted EtOAc (2 x 10 mL), dried over MgSO₄ and concentrated in vacuo. The resulting compound was subjected to the next reaction without further purification.

H NMR (200 MHz, CDCl₃) δ 7.39-6.90 (m), 6.97 -6.90 (m), 6.84 (d, J = 2.6 Hz, 1H), 6.51 (s, 1H, ArH), 6.26 (s, 1H, ArH), 5.48-5.17 (m), 5.17-4.92 (m), 3.92 (s, 3 H, ArOCH₃), 3.89 (s, 3H, ArOCH₃), 3.63 (s, 3H, -CO₂CH₃), 3.08-2.84 (m, 2H, PhCH₂CH(NHCBz)CO), 2.18 (s, 3H, ArCH₃), 1.45 (s, 9H, -CO₂C(CH₃)₃)

3-{2-Methyl-3-methoxy-5-[[N-[benzyloxy carbonyl]-R-phenylalanyl]-S-glycinyl methyl ester]phenyloxy}[N-t-Butoxycarbonyl-(R)-4-methoxy phenyl glycine pentafluorophenyl ester] (1.3.35)

A solution of the carboxylic acid 1.3.34 (40.3 mg, 0.051 mmol, 1.0 eq) in THF (1 mL) was combined with pentafluorophenol (28.3 mg, 0.15 mmol, 3.0 eq) and the mixture was cooled to 0 °C. Dicyclohexylcarbodiimide (DCC, 16 mg, 0.077 mmol, 1.5 eq) was added to the cooled solution and the mixture was stirred for 2h at 0 °C and overnight at rt. The reaction mixture was concentrated and purified by HPLC (M20 10/25 silica gel column, hexanes:EtOAc = 1:1) to afford the pentafluorophenyl ester 1.3.34 (29 mg, 60%) as a colorless oil. Rf
0.31 (1:1 hexanes:EtOAc ); IR (CHCl₃) 3684, 3620, 3417, 3298, 3038, 3035, 3031, 3028, 3024, 3022, 3019, 3010, 3008, 2979, 2937, 2433, 2400, 1790, 1741, 1707, 1673, 1583, 1520, 1465, 1456, 1442, 1420 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.45 (d, J = 9.2 Hz, 1H), 7.31 (bs, 4H), 7.23-7.14 (m, 3H), 7.07-6.94 (m, 4H), 6.85 (s, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 5.8 Hz, 1H), 6.56 (s, 1H), 6.42 (d, J = 7.9 Hz, 1H), 5.95 (s, 1H), 5.82 (d, J = 7.9 Hz, 1H), 5.52 (d, J = 7.4 Hz, 1H), 5.39-5.28 (m, 3H), 5.16-4.99 (m, 1H), 5.03 (s, 3H), 4.38 (s, 2H), 4.31 (m, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.82 (s, 1H), 3.80 (s, 2H), 3.69 (s, 1H), 3.67 (s, 3H), 3.65 (s, 1H), 3.64 (s, 1H), 3.05-2.98 (m, 3H), 2.83 (dd, J = 12.7, 3.5 Hz, 1H), 2.23 (s, 3H), 2.14 (s, 3H), 1.42 (s, 9H), 1.41 (s, 9H), [α]D + 35.1° (c 2.76, CHCl₃).

**Cyclic monomer 1.3.22a/1.3.22b:** Cyclization from 1.3.34 was performed similarly as described in the previous chapter. For the cyclization reaction from the pentafluorophenol 1.3.34, the precedent¹⁴ made by Chakraborty was used.
3.7 References and Notes


10. Gallagher, T.; Lamont, R. B.; Allen, D. G.; Clemens, I. R.; Newall, C. E.; Ramsay, M. V.; Rose, M.; Fortt, S. "Synthetic Studies directed towards the


Part II

Asymmetric Synthesis of an Arylglycinol.
Chapter 1.

Introduction
1.1. General.

Quinocarcin\(^1\) (2.1.1a) is a novel antitumor antibiotic isolated from the culture broths of *Streptomyces malanovinaceus*. It is the simplest member of the naphthyridinomycin\(^2\) and saframycin\(^3\) class of antitumor agents. It is known to display weak antimicrobial activity\(^1\) against gram-positive microbes and, as its citrate salt,\(^4\) it displays promising anti-tumor activity against several lines of solid mammalian carcinomas including St-4 gastric carcinoma, Co-3 human colon carcinoma and P 388 leukemia.

\[ \text{Fig 2.1.1. Structure of quinocarcin and its family} \]

It is believed that quinocarcin binds to the minor groove of DNA or RNA non-covalently and irreversibly couples with the 2-amino group of guanine after it is reductively activated to produce a highly reactive iminium ion.\(^5\) For quinocarcinol (2.1.1b) which lacks the oxazolidine functionality, no activity was reported\(^6\) while DX-52-1 (2.1.1c) which has a labile nitrile group on the C\(_{2a}\) position, showed remarkable antitumor activities.
Scheme 2.1.1 Reaction Mechanism of Quinocarcin to DNA

In another mechanism suggested recently,\textsuperscript{7} quinocarcin produces superoxide \((O_2)^-\) (from molecular oxygen via a self redox disproportionation) which causes non-selective scission of DNA via Fenton-type\textsuperscript{8} chemistry.

After the discovery of quinocarcin in 1983, there have been many studies towards the total synthesis of quinocarcin and in 1985 a total synthesis \((\pm)-\)quinocarcinol\textsuperscript{9} (2.1.1b) was accomplished by Danishefsky's group. The first total synthesis of \((\pm)-\)quinocarcin was accomplished in Fukuyama's group.\textsuperscript{10}

Until the first asymmetric total synthesis of quinocarcin\textsuperscript{11} to which the work reported in this part of dissertation contributed, its absolute chemistry was not known, and there was controversy about the configuration of the oxazolidine ring. A computational model study on a representative DNA segment d(ATGCAT)\textsuperscript{5} suggested the 11R configuration as depicted in structure 2.1.1a. Exploration of an efficient route for the asymmetric synthesis of quinocarcin was set as a main goal along with the elucidation of its absolute structure and the configuration of the oxazolidine ring.
Scheme 2.1.2 Williams' Mechanism for Interaction of Quinocarcin with DNA

1.2. Retrosynthetic Analysis of Quinocarcin. Scheme 2.1.3. shown below is the retrosynthetic analysis of quinocarcin by which its total synthesis was successfully accomplished.\textsuperscript{11} For the asymmetric synthesis of quinocarcin and
elucidation of its absolute stereochemistry, it was necessary to start with either (R) or (S)-1-methoxy-3-methyl amino alcohol and we chose the (R)-amino alcohol 2.1.5, which is the target molecule in this dissertation.

1.3. Synthetic Background of Chiral Nonracemic Amino Alcohols. As a synthetic equivalent of amino alcohol, synthesis of the corresponding α-amino acid was considered. Because of their importance in life science, methods for the synthesis of chiral nonracemic α-amino acids have been extensively explored by many different groups and a lot of very good methods have been established.\(^\text{12}\) Many intermediates of the established methods can afford the amino alcohols directly by the change of a step or two. Also several methods are well established for the reduction of an amino acid to the corresponding amino alcohol without changing its optical purity.\(^\text{13}\)

Methods for the synthesis of amino acids can be categorized as shown in Scheme 2.1.4.
Racemic amino acid synthesis has been known for 100 years. Mainly they were made by a Strecker type synthesis or by nucleophilic substitution of a leaving group at the α-position.

Scheme 2.1.4. General Methods for the Synthesis of Chiral Nonracemic Amino Acid

Though many optically pure chiral amino acids were obtained from the racemic ones using methods such as fractional crystallization, chromatography on columns with chiral stationary phases, enzymatic resolution (differentiation) by esterases, amidases and hydantoinases, these are not applicable to a wide range of molecules and are limited.

Synthetic methods for chiral nonracemic amino acids were developed during the last 3 decades and these can be divided into 4 categories such as nucleophilic/
electrophilic amination,\textsuperscript{15} asymmetric Strecker synthesis,\textsuperscript{16} chiral glycine equivalent method\textsuperscript{17} and asymmetric catalytic hydrogenation.\textsuperscript{18}

**a: asymmetric Strecker synthesis**

\[
\begin{align*}
R^*\text{H} & \xrightarrow{\text{CN}, \text{Lewis acid}} R^*\text{CN} \\
R^*\text{H} & \xrightarrow{\text{CN}, \text{Lewis acid}} R^*\text{CN} \\
R^*\text{COX} & \xrightarrow{\text{Base or Lewis acid, N}_2^+, \text{or Base, Br}^- \text{then N}_2^+, \text{reduction}} R^*\text{COX}^* \\
R^*\text{COX} & \xrightarrow{\text{Base or Lewis acid, N}_2^+, \text{or Base, Br}^- \text{then N}_2^+, \text{reduction}} R^*\text{COX}^* \\
R^*\text{NH} & \xrightarrow{\text{acidic hydrolysis}} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{acetic acid or reduction, removal of X}^*} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{L-Amino Acid}} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{D-Amino Acid}} R^*\text{NH}_2
\end{align*}
\]

**b: Nucleophilic/electrophilic amination**

\[
\begin{align*}
R^*\text{H} & \xrightarrow{\text{CN}, \text{Lewis acid}} R^*\text{CN} \\
R^*\text{H} & \xrightarrow{\text{CN}, \text{Lewis acid}} R^*\text{CN} \\
R^*\text{COX} & \xrightarrow{\text{Base or Lewis acid, N}_2^+, \text{or Base, Br}^- \text{then N}_2^+, \text{reduction}} R^*\text{COX}^* \\
R^*\text{COX} & \xrightarrow{\text{Base or Lewis acid, N}_2^+, \text{or Base, Br}^- \text{then N}_2^+, \text{reduction}} R^*\text{COX}^* \\
R^*\text{NH} & \xrightarrow{\text{acidic hydrolysis}} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{acetic acid or reduction, removal of X}^*} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{L-Amino Acid}} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{D-Amino Acid}} R^*\text{NH}_2
\end{align*}
\]

**c: chiral glycine equivalent method**

\[
\begin{align*}
R^*\text{CO}_2R & \xrightarrow{\text{Base then R}^+, \text{or Br}^- \text{then R}^+} R^*\text{CO}_2R \\
R^*\text{CO}_2R & \xrightarrow{\text{Base then R}^+, \text{or Br}^- \text{then R}^+} R^*\text{CO}_2R \\
R^*\text{NH} & \xrightarrow{\text{hydrolysis or reduction of X}^*} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{acetic acid or reduction, removal of X}^*} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{L-Amino Acid}} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{D-Amino Acid}} R^*\text{NH}_2
\end{align*}
\]

**d: chiral catalytic hydrogenation**

\[
\begin{align*}
R^*\text{CO}_2R & \xrightarrow{\text{chiral catalytic hydrogenation}} R^*\text{CO}_2R \\
R^*\text{CO}_2R & \xrightarrow{\text{chiral catalytic hydrogenation}} R^*\text{CO}_2R \\
R^*\text{NH} & \xrightarrow{\text{hydrolysis or reduction of X}^*} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{acetic acid or reduction, removal of X}^*} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{L-Amino Acid}} R^*\text{NH}_2 \\
R^*\text{NH}_2 & \xrightarrow{\text{D-Amino Acid}} R^*\text{NH}_2
\end{align*}
\]

**Scheme 2.1.5. Methods for Synthesis of Chiral Nonracemic Amino Acids.**

In the case of arylglycines, one of which was made as an intermediate for the requisite amino alcohol 2.1.5, the choice is limited. It is difficult to obtain arylglycines in optically pure form due to their ease of racemization at the $\alpha$-methine carbon under basic conditions (see also Table 1.2.3 in Part 1, Chapter 2), which are often the conditions required for generation of aryl glycines or removal of chiral auxiliaries.

Of these methods, we first chose the method developed by H. Kunz which utilized the asymmetric Strecker synthesis. This method worked well for several kinds of
arylglycines. The intermediate amino nitrile is known to be transformed to the amino acid under acidic conditions without the problem of racemization and the requisite auxiliary could be easily made and recovered. We embarked on a synthesis of (R)-1-methoxy-3-methyl amino alcohol using this method.
1.4 References and Notes


4 Fujimoto, K.; Oka, T.; Morimoto, M. "Antitumor Activity of a Novel Antitumor Antibiotic, Quinocarmycin Citrate (KW 2152)." Cancer Res. 1987, 47, 1516-1522.


8 Lesko, S. A.; Lorentzen, R. J.; Ts's, P.O.P. "Role of Superoxide in Deoxyribo- nucleic Acid Strand Scission." Biochemistry 1980, 19, 3023-3028.


Chapter 2

Asymmetric Synthesis of

(2R)-2-Amino-2-(2'-methoxy-6'-methylphenyl)ethyl Alcohol
2.1. Amino Alcohol Synthesis via Asymmetric Strecker Synthesis

Introduction  As a synthetic route to non-proteinogenic amino acids, the Strecker synthesis has been used in an asymmetric sense to introduce the "CN-" nucleophilically as an equivalent of the carboxylic acid group.

\[
\text{RCHO} + \text{NaCN} + \text{NH}_4\text{Cl} \xrightarrow{\text{Strecker Synthesis}} \text{RCHCN} \xrightarrow{\text{Hydrolysis}} \text{RCHCO}_2\text{H}
\]

Scheme 2.2.1. Amino Acid Synthesis by the Strecker Method

Stereoselective introduction of "CN-" was achieved by utilizing several kinds of chiral template such as the pentapivaloyl galactosyl amine 2.2.1, (4S, 5R)-5-amino-4-phenyl-1,3-dioxane 2.2.2 or (R)/(S) methylbenzylamine 2.2.3 together with HCN4, TMSCN5 or NaCN5 after formation of the imine of the substrate aldehyde. The optical purity was 78 ~ 85 % for 2.2.1 and 50 ~ 75 % for 2.2.2 and 2.2.3. However, after recrystallization, a highly enriched or even pure diastereomer was obtained. Of these, only 2.2.1 could be recovered and regenerated without destruction of the chiral template.

![Chiral Templates](image.png)

Figure 2.2.1. Several Chiral Templates
In the case of pentapivaloyl galactosylamine 2.2.1, which was used for synthesis of the desired amino acid (amino alcohol), the structure of the intermediate imine 2.2.4 is proposed as it is shown below because of interaction between the C=N p orbital and the σ* orbital of the C1-O bond, and cyanide anion is believed to attack from the back side (C1-O side) of the sugar because of steric hindrance by the -OPiv group at C2, predominantly forming the αR diastereomer. Using this method, several unusual amino acids were obtained in 78 ~ 84 % yields with 75 ~ 85 % e.e.

![Reaction scheme](image)

**Scheme 2.2.2. Examples of Asymmetric Strecker Synthesis.**

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>Lewis (mol. %)</th>
<th>temp/ time</th>
<th>αR:αS (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-tolyl</td>
<td>2-propanol</td>
<td>ZnCl2 (100)</td>
<td>0 °C/ 1 h</td>
<td>6.5:1 (78%)</td>
</tr>
<tr>
<td>p-NO2-C6H4</td>
<td>2-propanol</td>
<td>ZnCl2 (5)</td>
<td>20 °C/ 48 h</td>
<td>7:1 (88%)</td>
</tr>
<tr>
<td>o-NO2-C6H4</td>
<td>THF</td>
<td>SnCl4 (130)</td>
<td>-30 °C/ 8 h</td>
<td>only R (91%)</td>
</tr>
<tr>
<td>p-Cl-C6H4</td>
<td>THF</td>
<td>SnCl4 (130)</td>
<td>-78 ~ -30 °C/ 8 h</td>
<td>11:1 (84%)</td>
</tr>
<tr>
<td>(CH3)3C-</td>
<td>THF</td>
<td>SnCl4 (130)</td>
<td>-78 ~ -10 °C/ 3 h</td>
<td>13:1 (86%)</td>
</tr>
</tbody>
</table>

**Result and Discussion**  With this precedent, synthesis of our amino alcohol 2.1.5 was attempted starting with the synthesis of galactosyl amine 2.2.1. For the synthesis
of the chiral auxiliary, D-galactose was protected with pivaloyl chloride smoothly in
the presence of a catalytic amount of DMAP to afford only the β-anomer, and the
azide group was introduced at C₁ in 85–91 % yield using SnCl₄ and trimethylsilyl
azide.

\[
\begin{align*}
\text{PivO} & \quad \text{OPiv} & \quad \text{OPiv} & \quad \text{OPiv} \\
\text{PivO} & \quad \text{OPiv} & \quad \text{OPiv} & \quad \text{OPiv} \\
\text{rt. 20 hrs} & \quad 96 \% & \quad \alpha: \beta = 1:9 & \quad \text{1. Raney-Ni, H₂, HCl} \\
\text{PivO} & \quad \text{OPiv} & \quad \text{OPiv} & \quad \text{OPiv} \\
\text{N₃} & \quad \text{2. NaHCO₃} & \quad 62 \% & \quad \text{β-only}
\end{align*}
\]

Scheme 2.2.3 Synthesis of Sugar Template

The ratio of α:β anomer, based on the integration of anomic proton at 4.62 ppm (β-
anomer, J₁,₂ = 4.1 Hz) and 5.65 ppm (α-anomer, J₁,₂ = 7.9 Hz), was 1.6:1 ~ 1:10
depending upon the reaction conditions. Prolonged reaction time increased the ratio
of α anomer (Table 2.2.2, entry 2). Fortunately, irrespective of the ratio of the
mixture, only β-D-galactosyl amine 2.2.1 was obtained (β:α = 99:1) after reduction of
the azide.

Table 2.2.2. Ratio of α/β Anomers of Pentapivaloylgalactosyl Azide 2.2.6

<table>
<thead>
<tr>
<th>entry</th>
<th>s.m.</th>
<th>TMSN₃</th>
<th>SnCl₄</th>
<th>temp./ time</th>
<th>α:β (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-OPiv</td>
<td>3.0 eq</td>
<td>1.2 eq</td>
<td>rt/ 6 h</td>
<td>1:3 (87)</td>
</tr>
<tr>
<td>2</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
<td>rt/ 48 h</td>
<td>1.6:1(85)</td>
</tr>
<tr>
<td>3</td>
<td>&quot;</td>
<td>1.0 eq</td>
<td>0.85</td>
<td>rt/ 4 h</td>
<td>1:10(96)</td>
</tr>
</tbody>
</table>
The resulting amine was then coupled with 1-methoxy-3-methylbenzaldehyde, which was obtained by oxidation of 2,3-dimethylanisole,\textsuperscript{9} to form the Schiff base in

![Schiff base formation](image)

**Scheme 2.2.4** Formation of Schiff Base

### Table 2.2.3 Formation of Schiff Base

<table>
<thead>
<tr>
<th>entry</th>
<th>starting material</th>
<th>method</th>
<th>AcOH (eq)</th>
<th>rxn time</th>
<th>α:β ratio (% yield)\textsuperscript{a)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.2.1</td>
<td>d</td>
<td>1.0</td>
<td>24 h</td>
<td>1:1.3 (95)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>c</td>
<td>1.0</td>
<td>26 h</td>
<td>7.1:1 (96)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>c</td>
<td>0.5</td>
<td>30 h</td>
<td>5.0:1 (90)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>c</td>
<td>0.3</td>
<td>8 h</td>
<td>1:4.0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>c</td>
<td>0.05</td>
<td>14 h</td>
<td>1:7.2 (84)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>c</td>
<td>none</td>
<td>20 h</td>
<td>1:4.5 (49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48 h</td>
<td>1:5.0 (79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>71 h</td>
<td>17.0 (78)</td>
</tr>
<tr>
<td>7</td>
<td>2.2.1-HCl</td>
<td>c</td>
<td>none</td>
<td>24 h</td>
<td>2.0:1 (83)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93 h</td>
<td>4.3:1 (90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>194 h</td>
<td>4.3:1 (90)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>e</td>
<td>none</td>
<td>25 h</td>
<td>3.0:1 (86)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>72 h</td>
<td>3.0:1 (90)</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>d</td>
<td>none</td>
<td>20 h</td>
<td>2.7:1 (92)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>143 h</td>
<td>2.4:1 (93)</td>
</tr>
</tbody>
</table>

\textsuperscript{a) ratio and yield was determined by NMR (200 MHz) based on the anomeric proton. [H\textsubscript{7}(α) = 8.76 ppm, H\textsubscript{7}(β) = 8.93 ppm] after reaction mixture was taken and pumped in vacuo. b) reaction was performed uniformly in n-heptane. c) rt, molecular sieve (4 Å) d) reflux, Dean-Stark apparatus was used to remove H\textsubscript{2}O e) reflux, molecular sieve (4 Å)
79 \sim 96\% \text{ yield. Interestingly, the ratio of the } \alpha \text{ and } \beta \text{ anomers of the Schiff base was dependent on the amount of the AcOH, reaction temperature and reaction time.}

For example, the \alpha \text{ anomer was obtained as a major product at rt with more than 0.5 eq. of AcOH (entry 2.3), but with less than 0.3 eq of AcOH (entry 4.5.6), the } \beta \text{-anomer was preponderant. With prolonged reaction time, the ratio of } \beta/\alpha \text{ anomer increased (entry 6), but at high temperature, the ratio was not as high as at rt. However, in contrast to the case of free amine, the HCl salt of the galactosylamine preferred to form the } \alpha \text{ anomer as a major compound irrespective of reaction time and temperature (entries 7, 8, 9).}

Separation of these air and silica gel sensitive imines was done by recrystallization from n-heptane to afford pure } \alpha \text{-anomer (36.9 \%) from the } \alpha \text{ anomer enriched mixture } (\alpha: \beta = 2.8:1, \text{ yield of mixture } = 84.9 \%).

With pure } \beta\text{-D-galactosylimine 2.2.8, asymmetric Strecker synthesis was performed and a mixture of 4 products were obtained in total 90\% \text{ yield. Their ratio was determined by NMR (200 MHz) analysis based on the anomic proton } [H_\alpha = 5.32 \text{ ppm, } H_\beta = 4.78 \text{ ppm}] \text{ and the methyl peak of aromatic ring } (\beta S: \alpha S: \beta R: \alpha R = 2.30, 2.14, 2.07, 2.05 \text{ ppm}, \text{ and by HPLC analysis of the amino acid obtained after the hydrolysis of the aminonitrile (see later). The ratio was } \beta S: \beta R: \alpha S: \alpha R = 4.5:4.6:1.0:7.2 \text{ (i.e., } R:S = 2.1:1, \alpha: \beta = 0.9:1 \text{) and this is quite disappointing when compared with the precedent\textsuperscript{1} which showed at least 6.5:1 } (R:S) \text{ ratio and only trace amounts of } \alpha \text{-anomer. A better result was obtained from } \alpha \text{-imine 2.2.9 under the same conditions (Table 2.2.4, entry 2) and after a single crystallization in n-heptane, a mixture of products was obtained in the ratio of } \beta S: \beta R: \alpha S: \alpha R = 1:37:7:62 \text{ (R:S =}
12.4:1, α:β = 2.0:1). The D:L ratio of the amino acid derived from this mixture was 14.1:1 by HPLC.

Scheme 2.2.5. Asymmetric Strecker Synthesis

Table 2.2.4. Ratio of the Diastereomers for Aminonitriles

<table>
<thead>
<tr>
<th>starting material</th>
<th>αR (2.2.13)</th>
<th>αS (2.2.12)</th>
<th>βR (2.2.11)</th>
<th>βS (2.2.10)</th>
<th>α:β&lt;sup&gt;a&lt;/sup&gt;</th>
<th>R:S&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2.8</td>
<td>7.1</td>
<td>1</td>
<td>4.5</td>
<td>4.6</td>
<td>1:1:1</td>
<td>2.1:1</td>
</tr>
<tr>
<td>2.2.9</td>
<td>10.3</td>
<td>2.0</td>
<td>3.4</td>
<td>1</td>
<td>2.8:1</td>
<td>4.6:1</td>
</tr>
<tr>
<td>2.2.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>62</td>
<td>7</td>
<td>37</td>
<td>1</td>
<td>1.8:1 (2:1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12.4:1 (14.1:1)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> calculated ratio, i.e., ratio = (αR+αS):(βS+βR). <sup>b</sup> ratio was measured after crystallization of crude product. <sup>c</sup> ratio of anomeric proton observed by NMR. <sup>d</sup> ratio of amino acid measured with HPLC (equipped with Chiralpak<sup>®</sup>) after hydrolysis of crystallized aminonitriles. i.e., ratio = (αR+βR):(αS+βS).

Hydrolysis of recrystallized aminonitrile in methanolic 2N HCl afforded the amino nitrile 2.2.14 along with tetrapivaloyl galactose 2.216. The resulting aminonitrile
Scheme 2.2.6 Hydrolysis of Aminonitriles

2.214 was further hydrolyzed using vigorous acidic conditions to give the desired amino acid 2.2.15 in quantitative yield. The recovered auxiliary 2.2.16 was converted to the pentapivaloyl galactose 2.2.5 upon treatment with pivaloyl chloride, pyridine and DMAP.

Assignment of absolute stereochemistry to the synthetic amino acid 2.2.15 was performed using HPLC equipped with chiral column (chiralpak®, Daicel Instruments Co. 4.6 mm x 250 mm). This column eluted standard D-phenylglycine ($t_{ret} = 28.0$ min) first over the L-phenylglycine ($t_{ret} = 30.5$ min) and in case of synthetic amino acid 2.2.15, after neutralization with sodium mono/di-phosphate buffer to pH = 7, it showed two peaks with the ratio of 14.1:1 ($t_{ret} = 25.8$ min, 30.8 min respectively). Based upon the result from standard (D)/(L)-phenyl glycine and optical rotation (Table 2.2.4), the first peak was tentatively assigned as (D)-1-methoxy-3-methyl-phenylglycine. When it was neutralized with 0.01N NaOH, the D:L ratio was dropped to 6.8:1 indicating the base sensitivity of the synthetic amino acid.
<table>
<thead>
<tr>
<th>entry</th>
<th>compounds</th>
<th>D:L ratio</th>
<th>t_{rel} (min.)</th>
<th>[\alpha]\text{lp}^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(D)-Phenylglycine</td>
<td>1:0</td>
<td>28</td>
<td>-155°</td>
</tr>
<tr>
<td>2</td>
<td>(L)-Phenylglycine</td>
<td>0:1</td>
<td>30.5</td>
<td>+155°</td>
</tr>
<tr>
<td>3</td>
<td>2.2.15 (buffer)\text{b}</td>
<td>14.1:1</td>
<td>25.9, 30.9</td>
<td>-65.2°</td>
</tr>
<tr>
<td>4</td>
<td>2.2.15 (0.01 N NaOH)</td>
<td>6.8:1</td>
<td>25.3, 30.1</td>
<td></td>
</tr>
</tbody>
</table>

a) 1 N HCl was used as a solvent. b) Mixture of NaH₂PO₄/Na₂HPO₄ was used

Table 2.2.5. Assignment of the Absolute Chemistry

Purification of 2.2.15 from the side product NH₄Cl was attempted using the ion-exchange resin (Amberite IR-120, -SO₃H type) but different from the case of phenylglycine or p-nitrophenylglycine\textsuperscript{2}, it was not eluted with the 3% NH₄OH at all from the resin. Trimethylamine was successful for this purpose but the trimethylammonium salt was not separable from the amino acid.

From the crude product, desired amino alcohol 2.2.17 was obtained after reduction with BF₃·Et₂O/ BH₃·Et₂O in a vigorous condition.\textsuperscript{10} Protected amino acids are known to be reduced smoothly with LiAlH₄, DIBAL and BH₃·SMe₂,\textsuperscript{11} but unprotected amino acids such as 2.2.15 require harsh conditions. The yield of this process was poor and racemization seemed to occur during the reduction because of the 6 N NaOH used. The optical purity of the product was 6.5:1 (D:L) by NMR based on the integrated area of methoxy peaks of (+)-MTPA amide 2.2.18.\textsuperscript{12}
Scheme 2.2.7. Reduction of Amino Acid and Determination of Optical Purity

Conclusion Though the desired amino alcohol was obtained using the method described above, this method was not suitable for the synthesis of large amounts of amino alcohol because of low yields in the synthesis of the Schiff base and amino nitrile, difficulties in reduction and purification of the amino acid, and low optical purity.

2.2 Amino Alcohol Synthesis via Nucleophilic Azidation of Epoxy Alcohol.

Introduction. After the discovery of stereoselective epoxidation of allyl alcohol by Sharpless and Katsuki in 1980, it has been utilized in many research groups for the synthesis of various kinds of natural and unnatural compounds because of its uniqueness and high asymmetric induction.

Soon after the discovery of this method followed the development of synthetic methodology for synthesis of α-amino acids as shown in Scheme 2.2.8. Azidation of the epoxy alcohol 2.2.19 can be achieved by several kinds of reagent such as NaN₃/NH₄Cl, [Ti(O-i-Pr)₂(N₃)₂], Me₃SiN₃/Et₂AlCl, Regioselectivity of azidation varies depending upon substrate and azidation reagent but, in case of
2.2.19, azidation occurred exclusively at C₃, presumably owing to stabilization of the carbocation at C₃ by a neighbouring aromatic group.

\[
\text{Ph} \xrightarrow{\text{Ti(OiPr)₄, (-)-DIPT}} \text{PhOH} \xrightarrow{89\%} \text{PhCHO} \xrightarrow{85\%} \text{PhCO}_2\text{H} \xrightarrow{76\%} \text{PhCO}_2\text{H}
\]

2.2.19 (> 98 % ee)  2.2.20 (> 98 % ee)

\[
\text{Ph} \xrightarrow{\text{RuCl₃, H₂O₂}} \text{PhNH}_2
\]

Phenylglycine (86 % ee)

2.2.23 (> 98 % ee)  Phenylalanine (> 98 % ee)

**Scheme 2.2.8. Synthesis of Amino Alcohol from 2,3-Epoxy Alcohol**

A drawback for this procedure is racemization during the oxidative cleavage of the diol functionality. When compared with phenylalanine formation reaction from 2.2.23, racemization is believed to occur through the azidoaldehyde 2.2.21 whose methine proton is highly acidic because of the neighboring phenyl and carbonyl group.

For the synthesis of the desired amino alcohol, it was expected that reduction of azido aldehyde would produce an azido alcohol such as 2.2.27 and subsequent reduction of azide could provide the desired amino alcohol 2.2.28 as shown in Scheme 2.2.9.
Results and Discussion  As a model compound, azido diol 2.2.20 was prepared from 2.2.19 in 77% yield by 12 h refluxing with NH₄Cl/NaN₃ in aqueous MeOH. During this process, the product from azidation at C₂ or Payne rearrangement was not observed.

Azidodiol 2.2.20 was oxidatively cleaved using NaIO₄ in methanolic solution and resulting unstable aldehyde was reduced with NaBH₄ without separation to provide the azido alcohol 2.2.29 in good yield. Reduction of the azide group provided the amino alcohol 2.2.30 which was almost pure according to optical rotation and ¹H NMR of its (+)-MTPA amide. Protection of amino alcohol (2.2.30) without base was low (36%), but coupling with (+)-MTPA was smoothly accomplished in 88% yield. The ratio of (S):(R)-amino alcohol was 5:95 based on the integration of -OMe peak by NMR and racemization during the oxidative cleavage does not seem to occur during this procedure.
Scheme 2.2.11. Oxidative Cleavage of Azido Alcohol and Reduction.

Following this successful model study, allyl alcohol 2.2.33 was made from aldehyde 2.2.32. Reaction of 2-methoxy-6-methylbenzaldehyde with the stabilized phosphonium ylide afforded only the E-cinnamyl ester 2.2.32 in 95% yield which was reduced with DIBAL-H to the corresponding cinnamyl alcohol. Unfortunately, Sharpless epoxidation was unsuccessful with this substrate and starting material 2.2.33 was recovered in 86%.

Scheme 2.2.12 Preparation of 1-Methoxy-3-methylcinnamyl Alcohol and Attempted Sharpless Epoxidation.
It was later found\(^{21}\) that substituted cinnamyl alcohols with electron donating groups such as \(\alpha\)- or \(\rho\)-methoxy stabilize the benzylic carbocation center so much that the epoxide can be opened even at \(-20\) °C by various nucleophiles, eventually poisoning the catalyst (1/20 eq in typical condition) by irreversible formation of a complex with the catalyst.

![Scheme 2.2.13. Poisoning of Catalyst](image)

When the reaction was performed at \(-78\) °C with excess catalyst (1.6 eq. Ti(O-iPr)\(_4\)/ 2.3 eq. \((-\)-DIPT to overcome this problem, no reaction occurred over 2.5 h but at \(-14\) °C, a tailing spot started to appear on TLC. Assuming this is the unstable epoxide, \textit{in situ} nucleophilic azidation was attempted by addition of TMSN\(_3\) at \(-78\) °C but only traces of unidentifiable products were obtained. Reaction with Ti(O-i-Pr)\(_2\)(N\(_3\))\(_2\)\(^{17}\) instead of TMSN\(_3\) was also failed.

The epoxide \(2.2.34\) was very unstable and even without Lewis acid catalyst seems to open. When cinnamyl alcohol \(2.2.33\) was treated with m-CPBA, no epoxide was obtained but its m-CPBA adduct\(^{22}\) was produced in 88 % yield.

In 1981, A. J. Pearson and C. W. Ong published a paper\(^{23}\) in which allyl alcohol was oxidized in the presence of deactivated butadiene as its Fe(CO)\(_3\) complex without competing demetallation. A similar result was also reported by R. Gree in 1988.\(^{24}\)
Scheme 2.2.14 Sharpless Oxidation in the Presence of $\eta^4$-butadiene-Fe(CO)$_3$ Complex.

Using the same analogy, reduction of the electron donating ability of the 2-methoxy-3 methylphenyl ring was attempted by introducing a chromium tricarbonyl moiety onto the phenyl group of substrate 2.2.25 following the precedent.$^{25}$

Scheme 2.2.15. Complexation of Cinnamyl Ester and Its Epoxidation

Complexation of cinnamyl alcohol 2.2.33 was not clean but methyl cinnamyl ester provided the corresponding complex in 50 % yield. Reduction of the complex was also successful. However, when it was subjected to the Sharpless epoxidation,
oxidative demetallation occurred exclusively as feared and cinnamyl alcohol 2.2.33 was obtained in 87% yield. Later, it was also found that a chromium carbonyl moiety complexed to an aryl ring stabilizes a neighboring carbocationic center. Further efforts were not made because of this problem.

**Conclusion** Because of the problems mentioned above, further attempts to prepare the amino alcohol were not made. Instead, we switched to the electrophilic asymmetric azidation method developed by Evans et al.

2.3. Amino Alcohol Synthesis via Electrophilic Azidation

**Introduction** Electrophilic stereoselective amination\(^{27}\) (azidation\(^{28}\)) is very important for the synthesis of amino acids. Various amino acids can be made in high optical purity using this methodology. Chiral auxiliaries used in this method are exemplified by 2.2.36\(^{29}\), 2.2.37\(^{30}\), 2.2.38\(^{28}\), 2.2.39.\(^{28}\) Trisyl azide\(^{29}\) or di-t-butyl azocarboxylate\(^{28}\) are often used as aminating agent. In some cases, stereoselective halogenation is followed by a nucleophilic azide substitution reaction to provide the amino acid precursor but with reversed stereochemistry. The same chiral auxiliaries have been used for stereocontrolled enolate alkylations and aldol reactions.\(^{28}\)

![Scheme 2.2.16 Chiral Auxiliaries for Azidation/ Amination](image)

---

\(^{26}\) Further

\(^{27}\) Electrophilic stereoselective amination

\(^{28}\) Azidation

\(^{29}\) Trisyl azide

\(^{30}\) Di-t-butyl azocarboxylate
The stereodirecting effects of auxiliaries such as 2.2.36, 2.2.37 originate from steric hindrance between the approaching electrophile and the $C_4$ substituent of the auxiliaries.

\[
\begin{array}{c}
\text{R} \quad \text{R} \\
\text{K} \quad \text{K} \\
\text{H} \quad \text{E} \\
\text{Me} \quad \text{Me} \\
\text{Ph} \quad \text{Ph}
\end{array}
\]

Scheme 2.2.17. Origin of Selectivity of Electrophilic Azidation

The enolates are not freely rotating because of chelation with metallic ion and, $Z$-enolates are preferred over $E$-enolates because of the steric congestion with an oxazolidinone ring moiety.

**Results and Discussion.** For the synthesis of the amino alcohol 2.1.5, we first prepared the requisite phenylacetic acid using two different methods as shown in

\[
\begin{array}{c}
\text{CH}_3O \quad \text{CHO} \\
\text{CH}_3 \quad \text{CH}_3 \\
2.2.40 \quad 0 \degree C, 45 \min \quad 100 \% \quad \text{Ph}_3\text{P, CBr}_4
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3O \quad \text{Br} \\
\text{CH}_3 \quad \text{CH}_3 \\
2.2.41 \quad \text{n-But}, \text{TMSCl} \quad \text{-78} \degree \text{C} \to \text{rt}
\end{array}
\]

\[
\begin{array}{c}
\text{MeSCH} \quad \text{SiMe}_3 \\
\text{OMe} \\
\text{SOM}
\end{array}
\]

\[
\begin{array}{c}
\text{MeSCH} \quad \text{SOM} \\
\text{Triton B, } \Delta, 24 \text{ h} \\
\text{91} \%
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3O \quad \text{CO}_2X \\
\text{CH}_3 \quad \text{CH}_3 \\
\text{X} = \text{H, OMe, SME} \\
\text{2.2.43}
\end{array}
\]

Scheme 2.2.18 Preparation of 2-Methoxy-6-phenylacetic Acid.
scheme 2.2.18. In route A, aldehyde 2.2.40 was converted to a dibromo vinyl compound 2.2.41 following the protocol by Corey.31 This was then transformed into a trimethylsilyl acetylene by treatment with n-BuLi and TMSCl. *In situ* hydroboration of the compound32 followed by oxidative workup afforded the phenylacetic acid 2.2.43 in total yield of 43%. More conveniently, in route B, aldehyde 2.2.40 was condensed with MeSCH₂SOMe33 in the presence of Triton B® to afford the sulfinyl complex 2.2.42 as a 5:1 mixture of E:Z isomers. Hydrolysis of the product gave a mixture of the phenylacetic acid 2.2.43 and its methyl/thiomethyl ester. After hydrolysis of the esters under basic conditions, the combined material was crystallized in Et₂O to afford the phenylacetic acid 2.2.43 in 66% overall yield.

Phenylacetic acid 2.2.43 was coupled with lithium oxazolidinone after transformation to the mixed pivaloyl anhydride following precedents.28, 29 The resulting imide was azidated using KHMDS and trisyl azide. The diastereomeric excess of the crude product was at least 94% based on the integration of the -OMe peaks at 3.79 and 3.64 ppm. Column chromatography (SiO₂, hexanes:EtOAc = 20:3) and recrystallization from a hexanes/EtOAc mixture afforded the pure azidoimidate 2.2.45 in 88% yield.

![Scheme 2.2.19](image)

**Scheme 2.2.19.** Coupling of Chiral Auxiliary and Azidation.
Conversion of the azido imidate 2.2.45 to the corresponding amino alcohol 2.1.5 was attempted in three different ways. When it was reduced\textsuperscript{34} with LiAlH\textsubscript{4}, it directly afforded our desired amino alcohol 2.1.5 in 54–57% with high optical purity along with oxazolidinone in 37–59% (\([\alpha]_D\)\textsubscript{Recovered} = 173.6°, \([\alpha]_D\)\textsubscript{Lit} = 163.7°). But this reaction was very difficult to work up because of large amount of aluminum hydroxide formed after quenching of the reaction with water and was not used any more after we found another reduction method with NaBH\textsubscript{4}.\textsuperscript{35}

\[\begin{align*}
2.2.45 & \xrightarrow{\text{NaBH}_4, 0–5 \degree \text{C}, 42 \text{ h}} 83 \% \quad 2.2.46 \\
& \xrightarrow{\text{LiOH, H}_2\text{O}_2, 0 \degree \text{C}, 1 \text{ h}} 87 \% \\
& \xrightarrow{\text{LH}, 0 \degree \text{C}, 6 \text{ h}} 54 \% \\
2.2.47 & \xrightarrow{\text{LiAlH}_4, 2.5 \%} \quad [\alpha]_D = -41.3 \degree \\
& \xrightarrow{1. \text{TBDMSCl, Et}_3\text{N, 2. (S)MTPA, EDC, HOBt}} \\
& \quad \text{de} > 100:1 \\
2.1.5 & \xrightarrow{\text{CH}_3 \text{NH}_2 \text{OTBDMS}} \\
& \xrightarrow{\text{MTPA}\text{-(R)} = \text{Ph}_3 \text{O}\text{MeCF}_3} \\
2.2.49
\end{align*}\]

**Scheme 2.2.20.** Conversion of Azidoimidate to Amino Alcohol

In the case of hydrolysis with *in situ* generated LiOOH, the azidoacetic acid was obtained in 75 ~ 87% yield along with 98% recovery of auxiliary but reduction of the resulting azidoacetic acid 2.2.47 was very poor. Of these, NaBH\textsubscript{4} was the best reagent for mild reduction of the azido imidate. It afforded azido alcohol 2.2.46 in
83% along with 96% recovery of the auxiliary. Reduction of the azide group smoothly provided the desired amino alcohol 2.1.5 in 76% yield (not optimized).

To determine the optical purity of the amino alcohol, it was first protected with TBDMSCl and then coupled with (R)-(−)-α-methoxy-α-((trifluoromethyl)phenylacetic

Figure 2.2.2. Determination of Optical Purity of Amino Alcohol 2.1.5.
acid\textsuperscript{12} in the presence of EDC\textsuperscript{36} and HOBT. Comparison of the Mosher's amide 2.2.49 with the one derived from its racemic analogue showed no sign of diastereomer based on the -OMe peaks. Enantiomeric excess of amino alcohol 2.2.48 was determined to be greater than 100:1.

**Conclusion** Using the methodology developed by Evans and associates, we could easily prepare large amounts (\(~ 10 \text{ g}\)) of the desired amino alcohol with high optical purity (de > 100:1).

This material was used in the synthesis of quinocarcin which was completed by my colleague Dr. Wen Bin Ho\textsuperscript{37} in 1992. Quinocarcin ([\(\alpha\)]\textsubscript{D}\textsuperscript{Synthetic} = -30\(^\circ\) (c 0.2, \(\text{H}_2\text{O}\)), [\(\alpha\)]\textsubscript{D}\textsuperscript{Natural} = -32\(^\circ\) (c 0.5, \(\text{H}_2\text{O}\))) is revealed to have the absolute chemistry as depicted in structure 2.1.1a.

\[
\text{(R)-(2-methoxy-6-methylphenyl)-} \\
\text{2-amino ethanol (2.1.5)} \\
\text{\quad (\text{-Quinocarcin}} \\
\text{\quad (2.2.1a))}
\]

**Scheme 2.2.21.** Total Synthesis of Quinocarcin from Amino Alcohol 2.1.5.
2.4 Experimental Section.

**General** Silica gel TLC plates were visualized with UV illumination followed by charring with either 5% anisaldehyde in (95:5:1) EtOH-AcOH-H₂SO₄ (char A), 0.3% ninhydrin in (97:3) nBuOH-AcOH (char B), or 2% vanillin in (98:2) EtOH-H₂SO₄ (char C). Melting points are uncorrected. The ¹H NMR signal assignments were based on selective homonuclear decoupling experiments while the ¹³C assignments were based on APT (attached proton test) experiments and proton coupling data. High resolution mass spectral (HRMS) data are reported in units of m/e for M⁺ or for the highest mass fragment derived from M⁺. All reactions were performed under inert (N₂ or Ar), moisture-free atmosphere except when working in aqueous media. Solvent were purified beyond reagent grade as follows: 1,4-dioxane, THF, & toluene were distilled from sodium + benzophenone; CH₂Cl₂ & DMF were distilled from CaH₂ and stored over 4Å molecular sieves; CHCl₃ was washed with H₂O, dried over K₂CO₃, and distilled from P₂O₅.

(+)N-(2-Methoxy-6-methylphenylidene)-2,3,4,6-tetra-O-pivaloyl-α-D-galactopyranosylsylamine (2.2.9)

In a 500 mL three necked flask was placed tetrapivaloylgalactosyl amine 2.2.7 (23.06 g, 44.72 mmol, 1.01 eq), 1-methoxy-3-methylbenzaldehyde (6.62 g, 44.7 mmol, 1.00 eq) and 4 Å molecular sieves (45.1 g). The mixture was degassed under vacuum for 1 h and n-heptane (340 mL) was added under Ar atmosphere. To this was added glacial AcOH (2.56 mL, 1.0 eq) and the mixture was stirred for 7 d at rt until the reaction was finished. The ratio of α:β was increased with time, but it did not exceed the ratio of 2.8:1. The reaction mixture was
filtered through Celite and concentrated in vacuo to give a yellow liquid (19.0 g) which was recrystallized from n-pentane (140 mL) at -13 °C. While the solution cooled, the desired product 2.2.9 forms as needle shaped crystals (α-imine), however, after 10 h, cubic shaped crystals (β-imine, 2.2.8) appeared on top of the α-imine. Recrystallization of the solids at rt in n-heptane afforded only α-imine (10.7 g, 36.9 %).

For 2.2.9: IR(CHCl₃): 3410, 2410, 2400, 1740 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz, RT): δ 8.76 (s, H₃N), 7.29 (t, J = 7.6 Hz, HAr), 6.86 (d, J = 7.7 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.69-5.59 (m, H₃, H₄), 5.38 (dd, J = 10.3, 4.4 Hz), 5.10 (d, J = 4.5 Hz, H₁), 4.85-4.05 (m, H₆, H₆'), 3.82 (s, 3H), 2.66 (s, 3H), 1.30 (s, 9H), 1.16 (s, 9H), 1.13 (s, 9H), 1.07 (s, 9H); ¹³C NMR(CDCl₃, 50 MHz, RT): δ 177.84 (s, -), 177.47 (s, -), 177.20 (s, -), 177.03 (s, -), 161.77 (d, +), 160.23 (s, -), 140.69 (s, -), 131.45 (d, +), 124.19 (d, +), 121.85 (s, -), 108.23 (d, +), 94.13 (d, +), 69.06 (d, +), 68.99 (d, +), 68.60 (d, +), 68.30 (d, +), 61.68 (t, -), 55.36 (q, +), 39.10 (s, -) 38.73 (s, -), 27.24 (q, +), 27.05 (q, +), 22.86 (q, +); [α]D²⁴: +163.3° (c 0.82, CHCl₃); HRMS. Found: 647.3671; calc’d for C₃₅H₅₃NO₁₀ : 647.3669. MS: m/e 648(44), 647 (100), 328 (12), 211 (10), 181 (15), 178 (16), 150 (22), 148 (22), 147 (10), 129 (10)

(+)-N-(2-Methoxy-6-methylphenylidene)-2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosylamine (2.2.8)

IR(CHCl₃): 3400, 2420, 2410, 1745 cm⁻¹; ¹H NMR(CDCl₃, 200 MHz, RT): δ 8.93 (s, 1 H), 7.24 (t, J = 7.8 Hz, 1H), 6.79 (d, J = 7.6 Hz, 1H), 6.74 (d, J = 8.5 Hz, 1H), 5.51 (d, J = 3.1 Hz, H₄, 1H), 5.40 (dd, J = 10.3, 8.4 Hz, H₂, 1H), 5.25 (dd, J = 10.3, 3.2 Hz, H₃), 4.76 (dd, J = 8.4 Hz, H₁), 4.31-4.04 (m, H₅, H₆, H₆'), 3.83 (s, 3H), 2.51 (s, 3H), 1.29 (s, 3H), 1.19 (s, 9H), 1.13 (s, 9H); HRMS.
N-(2,3,4,6-tetra-O-pivaloyl-β-D-galactopyranosyl-α-(1'-methoxy-3'-methyl)phenyl-α-aminonitrile. (2.2.13)

To a -40 °C solution of imine 2.2.9 (10.5 g, 16.21 mmol, 1.0 eq) dissolved in 1L THF was injected freshly distilled SnCl₄ (5.0 mL) and the mixture was stirred for 30 min at -40 °C. To the resulting yellow solution, TMSCN (6.48 mL, 48.6 mmol, 3.0 eq) was injected and stirred for 12 h between -45 °C ~ -25 °C, 1.5 h at 0 °C and 8 h at rt. The reaction was quenched by addition of sat. aqueous NaHCO₃ (500 mL) and after separation of organic layer, the aqueous layer was extracted with Et₂O (2 x 250 mL). The combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a yellow liquid (15.1 g, R/S ratio of the chiral center = 4.5/1, α/β ratio = 2.8/1) and this gum was crystallized in n-heptane to give desired product 2.2.11/2.2.13 as a 1:1.9 mixture (7.6 g, 2.2.11 = 24 %, 2.2.13 = 46 %) along with 5 % of 2.2.10/2.2.12. For analytical purposes, pure 2.2.11 and 2.2.13 were obtained by chromatography (SiO₂, hexanes:EtoAc = 5:1).

For 2.2.13: mp: 75-78 °C; Rf 0.40 (hexanes:EtoAc = 5:1); IR (CHCl₃): 3360, 2250, 1740 cm⁻¹; 1H NMR (CD₆D, 200 MHz, RT): δ 6.94 (t, J = 7.9 Hz), 6.59 (d, J = 7.5 Hz), 6.36 (d, J = 8.2 Hz), 5.87 (dd, J = 10.7, 4.8 Hz, H₂), 5.62 (dd, J = 3.2, 1.0 Hz, H₄), 5.51 (dd, J = 10.8, 3.3, H₃), 5.33 (d, J = 4.8 Hz, H₁), 5.01 (d, J = 12.1, H₇), 4.27-4.15 (m, H₅, H₆, H₆), 3.53 (d, J = 12.3 Hz, NH⁻), 3.36 (s, 3H), 2.05 (s, 3 H), 1.26 (s, 9H), 1.23 (s, 9H), 1.15 (s, 9H), 1.07 (s, 9H); ¹³C NMR (CDCl₃, 50 MHz, RT): 177.05
(s, -), 176.53 (s, -), 176.03 (s, -), 175.77 (s, -), 157.31 (s, -), 135.94 (s, -), 129.37 (d, +), 122.97 (d, +), 120.78 (s, -), 117.63 (s, -), 109.25 (d, +), 81.70 (d, +), 67.18 (d, +), 66.64 (d, +), 66.11 (d, +), 65.26 (d, +), 60.30 (t, -), 55.33 (q, +), 42.30 (d, +), 38.35 (s, -), 38.64 (s, -), 37.95 (s, -), 30.82 (s, -), 26.44 (q, +), 26.34 (q, +), 26.07 (q, +), 18.92 (q, +); [\alpha]_D^{24}: +118.7° (c 0.78, CHCl₃); HRMS. Found: 648.3745; calc'd for C₁₅H₁₄NO₁₀ (M⁺-CN): 648.3747 MS: m/e 648(41), 647 (100), 546 (12), 499 (12), 328 (24), 211 (22).

N-(2,3,4,6-tetra-O-pivaloyl-β-D)galactopyranosyl-β-(1'-methoxy-3'-methyl)phenyl-α-aminonitrile (2.2.11):

mp: 145-147 °C; Rf: 0.32 (hexanes:EtoAc = 5:1); ¹H NMR(C₆D₆, 200 MHz, RT): 8.691 (t, J = 7.9 Hz, 1H), 6.56 (d, J = 7.6 Hz, 1H), 6.29 (d, J = 8.2, 1H), 5.56 (dd, J = 3.4, 1.2 Hz, H₄), 5.37 (dd, J = 10.4, 8.8 Hz, H₂), 5.18 (dd, J = 10.4, 3.4 Hz, H₃), 5.08 (bd, J = 9.7 Hz, H₇), 4.33-4.16 (m, 2 H, H₆,H₆'), 3.75 (dd, J = 10.7, 8.7 Hz, H₁), 3.52 (bt, J = 7.0 Hz, H₅), 3.30 (bt, J = 8.7 Hz, 1H), 3.19 (s, 3H), 2.15 (s, 3H), 1.21 (s, 9H), 1.18 (s, 9H), 1.15 (s, 9H), 1.01 (s, 9H); [\alpha]_D^{24}: +9.4° (c 0.78, CHCl₃)

2-(1-methoxy-3-methyl)phenylglycine (2.2.15)

To a solution of aminonitrile 2.1.11/2.2.13 (673 mg, 0.99 mmol, 1.0 eq) dissolved in Et₂O (14 mL) was added methanolic 2N HCl (2 mL 10 N HCl + 8 mL MeOH) and the mixture was stirred for 23 h at rt until the reaction was finished. After removal of the solvent in vacuo, the residue was mixed with H₂O (30 mL), washed with Et₂O (3 x 30 mL) and hydrolyzed with 6 N HCl (37 mL) by
stirring it for 68 h at 80 °C. The reaction mixture was cooled and concentrated *in vacuo* to give a yellow solid 2.2.15 (252.2 mg, 100 %). For HPLC analysis, few milligrams of this product was neutralized to pH 7 using a mixture of mono and di sodium phosphate or 0.01 N NaOH solution and eluted at 50 °C with 0.3 mM aqueous CuSO₄ solution over chiral pak® column (Daicel Instruments Co. 4.6 mm x 250 mm). Two peaks were observed (t<sub>ret</sub> = 25.9, 20.9 min respectively, flow rate = 1 mL/min.) in 14:1 ratio for buffer neutralized product and 6.8:1 for NaOH neutralized product. Also from the organic layers galactosyl alcohol 2.2.16 (401 mg, 77.9 %) was obtained as a white solid after it was dried over MgSO₄, and concentrated. Tetrapivaloyl galactose 2.2.16 (168 mg, 0.033 mmol) was converted to pentapivaloyl galactose 2.2.5 (118 mg, 61 %) using the same conditions that were used to prepare it from D-galactose.

For 2.2.15: R<sub>f</sub>: 0.28 (H₂O:MeOH:CH₃CN = 1:1:5); ¹H NMR (200 MHz, D₂O): δ 7.26 (t, J = 8.0, 1H), 6.80 (bd, J =7.5 Hz, 2H), 5.17 (s, H-1), 3.66 (s, 3H), 2.25 (s, 3H); [α]<sub>D</sub>: -65.2 °(c 1.2, 1N HCl)

2-(R)-2-Amino-2-(2-methoxy-6-methylphenyl)ethyl Alcohol (2.217)

**Caution!** *This reaction is violent and not suitable not suitable for 0.5 ~ 1 mol scale large reaction. BH₃·SMe₂ should be added very slowly.*

Crude amino acid 2.2.15 (729 mg, 2.9 mmol, 1.0 eq) contaminated with ~ 1 eq. of NH₄Cl was dissolved in THF (20 mL) and refluxed for 2 h with 790 µL of BF₃·OEt₂ under Ar atmosphere. Another portion of 790 µL BF₃·OEt₂ was added and mixture was refluxed for 2 more h. To the refluxing mixture was added BH₃·SMe₂ (418 µL, 1.5 eq) over 20 min and 6 h later, the reaction was quenched with 500 µL 1:1 mixture of THF:H₂O. Reaction mixture was then basified with 6 N NaOH (2.5 mL) and refluxed
for 2 h. After cooling, the mixture was partitioned between Et₂O/water and the aqueous layer was acidified to pH = 1 and washed with Et₂O (30 mL x 2). The aqueous layer was then basified to pH = 11 and extracted with dichloromethane (30 mL x 2). The combined organic layer was dried (MgSO₄) and concentrated to afford amino alcohol 2.2.17 (186 mg, 35%).

For 2.2.17: identical compound was made using different route. see 2.1.5.

(2S)-(+) -2-azido-2-phenylethanol (2.2.29)

To a solution of azido diol 2.2.20 (24 mg, 0.12 mmol, 1.0 eq) in 2 mL MeOH, was added 1.5 mL of NaIO₄/MeOH (0.119 M, 1.0 eq) solution over 3 h and the reaction mixture was stirred for additional 1.5 h. The reaction mixture was then filtered through a Celite pad with ambient amount of MeOH and was concentrated to 4 mL. To this solution was added NaBH₄ (7.65 mg, 0.202 mmol, 1.65 eq) and it was stirred for 25 min at rt. The reaction mixture was concentrated and partitioned between dichloromethane (2 mL) and water (2 mL). After separation and extraction of the aqueous layer with dichloromethane (2 x 2 mL), the combined organic layers were dried over MgSO₄ and concentrated in vacuo to give a yellow oil 2.2.29. (17.7 mg, 88.5 %). For 2.2.29: Rf: 0.75 (hexanes:EtOAc = 1:1); IR (CHCl₃): 3600, 2150 cm⁻¹; ¹H NMR (200 MHz, CDCl₃, RT): δ 7.34-7.25 (m, 5H), 4.61 (t, J = 6.4 Hz, 1H, H₃), 3.68 (dd, J = 6.7, 6.4 Hz, H₁, H₁'), 1.91 (t, J = 6.7 Hz, -OH); ¹³C NMR (CDCl₃, 50 MHz): δ 135.56 (s, -), 128.30 (d, +), 128.09 (d, +), 126.48 (d, +), 67.17 (t, - , C-1), 65.83(d, +, C-2); [α]D2⁴: +196° (c 0.95, CHCl₃); HRMS: found (M⁺) 163.0747; calcld for C₈H₁₁NO: 163.0746. MS: m/e 167 (4), 135 (1), 133 (13), 132 (79), 121.920, 106 (23).
(S)-(+)-2-phenylglycinol (2.2.30)

To a solution of azidoalcohol 2.2.29 (200 mg, 1.22 mmol) dissolved in 2 mL of EtOH were added 50 drops of Raney-Ni suspension in EtOH and the mixture was stirred for 4.5 h under H₂ atmosphere. The reaction mixture was filtered through a Celite pad and concentrated to give the product 2.2.30 (162 mg, 97 %). For 2.2.30: Rf: 0.67; IR(CHCl₃): 3620, 3550-2800, 1600-1550 cm⁻¹; ¹H NMR (200 MHz, CDCl₃ + 1-Drop D₂O, RT): δ 7.37-7.32 (m, 5H), 4.04 (q, H₃), 3.74 (dd, J = 10.7, 4.4, 1H), 3.54 (dd, J = 10.6, 3.7 Hz, 1H); ¹³C NMR (CDCl₃, 50 MHz): δ 142.3 (s, -, C-3), 128.5 (d, +), 127.5 (d, +), 126.4 (d, +), 67.7 (t, -, C-1), 57.3 (d, +, C-2); [α]D²⁴: + 23.6° (c 0.85, MeOH); HRMS: found (MH⁺) 138.0931; calcd for C₈H₁₁O: 138.0919. MS: m/e 138 (1), 137 (0.2), 132 (2), 121 (1), 120 (1.3), 108 (1.1), 107 (31), 106 (100).

Methyl 1-methoxy-5-methylcinnamyl ester (2.2.32)

To a solution of 1-methoxy-3 methylbenzaldehyde (9.41 g, 62.7 mmol, 1.0 eq) dissolved in 330 mL benzene was added methyl triphenylphosphoranylidene acetate (25.0 g, 74.8 mmol, 1.20 eq) and the mixture was refluxed for 64 h until the reaction was completed. After cooling, 1 N HCl (700 mL) was added to the reaction mixture and the organic layer was separated, washed with brine (200 mL), and dried over MgSO₄. After evaporation of the solvent in vacuo and chromatography (SiO₂, hexanes: EtOAc = 5 :1), 12.3 g (95.2 %) of product 2.2.32 was obtained as a yellow liquid. For 2.2.32: Rf: 0.46 (hexanes:EtOAc); IR (CHCl₃) 3031, 3026, 3020, 3009, 2952, 2840, 1711, 1629, 1594, 1576, 1522, 1477; ¹H NMR (200 MHz, CDCl₃, RT): δ 7.92 (d, J = 16.4 Hz, 1H), 7.25 (t, J = 8.1 Hz, 1H), 6.81 (bt, 2H), 6.67 (d, J = 16.1, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 2.44 (s, 3H).
1-Methoxy-3-methylcinnamylalcohol (2.2.33)

To an ice bath cooled solution of cinnamyl ester 2.2.32 (11.0 g, 53.34 mmol, 1.0 eq) dissolved in 250 mL of dichloromethane was added 1.5 M solution of DIBAL-H (35.6 mL, 53.1 mmol, 1.0 eq) dropwise via cannula and the reaction mixture was stirred for 10 h at 0 °C. Additional DIBAL-H (50 mL, 26.5 mmol, 0.5 eq) was added and it was stirred for 56 hrs at rt to bring the reaction to completion. The reaction mixture was acidified with 1 N HCl to pH = 1 and it was separated, washed (brine) and dried over MgSO₄. After evaporation of the solvent, the crude product was chromatographed (SiO₂, hexanes:EtOAc = 5:1) to afford 9.0 g (94.5 %) of product 2.2.32 as a yellow liquid. For 2.2.32: Rf: 0.54 (hexanes:EtOAc = 1:1); IR (CHCl₃) 3613, 3029, 3019, 3009, 2975, 2941, 2873, 1596, 1577, 1522, 1469, 1433; NMR (200 MHz, D₂O, RT): δ 9.95 (t, J = 7.9 Hz, 1H), 7.67-7.47 (m, 2H), 7.17 (dt, J = 16.2, 5.8 Hz, 1H), 5.18 (d, J = 5.57, 2H), 4.66 (s, 3H), 3.20 (s, 3H); HRMS: found (M+) 178.0996; calcd for C₁₁H₁₄O: 178.0994. MS: m/e 178 (73), 176 (19), 151 (30), 149 (24), 122 (100).

Tricarbonyl (η⁶ methyl 1-methoxy-5-methylcinnamylacetate) Chromium (2.2.34)

To a 10 mL two-neck flask equipped with air condenser was added chromium hexacarbonyl (640 mg, 2.9 mmol, 3.3 eq) followed by freshly distilled 1,4-dioxane (5 mL) in a nitrogen atmosphere. To here was added 2 mL dioxane solution of 2.2.32 (182.4 mg, 0.88 mmol, 1.0 eq) by syringe and the mixture was refluxed for 2 days until the reaction was finished. The cooled reaction mixture was then concentrated in vacuo and column-chromatographed (SiO₂, hexanes:EtOAc =
2:1) to afford the product **2.2.34** as a yellow solid. For **2.2.34**: $R_f$: 0.30 (hexanes:EtOAc = 2:1) IR (CHCl₃): 3025, 3021, 3015, 1961, 1880, 1712, 1628, 1528, 1508, 1463, 1437 cm⁻¹; NMR (200 MHz, D₂O, RT): $\delta$ 7.49 (d, $J = 16.1$ Hz, 1H), 6.45 (d, $J = 16.1$ Hz, 1H), 5.58 (t, $J = 6.3$ Hz, 1H), 4.99 (d, $J = 6.74$, 1H), 4.78 (d, $J = 5.90$, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.37 (s, 3H); HRMS: found (M⁺) 342.0212; calcd for C₁₅H₁₄O₃Cr: 342.0195 MS: m/e 342 (2), 259 (2.0), 258 (7), 207 (1).

**Tricarbonyl (η⁶ 1-Methoxy-5-methylcinnamylalcohol) Chromium (2.2.35)**

To a solution of chromium tricarbonyl complex **2.2.34** (50.2 mg, 0.15 mmol, 1.0 eq) in 3 mL dichloromethane was added 240 μL (0.24 mmol, 1.6 eq) of DIBAL-H at - 30 °C and stirred for 2 h. Additional DIBAL-H (120 μL x 2) was added and the mixture was stirred for 1.5 h. The reaction was then quenched with 6 N methanolic HCl (50 μL) and 3 mL water was added. After separation, the aqueous layer was extracted with ambient amount of dichloromethane and the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The crude product was chromatographed (SiO₂, hexanes:EtOAc = 3:2) to afford 44.8 mg (97%) of the product **2.2.35** as a yellow solid. For **2.2.35**: $R_f$: 0.43 (hexanes:EtOAc = 1:1); $^1$H NMR (200 MHz, CDCl₃, RT): $\delta$ 6.38 (m, 2H), 5.52 (t, $J = 6.7$ Hz, 1H), 4.99 (d, $J = 6.7$ Hz, 1H), 4.80 (d, $J = 6.30$ Hz, 1H), 4.32 (bs, 2H), 3.73 (s, 3H), 2.23 (s, 3H), 1.56 (bs, 1H).

**1-Methylsulfinyl-1-methylthio-2-(2'-methoxy-6'-methylphenyl) ethylene (2.2.42).**

To a solution of **2.2.40** (22.4 g, 0.149 mol) in THF (50 mL) was added methyl methylsulfinyl methyl sulfide (20.6 mL, 0.197 mol) followed by Triton B (15 mL,
40% w/w, 33 mmol). The reaction mixture was refluxed for 24 h until the TLC showed the reaction to be complete. After cooling to room temperature, the reaction mixture was acidified with 1N HCl to pH = 1 and the THF was evaporated in vacuo. The mixture was partitioned between H₂O (50 mL) and CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated to give 52.2 g of crude product. Flash chromatography over silica gel, eluting with (6:1) hexanes-EtOAc, gave **2.2.42** (34.6 g, 91%, E/Z = 5:1) as a yellow liquid. For analytical purposes, pure samples of **E-2.2.42** and **Z-2.2.42** were obtained by PTLC. For **E-2.2.42**: Rf 0.47 in (1:1) EtOAc-hexanes; IR (CHCl₃) 3010, 1600, 1580, 1470, 1440, 1265, 1085, 1055 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.59 (s, 1H, C=CH), 7.21 (t, J = 7.9 Hz, 1H, Ar), 6.83 (d, J = 7.6 Hz, 1H, Ar), 6.74 (d, J = 8.5 Hz, 1H, Ar), 3.76 (s, 3H, OCH₃), 2.80 (s, 3H, SOCH₃), 2.10 (s, 3H, S(CH)₃), 1.53 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 50 MHz) δ 156.7 (Ar), 144.7 (Ar or C(SMe)SOME), 137.4 (Ar or C(SMe)SOME), 133.3 (Ar or CHAr), 129.0 (Ar or CHAr), 122.9 (Ar), 122.3 (Ar), 107.9 (Ar), 55.4 (O Me), 40.8 (SOME), 19.9 (ArCH₃ or SMe), 17.4 (ArCH₃ or SMe); HRMS calcd for C₁₂H₁₆OS₂ (M⁺ - O) 240.0643, found 240.0646. For **Z-2.2.42**: Rf 0.25 in (1:1) EtOAc-hexanes; mp 122-124 °C; IR (CHCl₃) 3010, 1600, 1580, 1470, 1440, 1265, 1085, 1055 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.24 (t, J = 8.0 Hz, H), 6.86 (d, J = 7.6 Hz, 1H), 6.76 (d, J = 7.91 Hz, 1H), 6.75 (s, C=CH), 3.80 (s, 3H, OCH₃), 2.66 (s, 3H), 2.60 (s, 3H), 2.30 (s, 3H, CH₃); ¹³C NMR (CDCl₃, 50 MHz) δ 155.3 (Ar), 146.7 (Ar or C(SMe)SOME), 136.8 (Ar or C(SMe)SOME), 129.7 (Ar or CHAr), 128.6 (Ar or CHAr), 122.1 (Ar), 121.8 (Ar), 107.4 (Ar), 54.6 (O Me), 38.2 (SOME), 19.5 (ArCH₃ or SMe), 17.6 (ArCH₃ or SMe); HRMS calcd for C₁₂H₁₆OS₂ (M⁺ - O) 240.0643, found 240.0622.
(2-Methoxy-6-methylphenyl)acetic Acid (2.2.43).

HCl (230 mL) was added dropwise to a solution of 2.2.42 (34.4 g, 0.140 mol) in Et₂O (320 mL). The resulting reddish mixture was refluxed for 72 h until the TLC showed the reaction to be complete. After cooling, the mixture was treated with NaOH 10 N to pH = 11 and washed with CH₂Cl₂ (3 x 200 mL). The aqueous layer was acidified to pH = 1 with 1 N HCl whereupon a pale yellow oil (= 30 g) separated out. This oil was dissolved in EtOAc and a crop of crystalline 2.3.43 (9.7 g) was collected. Incompletely hydrolyzed material (= 11 g) was obtained from the organic wash and this was refluxed in 10 N NaOH (10 mL) overnight. After cooling, the reaction mixture was washed with Et₂O (3 x 50 mL), acidified to pH = 1 and extracted with EtOAc (3 x 50 mL) to afford a yellow solid (2.2 g). This solid was combined with the mother liquor of the first crop and crystallized from EtOAc to give a second crop of 2.2.43 (7.8 g, total = 17.5 g or 72% yield): Rf 0.52 in (1:1) EtOAc-hexanes; mp 154-156 °C; IR (CHCl₃) 3510, 3010, 2950, 1715, 1590, 1480, 1270, 1090 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.15 (t, J = 8.0 Hz, 1H, ArH), 6.80 (d, J = 7.4 Hz, 1H, ArH), 6.74 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H, OCH₃), 3.72 (s, 2H, CH₂CO₂H), 2.28 (s, 3H, PhCH₃); ¹³C NMR (CDCl₃, 50 MHz) δ 177.5 (CO₂H), 156.9, 137.7, 127.7, 122.0, 120.4, 107.5 (Ar), 55.0 (PhOCH₃), 31.1 (CH₂CO₂H), 19.1 (PhCH₃); HRMS calcd for C₁₀H₁₂O₃ (M⁺) 180.0786, found 180.0794.

(4S,SR)-2-(2'-Methoxy-6'methylphenyl)acetyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one (2.2.44).

To a solution of 2.2.43 (30.0 g, 0.167 mol) in THF (1.2 L) was added fresh distilled pivaloyl chloride (21.5 mL, 0.174 mol) at
-78 °C followed by Et$_3$N (24.4 mL, 0.175 mol). The mixture was stirred at -78 °C for 15 min, at 0 °C for 45 min, then re-cooled to -78 °C. In a separate flask, 2.5 M n-BuLi (76.4 mL, 0.191 mol) was added to a solution of (4R, 5S)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (32.5 g, 0.183 mol) in THF (600 mL) at -78 °C and stirred for 15 min, then transferred to the flask containing pivalic anhydride via cannula. The mixture was stirred for 15 min at -78 °C and 9 h at room temperature until TLC analysis showed the reaction to be complete. The reaction was quenched with 2 M KHSO$_4$ (350 mL) and, after evaporation of the THF, was extracted with EtOAc (3 x 500 mL). The combined organic layers were washed with brine (250 mL), dried over MgSO$_4$, filtered and concentrated to give the crude product. Crystallization from (3:1) EtOAc-hexanes afforded the product 2.2.44 (41.6 g, 73% yield) as a white solid. R$_f$ 0.43 in (4:1) hexanes-EtOAc; mp 149-151 °C; [α]$_D$ -14.1° (c 1.95, CHCl$_3$); IR (CHCl$_3$) 3010, 1785, 1715, 1590, 1480, 1360, 1270, 1245, 1200 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) δ 7.49-7.26 (m, 5H), 7.17 (t, $J = 7.9$ Hz, 1 H, ArH), 6.83 (d, $J = 7.3$ Hz, 1H,ArH), 6.76 (d, $J = 8.1$ Hz, 1H, ArH), 5.73 (d, $J = 7.6$ Hz, 1H, PhCH), 4.80 (dq, $J = 7.6$, 6.6 Hz, 1H, MeCH), 4.39 (d, $J = 18.2$ Hz, 1 H, 1/2 PhCH$_2$N), 4.27 (d, $J = 18.2$ Hz, 1H, 1/2 PhCH$_2$N), 3.79 (s, 3H, PhOCH$_3$), 2.26 (s, 3H, PhCH$_3$), 0.92 (d, $J = 6.6$ Hz, 3H, CH$_3$CHN); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 170.8 (CH$_2$CON), 157.6 (Ph), 153.6 (NCO), 138.2, 133.4, 128.7 127.8, 125.6, 122.6, 121.5, 108.07 (Ar/Ph), 79.0 (PhCHN), 55.6, 54.9 (NCH$_2$CH$_3$), 33.5 (PhCH$_2$CON), 19.8 (CH$_3$Ph), 14.5 (CH$_3$CHN); HRMS calcd for C$_{20}$H$_{21}$NO$_4$ (M$^+$) 339.1471, found 339.1485.

(4S,5R,2'R')-2-Azido-2-(2'-methoxy-6'methylphenyl)acetyl-4-methyl-5-phenyl-1,3-oxazolidin-2-one (2.2.45). A solution of KN(SiMe$_3$)$_2$ (117 mL, a 0.5 M in toluene, 0.0587 mol) was added to a solution of 2.2.44 (20.0 g, 0.059 mol) in dry THF (800 mL) at -78 °C via cannula over 5 min, and the stirring continued for 15 min. To
this cold enolate solution was added a solution of trisylazide at -78 °C (22.7 g, 0.073 mol) in THF (200 mL) over 3 min via cannula. After 2 min at -78 °C, glacial acetic acid (10.1 mL, 0.177 mol) was injected in one portion, followed by immediate heating to room temperature. After 18 h of stirring, the bulk of the THF was removed and the residue dissolved in EtOAc (750 mL), washed with saturated NaHCO₃ (250 mL) followed by brine (250 mL) and dried over MgSO₄. After filtration and concentration, the resulting yellow gum (= 25 g) was purified by flash chromatography over SiO₂, eluting with (20:3) hexanes-EtOAc to afford the desired product 2.2.45 (19.7 g, 88% yield) as a white solid: Rf ≈ 0.43 in (4:1) hexanes-EtOAc; mp 104 - 106 °C; [α]D - 280.7° (c 0.71, CHCl₃); IR (CHCl₃) 3020, 2405, 2120, 1790, 1730, 1540, 1470, 1360, 1200 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.44-7.19 (m, 6H), 6.91 (d, J = 7.6 Hz, 1H, ArH), 6.80 (d, J = 8.2 Hz, 1H, ArH), 5.71 (s, 1H, CHN₃), 5.49 (d, J = 7.6 Hz, 1H, PhCHO) 4.66 (dq, J = 7.6, 6.6 Hz, 1H, MeCHN), 3.81 (s, 3H, PhOCH₃), 2.49 (s, 3H, PhCH₃) 1.02 (d, J = 6.6 Hz, 3H, CH₃CHN); ¹³C NMR (CDCl₃, 50 MHz) δ 169.6 N₃CHCO), 156.6 (Ph), 152.2 (NCO₂), 140 6, 132.7, 129.9, 128.7, 128.6, 125.5, 124.1, 121.8, 109.7 (Ar/Ph), 79.7 (PhCHO), 61.0 (CHN₃), 56.5 (PhOCH₃), 56.1 (NCHMe) 19.6 (PhCH₃), 14.3 (NCHCH₃); HRMS calcd for C₂₀H₂₀N₂O₄ (M⁺ - N₂) 352.1423, found 352.1427.

2(R)-Azido-2-(2-methoxy-6-methylphenyl)acetic Acid (2.2.47)

To a solution containing azido imidate 2.2.45 (502.9 mg, 1.3 mmol, 1.0 eq) dissolved in (3 : 1) THF:H₂O mixture (23 mL) was added LiOH·H₂O (113.5 mg, 2.7 mmol, 2.1 eq) at 0 °C followed by H₂O₂ (30 % in H₂O, 588 mL) and the reaction mixture was stirred for 1 h
0 °C. After quenching of the reaction with NaHSO₃ (11.4 mL) and evaporation of THF in vacuo, reaction mixture was washed with Et₂O (3 x 30 mL) and aqueous layer was acidified to pH = 1 with 0.2 N HCl, extracted with EtOAc (4 x 30 mL) and dried over Na₂SO₄. After filtration and evaporation of the solvent, product was obtained as a yellow gum (263 mg) and 165 mg of this gum was column chromatographed over SiO₂ with (5:1) hexanes-EtOAc mixture to give the purified product (124.1 mg, 68.4 %) as a yellow solid. For 2.2.47: Rf: 0.23 (hexanes:EtOAc = 1:1); mp: 117.5-119 °C; [α]D²⁴: -173.0° (c, 1.37, CHCl₃); IR (CHCl₃): 3520 (br), 3000 (m), 2950 (br), 2120 (s, -N₃), 1770 (s), 1730 (s), 1590 (s), 1480 (s), 1280 (s), 1085 (s) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz): δ 9.72-9.30 (bs, 1 H, -OH), 7.27 (t, J = 7.94, 1 H), 6.87 (d, J = 7.68, 1 H), 6.82 (d, J = 8.21, 1 H), 5.34 (s, 1 H) 3.81 (s, 3 H, -OMe), 2.39 (s, 3 H, -Me); ¹³C NMR (CDCl₃, 50 MHz): δ 175.50 (s, +), 157.29 (s, +), 138.70 (s, +), 130.23 (d, -), 123.56 (d, -), 121.47 (s, +), 109.14 (d, -), 58.37 (d, -), 55.59 (q, -), 19.50 (q, -); HRMS calcd for C₁₀H₁₃N₃O₂ (M⁺) 221.0800, found 221.0796.

(2R)-2-Azido-2-(2'-methoxy-6'-methylphenyl)ethanol (2.2.46).

To a solution of 2.2.45 (17.3 g, 0.0455 mol) (2:1) dissolved in THF-H₂O (800 mL) was added NaBH₄ (7.0 g, 0.185 mol) at 0 °C. After stirring at 5 °C for 42 h TLC analysis showed the reaction to be complete. The reaction was quenched with 1.6 M NaH₂PO₄ (63 mL) solution and the bulk of the THF was removed. The resulting gum was partitioned between EtOAc (4 x 300 mL) and brine (200 mL). The organic layer was dried over MgSO₄, filtered and concentrated to give the crude product which was purified by flash chromatography over silica gel, eluting with (4:1) hexanes-EtOAc to afford 2.2.46 as a yellow gum (7.9 g, 83% yield) along with 7.7 g (96 %) of recovered
auxiliary. For 2.2.46: Rf 0.62 in (4:1) hexanes-EtOAc; [α]D -154.5° (c 1.75, CHCl3); IR (CHCl3) 3600, 3010, 2850, 2020, 1590, 1475, 1260, 1190, 1135 cm⁻¹; ¹H NMR (CDCl3 + 1 drop D₂O, 200 MHz) δ 7.19 (t, J = 8.0 Hz, 1 H), 6.82 (d, J = 7.4 Hz, 1 H), 6.79 (d, J = 8.2 Hz, 1 H), 5.22 (dd, J = 9.2, 4.6 Hz, 1 H, CHN₃), 4.13 (dd, J = 11.5, 9.1 Hz, 1 H, 1/2 CH₂OH), 3.83 (s, 3 H, PhOCH₃), 3.75 (dd, J = 11.5, 4.6 Hz, 1 H, 1/2 CH₂OH), 2.42 (s, 3 H, PhCH₃); ¹³C NMR (CDCl₃, 50 MHz) δ 158.7, 139.3, 130.0, 124.5, 122.5, 109.7 (Ar), 64.3 (CH₂OH), 62.8 (CHN₃), 56.3 (PhOCH₃), 21.1 (PhCH₃); HRMS caled for C₁₀H₁₃N₃O₂ (M⁺) 207.1008, found 207.1005.

(2R)-2-Amino-2-(2'-methoxy-6'-methy1phenyl)ethyl Alcohol (2.1.5).

To a solution of azido alcohol 2.2.46 (164 mg, 0.790 mmol) in absolute EtOH (4 mL) was added 10% Pd/C (13 mg). The mixture was stirred under H₂ at room temperature for 24 h when TLC analysis showed the reaction to be complete. The catalyst was filtered off through a Celite pad and the solvent removed to give the crude product which was purified by flash chromatography over silica gel, eluting with 100:20:1 CHCl₃-MeOH-NH₄OH, to afford the amino alcohol 2.1.5 (113 mg, 78% yield) as a white solid: Rf 0.08-0.28 in 100:20:1 CHCl₃-MeOH-NH₄OH; mp 132-134 °C; [α]D -40.5° (c 0.95, CHCl₃); IR (CHCl₃) 3620, 3420, 3010, 2980, 1600, 1585, 1475, 1280, 1265, 1250, 1080, 1035 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 7.12 (t, J = 7.9, 1 H, ArH), 6.80-6.75 (m, 2 H, ArH), 4.15 (dd, J = 9.9, 5.3 Hz, 1 H), 3.83 (s, 3 H, PhOCH₃), 3.78 (t, J = 9.9, 1 H), 3.55 (dd, J = 10.0, 5.3 Hz, 1 H), 2.35 (s, 3 H, PhCH₃), 2.41-2.18 (bs, 2 H, NH₂); ¹³C NMR (CDCl₃, 50 MHz) δ 158.4, 137.0,
128.5, 127.7, 123.3, 109.2 (Ar), 64.1 (CH$_2$OH), 55.1 (PhOCH$_3$), 53.5 (PhCHNH$_2$), 20.3 (PhCH$_3$); HRMS calcd for C$_9$H$_{12}$NO (M$^+$ - CH$_2$OH) 150.0919, found 150.0919.

(2R)-2-((+)-α-Methoxy-α-trifluoromethylphenylacetyl)amino-2-(2′-methoxy-6′-methylphenyl)ethyl ́Buylidimethylsilyl Ether (2.2.49)

To a solution of 2.1.5 (99 mg, 0.54 mmol) in CH$_2$Cl$_2$ (10 mL) was added ́BuMe$_2$SiCl (116 mg, 10.8 mmol) followed by Et$_3$N (220 mL, 2.92 mmol). This mixture was stirred at room temperature for 23 h when TLC analysis showed the reaction to be complete. The solvent was removed and the residue purified by flash chromatography over silica gel, eluting with (10:1) CHCl$_3$-MeOH, to afford (2R)-2-amino-2-(2′-methoxy-6′-methylphenyl)ethyl ́butyldimethylsilyl ether (159 mg, 100% yield) as a pale yellow oil: R$_f$ 0.55 in (100:20:1) CHCl$_3$:MeOH:NH$_4$OH; [α]$_D$ -8.26° (c 0.71, CHCl$_3$); IR (CHCl$_3$) 3690, 3015, 2400, 1740, 1525, 1480, 1425, 1220 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) δ 7.09 (t, $J$ = 7.9 Hz, 1 H, ArH), 6.75 (d, $J$ = 7.8 Hz, 1 H, ArH), 6.71 (d, $J$ = 7.46 Hz, 1 H, ArH), 4.26 (dd, $J$ = 8.2, 6.3 Hz, 1 H, CHNH$_2$), 3.94-3.69 (m, 2 H, CH$_2$OSi), 3.79 (s, 3 H, PhOCH$_3$), 3.46 (bs, 2 H, NH$_2$), 2.34 (s, 3 H, PhCH$_3$), 0.82 (s, 9 H, (CH$_3$)$_3$CSi), -0.02 (s, 3 H, CH$_3$Si), -0.07 (s, 3 H, CH$_3$Si); $^{13}$C NMR (CDCl$_3$) δ 159, 138.8, 128.6, 126.7, 124.1, 109.7 (Ar), 66.2 (CH$_2$OSi), 55.8 (PhOCH$_3$), 54.2 (CHNH$_2$), 26.5 ((CH$_3$)$_3$CSi), 21.2 (CH$_3$Ar), 18.9 (Me$_3$CSi), -4.8 (CH$_3$Si); HRMS calcd for C$_{16}$H$_{26}$O$_2$Si (M$^+$ - NH$_3$) 278.1702, found 278.1822. To a vial containing HOBT (16 mg, 0.11 mmol) and EDC (18 mg, 0.093 mmol) in CH$_2$Cl$_2$ (1 mL) was added (+)-α-methoxy-α-trifluoromethylphenylacetic acid (14.3 mg, 0.061 mmol) and (2R)-2-amino-2-(2′-methoxy-6′-methylphenyl)ethyl ́butyldimethylsilyl ether (15 mg, 0.051 mmol) in CH$_2$Cl$_2$ (180 mL). The reaction
mixture was stirred at room temperature for 13 h when TLC analysis showed the reaction to be complete. After concentration, the crude product was purified by PTLC on silica gel to give 2.2.49 (18 mg, 68 % yield) as a colorless oil. A wide band was cut to prevent accidental separation of the diastereomeric Mosher amide ($R_f$ 0.69). For compound 2.2.49: $R_f$ 0.73 in (5:1) hexanes-EtOAc; [α]$^D_{D}$ -29.9° (c, 1.20, CHCl$_3$); IR (CHCl$_3$) 2940, 3010, 2970, 2940, 1700, 1520, 1475, 1275, 1260 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) δ 7.66 (bd, $J = 9.3$ Hz, 1 H), 7.41-7.24 (m, 5 H, ArH), 7.11 (t, $J = 8.0$ Hz, 1 H, ArH), 6.79 (d, $J = 7.6$ Hz, 1 H, ArH), 6.63 (d, $J = 8.2$ Hz, 1 H, ArH), 5.54 (dt, $J = 9.3$, 7.5 Hz, 1 H, PhCH$_2$NH), 3.94 (dd, $J = 10.0$, 7.9 Hz, 1 H, 1/2 CH$_2$OSi), 3.79 (dd, $J = 10.0$, 7.0 Hz, 1 H, 1/2 CH$_2$OSi), 3.53 (s, 6 H, PhOCH$_3$ and CH$_3$OCCF$_3$), 2.47 (s, 3 H, PhCH$_3$), 0.81 (s, 9 H, (CH$_3$)$_3$Si), -0.03 (s, 3 H, CH$_3$Si), -0.09 (s, 3 H, CH$_3$Si); HRMS calcd for C$_{26}$H$_{37}$NO$_4$SiF$_3$ (MH$^+$) 512.2443, found 512.2511.
2.5. References and Notes


5  Similar to this method, alkyl group was introduced to chiral imino ester. Yamamoto, Y.; Ito, W. "Studies on the Reaction of \( \alpha \)-Iminoesters with Organometallic Compounds." *Tetrahedron*, 1988, 44, 5415-5423.


7  0.05 eq. of DMAP was used to accelerate the reaction.


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22 Reaction was done at rt; product is tentatively assigned as C (2) adduct.


30 2.2.36, 2.2.37 can be purchased from Aldrich Chemical Co. or can be prepared according to the procedure by: Evans, D. A.; Bartroli, J.; Shih, T. L. "Enantioselective


Chapter 3

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Part I

Chapter 1


Chapter 2


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Chapter 2


5 Similar to this method, alkyl group was introduced to chiral imino ester. Yamamoto, Y.; Ito, W. "Studies on the Reaction of α-Iminoesters with Organometallic Compounds." *Tetrahedron*, 1988, 44, 5415-5423.


7 0.05 eq. of DMAP was used to accelerate the reaction.


16 Onaka, M.; Sugita, K.; Izumi, Y. "Regioselective Ring-Opening Reactions of 2,3-Epoxyp Alcohol with Sodium Azide Supported on Zeolite CaY." *Chem. Lett.* 1986, 1327-1328.

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22. Reaction was done at rt; product is tentatively assigned as C (2) adduct.


30 2.2.36, 2.2.37 can be purchased form Aldrich Chemical Co. or can be prepared according to the procedure by: Evans, D. A.; Bartroli, J.; Shih, T. L. "Enantioselective Aldol Condensations. 2. Erythro-Selective Chiral Aldol Condensations via Boron Enolates." J. Am. Chem. Soc. 1981, 103, 2127-2129


