STUDIES TOWARD THE TOTAL SYNTHESIS OF
HYPERASPIN

DISSERTATION

Presented in Partial Fulfillment of the Requirements for the Degree
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By

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ABSTRACT

Ladybird beetles, commonly referred to as ladybugs, are part of the Coccinellidae family, which comprises approximately 5,200 species worldwide. Folk wisdom attributes good fortune to these insects, while farmers leverage their voracious appetites for aphids for pest control. Notably, in the 1880s, several of the species were imported to California to control insects which were threatening to destroy citrus orchards.

Ladybird beetles employ a chemical defense mechanism known as reflex bleeding. When perturbed, Ladybird beetles exude a bitter, toxic, foul-smelling fluid called hemolymph. Hemolymph is known to contain several alkaloids, including hyperaspine, an alkaloid with a fused-decalin ring system characterized by four stereogenic centers. The structure of hyperaspine, along with adaline, calvine, adalinine, and other alkaloids isolated from the Coccinellidae family, is based on 2-methylperhydro-9b-azaphenalene.

My research has focused on a synthesis of (+)-hyperaspine with the intent of extending N-acyliminium ion cyclization methodology. N-Acyliminium ion cyclizations have been used for carbon-carbon and carbon-heteroatom bond formation since the 1950s. Reactions involving such ions work similarly to the Mannich and Pictet-Spengler reactions, but overcome limitations in iminium ion reactivity inherent to such reactions. N-Acyliminium ion cyclizations have been reported with a wide spectrum of nucleophiles, including aromatic structures, heterocycles, alkenes, alkynes, and enol/enolates. They also frequently proceed with good stereocontrol.

We envisioned accessing (+)-hyperaspine through an N-acyliminium ion cyclization that would afford the A ring with control of the two stereogenic centers at C₄a and C₆. The
cyclization precursor was to be prepared from two key fragments, a chiral alcohol and a chiral carboxylic acid. The stereocenter at C₈ was to be introduced via Evans’ chiral oxazolidinone chemistry to afford the chiral carboxylic acid, which would control stereochemistry at C₄ₐ and C₆. The stereocenter at C₃ was to be derived from β-hydroxybutyrate, the aforementioned chiral alcohol.

This dissertation will focus on the various approaches to the N-acyliminium ion intermediate through the investigation of several different pathways. Each of these pathways concentrates on the oxidation state of C₄ₐ to access the relevant urethane. Once the correct oxidation state was achieved, systems utilizing commercially available butyl isocyanate and 4-pentenoic acid were employed with promising results. The butyl isocyanate system allowed us to form the appropriate N,O-acetal, while the 4-pentenoic acid system allowed us to utilize the N-acyliminium ion intermediate.

We re-attempted to synthesize (+)-hyperaspine with sound methodology, however, we could not generate the N-acyliminium ion precursor 72. In conclusion, although we were not able to successfully synthesize hyperaspine, we were still able to demonstrate that N-acyliminium ion cyclizations are useful on substrates with a urethane functional group. The branched chain of the substrate for hyperaspine limited our ability to demonstrate that while N-acyliminium ions can construct this carbon-carbon bond, it can do so in a stereoselective manner.
To My Parents, Arun and Darshana
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I am indebted to Professor David J. Hart for giving me the opportunity to complete my doctoral research under his guidance. His attention to detail and patience has allowed me to persevere and attain my goal. I appreciate his investment in time and financial assistance which has allowed me to finish my dissertation. I am also grateful to have learned from an excellent teacher; his thoroughness and clarity while teaching has served as an admirable example.

I would also like to extend my gratitude towards Dr. Jon Parquette and Dr. Matt Platz for serving on my committee. I have had the pleasure of teaching for Dr. Platz on more than one occasion, and I feel fortunate to have forged a friendship with him. He has served as a great mentor throughout my education.

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Lastly, I would like to thank God. In a world where it seems very few believe in His existence, He has been the source of my strength. My life is blessed and I owe God for all that I have.
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<td>AIBN</td>
<td>azo-<em>bis</em>-isobutryonitrile</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>ax</td>
<td>axial</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad (spectral)</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>CSA</td>
<td>camphorsulfonic acid)</td>
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<td>COSY</td>
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<tr>
<td>4-DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>d</td>
<td>day or doublet (spectral)</td>
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<tr>
<td>DEPT</td>
<td>Distortionless Enhancement by Polarization Transfer (spectral)</td>
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<td>DHP</td>
<td>dihydropyran</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>eq</td>
<td>equatorial or equivalent</td>
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<td>Et</td>
<td>ethyl</td>
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</table>
g  gram
h  hour
HMDS  hexamethyldisilylamide
HMPA  hexamethylphosphoramide
HMQC  Heteronuclear Multiple Quantum Coherence (spectral)
i-Pr  isopropyl
IR  infrared
J  coupling constant (spectral)
LDA  lithium diisopropylamide
m  meta
m  multiplet (spectral)
M  molecular ion (spectral)
MCPBA  meta-chloroperoxybenzoic acid
Me  methyl
min  minute
mL  milliliter
mM  millimolar
MOM  methoxymethyl
MS  molecular sieves
n-Bu  normal-butyl
NBS  N-bromosuccinimide
NMR  nuclear magnetic resonance

xvi
nOe  nuclear Overhauser effect

NOESY  nuclear overhauser effect spectroscopy

o  ortho

p  para

PCC  pyridinium chlorochromate

Ph  phenyl

Piv  pivaloyl

PPTS  pyridinium para-toluenesulfonate

py or pyr  pyridine

q  quartet

rt  room temperature

s  second or singlet (spectral)

t  triplet (spectral)

TBAF  tetra-\(n\)-butylammonium fluoride

TBDPS  \(tert\)-butyldiphenylsilyl

TBS  \(tert\)-butyldimethylsilyl

\(t\)-Bu  \(tert\)-butyl

TCC  \(trans\)-cumylecyclohexyl

Tf  trifluoromethanesulfonyl

TFA  trifluoracetic acid

TFAA  trifluoracetic anhydride

THP  tetrahydropyranyl
THF  tetrahydrofuran
TMS  trimethylsilyl
Ts   \textit{para}-toluenesulfonyl
CHAPTER 1

The Ladybug Alkaloids

1.1.1 Statement of Problem

This thesis will describe a synthetic approach to hyperaspine (1), an alkaloid secreted by the ladybug *Hyperaspis campestris* when it is under attack by a predator (Figure 1). The reasons for undertaking this project were two-fold: (1) to determine the absolute configuration of hyperaspine, which was unknown at the inception of this project and (2) to see if *N*-acyliminium ion cyclization methodology could be extended to the synthesis of the oxa-aza-decalins, the core heterocycle of hyperaspine.

To help the reader place this research in context, I will first provide some background information. This chapter will begin with an introduction to the ladybug alkaloids including their structures, isolation, biology, and biosynthesis. Details of the isolation and structure determination of hyperaspine will then be described, followed by a discussion of other studies directed toward the synthesis of hyperaspine. Chapter 2 will begin with a discussion of the synthetic plan that forms the basis of this research. A description of our own attempts to execute the plan will follow. Chapter 3 will present the experimental details of the research.

![Hyperaspine](image)

**Figure 1.** Hyperaspine
1.1.2 Introduction – Background of the Ladybug Alkaloids

Ladybird beetles, commonly referred to as ladybugs, are part of the Coccinellidae family, which comprises approximately 5,200 species worldwide. Folk wisdom attributes good fortune to these insects, while farmers leverage their voracious appetites for aphids to control pests. Notably, in the 1880s, several of the species were imported to California to control insects which were threatening to destroy citrus orchards.

Ladybird beetles employ a chemical defense mechanism known as reflex bleeding. When perturbed, Ladybird beetles exude a bitter, toxic, foul-smelling fluid called hemolymph. Hemolymph is known to contain several alkaloids, including hyperaspine, an alkaloid with a fused-oxo-aza-decalin ring system characterized by four stereogenic centers. Some other alkaloids isolated from hemolymph include adaline (2), calvine (3), and adalinine (4) (Figure 2).

1.1.3 History

As mentioned above, hemolymph is part of the ladybug chemical defense mechanism, used to deter predators, especially ants. The bitter taste of hemolymph was reported in the 18th century and referred to numerous times in the literature. In an early
study, Tursch and co-workers isolated some of the bitter alkaloids from hemolymph from 1600 ladybugs. The ladybugs were “blended” at room temperature in methanol and the blended material was subjected to centrifugation. The supernatant was separated and partitioned between methanol and \textit{n}-pentane. The researchers further fractionated the methanolic phase and monitored each subsequent extract by sampling it for the bitter taste indicative of the presence of the alkaloids. Once the bitter fractions were located, the fractions were concentrated and subjected to repeated column chromatography over alumina.

![Figure 3. Coccinelline and precoccinelline](image)

Two compounds were isolated and characterized from the purification. Coccinelline (5) was the major alkaloid and precoccinelline (6) was isolated in a much smaller quantity (Figure 3). Reduction of coccinelline with either ferrous sulfate or by catalytic hydrogenation (PtO$_2$) converted coccinelline to precoccinelline. It was determined that coccinelline was the compound responsible for the bitter taste of hemolymph but not its peculiar smell. The structure of coccinelline was first determined by mass spectrometry, NMR, UV, IR in 1971 and then definitely established by single-crystal X-ray diffraction analysis on the hemi-chloride of coccinelline.$^{4,5}$

1.1.4 Structural Sub-types

The alkaloids described thus far represent only a few of the ladybird alkaloids. The ladybird beetle excretes dozens of different alkaloids as part of its chemical defense system. Over 50 of these alkaloids have been isolated and characterized to date. These
alkaloids can be classified in several structural families including, pyrrolidines, piperdines, homotropanes, 2-methylperhydro-9b-azaphenalenes, azamacrolides, “dimeric” alkaloids, and long-chain and quinoline derivatives. As eluded to in section 1.1.3, the first compounds isolated from the ladybirds were coccinelline (5) and preococcinelline (6). These were followed by hippodamine (7), its N-oxide analog convergine, and myrrhine (8). All of these compounds belong to the 2-methylperhydro-9b-azaphenalene (9) family and are stereoisomers of each other (Figure 4). The structures of 6-8 (Figures 3 and 4) were determined by NMR and mass spectrometry. Even though the spectra are identical for 6-8 because they are all stereoisomers of each other, they were distinguished by IR spectroscopy.

![Figure 4. 2-Methylperhydro-9b-azaphenalene family](image)

### 1.1.5 Biology

Although the bioactivity of ladybug alkaloids is not well known, it is clear that they have insect repellant properties. For example, a 0.5% solution of coccinelline was mostly refused when given to a species of ants known to be thirsty.

Curiously, ladybugs exhibit a range of colors; and while the colors are attributed to beta-carotenoids, the colors themselves are not indicative of whether alkaloids are present. This class of alkaloids is present in gray-colored ladybugs such as Pullus auretius, Pullus suturalis, Rhizobius litura, and Aphidecta obliterate. Conversely, not all ladybugs that exhibit colors contain bitter alkaloids.
1.1.6 Biosynthesis

As previously mentioned, the ladybug alkaloids can be categorized into several classes of compounds. Laurent and co-workers have studied the biosynthesis of adaline (2) and adalinine (4), two alkaloids that belong to the piperdine family, which is related to the 2-methylperhydro-9b-azaphenalene family (9), to which hyperaspine belongs.\textsuperscript{11} If we examine the relationship between polyacetate structures and some of the ladybug alkaloids, this relationship becomes clearer (Figure 5).

\textbf{Figure 5.} Polyketoacid relationships
Hyperaspine (1), as well as adaline (2) and adalinine (4), are related alkaloids. In Figure 5, we can see how polyketoacid 10 can easily become the skeleton of what can later become hyperaspine (1), adaline (2), and adalinine (4). The asterisks in Figure 5 represent reduced ketones, to show how the linear chains are derived from polyacetates. The linear chain of polyketoacid 10 may react with ammonia, followed by a reductive amination, and then by a Mannich reaction to afford the key carbocycle skeleton 9. The hyperaspine skeleton (12) may be obtained in a similar manner. Polyketide 11 can react with ammonia to generate the imine, followed by a Mannich reaction and reaction with an equivalent of formaldehyde to install one more carbon. Finally the relationship between hyperaspine (1), adaline (2), and adaline (4) becomes clearer when we start with the same polyketide 11 and react it with ammonia followed by a Mannich reaction. These transformations suggest a relationship between structures that do not look like they are derived from the same biosynthetic pathway.

While the biosynthetic pathway of hyperaspine (1) has not been studied, there is a clearer understanding for adaline (2) and adalinine (4) due to isotope labeling studies. In a proposed biosynthetic pathway of (-)-adaline (2), the C\textsubscript{13} structure can be derived from the C\textsubscript{14} linear chain of polyketoacid 14 (Scheme 1). The asterisks denote C-14 isotope labels. The chain first undergoes a decarboxylation reaction. Once the chain is shortened, it undergoes reductive amination followed by intramolecular cyclization. Carbocycle 15 is formed and the tetrahydropyridine can undergo an intramolecular Mannich to afford (-)-adaline. Studies based on labeled acetate failed to prove the hypothesis because there was low incorporation of the acetate with C-14 radioisotopes. This is a known problem amongst these types of insects. A scheme for degrading (-)-adaline to benzoic acid (not shown here) was developed to isolate the one of the radioactively labeled carbons so that it was easier to detect the rate of incorporation. This experiment proved that adaline (2) was indeed derived from 14.
In a subsequent experiment, it was shown that there is a biogenetic relationship between adaline (2) and adalinine (4) and the enzymes that carry out this transformation are stereospecific. Radioactively labeled (-)-adaline was fed to four beetles for twenty days. The ladybug extract was monitored and analyzed by GC-MS. When the ladybugs were fed radioactive (+)-adaline, no radioactive adalinine was detected. This supports the hypothesis that adalinine is biosynthesized from adaline, and the enzymes that carry out this transformation are stereospecific. Although the biogenetic relationship was established, the researchers were unable to prove the mechanism for this transformation, but proposed that the mechanism must involve a retro-Mannich reaction.8

In a similar study, researchers in Belgium were able to prove that coccinelline was synthesized endogenously through a polyacetate pathway.4 Up until this point, it was not clear whether ladybugs were producing the alkaloids endogenously, or if they were obtaining it through their prey such as aphids. Coccinelline and precoccinelline were found in the eggs and larvae of ladybugs, but not in aphids.4 Radioactively labeled acetate was fed to ladybugs and was consequently detected in coccinelline that was produced. Although coccinelline and precoccinelline are synthesized endogenously, the data showed that there is no relation between the diet of ladybugs and alkaloid synthesis.
Hyperaspine – A Brief Review

1.2.1 Isolation of Hyperaspine

Lebrun and co-workers reported the isolation of hyperaspine (1) in 2001. A methanol extract obtained from 203 specimens of *Hyperaspis campestris*, a newly discovered tribe of the ladybird family collected in Bulgaria, gave 20 mg of a mixture of compounds. The extract was chromatographed over two successive silica gel columns, via flash chromatography [eluted in EtOAc/hexane/NH₄OH (8:2:0.1)], to afford 400 µg of a new compound that Lebrun and co-workers named hyperaspine.

1.2.2 Structure Elucidation

The structure of hyperaspine was determined using a combination of mass spectorometry, infrared spectroscopy and, largely, 1D and 2D NMR spectroscopy. High resolution mass spectrometry indicated the molecular formula to be C₁₉H₃₀N₂O₃ (m/z 334.2236). The base peak appeared at m/z 152.1070, calculated for C₉H₁₄NO, and indicated facile loss of a pentyl group and a pyrrole carboxylate moiety. The presence of the pyrrole carboxylate fragment was confirmed by the UV spectrum (λₘₐₓ 263 nm, ε 3650). A second diagnostic peak at m/z 263.1399, calculated for C₁₄H₁₀N₂O₃, indicated the loss of a pentyl chain; and thus, established the two major substituents of this novel alkaloid. The ¹H/¹H COSY, HMQC, and HMBC spectra revealed a perhydropyrido [1,2-c][1,3]oxazine skeleton (16), a secondary methyl group (d at δ 1.15, J = 6.6 Hz), a 2-pyrrolecarboxylate group, and a n-pentyl side chain based on comparison with data from the literature. The methyl group, pyrrole carboxylate, and pentyl side chain were placed at the C₃, C₆, and C₈, respectively based on COSY and HMBC correlations. A doublet at δ 4.22 and 4.77 ppm with identical large coupling constants (J = 10.8 Hz) signified geminal coupling; meaning that these two protons were isolated and between the oxygen and nitrogen. The proton at δ 4.22 had an HMBC correlation with three
carbons, while enhancing two proton signals. The other proton at δ 4.77 had an HMBC correlation with four carbons and two proton signals. The fourth carbon correlation signified W-coupling which would only occur for an equatorial proton. Once the C_1 position was firmly established, the other correlations became easier to decipher as well as the positions of substitution. The axial proton at C_1 had a nOe with two protons, both of which must be axial as well, therefore no substituent existed on this ring in the axial orientation. The next downfield proton was at δ 3.60, which must be the axial proton at C_3. The splitting pattern, (ddq, J = 12.0, 6.6, 4.2 Hz), could only occur with a methyl substituent attached to the same carbon to yield a quartet, otherwise it would just be ddd, with a large geminal coupling constant. Another proton signal of interest was the signal at δ 5.10 (dddd, J = 11.0, 11.0, 5.0, 5.0) which was a methine by $^{13}$C experiments. The downfield nature of the proton and carbon signified that this position was associated with the pyrrole carboxylate moiety. The final methine, therefore had to be associated with the pentyl side chain. $^1$H/$^1$H COSY and HMQC correlations determined that these methines were the C_6 and C_8 positions attached to the carboxylate and pentyl side chain, respectively.

Lebrun and co-workers speculated that hyperaspine preferred a cis conformation based on the lack of Bohlmann bands in the IR spectrum. In addition, the diastereotopic protons at C_1 had a coupling constant of $J_{\text{gem}} = 10.8$ Hz. This matched coupling constants for similar systems wherein the cis conformation gave a $J_{\text{gem}}$ of 10 Hz and trans conformations gave a $J_{\text{gem}}$ of 8 Hz.\textsuperscript{15,16}

The preferred conformation of hyperaspine (1) was assigned based on the behavior of similar alkaloids isolated from ladybugs. The preferred conformation was tentatively assigned the cis conformation 17 shown in Figure 7. The trans conformation
In this section, we focus on the conformational preferences of hyperaspine. Figure 7 illustrates the three-dimensional conformation of hyperaspine.

The cis conformation of hyperaspine is characterized by the 1,3-diaxial interaction between the pentyl side chain and the pyrrole ester. In addition to this steric interaction, there is an unfavorable dipole interaction between the nitrogen lone pair and the N,O-acetal oxygen lone pair. Both of these factors are absent in the cis conformation. In the cis conformation, both the pyrrole ester and pentyl side chain are equatorial. Additionally, the nitrogen lone pair aligns with the sigma star orbital of the C-O bond.

The structure of hyperaspine was eventually confirmed by total synthesis. In 2005, Braekman and co-workers prepared racemic hyperaspine. They were able to establish HPLC conditions to separate both enantiomers. They were then able to match the retention time of an authentic sample of hyperaspine with one of the enantiomers by co-injecting the samples. The synthetic enantiomer of interest was isolated by HPLC and the absolute configuration was established as 3S, 4aS, 6R, 8S, based on a comparison of retention times of both enantiomers of hyperaspine with synthetic hyperaspine prepared in other laboratories. The details of this synthetic work will be discussed in the next section.

Recall that one of the objectives of my research was to determine the absolute configuration of hyperaspine. The work of Braekman accomplished this and task and
thus, this objective became a moot point some time after my research began. Nonetheless, this objective influenced our synthetic plan. Hopefully this will be clear to the reader as I proceed. It is clear that “synthesis” was ultimately the tool used to determine the absolute configuration of 1.

1.2.3 Syntheses of Hyperaspine

Ma Synthesis of 8-epi-hyperaspine

The first attempt at a total synthesis of hyperaspine was carried out shortly after its isolation and structure determination, but failed to afford the relative stereochemistry established by Lebrun. This synthesis afforded 8-epi-hyperaspine (34). A synthesis of 34 is shown in Schemes 2-5. Ethyl acetoacetate was stereoselectively reduced to (S)-alcohol 19 using baker’s yeast. The alcohol was protected as the benzyl ether (20) with benzyl 2,2,2-trichloroacetimidate. The ester moiety was then partially reduced with DIBAL to the aldehyde, which was immediately subjected to a Wittig reaction to afford α,β-unsaturated ester 21.

Scheme 2. Synthesis of ester 23. (a) 2,2,2-trichloroacetimidate, TfOH, 78%; (b) DIBAL, (c) Ph₃P=CHCO₂Et, 90%; (d) (S)-benzyl-α-methylbenzylamine, n-BuLi, THF, 85%; (e) Pd(OH)₂/C, (f) TBDMScI/Et₃N, 77%.
In a diastereoselective Michael addition, lithium (S)-N-benzyl-α-methylbenzylamide was subjected to α,β-unsaturated ester 21 to provide the β-amino ester 22. The other diastereomer was not detected and therefore a 98% de was reported for this step. A transition state in which the lithium coordinates to both the oxygen of the ester and the nitrogen of the amine in a chair transition state was presented to rationalize the observed stereochemistry (Figure 8).

Figure 8. Diastereoselective Michael Addition

Hydrogenolysis of 22 over Pearlman’s catalyst removed both benzyl protecting groups. Silyl ether protection of the alcohol gave chiral β-amino ester 23.

Scheme 3. β-elimination problem. (a) 3-oxooctanoic acid ethyl ester, MgSO₄, 4 Å molecular sieves, 85%; (b) KOTBu, THF, Δ, 79%.

The synthesis continued with application of a method developed by Ma for assembling 4-hydroxy-2,6-disubstituted piperidines from β-amino acid derivatives. The plan was to
use this methodology to establish the relative stereochemistry at C_{4a} and C_8 of hyperaspine (Scheme 3). In the first step, silyl ether 23 was condensed with 3-oxooctanoic acid ethyl ester. In the original methodology, the procedure used acidic conditions. Since the silyl ether was acid labile, however, the reaction was run neat with MgSO\_4 and 4 Å MS to remove water. Under these mild conditions, vinylogous urethane 26 was obtained 85% yield. The next step was to cyclize the diester under Dieckmann conditions to generate unsaturated ester 27. Initially, sodium ethoxide in refluxing ethanol was employed. These conditions, however, afforded the β-elimination products 28 and 29. To reduce the amount of β-elimination, the base was changed to a large bulkier base, potassium tert-butoxide, which gave the desired condensation product 27. The β-keto ester was hydrolyzed and decarboxylated under reflux in aqueous NaOH to afford the vinylogous amide 30 (Scheme 4). The alcohol was reprotected as a silyl ether and the amine was protected with a BOC group to afford 31.

![Scheme 4](image)

**Scheme 4.** Synthesis of ketone 33. (a) aq. NaOH, EtOH, Δ, 81%; (b) TBDMSCl/imidazole, (c) n-BuLi; (BOC)_2O, 90%; (d) Pd/C/H\_2, MeOH, 95%; (e) TFA, (f) 37% HCHO, 80%.

The next task was reduction of the C\_7-C\_8 double bond. Whereas the authors expected the *trans* product, reduction of 31 by catalytic hydrogenation over palladium on
charcoal gave only cis-2,6-disubstituted piperidine 32. Cleavage of the protecting groups and formation of the N,O-acetal gave 33.

Several other methods of hydrogenation were also examined including sodium borohydride, sodium cyanoborohydride, and catalytic hydrogenations over platinum. Ma and co-workers also tried to hydrogenate the unprotected amine 30, but all cases resulted in the cis relationship between C\textsubscript{4a} and C\textsubscript{8}. It is likely that conformations which favored an axial disposition of the C\textsubscript{4a} substituent are responsible for the observed stereochemistry. This assumes that the course of this reaction is solely kinetically driven. Given the observed result, the Ma group was only able to synthesize the C\textsubscript{8}-epimer of hyperaspine. The synthesis was finished by reaction of ketone 33 with the L-Selectride at -78 °C to afford the axial alcohol, followed by esterification with pyrrole-2-carboxylic acid (Scheme 5).

![Scheme 5](image.png)

**Scheme 5.** Synthesis of hyperaspine isomer. (a) Pd/C/H\textsubscript{2}/MeOH; (b) 37% HCHO; (c) Dess-Martin oxidation, 90% (3 steps); (d) L-Selectride, THF, -78 °C; (e) pyrrole 2-carboxylic acid chloride, 66%.

The reduction of the ketone produced the opposite stereochemistry at C\textsubscript{6} to that required by hyperaspine. Thus, this total synthesis produced the incorrect relative stereochemistry at both the C\textsubscript{6} and C\textsubscript{8} positions (34).

**Ma’s Synthesis of Hyperaspine**

In a subsequent paper, Ma and Zhu synthesized hyperaspine with the proper relative stereochemistry.\textsuperscript{19} The synthesis utilized similar methodology, however the authors “bought” the C\textsubscript{8} stereogenic center, rather than hydrogenating the enamine. The synthesis (Schemes 6-7) started with the preparation of two intermediates, homopropargylic alcohol 36 and β-amino ester 38. Alcohol 36 was prepared by treating
ethyl propiolate with \( n \)-BuLi followed by trapping of the anion with (S)-propylene oxide (35) in the presence of a Lewis acid. \( \beta \)-Amino ester 38 was prepared by diastereoselective Michael addition of lithium (S)-N-benzyl-\( \alpha \)-methylbenzylamide to (E)-2-nonenonoic acid ethyl ester (37), followed by hydrogenolysis of the benzyl groups. Both intermediates (36 and 38) were combined in DMF to afford enamine 41 as an inseparable mixture of geometric isomers. Enamine 41 was hydrogenated, according methodology established in previous work, and the resulting mixture of stereoisomers was protected as the \( N,O \)-acetal using formaldehyde.²⁰,²¹ The 6.3:1 mixture (by \(^1\)H NMR) of isomers 42 and 43 resulting from the hydrogenation were inseparable by column chromatography.

Scheme 6. Diester synthesis. (a) ethyl propiolate, \( n \)-BuLi; BF\(_3\)·OEt\(_2\)/THF, -90°C, 87%; (b) lithium (S)-N-\( \alpha \)-methylbenzylamide; (c) Pd/C, H\(_2\), 89%; (d) DMF, 60-70°C, 83%.
Catalytic sodium ethoxide was added to the diester mixture to afford the expected Dieckmann product. A Krapcho decarboxylation provided ketones 44 and 45 which were separated by chromatography.

![Scheme 7. Synthesis of hyperaspine.](image)

The major product (45) was isolated in 60% yield from the mixture of 42 and 43. Reduction of the ketone with L-Selectride afforded axial alcohol 46 as a single isomer. Since this alcohol had the incorrect stereochemistry, the alcohol was inverted via Mitsunobu conditions and esterified to produce the (3S, 4aS, 6R, 8S)-hyperaspine (1). This was the first total synthesis of the correct relative stereochemistry of hyperaspine. Up until this point, the absolute stereochemistry of hyperaspine had not been established since very little material was procured from the isolation.

**Braekman Synthesis of hyperaspine**

In 2005, Braekman and co-workers published a total synthesis of (±)-hyperaspine and established the absolute configuration (Section 1.2.2). This synthesis began with anodic oxidation of piperidinone acetal 47, under Shono’s conditions, to afford N,O-acetal 48 (Scheme 8). The methoxy moiety was reacted with a silyl enol ether to install the
acetonyl group. The resulting ketone 49 was reduced with lithium tri-tert-butoxyaluminum hydride to afford the secondary alcohol 50. This well-known reaction was stereoselective. One rationalization of this observation is to invoke lithium coordination to the nitrogen of the piperidine ring and the carbonyl oxygen of the ketone (Figure 9). Hydride delivery from the bottom face of a chair transition state avoids steric interactions with the carbamate moiety.

![Chemical structure](image)

**Scheme 8.** Stereoselectivity of hydride reduction. (a) MeOH, K₂CO₃, Et₃N·OTs, 6.3 F/mol, 98%; (b) CH₂=C(OTMS)CH₃, TMSOTF, CH₂Cl₂, -78 °C, 76%; (c) LiAlH(O-tBu)₃, THF, 91%.

![Chemical structure](image)

**Figure 9.** Stereoselective Reduction of Ketone of 49

Continuing with the synthesis, the secondary alcohol was protected as acetate 51 and then a second anodic-oxidation was conducted to afford the N,O-acetal 52. The acetate
protecting group was removed to reveal the secondary alcohol which immediately cyclized to form cyclic carbamate 53.

![Chemical structure and reaction scheme](attachment:image)

Scheme 9. Synthesis of vinylogous amide. (a) Ac₂O, pyr., 82%; (b) MeOH, K₂CO₃, Et₄N-OTf, 16F/mol, 74%; (c) K₂CO₃, MeOH, 57%; (d) pTsOH, CH₂Cl₂, 100%.

At this point, the authors comment on the elucidation of the relative stereochemistry of 53 via coupling constants. They note the coupling constants show that the protons at C₄a and C₃ are axial to each other as well as the methoxy group at C₈. Satisfied with the relative stereochemistry at C₃ and C₄a, the stereocenter at C₈ was destroyed by elimination of methanol to give 54 as shown in Scheme 9.

![Additional chemical structures and reactions](attachment:image)

Scheme 10. Addition of pentyl side chain. (a) C₅H₁₁MgBr, CuCN, THF, -78 °C, 79%; (b) TMSOCH₂CH₂OTMS, TMSOTf, CH₂Cl₂, 90%.
The pentyl side chain was introduced as shown in Scheme 10. Enone 54 was subjected to a diastereoselective Michael addition utilizing an organocuprate to introduce the pentyl side chain. This reaction gave a 9:1 mixture of 55a and 55b, which were easily separable by chromatography. The relative stereochemistry at C3, C4a, and C8 were established via NOESY experiments at a later stage for N,O-acetal 59. For example, the most important correlations were between H1ax, H3ax, and H4a, between H4ax and H8ax, between H8ax and 9-CH3, and between H1eq and H8ax.

Scheme 11. Synthesis of hyperaspine core. (a) KOH, EtOH, reflux, 87%; (b) MeOH, HCl, 60 °C, 88%; (c) HCHO, MeOH, 94%.

In order to form the N,O-acetal from the carbamate, it was necessary to protect the ketone as ketal 56. The carbamate was hydrolyzed under basic conditions to give amino alcohol 57 (Scheme 11). The ketal was hydrolyzed to give ketone 58, which was then subjected to formaldehyde to form the desired N,O-acetal 59.

Scheme 12. Synthesis of hyperaspine. (a) NaBH₄, MeOH, 80%; (b) pyrrole-2-carboxylic acid, DMAP, Ph₃P, PhH, 33%.
Although the Ma group used L-Selectride to reduce ketone 59 to alcohol 60b, followed by inversion under Mitsunobu conditions to give 1, Braekman could not reproduce this result. It was hypothesized that alcohol 60a was too sterically congested to allow the inversion, resulting in esterification with retention of configuration. Instead of using L-Selectride, they used sodium borohydride to reduce the ketone into inseparable alcohols 60a and 60b (Scheme 12). The alcohols were esterified and the pyrrole esters were separated via column chromatography to afford hyperaspine (1) and its C6 epimer (61) (Scheme 12).

Comins’ Synthesis of (+)-hyperaspine

Comins and Sahn reported the most recent synthesis of (+)-hyperaspine.22 They utilized dihydropyridones as synthetic intermediates. This total synthesis provided another example of the wide utility of dihydropyridones to access a variety of alkaloids.

The synthesis began with treatment of 4-methoxy-3-(triisopropylsilyl)pyridine with (+)-TCC chloroformate to afford the 1-acyliminium salt 62. Comins then utilized the chiral N-acyliminium ion to induce stereochemistry on the aromatic ring through reaction of 63 with the zinc enolate of acetone. The resulting ketone (64) was reduced with L-Selectride followed by basic methanolysis to afford non-racemic alcohol 65 (98% de). The relative stereochemistry was confirmed via nOe analysis of the bicyclic carbamate that resulted when the alcohol was treated with phosgene and base. Comins and Sahn noted that, based on previous approaches, the bicyclic N,O-acetal had to be constructed early in the synthesis. After many different attempts, they found that they could use phase transfer-catalysis. Thus, alcohol 65 was treated with K2CO3, CH2Br2, and Aliquat 336 to afford the desired aminal 66. The TIPS group was protodesilylated in dilute acid to generate the dihydropyridinone 67 in near quantitative yield. As one can see, this intermediate is only a few steps from hyperaspine, which is why these synthetic intermediates are so attractive.
To complete the synthesis, treatment of the enone, with a pentylcuprate installed the \( n \)-pentyl side chain with complete diastereoselectivity to give 68a and 68b. Ma and Braekman had both reported unsuccessful stereoselective reductions of this bicyclic ketone. Comins and Sahn found that a dissolving metal reduction with lithium afforded the desired alcohol as the major diastereomer (Scheme 14). Acylation of the alcohol \textit{in situ} provided the final product in 50% yield (1).

**Scheme 13.** Synthesis of ketone 66. (a) LDA; ZnCl\(_2\); (b) H\(_3\)O\(^+\), >93% de, 72%, pure; (c) L-Selectride; (d) K\(_2\)CO\(_3\), MeOH, > 98% de, 80%; (e) 10% DMSO/THF, K\(_2\)CO\(_3\), CH\(_2\)Br\(_2\), Aliquat 336; (f) 10% HCl, THF, 97%; (g) C\(_5\)H\(_{11}\)MgBr, Cul, THF, -78 °C, 92%.

**Scheme 14.** Synthesis of hyperaspine. (a) Li/NH\(_3\), Et\(_2\)O, -55 °C, 70%; (b) Li/NH\(_3\); (c) pyrrole-2-COCl, TEA, 50%.
To summarize, hyperaspine represents an example of a ladybird alkaloid which shows some interesting structural features. We have briefly discussed some related alkaloids in the same family as hyperaspine, the biosynthetic origins of hyperaspine, as well as a brief survey of prior syntheses of hyperaspine. While the total synthesis of hyperaspine has been accomplished, each synthesis utilized a different methodology and approach from the one that will be presented in the next chapter. The next section will focus on the utility of N-acyliminium ion ring closure methodology can be applied towards the total hyperaspine.
CHAPTER 2

Background

2.1.1 Synthetic Plan

In this chapter I will present the results and discuss our approaches, towards a synthesis of hyperaspine. As was noted in section 1.1.1, the plan revolved around an $N$-acyliminium ion initiated cyclization which was to construct the $C_{4a}$-$C_5$ bond to construct the A-ring with control of $C_{4a}$ and $C_6$ stereochemistry. An outline of the plan is described below in Scheme 15:

Scheme 15. Retrosynthetic Plan
The synthesis was to begin with carboxylic acid 69 and alcohol 70. The carboxylic acid was to be converted to an isocyanate through a Curtius rearrangement and then trapped with alcohol 70 to form urethane 71. It was projected that the dimethyl acetal would then be deprotected to reveal the aldehyde, which would immediately condense with the urethane nitrogen to form N-acyliminium ion 72. Variations on this theme were also considered. For example it was imagined that the required oxidation state at C4a might also be accessed by oxidation of a C4a alcohol oxidation or reduction of a C4a carboxylic acid derivative.

Figure 10 illustrates why the N-acyliminium ion cyclization was expected to control the stereocenters at C4a and C6 of hyperaspine. The projected N-acyliminium ion 72 could cyclized from either conformation 72a or 72b.

Cyclization from conformation 72a would provide 73a if the cyclization involved anti-periplanar addition of the electrophilic N-acyliminium ion and nucleophile (hydroxide equivalent) across the carbon-carbon double bond. On the other hand, cyclization from conformation 72b, in a similar manner, would provide 73b. It was projected that conformation 72a would be lower in energy than conformation 72b due to the absence of allylic strain present in 72b (see Figure 11). Furthermore, it was projected that cyclization product 73a would be more stable than 73b for the same reason. Thus,
regardless of whether the cyclization had an early or late transition state, 73a was anticipated to be the product. Naturally 73a has precisely the stereochemistry required by hyperaspine if the C₆ pyrrole carboxylate was introduced with inversion of stereochemistry. In principle, if the stereochemistry could be independently controlled at C₈ (acid fragment) and C₃ (acetal fragment), the stereochemistry centers at C₄a and C₆ would follow as required.

It is notable that this plan suggests that diastereomers of 71 would be expected to provide diastereomers of hyperaspine in a predictable manner. For example, 74 would be expected to provide 75, the C₃ epimer of 73a. Cyclization substrate 76 would be expected to afford the enantiomer of 75, and substrate 78 would most likely give 79, the enantiomer of 73a.

With this plan in mind, we will briefly examine some background information about N-acyliminium ions and N-acyliminium ion initiated cyclizations.

Figure 11. Diastereomers of Hyperaspine.
2.1.2 \textit{N}-Acyliminium Ions

So what exactly are \textit{N}-acyliminium ions and why are they useful? If we examine a simple carbonyl such as an aldehyde or ketone \textbf{80} we can activate it via protonation (Figure 12). Likewise, we can use this same logic with an imine. Once protonated, we activate the imine \textbf{82} as an iminium ion \textbf{83}, rendering it more reactive.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{protonation.png}
\caption{Reactivity of Protonated Species}
\end{figure}

The Mannich and Pictet-Spengler reactions use this type of iminium ion chemistry to construct carbon-carbon and carbon-heteroatom bonds.\textsuperscript{24,25} The electrophilicity of iminium ions, however, may not be sufficient for some applications. If we take that same imine and place an electron-withdrawing group such as an acyl group on the nitrogen, we produce an iminium ion even more reactive than that derived from a simple protonation (\textbf{85}). Thus, in cases where the reactivity of a simple iminium ion is insufficient, one can acylate the imine to make it more reactive. This is known to be particularly useful for alkaloid synthesis as it serves as a platform for alpha amidoalkylation.\textsuperscript{26,27}

An example of how an iminium ion may not be reactive enough is shown in Figure 13. In Belleau’s synthesis of erythrinane,\textsuperscript{28} he was unable to form the spirocyclic
amine 87 via an iminium ion cyclization despite the electron-rich aromatic ring. Belleau changed his approach and generated an N-acyliminium ion intermediate, which cyclized to the spirocyclic lactam 89 upon treatment of a suitable precursor of 88 with polyphosphoric acid.

![Chemical structure](image.png)

**Figure 13.** N-Acyliminium ion reactivity.

One of the hallmarks of N-acyliminium ion cyclizations is stereoselectivity. Figure 14 illustrates an example by the Speckamp group where good stereocontrol is observed.29 The ethoxy group of 90 was ionized upon treatment with formic acid, and the resulting N-acyliminium ion 91 was presumably formed. Cyclization via antiperiplanar addition of the N-acyliminium ion and formate across the olefin (a typical electrophilic addition), via a chair-like transition state, rationalizes the stereochemical course of the cyclization.

![Chemical structure](image.png)

**Figure 14.** Stereocontrol of N-acyliminium ions.
Another example that serves as precedence for the proposed hyperaspine synthesis, is shown in Scheme 16. Dimethyl acetal amide 93 was treated with formic acid, presumably to afford the aldehyde, which reacted with the amide to form N-acyliminium ion 94. Cyclization of 94, with formic acid as the terminator, gave bicyclic lactam 95. The formate ester was hydrolyzed to afford alcohol 96 with the desired relative stereochemistry. With this background, we will now move to attempts to execute the proposed research.


2.1.3 Synthesis of Alcohol Fragment

The first steps toward execution of the plan shown in Scheme 15 involved the development of an enantioselective synthesis of 70. Preliminary work began with readily available and inexpensive ethyl acetoacetate 97. Reduction of 97 with baker’s yeast according to literature precedence gave (S)-alcohol 98 in 50% yield. This reaction provided large quantities of the desired alcohol, however, as we will see later, the % ee
was moderate and it would become necessary to purchase alcohol 98 in the actual synthesis towards hyperaspine. The alcohol was protected as an acetal with dihydropyran to generate THP ether 99a.

Scheme 17. Synthesis of Alcohol Fragment. (a) Baker's Yeast, sucrose, H2O, 50%; (b) DHP, CSA, Et2O, 0 °C; (c), LiAlH4, Et2O, 80% (2 steps); (d) SO3-pyridine, Et3N, DMSO-CH2Cl2, 80%; (e) MeOH, p-TsOH, 86%.

This reaction always gave 99a contaminated with bis-acetal 99b, presumably formed by addition of water to two moles of dihydropyran. The desired ester 99a could not be separated from 99b, although the ratio of 99a:99b was estimated to be 1.0:0.3 based on integration of appropriate signals in the 1H NMR spectra of the mixture. Treatment of the mixture of 99a and 99b with lithium aluminum hydride gave a mixture of alcohol 100 and 99b, which were easily separated by column chromatography over silica gel. The overall yield of 100 from 99a was 82%. It is interesting that 99b was obtained as a single diastereomer, presumably with the indicated stereochemistry based on the appearance of only 5 signals in its 13C spectrum. These signals in the 13C spectrum suggest symmetry in the molecule which upon inspection of 99b can occur from the meso compound or the C2-symmetric compound, which is the dl-pair (see Figure 15). The alcohol was oxidized to aldehyde 101 with sulfur trioxide-pyridine complex in the presence of triethylamine and dimethyl sulfoxide.31 We found that Swern oxidation
conditions were less satisfying as they did not completely convert the alcohol to the aldehyde, and approximately 50% of the starting alcohol was recovered. The THP ether was then removed and the aldehyde was protected in one step using excess methanol in the presence of a catalytic amount of p-toluenesulfonic acid to afford desired alcohol 70 in 86% yield.

It was necessary to determine the enantiomeric excess (% ee) of alcohol 70 before continuing with the synthesis. Recall that hyperaspine has four stereogenic centers thus it was important that both the C₃ and C₈ stereocenters of 73 have high optical purity to decrease the amount of minor stereoisomers that would make characterization difficult (see Figure 11). The Mosher ester method was used to determine the % ee of 70. Alcohol 70 was esterified with the (S)-Mosher’s acid (102) to afford ester 103a. The signals in the ¹⁹F NMR of spectrum 103a were not resolved, however, the ¹H NMR provided enough data to determine the enantiomeric excess. For example, the C₃ methine and C₄ methyl signals appeared at δ 4.42 and 1.31 in 103a and at δ 4.21 and 1.38 in 103b. Integration of these signals revealed a 92.5:7.5 ratio of 103a and 103b respectively. This reflects an 85% ee for alcohol 70 (assuming no kinetic resolution occurred in the esterification), which is what we will call “Baker’s Yeast alcohol.” When a sample of 70 prepared from commercially available (S)-98 was analyzed in the same manner, it had an enantiomeric excess of 98%. Clearly the route with purchased alcohol was superior.
2.1.4 Synthesis of Alternate C₃-C₄a Fragments

In section 2.1.1 it was mentioned that acid and alcohol oxidation states at C₄a were also anticipated to provide an entry to the required N-acyliminium ion 72. This is shown in more detail in Scheme 18.

![Diagram](attachment:image)

**Scheme 18.** Different Routes to Intermediate 72

The necessary C₃-C₄a fragments for these alternative plans were prepared as shown in Scheme 19. Beginning with previously prepared THP-ether alcohol 99, the alcohol was esterified with pivaloyl chloride to provide pivalate ester 107 in 89% yield. The THP-ether was removed via an acetal exchange reaction with methanol under catalytic acidic conditions to afford pivalate alcohol 108 in 80% yield. Finally, commercially available acid 109 was esterified to give thioester 110 using 1,3-dicyclohexylcarbodiimide, 4-dimethylaminopyridine, and benzenethiol in 47% yield.34

![Diagram](attachment:image)

**Scheme 19.** Alternate alcohol fragments. (a) PivCl, Et₃N, CH₂Cl₂, 89%; (b) MeOH, p-TsOH, 80%. (b) DCC, 4-DMAP, PhSH, 47%.
2.1.5 Synthesis of Carboxylic Acid Fragment

The second integral piece required by the plan described in Scheme 15 is chiral carboxylic acid 69. Both enantiomers of the carboxylic acid were synthesized in order to investigate the influence of allylic strain on the stereochemical course of the $N$-acyliminium ion cyclization. It was hypothesized that the substituent at $C_8$ would be solely responsible for dictating the relative stereochemistry at $C_{4a}$ and $C_6$. For example, it was predicted that 74 would give 75 (Figure 11) and the diastereomers 78 would provide only 79 (see Figure 11). This point will become clearer when we discuss the model systems later in the chapter.

The synthesis of 69a began with the natural isomer of norephedrine (111a), which was heated with diethyl carbonate under basic conditions to afford oxazolidinone 112a in quantitative yield (Scheme 20). The anion derived from oxazolidinone 112a and $n$-BuLi was $N$-acylated with heptonyl chloride at -70 °C to give imide 113a (Scheme 20) in 80% yield. Deprotonation of imide 113a with sodium hexamethyldisilazane at -100 °C, followed by alkylation of the enolate with allyl bromide gave 114a in 72% yield. The chiral auxiliary was removed with basic hydrogen peroxide to generate desired (S)-carboxylic acid 69a in quantitative yield. This stereoselective synthesis uses methodology developed by the Evans laboratories that has been widely used. The auxiliary can be recycled and used again in the synthesis. The same synthesis was utilized to prepare (R)-carboxylic acid 69b as described in Scheme 21 without comment.
Scheme 20. (S)-Carboxylic Acid. (a) CO(OEt)$_2$, K$_2$CO$_3$, $\Delta$, 100%; (b) CH$_3$(CH$_2$)$_3$COCl, n-BuLi, -70 ºC, 80%; (c) NaHMDS, CH$_2$=CHCH$_2$Br, -100 ºC $\rightarrow$ -70 ºC, 72%; (d) 30% aq. H$_2$O$_2$, LiOH·H$_2$O, CH$_2$Cl$_2$, 0 ºC $\rightarrow$ rt, 100%.

Scheme 21. (R)-Carboxylic acid. (a) CO(OEt)$_2$, K$_2$CO$_3$, $\Delta$, 74%; (b) CH$_3$(CH$_2$)$_3$COCl, n-BuLi, -70 ºC, 88%; (c) NaHMDS, Allyl-Br, -100 ºC $\rightarrow$ -70 ºC, 85%; (d) 30% aq. H$_2$O$_2$, LiOH·H$_2$O, CH$_2$Cl$_2$, 0 ºC $\rightarrow$ rt, 100%.
The enantiomeric excess of both carboxylic acids had to be determined, Mosher esters of the alcohols derived from reduction of acids 69a and 69b were not helpful. No well-resolved signals were observed in either the $^{19}$F or $^1$H or $^{13}$C NMR spectra of these esters. The $^{13}$C NMR of imide 114a, however showed diagnostic signals for the minor diastereomer (115). Authentic diastereomer 115 was synthesized in 45% yield by acylating oxazolidinone 112a with the acid chloride of (R)-carboxylic acid 69b. A standard solution of imide 114a was prepared in a NMR tube and 1% aliquots of imide 115 were sequentially added to measure the level at which it could be detected. This was repeated for imide 114b. It was determined that the level of detection was at least 4% for imide 114a, thereby suggesting an enantiomeric excess of 92% for this material and thus, acid 69a. The same $^{13}$C analysis for imide 114b detected as little as 3% of the minor diastereomer, thereby suggesting an enantiomeric excess of 94% for 114b and the derived acid 69b.

![Diastereomeric Imides](image)

**Figure 17.** Diastereomeric Imides.

### 2.1.6 Attempts to Generate N-Acyliminium ion 72 via Alcohol 106

We will now move to the critical stage of this project, generation and cyclization of N-acyliminium ion 72. As a reminder, three approaches to this ion had been imagined (see Section 2.11). These are reported graphically in Scheme 22. We will first examine Path A. The required urethane 106 was prepared as shown in Scheme 23:
Treatment of carboxylic acid 69a with diphenylphosphoryl azide and triethylamine under reflux generated the isocyanate in situ. The isocyanate was trapped with alcohol 70 (2.1 equivalents) to afford urethane 116 in a modest 49% yield. The pivalate group was removed via aminolysis to reveal alcohol 106 in quantitative yield. From here we attempted to oxidize the alcohol to the aldehyde with the Dess-Martin periodinane, however, neither cyclized product nor starting material was isolated. 35
\(^1\)H NMR analysis of reaction mixture suggested that the corresponding carboxylic acid had occurred (Figure 18). The \(^1\)H NMR exhibited a peak in the carboxylic acid region, while lacking any appropriate signals for materials derived from the \(N\)-acyliminium ion, or the starting material. This approach was abandoned and we next turned to Path B.

![Figure 18. Dess-Martin Oxidation](image)

### 2.1.7 Attempts to Generate \(N\)-Acyliminium Ion 72 via Acid Derivatives Such as 104 and 105

Since the alcohol oxidation state did not produce any desired results, our efforts turned to the carboxylic acid oxidation state. (S)-Carboxylic acid 69a was converted to the isocyanate using conditions similar to those previously described (diphenylphosphoryl azide), however, the readily available and inexpensive ethyl \(\beta\)-hydroxybutyrate was used to trap the isocyanate to give the corresponding urethane (118) (see Scheme 24). We tried to proceed from 118 in two ways: (1) reduction of 118 to the aldehyde and (2) cyclization of 118 to the imide followed by reduction of the imide to the aldehyde oxidation state. The first approach met with failure. Even reagents such as LiBH\(_4\) in various solvents, NaBH\(_4\) in methanol, and LiAlH\(_4\) in diethyl ether gave none of the expected alcohol.\(^{37}\) The second approach was also disappointing. Reagents such as NaH in tetrahydrofuran and AlMe\(_3\) (known to cyclized esters) gave none of the desired imide.\(^{38}\)
Given these disappointing results, a different approach to imide 120 was investigated based on the following literature precedent. Shibuya had shown that phenylisothiocyanate and 82 could be converted to afford imide 120 as shown in Scheme 25.  

This reaction was repeated as a technique check in 31% yield. Encouraged by this result, we moved to the model system shown in Scheme 27. Commercially available n-butylamine (121) was converted to thioisocyanate 122 in 77% yield by reacting the amine with carbon disulfide and base, followed by hydrogen peroxide (Scheme 27). The thioisocyanate was subjected to 3-hydroxybutyric acid, silver trifluoracetate, and triethylamine to afford the desired cyclized product 123 in 3% yield. Despite the low yield, enough material was procured to use in the next reaction. The most reactive carbonyl group of the imide was reduced to the hemiaminal using sodium borohydride-HCl in ethanol. Treatment of this crude product with p-toluenesulfonic acid gave N,S-acetal 124 in 48% overall yield.
Encouraged by these results, but disappointed with the poor yield of 123, we attempted to access this imide through a different route. The plan was to return to Scheme 22, but to replace the ester with a more reactive thioester. In practice (Scheme 27), commercially available butyl isocyanate (125) was trapped with previously prepared thioester 110 to afford urethane 126 in 60% yield. Again, we attempted to cyclize the urethane under basic conditions (NaH), however, a mixture of products was obtained (Scheme 27). The β-substituted thioester (127) was isolated in 26% yield and amide 130 was isolated in 24% yield.

The structures of these products were apparent from their spectral data. In addition, a mixture of 128 and 129 was isolated as an inseparable 3:2 mixture, respectively. The yields of 128 and 129 were 35% and 24%, respectively, based on the aforementioned
ratios. The formation of these products can be rationalized by the events shown in Scheme 28.

![Scheme 28. Mechanism for Formation of Products 127-130.]

Given the disappointing results shown in Schemes 25-27 we next turned to Path C (Scheme 22).

### 2.1.8 Attempts to Generate N-Acyliminium Ion of 72 via urethane 71

The original retrosynthetic plan (Scheme 15) involved urethane intermediate 71. Our efforts began with attempts to prepare this key intermediate. The aforementioned (S)-carboxylic acid 69a was treated with diphenylphosphoryl azide and triethylamine in refluxing benzene to afford the corresponding isocyanate in situ (Scheme 29). The isocyanate was trapped with dimethyl acetal 70 to afford urethane (38%) as well as urea 131 (10%). Under these conditions it was impossible to avoid formation of urea 131. This side product was presumed to be formed from amine 134 and isocyanate 135. Amine 134 was most likely formed by hydrolysis of the isocyanate by water, or by β-elimination of from a possible aldehyde (or enol) intermediate (Figure 19). For example, acid-mediated hydrolysis of 71 might give 132. The proton alpha to the aldehyde might
be deprotonated, followed by expulsion of the carbamate and loss of carbon dioxide to give amine 134. Reaction of the primary amine with another molecule of isocyanate 135, formed from the Curtius rearrangement, would afford the observed urea 131.

Formation of the urea proved to be problematic since initial column chromatography efforts over silica gel could not separate the two products (71 and 131). NMR analysis of the mixture of products suggested that the ratio of desired product and urea was 8:1. An initial attempt to cyclize intermediate 71 via \(N\)-acyliminium ion, however, gave only unidentified decomposition products. TLC and NMR analysis. At this point, we directed our efforts towards model studies.

Up until this point, pure urethane 71 had not been obtained and it was thought that this might be the source of problems. Therefore, we focused on the preparation of pure isocyanate 135, since this seemed to be the crucial step. Recall that carboxylic acid 69a
was treated with diphenylphosphoryl azide and triethylamine, which also afforded organophosphorous compounds as reaction products. The isocyanate was too reactive to purify by column chromatography. It seemed logical to prepare the isocyanate by another method if this was indeed the source of problems, but first we decided to use a simpler isocyanate in model studies.

2.1.9 Model studies with aldehyde oxidation state

Butyl Isocyanate

Since \( n \)-butylisocyanate (136) was commercially available, this became the starting point of our model studies. Aliphatic isocyanate 136 was reacted with racemic dimethyl acetal 137 in refluxing benzene to afford urethane 138 in 73% yield (Scheme 29).

This result suggested that if isocyanate 135 could be generated as a pure material, the synthesis of urethane 71 as a pure material should be possible. We next tried to accomplish the initial cyclization of the B-ring through the ionization of the acetal. Urethane 138 was reacted with (\(-\))-camphorsulfonic acid in methanol at room temperature and then heated to reflux. No reaction occurred. The solvent was changed to ethanol in order to observe whether any ionization was occurring by looking for a mixed acetal. No reaction occurred in this solvent. Finally the solvent was changed to methylene chloride and the desired cyclization occurred within six hours in 52% yield to afford \( N,O \)-acetal 139. Further examination of 139 revealed a 5:1 mixture of the trans:cis isomers. This ratio was based on integration of \(^1\)H NMR signals at \( \delta \) 4.59 (139a) and 4.74 (139b).

![Scheme 30](image)

**Scheme 30.** Butyl isocyanate model system. (a) \( rac \)-4,4-dimethoxybutan-2-ol (137), PhH, \( \Delta \), 73%; (b) CSA, \( \text{CH}_2\text{Cl}_2 \), 52%.
The relative stereochemistry of the major product was determined through analysis of nOe and $^1$H NMR spectra. The following is a summary of the key nOe enhancements observed for the major and minor diastereomers 139a and 139b:

![Chemical Structure](image)

**Proton Irradiated** | $\delta$ (ppm) | nOe observed (%) | $\delta$ (ppm) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C(5)OCH$_3$</td>
<td>3.36</td>
<td>0.25 C(4)H eq</td>
<td>2.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.41 C(5)H eq</td>
<td>4.41</td>
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<tr>
<td>C(5) H</td>
<td>4.41</td>
<td>1.96 C(4)H eq</td>
<td>1.65</td>
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<tr>
<td></td>
<td></td>
<td>0.83 C(4)H ax</td>
<td>2.05</td>
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<td></td>
<td>0.77 C(7)H</td>
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<td>1.25 C(5)OCH$_3$</td>
<td>3.36</td>
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<td>0.68 C(7)H</td>
<td>3.53</td>
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<tr>
<td>C(3) H</td>
<td>4.59</td>
<td>1.51 C(3)CH$_3$</td>
<td>1.35</td>
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<td></td>
<td>0.73 C(4)H eq</td>
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<tr>
<td></td>
<td></td>
<td>0.19 C(5)OCH$_3$</td>
<td>3.36</td>
</tr>
</tbody>
</table>

![Chemical Structure](image)

**Proton Irradiated** | $\delta$ (ppm) | nOe observed (%) | $\delta$ (ppm) |
<table>
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<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C(5) H</td>
<td>4.74</td>
<td>0.90 C(4)H eq</td>
<td>2.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.42 C(5)OCH$_3$</td>
<td>3.30</td>
</tr>
</tbody>
</table>

*Table 1.* Summary of key nOe signals for 139a and 139b.

From the data it was apparent that 139a is the major isomer because of the proximity of the C$_3$ proton and the methoxy substituent at C$_5$. Conversely, we saw a proximal relationship between the C$_5$ proton and the C$_4$ equatorial proton, but no significant nOe
with the C₃ substituents. We speculate that the C₃ proton is in the axial position in 139b and is too far away from the C₅ axial proton to register a signal enhancement in the minor diastereomer. The major isomer has no allylic strain between the N-butyl side chain and the methoxy group and allows the methyl substituent to be equatorial. We will see that this observation is also seen in the next model system. Given this encouraging result, we next moved to a model system in which we could examine an N-acyliminium ion cyclization.

4-Pentenoic Acid

Encouraged by these results, we moved to the 3-buten-1-yl isocyanate (140d). It was anticipated that this isocyanate would provide an N,O-acetal of type 139, only with an olefin in the side chain that could be used to model the key N-acyliminium ion cyclization.

The simplest way to prepare the required isocyanate was to begin with commercially available 4-pentenoic acid 140a. 4-Pentenoic acid (140a) was reacted with an equimolar amount of oxalyl chloride at 0 °C for six hours and then distilled at reduced pressure to afford the pure acid chloride 140b in 82% yield.

Scheme 31. 4-Pentenoic acid model system. (a) (COCl)₂, 0 °C; (b) NaN₃, acetone-H₂O; (c) rac-4,4-dimethoxybutan-2-ol (140e), 38%; (d) CSA, CH₂Cl₂, 66%; (e) HCOOH, CH₂Cl₂, 57%; (f) NaOH, H₂O, MeOH, 87%; (g) IBX, CH₃CN, Δ, 29%.
The acid chloride was dissolved in reagent-grade acetone and cooled to 0 °C. Sodium azide was dissolved in a minimal amount of water and added to the cooled solution to afford acyl azide 140c. The acyl azide was used without purification and redissolved in benzene and heated under reflux to afford the isocyanate 140d in situ. The isocyanate was treated with dimethyl acetal 137 to afford urethane 141 in moderate yield (38%). The urethane was also treated with camphorsulfonic acid, similar to the system previously mentioned, in methylene chloride to afford a mixture of $N,O$-acetals 142a and 142b in 66% yield. Based on the saturated system (139a and 139b), 142a was expected to be the major product. $^1$H and $^{13}$C NMR analysis showed that there was largely one isomer, as opposed to the 5:1 mixture in the saturated system. A summary of the key nOe signals are presented in Table 2 for isomer 142a.

From Table 2 we can see that there is a nOe between the methoxy substituent at C5 and the proton at C3, while no relationship exists between the methoxy group at C5 and the methyl group at C3. This is the key signal which clearly shows the methoxy substituent and methyl substituent are trans to each other and one of the substituents is in the axial position. We would not expect to see a nOe between these substituents if they were both equatorial.

<table>
<thead>
<tr>
<th>Proton Irradiated</th>
<th>$\delta$ (ppm)</th>
<th>nOe observed (%)</th>
<th>$\delta$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(5)OCH$_3$</td>
<td>2.77</td>
<td>0.93 C(4)H eq</td>
<td>1.33</td>
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<tr>
<td></td>
<td></td>
<td>1.49 C(5)H</td>
<td>3.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.83 C(3)H</td>
<td>4.41</td>
</tr>
<tr>
<td>C(5) H</td>
<td>3.90</td>
<td>1.30 C(4)H ax</td>
<td>1.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.90 C(4)H eq</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85 C(8)H</td>
<td>2.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.23 C(5)OCH$_3$</td>
<td>2.77</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.85 C(7)H</td>
<td>3.19</td>
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<tr>
<td></td>
<td></td>
<td>0.76 C(7)H</td>
<td>3.54</td>
</tr>
<tr>
<td>C(3) H</td>
<td>4.31</td>
<td>1.43 C(3)CH$_3$</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.49 C(4)H eq</td>
<td>1.33</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 C(5)OCH$_3$</td>
<td>2.77</td>
</tr>
</tbody>
</table>

*Table 2. Summary of nOe signals for 142a.*
in the 1,3 position and trans. The splitting pattern of the proton at C₃ confirms that the proton is in the axial position (see appendix).

We now had a substrate with which we could generate the N-acyliminium ion. N,O-acetal was reacted with concentrated formic acid, and to our delight, we were able to close the A-ring to afford a mixture of isomers 143a and 143b along with other materials.

It was clear from NMR analysis that we had the desired bicyclic compound; however, it was unclear what relative stereochemistry had been produced and which isomer was the major compound, because there were three stereogenic centers. We were able to tentatively assign the relative stereochemistry between C₄ₐ and C₆, but C₃ remained unclear. Table 3 summarizes some of the key nOe’s between relevant signals. We arbitrarily assigned H₄ₐ in the axial position assuming that the formate ester would occupy the equatorial position. We also based this assumption on the splitting pattern of H₆. H₆ had a triplet of triplet pattern (J = 10, 5 Hz), which indicated that it was split from H₇eq and H₅eq (J = 5 Hz), and then split from the protons trans to it at the same positions (J = 10 Hz). If H₆ were equatorial, we would not see a clear distinct pattern such as the tt pattern that was observed; we would expect to see a pentet if it were equatorial.

Additionally, from the table we can see that there is a significant relationship between H₄ₐ, H₆, and H₈ax. From subsequent experiments, we were able to establish that the
methyl group was in the axial position, however, the nOe data from 143a and 143b did not elucidate this orientation. Since we were unable to definitively assign the relative stereochemistry for all compounds produced in the cyclization of 142, we attempted destroy one of the stereogenic centers to make the analysis simpler. The formate ester was hydrolyzed with aqueous sodium hydroxide to alcohol 144 in excellent yield (87%). The $^1$H NMR was extremely complex (see appendix), but both $^{13}$C NMR and HRMS suggested that the desired alcohol had been obtained. We next attempted to oxidize the mixture of alcohols to a C$_6$ ketone. Thus, the presumed mixture of alcohols 144 was treated with IBX in refluxing acetonitrile to give enamides 145a and 145b.

<table>
<thead>
<tr>
<th>Varshneva (500 MHz) δ ppm</th>
<th>H/C</th>
<th>Brackman (300 MHz)δ ppm</th>
</tr>
</thead>
</table>

$^1$H data

<table>
<thead>
<tr>
<th>1.47 (d, $J = 7$ Hz, 3H)</th>
<th>CHCH$_3$</th>
<th>1.47 (d, $J = 6.2$ Hz, 3H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.88 (broad q, $J = 11.6$ Hz, 1H)</td>
<td>CHCH$_2$CH</td>
<td>1.88 (broad q, $J = 11.6$ Hz, 1H)</td>
</tr>
<tr>
<td>2.23 (ddd, $J = 14$, 3.6, 1.9 Hz, 1H)</td>
<td>CH$_2$C=O</td>
<td>2.23 (ddd, $J = 14$, 3.6, 1.9 Hz, 1H)</td>
</tr>
<tr>
<td>2.51 (m, 2H)</td>
<td>OCHCH$_2$</td>
<td>2.51 (m, 2H)</td>
</tr>
<tr>
<td>4.14 (m, 1H)</td>
<td>NCH</td>
<td>4.14 (m, 1H)</td>
</tr>
<tr>
<td>4.57 (m, 1H)</td>
<td>OCH</td>
<td>4.57 (m, 1H)</td>
</tr>
<tr>
<td>5.52 (d, $J = 8.3$ Hz, 1H)</td>
<td>=CHC=O</td>
<td>5.52 (d, $J = 8.3$ Hz, 1H)</td>
</tr>
<tr>
<td>8.01 (d, $J = 8.3$ Hz, 1H)</td>
<td>=CHN</td>
<td>8.01 (d, $J = 8.3$ Hz, 1H)</td>
</tr>
</tbody>
</table>

$^{13}$C data

| 21.1 C$_9$ | 21.1 C$_9$ |
| 35.9 | 35.9 |
| 42.4 | 42.4 |
| 53.7 | 53.7 |
| 74.7 C$_3$ | 74.7 C$_3$ |
| 110.0 C$_7$ | 110.0 C$_7$ |
| 143.8 C$_8$ | 143.8 C$_8$ |
| 150.2 C$_1$ | 150.2 C$_1$ |
| 192.2 C$_6$ | 192.2 C$_6$ |

C$_4$, C$_{4s}$, C$_5$

Table 4. Comparison of data for 145b.
The overoxidation at C7 and C8 was a surprise, but after the fact is reasonable based on the known oxidation of ketones to enones with this reagent.\textsuperscript{35c} In fact, this overoxidation was fortunate because 145b is an intermediate in the Braekman synthesis hyperaspine. We compared the spectral data provided by Braekman for 145b, and indeed, the data matched (\textsuperscript{1}H and \textsuperscript{13}C) (see Table 4).

\begin{table}
\centering
\begin{tabular}{lccc}
Proton Irradiated & \(\delta\) (ppm) & nOe observed (%) & \(\delta\) (ppm) \\
\hline
C(3)CH₃ & 1.49 & 1.44 C(4a)H & 1.60 \\
& & 1.50 C(3)H & 4.80 \\
C(4a)H & 4.80 & 1.23 C(3)CH₃ & 1.49 \\
& & 2.14 C(4)H & 4.63 \\
\hline
\end{tabular}
\caption{Summary of nOe signals for 145a and 145b.}
\end{table}

The spectral analysis became easier with one stereogenic center destroyed, but the isomers were still inseparable. Nonetheless, it was apparent that the 145a and 145b had been formed as a 2:1 mixture, respectively. Further inspection of nOe data (summarized...
in Table 5) confirmed 145a was the major stereoisomer. For example, there was a significant nOe between H₄ₐ and the methyl group at C₃ in 145a which was lacking in 145b. The stereoisomers were inseparable and nOe data obtained for 145a and 145b were extracted from a mixture of these isomers as well as some minor undetermined products, but gave valuable information about the relative stereochemistry of 145a and 145b. Recall from our earlier discussion of the N-acyliminium ion cyclization approach to hyperaspine, both allylic strain and the propensity of the C₃ methyl group to be equatorial were expected to cooperate to yield the appropriate stereochemistry (Figure 20). The stereochemical outcome of the cyclization of 142 to 143a and 143b suggests that C₃ methyl group is not as important as initially hypothesized. In fact it seems that the effect of the methyl group is minimal at best (2:1).

Figure 20. Stereochemical outcome of N-acyliminium ion.

The outcome of both model systems (Schemes 30-31) were encouraging. Not only were we able to synthesize the elusive urethane substrate in respectable yields and purity, but we were also able to demonstrate that the N-acyliminium ion ring closure could be extended to systems with the urethane functional group. This novel extension is the first of its type.
We next returned to the total synthesis of hyperaspine. The methodology of converting 4-pentenoic acid to the isocyanate 140d and urethane 141 was applied to (S)-carboxylic acid 69a (Scheme 32). Carboxylic acid 69a was converted to acid chloride 146 upon treatment with a stoichiometric amount of oxalyl chloride at 0 °C. The excess volatiles were removed in vacuo and acid chloride 146 was reacted with sodium azide dissolved in aqueous acetone afford the desired acyl azide 147. The acyl azide was immediately used for the Curtius rearrangement. The presumed intermediate isocyanate 148 was trapped with alcohol 70 to afford desired urethane 71 in 45% yield after purification by column chromatography. Satisfied with the purity of the urethane (71), we were now able to attempt conversion to the N,O-acetal corresponding to 139 (Scheme 30) or 142 (Scheme 31). The attempts are summarized in Table 6.

![Scheme 32. Alternate preparation of urethane 71. (a) (COCl)_2, 0 °C; (b) NaN₃, acetone-H₂O, 0 °C; (c) PhH, Δ; (d) alcohol 70, 45%.](image)

Our first attempt naturally began with CSA. Similar to the model systems described earlier, we began with catalytic amounts of CSA at room temperature. None of
the desired $N,O$-acetal was detected by NMR. Increasing the concentration of CSA and increasing the temperature led to no improvement. The same process was repeated with the acids listed in Table 6. The results from each attempt basically yielded no results. We were able to identify crotonaldehyde (in small amounts) by $^1$H NMR spectroscopy. None of the desired $N,O$-acetal, however, was obtained.

The identification of crotonaldehyde suggested a $\beta$-elimination was occurring. The primary amine, however, was not isolated. An authentic sample of the primary amine was prepared as shown in Scheme 32. It was still difficult to determine whether

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Equivalents</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Crotonaldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSA</td>
<td>0.05 $\rightarrow$ 1.0</td>
<td>CH$_2$Cl$_2$</td>
<td>r.t $\rightarrow$ Δ</td>
<td>yes</td>
</tr>
<tr>
<td>TFA</td>
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<td>r.t $\rightarrow$ Δ</td>
<td>yes</td>
</tr>
<tr>
<td>BF$_3$·OEt$_2$</td>
<td>0.05 $\rightarrow$ 1.0</td>
<td>CH$_2$Cl$_2$</td>
<td>r.t $\rightarrow$ Δ</td>
<td>yes</td>
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<tr>
<td>TiCl$_4$</td>
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<td>CH$_2$Cl$_2$</td>
<td>r.t $\rightarrow$ Δ</td>
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<tr>
<td>TMSOTf</td>
<td>0.05</td>
<td>CH$_2$Cl$_2$</td>
<td>r.t $\rightarrow$ Δ</td>
<td>yes</td>
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<tr>
<td>Benzenesulfonic Acid</td>
<td>0.05</td>
<td>PhH</td>
<td>r.t $\rightarrow$ Δ</td>
<td>no</td>
</tr>
<tr>
<td>$p$-TsOH</td>
<td>0.05 $\rightarrow$ 1.0</td>
<td>PhH</td>
<td>r.t $\rightarrow$ Δ</td>
<td>yes</td>
</tr>
</tbody>
</table>

Table 6. Cyclization Attempts.
the primary amine was formed. This brought my efforts towards hyperaspine to a conclusion.

**Scheme 33.** Synthesis of racemic amine 155. (a) CH₃(CH₂)₅COCl, n-BuLi, -70 °C; (b) NaHMDS, CH₂=CHCH₂Br, -70 °C, 69%; (c) 30% aq. H₂O₂, LiOH·H₂O, CH₂Cl₂, 0 °C→rt, 100% (d) Δ, t-BuOH, 35%; (e) TFA 68%.

**Conclusions and Future Directions**

Despite the inability to utilize an N-acyliminium ion cyclization in a total synthesis of hyperaspine, we were still able to demonstrate an extension of this methodology in the model systems. As previously stated, the substrates for generating an N-acyliminium ion has not included urethanes, and the 4-pentenoic acid model system was the first of this kind.

It is apparent that the branched hydrocarbon interfered with the cyclization of 71 to N,O-acetal 149. All of the different oxidation states at C₄a were investigated, and through the model systems, the aldehyde oxidation state was the one with the most encouraging results.

The minimal results obtained with 71 suggest that the acids we had hoped would “activate” the acetal for cyclization to 156, also activates the methane oxygen (or oxygens) such that β-elimination competes with cyclization (perhaps to the exclusion of
cyclization). A logical solution to this problem would be to move to a substrate of type 156. The thioacetal could be activated by “soft” Lewis acids that would be more likely to ignore the “hard” Lewis base oxygens of the urethane. In this way, one might be able to turn on the desired ionization and avoid the presumed β-elimination problem. A logical first choice for a soft Lewis acid would be Hg$^{2+}$, which has a high affinity for sulfur (in fact, this is where the term “mercaptan” comes from). Only time and experimentation would determine if this proposed continuation of the $N$-acyliminium ion approach to hyperaspine would succeed.

![Scheme 34. Thioacetal](image)

In conclusion, although we were not able to successfully synthesize hyperaspine, we were still able to demonstrate that $N$-acyliminium ion cyclizations are useful on substrates with a urethane functional group. The branched chain of the substrate for hyperaspine limited our ability to demonstrate that while $N$-acyliminium ions can construct this carbon-carbon bond, it can do so in a stereoselective manner.
CHAPTER 3
EXPERIMENTAL PROCEDURES

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on Bruker DPX-250, Bruker DPX-400, or Bruker DRX-500 spectrometers and are recorded in parts per million from internal chloroform, benzene, methylene chloride on the δ scale and are reported as follows: chemical shift [multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, m=multiplet), coupling constant(s) in hertz, integration, interpretation]. ¹³C NMR data were recorded and on either a Bruker DPX-400 or Bruker DRX-500 spectrometer and are reported as follows: chemical shift (multiplicity as determined from DEPT and/or HMQC experiments). ¹H NMR and NOESY experiments were recorded on a Bruker DRX-500 spectrometer and samples were degassed by three consecutive freeze-pump-thaw cycles using liquid nitrogen and house vacuum, followed by back-filling with argon.

Unless otherwise, noted, all reactions were carried out under argon or nitrogen using flame or oven-dried glassware and standard syringe, cannula, and septa techniques, when necessary. Unless specified, commercial reagents were used without further purification. Benzene, diethyl ether, and tetrahydrofuran were distilled from sodium benzophenone ketyl under argon. Methylene chloride, triethylamine, dimethylsulfoxide, and toluene were distilled from calcium hydride under argon. Flash column chromatography was performed using Scientific Adsorbents Incorporated (SAI) 32-60 mm, pore size 60 Å silica gel with solvent systems indicated. Analytical thin layer chromatography was performed using SAI 250 mm glass-backed F254 silica gel plates that were visualized by fluorescence upon 254 nm irradiation then by staining upon heating.
with 10% phosphomolybdic acid (61 g PMA in 1 L 95% ethanol) or potassium permanganate (3 g KMnO₄; 20 g K₂CO₃; 5 mL of 5% aq NaOH; 300 mL H₂O). Solvent removal was affected by rotary evaporation under house vacuum (~25-40 mmHg).

Combustion analysis was performed at Atlantic Microlab, Norcross, Georgia. Mass spectra were recorded on either a 70eV Kratos VG 70-250-S or a Kratos MS-30 at The Ohio State University Center for Mass Spectrometric Analysis or The Ohio State University Campus Chemical Instrumentation Center.
(S)-Ethyl 3-hydroxybutanoate (98).\textsuperscript{29} A 3-L, 3-necked round-bottom flask equipped with mechanical stirrer, bubble counter, and stopper was charged with 1.2 L of tap water, 225 g of sucrose, and 150 g of baker’s yeast. The ingredients were added with continuous stirring. The mixture was stirred for 1 h at approximately 27 °C. After 1 h, 15 g (0.115 mol) of ethyl acetoacetate was added and the fermenting suspension was stirred for another 24 h at room temperature. A solution of 150 g sucrose in 750-mL of tap water, warmed to approximately 40 °C, was then added followed by an additional 15.0 g (0.115 mmol) of ethyl acetoacetate. Stirring was continued for 84 h at room temperature after which the reaction was complete by TLC (silica gel, 30% EtOAc/hexanes, \textit{p}-anisaldehyde stain). The heterogeneous mixture was filtered through a sintered glass funnel packed with 60 g of celite. The filtrate was collected, saturated with NaCl, and extracted with five 500-mL portions of diethyl ether. The combined ether extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo (water bath at 35 °C). The residue was distilled at reduced pressure to afford 21.7 g (71%) of ester 98 as a pale yellow oil: bp 71-90 °C (40 torr) [lit.\textsuperscript{29} 71–73°C (12 torr)]; [\(\alpha\)]\textsubscript{D}\textsuperscript{33} +37.5° (c 1.30, CHCl₃); \textsuperscript{1}H NMR (400 MHz, CDCl₃) \(\delta\) 1.22 (d, \(J = \) 8 Hz, 3H, CHCH₃), 1.28 (t, \(J = \) 8 Hz, 3H, CH₂CH₃), 2.42 (10.5, 8 Hz, 1H, CHCH₂), 2.50 (dd, \(J = \) 10.5, 2 Hz, 1H, CHCH₂), 2.95 (broad s, 1H, OH), 4.29 (m, 1H, CHO).
(S)-Ethyl 3-(tetrahydro-2H-pyran-2-ylxy)butanoate (99a). A solution of 25.3 g (185 mmol) of alcohol 98 in 350 mL of diethyl ether was placed in a 1-L flask and cooled to 0 °C in an ice-bath. To the solution was added 20.2 mL (18.62 g, 221 mmol) of dihydropyran via syringe. To the stirred solution was added 2.13 g (9.16 mmol) of CSA in one portion. The mixture was stirred for 2 h and allowed to warm to room temperature. The mixture was stirred for additional 18 h, after which time the reaction seemed complete by TLC (silica gel, 15% EtOAc/hexanes). To the mixture was added approximately 100 mL of saturated aqueous NaHCO₃, followed by transfer to a large separatory funnel. The organic phase was separated and the aqueous phase was extracted with three 100-mL portions of ethyl acetate. The combined organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (900 g of silica gel, 15%EtOAc/hexanes) to afford 33.6 g of an inseparable mixture of the desired product 99a and the dimer of DHP 99b, respectively, as a colorless oil. This material was approximately a 1:0.3 mixture of 99a and 99b, respectively, based upon integration of ¹H NMR signals at δ 4.70, 4.75 (99a) and 4.96 (99b). The spectral data for 99a extracted from the mixture follows: IR (neat, of mixture) 1737 cm⁻¹; ¹H NMR (signals due to 99a which represent a 1:1 mixture of
diastereomers, CDCl₃, 500 MHz) δ 1.21 (d, J = 6 Hz, 1.5 H, CHCH₃), 1.31 (d, J = 6 Hz, 1.5 H, CHCH₃), 1.26 (m, 3H, CH₂CH₃), 1.47-1.60 (m, 7H, CH₂-manifold), 2.37-2.70 (m, 2H, CH₂C=O), 3.50 (m, 1H, CHO), 3.85 (m, 0.5H, OCHO), 3.91 (m, 0.5H, OCHO), 4.14 (q, J = 8 Hz, 2H, OCH₂CH₃), 4.70 (t, J = 3 Hz, 0.5H, OCHCH₂), 4.76 (t, J = 3 Hz, 0.5H, OCHCH₂); ¹³C NMR (signals due to 99a which represent a 1:1 mixture of diastereomers, CDCl₃, 125 MHz) δ 14.2 (q), 14.2 (q), 19.4 (t), 19.4 (q), 19.8 (t), 21.9 (q), 25.4 (t), 30.9 (t), 31.0 (t), 41.2 (t), 42.8 (t), 60.3 (t), 60.3 (t), 62.1 (t), 62.8 (t), 68.8 (t), 68.6 (d), 71.1 (d), 96.0 (d), 92.3 (d), 171.5 (s), 171.5 (s); HRMS (EI) for C₁₁H₂₀O₄Na calculated for m/e 239.1259, found m/e 239.1260. ¹H NMR (signals due to 99b isolated from the subsequent reaction, CDCl₃, 500 MHz) δ 1.50-1.66 (m, 8H, CH₂-manifold), 1.73-1.80 (m, 2H, CH₂-manifold), 1.80-1.92 (m, 2H, CH₂-manifold), 3.54 (m, 2H, OCH₂), 3.88 (m, 2H, OCH₂), 4.95 (t, J = 3 Hz, 2H, OCH); ¹³C NMR (signals due to 99b isolated from the subsequent reaction, CDCl₃, 125 MHz) δ 19.8 (t), 25.5 (t), 30.7 (t), 63.0 (t), 94.7 (d).
(S)-3-(Tetrahydro-2H-pyran-2-yloxy)butan-1-ol (100). An oven-dried 500-mL 3-necked round-bottom flask was placed under argon, charged with 233 mL of dry Et₂O, and was cooled in an ice-bath. To the solution was added 1.75 g (46.2 mmol) of LiAlH₄ in one portion. To the stirred mixture was added 10.0 g (46.2 mmol) of ester 99a via Pasteur pipette. The mixture was stirred and allowed to warm to room temperature over a period of 2 h after which time the reaction seemed complete by TLC (silica gel, eluted with 30% EtOAc/hexanes). To the stirred solution was sequentially added 2 mL of H₂O, 4 mL of 1 N aqueous NaOH, and 6 mL of H₂O. The mixture was filtered using a Buchner funnel and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography over 300 g SiO₂ gel (eluted with EtOAc/hexanes, 3:7, gradually changed to 1:1) to afford 8.0 g (84% from ethyl 3-hydroxybutanoate) of alcohol 100 as a colorless oil: [α]₂⁰⁺₁₆.₂° (c 1.12, CHCl₃); IR (neat) 3416 cm⁻¹; ¹H NMR (signals due to a 1:1 diastereomeric ratio of alcohol 100, C₆D₆, 500 MHz) δ 0.99 (d, J = 6 Hz, 1.5H, CHCH₃), 1.15 (m, 1H, CH₂), 1.20 (m, 1H, CH₂), 1.25 (d, J = 6 Hz, 1.5H, CHCH₃), 1.30 (m, 1H, CH₂), 1.35 (m, 1H, CH₂), 1.57-1.70 (m, 4H, CH₂-manifold), 2.20 (broad s, 0.5 H, OH), 3.03 (broad s, 0.5H, OH), 3.20 (m, 0.5H, CH₂), 3.32 (m, 0.5H,
CH$_2$), 3.50-4.03 (m, 3.5H, CH$_2$-manifold, CHO), 4.42 (t, $J = 3$Hz, 0.5H, OCHO), 4.68 (t, $J = 3$Hz, 0.5H, OCHO); $^{13}$C NMR (C$_6$D$_6$, 125 MHz) $\delta$ 19.9 (q), 20.8 (2 carbons, t), 22.1 (q), 25.5 (t), 25.9 (t), 31.5 (t), 31.7 (t), 39.7 (t), 40.0 (t), 59.9 (t), 59.9 (t), 62.2 (t), 63.7 (t), 70.2 (d), 73.0 (d), 97.5 (d), 99.2 (d); HRMS (EI) mass calculated for C$_9$H$_{18}$O$_3$Na$^+$ $m/e$ 197.1154, found $m/e$ 197.1154. Prior to the elution of 100, 1.15 g (14%) of 99b was isolated (eluted with EtOAc/hexanes 3:7) as a colorless oil: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.50-1.66 (m, 8H, CH$_2$-manifold), 1.73-1.80 (m, 2H, CH$_2$-manifold), 1.80-1.92 (m, 2H, CH$_2$-manifold), 3.54 (m, 2H, OCH$_2$), 3.88 (m, 2H, OCH$_2$), 4.95 (t, $J = 3$ Hz, 2H, OCH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 19.8 (t), 25.5 (t), 30.7 (t), 63.0 (t), 94.7 (d).
(S)-3-(Tetrahydro-2H-pyran-2-yloxy)butanal (101). A 1000-mL 3-necked flask was charged with 10.0 g (58.0 mmol) of alcohol 100 and 330 mL of a 1:1 mixture of DMSO-CH₂Cl₂. The mixture was cooled in an ice-bath and 65.0 mL (462 mmol) of Et₃N was added via syringe. The reaction mixture was allowed to stir cold for several minutes, followed by the addition of 37.0 g (232.0 mmol) of sulfur trioxide-pyridine complex in one portion. The reaction mixture was stirred for 1 h while progress was monitored by TLC (silica gel, 30% EtOAc/hexanes). The reaction was quenched with 100 mL saturated aqueous NH₄Cl, following which it was poured into a separatory funnel and extracted with four 100-mL portions of dichloromethane. The organic extracts were combined and carefully concentrated in vacuo. The residue was subjected to column chromatography over 450 g of SiO₂ gel [eluted with a gradient of 10-30% Et₂O/petroleum ether (bp 35-60 °C)]. Appropriate fractions were pooled and concentrated in vacuo. The residue was chromatographed in the same manner over 900 g of SiO₂ gel and appropriate fractions were concentrated to yield 7.9 g (78%) of aldehyde 101 as a pale yellow oil: [α]D²³ +13.7° (c 1.0, CHCl₃); IR (neat): 1726 cm⁻¹; ¹H NMR (signals due to a 1:1 diastereomeric ratio of aldehyde 101, C₆D₆, 500 MHz) δ 0.9 (d, J = 7.5 Hz, 1.5H, CH₃),
1.15 (d, \( J = 7.5 \) Hz, 1.5H, CH\textsubscript{3}), 1.16-1.31 (m, 3H, CH\textsubscript{2}-manifold), 1.40-1.52 (m, 2H, CH\textsubscript{2}-manifold), 1.53-1.65 (m, 1H, CH\textsubscript{2}-manifold), 1.9 (dd, \( J = 15, 5, 1.5 \) Hz, 0.5H, CH\textsubscript{2}C=O), 2.0 (ddd, \( J = 15, 5, 1.5 \) Hz, 0.5H, CH\textsubscript{2}C=O), 2.2 (ddd, \( J = 16, 7, 2.5 \) Hz, 0.5 H, CH\textsubscript{2}C=O), 2.37 (ddd, \( J = 15, 7.7, 3 \) Hz, 0.5H, CH\textsubscript{2}C=O), 3.29 (m, 1H, CH\textsubscript{2}O), 3.67 (dt, \( J = 10.4, 3.4 \) Hz , 0.5H, CH\textsubscript{2}O), 3.73 (dt, \( J = 10.4, 3.4 \) Hz ,0.5H, CH\textsubscript{2}O ), 4.03 (m, 0.5H, OCHCH\textsubscript{3}), 4.11 (m, 0.5H, OCHCH\textsubscript{3}), 4.53 (t, \( J = 4 \) Hz, 0.5H, OCHO), 4.59 (t, \( J = 4 \) Hz, 0.5H, OCHO), 9.48 (s, 0.5H, CHO), 9.58 (s, 0.5 CHO); \(^{13}\text{C NMR (C}_{6}\text{D}_{6}, 125 MHz) \delta \)

19.6 (q), 19.8 (2 carbons, t), 22.1 (q), 25.1 (t), 25.8 (t), 31.2 (t), 31.3 (t), 50.7 (t), 51.1 (t), 62.2 (t), 62.3 (t), 67.3(d), 69.4 (d), 96.4 (d), 98.8 (d), 199.3 (d), 199.6 (d); HRMS (EI) mass calculated for C\textsubscript{9}H\textsubscript{16}O\textsubscript{3}Na\textsuperscript{+} \( m/e \) 195.0997, found \( m/e \) 195.0997.
(S)-4,4-Dimethoxybutan-2-ol (70). A solution of 12.1 g (71.1 mmol) of aldehyde 101 was in 150 mL of dry methanol was placed under argon at 0 °C in a 1000-mL one necked round-bottom flask. To the solution was added 0.676 g (3.55 mmol) of p-toluenesulfonic acid monohydrate in one portion. The mixture was stirred and, after removing the cold bath, was allowed to warm to room temperature under argon. The reaction was monitored via TLC (silica gel, eluted with 20% EtOAc/hexanes). After 10 h, approximately 50 mL of saturated aqueous NaHCO3 was added. The flask was equipped with a still head and methanol was removed by distillation at one atmosphere. The resulting aqueous residue was transferred to a separatory funnel and extracted with four 75-mL portions of CH2Cl2. The extracts were combined, washed with 100 mL of brine and the solvent was removed by atmospheric distillation. The residue was purified by flash column chromatography over 300 g SiO2 gel [eluted with diethyl ether-petroleum ether (bp 35–60 °C), 7:3] and concentrated via atmospheric distillation to afford 9.30 g (97%) of 70 as a yellow oil: [α]23D +26.3° (c 1.04, CH3OH); IR (neat) 3440 cm⁻¹; ¹H NMR (CD6, 500 MHz) 1.07 (d, J = 6.5 Hz, 3H, CHCH3), 1.56 (ddd, J = 14, 7, 5 Hz, 1H,
CH$_2$), 1.70 (ddd, $J = 15$, 8, 7 Hz, 1H, CH$_2$), 2.41 (d, $J = 3$ Hz, 1H, OH), 3.04 (s, 3H, OCH$_3$), 3.05 (s, 3H, OCH$_3$), 3.88 (m, 1H, OCH), 4.40 (t, $J = 5$ Hz, 1H, OCHO); $^{13}$C NMR (C$_6$D$_6$, 125 MHz) $\delta$ 23.5 (q), 41.3 (t), 52.0 (q), 52.6 (q), 64.2 (d), 103.9 (d); HRMS (EI) mass calculated for C$_6$H$_{14}$O$_3$Na$^+$ m/e 157.0841, found m/e 157.0843.
(2S)-(S)-4,4-Dimethoxybutan-2-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (103a). A dry, 2-necked, 10-mL pear-shaped flask was charged with 75 mg (0.56 mmol) of chiral alcohol 70 (prepared from purchased ethyl 3-hydroxybutanoate) and 2 mL of dry CH$_2$Cl$_2$. To the solution were added, in sequence, 0.173 g (0.84 mmol) of DCC and 34 mg (0.28 mmol) of 4-DMAP. To the stirred mixture was added 0.15 mL (0.200 g, 0.85 mmol) of (S)-Mosher’s Acid in one portion. A cream-colored solid, that turned white as the reaction progressed, precipitated from the mixture. The mixture was stirred for 24 h and monitored by TLC (silica gel, 20% EtOAc/hexanes). After the reaction seemed complete, the mixture was filtered. The filter cake was washed with approximately 50 mL of CH$_2$Cl$_2$ repeatedly to ensure quantitative filtration. The filtrate was concentrated in vacuo. The crude material was purified by flash chromatography over 10 g silica gel (eluted with EtOAc-hexanes, 1:9) to afford 0.148 g (76%) of ester 103a as a colorless oil: $[\alpha]_D^{23}$ = -32.7$^\circ$ (c 1.02, CHCl$_3$); IR(neat) 1746 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 1.31 (d, $J$ = 6.5 Hz, 3H, CH$_3$), 1.77-2.05 (m, 2H, CH$_2$), 3.29 (s, 3H, OCH$_3$), 3.31 (s, 3H, OCH$_3$), 3.55 (s, 3H, COCH$_3$), 4.41 (dd, $J$ = 7.7, 7.1 Hz, 1H, CH(OCH$_3$)$_2$), 5.25 (m, 1H, OCH), 7.4 (m, 3H, ArH), 7.55 (m, 2H, ArH); $^{13}$C NMR
(C₆D₆, 125 MHz) δ 19.7 (q), 38.8 (t), 52.5 (d), 52.6 (d), 55.2 (d), 71.0 (d), 101.7 (q),
123.1-133.1 (d, s), 166.16 (s). This material had an enantiomeric excess of 98% based on
integration of the methine signals in the ¹H NMR spectrum at 4.39 (major) and 4.18
(minor) ppm (1.00:0.01 ratio).
(2S)-(S)-4,4-Dimethoxybutan-2-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (8).

A dry, 2-necked, 10-mL pear-shaped flask was charged with 75 mg (0.782 mmol) of chiral alcohol 70 and 2 mL of dry CH₂Cl₂. To the solution were added, in sequence, 265 mg (1.28 mmol) of DCC and 45 mg (0.37 mmol) of 4-DMAP. To the stirred mixture was added 0.20 mL (265 mg, 1.13 mmol) of (S)-Mosher’s acid in one portion. A cream-colored solid, that turned white as the reaction progressed, precipitated from the mixture. The mixture was stirred for 24 h and monitored by TLC (silica gel, 20% EtOAc/hexanes). After the reaction seemed complete, the mixture was filtered. The filter cake was washed with approximately 50 mL of CH₂Cl₂. The filtrate was concentrated in vacuo. The crude material was purified by flash chromatography over 10 g silica gel (eluted with EtOAc-hexanes, 1:9) to afford 0.126 g (48%) of 103a as a colorless oil: [α]₂³⁰°⁻⁹.¹° (c 1.02, CHCl₃); IR (neat) 1745 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 1.31 (d, J = 6.5 Hz, 3H, CH₃), 1.77-2.05 (m, 2H, CH₂), 3.29 (s, 3H, OCH₃), 3.31 (s, 3H, OCH₃), 3.55 (s, 3H, COCH₃), 4.41 (dd, J = 7.7, 7.1 Hz, 1H, CH(OCH₃)₂), 5.25 (m, 1H, OCH), 7.4 (m, 3H, ArH), 7.55 (m, 2H, ArH). This material had an enantiomeric excess of 82-86% based on integration of the methine signals in the ¹H NMR spectrum at 4.42 (major) and 4.21 (minor) ppm (95:7 ratio). This ratio was cross-verified by integration of the methyl doublets at 1.31 and 1.38 ppm.
(2S)-(R,S)-4,4-Dimethoxybutan-2-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (103c). A dry, 2-necked, 10-mL pear-shaped flask was charged with 0.126 g (0.76 mmol) of racemic alcohol 70 and 2 mL of dry CH₂Cl₂. To the solution were added, in sequence, 0.239 g (1.15 mmol) of DCC and 0.053 g (0.43 mmol) of 4-DMAP. To the stirred mixture was added 0.2 mL (0.262 g, 1.11 mmol) of (S)-Mosher’s acid in one portion. A cream-colored solid, that turned white as the reaction proceeded, precipitated from the mixture. The mixture was stirred for 24 h and monitored by TLC (silica gel, 20% EtOAc/hexanes). The mixture was filtered via gravity to remove the precipitate (dicyclohexyl urea) and the filter cake was washed with approximately 25 mL of CH₂Cl₂. The filtrate was concentrated *in vacuo* to afford 0.310 g of crude material which was subjected to flash chromatography over 10 g silica gel (eluted with 10 % EtOAc/hexanes) to afford 0.154 g (58%) of esters 103c as a colorless oil:  IR (neat) 1746 cm⁻¹; ¹H NMR (signals represent a 1:1 mixture of diastereomeric esters 103c, CDCl₃, 500 MHz) δ 1.31 (d, J = 6.5 Hz, 1.5H, CH₃), 1.38 (d, J = 6.5 Hz, 1.5H, CH₃), 1.77-2.05 (m, 2H, CH₂), 3.24 (s, 1.5H, OCH₃), 3.28 (s, 1.5H, OCH₃), 3.31 (s, 1.5H, OCH₃), 3.33 (s, 1.5H, OCH₃), 3.55
(s, 1.5H, OCH₃), 3.58 (s, 1.5H, OCH₃), 4.21 (dd, J = 7.7, 7.1 Hz, 0.5H, CH(OCH₃)₂),
4.41 (dd, J = 7.7, 7.1 Hz, 0.5H, CH(OCH₃)₂), 5.25 (m, 1H, OCH), 7.4 (m, 3H, ArH), 7.5
(m, 2H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 19.9 (q), 20.1 (q), 38.7 (t), 38.8 (t), 52.7
(q), 52.8 (q), 53.3 (q), 53.6 (q), 55.3 (q), 55.4 (q), 70.9 (d), 71.0 (d), 101.3 (d), 101.4 (d),
127.2 (d), 127.4 (d), 128.4 (d), 129.5 (2 carbons, d), 129.6 (d), 132.3 (s), 132.5 (s), 165.8
(s), 166.0 (s), signals due to the CF₃ and C(C=O) carbons were not readily seen; HRMS
(EI) mass calculated for C₁₆H₂₁F₃O₅Na m/e 373.1239, found m/e 373.1240.
(S)-3-(Tetrahydro-2H-pyran-2-yloxy)butyl pivalate (107). A 100-mL, 3-necked flask was charged with 1.44 g (8.36 mmol) of alcohol 100 in 40 mL of dry CH₂Cl₂ and cooled to 0 °C in an ice-bath. To the solution was added 1.40 mL (1.00 g, 10.1 mmol) of Et₃N via syringe followed by the addition of 0.105 g (0.86 mmol) of 4-DMAP. The mixture was stirred for 5 min and 1.0 mL (1.11 g, 9.20 mmol) of pivaloyl chloride was added dropwise. The reaction was stirred for 12 h and monitored via TLC (silica gel, 50% EtOAc/hexanes). Once the reaction was complete, the mixture was quenched with 10 mL of 1 N aqueous HCl. The mixture was poured into a separatory funnel and extracted with three 30-mL portions of CH₂Cl₂. The organic layers were collected, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was subjected to column chromatography (eluted with 15% EtOAc/hexanes) to afford 1.92 g (89%) of pivalate 107 as a colorless oil: IR (neat) 1729 cm⁻¹; ¹H NMR (these signals represent a diastereomeric mixture, CDCl₃, 500 MHz) δ 1.18 (t, J = 6 Hz, 1.5H, CH₃), 1.20 (s, 9H, C(CH₃)₃), 1.29 (d, J = 6 Hz, 1.5H, CH₃), 1.50-1.90 (m, 8H, CH₂-manifold), 3.50 (m, 1H, OCH₂), 3.82 (m, 1H, OCHCH₃, OCH₂), 3.94 (m, 1H, OCHCH₃, OCH₂), 4.02 (t, J = 6 Hz, 1H, CH₂OPiv), 4.22 (t, J = 6 Hz, 1H, CH₂OPiv), 4.61 (t, J = 2 Hz, 0.5H, OCHO), 4.75 (t,
\( J = 2 \text{ Hz}, 0.5\text{H}, \text{OCHO} \); \(^{13}\text{C NMR} (\text{CDCl}_3, 125 \text{ MHz}) \delta 19.2 \text{ (q)}, 19.4 \text{ (t)}, 20.0 \text{ (t)}, 22.0 \text{ (q)}, 25.43 \text{ (t)}, 26.49 \text{ (t)}, 27.17 \text{ (q)}, 27.17 \text{ (q)}, 31.0 \text{ (t)}, 31.1 \text{ (t)}, 35.8 \text{ (t)}, 36.4 \text{ (t)}, 38.7 \text{ (s)}, 61.2 \text{ (t)}, 61.4 \text{ (t)}, 62.2 \text{ (t)}, 62.9 \text{ (t)}, 67.5 \text{ (d)}, 71.4 \text{ (d)}, 95.1 \text{ (d)}, 99.4 \text{ (d)}, 178.5 \text{ (s)}, 178.6 \text{ (s)}; \text{HRMS (EI) for C}_{14}\text{H}_{26}\text{O}_{4}\text{Na calculated for } m/e 281.1729, \text{found } m/e 281.1736.\)
(S)-3-Hydroxybutyl pivalate (108). To a solution of 1.92 g (7.43 mmol) of alcohol 107 (from ethylacetoacetate) in 22 mL of dry methanol was added 70 mg (0.37 mmol) of p-toluenesulfonic acid monohydrate. The mixture was stirred for 12 h at room temperature, and then 10 mL of saturated aqueous NaHCO₃ was added. The mixture was concentrated and the residue was partitioned with 20 mL of CH₂Cl₂. The aqueous phase was extracted with two 20-mL portions of CH₂Cl₂. The combined organic phases were dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by chromatography over 70 g of flash silica gel (eluted with EtOAc/hexanes, 3:7) to afford 1.03 g (80%) of pivalate 108 as a colorless oil: [α]D \text{23} ^{23} +14.0° (c 1.02, CHCl₃); IR (neat) 3444 (broad), 1729, 1711 cm⁻¹; ¹H NMR (C₆D₆, 500 MHz) δ 1.03 (d, J = 7 Hz, 3H, CH₃), 1.21 (s, 9H, C(CH₃)₃), 1.54 (m, 2H, CH₂), 1.68 (broad s, 1H, OH), 3.67 (m, 1H, OCH), 4.09 (m, 1H, OCH₂), 4.30 (m, 1H, OCH₂); ¹³C NMR (C₆D₆, 125 MHz) δ 22.6 (q), 27.3 (q), 38.5 (t), 38.7 (s), 61.8 (t), 64.6 (d), 178.1 (s); HRMS (EI) for C₉H₁₈O₃Na calculated for m/e 197.1154, found m/e 197.1152.
**S-Phenyl 3-hydroxybutanethioate (110).** A dry 3-necked round-bottom flask was charged with 10.4 g (100 mmol) of β-hydroxybutyric acid in 1500 mL of dry CH₂Cl₂ and cooled in an ice-bath. To the cooled solution was added 0.561 (5.0 mmol) of 4-(dimethylamino) pyridine, followed by addition of 24.8 g (120 mmol) of dicyclohexyl-carbodiimide in one portion. To the cooled solution was added 12.3 mL (13.2 g, 120 mmol) of thiophenol in one portion via syringe. The mixture was stirred cold for 2 h, allowed to warm to room temperature, and then allowed to stir for an additional 10 h. A white precipitate formed during the course of the reaction. When the reaction was complete by TLC analysis (silica gel, 50% EtOAc/hexanes), the mixture was filtered through a small layer (approximately 20 cm thick) of regular silica gel placed over the sintered glass disk in a Buchner funnel. The silica gel was washed with approximately 250 mL of CH₂Cl₂, and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography over 300 g of silica gel (eluted with ethyl acetate-hexanes, 1:4) to afford 9.15 g (47%) of thioester 110 as a pale yellow oil: IR (neat) 3394, 1703 cm⁻¹;¹H NMR (CDCl₃, 500 MHz) δ 1.27 (d, J = 6 Hz, 3H, CH₃), 2.77-2.88 (m, 2H,
CH$_2$), 4.30 (m, 1H, CHO), 7.44 (s, 5H, ArH) (signal due to OH not observed); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 22.5 (q), 51.6 (t), 64.9 (d), 127.1 (s), 129.3 (d), 129.7 (d), 134.5 (d), 197.8 (s); HRMS (EI) mass calculated for C$_{10}$H$_{12}$O$_2$SNa$^+$ $m/e$ 219.0456, found $m/e$ 219.0454.
(4R,5S)-4-Methyl-5-phenyloxazolidin-2-one (112a). A dry 1-necked round-bottom flask was charged with 49.9 g (330 mmol) of (1S,2R)-norephedrine, 4.6 g (33.2 mmol) of potassium carbonate and 83 mL (80.4 g, 681 mmol) of diethyl carbonate. The flask was fitted with a distillation head and the mixture was heated in an oil bath at 135 °C. Distillation of ethanol began after 1.5 h and was complete after 3.5 h (60 mL of distillate was collected). The oil bath was removed and the mixture was cooled to room temperature. The yellow residue was diluted with 200 mL of CH₂Cl₂ and transferred to a separatory funnel. The organic layer was washed with 200 mL of H₂O, 200 mL of brine, and was then dried over Na₂SO₄. The organic layer was filtered and concentrated *in vacuo* to afford a white residue which was subsequently recrystallized from approximately 150 mL of EtOAc/hexanes (2:1) to afford 50.7 g (87%) of oxazolidinone 112a as dense, white crystals: mp 112-115°C (lit. 39 mp 121-122 °C); ¹H NMR δ 0.83 (d, J = 6.7 Hz, 3H, CH₃), 4.21 (dq, J = 7, 7 Hz, 1H, NH), 5.45 (broad s, 1H, NH), 5.73 (d, J = 7.5, 1H, OCH), 7.30-7.44 (m, 5H, ArH).
(4R,5S)-3-Heptanoyl-4-methyl-5-phenyloxazolidin-2-one (15). A 3-necked round-bottom flask was charged with 22.4 g (126 mmol) of oxazolidinone 13 in 650 mL of dry THF. The solution was cooled to -65 °C. To the cold solution was added 13.9 mL (139 mmol) of a 10 M solution of n-BuLi/hexanes via syringe at a rate such that the temperature did not rise above -55 °C. Once all of the n-BuLi was added, 23.4 mL (22.5 g, 151 mmol) of heptanoyl chloride was added via syringe at a rate such that the temperature did not rise above -55 °C. The reaction mixture was stirred for 1.5 h at which point it was complete by TLC (silica gel, 30% EtOAc/hexanes). Approximately 200 mL saturated aqueous NH₄Cl was added to the mixture followed by transfer to a separatory funnel. The organic layer was separated and the aqueous layer was washed with two 100-mL portions of EtOAc. The organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to obtain a solid pale yellow residue. The residue was triturated with approximately 250 mL cold pentane and dried under vacuum for several hours to afford 33.6 g (92%) of imide 15 as a white, crystalline solid: mp 63-66 °C; ¹H
NMR (CDCl₃, 500 MHz) δ 0.92 (m, 6H, CH₃), 1.29-1.45 (m, 6H, CH₂CH₂CH₂), 1.64-1.74 (m, 2H, CH₂CH₂C=O), 2.90 (dt, J = 9, 7.5 Hz, 1H, CH₂C=O), 2.99 (dt, J = 9, 7 Hz, 1H, CH₂C=O), 4.78 (dq, J = 7, 7 Hz, 1H, CHCH₃), 5.67 (d, J = 7 Hz, 1H, CHAr), 7.30-7.36 (m, 5H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 14.0 (q), 14.6 (q), 22.5 (t), 24.3 (t), 28.8 (t), 31.5 (t), 35.6 (t), 54.8 (d), 79.0 (d), 125.6 (d), 128.70 (d), 128.74 (d), 133.4 (s), 153.0 (s), 173.2 (s).
(4\text{R},5\text{S})-3-((\text{S})-2-Allylheptanoyl)-4-methyl-5-phenyloxazolidin-2-one (114a). To a 3-necked flask was added 1000 mL of dry THF and 33.6 g (116 mmol) of imide 113a followed by cooling to an internal temperature of -100 °C (dry ice/isopropanol/liquid N\textsubscript{2}). To the solution was added 139 mL (139 mmol) of a 1 M solution of NaHMDS/THF while maintaining the temperature below -60 °C. The internal temperature was returned to -100 °C, followed by addition of 14.7 mL (21.1 g, 174 mmol) of allyl bromide via syringe in one portion. The mixture was allowed to stir overnight (12 h) while it warmed to room temperature at which point it was complete by TLC (silica gel, 20% EtOAc/hexanes). The reaction was quenched by addition of 100 mL of saturated aqueous NH\textsubscript{4}Cl. The mixture was transferred to a separatory funnel and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with three 400-mL portions of EtOAc. The organic layers were combined, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated \textit{in vacuo}. The residue was purified by flash chromatography over 900 g of silica gel (eluted with 15% EtOAc/hexanes) to afford 28.2 g (74%) of imide 114a as a pale yellow, viscous oil: IR (neat) 1784, 1694 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \textdelta 0.88
(d, $J = 6.7$ Hz, 3H, CHCH$_3$), 0.91 (t, $J = 7$ Hz, 3H, CH$_2$CH$_3$), 1.27-1.38 (m, 6H, CH$_2$CH$_2$CH$_2$), 1.52 (m, 1H, CHCH$_2$), 1.72 (m, 1H, CHCH$_2$), 2.32 (m, 1H, =CHCH$_2$), 2.45 (m, 1H, =CHCH$_2$), 3.93 (m, 1H, CHC=O), 4.71 (dq, $J = 7$, 7 Hz, 1H, NCH), 5.01 (dd, $J = 11$, 2 Hz, 1H, =CH$_2$), 5.04 (dd, $J = 14$, 2 Hz, 1H, =CH$_2$), 5.65 (d, $J = 7$ Hz, 1H, OCH), 5.82 (ddt, $J = 14$, 11, 6 Hz, 1H, CH=CH$_2$), 7.30-7.45 (m, 5H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 14.0 (q), 14.6 (q), 22.5 (t), 26.9 (t), 31.6 (t), 31.8 (t), 36.8 (t), 42.4 (d), 55.0 (d), 78.7 (d), 117.0 (t), 125.6 (d), 128.69 (d), 128.73 (d), 133.4 (s), 135.3 (d), 152.8 (s), 176.0 (s); HRMS (EI) for C$_{20}$H$_{27}$O$_3$Na calculated for $m/e$ 352.1889, found $m/e$ 352.1884.
(S)-2-Allenheptanoic acid (69a). To a 1-necked, 1-L flask was added 28.2 g (85.6 mmol) of 114a in 430 mL of a 4:1 mixture of THF-H2O. The solution was cooled in an ice-bath and 35 mL of a 30% aqueous solution of H2O2 was added, followed by 5.75 g (137 mmol) of lithium hydroxide monohydrate. The mixture was stirred for 6 h and monitored by TLC (silica gel, 15% EtOAc/hexanes). When reaction was complete, 15 g of Na2SO3 was added, the mixture was transferred to a round-bottomed flask and the organic volatiles were removed in vacuo. The residue (pH ~11) was transferred to a separatory funnel and the mixture was extracted with four 50-mL portions of CH2Cl2. The aqueous layer was acidified to pH ~1 with concentrated HCl (approximately 12 mL), and was extracted with four 50-mL portions of CH2Cl2. The organic layers from the second extraction were collected and concentrated to afford 14.6 g (100%) of acid 69a as a pale yellow oil: $[\alpha]_D^{23}$ -13.0° (c 1.12, CHCl3); IR (neat) 3000 cm⁻¹ (broad), 1706 cm⁻¹; $^1$H NMR (CDCl3, 500 MHz) $\delta$ 0.90 (t, $J = 6.5$ Hz, 3H, CH3), 1.23-1.40 (m, 6H, CH2), 1.52 (m, 1H, CH2CH), 1.66 (m, 1H, CH2CH), 2.28 (m, 1H, =CHCH2), 2.40 (m, 1H,
=CHCH₂), 2.47 (m, 1H, CHC=O), 5.05 (dd, J = 11, 2 Hz, 1H, =CH₂), 5.10 (dd, J = 14, 2 Hz, 1H, =CH₂), 5.80 (ddt, J = 14, 11, 6 Hz, 1H, =CH), the CO₂H signal was not recorded; 

\(^{13}\)C NMR (CDCl₃, 125 MHz) \(\delta\) 14.0 (q), 22.4 (t), 26.8 (t), 31.5 (t), 31.7 (t), 36.1 (t), 45.1 (d), 116.9 (t), 125.2 (d), the CO₂H carbon signal was too weak to be recorded; HRMS (EI) for C₁₀H₁₈O₂Na calculated for m/e 193.1204, found m/e 193.1200.

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(4R,5S)-4-Methyl-5-phenyloxazolidin-2-one (112b). A dry 1-necked round-bottom flask was charged with 50.1 g (331 mmol) of (1R,2S)-norephedrine, 4.6 g (33.2 mmol) of potassium carbonate and 83 mL (80.4 g, 681 mmol) of diethyl carbonate. The flask was fitted with a distillation head and the mixture was heated in an oil bath at 135 ºC. After 2 h of continuous heating, rapid distillation of alcohol began which was complete after 3.5 h (60 mL of distillate was collected). After the distillation ceased, the oil bath was removed and the mixture was cooled to room temperature. The residue was diluted with 200 mL of CH₂Cl₂ and transferred to a separatory funnel. The organic layer was washed sequentially with 200 mL of H₂O, 200 mL of brine, and was then dried over Na₂SO₄. The organic layer was filtered and concentrated in vacuo to afford a white residue which was subsequently recrystallized from approximately 150 mL of EtOAc/hexanes (2:1) to afford 43.6 g (74%) of 112b as a white, granular solid: mp 107-108.5 ºC (lit. mp 102-105 ºC); ¹H NMR δ 0.83 (d, J = 6.7 Hz, 3H, CH₃), 4.21 (dq, J = 7, 7 Hz, 1H, NHCH), 5.45 (broad s, 1H, NH), 5.73 (d, J = 7.5 Hz, 1H, OCH), 7.30-7.44 (m, 5H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 17.5, 52.4, 81.0, 125.9, 128.5, 128.5, 134.9, 159.4.
(4S,5R)-3-Heptanoyl-4-methyl-5-phenyloxazolidin-2-one (113b). A 3-necked round-bottom flask was charged with 19.0 g (107 mmol) of oxazolidinone 112b and 650 mL of dry THF. The solution was cooled to -72 °C. To the cold solution was added 11.7 mL (117 mmol) of a 10 M solution of n-BuLi/hexanes via syringe at a rate such that the temperature did not rise above -55 °C. After all of the n-BuLi was added, the solution was cooled to -70 °C, following which 20 mL (19.1 g, 128 mmol) of heptanoyl chloride was added via syringe at a rate such that the temperature did not rise above -55 °C. The reaction mixture was stirred for 1.5 h at which point it was complete by TLC (silica gel, 30% EtOAc/hexanes). Approximately 200 mL of saturated aqueous NH₄Cl was added to the mixture followed by transfer to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with two 100-mL portions of EtOAc. The organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to obtain a solid pale yellow residue. The residue was trituated with approximately 250 mL of cold pentane and dried under vacuum for several hours to afford 27.5 (88%) of imide 113b as a white crystalline solid: mp 66.5-67.5 °C; IR (thin film) 1783, 1707, 1694 cm⁻¹; ¹H NMR
(CDCl₃, 500 MHz) δ 0.92 (m, 6H, CH₃), 1.29-1.45 (m, 6H, CH₂CH₂CH₂), 1.64-1.74 (m, 2H, CH₂CH₂C=O), 2.90 (dt, J = 9, 7.5 Hz, 1H, CH₂C=O), 2.99 (dt, J = 9, 7 Hz, 1H, CH₂C=O), 4.78 (dq, J = 7, 7 Hz, 1H, CHCH₃), 5.67 (d, J = 7 Hz, 1H, CHAr), 7.30-7.36 (m, 5H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 14.0 (q), 14.6 (q), 22.5 (t), 24.3 (t), 28.8 (t), 31.5 (t), 35.6 (t), 54.8 (d), 79.0 (d), 125.6 (d), 128.71 (d), 128.75 (d), 133.4 (s), 153.0 (s), 173.2 (s); HRMS (EI) for C₁₇H₂₃O₃Na calculated for m/e 312.1576, found m/e 312.1563.
(4S,5R)-3-((R)-2-Allyheptanoyl)-4-methyl-5-phenyloxazolidin-2-one (114b). To a 3-necked flask was added 1000 mL of dry THF and 18.0 g (62.2 mmol) of imide 113b followed by cooling to an internal temperature of -100 ºC (dry ice/isopropanol/liquid N₂ bath). To the solution was added 60 mL (60 mmol) of a 1 M solution of NaHMDS/THF at a rate such that the temperature did not rise above -60 ºC. Once the bath was completely added, the internal temperature was returned to -100 ºC, following which 7.9 mL (11.3 g, 93.3 mmol) of allyl bromide was added via syringe in one portion. The mixture was allowed to stir for 8 h while it warmed to room temperature at which point it was complete by TLC (silica gel, 30% EtOAc/hexanes). The reaction was quenched by addition of 100 mL of saturated aqueous NH₄Cl. The mixture was transferred to a separatory funnel and the organic layer was separated from the aqueous layer. The aqueous layer was washed with three 400-mL portions of EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over 900 g of silica gel (eluted with 15 % EtOAc/hexanes) to afford 17.5 g (85%) of 114b as a pale yellow, viscous oil. IR (neat)
1781, 1698 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.88-0.93 (m, 6H, CH\(_3\)), 1.27-1.38 (m, 6H, CH\(_2\)CH\(_2\)CH\(_2\)), 1.52 (m, 1H, CHCH\(_2\)), 1.72 (m, 1H, CHCH\(_2\)), 2.32 (m, 1H, =CHCH\(_2\)), 2.45 (m, 1H, =CHCH\(_2\)), 3.93 (m, 1H, CHC=O), 4.71 (dq, \(J = 7, 7\) Hz, 1H, NCH), 5.01 (dd, \(J = 11, 2\) Hz, 1H, CH=CH\(_2\)), 5.04 (dd, \(J = 14, 2\) Hz, 1H, CH=CH\(_2\)), 5.65 (d, \(J = 7\) Hz, 1H, OCH), 5.82 (ddt, \(J = 14, 11, 6\) Hz, 1H, CH=CH\(_2\)), 7.30-7.45 (m, 5H, ArH); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 14.0 (q), 14.6 (q), 22.5 (t), 26.9 (t), 31.6 (t), 31.8 (t), 36.8 (t), 42.4 (d), 55.0 (d), 78.7 (d), 117.0 (t), 125.6 (d), 128.7 (d), 128.7 (d), 133.4 (s), 135.3 (d), 152.8 (s), 176.0 (s); HRMS (EI) for C\(_{20}\)H\(_{27}\)O\(_3\)Na calculated for \(m/e\) 352.1889, found \(m/e\) 352.1880.
(R)-2-Butyric acid (69b). To a 1-necked, 1-L flask was added 17.5 g (53.1 mmol) of 114b in 265 mL of a 4:1 mixture of THF-H2O. The solution was cooled in an ice-bath and 21.6 mL of a 30% aqueous solution of H2O2 was added, followed by 3.57 g (85.1 mmol) of lithium hydroxide monohydrate. The mixture was stirred for 6 h and monitored by TLC (silica gel, 15% EtOAc/hexanes). When reaction seemed complete, 10 g of Na2SO3 was added to quench the reaction. Then the mixture was transferred to a round-bottomed flask and the organic volatiles were removed in vacuo. The residue (pH ~11) was transferred to a separatory funnel and the mixture was extracted with four 50-mL portions of CH2Cl2. The aqueous layer was acidified to pH ~1 with concentrated HCl (approximately 12 mL), and was extracted with four 50-mL portions of CH2Cl2. The organic layers from the second extraction were collected and concentrated to afford 9.0 g (100%) of acid 69b as a pale yellow oil: [α]D23 +10.5° (c 1.05, CHCl3); IR (neat) 2930 (broad), 1707 cm⁻¹; ¹H NMR (CDCl3, 500 MHz) δ 0.90 (t, J = 6.5 Hz, 3H, CH3), 1.23-1.40 (m, 6H, CH2), 1.52 (m, 1H, CH3CH), 1.66 (m, 1H, CH2CH), 2.28 (m, 1H, =CHCH2), 2.40 (m, 1H, =CHCH2), 2.47 (m, 1H, CHC=O), 5.05 (dd, J = 11, 2 Hz, 1H, =CHCH2).
=CH_2), 5.10 (dd, J = 14, 2 Hz, 1H, =CH_2), 5.80 (ddt, J = 14, 11, 6 Hz, 1H, =CH); $^{13}$C
NMR (CDCl₃, 125 MHz) δ 14.0 (q), 22.4 (t), 26.8 (t), 31.5 (t), 31.7 (t), 36.1 (t), 45.1 (d), 116.9 (t), 125.2 (d), carbonyl signal was too weak to be seen.
(4R,5S)-3-((R)-2-Allylheptanoyl)-4-methyl-5-phenyloxazolidin-2-one (115). A dry 2-necked flask containing 0.30 g (1.76 mmol) of carboxylic acid 69b was cooled in an ice bath and 0.17 mL (0.25 g, 1.93 mmol) of oxalyl chloride was added. The mixture was stirred cold for 4 h and bubbling occurred periodically. Once the bubbling ceased and the reaction was determined complete by IR, the volatiles were removed in vacuo to afford 0.333 g (100%) of a colorless oil which was directly used in the subsequent reaction: IR (neat) 1795 cm⁻¹.

A solution of 0.240 g (1.35 mmol) of oxazolidinone 112a and 10 mL of dry THF was prepared in a dry 3-necked flask, and cooled to an internal temperature of -70 °C. To the cooled solution was added 1.0 mL (2 mmol) of a 2 M solution of n-BuLi/hexanes via syringe, maintaining the temperature below -60 °C. After 15 minutes, the aforementioned acid chloride (0.333 g, 1.74 mmol) was added via cannulation with a 3 mL rinse with dry THF. The reaction was complete after 2 h by TLC analysis (silica gel, 20% EtOAc/hexanes). To the reaction mixture was added 10 mL of saturated aqueous NH₄Cl. The mixture was transferred to a separatory funnel and the organic layer was separated.
The aqueous layer was washed with three 50-mL portions of EtOAc. The organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The residue was purified by flash chromatography over 20 g of silica gel (eluted with 15% EtOAc/hexanes) to afford 0.200 g (45%) of imide \textbf{115} as a pale yellow oil:  $[\alpha]_{D}^{21} + 6.3^\circ$ (c 1.05, CH$_3$OH); IR (neat) 1782, 1698 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 0.88-0.93 (m, 6H, CH$_3$), 1.27-1.38 (m, 6H, CH$_2$CH$_2$CH$_2$), 1.52 (m, 1H, CHCH$_3$), 1.72 (m, 1H, CHCH$_2$), 2.32 (m, 1H, =CHCH$_2$), 2.45 (m, 1H, =CHCH$_2$), 3.93 (m, 1H, CHC=O), 4.71 (dq, $J$ = 7, 7 Hz, 1H, NCH), 5.01 (dd, $J$ = 11, 2 Hz, 1H, =CH$_2$), 5.04 (dd, $J$ = 14, 2 Hz, 1H, =CH$_2$), 5.65 (d, $J$ = 7 Hz, 1H, OCH), 5.82 (ddt, $J$ = 14, 11, 6 Hz, 1H, =CH), 7.30-7.45 (m, 5H, ArH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 13.9 (q), 14.4 (q), 22.4 (t), 26.5 (t), 31.7 (t), 31.9 (t), 36.4 (t), 42.5 (d), 54.8 (d), 78.6 (d), 116.7 (t), 125.6 (d), 128.6 (d), 128.6 (d), 133.4 (s), 135.6 (d), 152.7 (s), 175.8 (s).
The determination of Enantiomeric Excess of (69a) and (69b). A solution of 100 mg of imide 114a in 1 mL of CDCl₃ was placed in an NMR tube. A solution of 100 mg of imide 115 in 1 mL of CDCl₃ was added in 10 μL aliquots and the ¹³C NMR spectra of the 114a/115 mixtures were recorded. The signals due to the presence of imide 115 were evident at 25.1 and 39.5 ppm. It was determined that ¹³C analysis could detect as little as 4% of 115 in 114a, thereby resulting in an enantiomeric excess of at least 92% for carboxylic acid 69a by ¹³C analysis.

A solution of 100 mg of imide 115 in 1 mL of CDCl₃ was placed in an NMR tube. A solution of 100 mg of imide 114a in 1 mL of CDCl₃ was added in 10 μL aliquots and the ¹³C NMR spectra of the 115/114a mixtures were recorded. The signals due to the presence of imide 114a were evident at 25.1, 39.5, and 134.8 ppm. It was determined that ¹³C analysis could detect as little as 3% of 114a in 115, thereby resulting in an enantiomeric excess of at least 94% for carboxylic acid 69b by ¹³C analysis.
**(S)-4-(Pivaloyloxy)butan-2-yl (S)-non-1-en-4-ylcarbamate (116).** A 3-necked round-bottom flask, fitted with a reflux condenser, was charged with 1.00 g (5.87 mmol) of carboxylic acid 69a and 15 mL of dry benzene. To the stirred solution at room temperature was added 0.85 mL (0.617 g, 6.10 mmol) of Et<sub>3</sub>N via syringe, followed by the addition of 1.3 mL (1.62 g, 5.88 mmol) of diphenylphosphoryl azide in one portion. The reaction was heated under reflux for 30 min and the progress of the reaction was monitored via TLC (silica gel, 30% EtOAc/hexanes) and IR. To the resulting solution of isocyanate was added 1.13 g (6.49 mmol) of alcohol 108 and the mixture was allowed to stir under reflux for 18 h. To the reaction mixture was added an additional 0.51 g (2.93 mmol) of 108, followed by heating under reflux for another 18 h. The reaction was still not complete and an additional 0.19 g (1.10 mmol) of 108 was added. Heating was continued and the reaction was complete after 7 h by TLC analysis (silica gel, 30% EtOAc/hexanes). The reaction mixture was cooled to room temperature and 10 mL of
5\% aqueous citric acid was added. The mixture was transferred to a separatory funnel and the benzene layer was separated. The aqueous layer was extracted with two 20-mL portions of benzene. The organic layers were combined, dried over Na$_2$SO$_4$, filtered, and concentrated \textit{in vacuo}. The residue was purified by flash chromatography over 100 g of silica gel (eluted with 25\% EtOAc/hexanes) to afford 0.978 g (49\%) of 116 as a pale yellow oil: IR (neat) 1729, 1700 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 0.90 (t, $J$ = 8.3 Hz, 3H, CH$_2$CH$_3$), 1.20-1.60 (m with s at 1.20, 20H, C(CH$_3$)$_3$, CHCH$_3$ and CH$_2$ manifold), 1.78-1.93 (m, 2H, CH$_2$CHCH$_3$), 2.18 (m, 1H, =CHCH$_2$), 2.25 (m, 1H, =CHCH$_2$), 3.68 (m, 1H, NHCH$_2$), 4.11 (m, 2H, OCH$_2$), 4.40 (s, 1H, NH), 4.90 (m, 1H, OCH), 5.09 (d, $J$ = 12 Hz, 2H, =CH$_2$), 5.77 (m, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 14.0, 20.9, 22.5, 25.6, 31.7, 34.6, 39.6, 39.9, 50.6, 58.5, 68.0, 117.8, 134.3, 157.0, 181.0, two aliphatic signals were not observed and several impurity signals were observed; HRMS (EI) calculated for C$_{19}$H$_{35}$O$_4$Na $m/z$ 364.2458, found $m/z$ 364.2475.
Preparation of (S)-4-Hydroxybutan-2-yl (S)-non-1-en-4-ylcarbamate (106). A 2-necked round-bottom flask was charged with 0.053 g (0.155 mmol) of urethane 116 and 8 mL of methanol. To the solution, 8 mL of a 40 % aqueous solution of dimethylamine was added and the reaction was refluxed for 2 d; it was found to be complete by TLC (15 % EtOAc/hexanes). The mixture was transferred to a flask and the organic volatiles were removed in vacuo to afford a solid residue. The residue was purified by flash chromatography over 3 g of silica gel (eluted in 30 % EtOAc/hexanes) to afford 40 mg of alcohol 106 in quantitative yield as a beige solid: mp 50-51 °C; IR (neat) 3322 (broad), 1693 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.90 (t, \(J = 8\) Hz, 3H, \(\text{CH}_2\text{CH}_3\)), 1.28-1.90 (m, 14H, \(\text{CH}_2\)-manifold, \(\text{CHCH}_3\)), 2.17 (m, 1H, =CHCH\(_2\)), 2.30 (m, 1H, =CHCH\(_2\)), 3.60 (m, 2H, OCH\(_2\)), 3.70 (m, 1H, NHCH), 4.47 (s, 1H, NH), 5.03 (m, 1H, OCH), 5.10 (d, \(J = \))
13.5 Hz, 2H, =CH$_2$), 5.77 (m, 1H, =CH); $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ 14.0, 20.4, 22.6, 25.6, 27.2, 31.7, 35.1, 38.7, 50.5, 60.9, 117.8, 134.4, 178.5; HRME (EI) calculated for C$_{14}$H$_{27}$NO$_3$Na $m/e$ 280.188312, found $m/e$ 280.18914.
(S)-1-(Ethoxycarbonyl)propan-2-yl (S)-non-1-en-4-yl carbamate) (118). A dry 3-necked round-bottom flask was charged with 3.99 g (23.4 mmol) of carboxylic acid 69a and 50 mL of dry benzene. To the stirred solution, at room temperature, was added 3.2 mL (2.37 g, 23.4 mmol) of Et$_3$N via syringe, followed by addition of 5.2 mL (6.45 g, 23.4 mmol) of diphenylphosphoryl azide in one portion. The reaction mixture was heated to reflux for one hour and 3.51 g (26.5 mmol) of alcohol 98 was added via Pasteur pipette. The reaction mixture was heated under reflux for 36 h and an additional 1.60 g (11.9 mmol) of alcohol 98 was added. The mixture was heated for an additional 36 h under reflux, at which point the reaction was complete by TLC (silica gel, 20% EtOAc/hexanes). The mixture was cooled to room temperature and 20 mL of 5% aqueous citric acid was added. The mixture was transferred to a separatory funnel and the benzene layer was separated. The aqueous layer was extracted with two 20-mL portions of benzene. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and
concentrated in vacuo. The residue was purified by flash chromatography over 500 g of silica gel (eluted with 20% EtOAc/hexanes) to afford 5.43 g (77%) of desired urethane 118 as a beige solid: mp 34-35 °C; \([\alpha]^{23}_D\) -18.9° (c 1.07, CH3OH); IR (thin film) 3342, 1738, 1701 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 0.90 (t, \(J = 6.5\) Hz, 3H, CH\(_2\)CH\(_3\)), 1.28 (t, \(J = 6\) Hz, 3H, OCH\(_2\)CH\(_3\)), 1.20-1.40 (m, 10H, CH\(_2\)-manifold and CHCH\(_3\)), 1.48 (m, 1H, NHCHCH\(_2\)), 2.20 (m, 1H, =CHCH\(_2\)), 2.27 (m, 1H, =CHCH\(_2\)), 2.50 (dd, \(J = 14, 8\) Hz, 1H, CH\(_2\)CH\(_3\)), 2.63 (dd, \(J = 14, 10\) Hz, 1H, CH\(_2\)C=O), 3.68 (m, 1H, NHCH), 4.15 (q, \(J = 14, 2\) Hz, 2H, OCH\(_2\)), 4.42 (d, \(J = 8\) Hz, 1H, NH), 5.08 (d, \(J = 11\) Hz, 2H, =CH\(_2\)), 5.17 (m, 1H, CHCH\(_3\)), 5.78 (m, 1H, =CH); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) 14.0 (q), 14.2 (q), 20.2 (q), 22.6 (t), 25.6 (t), 31.7 (t), 34.6 (t), 39.5 (t), 41.3 (t), 50.5 (d), 60.5 (t), 67.6 (d), 117.7 (t), 134.4 (d), 155.3 (s), 170.5 (s); HRMS (EI) for C\(_{19}\)H\(_{29}\)NO\(_4\)Na calculated for m/e 322.1994, found m/e 322.1992.
1-Isothiocyanatobutane (119). To a stirred solution of 10.0 mL (7.4 g, 101 mmol) of n-butylamine and 4.1 g (101 mol) of NaOH in 100 mL of 10% aqueous THF was added 34 mL (43.0 g, 565 mmol) of carbon disulfide with cooling in an ice-bath. The mixture was stirred for 30 min and then 34 mL of 30% aqueous H₂O₂ was added dropwise via an addition funnel while maintaining the temperature below 40 ºC. Once addition of the peroxide was completed, the reaction was adjusted from pH 8.5 to pH 6.5 with concentrated HCl monitored using pH paper. The organic solvent was removed via atmospheric distillation to afford a residue which was dissolved in 75 mL of EtOAc. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with three 75-mL portions of EtOAc. The combined organic layers were concentrated via atmospheric distillation to afford a residue oil. The residue was purified by distillation at reduced pressure (80-100 ºC at 50 torr [lit. 83-85 ºC at 50 torr]) to afford 8.9 g (77%) of isothiocyanate 122 as a colorless oil: IR (neat) 2174, 2100 cm⁻¹; ¹H NMR (CDCl₃, 250 MHz) δ 0.97 (t, J = 6.8 Hz, 3H, CH₃), 1.48 (sextet, J = 7 Hz, 2H, CH₂CH₃), 1.69 (quintet, J = 7 Hz, 2H, CH₂CH₃), 3.52 (t, J = 6.8 Hz, 2H, NCH₂); ¹³C NMR (CDCl₃, 100 MHz) δ 13.2 (q), 19.8 (t), 31.9 (t), 44.7 (t), the N=C=S carbon was not observed.
3-Butyl-6-methyl-1,3-oxazinane-2,4-dione (123). A dry 3-necked round-bottom flask was charged with 2.00 g (17.4 mmol) of isothiocyanate 122 and 87 mL of dry CH$_3$CN. To the solution was added 2.17 g (1.92 mL, 20.8 mmol) of racemic β-hydroxybutyric acid in one portion, followed by addition of 9.2 g (41.6 mmol) of silver trifluoracetate. To the reaction mixture was added 8.7 mL (6.46 g, 62.8 mmol) of Et$_3$N via syringe. The mixture was heated to reflux and the reaction was monitored via $^1$H NMR and IR. After six hours the mixture was cooled to room temperature, filtered through a pad of celite, and the filtrate was concentrated in vacuo. The residue was dissolved in 50 mL of EtOAc and washed with 50 mL of H$_2$O. The organic phase was dried over Na$_2$SO$_4$, concentrated in vacuo and the residue was purified by flash chromatography over 250 g of flash silica gel (eluted with EtOAc/hexanes, 1:4 increasing to 3:7) to afford 0.100 g (3%) of the desired imide 123 as a yellow oil: IR (neat) 1757, 1698 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 500 MHz) δ 0.94 (t, $J = 7$ Hz, 3H, CH$_3$), 1.34 (sextet, $J = 8$ Hz, 2H, CH$_2$CH$_3$), 1.48 (d, $J = 5.5$ Hz, 3H, CHCH$_3$), 1.58 (m, 2H, CH$_2$CH$_2$CH$_3$), 2.46 (dd, $J = 16$, 11.5 Hz, 1H, CH$_2$C=O), 2.91 (dd, $J = 16$, 5 Hz, 1H, CH$_2$C=O), 3.78 (m, 2H, NCH$_2$), 4.60 (m, 1H, CH); $^{13}$C NMR
(CDCl₃, 125 MHz) δ 13.7 (q), 20.0 (t), 20.2 (q), 30.0 (t), 38.3 (t), 41.9 (t), 70.5 (d), 151.6 (s), 167.9 (s); HRMS (El) for C₉H₁₅NO₃Na calculated for m/e 208.0950, found m/e 308.0954.
cis- and trans-3-Butyl-6-methyl-4-(phenylthio)-1,3-oxazinan-2-one (124). A dry 3-necked flask was charged with 104 mg (0.561 mmol) of imide 123 and 5 mL of dry ethanol, and cooled to an internal temperature of 0 °C. To the stirred solution was added 57 mg (1.50 mmol) of NaBH₄ in one portion, followed by the dropwise addition of 0.4 mL of 2N HCl/EtOH every few min to buffer the reaction. After all of the ethanolic solution was added, the pH began to decrease below 9. The mixture was acidified with 2 N HCl/EtOH to approximately pH 1 and stirred for 10 min, and 1% KOH/EtOH was then added to basicify the reaction to pH 9. The reaction mixture was partitioned between 20 mL of H₂O and 20 mL of CH₂Cl₂. The CH₂Cl₂ phase was separated and the aqueous layer was extracted with three 20-mL portions of CH₂Cl₂. The organic phases were dried over Na₂SO₄, filtered, and concentrated in vacuo. To the residue was added 0.06 mL (62 mg, 0.563 mmol) of thiophenol, followed by 1 mg (0.005 mmol) of p-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 10 min at which point it was complete by TLC analysis (silica gel, 30% EtOAc/hexanes). To the mixture was added 10 mL of saturated aqueous NaHCO₃. The mixture was transferred to a separatory funnel and the aqueous layer was extracted with three 20-mL portions of CH₂Cl₂. The
organic layers were combined, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over 5 g of silica gel (eluted with 30% EtOAc/hexanes) to afford 75 mg (48%) of 124 as a pale yellow oil. This material was about 85% trans-124 based on integration of selected ¹H NMR signals. The remaining material was largely cis-124 with a small amount of other minor products. The mixture exhibited the following spectral data: IR (neat) 1697 cm⁻¹; HRMS (EI) calculated for C₁₅H₂₁NO₂SNa⁺ m/z 302.1185, found m/z 302.1187; NMR data for trans-124 (extracted from the mixture with help from a COSY spectrum) follow: ¹H NMR (signals due to trans-124, CDCl₃, 500 MHz) δ 0.93 (t, J = 5.5 Hz, 3H, CH₂CH₃), 1.34 (m, 2H, CH₂CH₃), 1.52-1.70 (m, 2H, NCH₂CH₂), 1.99 (dt, J = 15, 4 Hz, 1H, OCH₂-equatorial), 2.14 (dt, J = 12, 1.5 Hz, 1H, OCH₂-axial), 3.30 (m, 1H, NHCH₂), 3.62 (m, 1H, NHCH₂), 4.68 (dd, J = 2, 2 Hz, 1H, NCHS), 4.83 (m, 1H, OCH); ¹³C NMR (signals due to trans-124, CDCl₃, 100 MHz) δ 13.7 (q), 20.0 (t), 20.7 (q), 29.4 (t), 35.6 (t), 47.9 (t), 65.8 (d), 69.9 (d), 128.5 (d), 129.4 (d), 132.8 (s), 133.7 (d), 152.3 (s). ¹³C NMR data for cis-124 (extracted from spectra of mixture) follow: (CDCl₃, 100 MHz) δ 13.6 (q), 19.9 (t), 20.1 (q), 29.0 (t), 37.0 (t), 45.4 (t), 63.0 (d), 70.9 (d), 129.0 (d), 129.3 (d), 132.8 (s), 134.8 (d), 154.2 (s).
1-((Phenylthio)carbonyl)propan-2-yl butylcarbamate (126). A dry 3-necked flask was charged with 200 mg (2.01 mmol) of butylisocyanate and 10 mL of dry benzene at room temperature. To the solution was added 793 mg (4.04 mmol) of thioester 110 via Pasteur pipette, followed by warming at 60 °C. The reaction was complete by TLC (silica gel, 20% EtOAc/hexanes) after 18 h. The mixture was cooled to room temperature and the volatiles were removed \textit{in vacuo}. The residue was purified by flash chromatography over 50 g of silica gel (eluted with 20% EtOAc/hexanes) to afford 357 mg (60%) of carbamate 126 as a pale yellow oil: IR (neat with H₂O present) 1703 (broad) cm⁻¹; ¹H NMR (CDCl₃, 500 MHz) δ 0.93 (t, J = 6.8 Hz, 3H, CH₃), 1.30-1.43 (m, 5H, CH₂), 1.43-1.54 (m, 2H, NHCH₂CH₂), 2.82 (dd, J = 14.8, 6 Hz, 1H, CH₂C=O), 2.98 (dd, J = 9.5, 6.5 Hz, 1H, CH₂C=O), 3.18 (m, 2H, NCH₂), 4.62 (s, 1H, NH), 5.23 (m, 1H, OCH), 7.40 (s, 5H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 13.7, 19.9, 20.2, 32.0, 40.7, 49.5, 67.7, 127.5, 129.2, 129.4, 134.4, 155.7, 194.1.
Attempted Preparation of 3-Butyl-6-methyl-1,3-oxazinane-2,4-dione (129). A dry 3-necked round-bottom flask was charged with 28 mg of a 60% oil dispersion of sodium hydride (0.708 mmol), 6 mL of dry THF, and cooled in an ice-bath. To the cooled solution was added 0.200 g (0.677 mmol) of urethane 126 in one portion via Pasteur pipette. Another 28 mg (0.708 mmol) of the sodium hydride oil dispersion was added to the mixture over the course of 1 h at which point the reaction was complete by TLC (silica gel, 25% EtOAc/hexanes). To the mixture was added 2 mL of H₂O via Pasteur pipette and the contents of the flask were transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with three 20-mL portions of EtOAc. The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over 40 g of silica gel.
(eluted with 20→100% EtOAc/hexanes) to afford, in order of elution, 100 mg (26%) of 127, 90 mg of an inseparable 3:2 mixture of 128 (35%) and 129 (24%), and 15 mg (16%) of 130 as pale yellow oils: Data for 127: 1H NMR (CDCl₃, 400 MHz) δ 1.38 (d, J = 6.8 Hz, 3H, CH₃), 2.77 (dd, J = 15.2, 8.8 Hz, 1H, CH₂), 2.98 (dd, J = 15.2, 5.2 Hz, 1H, CH₂), 3.72 (m, 1H, CH), 7.20-7.54 (m, 10H, ArH). This material contained impurities in the δ 0.80-1.30 region and thus, the yield is probably lower than reported. Data for 128: The following peaks due to 128 were visible in the mixture: 1H NMR (CDCl₃, 400 MHz) δ 2.26 (dd, J = 14.6, 7.6 Hz, 1H, CH₂C=O), 2.52 (dd, J = 14.4, 6.4 Hz, 1H, CH₂C=O), 3.25 (m, 2H, NHCH₂), 3.69 (m, 1H, SCH), 5.65 (bs, 1H, NH), 7.20-7.45 (m, 5H, ArH); signals for other portions of 128 were apparent, but overlapped with signals from 129. Data for 129: The following peaks due to 129 were visible in the mixture: 1H NMR (CDCl₃, 400 MHz) δ 2.60 (dd, J = 14, 11 Hz, 1H, CH₂C=O), 2.77 (dd, J = 15.4, 1.5 Hz, 1H, CH₂C=O), 3.71 (m, 2H, NHCH₂), 4.57 (m, 1H, OCH). Data for 130: 1H NMR (CDCl₃, 400 MHz) δ 0.90 (t, J = 9 Hz, 3H, CH₃), 1.37 (m, 2H, CH₂CH₃), 1.50 (m, 2H, CH₂CH₂CH₃), 1.85 (d, J = 5.5 Hz, 3H, =CCH₃), 3.30 (m, 2H, NHCH₂), 5.62 (broad s, 1H, NH), 5.80 (d, J = 13 Hz, 1H, =CHC=O), 6.84 (m, 1H, =CHCH₃).
4,4-Dimethoxybutan-2-yl butylcarbamate (138). A 3-necked round-bottom flask was charged with 0.634 g (0.72 mL, 6.39 mmol) of freshly distilled butylisocyanate and 15 mL of dry benzene. To the solution was added 1.717 g (12.8 mmol) of racemic alcohol 137 in one portion via Pasteur pipette. The mixture was stirred at 60 ºC for 8 h, cooled to room temperature, and the volatiles were removed in vacuo. The residue was purified by flash chromatography over 200 g of silica gel (eluted with 20% EtOAc/hexanes) to afford 1.1 g (73%) of 138 as a pale yellow oil: IR (neat) 3349, 1698 (broad) cm⁻¹; ¹H NMR (C₆D₆, 500 MHz) δ 0.72 (t, J = 6 Hz, 3H, CH₂CH₃), 1.24 (m, 2H, CH₂CH₃), 1.13 (m, 2H, CH₂CH₂CH₃), 1.20 (d, J = 6 Hz, 3H, CHCH₃), 1.80 (ddd, J = 14, 6.5, 5 Hz, 1H, CHCH₂), 2.02 (ddd, J = 15, 8, 5 Hz, 1H, CHCH₃), 2.95 (m, 2H, NHCH₂), 3.15 (s, 3H, OCH₃), 3.16 (s, 3H, OCH₃), 4.09 (broad s, 1H, NH), 4.57 (dd, J = 6.8, 5 Hz, 1H, CH(OCH₃)₂), 5.71 (m, 1H, CHO); ¹³C NMR (C₆D₆, 125 MHz) δ 13.6 (q), 19.8 (t), 20.7 (q), 32.1 (t), 39.7 (t), 40.5 (t), 51.5 (q), 52.9 (q), 67.9 (d), 101.9 (d), 155.8 (s). HRMS (EI) for C₁₁H₂₃NO₄Na calculated for m/e 256.1525, found m/e 256.1529.
rel-(4S,6S)-3-Butyl-4-methoxy-6-methyl-1,3-oxazinan-2-one (139a) and rel-(4S,6R)-3-Butyl-4-methoxy-6-methyl-1,3-oxazinan-2-one (139b). A 3-necked round-bottom flask was charged with 0.481 g (2.06 mmol) of urethane 138 and 10 mL of dry CH₂Cl₂. To the solution was added 48 mg (0.20 mmol) of (-)-camphorsulfonic acid in one portion. The reaction mixture was stirred for 12 h while progress was monitored by TLC (silica gel, 20% EtOAc/hexanes). The mixture was transferred to a 1-necked flask and the volatiles were removed in vacuo. The residue was purified by flash chromatography over 40 g of silica gel (eluted with 40% EtOAc/hexanes) to afford 0.215 g (52%) of an inseparable mixture of N,O-acetals 139a and 139b as an orange oil. This material was approximately a 5:1 mixture of 139a and 139b, respectively, based upon integration of ¹H NMR signals at δ 4.59 (139a) and 4.74 (139b): IR (neat) 1701 cm⁻¹; ¹H NMR (signals due to 139a: CDCl₃, 400 MHz) δ 0.93 (t, J = 8 Hz, 3H, CH₂CH₃), 1.25-1.40 (m with d, J = 6 Hz, at 1.36, 5H, CHCH₃, CH₂CH₃), 1.51-1.72 (m, 3H, OCHCH₂, CH₂), 2.06 (dt, J = 14, 2 Hz, 1H, CHCH₂), 3.20 (m, 1H, NHCH₂), 3.36 (s, 3H, OCH₃), 3.53 (m, 1H, NHCH₂), 4.41 (dd, J = 3.2, 2.6 Hz, 1H, NHCH), 4.59 (m, 1H, OCH); ¹³C NMR (signals due to 139a: CDCl₃, 100 MHz) δ 13.9 (q), 20.1 (t), 20.7 (q), 30.1 (t), 33.2 (t), 48.3 (t), 106
55.5 (q), 69.0 (d), 85.5 (d), 152.6 (s). The following diagnostic signals for 139b were observed: $^1$H NMR (signals due to 139b, CDCl$_3$, 400 MHz), $\delta$ 1.9 (ddd, $J = 13.9, 10.4, 7.6$ Hz, 1H, OCHCH$_2$), 2.2 (ddd, $J = 14, 6.4, 2.8$ Hz, 1H, OCHCH$_2$), 3.3 (s, 3H, OCH$_3$), 4.3 (m, 1H, OCH), 4.74 (dd, $J = 8, 7.6$ Hz, 1H, NCHO). HRMS (EI) for C$_{10}$H$_{19}$NO$_3$ calculated for $m/e$ 224.1263, found $m/e$ 224.1270. Several $^{13}$C NMR signals due to 139b also appeared in the spectrum of the mixture (see Appendix).
Pent-4-enoyl chloride (140b). A dry 2-necked round-bottom flask was charged with 2.00 g (20 mmol) of freshly distilled 4-pentenoic acid and cooled to 0 °C (dry ice/ice/H₂O bath). To the solution was added 1.9 mL (2.8 g, 22.0 mmol) of oxalyl chloride via syringe in a dropwise manner. The reaction mixture was allowed to stir cold for approximately 30 min and then allowed to warm to room temperature. The reaction mixture was stirred for 4 h additionally while progress was monitored by IR. The mixture was transferred to a 5-mL conical flask fitted with a Hickman distillation head, water condenser, thermometer, and magnetic stir bar. The excess oxalyl chloride was distilled at 85 °C and one atmosphere. During distillation, pressure was slowly reduced to 45 torr while maintaining the oil bath temperature at 85 °C until all of the desired acid chloride had been collected to afford 1.00 g (42%) of 140b as a colorless oil: bp 85 °C (45 torr (lit. 44 40-42 °C [20 torr]); IR (neat) 1797 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 2.46 (q, J = 7 Hz, 2H, =CHCH₂), 3.02 (t, J = 7 Hz, 2H, CH₂C=O), 5.09 (dd, J = 8, 2 Hz, 1H, =CH₂), 5.12 (dd, J = 14, 2 Hz, 1H, =CH₂), 5.79 (tt, J = 14, 7 Hz, 1H, =CH).
4,4-Dimethoxybutan-2-yl but-3-enylcarbamate (141). A dry 3-necked flask was charged with 1.97 g (16.6 mmol) of acid chloride 140b and 8 mL of acetone, and cooled in an ice-bath. To the cooled solution was added 1.19 g (18.3 mmol) of NaN₃ and 0.5 mL of H₂O in one portion. The reaction mixture was stirred cold for 1 h and monitored by IR. When complete, the mixture was poured over crushed ice and extracted with three 20-mL portions of cold pentane. The organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo to afford 2.03 g (98%) of the desired acyl azide 140c as a colorless oil: IR (neat with acetone) 2134, 1716 cm⁻¹. A dry 3-necked, round-bottom flask was charged with 0.816 g (6.52 mmol) of aforementioned acyl azide and 32 mL of dry benzene, and heated to 60 °C for 1 h during which time rapid bubbling ensued. To the heated solution was added 1.75 g (13.0 mmol) of racemic alcohol 137 via Pasteur pipette in one portion. Heating was continued for 10 h at which point, the reaction was complete by IR. The mixture was cooled to room temperature and the volatiles were removed in vacuo. The resulting residue was purified by flash chromatography over 60 g
of silica gel (eluted with 20% EtOAc/hexanes) to afford 0.575 g (38%) of 141 as a pale yellow oil: IR (neat) 3340, 1698 cm\(^{-1}\); \(^1\)H NMR (C\(_6\)D\(_6\), 500 MHz) \(\delta\) 1.30 (d, \(J = 6.8\) Hz, 3H, CHCH\(_3\)), 1.91 (ddd, \(J = 12, 8, 5\) Hz, 1H, CHCH\(_2\)), 2.0 (m, 2H, =CHCH\(_2\)), 2.13 (ddd, \(J = 12, 8, 5\) Hz, 1H, CHCH\(_2\)), 3.11 (m, 2H, NHCH\(_2\)), 3.27 (s, 3H, OCH\(_3\)), 3.28 (s, 3H, OCH\(_3\)), 4.27 (broad s, 1H, NH), 4.67 (dd, \(J = 7, 3\) Hz, 1H, CH(OCH\(_3\))\(_2\)), 4.99 – 5.01 (m, 2H, =CH\(_2\)), 5.33 (sextet, \(J = 8\) Hz, 1H, CHO), 5.58 (m, 1H, =CH); \(^{13}\)C NMR (C\(_6\)D\(_6\), 125 MHz) \(\delta\) 20.8 (q), 34.4 (t), 39.9 (t), 40.2 (t), 51.7 (q), 53.1 (q), 68.3 (d), 102.1 (d), 116.7 (t), 135.6 (d), 156.0 (s); HRMS (EI) calculated for C\(_{11}\)H\(_{21}\)NO\(_4\)Na \(\text{m/e}\) 254.1368, found \(\text{m/e}\) 254.1375.
rel-(4S,6S)-3-(But-3-enyl)-4-methoxy-6-methyl-1,3-oxazinan-2-one (142a) and rel-(4S,6R)-3-(but-3-enyl)-4-methoxy-6-methyl-1,3-oxazinan-2-one (142b). A dry 3-necked, round-bottom flask was charged with 575 mg (2.45 mmol) of urethane 141 and 8 mL of dry CH₂Cl₂, and cooled in an ice-bath. To the mixture was added 57 mg (0.245 mmol) of (-)-camphorsulfonic acid in one portion. The reaction mixture was monitored by TLC (silica gel, 20% EtOAc/hexanes) and was complete after 8 h. To the reaction mixture was added 0.5 mL of saturated aqueous NaHCO₃. The organic volatiles were removed in vacuo and the residue was dried over Na₂SO₄. The dried residue was purified by flash chromatography over 40 g of silica gel (eluted with 40% EtOAc/hexanes) to afford 320 mg (66%) of an inseparable mixture of desired N,O-acetals 142a and 142b as a pale yellow oil. This material was approximately an 11:1 mixture of 142a and 142b, respectively, based upon integration of ¹H NMR signals at δ 4.30 (142a) and 4.15 (142b):

¹H NMR (signals due to 142a, C₆D₆, 500 MHz) δ 0.94 (d, J = 7.5 Hz, 3H, CH₃), 1.04 (ddd, J = 12, 10, 2 Hz, 1H, axial-CHCH₂CH), 1.33 (d, J = 14 Hz, 1H, equatorial-CHCH₂CH), 2.37 (m, 1H, =CHCH₂), 2.44 (m, 1H, =CHCH₂), 2.77 (s, 3H, OCH₃), 3.19
(m, pentet, $J = 5\text{ Hz}$, 1H, NHCH$_2$), 3.54 (ddd, $J = 12.6, 8.5, 6\text{ Hz}$, 1H, NHCH$_2$), 3.9 (broad, s, 1H, OCHN), 4.31 (m, 1H, CHCH$_3$), 4.95 (dd, $J = 8, 2\text{ Hz}$, 1H, =CH$_2$), 5.03 (dd, $J = 15.5, 2\text{ Hz}$, 1H, =CH$_2$), 5.71 (m, 1H, =CH); $^{13}$C NMR (signals due to 142a, C$_6$D$_6$, 125 MHz) $\delta$ 20.5 (q), 32.92 (t), 32.96 (t), 48.2 (t), 54.5 (q), 68.3 (d), 85.9 (d), 116.4 (t), 135.8 (d), 151.7 (s); HRMS (EI) calculated for C$_{10}$H$_{17}$NO$_3$Na $m/e$ 222.1106, found $m/e$ 222.1096.
Octahydro-3-methyl-1-oxopyrido[1,2-c][1,3]oxazin-6-yl formate (143). A dry 2-necked, round-bottom flask was charged with 100 mg (0.50 mmol) of \(N,O\)-acetal 142 and 0.1 mL of dry \(CH_2Cl_2\). The reaction mixture was stirred rapidly and cooled in an ice-bath. To the cooled solution was added 1 mL (1.22 g, 26.5 mmol) of 99% formic acid in a rapid manner via Pasteur pipette. The reaction was complete by TLC (silica gel, 70% EtOAc/hexanes) after 2.5 h. The excess formic acid was removed \textit{in vacuo} and the residue was dissolved in 1 mL of saturated aqueous NaHCO\(_3\) and stirred for several minutes. The solution was diluted with 10 mL of saturated aqueous NaHCO\(_3\) and the aqueous layer was extracted with three 10-mL portions of \(CH_2Cl_2\). The organic layers were dried over Na\(_2\)SO\(_4\), filtered, and concentrated \textit{in vacuo}. The residue was purified by flash chromatography over 5 g silica gel (eluted with 70% EtOAc/hexanes) to afford 61 mg (57%) of a mixture of formate esters as a colorless oil. This material was an approximately 2:1 mixture of 143a and 143b, respectively, based on integration of \(^1\)H NMR signal at \(\delta\) 5.00 (143a) and 4.90 (143b). This material also contained at least one (possibly two) additional minor compounds (possibly stereoisomeric formates at \(C_6\)) that are estimated to comprise no more than 10% of the product mixture (based on NMR spectra). Spectral data for 37a extracted from the mixture, with help from the \(^1\)H-\(^1\)H and
$^1$H-$^{13}$C COSY spectra (see appendix) follow: $^1$H NMR (signals due to the major
diastereomer 143a, CDCl$_3$, 500 MHz) $\delta$ 1.33 (d, $J = 7$ Hz, 3H, CH$_3$), 1.51-1.62 (m, 2H, H$_7$, H$_5$), 1.74 (dt, $J = 14$, 3 Hz, 1H, H$_{4e}$), 1.96-2.06 (m, 3H, H$_7$, H$_5$, H$_{4ax}$), 2.75 (ddd, $J = 13.5$, 13.5, 2.5 Hz, 1H, H$_{8ax}$), 3.89 (m, 1H, H$_{4a}$), 4.40 (m, 1H, H$_3$), 4.46 (ddd, $J = 12$, 5, 2 Hz, 1H, H$_{8c}$), 4.99 (tt, $J = 10$, 5 Hz, 1H, H$_6$), 7.99 (s, 1H, CHO); $^{13}$C NMR (signals due to
143a, CDCl$_3$, 125 MHz), 20.3 (q), 30.8 (t), 34.1 (t), 37.9 (t), 42.8 (t), 50.2 (d), 70.0 (d),
70.1 (d), 153.1 (s), 160.0 (d). Diagnostic signals for 143b: $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$
2.77 (dt, $J = 12.4$, 11.3, 2.5 Hz, 1H, H$_{8ax}$), 3.40 (m, 1H, H$_{4a}$), 4.3 (m, 1H, H$_3$), 4.55 (ddd, $J = 12$, 5, 2, 1H, H$_{8eq}$), 4.9 (tt, $J = 10$, 5 Hz, 1H, H$_6$); $^{13}$C (signals due to 143b, CDCl$_3$,
125 MHz) $\delta$ 20.7 (q), 30.3 (t), 36.8 (t), 38.3 (t), 42.2 (t), 51.6 (d), 69.6 (d), 71.7 (d), 153.3
(s), 160.1 (d); HRMS of mixture (EI) calculated for C$_{15}$H$_{15}$NO$_4$Na $m/e$ 236.0899, found
$m/e$ 236.0903.
Hexahydro-6-hydroxy-3-methylpyrido[1,2-c][1,3]oxazin-1(3H)-one (144). A 1-necked flask was charged with 150 mg (0.70 mmol) of formate esters 143a and 143b and 1 mL of methanol. To the stirred solution was added 39 mg (0.975 mmol) of crushed NaOH pellets in one portion, followed by 0.2 mL of H2O. The reaction mixture was stirred at room temperature and was complete by TLC (silica gel, 60% EtOAc/hexanes) after 20 min. The mixture was diluted with 5 mL of CH2Cl2 and transferred to a 10-mL test tube. The organic layer was separated via Pasteur pipette, dried over Na2SO4, and concentrated in vacuo to afford 0.103 g (87%) of a mixture of alcohols 144a and 144b as a white, semi-solid. Due to the presence of stereoisomers (and possibly other materials), the 1H NMR and the 13C NMR spectra of this material were complex. The major components of the mixture appeared to be 144a and 144b, present in an approximately 2:1 ratio, respectively, based on the presence of H6 as tt (J = 8.5, 4 Hz) at δ 3.7 (144b) and 3.8 (144a).

The stereochemical assignments are based on subsequent experiments. The spectrum also revealed other peaks in the expected chemical shift ranges (including a broad OH signal at δ 3.0), but they are too complex to report here (see appendix). The 13C NMR spectrum of the mixture was also complex, but, did show (in addition to minor signals) 18 carbons suspected to be due to the major isomer 144a: (CDCl3, 125 MHz) δ 20.4 (q), 34.4 (t),
34.6 (t), 41.7 (t), 43.4 (t), 50.6 (d), 68.2 (d), 70.2 (d), 153.7 (s); and the minor isomer 144b: (CDCl<sub>3</sub>, 125 MHz) δ 20.8 (q), 34.1 (t), 37.1 (t), 42.2 (t), 42.8 (t), 53.5 (d), 67.6 (d), 72.0 (d), 153.8 (s). The mixture gave a mass spectrum of stereoisomers: HRMS (EI) for C<sub>9</sub>H<sub>15</sub>NO<sub>3</sub>Na calculated for m/e 208.0950, found m/e 208.0951.
rel-(3R,4aS)-3,4,4a,5-Tetrahydro-3-methylpyrido[1,2-c][1,3]oxazine-1,6-dione (145a) and rel-(3S,4aS)-3,4,4a,5-Tetrahydro-3-methylpyrido[1,2-c][1,3]oxazine-1,6-dione (145b). A dry 2-necked round bottom flask fitted with a water condenser was charged with 100 mg (0.540 mmol) of alcohol 144 and 5 mL of dry CH₃CN. To the stirred solution was added 453 mg (1.618 mmol) of IBX in one portion. The reaction mixture was heated to reflux under argon. The reaction was complete by TLC (silica gel, 50% EtOAc/hexanes) after 8 h. The mixture was cooled to room temperature and filtered over a pad of celite. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography over 6 g of silica gel (eluted with 50% EtOAc/hexanes) to afford 14 mg (29%) of an inseparable mixture of enones 145a and 145b as a pale yellow oil. The ratio of 145a: 145b was 3:2 respectively, based on integration of the ¹H NMR signals at δ 4.2 (145b) and 4.3 (145a). This material also contained some minor impurities.

Signals due to 145a follow: ¹H NMR (CDCl₃, 500 MHz) δ 1.49 (d, J = 7 Hz, 3H, CHCH₃), 2.08-2.28 (m, 2H, CHCH₂CH), 2.47-2.67 (m, 2H, CH₂C=O), 4.28 (m, 1H, NCH), 4.78 (m, 1H, OCH), 5.53 (d, J = 8 Hz, 1H, =CHC=O), 8.05 (d, J = 7.5 Hz, 1H, =CHN); ¹³C NMR (CDCl₃, 125 MHz) δ 19.8 (q), 33.0 (t), 42.5 (t), 50.2 (d), 72.8 (d),
110.0 (d), 143.8 (d), 149.96 (s), 192.1 (s). Signals due to 145b follow: $^1\text{H NMR (CDCl}_3\text{)}$ δ 1.47 (d, $J = 6 \text{ Hz}$, 3H, CHCH$_3$), 4.14 (m, 1H, NCH), 4.58 (m, 1H, OCH), 5.53 (d, $J = 8 \text{ Hz}$, 1H, =CHC=O), 8.05 (d, $J = 7.5 \text{ Hz}$, 1H, =CHN); $^{13}\text{C NMR (CDCl}_3\text{, 125 MHz)}$ δ 20.9 (q), 35.7 (t), 42.2 (t), 53.5 (d), 74.2 (d), 109.8 (d), 143.6 (d), 149.86 (s), 192.9 (s). The following data were recorded on the mixture: IR (neat) 1714, 1668 cm$^{-1}$; HRMS (EI) calculated for C$_9$H$_{11}$NO$_3$Na $m/e$ 204.0637, found $m/e$ 204.0633. The NMR for 145b data agree with those reported for enantiomerically pure material.\textsuperscript{17}
(S)-4,4-Dimethoxybutan-2-yl (S)-non-1-en-4-ylcarbamate (71). A 2-necked round-bottom flask was charged with 1.69 g (9.92 mmol) of carboxylic acid 69a, 50 mL of dry benzene, and stirred at room temperature. To the solution was added 1.38 mL (1.00 g, 9.88 mmol) of Et$_3$N via syringe, followed by addition of 2.2 mL (2.73 g, 9.92 mmol) of diphenylphosphoryl azide. The mixture was heated to reflux for 1 h at which point it was complete by IR analysis. To the reaction mixture was added 1.60 g (11.9 mmol) of alcohol 6 via Pasteur pipette and the mixture was warmed under reflux for 36 h. The reaction was complete by TLC (silica gel, 15% EtOAc/hexanes). The mixture was then cooled to room temperature and 10 mL of 5% aqueous citric acid was added and the mixture was transferred to a separatory funnel. The benzene layer was separated and the aqueous layer was extracted with three 30-mL portions of benzene. The organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was purified by flash chromatography over 100 g of silica gel (eluted with 15% EtOAc/hexanes) to afford 0.760 g of an inseparable mixture of 71 and 131 as a colorless oil. This material was
approximately a 8:1 mixture of 71 and 131, respectively, based upon integration of $^1$H NMR signals at $\delta$ 5.65 (71) and 5.68 (131). A small portion of this mixture (120 mg) was separated by HPLC (eluted with 40→60% CH$_3$CN:H$_2$O) to afford 80 mg (74%) of 71 and 14 mg (100%) of 131. The spectral data for each pure sample is as follows, 71: IR (neat) 1693 cm$^{-1}$; $^1$H NMR (signals due to 71, C$_6$D$_6$, 500 MHz) $\delta$ 0.87 (t, $J = 8$ Hz, 3H, CH$_2$CH$_3$), 1.03-1.27 (m, 8H, CH$_2$-manifold), 1.15 (d, $J = 8$ Hz, 3H, CHCH$_3$), 1.82 (ddd, $J = 14$, 6.5, 5 Hz, 1H, OCHCH$_2$), 1.92 (m, 1H, =CHCH$_2$), 2.04 (m, 2H, OCHCH$_2$, =CHCH$_2$), 3.17 (s, 3H, OCH$_3$), 3.20 (s, 3H, OCH$_3$), 3.75 (m, 1H, NCH), 4.0 (s, 1H, NH), 4.58 (dd, $J = 6.5$, 5.0 Hz, 1H, OCHO), 4.94-4.98 (m, 2H, =CH ), 5.23 (m, 1H, CHO), 5.64 (m, 1H, =CH); $^{13}$C NMR (signals due to 71, C$_6$D$_6$, 125 MHz) $\delta$ 13.8 (q), 20.5 (q), 22.6 (t), 25.5 (t), 31.6 (t), 34.5 (t), 39.5 (t), 39.6 (t), 50.2 (d), 51.3 (d), 52.9 (q), 67.8 (d), 101.8 (d), 117.0 (t), 134.7 (d), 155.4 (s); HRMS (EI) for C$_{16}$H$_{31}$NO$_4$Na calculated $m$/$e$ 324.2151, found $m$/$e$ 324.2149. 131: IR (thin film) 3330, 1626 cm$^{-1}$; 1H NMR (signals due to 24b, C$_6$D$_6$, 500 MHz) $\delta$ 0.90 (t, $J = 7$ Hz, 6H, CH$_3$), 1.14-1.40 (m, 16H, CH$_2$CH$_2$CH$_2$CH$_2$), 2.05 (ddd, $J = 14$, 7, 7 Hz, 2H, =CHCH$_2$), 2.19 (ddd, $J = 14$, 7, 7 Hz, 2H, =CHCH$_2$), 3.33 (s, 1H, NH), 3.35 (s, 1H, NH), 3.96 (m, 2H, NCH), 5.01-5.08 (m, 4H, =CH$_2$), 5.78 (m, 2H, =CH); $^{13}$C NMR (signals due to 131, C$_6$D$_6$, 125 MHz) $\delta$ 14.2, 23.0, 26.0, 32.1, 35.4, 40.4, 49.4, 117.0, 135.7, 157.0; HRMS (EI) for C$_{19}$H$_{36}$NO$_2$Na calculated $m$/$e$ 309.2906, found $m$/$e$ 309.2908.
(S)-4,4-Dimethoxybutan-2-yl (S)-non-1-en-4-ylcarbamate (71). A dry 2-necked round-bottom flask was charged with 0.500 g (2.9 mmol) of carboxylic acid 69a and cooled to 0 ºC (dry ice/ice/H₂O bath). To the solution was added 0.3 mL (0.410 g, 3.23 mmol) of oxalyl chloride via syringe in a dropwise manner. The reaction mixture was allowed to stir cold for approximately 30 min and then allowed to warm to room temperature. The reaction mixture was stirred for another 8 h while progress was monitored by IR. The excess oxalyl chloride was removed in vacuo to afford 0.548 g (99%) of desired acid chloride 146 as a colorless oil, immediately used in the next reaction. A dry 3-necked flask was charged with 0.548 g (16.6 mmol) of acid chloride 146 and 1.5 mL of acetone, and cooled in an ice-bath. To the cooled solution was added 0.208 g (3.2 mmol) of NaN₃ and 0.1 mL of H₂O in one portion. The reaction mixture was stirred cold for 1 h and monitored by IR. When the reaction was complete, the mixture was poured over crushed ice and extracted with three 20-mL portions of cold
hexanes. The organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to afford 0.504 g (89%) of the desired acyl azide **147** as a colorless oil: IR (neat with acetone) 2134, 1713 cm$^{-1}$. A dry 3-necked, round-bottom flask was charged with 0.504 g (2.58 mmol) of aforementioned acyl azide and 8 mL of dry benzene, and heated to 60 °C for 1 h during which time rapid bubbling ensued. To the heated solution was added 0.820 g (6.11 mmol) of alcohol **70** via Pasteur pipette in one portion. Heating was continued for 12 h at which point, another 0.206 g (1.54 mmol) of **70** was added. Heating was continued for 10 h at which point the reaction was complete by IR. The mixture was cooled to room temperature and the volatiles were removed in vacuo. The resulting residue was purified by flash chromatography over 60 g of silica gel (eluted with 20% EtOAc/hexanes) to afford 0.334 g (43%) of **71** as a pale yellow oil: IR (neat) 1693 cm$^{-1}$; $^1$H NMR (C$_6$D$_6$, 500 MHz) $\delta$ 0.87 (t, $J = 8$ Hz, 3H, CH$_2$CH$_3$), 1.03-1.27 (m, 8H, CH$_2$-manifold), 1.15 (d, $J = 8$ Hz, 3H, CHCH$_3$), 1.82 (ddd, $J = 14$, 6.5, 5 Hz, 1H, OCHCH$_2$), 1.92 (m, 1H, =CHCH$_2$), 2.04 (m, 2H, OCHCH$_2$, =CHCH$_2$), 3.17 (s, 3H, OCH$_3$), 3.20 (s, 3H, OCH$_3$), 3.75 (m, 1H, NCH), 4.0 (s, 1H, NH), 4.58 (dd, $J = 6.5$, 5.0 Hz, 1H, OCHO), 4.94-4.98 (m, 2H, =CH$_2$), 5.23 (m, 1H, CHO), 5.64 (m, 1H, =CH); $^{13}$C NMR (C$_6$D$_6$, 125 MHz) $\delta$ 13.8 (q), 20.5 (q), 22.6 (t), 25.5 (t), 31.6 (t), 34.5 (t), 39.5 (t), 39.6 (t), 50.2 (d), 51.3 (d), 52.9 (q), 67.8 (d), 101.8 (d), 117.0 (t), 134.7 (d), 155.4 (s); HRMS (EI) for C$_{16}$H$_{31}$NO$_4$Na calculated $m/e$ 324.2151, found $m/e$ 324.2149.
REFERENCES


APPENDIX

SPECTRAL DATA
98
PV-III-219
(500 MHz, CDCl₃)
99a
PV-IV-86
(500 MHz, CDCl₃)

* = signals due to 99b
99b
PV-IV-86
(125 MHz, CDCl₃)

* = signals due to 99b
PV-IV-112
(500 MHz, C$_6$D$_6$)
100
PV-IV-112
(125 MHz, C₆D₆)
$^{99b}$

(CDCl$_3$, 500 MHz)
101
PV-IV-114
(500 MHz, C₆D₆)
OTHP

PV-IV-114
(500 MHz, C₆D₆)
PV-IV-114
(125 MHz, C₆D₆)
70
PV-IV-118
(500 MHz, C₆D₆)
PV-IV-118
(500 MHz, C$_6$D$_6$)
PV-IV-118
(125 MHz, C₆D₆)
103a

PV-IV-119
(CDCl₃, 500 MHz)
103a
PV-IV-119
(CDC13, 125 MHz)
103a
PV-III-240
(500 MHz, CDCl₃)
$\text{H}_3\text{CO}$

$\text{O}$

$\text{O}$

$\text{CF}_3$

$\text{Ph}$

103a

PV-III-240

(500 MHz, CDCl$_3$)
PV-III-235
(125 MHz, CDCl₃)
107
PV-III-206
(500 MHz, C₆D₆)
107
PV-III-206
(125 MHz, C₆D₆)
PV-III-209
(500 MHz, C₆D₆)
PV-III-209
(125 MHz, C₆D₆)
110
PV-IV-43
(CDCl$_3$, 500 MHz)
110
PV-IV-43
(CDCl$_3$, 125 MHz)
112b
PV-IV-100
(500 MHz, CDCl₃)
112b
PV-IV-100
(125 MHz, CDCl₃)
113b
PV-IV-102
(500 MHz, CDCl₃)
113b
PV-IV-102
(125 MHz, CDCl$_3$)
114b
PV-IV-104
(CDCl₃, 125 MHz)
69a
PV-IV-105
(CDCl₃, 500 MHz)
PV-IV-99
(500 MHz, CDCl3)
113a
PV-IV-101
(500 MHz, CDCl₃)
Current Data Parameters
NAME: PV-IV-101
EXPNO: 2
PROCNO: 1

F2 - Acquisition Parameters
Date: 20061012
Time: 19.12
INSTRUM: spect
PROBHD: 5 mm Multinucl
PULPROG: zgpg30
TD: 65536
SOLVENT: CDCl3
NS: 242
DS: 4
SWH: 30030.029 Hz
FIDRES: 0.458222 Hz
AQ: 1.0912344 sec
R: 8192
DW: 16.650 usec
DE: 6.00 usec
TE: 300.2 K
D1: 2.000000 sec
G1: 0.000000 sec
DELTA: 1.899999 sec
MCREST: 0.000000 sec
MCRWK: 0.015000 sec

======== CHANNEL f1 ========
NUC1: 13C
P1: 13.00 usec
PL1: 3.00 dB
SFO1: 125.742702 MHz

======== CHANNEL f2 ========
CPDPRG: waltz16
NUC2: 1H
PCPD2: 100.00 usec
PL2: -1.00 dB
PL12: 18.80 dB
PL13: 120.00 dB
SFO2: 500.02200 MHz

F2 - Processing parameters
SI: 32768
SF: 125.73013 MHz
W: 1.00 Hz
SSB: 0
LB: 1.00 Hz
PC: 1.00

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113a
PV-IV-101
(125 MHz, CDCl3)
114a
PV-IV-103
(CDCl$_3$, 500 MHz)
PV-IV-103 (CDCl$_3$, 125 MHz)

114a
PV-IV-106 (CDCl₃, 500 MHz)
115
PV-IV-111
(CDCl₃, 500 MHz)
PV-III-197
(CDCl₃, 400 MHz)
106
PV-III-203
(CDCl$_3$, 500 MHz)
106
PV-III-203
(CDCl$_3$, 125 MHz)
118
PV-III-172
(CDCl₃, 500 MHz)
118
PV-III-172
(CDCl₃, 125 MHz)
122
PV-III-304
(CDCl₃, 100 MHz)
PV-IV-6
(CDCl₃, 500 MHz)
PV-IV-15
(CDCl$_3$, 500 MHz)
124
PV-IV-15
(CDCl₃, 125 MHz)
PV-IV-37
(CDCl₃, 400 MHz)
130
PV-IV-37
(CDCl₃, 400 MHz)
138
PV-IV-55
(CDCl$_3$, 500 MHz)
139a
PV-IV-61
(CDCl₃, 125 MHz)

139b

* = signals due to 139b
140b
PV-IV-63
(CDCl₃, 400 MHz)
* = impurities

141
PV-IV-72
(CDCl₃, 500 MHz)

192
PV-IV-72
(CDCl₃, 125 MHz)
$^{142a}$

**PV-IV-73**

(CDCl$_3$, 500 MHz)

$^{142b}$

* = signals due to $^{142a}$

o = signals due to $^{142b}$

* = signals due to EtOAc

ppm
192a
PV-IV-73
(CDCl₃, 125 MHz)

192b
37a
PV-IV-74
(CDCl3, 500 MHz)

* = signals due to 37a
o = signals due to 37b
143a
PV-IV-74
(CDCl₃, 125 MHz)

* = signals due to 143a
o = signals due to 143b
PV-IV-80
(CDCl₃, 500 MHz)
144a
PV-IV-80
(CDCl₃, 125 MHz)

144b