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THE SYNTHESIS OF NOVEL, VICINAL DIAMINES FOR THE INVESTIGATION OF ORGANOLITHIUM COMPOUNDS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

By

Jeffrey Duane Akester, B.A.

The Ohio State University

1997

Dissertation Committee:
Dr. Gideon Fraenkel, Adviser
Dr. John Swenton
Dr. David Hart

Approved by
Dr. Gideon Fraenkel
Chemistry Department
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Jeffrey Duane Akester

1997
ABSTRACT

The main objective of this dissertation is the development of new, efficient procedures which can be used to make a variety of previously unknown vicinal diamines. The synthesis of \((2S,2'S)-1,1'-(\text{cis}-1,2\text{-cyclopentylene})\text{bis}[2-methylpyrroloidine}\) \((2-7)\), \(\text{meso-}N,N',N',N'\text{-tetramethyl-2,3-butanediamine}\) \((3-5)\), \(\text{cis-}N,N'\text{-dimethyl-1,2-cyclohexanediame}\) \((4-5)\), and the attempted synthesis of \(N,N',N',N'\text{-tetramethyl-2,3-dimethyl-2,3-butanediamine}\) are described. Such compounds have potential as organolithium ligands. The X-ray crystal structure of the monopicrate salt of \((2-7)\) was thoroughly examined. Variable temperature NMR studies were conducted on the complexes of \(\text{meso-}N,N',N',N'\text{-tetramethyl-2,3-butanediamine}\) with \([1,3\text{-bis}(\text{trimethylsilyl})\text{allyl}]\text{lithium}\) in deuterated diethyl ether \((6-1)\) and with \([\alpha-(\text{trimethylsilyl})\text{benzyl}]\text{lithium}\) in deuterated THF \((6-2)\). For complex \((6-2)\), the phenyl ring rotation was determined to have an entropy of activation \((\Delta S^\ddagger)\) of -25.0 eu and an enthalpy of activation \((\Delta H^\ddagger)\) of 19.7 kcal / mol. Included in this work is a literature search of chiral diamines used as ligands for asymmetric synthesis (as of 1995) and a literature search of compounds with a vicinal diamine functionality investigated for biological activity (as of 1994).
ACKNOWLEDGMENTS

I would first like to thank Professor Gideon Fraenkel for the wisdom and guidance he has provided me. This work would not have been possible without his creativity and experience.

I would like to thank the following members of the Fraenkel group who have encouraged and inspired me during my project: Kevin Martin, Joe Duncan, Fayang Qiu, Albert Chow, Sharon Boyd, Dr. Jose Cabral, Sheela Subramanian, Dr. Wang, and Carolina Iwamoto. Also, I would like to express my gratitude to the following people who have been good friends to me at Ohio State: Kristy Martin, Tony Skufca, Bobbie Cassity, Dr. Robert Feiertag, Dr. Gordon Renkes, Johnny Royal, Jeannette Painter, Tim Henthorne, Tom Ruff, Kevin Dill, and John & Jerry in the machine shop.

Furthermore, I would like to include a special thanks to my father, Jack and step-mother, Sallie for their love and support throughout my life. This achievement nor any of my accomplishments in the past would have been possible without you. Finally, I would like to acknowledge the financial support for the group donated by the American Cyanamid Company when funding cuts and a recession severely limited our resources and budget.
VITA

November 17, 1969 ............ Born, Wilmington, Delaware
May, 1987 ....................... H.S. Diploma, Pennington Prep.
Pennington, New Jersey
The American Cyanamid Company
Pearl River, New York.
May, 1991 ....................... B.A., Chemistry
Drew University
Madison, New Jersey
September, 1991 - June, 1996
Graduate Teaching Associate
Department of Chemistry
The Ohio State University
Columbus, Ohio
March 4, 1993 ................. Nominated and Finalist for the
1993 Graduate Associate Teaching
Award
June 16, 1994 ................. Recipient of the 1994 DuPont
Fluoroproducts Award Scholarship
December 7, 1994 ............. Recipient of the 1994 Graduate
Student Alumni Research Award
March 3, 1995 ................. Nominated and Finalist for the
1995 Graduate Associate Teaching
Award
June 6, 1996 ................. Graduate Research Ethics
Workshop Bloomington, Indiana
PUBLICATIONS

Research Publication


FIELD OF STUDY

Major Field: Chemistry

Synthesis of Vicinal Diamines and the studies of their Organolithium Complexes under Professor Gideon Fraenkel.
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<td>FULL NAME</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Ar</td>
<td>argon gas</td>
</tr>
<tr>
<td>ATM</td>
<td>atmospheric pressure</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>n-BuLi</td>
<td>normal butyllithium</td>
</tr>
<tr>
<td>s-BuLi</td>
<td>secondary butyllithium</td>
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<tr>
<td>t-BuLi</td>
<td>tertiary butyllithium</td>
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<tr>
<td>CAL.</td>
<td>calculated</td>
</tr>
<tr>
<td>CAT</td>
<td>catalyst</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td>GC/MS/IR</td>
<td>gas chromatography / mass spectrum / infrared</td>
</tr>
<tr>
<td>HMPT</td>
<td>hexamethyl phosphoric triamide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PSI</td>
<td>pounds of pressure per square inch</td>
</tr>
<tr>
<td>RBF</td>
<td>round bottom flask</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
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(5-2)  

(5-3)  

(5-4)  

(5-5)
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(6-2)
PART I. ORGANOLITHIUM COMPOUNDS

Organolithium compounds form the largest single group of synthetically useful organometallic compounds, and daily there are announcements of "novel, versatile" R-Li species. Almost any page of the organic section of JACS or any organic journal is likely to mention organolithium compounds at least once. New developments were reviewed annually in the Annual Surveys of the Journal of Organometallic Chemistry, in Specialist Periodical Reports, and in Annual Reports of the Chemical Society.

Some comments on experimental matters are now in order. The alkyllithiums are soluble and stable in alkane solvents, though less reactive than in ethers. Benzene and toluene are good solvents for RLi species; they tend to become metalated in the presence of vicinal diamines.\textsuperscript{1} Ethers are commonly used, especially diethyl ether and THF. Further they have low melting points, thus useful, when perdeuterated as solvents for NMR studies. While diethyl ether is more stable to RLi compounds, THF provides a more reactive medium both for formation of the lithium compounds as well
as their reactions. Tertiary amines, especially vicinal tertiary diamines, catalyze the reactions of RLi compounds and are employed as additives in these reaction mixtures. HMPT is known to promote formation of solvent separated ion pairs of Li carbanide salts, often highly and selectively reactive.

Organolithium compounds must be handled under conditions strictly anhydrous and oxygen free,

\[
RLi + H_2O \rightleftharpoons RH + LiOH \quad (A)
\]

\[
RLi + O_2 \rightarrow ROO^+Li \stackrel{RLi}{\rightarrow} RO^+Li^+ \quad (B)
\]

Scheme 1. Hydrolysis and oxygenation of organolithium compounds

since hydrolysis (A) and oxygenation to alkoxides (B) are extremely fast reactions. (see scheme 1) It is also advisable, when ethers are used, that reactions be run at low temperature to slow down RLi promoted 1,1 and 1,2 elimination reactions. (see scheme 2)

Scheme 2. RLi promoted 1,1 and 1,2 elimination reactions.

Reactions in which RLi species are used should be carried out under N\textsubscript{2} or Ar atmosphere. In case of using Li metal, only Ar is suitable since Li reacts with N\textsubscript{2}.
Given the fundamental requirements of organolithium experimental procedures, let us consider the real identity of an organolithium compound. Although the simple formula “R-Li” is usually adequate for representing organolithium compounds in equations, such species do not normally exist in the free state. In solution, most organolithiums are associated aggregates, and in the presence of electron donors from coordination complexes. There has been much speculation about the exact nature of the carbon-lithium bond. A high degree of ionic character is predicted by an unsophisticated comparison of electronegativities\(^2\), by extended Huckel molecular orbital calculations, and ab initio calculations.\(^3\) However, many of the physical properties of simple organolithium compounds, such as low melting points and solubility in hydrocarbon solvents, are clearly incompatible with highly ionic structures, and thus more complex types of bonding must be involved within their structures.\(^4\)

Considering the enormous popularity of organolithium compounds with both synthetic chemists and theoreticians, it is surprising that so little is known about their true nature. Questions regarding organolithium compounds include: How are \((\text{RLi})_n\) species aggregated, and what holds them together?, How long do the aggregates stay together, and how do the carbon-lithium bonds scramble?, Are some \(\text{RLi}\) species ion paired, and what structures do they assume?, Why is the reactivity of organolithium compounds often increased by the presence of tertiary ligands such as \(\text{N,N,N',N'-tetramethylethylenediamine (TMEDA)}\)? (see scheme 3)
Organolithium compounds exhibit an astonishing array of structures including unsolvated monomers, octahedral hexamers, tetramers, and when coordinated to electron donors, cubic tetramers, bridged dimers, and monomers. The bonding in the associated species is electron deficient, and organolithium aggregates can behave, paradoxically, both as electron poor reagents (Lewis acids) and as electron rich reagents (Bronsted bases or nucleophiles) in organic reactions.

Scheme 4. Proposed aggregate structures of bridged dimer, 1, cubic tetramer, 2, octahedral hexamer, 3, and tridentately complexed monomer, 4.
A Lewis base interacts with a RLi compound by coordinating to Li. This coordination tends to reduce the degree of association. In general, the stronger the electron donor, the lower the resulting degree of association. The progression, solvated tetramer \( \rightarrow \) dimer \( \rightarrow \) monomer, is exothermic in the disassociating direction due to the increase in coordination of Li. With very strong electron donors, particularly triamines, even monomeric complexes have been reported. The overall effect of electron donor solvents is to reduce the electron deficiency of organolithium reagents, while at the same time increasing their carbanionic character, and thus increase both their nucleophilicity and basicity.

NMR (\(^1\)H, \(^{13}\)C, \(^7\)Li, \(^6\)Li) of organolithium compounds provides insight into structure, relaxation, and exchange dynamics.\(^{5a,b,c}\) There is spin coupling between \(^{13}\)C and directly bonded lithium. In the case of \(^7\)Li, nuclear electric quadrupole induced relaxation is often fast enough to average the \(^{13}\)C, \(^7\)Li spin coupling, an effect that has been named “scalar relaxation of the second kind”. However, the quadrupole moment of \(^6\)Li, being only 1/90 of that of \(^7\)Li, allows observation of one bond \(^{13}\)C, \(^6\)Li spin coupling at low temperature.
Thus, organolithium compounds have been prepared enriched in $^6$Li. From the multiplicity of $^{13}$C NMR for lithium-6 bound carbon one can determine how many $^6$Li's are coupled, therefore bonded to each carbon. The different multiplicates are listed in Table 1. Values are also included for the case of $^{7}$Li at slow $^7$Li relaxation.

With increasing temperature the $^{13}$C, $^6$Li coupling becomes progressively averages due to intermolecular C, Li bond exchange.

In addition to $^{13}$C, $^6$Li spin coupling $^{13}$C NMR of organolithium compounds exhibit shifts characteristic of the state of aggregation. As a result these studies provide access to the thermodynamics of interconversion of aggregates, the dynamics
of $^{13}$C, $^6$Li bond exchange$^{6a,b}$ as well as different fast equilibrium ligand lithium exchanges and coordinated lithium-carbanion reorientation processes.$^{7a,b}$

NMR lineshape analysis$^{5a-s}$ is one of the few techniques which allows determination of the dynamics and study of the mechanisms of fast reactions at equilibrium.$^{9a-c}$

PART II VICINAL, TERTIARY DIAMINES

We now examine the ligands which are often used to enhance the reactivity of organolithium compounds. Though several types of organolithium ligands have been used, this discussion will focus exclusively on vicinal, tertiary diamines. To date, vicinal tertiary diamines are best known for their remarkable ability to catalyze the reactions of organolithium compounds, though more recent work has been focused on the possible pharmacological activity of these compounds. We will first discuss the synthesis of cis-vicinal diamines and their potential as organolithium catalysts, then explore their recently discovered ability to act as pharmaceutical agents.

It was long known that TMEDA promotes the lithiation of organic compounds and that this ligand forms di bidentately complexed Li bridged dimers with organolithium compounds. Cis-vicinal, tertiary diamines should promote the formation of such complexes and possibly also enhance reactivity of RLi species even more than TMEDA. Thus, the Fraenkel group was interested in trying out such cis diamines. Unfortunately, at the time the published methods to prepare such cis diamines were
inefficient and expensive. That such compounds were not readily available explains the paucity of information on them and why they were not tried out.

Here are summarized some earlier attempts to prepare cis-diamines. For example, Toftlund and Pederson\textsuperscript{10} prepared cis-1,2-diaminocyclopentane by reducing the nickel complex of amphi-1,2-cyclopentanedioneoxime as shown in scheme 5.

![Scheme 5. Toftlund and Pederson Cis-vicinal Diamine Synthesis, 1972.]

This procedure yields only a 4\% conversion of starting material to the desired cis-vicinal diamine.

Another synthesis of cis-1,2-diaminocyclopentane was carried out by Potter, Coleman, and Monro\textsuperscript{11} in 1975. Their synthesis involved the catalytic hydrogenation of cis-1,2-diazidocyclopentane as shown in scheme 6. The cis-diazide was obtained in 27\% yield and no yield or experimental data were reported for the final product.
Scheme 6. Potter, Coleman, and Monro Synthesis of Cis-vicinal Diamines, 1975

The Sharpless method, published in 1977, employed a very expensive and toxic alkylimido-osmium reagent. (see scheme 7)


Backvall reported a PdCl₂ promoted diamination of olefins in 1978, however this procedure appears to be limited to open chain olefins. (see scheme 8)
Both of the previous two procedures have the disadvantages of requiring an alkene functionality to activate diamination. It would be much more synthetically useful to develop procedures that employed a variety of functional groups as cis diamine precursors. Realizing the potential utility of synthetic procedures for cis vicinal diamines which could act as organolithium ligands, Fraenkel initiated research projects to develop the most efficient methodology for diamine synthesis. We will now examine some of the synthetic strategies for vicinal diamine synthesis developed by the Fraenkel group over the past 10 years.

The first route attempted by the Fraenkel group involved a synthesis of \( \beta \)-lactam via dipolar addition of N-chlorosulfonyl isocyanate to cyclopentene following the 1971 procedure of Bestian and co-workers. The \( \beta \)-lactam intermediate was isolated, converted to an azide and allowed to undergo a Curtius rearrangement. The bicyclic urea produced was then hydrolyzed and alkylated to obtain the cis-vicinal diamine. (see scheme 9) Unfortunately, this procedure involves harsh conditions and an 8% overall yield of cis vicinal diamine based on cyclopentene.
The group's second synthetic effort employed a reductive amination of 2-N,N-dimethylaminocyclopentanone in a buffered medium with dimethylamine using sodium borohydride. The imminium intermediate is reduced via borohydride attack from the less hindered side giving the cis product. Unfortunately, when the procedure was run with piperidine, mixtures of cis vicinal diamine and the cis vicinal aminoalcohol were obtained. (see scheme 10) A search for conditions which would favor formation of cis diamine was unsuccessful.

Fraenkel and Rosenzweig later developed an alternative cis-vicinal diamine synthesis that represented a significant improvement on all previous methods. The key to their synthesis was to generate and isolate the more stable amino-enamine which, when subject to catalytic hydrogenation, reduced exclusively from the less hindered side to yield the desired diastereomerically pure, cis vicinal diamine (see scheme 11)

In the illustration, a diester is converted to 1,2-bis(trimethylsiloxy)cyclopentene (B). The latter is reacted with 1 equivalent of piperidine to yield the aminoketone (C), which is condensed with a second equivalent of piperidine under Dean Stark conditions to produce the synthetically useful amino-enamine (D). This compound undergoes catalytic hydrogenation (5% Pd on C) on the unhindered side to give, exclusively cis vicinal diamine (E).

Advances have been made in the area of asymmetric synthesis over the past ten years, for example in the utilization of external chiral ligands as asymmetric controls. The Fraenkel and Rosenzweig synthesis was used as a starting point for the development of chiral, cis-vicinal, tertiary diamines which have potential as chiral ligands for the asymmetric control of organolithium compounds. Scheme 12 on the
next page lists of most of the chiral diamines which have been synthesized and employed as ligands for asymmetric synthesis as of a 1995 literature search. As shown, there are currently about two dozen chiral diamine ligands known. However, the majority of these ligands, with the exception of (-)sparteine, are not commonly employed as ligands for organolithium compounds. Since (-)sparteine can be isolated from the Lupin flower and is commercially available from several sources, it has been the only chiral diamine to undergo a thorough investigation. Research investigations which employ (-)sparteine as a chiral organolithium ligand demonstrate that it influences the stereochemical reactivity of organolithium compounds in most cases. Since organolithium compounds are used in the synthesis of chiral drugs and in polymerization reactions that are a source of commercial rubber, the stereochemical manipulation of organolithium reagents is important.

It is now appropriate to discuss the pharmacological role of chiral vicinal diamines. Several types of amines have long been recognized to be physiologically active. For example, polyamines, including vicinal diamines, are known to play a role in metabolism, controlling cell growth and cell division. Spermine and spermidine are straight chain polyamines which complex with DNA, RNA, and t-RNA to change the conformations of these host molecules. Among diamines which are not found in living organisms, some are antineoplastic (inhibit tumor formation), whereas others are metastatic, bacteriacidyl, or act as neurotoxins.
Scheme 12. Chiral Diamines used as Ligands for Asymmetric Synthesis as of 1995. 
*The corresponding references are given beside each structure.
It is believed that the pharmacological potential of these substances is enhanced when the diamine's amino groups are oriented cis to one another. Scheme 13 on the next page contains a list of most compounds with a vicinal diamine functionality that have been investigated for biological activity as of a 1994 literature search. Currently, the most potent agent against testicular cancer is a platinum complex of cis-1,2-diaminocyclohexane. The effectiveness of this drug is believed to directly result from the cis arrangement of its amino groups.

Quite recently a family of cis vicinal diamines was used for a specific pharmacological study. It was determined that the cis vicinal diamine functionality in (+/-)-3,4-dichloro-N-methyl-N-[2-(1-pyrrolidinylcyclohexanyl)]benzamide binds selectively and strongly to guinea pig brain sigma receptors. Sigma receptors, which are located throughout the brain and nervous system, have received attention recently because of their involvement with psychotomimetic effects that occur after ingestion of opioid and dopamine drugs such as benzomorphans and phencyclidine (PCP). Tardive diskinesia, a violent movement disorder which occurs after the administration of antipsychotic drugs, has been correlated with activation of sigma receptors. The physiological functions of these receptors are not well understood, thus their binding properties need to be investigated using selectively designed probes. Some compounds that have a vicinal diamine functionality have been found to complex with sigma receptors. (see scheme 14)
Scheme 13. Compounds with a vicinal diamine functionality that have been investigated for biological activity as of 1994.

*The corresponding references are given beside each structure.
Structure activity relationships have demonstrated that the cis isomer of (+/-)-1 is a more selective probe for sigma receptors than the trans isomer (+/-)-2. This compound was previously investigated by Searle & Company as a non-dopamine, non-opoid, non-PCP anticonvulsant with a high therapeutic index.

Scheme 14. Compounds with a vicinal diamine functionality that have been used in sigma brain receptor research, 1990.

Recent studies show that cis vicinal diamines have potential as pharmaceutical agents. The main objective of this dissertation is the development of new, efficient procedures which can be used to make a variety of unknown vicinal diamines. These compounds can then be investigated for their use as ligands for organolithium chemistry and investigated for biological activity as new pharmaceutical compounds.
CHAPTER 2

SYNTHESIS OF (2S,2'S)-1,1'-
(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine]

This work represents a combination of synthetic methodologies developed by Professor Peter Beak\textsuperscript{38a,b} at the University of Illinois and Professor Gideon Fraenkel\textsuperscript{39a,b} at the Ohio State University. Professor Beak was responsible for an efficient procedure by which enantiomerically pure, $\alpha$-alkyl pyrrolidines have been produced. (see scheme 15)

\begin{center}
\begin{tikzpicture}
\node[below] at (0,0) {BOC};
\node[below] at (2,0) {BOC};
\draw[->] (0,0) -- (2,0);
\node[below] at (1,0) {-Sparteine};
\node[below] at (4,0) {Electrophile (E)};
\node[below] at (6,0) {Et$_2$O};
\node[below] at (8,0) {Et$_2$O};
\node[below] at (10,0) {6 hrs};
\node[below] at (10,0) {sec-BuLi / (Spart) / Et$_2$O / -78$^\circ$C / 6 hrs};
\end{tikzpicture}
\end{center}

Scheme 15. Beak's 2-Alkylpyrrolidine Synthesis

However, such compounds had not previously been employed in the synthesis of optically pure, cis vicinal, tertiary diamines. Given the methodology for the synthesis of cis vicinal diamines established by the Fraenkel group, (see scheme 16)
it seemed the next logical step to exploit both the Beak and Fraenkel procedures for the first synthesis of a new class of chiral, cis vicinal, tertiary diamines.

The idea was to prepare (2S)-2-methylpyrrolidine using Beak's procedure; ie metalate tert-butyl 1-pyrrolidinecarboxylate in the presence of (-)-sparteine, then methylate the resulting lithium compound using dimethyl sulfate. The resulting free amine could be used in a Fraenkel-Rosenzweig procedure to prepare a chiral, enantiomerically pure, cis-vicinal diamine. Page 21 (see scheme 17) describes the scheme used to prepare (2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine].

There are two important comments concerning the experimental procedure which should be mentioned. The first pertains to the synthesis of tert-butyl 1-pyrrolidinecarboxylate (2-1). The procedure originally used to protect the amine with t-BOC involved the reaction of pyrrolidine with tert-butoxycarbonyl azide. (see scheme 18)
The BOC azide was easily made from the reaction of tert-butyl carbazate with sodium nitrite in acetic acid.\textsuperscript{9c} However, in one incident, upon distillation of the BOC azide there was a violent explosion as the compound suddenly decomposed into nitrogen and carbon dioxide. The BOC dicarbonate was found to be a much safer and effective BOC protecting reagent compared to the BOC azide.

The second comment concerns the hydrolysis of tert-butyl (2S)-2-methyl-1-pyrrolidinecarboxylate (2-2). The procedure published by Professor Beak\textsuperscript{38a,b} which employed refluxing the carbamate in ethanol for 4 hours with 4 equivalents of sodium hydroxide was found to racemize the stereogenic center $\alpha$ to the nitrogen. (see scheme 19)
Scheme 17. Synthesis of (2S,2'S)-1,1’-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine]
Scheme 19. tert-Butyl (2S)-2-methyl-1-pyrrolidinecarboxylate Racemization

The (2S)-2-methylpyrrolidine prepared by Beak's procedure was found to have only 67% enantiomeric excess and was found to racemize further with longer reflux times.

In contrast, the (2S)-2-methylpyrrolidine (2-4) prepared by stirring the carbamate in 6 M hydrochloric acid at 0 °C, followed by stirring at room temperature was found to be in 99% enantiomeric excess.

It should be noted the above procedure affords an 46.8% overall conversion of pyrrolidine to (2-7). Several analogs of the 1,2-dipyrrolidinyl and 1,2-dipiperidinylcyclopentane had been prepared by the Fraenkel group in the past, however no chiral analogs of these compounds were explored. It is believed that the alkyl groups which create stereogenic centers α to the pyrrolidinyl nitrogen in the chiral diamine will induce a "chiral cleft" as the molecule complexes with organolithium compounds and may influence their stereochemical reactivity.
While (-)-sparteine is used in the above synthesis, it was only chosen as a chiral diamine ligand because it was available in optically pure form and its stereochemical influence was well established. Discovering a chiral diamines which have similar stereochemical properties and could be manufactured at a lower cost would be extremely useful.

The chiral, cis diamine (2-7) was mono protonated with picric acid and the picrate salt was submitted to Dr. Judy Gallucci for X-ray crystal analysis. In addition to the picrate salt, both the hydrobromic salt and the hydrochloric salt were attempted. Unfortunately, these acids did not produce nice crystals but instead yielded oils. The crystal structures are shown in Figures 1 and 2.

The crystal used for data collection was a multi-faceted brown chunk. Examination of the diffraction pattern on a Rigaku AFC5S diffractometer indicated a monoclinic crystal system with systematic absences of 0k0, k = 2n + 1. The crystal should contain one enantiomer of the diamine so that the space group is uniquely determined as P21. Unit cell constants were obtained by a symmetry restricted least-squares fit of the diffractometer setting angles for 25 reflections in the 2θ range 21 to 29° with MoKα radiation (λ(MoKα) = 0.70930 Å).

Six standard reflections were measured after every 150 reflections during data collection and indicated that the crystal was stable. Data reduction was done with the TEXSAN package.40
The structure was solved by the direct methods procedure in SHELXS-86. The correct enantiomer was chosen based on the known chirality at an asymmetric center. Full-matrix least-squares refinements on \( F^2 \) were performed in SHELXL-93; the function minimized was \( \Sigma w (F_o^2 - F_c^2)^2 \). Atom C(13) appears to be disordered over two sites which are labeled as C(13A) and C(13B). It was necessary to introduce a bond length restraint of 1.46 Å for the C(12)-C(13A) and the C(12)-C(13B) bonds.

The occupancy factor for C(13A) was refined and that for C(13B) was restricted accordingly; both atoms were refined only isotopically. A hydrogen atom bonded to N(2) was located in a difference electron density map and refined isotropically. So the picrate molecule is an anion while the diamine is a cation and they exist in the crystal in a 1:1 ratio. The other hydrogen atoms are included in the structure using a riding model, i.e., they ride on the atoms to which they are bonded. The final refinement cycle was based on all 2862 unique intensities and 304 variables and resulted in agreement indices of R(F) = 0.144 and \( R_w(F^2) = 0.186 \). For the subset of intensities with \( F_o^2 > 2\sigma(F_o^2) \) (1490 reflections) the R(F) value is 0.058. The final difference electron density map contains maximum and minimum peak heights of 0.21 and -0.15 e/Å. Scattering factors are from the International tables for X-ray Crystallography and include the terms for anomalous dispersion. Since P2 is a polar space group, SHELXL-93 applied a polar axis restraint according to the method of Flack and Schwarzenbach.
Compound: \((2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine]\)

Formula: \((\text{C}_{13}\text{H}_{29}\text{N}_{2})^+ (\text{C}_6\text{H}_2\text{N}_3\text{O}_7)^-\)

Formula Wt.: 465.51

Space Group: \(P2_1\)

\(a, \text{Å}: 9.015(2)\)

\(b, \text{Å}: 13.526(1)\)

\(c, \text{Å}: 9.743(1)\)

\(\beta, \text{deg}: 92.90(1)\)

Volume, \(\text{Å}^3\): 1186.5

\(Z: 2\)

Density (calc), g/cm\(^3\): 1.30

Crystal size, mm: 0.23 X 0.38 X 0.38

Radiation: \(M\alpha K\alpha\) with graphite monochromator

Linear abs. coeff., cm\(^{-1}\): 0.99

Temperature: ambient

\(2\theta\) limits: \(4^\circ \leq 2\theta \leq 55^\circ\)

Scan speed: \(4^\circ /\text{min in} \ \text{w with maximum 4 scans} / \text{ref.}\)

Table 2: Crystallographic details for X-ray analysis
Table 2. (continued)

**Background time / scan time:** 0.5

**Scan range:** \((1.30 + 0.35 \tan \theta)^\circ\) in \(\omega\)

**Data Collected:** +\(h\), +\(k\), +\(l\)

**Scan type:** \(\omega - 2\theta\)

**Unique data:** 2862

**Unique data, with \(F_o^2 > 2\sigma(F_o^2)\):** 1490

**Final number of variables:** 304

\[ R_w(F^2) : 0.186 \quad \text{based on all the data} \]
\[ R(F) : 0.144 \]

**Error in observation of unit weight:** 1.01

\[ R(\text{on } F \text{ for } F_o^2 > 2\sigma(F_o^2)) : 0.058 \quad \text{(based on 1490 reflections)} \]

\[ R_w(F^2) = \left[ \Sigma w (F_o^2 - F_c^2)^2 / \Sigma w F_o^4 \right]^{1/2} \]

\[ R(F) = \Sigma ||F_o|| - |F_c| / \Sigma |F_o| \]

\[ w = 1 / [\sigma^2(F_o^2) + (0.0831 \ast P)^2 + 0.2089P] \]

and \( P = 1/3 \) (maximum of \((0 \text{ or } F_o^2)\) + 2/3 \((F_c)^2\))

The positional and thermal parameters refined to reasonable values during least-squares refinements. The geometry about the N2 atom is tetrahedral. The N2 atom is involved in a hydrogen bond with the O1 atom of the picrate molecule. The hydrogen bonding parameters for the \(N(2) --- H(N2) --- O1\) diamine-picrate bond are:
N(2)—H(N2) 0.88(5) Å
H(N2)—O1 2.04(5) Å
N(2)—O1 2.809(5) Å
N(2)—H(N2)—O(1) 145(4)°

Additional geometry of interest: N(2)—N(1) 2.894(6) Å

Table 3 contains the torsion angles of various 3 atom planes in the 5-membered all carbon ring. Planes 2 and 3 indicate that the C2 is the flap atom in the 5-membered ring, i.e., C1, C3, C4, and C5 lie essentially in a plane and C2 lies significantly out of this plane (see Figure 3). This is confirmed by the small torsion angle of 1.8° for C3-C4-C5-C1. The angle between the C2-N2 bond and the C3-C4-C5 plane is 7.1(8)°. The angle between the C1-N1 bond and the C3-C4-C5 plane is 63.3(8)°. The H(N2) atom is 0.3 Å out of the plane defined by N1, N2 and O1.

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(continued)

Table 3: Torsion angles for (2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrroloidine] monopicate

27
Table 3: (continued)

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Table 3: (continued)

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<td>113.2(15)</td>
<td>C11-N2-C14-C13B</td>
<td>-11.3(15)</td>
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Figure 1. X-ray crystal structure of (2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine] monopicrate
Figure 2. X-ray crystal structure of (2S,2'S)-1,1'-\(\text{cis}-1,2\)-Cyclopentylene)bis[2-methylpyrrolidine].
Figure 3. Side view of cyclopentane ring in (2S,2'S)-1,1'-(cis-1,2-
Cyclopentylene)bis[2-methylpyrrolidine] monopicrate

Figure 4. The three center hydrogen bond in (2S,2'S)-1,1'-(cis-1,2-
Cyclopentylene)bis[2-methylpyrrolidine] monopicrate
It is now appropriate to comment on the X-ray structure of \((2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine]\) monopicrate. Clearly the acid proton is closer to N2 than N1. The N2 atom is involved in a hydrogen bond with O1 of the picrate (see Figure 4). The N1 atom may also be part of a hydrogen bond with N2. The interaction of H3 with N2 is much stronger than with N1. The configuration about the acid proton (N2, N1, O1) may be described as a three center hydrogen bond.

While the N2-H3-N1 angle of 98° is not unusual for a three center hydrogen bond, the N1-H2 distance of 2.89 Å is close to the sum of the Van der Waals radii, 1 Å for H and 1.55 Å for N. Note that H lies 0.3 Å to one side of the N1-N1-O1 plane.

With regard to the cyclopentane moiety C1 is -0.05 Å and C2 is 0.54 Å from the plane defined by the three CH2 carbons, C3, C4, and C5. As shown in the drawings (Figure 3), C3, C4, C5, and C1 lie essentially in a plane with C2 as the flap atom. This is also seen in the C-C torsional angles. Relative to the cyclopentane framework N2 on the flap atom lies pseudoequatorial, while N1 (neutral) at C1 is pseudoaxial. A cisoid arrangement is supported by the method of synthesis. Similar results developed in the crystallographic study of cis-1,2-bis(N,N-dimethylamino)cyclopentane monopicrate.

The C2-N2 bond length of 1.488 Å is significantly longer than the C1-N1 bond length of 1.457 Å; these results are similar to the bond lengths determined crystallographically for the monopicrate of cis-1,2-bis(N,N-dimethylamino)
cyclopentane, 1.487 Å for C-N⁺ and 1.455 Å for C-N. In fact, a survey of such bond lengths in the Cambridge Structural Database shows average values of 1.499 Å for C(sp³)-N⁺ and 1.469 Å for C(sp³)-N. This bond lengthening would be expected on the basis that positive charge in the nitrogen should reduce electron density associated with the C-N⁺ bond compared to the neutral C-N bond.

In drawing the structure of (2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine] monopicate, we have assumed 2S stereochemistry on the pyrrolidinyl group as obtained from optical rotation data for the (2S)-2-methylpyrrolidine starting material. The general aspects of the cyclopentane structure, the envelope with a flap out of the plane, are well known. What is new in this work is the arrangement of substituents cisoid with maximum separation to insure minimum repulsion.
CHAPTER 3

SYNTHESIS OF meso-$N,N,N',N'$-Tetramethyl-2,3-butanediamine

This work represents the first synthesis of diastereomERICALLY pure meso-$N,N,N',N'$-tetramethyl-2,3-butanediamine. Such diamines have potential as ligands for organolithium compounds. The synthesis developed involves a five step procedure beginning with common and inexpensive starting materials. (see scheme 20) The first step of the procedure is a modification of the Ruhlmann synthesis. The acid catalyzed condensation of $\text{N,N'}$-dimethylurea with 3-hydroxybutanone to form imidazolinone (3-1) is complete within 12 hours in refluxing cumene at 135 °C. When the reaction was run at reflux in lower boiling solvents such as benzene and toluene, only starting material was recovered; using reactant concentrations $> 0.1 \text{ M}$ resulted in reduced yields of desired product. It is believed that a dilute reactant concentration favors the cyclization over the polymerization of the reactants. (see scheme 21)

Catalytic hydrogenation of imidazolinones is slow due to their heteroaromatic stability. In 1945, Duschinsky and Dolan reported the hydrogenation of the
imidazolinone functionality. They reduced 4-methyl-5-benzimidazolin-2-one over platinum oxide in glacial acetic acid at 1,300 PSI of hydrogen. (see scheme 22)

Duschinsky and Dolan$^{54}$ later discovered in 1948 that N,N’-diacylation of the imidazolinone system reduced the aromatic character of the compound to the extent that the N,N’-diacylated molecules underwent hydrogenation over palladium on carbon.

In the second report of a successful reduction of imidazolinones in a 1958 US patent, Simon$^{55}$ employed high pressure (125 atms), high temperature (140 ° C), and a large excess of Raney nickel catalyst (10 parts catalyst to 1 part imidazolinone). Furthermore, no yields or proof of stereochemistry were reported. (see scheme 23)

In 1961, Bauer$^{56}$ reported the room temperature, atmospheric pressure hydrogenation of N,N’-diacylated imidazolinone over platinum oxide.

While the procedures were successful for the reduction of N-protonated and N-acylated imidazolinone systems, much less was known about their ability to hydrogenate N-alkylated imidazolinones. Both 10% palladium on carbon and Raney nickel (W-2) were found to be ineffective as hydrogenation catalysts for the N-alkylated derivative (3-1). Furthermore, an attempt to reduce the N-alkylated imidazolinones using Raney nickel$^{57a,b}$ in refluxing isopropyl alcohol yielded a variety of products. Our results demonstrate that 1,500 PSI of hydrogen in glacial acetic acid at room temperature employing platinum oxide as a catalyst will reduce (3-1) over the course of 5 to 7 days to give (3-2).
1) Dilute reactants

\[ \text{NH}_2\text{NH}_2 + \text{O}_2\text{H} \rightarrow \text{N}_2\text{H}_4 + \text{O}_2\text{H} \]

Cyclization

2) Concentrated reactants (abbreviated, proposed mechanism)

Steps A through D

Free Rotation

Polymerization

Scheme 21 (Proposed urea condensation mechanism)

Scheme 23. Simon's Raney Nickel Imidazolinone Reduction, 1958

When the hydrogenation of the imidazolinone was run at a higher temperature (65 °C), the reaction time was decreased to 3 to 5 days, but the yield was lowered to 35%.

While N-alkylated imidazolinones are difficult to hydrogenate, their reduction products, imidazolidinones (cyclic ureas), are even more resistant to hydrolysis. The hydrolysis of tetra-alkylated ureas was attempted over several years by students in the
Fraenkel group using a variety of conditions. Unfortunately, none of these attempts were successful.

After some investigation, we found that (3-2) was effectively hydrolyzed to the corresponding cis vicinal diamine dihydrochloride salt by refluxing the compounds in 6 M hydrochloric acid for 1 week.\textsuperscript{59a,b} Neutralization of the salt (3-3) with aqueous sodium hydroxide afforded the corresponding diamine (3-4) in 94% yield.

Once (3-4) had been isolated, it was methylated using standard Eschweiler-Clarke\textsuperscript{59a,b} chemistry. The N-methyl diamine was refluxed at 80 °C for 24 hours with 2.1 equivalents of aqueous 37.5% formaldehyde and 2.1 equivalents of aqueous 90.8% formic acid. Work up yielded 81% of diastereomERICally pure meso-\(N,N,N',N'\)-tetramethyl-2,3-butanediamine (3-5). Thus, this procedure yields a 14% overall conversion of 1,3-dimethylurea and 3-hydroxy butanone to the vicinal diamine.

It is believed that the cis methyls on the ethane bridge of the bidentately lithium complexed diamine will create a less symmetric environment for the organolithium when this compound is compared to using TMEDA as a ligand. Chapter 6 describes our NMR studies of (3-5) complexed with [1,3-bis (trimethylsilyl)allyl]lithium in deuterated diethyl ether and of (3-5) complexed with [\(\alpha\)-trimethylsilylbenzyl]lithium in deuterated THF.
CHAPTER 4

SYNTHESIS OF cis-N,N'-Dimethyl-1,2-cyclohexanediamine

This chapter describes the synthesis of diastereomerically pure cis-N,N'-dimethyl-1,2-cyclohexanediamine and is a variation of the chemistry described in chapter 3. The synthesis developed involves a five step procedure beginning with common and inexpensive starting materials. (see scheme 24)

There are two advantages to this route. First, the ring size and substitution on the diamine ring may be varied by use of different known acyloin products. Second, it is simple and inexpensive to obtain N-alkylated ureas. Thus, this procedure could be used to prepare new members of this family of diamines.

In the first step in the synthesis (the acyloin reaction)\textsuperscript{60a,b,c}, diesters are reductively cyclized to 1,2-disiloxycycloalkenes by the action of sodium and TMSCl. It is believed that trimethylsilylchloride acts as an alkoxide scavenger to inhibit any Claisen-Dieckmann condensation products. Dilute reactant concentrations (0.1 M) favor the cyclization of the diradical to produce the disiloxycycloalkenes rather
than polymerization at higher concentrations. The reaction produces yields in the 50% to 80% range and the remainder of the product is most likely a mixture of polymers produced from the intermolecular coupling. All reagents must be freshly
distilled before use since explosions have been reported in cases where the reagents were wet or impure.

In the second step of the synthesis, N,N'-dimethylurea condenses with 1,2-disiloxycyclohexene in the presence of a catalytic amount of para-toluenesulfonic under Dean-Stark conditions in refluxing cumene over 12 hours.\(^{61a,b,c}\)

The reaction did not take place at reflux in lower boiling solvents such as benzene or toluene. The hydrogenation of the imidazolinone (4-2) over a catalytic amount of platinum oxide in glacial acetic acid produced a relatively low yield of \textit{cis}-hexahydro-1,3-dimethyl-2-benzimidazolidinone (4-3).

(4-3) was then refluxed in 6 M hydrochloric acid for 2 weeks to produce the dihydrochloride salt (4-4) of the secondary diamine. The secondary diamine was regenerated using a 40% sodium hydroxide solution. Proton and carbon NMR analysis confirmed that the amine was \textit{cis}-N,N'-dimethyl-1,2-cyclohexanediamine (4-5). Due to insufficient material, it was not possible to reductively alkylate this sample using Eschweiler-Clarke conditions.

Subsequent to this work, this method has been applied to the preparation of several cyclic analogs of these diamines with the ring sizes 7 through 9.\(^{62}\) As mentioned, these compounds could potentially be used as organolithium ligands. In such complexes, it has been suggested that the ring on one side of the ethane bridge may create a less symmetric environment for carbanions.
CHAPTER 5

ATTEMPTED SYNTHESIS OF \( N,N,N',N'\text{-}\text{tetramethyl-2,3-dimethyl-2,3-butanediamine} \)

This work is a continuation of some previous experiments concerning the synthesis of highly substituted vicinal diamines. This particular investigation was initiated when Dr. Robert Crabtree of Yale University presented a seminar at The Ohio State University in the summer of 1994. During Crabtree's studies of amino substituted radicals, the group reported that isopropylamine and 3-aminopentane form radicals under the influence of mercury and ultraviolet irradiation and dimerize to a small extent to form diamines. Such compounds are not readily available via any simple route. It was decided to further explore this chemistry in an attempt to prepare \( N,N,N',N'\)-tetramethyl-2,3-dimethyl-2,3-butanediamine, a permethylated and strained analog of TMEDA. At the time of this investigation, we were not aware of any published synthesis of this compound and were interested in employing this diamine as an organolithium ligand. This compound cannot undergo elimination of Li NMe\(_2\) as does TMEDA since all of the bridge positions are blocked.
by methyls. In addition, the bulk of the ligand may help favor formation of complexed
dimers which are generally more reactive than tetramers and other aggregates.

To begin this investigation, Crabtree’s results were reproduced,
isopropylamine was exposed to ultraviolet light (Hg vapor) in the presence of
mercury in gaseous ammonia over the course of a week to yield the vicinal diamine,
2,3-dimethyl-2,3-butanediamine. (see scheme 25) The diamine was isolated as its
oxalate salt and later regenerated from 20% aqueous sodium hydroxide.

\[
\begin{align*}
\text{NH}_2 + \text{Hg} & \quad 1) \text{hv (Hg vapor)} \quad \text{HO} \\
& \quad \text{anhydrous NH}_3 \\
& \quad 2) \text{Oxalic acid} \\
\end{align*}
\]

Scheme 25. Crabtree’s synthesis of 2,3-Dimethyl-2,3-butanediamine.

The one disadvantage of this method is that it is only possible to synthesize very small
amounts (1 to 2 grams) of the diamine per week.

After accumulating the diamine, several efforts were directed to prepare the
tertiary diamine. The most obvious route was an Eschweiler-Clarke reaction using
formaldehyde and formic acid. Unfortunately, this reaction produced the unwanted
aminal. (see scheme 26) Apparently, cyclization via attack of the second nitrogen on
the intermediate iminium carbon is faster than intermolecular reduction by hydride.
(see scheme 27) The Eschweiler-Clarke reaction was attempted a second time
employing sodium cyanoborohydride as the reducing agent, but this reaction also
yielded the aminal.
Scheme 26. The Eschweiler-Clarke reaction produces an aminal from 2,3-Dimethyl-2,3-butanediamine.

Scheme 27. Cyclization of diamine to yield aminal.

An alternative method for the exhaustive methylation of amines is the reaction with excess iodomethane in the presence of a mild base. (see scheme 28) This reaction produced a white solid with a melting point of 198 °C. When a small amount of the solid was dissolved in an ethanol / silver nitrate solution, a pale white silver iodide precipitate formed confirming the solid as an iodide salt. The salt was completely insoluble in water, dimethyl sulfoxide, hexamethyl phosphoramide, dimethyl formamide, acetonitrile, acetone, and tetrahydrofuran, but was slightly soluble in trifluoroacetic acid.

Scheme 28. The reaction of 2,3-dimethyl-2,3-butanediamine with iodomethane to yield hexamethylaziridinium iodide.
NMR analysis in TFA-d confirmed that the solid was hexamethylaziridinium iodide. (5-3) had previously been prepared by Lillocci via an alternative method. An attempt was made to reduce (5-3) with lithium aluminium hydride in tetrahydrofuran, but no product could be isolated from the reaction mixture. It may be possible to react (5-3) with one equivalent of dimethylamine in a polar solvent such as methanol to produce \( N,N,N',N' \)-tetramethyl-2,3-dimethyl-2,3-butanediamine. This reaction deserves further investigation.

After two unsuccessful attempts at synthesizing the desired ligand, we decided to approach the problem from a simple angle. The easiest way to prepare this ligand would be to directly connect two molecules of \( N,N \)-dimethylisopropylamine via a radical dimerization. This molecule should react in an analogous manner to isopropylamine and produce the desired ligand in one step. Much to our dismay, the \( N,N \)-dimethylisopropylamine coupled via the \( N \)-methyl radical to yield \( N,N' \)-diisopropyl-\( N,N' \)-dimethylethylenediamine (2%), instead of the desired compound via secondary radical coupling. (see scheme 29) An explanation for the \( N \)-methyl radical coupling may be that the two secondary radicals are too sterically hindered by the dimethylamino groups and thus prevented from achieving close proximity.

\[
\begin{align*}
\text{N} + \text{Hg} & \quad \xrightarrow{1) \text{hv (Hg vapor)}} \quad \text{O} \\
& \quad \text{anhydrous NH}_3 (g) \quad \rightarrow \quad \text{N} \quad \xrightarrow{2) \text{Oxalic acid}} \quad \text{N} \\
& \quad \text{20% NaOH} \quad \rightarrow \quad \text{N} \quad \text{Ether}
\end{align*}
\]

Scheme 29. The radical dimerization of N,N-dimethylisopropylamine.
After three unsuccessful attempts, it was decided that the project should be set aside until a method was discovered to synthesize this compound. About one year later, a publication was found that claimed the synthesis of \( N,N,N',N' \)-tetramethyl-2,3-dimethyl-2,3-butanediamine. In 1926, Velghe, while investigating the reactions of nitriles with Grignard reagents, prepared some permethylated diamines. Velghe\(^6\) published the following procedure in the Bulletin of the Academy of Belgium as a method to prepare our desired ligand. (see scheme 30) We were unable to find any other syntheses of this compound. This procedure was attempted using the vague experimental procedure given by Velghe. A reaction occurred immediately and was slightly exothermic. Unfortunately, none of the desired tertiary, vicinal diamine was recovered from the work up of the reaction mixture. GC/MS analysis of the crude organic product indicated that there was a large amount of unreacted starting material and that 8 minor products were produced by the reaction.

\[
\begin{align*}
\text{Scheme 30. Velghe's reported procedure for the synthesis of} \\
N,N,N',N'\text{-tetramethyl-2,3-dimethyl-2,3-butanediamine, 1926.}
\end{align*}
\]

Claude Yoder sent us an experimental procedure (identical to Velghe’s work) which he claimed was used by one of his students to prepare \( N,N,N',N' \)-tetramethyl-
2,3-dimethyl-2,3-butanediamine. Unfortunately, Yoder's procedure did not yield the desired diamine and produced results identical to Velghe's procedure. Further investigation needs to be done to synthesize this compound.
CHAPTER 6

NMR STUDIES OF [1,3-Bis(trimethylsilyl)allyl]lithium
COMPLEXED WITH meso-N,N,N',N'-Tetramethyl-2,3-butanediamine
&
[α-(Trimethylsilyl)benzyl]lithium
COMPLEXED WITH meso-N,N,N',N'-Tetramethyl-2,3-butanediamine

In previous work, NMR studies of the complex of [1,3-bis
(trimethylsilyl)allyl]lithium with TMEDA established that the bidentately
complexed ligand is asymmetrically sited with respect to the allyl loop, thus the
complexed ion-pair has a preferred structure. By 150 K, the two terminal
carbons are magnetically non-equivalent and the N-methyls of complexed TMEDA
give rise to a broadened doublet. The NMR data are consistent with proposed
structure A (scheme 31) except one would expect the N-methyls to give rise to
four $^{13}$C resonances. This observation was rationalized by the proposal that
perhaps there is a fast, momentary, reversible N,Li dissociation, accompanied by
inversion at nitrogen while the bond was dissociated.

With increasing temperature above 150 K, there is progressive averaging in
the NMR of A of the $C_1$, $C_3$, and $N$-$CH_3$ doublets to single lines at their respective
centers. NMR line shape analysis gave the same rates for both line shapes, hence they must be due to the same process. It was proposed that the process involved the reorientation of coordinated lithium with respect to allyl anion within the ion-pair. Several other examples of this effect have been seen, each with $\Delta H^\circ$ of 7 to 8 kcal/mol respectively.\textsuperscript{65b,c} These are the first observed examples of dynamic

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.8\textwidth]{image.png}};
\end{tikzpicture}
\end{center}

Scheme 31. [1,3-bis(trimethylsilyl)allyl]lithium complexed with diamines.

measurements of ion-ion reorientation within ion-pairs. It was felt that the preceding proposal would be strengthened if a vicinal diamine coordinated allyl lithium could be found which exhibited all different $N$-methyls. For example, the complex corresponding to A (scheme 31), with meso-$N,N,N',N'$-tetramethyl-2,3-butanediamine instead of TMEDA, should take the form B and due to its less symmetric structure would be more likely to show four magnetically non-equivalent $N$-methyls.

\textit{meso-$N,N,N',N'$-tetramethyl-2,3-butanediamine was prepared diastereomerically pure and investigated as a ligand for [1,3-bis(trimethylsilyl)]allyl]lithium. 1,3-Bis(trimethylsilyl)propene was deprotonated using 1.3 M sec-butyl lithium in pentane at room temperature in the presence of an equivalent of}
meso-$N,N,N',N'$-tetramethyl-2,3-butanediamine (scheme 32). The sample was charged into an NMR tube and the solvent replaced with deuterated diethyl ether. Proton NMR of the allyl moiety shows vicinal coupling of 12 Hz (a 1:2:1 triplet for $H_2$ and a 1:1 doublet for $H_1$ of 12 Hz) indicating that the two silyl groups are exo, as shown in B (scheme 31).

Scheme 32. The reaction of 1,3-bis(trimethylsilyl)propene with meso-$N,N,N',N'$-tetramethyl-2,3-butanediamine in the presence of sec-butyllithium.

Unfortunately, by 180 K the material precipitated out of solution, so not all of the behavior seen for A previously could be observed for proposed B. For example, $C_1$ and $C_3$ gave rise to just a broad resonance which turns into a poorly resolved doublet by 180 K. The important point is that the $N$-methyls appear as a set of four well spaced resonances of equal intensity, confirming the proposed structure B. Of course, their shift assignments cannot be made, although a reasonable choice can be proposed. Figure 6 shows the low temperature $^{13}$C NMR spectrum. Different parts of this low temperature spectrum are shown expanded at the bottom of the stack plots showing the effect of increasing temperature.

The clearest indication of the operation of dynamic processes is manifested by the temperature dependent behavior of the NCH$_3$$^{13}$C resonances.
The four peaks of equal intensity broaden equally between 200 K and 180 K, indicating an operation common of a dynamic process. By 210 K, peak C and D begin to average as have also E with F (scheme 33). By 220 K, a fourth

\[\text{Scheme 33. The N-methyl resonances of meso-N,N,N',N'-tetramethyl-2,3-butanediamine complexed with [1,3-bis(trimethylsilyl)allyl]lithium.}\]

resonance, G appears at the same shift (43.5 ppm) as N\(\text{CH}_3\) in pure meso-\(N,N,N',N'\)-tetramethyl-2,3-butanediamine. Above 230 K, it is apparent that a second process is averaging C with E and D with F, or C with F and D with E. Finally, a third process averages all five resonances to a single line by 293 K. This latter process is without a doubt the exchange of meso-\(N,N,N',N'\)-tetramethyl-2,3-butanediamine between its free and complexed state.

The following discussion is speculative in the sense that there are more and less reasonable choices to be made. Inspection of proposed structure, B reveals that inversion at nitrogen would average N\(\text{CH}_3\), W with X and Y with Z,
Figure 5. The $^1$H NMR of (6-1) in diethyl ether-d$_{10}$ for the C-methyl (9.8 PPM) carbons from 293 K to 180 K.
Figure 6. The $^{13}$C NMR of (6-1) in diethyl ether-d$_{10}$ of the N-methyl (43.5 PPM) carbons from 293 K to 180 K. The N-methyl resonances resolve to give four peaks (49.0, 45.9, 44.4, 42.0 PPM) by 190 K.
Figure 7. The $^{13}$C NMR of (6-1) in diethyl ether-d$_{10}$ for C$_1$ & C$_3$ of the anion (68.1 PPM) and the ethane bridge(63.4 PPM) carbons from 250 K to 180 K.
Figure 8. The $^{13}\text{C}$ NMR of (6-1) in diethyl ether-d$_{10}$ for the C$_2$ of allyl (155.2 PPM) carbon from 250 K to 180 K.
process i, while reorientation r, of the ions with respect to each other would
average W with Y and X with Z (scheme 34). Let us assume that the syn N-

\[
\text{Scheme 34. Possible reorientation processes of meso-N,N,N',N'-}
\text{tetramethyi-2,3-butanediamine complexed with [1,3-bis (trimethylsi}
\text{lyl)allyl]lithium.}
\]

methyls with respect to the plane of the coordinated ligand should have shifts more
similar to each other than the N-methyls on opposite sides. Then, the signal
averaging seen at lowest temperature is due to the fast reorientation and the
second averaging observed at higher temperature arises from inversion at nitrogen.
In principle, all of this could easily be simulated since the system is one of four
uncoupled half spins exchanging sites. It is obvious that the first two slowest
processes have different rates since a common rate constant for both failed to
reproduce the observed spectra. It was thought that only the faster process
perturbed the line shapes at the lowest temperature. This assumption turned out to
be incorrect since the line widths for the broad averaged, single C,D and E,F resonances, respectively, change very little with increasing temperature between 210 K and 240 K. Thus, two processes contribute: first, the tumbling-reorientation which would average C with D and E with F and narrow the averaged resonances, and second, the inversions at nitrogen which would, at the same time, broaden the C,D peak and the E,F peak. Clearly all these processes perturb the N-methyl resonances over most of the temperature range observed. Choosing the correct set of three different rate constants would be virtually impossible.

An alternative explanation; that the bidentately complexed system dissociates to monodentately complexed lithium would explain the appearance of "free" NCH₃ in the ¹³C NMR, but then one would expect to observe a new resonance for the methyls in the complexed nitrogen of the new species; this is not seen. The "complexed" NCH₃ 's show averaged shifts at higher temperature; not altogether new ones.

The behavior of the remainder of the spectrum is not definitive at this time. In addition, from the appearance of ¹³C₂ of allyl at low temperature there is a second species (< 10%) which necessarily complicates interpretation of these data. The two ¹³C₂ signals average with increasing temperature. All the results with meso-N,N',N'-tetramethyl-2,3-butanediamine support the unsymmetrical nesting
of Li⁺ complexed ligand with the allyl anion. Further, three dynamic effects have been qualitatively identified.

A second species for which we proposed to investigate the structure and behavior of ion-pairs consists of amine complexes of [α-(trimethylsilyl)benzyl] lithium. Studies of this compound complexed to different ligands generated fresh insight into the nature of bonding within the ion-pair. Complexes with TMEDA and N,N',N'',N'''-pentamethyldiethylenetriamine appear to be only partially delocalized. With triamine a $^{13}$C, $^6$Li spin coupling of 4 Hz was observed at low temperature. The complex with meso-$N,N,N',N''$-tetramethyl-2,3-butanediamine was prepared by deprotonating α-(trimethylsilyl)toluene with 2.5 M n-butyl lithium in diethyl ether at room temperature in the presence of an equivalent of the diamine. Samples were dissolved in deuterated tetrahydrofuran for NMR studies. Down to 200 K this sample showed none of the magnetic nonequivalencies characteristic of ion-paired lithium carbanide salts. The sample precipitated out below 200 K. NMR spectra showed some selective broadening of $^{13}$C resonances at reduced temperatures; for example the $N$-methyl $^{13}$C resonance. It is likely that the dynamic processes which average shifts for nonequivalent sites in these complexes are still too fast by 200 K to permit observations of the nonequivalent carbons. However, rotation around the phenyl-benzyl bond is slow enough by 200 K. At 250 K, the two ortho carbons form a well spaced, clean doublet, see figure 13. NMR line shape analysis of the signal averaging of the ortho carbons
resonances which takes place above 250 K gives rise to $\Delta H^\circ$ of 19.7 kcal / mol with $\Delta S^\circ$ of -25 eu; similar to values obtained using other ligands.$^{67}$ The Erying plot is shown in figure 14 and the 2 X 2 matrix for the dynamic analysis of phenyl ring rotation of 6-2 in THF-d$_8$ is shown in scheme 31. The line shapes for the $^{13}$C NMR spectrum of 6-2 as a function of temperature are illustrated in figures 9 through 12.

Future work on this problem should include studies of a ring substituted analog to increase solubility at low temperature and thus allow NMR studies at lower temperature than possible with the present sample.

$$\begin{bmatrix}
2\Pi(\Delta v_1) & k \\
-k/T - k & 
\end{bmatrix}
\begin{bmatrix}
\rho_1 \\
\rho_2 \\
\end{bmatrix}
= iC
\begin{bmatrix}
1 \\
1 \\
\end{bmatrix}
$$

$\text{Abs (v) = -Im (} \rho_1 + \rho_2 \text{)}$

Scheme 31. The 2 X 2 matrix for the dynamic analysis of phenyl ring rotation of 6-2 in THF-d$_8$ using the ortho carbon resonances.
Figure 9. The $^{13}$C NMR of (6-2) in THF-$d_8$ for the trimethylsilyl (2.9 PPM) and C-methyl (7.6 PPM) carbons from 295 K to 200 K.
Figure 10. The $^{13}$C NMR of (6-2) in THF-d$_6$ for the N-methyl (40.7 PPM) and α-C anion (40.5 PPM) carbon from 295 K to 200 K.
Figure 11. The $^{13}$C NMR of (6-2) in THF-$d_6$ for the ethane bridge (62.9 PPM) carbons from 295 K to 200 K.
Figure 12. The $^{13}$C NMR of (6-2) in THF-$d_8$ for the phenyl ring (ipso 160.1, meta 128.1, ortho 120.4, para 107.8 PPM) carbons from 295 K to 200 K. The ortho carbon resonances resolve to give a clean 1:1 doublet (121.5, 118.4 PPM) by 250 K.
Figure 13. The $^{13}$C NMR line shapes for the ortho carbon resonance of [α-(trimethylsilyl)benzyl]lithium complexed with meso-\(N,N',N''\)-tetramethyl-2,3-butanediamine in THF-\(d_8\). Left) observed; Right) calculated, to fit with first order rate constant for rotation about the ring benzyl bond.
Figure 13. (continued) The $^{13}$C NMR line shapes for the ortho carbon resonance of [α-(trimethylsilyl)benzyl]lithium complexed with meso-$N,N',N''$-tetramethyl-2,3-butanediamine in THF-$d_8$. Left) observed; Right) calculated, to fit with first order rate constant for rotation about the ring benzyl bond.
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Line Width 3 Hz
Chemical Shift 120.4 PPM
Concentration 0.4 M
Solvent THF-d₈
R squared 0.9867

\[ y = -9.9121x + 36.338 \]

Slope = \(\Delta H^\ddagger / R\)
Intercept = \(\ln(k_B / h) + \Delta S^\ddagger / R\)
No. of observations 9
Slope 9912 K

Activation Parameters
Entropy of Activation: \(\Delta S^\ddagger = -25.0\) eu
Enthalpy of Activation \(\Delta H^\ddagger = 19.7\) kcal / mol

Table 4. Data used for the dynamic analysis of phenyl ring rotation in (6-2) in THF-d₈ using the ortho carbon resonances.
Figure 14. The Erying plot for the dynamic analysis of phenyl ring rotation of 6-2 in THF-d$_6$ using the ortho carbon resonances.
Conclusions

Through the course of our investigation, we have established new procedures for the synthesis of previously unknown vicinal diamines and further studied the dynamic processes that occur within the ion pairs of diamine / organolithium complexes. We have successfully developed syntheses for $(2S,2'S)-1,1'-(cis-1,2-cyclopentylene)bis[2-methylpyrroldidine]$ $(2-7)$, $meso-N,N,N',N'-tetramethyl-2,3-butanediamine$ $(3-5)$, and $cis-N,N'-dimethyl-1,2-cyclohexane diamine$ $(4-5)$. These synthetic procedures are important since new vicinal diamines have potential as ligands for organolithium compounds. Further work needs to be done on the synthesis of $N,N,N',N'-tetramethyl-2,3-dimethyl-2,3-butanediamine$, however our investigation describes the problems encountered with the most obvious routes.

Variable temperature NMR studies were conducted on the complexes of $meso-N,N,N',N'-tetramethyl-2,3-butanediamine$ with $[1,3\text{-bis}(\text{trimethylsilyl})\text{allyl}]\text{lithium}$ in deuterated diethyl ether $(6-1)$ and with $[\alpha-(\text{trimethylsilyl})\text{benzyl}]\text{lithium}$ in deuterated tetrahydrofuran $(6-2)$. For complex $(6-2)$, the phenyl ring rotation was determined to have an entropy of activation $(\Delta S^\circ)$ of $-25$ eu and an enthalpy of activation $(\Delta H^\circ)$ of 19.7 kcal / mol. These activation parameters are similar to earlier work on the same organolithium species complexed with TMEDA.
CHAPTER 7
EXPERIMENTAL SECTION

General Experimental

Any common solvents or reagents used in these experiments were purchased from The Ohio State University stores. All other chemicals were purchased from the Aldrich Chemical company. All deuterated solvents were purchased from Cambridge Isotopes. FT-NMR spectra were obtained on either Bruker AC-200 or Bruker AM-250 spectrometer. FT-NMR spectra of organolithium / diamine complexes were obtained on a Bruker MSL-300 spectrometer. All NMR spectra were referenced to the solvent and all shifts were reported in PPM. The GC/MS data were obtained on a Hewlett-Packard 5680 combination gas chromatography / infrared / mass spectrometer. All specific rotations were measured on a Perkin-Elmer 241 MC polarimeter at room temperature (25 °C) with a Sodium D lamp using a 1 mm slit width and a 2 mL cell that was 1 decimeter in length. All concentrations for optically active compounds are listed in g / mL. All melting points were determined using a Mel-Temp melting point apparatus in open capillary tubes and were uncorrected.
FT-IR spectra were obtained NEAT using a Perkin-Elmer 1600 series FT-Infrared spectrometer and were reported in reciprocal centimeters. A Parr Pressure Reaction Apparatus was used for all hydrogenation reactions run below 100 PSI. All other hydrogenations were performed using a 450 mL Parr stainless steel bomb (model 4562) with a maximum pressure rating of 2000 PSI. Platinum oxide (Adam’s catalyst) was always activated by perhydrogenation before use.

Preparation of Organolithium Compounds.

All glassware used in the preparation or reaction of organolithium compounds was baked overnight in an oven, assembled while still warm, and then flame dried under vacuum. The glassware systems were flushed at least twice with purified argon. All syringes were dried overnight in an oven and assembled while still warm. All solvents (diethyl ether, tetrahydrofuran, pentane) used in organolithium reactions were freshly distilled from sodium with benzophenone under purified argon. Before use, all cis-vicinal, diamine ligands were distilled from potassium hydroxide, and then distilled from calcium hydride to ensure that they were totally dry. Since organolithium compounds are extremely sensitive to moisture and oxygen, all reactions were carried out under a blanket of purified argon or in a dry box.

Titration of Organolithium Compounds.

Organolithium compounds which were used as synthetic reagents were titrated for their total alkoxide and base content before use. The total amount of base was determined by adding a 1 mL sample of the organolithium solution to a solution
of menthol (0.1 g) in tetrahydrofuran. The base was then titrated with a 0.1 M solution of benzoic acid in toluene with methylene blue as an indicator. The amount of alkoxide present in the organolithium solution was then determined by quenching a 1 mL sample with 0.2 mL of allyl bromide and performing the same titration listed above. The concentration of carbon bound base is the difference between the two titrations.

**Preparation of NMR samples:**

The NMR sample tubes (5 mm) were connected to a 14/20 female joint with a section of hard glass. The NMR tubes were stored in an oven (105 °C) to keep them dry. To prepare the NMR tube for an organolithium sample, a 14/20 male Schlenk adapter was attached to the tube and the tube flame dried under high vacuum. The NMR tube and organolithium sample were then placed in the dry box. The sample was charged into the tube either as a solid or solution. The tube was removed from the dry box and placed under high vacuum. Any residual solvent was slowly pumped into a cold trap and the tube evacuated to below 5 microns. Deuterated solvent (previously dried with sodium and benzophenone) was then vacuum transferred into the NMR tube. The solution in the NMR tube was degassed by using two liquid nitrogen freeze, vacuum pump, and room temperature thaw cycles. Finally, the NMR sample was frozen with liquid nitrogen, the head space was evacuated, and the top of the NMR tube heated with an oxygen / methane torch until the NMR tube was sealed off under glass. All NMR samples were stored in liquid nitrogen in a Dewar flask in a
-30°C refrigerator. Most samples could be used to obtain NMR spectra for two weeks or longer depending on the reactivity of the organolithium compound.

**tert-Butyl 1-pyrrolidinocarboxylate (2-1)**

Pyrrolidine (33.14 g, 0.466 mol) was dissolved in dichloromethane (350 mL) and charged into a RBF. Di-tert-butyldicarbonate (100.0 g, 0.459 mol) was dissolved in dichloromethane (100 mL) and the solution was introduced into the RBF through a pressurized addition funnel over 3 hours with cooling using an ice bath (carbon dioxide evolution, system must be vented). Once the addition was complete, the reaction solution was stirred for 18 hours at room temperature. The solvent was rotary evaporated to produce a light yellow liquid which fractionally distilled to yield (2-1) (75.55 g, 0.441 mol, 96%) at 71°C / 10 Torr. \( ^1 \text{H NMR (CDCl}_3, 200 \text{ MHz)} \delta 3.20 (m,4H), 1.74 (m,4H), 1.38 (s,9H); {^13} \text{C NMR (CDCl}_3, 50 \text{ MHz)} \delta 154.4, 78.7, 45.8, 45.5, 28.4, 25.6, 24.9; \text{GC/MS Calcd for C}_{9}H_{17}NO_{2}: 171. Found: 171.**

**tert-Butyl (2S)-2-methyl-1-pyrrolidinocarboxylate (2-2)**

(-)Sparteine (120.0 g, 0.512 mol) was dissolved in diethyl ether (1,500 mL) in a RBF. (2-1) (73.22 g, 0.427 mol) was dissolved in diethyl ether (100 mL) and charged into the RBF. The solution was stirred at room temperature for 5 minutes, then cooled to -78°C using an acetone / dry ice bath. Sec-butyllithium (1.3 M in cyclohexane, 394 mL, 0.512 mol) was syringed into the RBF and the solution stirred for 4 hours at -78°C. Dimethyl sulfate (61 mL, 0.641 mol) was charged into the RBF and the solution was allowed to warm to room temperature over 3 hours. The reaction
mixture was transferred to a 4 L separatory funnel and washed with water (2 x 1,000 mL), then the aqueous washes were combined. The aqueous washes were transferred to another funnel and extracted with diethyl ether (5 x 200 mL), then ether extracts were added to the reaction mixture. The mixture was washed with 5% aqueous H₃PO₄ (5 x 200 mL), then dried over magnesium sulfate (3 g, overnight). After vacuum filtration, the mixture was concentrated by rotary evaporation. The remaining liquid was fractionally distilled to yield (2-2) (71.21 g, 0.384 mol, 90%) at 102°C / 6 Torr in 99% ee based on the specific rotation. The specific rotation of (2-2) purified by chiral chromatography had been established by Beak.¹³a¹³ H NMR (CDCl₃, 200 MHz) δ 3.80 (m,1H), 3.28 (m,2H), 2.00 to 1.65 (m,4H), 1.40 (s,9H), 1.07 (d,3H); ¹³C NMR (CDCl₃, 50 MHz) δ 154.4, 78.7, 52.7, 46.2, 33.2, 28.5, 22.9, 20.6; [α]⁺²⁵ = +31° (C. 0.48, CHCl₃), Ref: [α]⁺²⁵ = +31.2° (C. 2.76, CHCl₃)

(2S)-2-Methylpyrrolidine hydrochloride (2-3) & (2S)-2-Methylpyrrolidine (2-4)

12 M Hydrochloric acid (94 mL, 1.13 mol) was charged into a RBF which was placed in an ice bath. (2-2) (104.1 g, 0.562 mol) was introduced into the RBF via a pressurized addition funnel over 2 hours (carbon dioxide evolution, system must be vented). Once addition was complete, the solution was allowed to warm to room temperature over 4 hours. (the monohydrochloride salt of the amine (2-3) can be isolated (94%) by rotary evaporating the reaction solution to dryness) The reaction solution was returned to the ice bath and 40% aqueous sodium hydroxide solution (120 mL) was added over 2 hours through the addition funnel. Upon basification (pH
= 11), a yellow layer oiled out of the solution. The oil was decanted and the aqueous solution was transferred to a separatory funnel, then extracted with pentane (3 x 50 mL). The organic materials were combined and dried over magnesium sulfate (0.5 g, overnight). Fractional distillation yielded (2-4) (39.39 g, 0.462 mol, 82%) at 95°C / 1 atm in 99% ee based on the specific rotation. The specific rotation of (2-4) purified by the fractional crystallization of the (-)hydrogen tartrate had been established by Ringdahl.\textsuperscript{68a,b} \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz) \(\delta\) 2.95 (m, 2H), 2.70 (m, 1H), 1.68 (m, 4H), 1.04 (d, 3H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 50 MHz) \(\delta\) 54.4, 46.6, 33.6, 25.6, 21.1; \([\alpha]_{D}^{25} = +19.8^\circ\) (C. 0.11, 95% EtOH), Ref\textsuperscript{68}; \([\alpha]_{D}^{25} = +20.0^\circ\) (C. 0.8, 95% EtOH)

(2RS)-2-[(2S)-2-Methyl-1-pyrrolidinyl]cyclopentanone (2-5)

Methanol (43 mL, 1.06 mol) and 1,2-bis(trimethylsiloxy)cyclopentene (41.73 g, 0.171 mol) were charged into a RBF and stirred for 5 minutes. (2-4) (14.58 g, 0.171 mol) was introduced into the RBF and the reaction solution was refluxed for 26 hours. The solvent was removed by rotary evaporation to produce a red liquid (30 mL). The amino-ketone (2-5) was not isolated (theoretical: 100% = 28.60 g, 0.171 mol), but used as a starting material for the next reaction. GC/MS analysis established that the crude material was roughly a 1:1 mixture of the R,S / S,S diastereomeric amino-ketones. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 200 MHz): spectrum is consistent with two diastereomers; \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 50 MHz): spectrum is consistent with two diastereomers, carbonyls \(\delta\) 219.8, 217.3; GC/MS Calcd for C\textsubscript{19}H\textsubscript{17}NO: 167. Found: 167.
(2S,2'S)-1,1'-[(1RS)-2-Cyclopenten-1,2-ylene]bis[2-methylpyrrolidine] (2-6)

The crude 1:1 mixture of R,S / S,S (2-5) (30 mL), benzene (65 mL, 0.727 mol), (2-4) (14.58 g, 0.171 mol), and p-toluenesulfonic acid monohydrate (0.13 g, 0.68 mmol) were charged into a RBF fitted with a Dean-Stark trap and reflux condenser. The reaction mixture was stirred and refluxed until water (3 mL) stopped collecting in the trap (12 hours). The solvent was rotary evaporated to produce a red liquid (40 mL) which fractionally distilled to yield (2-6) (30.32 g, 0.130 mol, 76%) at 125°C / 1 Torr. GC/MS analysis established that the product was a 1:1 mixture of the R,S,S / S,S,S diastereomeric amino-enamines. \(^1\)H NMR (CDCl\(_3\), 200 MHz): spectrum is consistent with two diastereomers, vinylic H's \(\delta 4.2\), \(^1^3\)C NMR (CDCl\(_3\), 50 MHz): spectrum is consistent with two diastereomers, alkene C's \(\delta 148.1, 125.1\); GC/MS Calcd for C\(_{15}\)H\(_{26}\)N\(_2\): 234. Found: 234.

(2S,2'S)-1,1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine] (2-7)

Ethyl acetate (240 mL), (2-6) (30.32 g, 0.130 mol), and 5% Pd on C (2.60 g) was charged into a Parr jar that was placed in a Parr hydrogenation apparatus. The jar was flushed with hydrogen 4 times and charged to 50 PSI, then rocked at room temperature for 3 hours. The reaction mixture was vacuum filtered through 1 cm of Celite, then the solvent was rotary evaporated to produce a red liquid (30 mL) which fractionally distilled to yield (2-7) (26.74 g, 0.113 mol, 87%) at 115°C / 1 Torr in 99% de based on the optical purity of (2-4) used as starting material. \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta 3.31 (m, 2H), 3.12 (m, 2H), 2.51 (m, 4H), 1.9 to 1.1 (m, 14H), 77
1.00 (d,6H); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 3.40 (m,1H), 3.30 (m,1H), 3.10 (m,1H),
3.05 (m,1H), 2.65 (m,1H), 2.50 (m,2H), 2.40 (m,1H), 1.90 (m,1H), 1.70 (m,9H),
1.50 (m,2H), 1.40 (m,1H), 1.25 (m,1H), 1.00 (d of d,6H); \(^1\)C NMR (CDCl\(_3\), 50 MHz) \(\delta\) 68.1, 58.8, 57.2, 56.1, 53.0, 48.2, 33.3, 32.3, 31.8, 22.9, 22.7, 22.5, 20.6,
19.4; \(^1\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 67.9, 58.5, 57.2, 56.1, 52.9, 48.2, 33.3, 32.3,
31.6, 22.8, 22.7, 22.5, 22.4, 20.5, 19.3; \([\alpha]^{25}_D = +117.6^\circ\) (C. 0.115, CHCl\(_3\)); GC/MS
Calcd for C\(_{15}\)H\(_{28}\)N\(_2\): 236. Found: 236.

(2S,2'S)-1.1'-(-cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine] dihydrochloride (2-8)

(2-7) (10.0 g, 0.042 mol) and 6 M hydrochloric acid (14 mL, 0.084 mol) were
introduced into a RBF and stirred for 5 minutes. The solution was rotary evaporated
to dryness to yield (2-8) (8.63 g, 0.028 mol, 66%) with a mp = 218° C. The NMR
spectrum of the monohydrochloride salt was observed. \(^1\)H NMR (D\(_2\)O, 200 MHz) \(\delta\)
4.20 (b,1H), 3.9 - 3.6 (2 x m, 5H), 3.2 (m,2H), 2.4 - 1.5 (m,14H), 1.3 (d,6H).

(2S,2'S)-1.1'-(cis-1,2-Cyclopentylene)bis[2-methylpyrrolidine] monopicrate (2-9)

(2-7) (0.500 g, 0.002 mol) and picric acid (0.916 g, 0.004 mol) in 95% ethanol (6.1 g
acid / 100 mL solution) were charged into a small, open vial. After 1 week, the
solvent had evaporated to yield light brown crystals of (2-9) (0.720 g, 77%) with a
mp = 191° C. X-ray analysis of the crystals by Dr. Judy Gallucci established the
structure of the diamine salt. (see pages 22 - 33)
1,3,4,5-Tetramethyl-4-imidazolin-2-one (3-1)

Cumene (1,000 mL), 1,3-dimethylurea (8.811 g, 0.100 mol), 3-hydroxy-2-butanone (8.811 g, 0.100 mol), and p-toluenesulfonic acid (1.98 g, 0.010 mol) were charged into a RBF which was fitted with a Dean-Stark trap and reflux condenser. (1,3-dimethylurea and 3-hydroxy-2-butanone were dried in a desiccator before use) This mixture was stirred and refluxed until water (roughly 4 mL) collection was complete (12 hours). The cumene was removed by allowing the condensing solvent to drain through the trap. The red liquid which remained was fractionally distilled to yield a yellow liquid (8.0 g) at 125°C / 3 Torr. The distilled crude product solidified upon standing at room temperature. The solid was vacuum filtered and washed with cold water (2 x 3 mL), then cold acetone (2 x 3 mL) to yield (3-1) (5.32 g, 0.038 mol, 38%) as a white solid (mp = 95°C). \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 2.75 (s, \(6H\)), 1.58 (s, \(6H\)); \(^13\)C NMR (CDCl\(_3\), 50 MHz) \(\delta\) 153.3, 112.9, 27.1, 8.4; GC/MS Calcd for C\(_7\)H\(_{12}\)N\(_2\)O: 140. Found: 140.

cis-1,3,4,5-Tetramethyl-2-imidazolidinone (3-2)

Acetic acid (170 mL), (3-1) (10.09 g, 0.072 mol), and platinum oxide (1.00 g, 0.004 mol) were charged into a Parr high pressure hydrogenator. The system was purged with hydrogen 3 times and pressurized to 1,500 PSI, then stirred at room temperature for 1 week. The reaction solution was vacuum filtered through 2 cm of Celite, then rotary evaporated to produce a yellow liquid which fractionally distilled to yield (3-2) (6.11 g, 0.043 mol, 60%) at 93°C / 1 Torr. \(^1\)H NMR (CDCl\(_3\), 200 MHz) \(\delta\) 3.35
(m,2H), 2.59 (s,6H), 0.95 (d,6H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 161.3, 54.8, 28.5, 12.1; GC/MS Calcd for C$_7$H$_{14}$N$_2$O: 142. Found: 142.

**meso-N,N'-Dimethyl-2,3-butanediamine dihydrochloride (3-3)**

12 M Hydrochloric acid (108 mL) and (3-2) (6.11 g, 0.043 mol) were introduced into a RBF attached to a reflux condenser. The mixture was stirred and refluxed for 1 week, then rotary evaporated to dryness to yield (3-3) (6.75 g, 0.036 mol, 83%) with a mp = 233°C. $^1$H NMR (D$_2$O, 200 MHz) $\delta$ 3.51 (m,2H), 2.63 (s,6H), 1.30 (d,6H); $^{13}$C NMR (D$_2$O, 50 MHz) $\delta$ 56.7, 31.3, 11.6.

**meso-N,N'-Dimethyl-2,3-butanediamine (3-4)**

(3-3) (6.75 g, 0.036 mol) was dissolved in aqueous 40% sodium hydroxide (10 mL). The solution was transferred to a separatory funnel, extracted with diethyl ether (3 x 10 mL), the organic layers were combined, then washed with saturated sodium chloride (3 mL). The organic layers were dried over sodium sulfate (0.5 g, 2 hrs), then fractionally distilled to yield (3-4) (4.00 g, 0.034 mol, 94%) at 135°C / 1 atm. $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 2.45 (m,2H), 2.29 (m,6H), 1.78 (m,2H), 0.90 (s,6H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 57.9, 34.4, 15.1; GC/MS Calcd for C$_6$H$_{16}$N$_2$: 116. Found: 116.

**meso-N,N',N'-Tetramethyl-2,3-butanediamine (3-5)**

Aqueous 37.5% formaldehyde solution (5.72 g, 0.071 mol), aqueous 90.8% formic acid solution (3.62 g, 0.071 mol), and (3-4) (4.00 g, 0.034 mol) were charged into a RBF which was attached to a reflux condenser. The reaction mixture was stirred and
refluxed for 24 hours, then diluted with 6 M hydrochloric acid (15 mL). The solution was transferred to a separatory funnel, extracted with diethyl ether (3 x 15 mL), then the organic layers were combined and discarded. The aqueous phase was transferred to a beaker, placed in an ice bath and made basic (pH = 11) by addition of aqueous 50% potassium hydroxide (20 mL). The basic solution was transferred to a separatory funnel, extracted with diethyl ether (3 x 25 mL), the organic layers were combined, then washed with saturated sodium chloride (20 mL). The organic layer was dried over sodium sulfate (0.5 g, 5 hrs), then fractionally distilled to yield (3-5) (3.97 g, 0.028 mol, 81%) at 145°C / 1 atm. 

\[ ^1H \text{ NMR (CDCl}_3, 200 MHz) \delta 2.3 \text{ (m, 2H), 2.14 (s, 12H), 0.88 (d, 6H); }^{13}C \text{ NMR (CDCl}_3, 50 MHz) \delta 62.0, 40.4, 7.6; \text{ GC/MS Calcd for C}_8H_{16}N_2: 144. \text{ Found: 144.} \]

**meso-N,N,N',N'-Tetramethyl-2,3-butanediamine dihydrochloride (3-6)**

12 M Hydrochloric acid (1.58 mL, 0.019 mol) and (3-5) (0.915 g, 0.006 mol) were charged into a RBF and stirred for 5 minutes. The solution was rotary evaporated to dryness to yield (3-6) (1.00 g, 0.0046 mol, 73%) with a mp = 218°C. 

\[ ^1H \text{ NMR (D}_2\text{O, 200 MHz) } \delta 3.80 \text{ (m, 2H), 2.91 (m, 12H), 1.47 (d, 6H); }^{13}C \text{ NMR (D}_2\text{O, 50 MHz) } \delta 61.4, 43.8, 36.4, 8.9. \]

**(1-Cyclohexen-1,2-yleneoxy)bis[trimethylsilane] (4-1)**

Toluene (700 mL) and sodium (27.1 g, 1.18 mol) were charged into a RBF fitted with a reflux condenser and pressurized addition funnel. The mixture was stirred and refluxed for 2 hours to produce a sodium dispersion. Toluene (250 mL), dimethyl
adipate (43.55 g, 0.250 mol), and trimethylsilylchloride (108.64 g, 1.00 mol) were introduced into the funnel and added to the reaction solution over 6 hours. The mixture was stirred and refluxed for 12 hours, then filtered through glass wool and vacuum filtered through 1 cm of Celite. The filtrate was rotary evaporated to produce a yellow liquid which fractionally distilled to yield (4-1) (28.97 g, 0.111 mol, 45%) at 130°C / 10 Torr. $^1$H NMR (CDCl$_3$, 200 MHz) δ 2.04 (m,4H), 1.57 (m,4H), 0.14 (s,18H); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 132.1, 29.7, 23.3, 0.8.

4,5,6,7-Tetrahydro-1,3-dimethyl-2-benzimidazolinone (4-2)
Cumene (500 mL), 1,3-dimethylurea (8.811 g, 0.100 mol), (4-1) (25.85 g, 0.100 mol), and p-toluenesulfonic acid (1.98 g, 0.010 mol) were charged into a RBF fitted with a Dean-Stark trap and reflux condenser. The mixture was stirred and refluxed until water (1.9 mL) collection was complete (12 hours). The cumene was removed by allowing the condensing solvent to drain through the trap. The remaining red liquid was fractionally distilled to yield (4-2) (9.21 g, 0.055 mol, 55%) at 155°C / 1.5 Torr. $^1$H NMR (CDCl$_3$, 200 MHz) δ 2.87 (s,6H), 2.05 (m,4H), 1.53 (m,4H); $^{13}$C NMR (CDCl$_3$, 50 MHz) δ 153.3, 116.2, 26.7, 22.2, 19.4; GC/MS Calcd for C$_9$H$_{14}$N$_2$O: 166. Found: 166.

cis-Hexahydro-1,3-dimethyl-2-benzimidazolidinone (4-3)
Acetic acid (150 mL), (4-2) (10.69 g, 0.064 mol), and platinum oxide (1.00 g, 4.39 mmol) were charged into a Parr hydrogenation apparatus. The system was purged with hydrogen 3 times, pressurized to 1,500 PSI, then stirred at room temperature for
68 hours. The mixture was vacuum filtered through 1 cm of Celite and the filtrate was rotary evaporated to produce a yellow liquid which fractionally distilled to yield (4-3) (2.88 g, 0.017 mol, 27%) at 126°C / 6 Torr. \( ^1\text{H NMR (CDCl}_3, 200 \text{ MHz)} \delta 3.14 \text{ (m,2H)}, 2.55 \text{ (s,6H)}, 1.7 \text{ to 1.1 (m,8H)}; ^{13}\text{C NMR (CDCl}_3, 50 \text{ MHz)} \delta 162.4, 55.2, 28.4, 25.2, 20.5; \text{GC/MS Calcd for C}_9\text{H}_{16}\text{N}_2\text{O: } 168. \text{Found: } 168.

cis-\text{N,N'-Dimethyl-1,2-cyclohexanediamine dihydrochloride (4-4)}

12 M Hydrochloric acid (18 mL) and (4-3) (1.21 g, 0.007 mol) were charged into a RBF fitted with a reflux condenser. The mixture was stirred and refluxed for 2 weeks, then rotary evaporated to dryness to yield (4-4) (0.60 g, 0.0028 mol, 40%) with a mp = 208°C. \( ^1\text{H NMR (D}_2\text{O, 200 MHz)} \delta 3.57 \text{ (m,2H)}, 2.66 \text{ (s,6H)}, 1.79 \text{ (m,4H)}, 1.46 \text{ (m,4H)}; ^{13}\text{C NMR (D}_2\text{O, 50 MHz)} \delta 57.5, 31.4, 23.0, 20.0.

cis-\text{N,N'-Dimethyl-1,2-cyclohexanediamine (4-5)}

(4-4) (0.60 g, 0.0028 mol) was dissolved in aqueous 40% sodium hydroxide (3 mL). A yellow layer oiled out of the aqueous phase and was confirmed as (4-5) by NMR and GC/MS analysis. \( ^1\text{H NMR (CDCl}_3, 200 \text{ MHz)} \delta 2.33 \text{ (m,2H)}, 2.15 \text{ (s,6H)}, 1.4 \text{ to 1.1 (m,4H)}; ^{13}\text{C NMR (CDCl}_3, 50 \text{ MHz)} \delta 58.5, 33.9, 27.2, 22.0; \text{GC/MS Calcd for C}_9\text{H}_{16}\text{N}_2: } 142. \text{Found: } 142.

2,3-\text{Dimethyl-2,3-butanediamine (5-1)}

Isopropylamine (50 mL, 0.587 mol) and mercury (3 mL) were charged into a 1 L quartz photochemical reaction tube fitted with a Dewar reflux condenser which contained antifreeze and was cooled to -30 °C using a refrigeration coil. The tube
was placed in a Rayonet reactor with Hg vapor UV lamps and anhydrous ammonia was bubbled through the tube. The reactor was run for 1 week, then the liquid which remained (15 mL) was decanted from the mercury. Saturated aqueous oxalic acid (70 mL) was added to the liquid until the solution was slightly acidic to litmus paper.

Upon standing, a white solid separated from the solution and was vacuum filtered to yield the oxalate salt (10.31 g, 0.050 mol) of (5-1) with a mp = 320°C. The salt was dissolved in aqueous 20% sodium hydroxide (40 mL) and transferred to a separatory funnel. The aqueous solution was extracted with diethyl ether (3 x 30 mL), the organic layers were combined, then washed with saturated sodium chloride (30 mL). The organic layer was dried over sodium sulfate (1 g, overnight) and fractionally distilled to yield (5-1) (2.76 g, 0.0024 mol, 0.8%) at 112°C / 1 atm.

H NMR (CDCl₃, 200 MHz) δ 0.98 (s,12H); NMR (CDCl₃, 50 MHz) δ 54.4, 26.1; GC/MS Calcd for C₆H₁₆N₂: 116. Found: 116.

1,3,4,4,5,5-Hexamethylimidazolidine (5-2)

Aqueous 90.8% formic acid (4.51 g, 0.089 mol), aqueous 37.5% formaldehyde (7.12 g, 0.089 mol), and (5-1) (2.53 g, 0.022 mol) were charged into a RBF fitted with a reflux condenser. The mixture was stirred and refluxed for 15 hours, then diluted with 6 M hydrochloric acid (15 mL). The solution was transferred to a separatory funnel and extracted with diethyl ether (3 x 20 mL), the organic layers were combined and discarded. The aqueous layer was made basic by addition of aqueous 50% potassium hydroxide (18 mL), then transferred to a separatory funnel and extracted
with diethyl ether (6 x 20 mL). The organic layers were combined, washed with saturated sodium chloride (10 mL) and dried over sodium sulfate (0.5 g, overnight).

The solution was rotary evaporated to yield a yellow liquid which was confirmed to be (5-2) (2.75 g, 0.018 mol, 80%) by NMR and GC/MS analysis. $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 3.39 (s,2H), 2.09 (s,6H), 0.80 (s,12H); $^1$C NMR (CDCl$_3$, 50 MHz) $\delta$ 75.9, 64.0, 32.7, 18.8; GC/MS Calcd for C$_9$H$_{20}$N$_2$: 156. Found: 156.

**Hexamethylaziridinium Iodide (5-3)**

Methanol (70 mL), (5-1) (7.30 g, 0.063 mol), iodomethane (26.7 g, 0.189 mol, 3 eq), and sodium bicarbonate (31.67 g, 0.377 mol, 6 eq) were charged into a RBF fitted with a reflux condenser. The mixture was stirred and refluxed for 24 hours. Iodomethane (26.7 g, 0.189 mol, 3 eq) was introduced into the RBF and the mixture refluxed for an additional 24 hours. The solution was rotary evaporated to dryness to yield a tan solid (70 g). The solid was extracted with boiling chloroform (4 x 70 mL). The organic extracts were combined and a light brown solid precipitated upon standing at room temperature. The solid was vacuum filtered to yield a crude iodide salt (6.24 g, mp = 166 °C). The solid was recrystallized from methanol to yield (5-3) (2.43 g, 0.009 mol, 14%) as a white solid (mp = 198 °C, Lit.$^{63}$: mp = 181 °C) which was soluble in TFA. $^1$H NMR (TFA-d, 200 MHz) $\delta$ 3.39 (s,6H), 2.06 (s,12H); $^1$H NMR (CD$_3$CN) $\delta$ 2.79 (s,6H), 1.46 (s,12H); $^{13}$C NMR (TFA-d, 50 MHz) $\delta$ 61.1, 41.7, 17.5.
**N,N'-Diisopropyl-N,N'-dimethylhexanediamine (5-4)**

N,N-Dimethylisopropylamine (50 mL, 0.410 mol) and mercury (3 mL) were charged into a 1 L quartz photochemical reaction tube fitted with a Dewar reflux condenser which contained antifreeze and was cooled to -30°C using a refrigeration coil. The tube was placed in a Rayonet reactor with Hg vapor UV lamps and anhydrous ammonia was bubbled through the tube. The reactor was run for 1 week, then the liquid which remained (5 mL) was decanted from the mercury. Saturated aqueous oxalic acid (25 mL) was added to the liquid until the solution was slightly acidic to litmus paper. Upon standing, a white solid separated from the solution and was vacuum filtered to yield the oxalate salt (5.25 g, 0.025 mol) of (5-4) with a mp = 320 °C. The salt was dissolved in aqueous 20% sodium hydroxide (20 mL) and transferred to a separatory funnel. The aqueous solution was extracted with diethyl ether (3 x 30 mL), the organic extracts were combined, then washed with saturated sodium chloride (30 mL). The organic layer was dried over sodium sulfate (1 g, overnight) and rotary evaporated to yield (5-4) (0.700 g, 0.004 mol, 2%). ¹H NMR (CDCl₃, 200 MHz) δ 2.71 (q,2H), 2.36 (s,4H), 2.11 (s,6H), 0.89 (d,12H); NMR (CDCl₃, 50 MHz) 5 53.9, 51.7, 37.5, 17.7; GC/MS Calcd for C₁₀H₁₄N₂: 172. Found: 172.

**2-(Dimethylamino)-2-methylpropionitrile (5-5)**

Sodium bisulfite (52.03 g, 0.500 mol) was dissolved in water (125 mL) and the solution charged into a RBF. Acetone (29.04 g, 0.500 mol) was loaded into the RBF
and the solution heated (60°C) and stirred for 10 minutes. Dimethylamine (22.54 g, 0.500 mol) was dissolved in water (60 mL) and the solution introduced into the RBF and stirred for 1 hour. Sodium cyanide (24.50 g, 0.500 mol) was dissolved in water (60 mL) and the solution charged into the RBF over 10 minutes through an addition funnel, then the solution stirred for half an hour. The mixture was transferred to a separatory funnel and the top organic layer was collected, then dried over sodium sulfate (0.5 g, overnight) and fractionally distilled to yield (5-5) (26.4 g, 0.235 mol, 47%) at 147°- 150°C / 1 atm. °H NMR (CDCl₃, 200 MHz) δ 2.29 (s,6H), 1.43 (s,6H), °C NMR (CDCl₃, 50 MHz) δ 119.5, 57.0, 40.6, 26.7; GC/MS Calcd for C₆H₁₂N₂: 112. Found: 112.

[1,3-Bis(trimethylsilyl)allyl]lithium complex with meso-N.N.N'-tetramethyl-2,3-butanediamine (6-1)

A 5 mL Schlenk flask equipped with a glass stopcock and a teflon stir bar was flame dried under vacuum and purged with argon twice. Pentane (1 mL, dry), 1,3-bis(trimethylsilyl)propene (0.155 g, 0.83 mmol), (3-5) (0.12 g, 0.83 mmol), and sec-butyllithium (0.83 mL, 1.08 mmol, 1.3 M in cyclohexane) were charged via syringe. The yellow solution was stirred at room temperature for 2 hours, then placed under vacuum (0.9 Torr) until all of the hydrocarbon solvent had been removed (1 hour) and a red oil remained. The system was purged with argon and pentane (1 mL, dry) was charged into the flask. The solution was transferred via syringe to a Schlenk NMR tube and placed on the dispersion pump vacuum line. The solvent was removed under vacuum (0.1 Torr) and deuterated diethyl ether (2 mL) was
transferred over to the tube. The sample (0.4 M) was frozen in liquid nitrogen and sealed off under glass using an oxygen - methane torch. $^1$H NMR (Et$_2$O-$d_{10}$, 300 MHz, 295 K) $\delta$ 6.70 (t, 1H), 2.6 (d, 2H), 2.5 (m, 2H), 2.31 (s, 12 H), 1.09 (d, 6H), -0.03 (s, 18H), $^{13}$C NMR (Et$_2$O-$d_{10}$, 75 MHz, 295 K) $\delta$ 155.2, 68.2, 63.4, 43.6, 9.9, 2.0.

[$\alpha$-(Trimethylsilyl)benzyl]lithium complex with meso-$N,N',N'$-tetramethyl-2,3-butanediamine (6-2)

A 5 mL Schlenk flask equipped with a glass stopcock and a teflon stir bar was flame dried under vacuum and purged with argon twice. Diethyl ether (1 mL, dry), $\alpha$-(trimethylsilyl)toluene (0.135 g, 0.83 mmol), (3-5) (0.12 g, 0.83 mmol), and n-butyllithium (0.43 mL, 1.08 mmol, 2.5 M in hexane) were charged via syringe. The yellow solution was stirred at room temperature for 2 hours, then placed under vacuum (0.9 Torr) until all of the solvent had been removed (1 hour) and an orange oil remained. The system was purged with argon and pentane (1 mL, dry) was charged into the flask. The solution was transferred via syringe to a Schlenk NMR tube and placed on the dispersion pump vacuum line. The solvent was removed under vacuum (0.1 Torr) and deuterated tetrahydrofuran (2 mL) was transferred over to the tube. The sample (0.4 M) was frozen in liquid nitrogen and sealed off under glass using an oxygen - methane torch. $^1$H NMR (THF-$d_8$, 300 MHz, 295 K) $\delta$ 6.44 (t, 2H), 6.30 (d, 2H), 5.67 (t, 1H), 2.4 (m, 2H), 2.2 (s, 1H), 2.13 (s, 12H), 0.90 (d, 6H), -0.04 (s, 9H), $^{13}$C NMR (THF-$d_8$, 75 MHz, 295 K) $\delta$ 160.1, 128.1, 120.3, 107.9, 62.9, 40.7, 40.5, 7.6, 2.9.
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# APPENDIX

## NMR SPECTRA

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\[ \text{Chemical Shifts:}  \] 

- **4.00 ppm**: 
- **6.00 ppm**: 
- **7.00 ppm**: 

\[ \text{Resonance Lines:}  \]

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Figure 62. The $^{13}$C NMR spectrum of (5-4) in CDCl$_3$. 
Figure 6.1. The $^1$H NMR spectrum of (S,S) in CDCl$_3$. 

Figure 6.3. The $^1$H NMR spectrum of (S,S) in CDCl$_3$. 

[Diagram of NMR spectrum with peaks labeled a, b, 6H, 6H, and integrals at 0.8, 2.3, 4.5, and 7.0 PPM.]
Figure 64. The $^{13}$C NMR spectrum of $(5-5)$ in CDCl$_3$. 

![NMR Spectrum Image]

$\text{Figure 64. The }^{13}\text{C NMR spectrum of (5-5) in CDCl}_3.$
Figure 65. The $^1$H NMR spectrum of (6-1) in EtO$_2$-d$_{10}$. 
Figure 66. The expanded $^1$H NMR spectrum of (6-1) in EtO$_2$-d$_{10}$. 
Figure 67. The $^{13}$C NMR spectrum of (6-1) in EtO$_2$-d$_{10}$. 
Figure 68. The $^1$H NMR spectrum of (6-2) in THF-$d_6$. 
Figure 69. The expanded $^1$H NMR spectrum of (6-2) in THF-$d_6$. 
Figure 70. The $^{13}$C NMR spectrum of (6-2) in THF-$d_8$. 