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Progress Towards the Total Synthesis of Bengazole A, an Antifungal Natural Product from a Marine Sponge *Jaspis* sp.

By

CYNTHIA MARIE SHAFER

B. S. (Oklahoma State University) 1992

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

in the

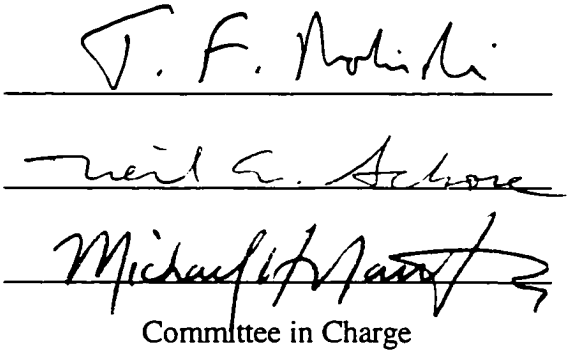
OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

Approved:



Committee in Charge

1998

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I would like to thank my advisor Dr. Tadeusz Molinski for sharing with me his enthusiasm for chemistry and his knowledge and unique laboratory techniques. Ted taught me to be an avid yet thorough scientist, and I am proud to be his first Ph.D. graduate. I would also like to thank Dr. Philip Searle, my friend and labmate, for teaching me numerous laboratory techniques and patiently answering many questions. Also many thanks for all of the Junior Mints! Former and current Molinski group members who have pored over NMR spectra and shared their lives with me: Tami Hong, Julia Munsch, Karl Bailey, Sarah Brantley, Melanie Franklin Cleland, Cary Freidman, Valerie Root, Matt Sage, and Ana Rueda, our visiting graduate student from Spain -- Thank you all! In addition, I am grateful to Nicole Ortega, Dan Morse, and Jed Hubbs, all of whom worked with me as undergraduate researchers. Special thanks to Xenia Beebe Searle for acting as my mentor early in my graduate school career. Her encouragement and wisdom were very much appreciated. To the other members of my thesis committee, Dr. Michael Nantz and Dr. Neil Schore, I thank you for your interest in my academic career and for writing numerous letters of recommendation and reading my dissertation.

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Cynthia Marie Shafer

March 1998

Chemistry

Progress Towards the Total Synthesis of Bengazole A, an Antifungal Natural Product from a Marine Sponge *Jaspis* sp.

Abstract

Bengazole A is a highly potent antifungal agent from a marine sponge of the genus *Jaspis* sp. The structure of bengazole A contains a *bis*-(oxazolyl)methanol moiety which is an unprecedented motif among natural products. In addition, bengazole A is the only known marine natural product that contains a C5 monosubstituted oxazole. This dissertation research describes work towards the total synthesis of bengazole A and the development of new synthetic methodology.

Chapter 2 details the initial work on the synthesis of bengazole A including the attempted synthesis of the undescribed 2-formyloxazoline. While efforts to prepare a 2-formyloxazoline were unsuccessful, a novel oxidative rearrangement of 2-methyloxazoline to a dihydrooxazinone was discovered.

Chapter 3 develops the methodology of the oxazoline-dihydrooxazinone oxidative rearrangement, describes the chemistry of 3-unsubstituted dihydrooxazinones, and utilizes the oxidative rearrangement for the synthesis of optically pure (*S*)-*tert*-leucine. The mechanism of the oxidative rearrangement was investigated by kinetic studies, isolation of an intermediate, and ^{13}C labeling studies. These studies led to refinement of the proposed mechanism of reaction.

Chapter 4 describes the preparation of an advanced intermediate incorporating C1-C9 of bengazole A by taking advantage of the ambident nucleophilicity of 2-lithiooxazole

with preferential C4 addition to aldehydes. The aldehyde used in the synthesis, a precursor to the bengazole side chain, C1-C6, was prepared from the inexpensive sugar D-galactose.

Chapter 5 outlines a synthetically useful preparation of C5 monosubstituted oxazoles for incorporation in the last stage of bengazole A synthesis. The methodology allows selective deprotonation-electrophilic addition at C5 of 2-methylthiooxazole for the construction of 5-substituted oxazoles. The methylthio group is then conveniently removed by reductive desulfurization with Raney nickel.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

abs	absolute
AIBN	2,2'-Azobisisobutyronitrile
AIDS	Aquired Immune Deficiency Syndrome
aq	aqueous
atm	atmosphere
CD	circular dichroism
DEPT	distortionless enhancement by polarization transfer
DMAP	*N*,*N*-dimethylaminopyridine
DMPU	*N*,*N*'-dimethylpropylene urea
DMSO	dimethylsulfoxide
DSS	3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt
ee	enantiomeric excess
GC	gas chromatography
GCMS	gas chromatography/mass spectrometry
GI_{50}	concentration which inhibits cell growth by 50%
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IC_{50}	concentration which inhibits effect by 50%
IR	infrared spectroscopy
K_D	dissociation constant
KHMDS	potassium hexamethyldisilazide
MIC	minimum inhibitory concentration
MS	molecular sieves
NBS	*N*-bromosuccinimide

NMO	*N*-morpholine *N*-oxide
nOe	nuclear Overhauser effect
NMR	nuclear magnetic resonance
NR	no reaction
NT	not tested
PDC	pyridinium dichromate
satd	saturated
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TPAP	tetrapropylammonium perruthenate
p-TSA	*para*-toluenesulfonic acid

CHAPTER 1. INTRODUCTION

1.1 General

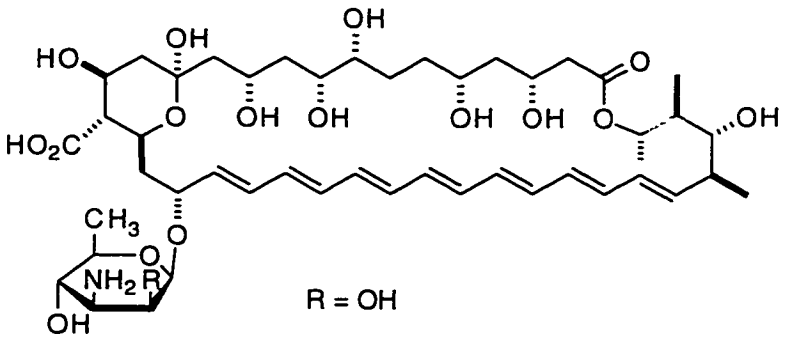
In the last decade, the incidence of fungal infections has increased significantly. AIDS, a disease that slowly weakens the immune system, is a major factor in the increasing number of fungal infections. Fifty-eight percent of the reported AIDS cases are associated with fungal infections, and the fourth most common life-threatening illness in AIDS patients is caused by the fungus, *Cryptococcus neoformans*.[1] Other fungal infections are a consequence of particular medical treatments.[1,2] Immunosuppressive drugs or procedures such as chemotherapy or bone marrow transplants impair the immune system. The weakened immune system renders the patient more susceptible to attack by opportunistic infectious agents, in particular yeasts and fungi. Patients who receive bone marrow transplants, for example, have an increased susceptibility to potentially fatal pneumonia caused by fungus *Aspergillus*.[2]

The pharmacopoeia lists many topical drugs for treatment of dermal or mucosal fungal infections such as athlete's foot or thrush, but very few drugs exist to treat disseminated fungal infections. The compounds used most commonly for systemic fungal infections are amphotericin B (**1**) and the azole drugs **4**-**6**,[3] but stringent limitations are placed on intravenous administrationif these agents because of their toxicity. Clearly, new drugs are needed.

1.1.1 Amphotericin B

Amphotericin B (**1**) is the only antifungal drug approved for intravenous use in the treatment of systemic fungal infections. It is fungicidal against a broad spectrum of fungal strains, but its severe side effects which include fever, chills, headache, vomiting, and nephrotoxicity limit its use to potentially fatal mycoses.[3] Amphotericin B (**1**) belongs to a

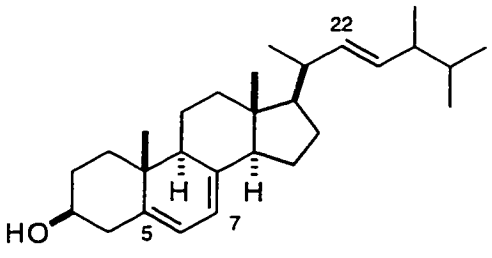
class of ~200 compounds known as polyene antibiotics that contains common structural elements-a macrolide ring, embodying a hydrophobic all *trans* conjugated polyene segment opposed by a hydrophilic polyol segment. The molecular structures of polyenes therefore resemble extended rods. Often the macrolide is glycosylated with the charged aminosugar, mycosamine (e.g. **1**).



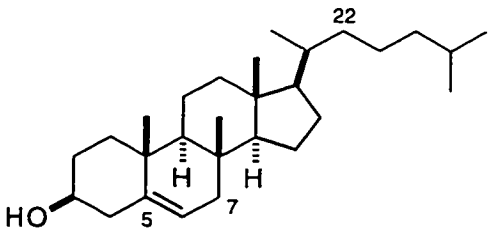
R = OH

1 Amphotericin B

The mechanism of action of amphotericin B (**1**) is complex but is believed to involve binding to ergosterol (**2**), the major sterol present in the fungal membrane, leading to increased permeability of the fungal cell membrane.



2 Ergosterol



3 Cholesterol

Several units of the non-covalent amphotericin B-ergosterol complex are thought to undergo self assembly to form a channel that spans the membrane bilayer. The ion permeable lumen is lined with the hydrophilic groups, and the hydrophobic exterior is

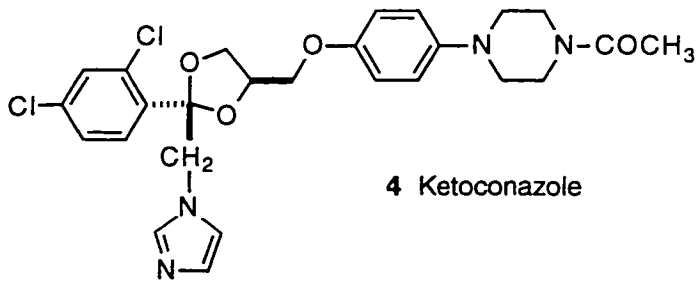
exposed to the lipid bilayer. Cations and other cellular constituents diffuse out of the cell through this hydrophilic lumen resulting in cell death.[4,5]

Amphotericin B's (**1**) severe side effects may be due in part to binding with cholesterol (**3**), the major sterol in mammalian cells, albeit with lower K_D than with ergosterol (**2**).[6]

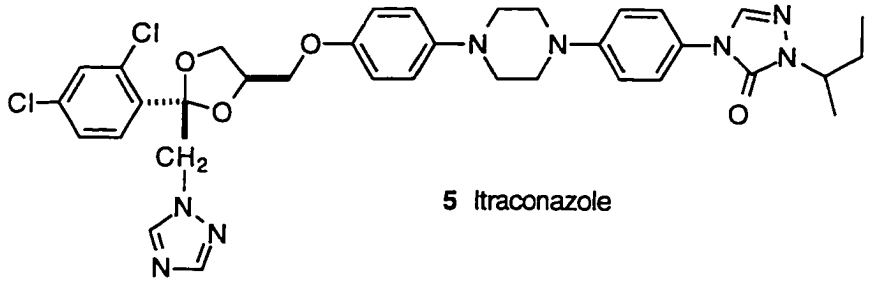
1.1.2 Azole Drugs

The molecular structure of azole antifungal drugs contains imidazole or triazole heterocycles (e.g. **4-6**). Imidazole compounds such as ketoconazole (**4**) were developed as antifungal drugs but induced hepatotoxicity with prolonged use. To circumvent this problem, the design of the structure of azole antifungals was refined giving the triazoles, itraconazole (**5**) and fluconazole (**6**). These compounds have excellent antifungal activity, oral availability, and metabolically stable triazole rings. They are also rapidly excreted. Fluconazole (**6**) is now the antifungal drug of choice in primary therapy.

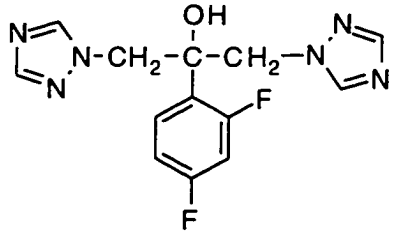
Azoles inhibit 14α-demethylase, a cytochrome P_{450}-dependent enzyme that oxidatively cleaves the C14 methyl group of lanosterol in the biosynthesis of ergosterol (**2**). Consequently, cell growth is suppressed in the presence of azoles.[7]



4 Ketoconazole



5 Itraconazole



6 Fluconazole

The azole drugs, in general, have a broad range of activity and low toxicity; however, they are fungistatic, not fungicidal. Consequently, maintenance therapy is necessary to prevent reinfection, and resistant strains of fungi have emerged.

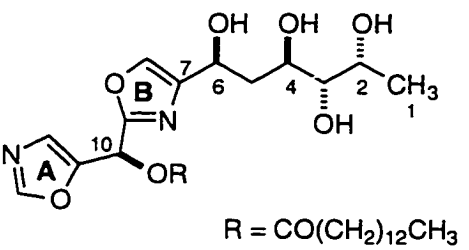
While resistance is not surprising with fungistatic drugs, it should not be overlooked that the polyene antibiotics have remarkably low rates of induced resistance. This is likely a consequence of the lethality of yeast mutations that might circumvent the essential role played by ergosterol in cell structure and function. Thus, while amphotericin B (**1**) has high attendant toxicity, the low incidence of resistance is an attractive property.

Since the few antifungal drugs currently used to treat systemic antifungal infections suffer from drawbacks such as toxic side effects or prolonged treatment, there is a need for new antifungals which overcome these limitations. To find leads for new antifungal drugs, research in the Molinski group has focused on the isolation of antifungal compounds from marine sponges. This effort led to the discovery of the antifungal activity of bengazole A (**7**),[8] a compound first isolated by Crews *et al.* from a marine sponge of the genus *Jaspis*

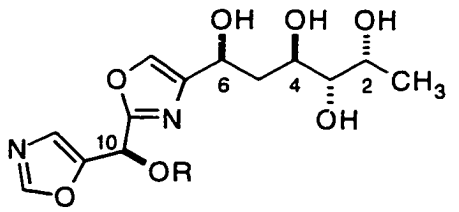
sp.[9] My dissertation research involves work towards the total synthesis of bengazole A (**7**).

1.2 Background of the Bengazole Natural Products

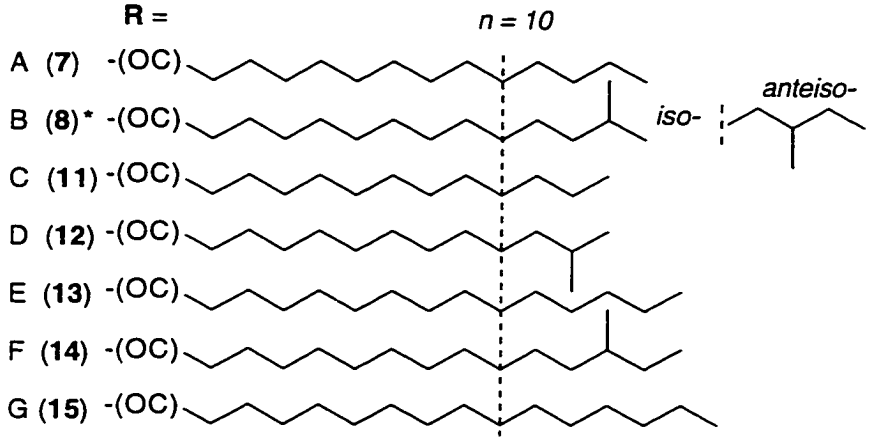
Bengazole A (**7**) is a marine natural product discovered by Adamczeski and coworkers in 1988 from a Fijian sponge of the order Choristida along with its homolog, bengazole B (**8**).[9] Bengazole A (**7**) contains two oxazole rings, structural elements which are rare in marine natural products. At the time of its discovery, only four other oxazole-containing metabolites had been isolated from marine organisms,[10-13] two of which, calyculin A (**9**) and halichondramide (**10**), were from sponges.[10,13] The structure of bengazole A (**7**) contains a *bis*-(oxazolyl)methanol moiety which is an unprecedented motif among natural products.[9]



7 Bengazole A



Bengazoles A-G



* Bengazole B (**8**) was isolated as an inseparable 5:1 mixture of *iso*- and *anteiso*- 15:0 fatty esters.[14]

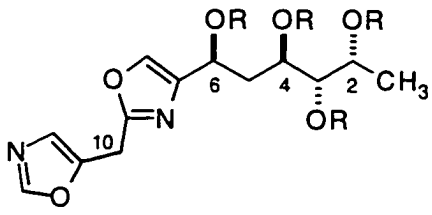
Figure 1. Bengazoles A-G (**7-8**, **11-15**)

Bengazoles A (**7**) and B (**8**) have also been isolated from a sponge of the genus *Jaspis* sp. from the Great Barrier Reef by the Molinski group (Department of Chemistry, University of California at Davis) along with new homologs, bengazole C-G (**11-15**, Figure 1).[8,14] The new bengazoles differ only in the composition of the fatty acyl side chain.[8,14]

1.2.1 Structural Variants of Bengazole A

A structural variant of the bengazole nucleus was discovered that lacks the C10 oxygen functionality.[15,16] Seven 10-desoxybengazoles, represented by structure **16**, were isolated from *Jaspis* cf. *coriacea*, collected in Papua New Guinea. The fatty acyl side chain, either a myristate (C_{14}) or pentadecanoate (C_{15}) ester, is present at one of the OH

groups on the tetraol side chain.[15] Digonazole, another 10-desoxybengazole isolated from the South African sponge *Jaspis digonoxea*, has a *n*-C_{21} ester at the C6 hydroxyl.[16]

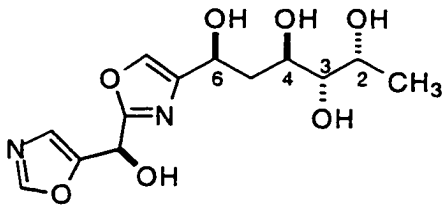


16 R = H, $CO(CH_2)_{12}Me$, $CO(CH_2)_{11}CHMe_2$, or $COC_{20}H_{41}$

1.2.2 Biological Activity of Bengazoles

Adamczeski *et al.* reported anthelminthic activity for **7** against the parasite *Nippostrongylus braziliensis*.[9] Bengazole A was later shown to exhibit *in vitro* antitumor activity against cultured cell lines of colon (COLO-205, GI_{50} 0.18 μM) and melanoma (SK-MEL-5, GI_{50} 1.13 μM).[15] Bengazoles A-G (**7-8**, **11-15**) show potent *in vitro* antifungal activity against the common human pathogen *Candida albicans* (MIC 1 μg/mL).[14,17]

The *in vitro* antifungal activity of **7** is comparable to that of amphotericin B (**1**). Further investigation has shown that bengazole A and amphotericin B may have a similar mode of action as the reactivity of **7** is also dependent on ergosterol (**2**).[8] If the long chain fatty ester is removed from bengazole A (**7**) giving compound **17**, all antifungal activity against *C. albicans* is abolished.[14] Whether bengazole A actually induces ion-permeable pore formation in membranes has not yet been established.



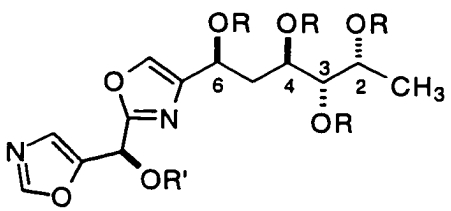
17

1.2.3 Absolute Configuration of Bengazole A

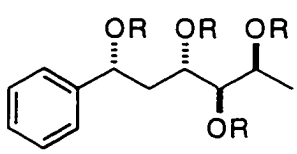
Adamczeski *et al.* identified the relative configuration of the chiral centers in the tetraol side chain of **7** (C1-C6) as 2*S**,3*R**,4*S**,6*R** by comparing nOe and vicinal ^1H coupling constants of a degradation product of bengazole A with those of models.[9] They were unable to determine the configuration of C10 and failed to address the absolute configuration. Thus, the stereochemical determination of **7** remained incomplete.

Dr. Philip Searle, a postdoctoral researcher in our lab, synthesized a variety of protected bengazole A analogs in order to obtain a crystal suitable for X-ray crystallography; however, only crystals of unsuitable dimensions were obtained.[14]

The complete configuration of **7** was successfully solved by chemical and chiroptical correlations. The modified Mosher's method[18] was used to determine 10*S* configuration, and the absolute stereochemistry of C2-C6 was deduced by comparison of the exciton coupling in the circular dichroism (CD) spectra of the tetra-*p*-bromobenzoate ester of bengazole (**18**) and a model compound **19** synthesized in 8 steps from L-fucose (20%).



18 R' = fatty acyl, R = *p*-BrBz



19 R = *p*-Br-Bz

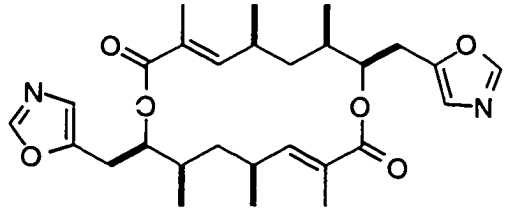
The CD spectra of **18** and **19** have Cotton effects of equal magnitude and wavelength but of opposite sign. This spectroscopic data indicated that the stereochemistry of C1-C6 in bengazole A is opposite of that in **19**, and thus the absolute configuration for bengazole A was assigned as 2*R*,3*S*,4*R*,6*S*,10*S*.[14] The configuration of this side chain, thus, correlates with D-fucose.

1.3 Review of Natural Products Containing Oxazoles

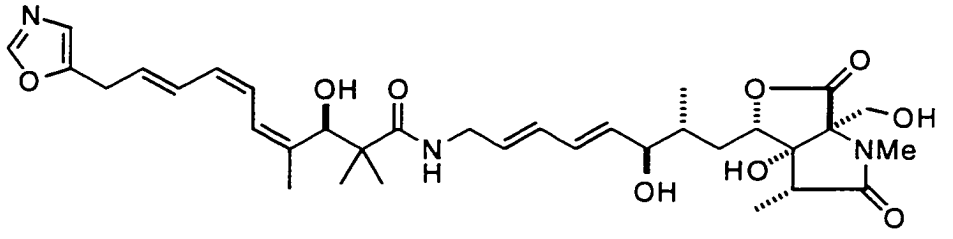
In the last 15 years, a number of oxazole containing marine natural products have been discovered. The majority of these compounds contain 2,4-disubstituted oxazoles which appear to result from mixed serine-polyketide biosynthesis.

The bengazole family of natural products contains two oxazole rings with differing substitution. Ring B is the common 2,4-disubstituted oxazole while ring A is a rare C5-monosubstituted oxazole. The other examples of naturally occurring 5-monosubstituted oxazoles are three bacterial products, conglobatin (**20**) and neooxazolomycin (**21**) and a related compound, oxazolomycin.[19-21]

The side chain of conglobatin (**20**) appears to be a tetraketide linked to the C5 position of oxazole (probably derived from *N*-formylglycine). The biosynthesis of oxazolomycin[22] has been studied and confirms a pentaketide origin of the C5 substituent.



20 Conglobatin



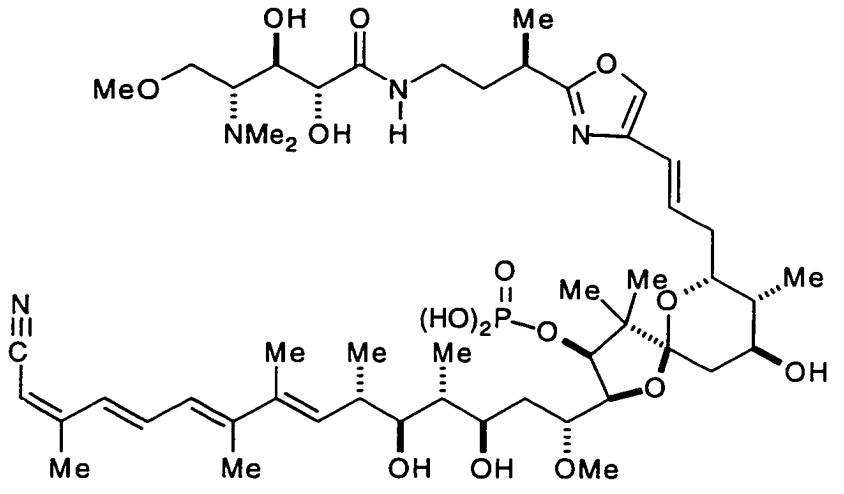
21 Neooxazolomycin

Lewis has reviewed naturally occurring oxazoles from microbial, plant and marine sources[23] This section will review a representative selection of important marine natural products containing oxazole rings.

1.3.1 Marine Natural Products Containing the Common Biogenic 2,4-Disubstituted Oxazole Ring

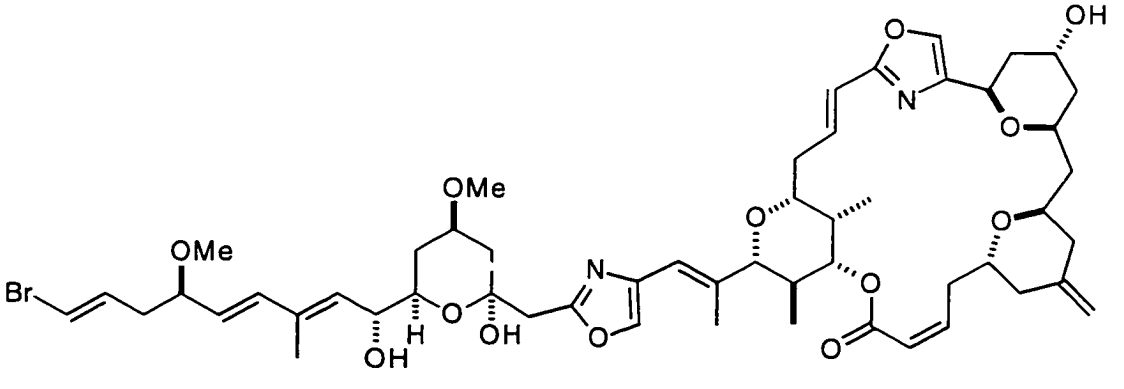
As stated previously, 2,4-disubstitution is the most common substitution pattern for marine derived oxazoles. In the one example studied to date, the biosynthesis of a 2,4 disubstituted oxazole arises from a serine amino acid residue by cyclodehydration-oxidation.[24]

Calyculin A (**9**) was isolated from a sponge *Discodermia calyx* and is a potent serine/threonine phosphatase inhibitor with IC_{50} values on the order of 1 nM.[10,25] The synthesis of **9** has been completed by Evans *et al.*[25] and Masemune *et al.*[26]



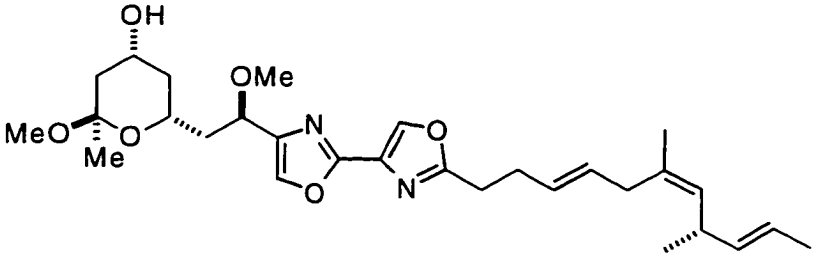
9 Calyculin A

Phorboxazoles A and B from the Indian ocean sponge *Phorbas* sp. have structures that contain two non-consecutive oxazole rings. Phorboxazole A (**22**) has impressive yet selective activity against solid colon tumors (HCT 116, IC_{50} 0.25 nM). Unlike many antimitotics, phorboxazole A does not inhibit tubulin polymerization. Instead **22** appears to arrest the cell cycle in the S phase.[27,28] Work on the total synthesis of phorboxazole A is currently under way in several laboratories.[29-32]



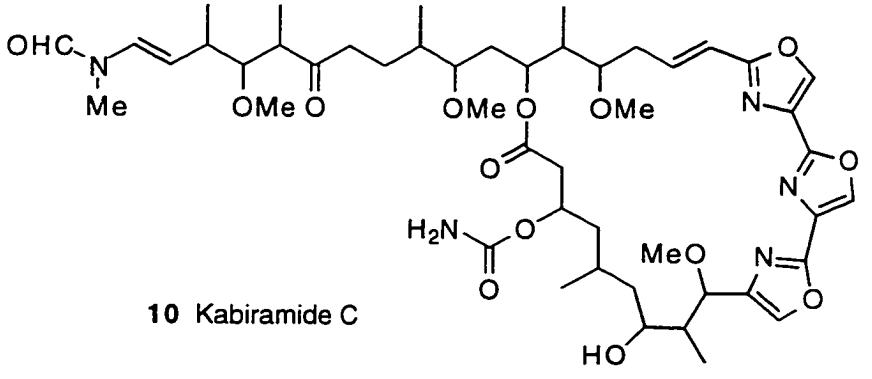
22 Phorboxazole A

Two families of marine natural products that contain contiguous 2,4-disubstituted oxazoles are the hennoxazoles and the halichondramides. Hennoxazole A (**23**) from the Pacific sponge *Polyfibrospongia* sp. is active against herpes simplex virus type I (IC_{50} 0.6 μg/mL).[33] The absolute configuration was assigned after completion of the synthesis of *ent*-**23**.[34,35]



23 Hennoxazole A

Kabiramide C (**10**) was isolated from the eggmasses of an unidentified nudibranch.[12] Kabiramide C (**10**) is one of about a dozen compounds in this class, all of which contain three contiguous 2,4-disubstituted oxazole rings.

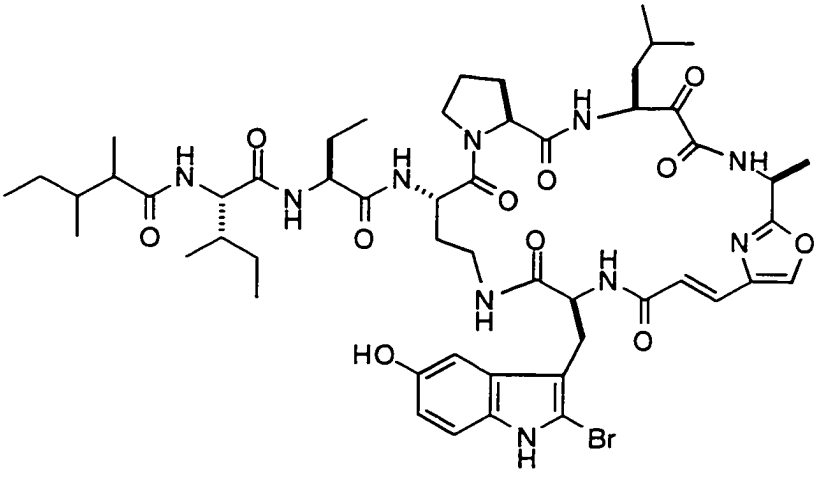


10 Kabiramide C

Other members of this family include the mycalolides from the sponge *Mycale* sp.,[36] the ulapualides, isolated from the eggmasses of the nudibranch *Hexabranchus sanguineus*,[11] and halichondramide, from the sponge *Halichondria* sp.[13,37] and also from its predator, the nudibranch *Hexabranchus sanguineus*.[37] All of the compounds have

shown potent antifungal or antitumor activity (IC_{50}'s of the mycalolides against B-16 melanoma cells are 0.5-1.0 ng/mL); however, *in vivo* experiments reveal these compounds to be highly toxic.[36] The mycalolides are potent inhibitors of actin polymerization.[38]

Keramamide D (**24**), isolated from a sponge of the genus *Theonella*, is a cyclic peptide containing an oxazole ring.[39] Keramamide D inhibits the superoxide generation response in human neutrophils (0.5 nM). Another compound of the keramamide family, keramamide F, has been the focus of a synthetic effort.[40] The discokiolides[41] and orbiculamide A[42] are other cyclic peptides containing oxazole rings.

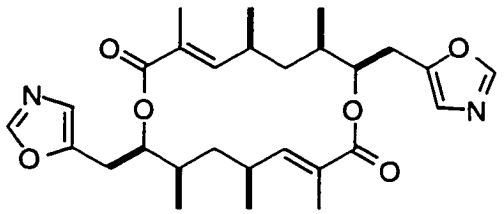


24 Keramamide D

1.3.2 Microbial Natural Products Containing a 5-Monosubstituted Oxazole Ring

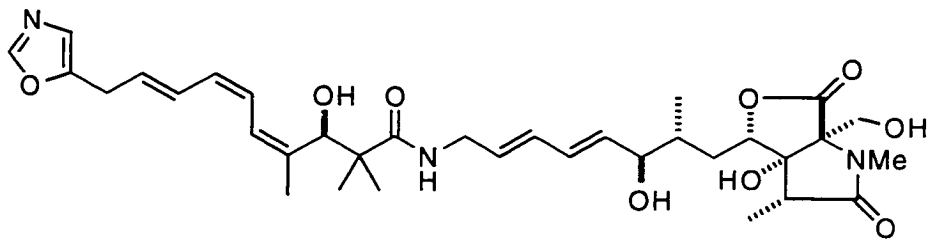
C5 monosubstituted oxazole rings are more rare in nature than the 2,4-disubstituted oxazole rings. At present, it is unknown how C5 monosubstituted oxazole rings arise biosynthetically although examination of structures **20** and **21** suggest *N*-formyl glycine as both polyketide starter unit and oxazole ring precursor. Conglobatin (**20**), isolated from *Streptomyces conglobatus* ATCC 31005, is the earliest example of a microbial natural product containing a C5 monosubstituted oxazole. Unlike the other oxazole containing

compounds reviewed here, conglobatin (**20**) shows no biological activity in antifungal, antibacterial, antiprotozoal or antitumor tests.[19]



20 Conglobatin

Neooxazolomycin (**21**)[21] and a congeneric β-lactone, oxazolomycin,[20] were isolated from *Streptomyces* sp. by a bioassay guided separation searching for Ehrlich ascites tumor inhibition. Both compounds also exhibited activity against P-388 leukemia and gram-positive bacteria. Neooxazolomycin has been synthesized by Kende *et al.*[43]



21 Neooxazolomycin

1.4 Research Objectives

After the complete configuration of **7** was determined, the purpose for the synthesis of **7** was to compare biological activity of the natural product with other analogs (structure-activity relationships) in order to gain additional insight into the mechanism of action of bengazole A. The research described in this dissertation outlines work toward the synthesis of bengazole A (**7**) and development of oxazole synthetic methodology for the

completion of the synthesis of bengazole A. To date, no synthesis of bengazole A or other members of the bengazole family has been reported.

1.5 Retrosynthetic Analysis

The initial retrosynthetic analysis of bengazole A (**7**) was derived from a (4*S*)-2-methyloxazoline-4-carboxylate ester, followed by oxidation of the methyl group to aldehyde **25** (Figure 2). Compound **25** would then be coupled with 5-lithio-2-trimethylsilyl-oxazole **26** as the ring A precursor to give **27**. It was envisioned that the chiral center at C4 on **25** would influence the diastereomeric ratio of coupling through chelation control.[44,45] Once rings A and B were coupled (**27**), the resultant alcohol would be protected and the C4 hydroxymethyl would be deprotected and transformed to an ester. The oxazoline would then be oxidized to an oxazole,[46,47] and the *bis*-(oxazolyl)methanol core would be coupled with the conjugate base of a carbohydrate-derived sulfone **28**. With the carbon skeleton intact, bengazole A (**7**) would be obtained by appropriate deprotection.

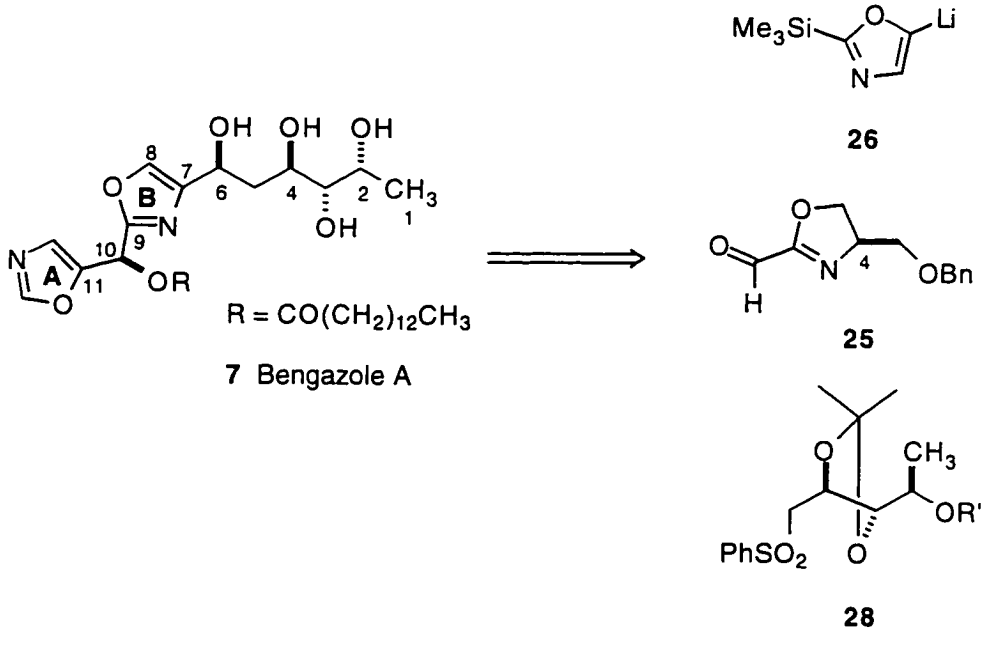
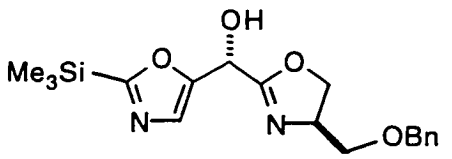


Figure 2. Retrosynthetic analysis of bengazole A: oxazoline precursor to ring B



27

1.6 Conclusion

In the event that the approach outlined above is unsuccessful, the retrosynthetic analysis in Figure 2 allows for alternate bond disconnections about C6-C7 and C10. It was necessary to take advantages of this flexibility, and a synthesis of an advanced oxazole-containing intermediate was eventually achieved *via* an alternate route (see Chapter 4).

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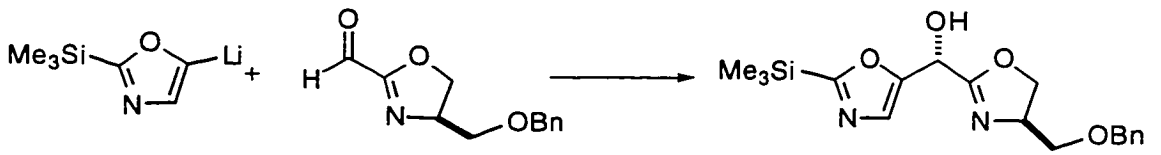
CHAPTER 2. SYNTHETIC APPROACHES TO C7-C13 FRAGMENT (RING A/RING B) OF BENGAZOLE A VIA OXAZOLINE PRECURSOR

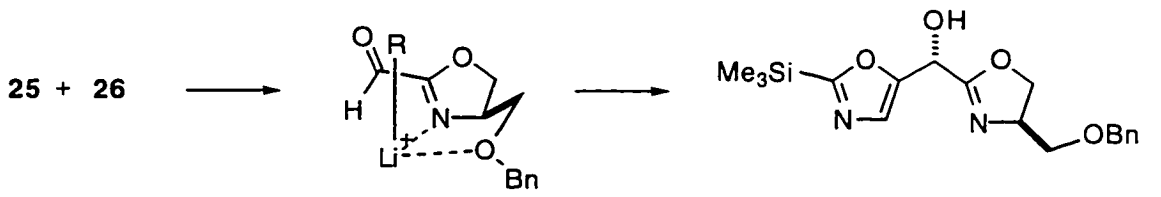
2.1 Introduction

As outlined in Chapter 1, the retrosynthetic scheme for bengazole A (**7**) requires formation of the *bis*-(oxazolyl)methanol core **27** (Figure 3) *via* 2-TMS-5-lithiooxazole **26** and aldehyde **25**. Literature precedence shows that high enantiomeric excess (92-99%) is obtained for nucleophilic addition of alkyl- and aryllithium compounds to 2-styryloxazolines (e.g. **29**).[1] The rationale for the high enantiomeric excess invokes chelation control by participation of lithium with the nitrogen and the benzyloxy group at C4. It was anticipated that 2-TMS-5-lithiooxazole **26** would add to 2-formyloxazolines and exhibit similar behavior. Figure 4 illustrates a possible transition state for asymmetric induction responsible for the configuration in **27**.



26 **25** **27**

Figure 3. Key intermediate (**27**) in the synthesis of bengazole A (**7**)



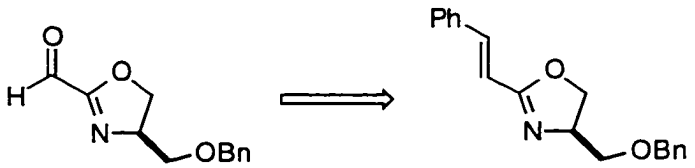
27

Figure 4. Chelation control leading to **27**

To examine the feasibility of this approach, 2-formyloxazoline (**25**) was required. The preparation of 2-formyloxazolines are not reported in the literature, but several syntheses were envisioned that would yield **25**. The attempts to prepare **25** are outlined in this chapter.

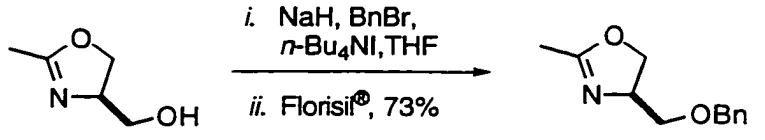
2.2 Attmepted Synthesis of 2-Formyloxazoline from 2-Styryloxazoline

Oxidative cleavage of the styryl C-C double bond in **29** was predicted to give **25**.

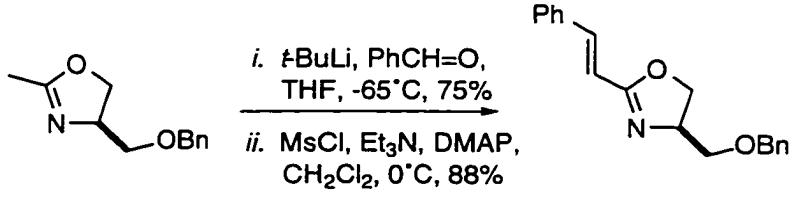


25 **29**

The requisite styrene **29** was obtained by a modification of the method reported by Meyers.[1] 4-Hydroxymethyl-2-methyl-oxazoline (**30**) was obtained by addition of L-serine ethyl ester hydrochloride and ethyl acetimidate hydrochloride. The ester was reduced to an alcohol with Red-Al®,[1] and the alcohol **30** was protected as a benzyl ether. Initially, the yields for the protection were low (20%), but, after considerable experimentation, an optimized yield of 74% was obtained by eliminating the aqueous workup, adsorbing the reaction mixture directly onto Florisil®, a neutral chromatography support, and eluting the product from a Florisil® column.[2] 2-Methyloxazoline **31c** was deprotonated with *t*-BuLi, and the anion added to benzaldehyde to form a secondary alcohol which was immediately subjected to elimination conditions. Direct dehydration of the alcohol in refluxing trifluoroacetic acid and dry toluene (Dean-Stark trap) gave substituted styrene **29** in low yield (18%).[1] Mesylation of the intermediate alcohol (MsCl, Et_3N, DMAP, CH_2Cl_2) and *in situ* elimination improved the yield to 88%.

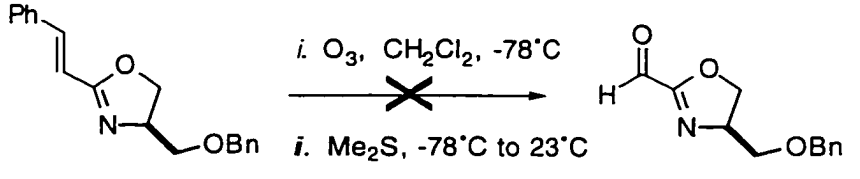


30 **31c**

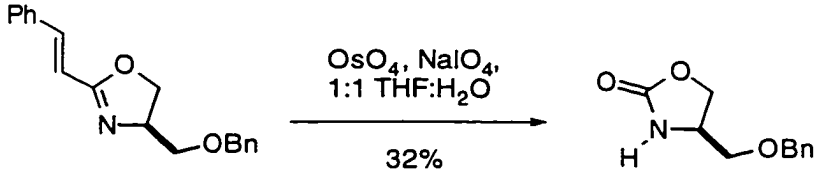


31c **29**

Ozonolysis[3] of **29** gave a mixture of products which were not further characterized, but no evidence of an aldehyde (^{1}H NMR) was observed. Ozonolysis most likely cleaved both imine bond and the olefin double bond. Use of osmium tetraoxide and sodium periodate[4,5] also failed to deliver **25** and gave only 2-oxazolidinone **32**.[6]



29 **25**

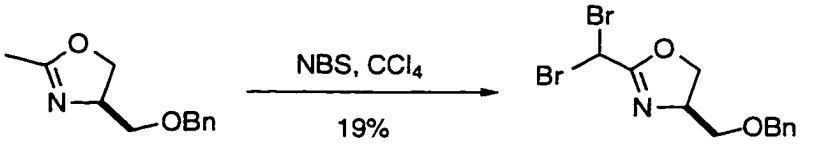


29 **32**

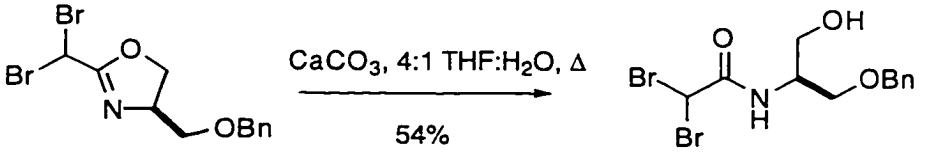
2.3 Attempted Synthesis of 2-Formyloxazoline from 2,2-Dibromomethyloxazoline

Indirect preparation of **25** was attempted by bromination of **31c** followed by hydrolysis. Treatment of **31c** with *N*-bromosuccinimide in carbon tetrachloride with irradiation from a tungsten lamp generally yielded a mixture of the mono-, di-, and tribrominated compounds. The highest yield of dibromide **33** was obtained when no additional illumination was used and the reaction was stopped before completion (19%; tribrominated compound 23%).

Hydrolysis of the dibrominated compound **33** was attempted using $CaCO_3$ in THF-H_2O under reflux. Only the ring-opened product **34** was obtained (56%). Silver nitrate in CH_3CN-H_2O (1:1) gave the same product **34** (23%).



31c **33**

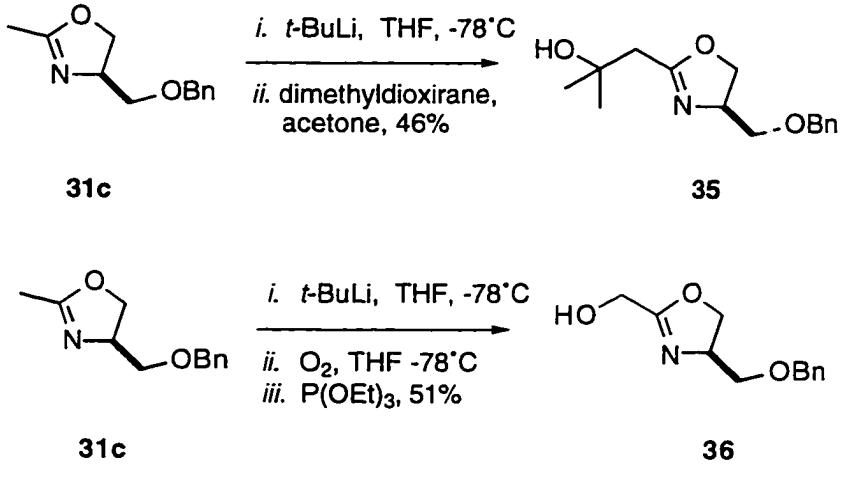


33 **34**

2.4 Attempted Synthesis of 2-Formyloxazoline from 2-Hydroxymethyloxazoline

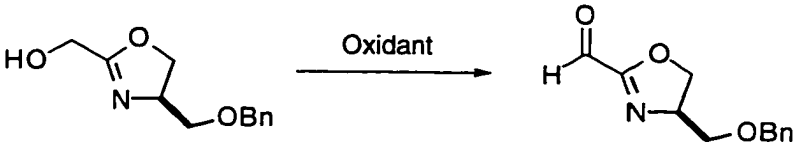
Application of the indirect oxidation methods described above were hampered by poor selectivity of oxidant or susceptibility of the oxazoline ring to hydrolytic ring opening. In order to circumvent these difficulties, a more straight-forward oxidation was attempted by direct oxidation of the anion of **31c**.

Deprotonation of **31c** with either *t*-BuLi or KHMDS in THF at -78°C followed by addition of 2-(phenylsulfonyl)-3-phenyl-oxaziridine[7,8] gave no reaction. A second attempt with dimethyldioxirane in acetone as the oxidant[9] gave the addition product of **31c** to acetone (**35**, 46%). Success was finally obtained by bubbling O_2 through a solution of the anion of **31c** (-78°C) and reducing the resulting hydroperoxide anion with triethylphosphite (**36**, 51%).



A variety of oxidants were tried to convert **36** to **25** (Table 1). Manganese oxide, a mild oxidant for the oxidation of allylic alcohols to aldehydes,[10,11] gave different results depending on the grade of MnO_2. With activated MnO_2 (Aldrich), no reaction occurred. Battery grade MnO_2 (Aldrich) gave no aldehyde but a new product **37**. The ^1H NMR spectrum of **37** showed a doublet at 7.90 ppm (J = 2.6 Hz, 84% by ^1H NMR). Similar results were obtained with pyridinium dichromate (PDC) in CH_2Cl_2. Swern's conditions ($(COCl)_2$, DMSO, Et_3N) resulted in an uncharacterizable mixture,[12] and tetra-*n*-propylammonium per-ruthenate (TPAP) and *N*-methyl morpholine *N*-oxide (NMO) in CH_2Cl_2 gave an unknown compound with an ^1H NMR signal at 8.1 ppm (singlet) which was not investigated further.[13,14]

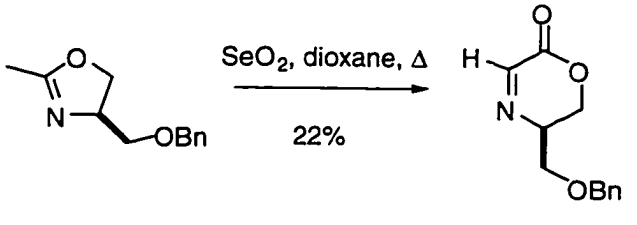
Table 1. Results from attempted oxidation of **36**



36 **25**

Oxidant	Characteristic ^1H NMR Signal (ppm)	Yield from 36 (%)	Product
MnO_2 (Activated)	–	–	NR
MnO_2 (Battery grade)	7.90 (d)	84 (by ^1H NMR)	**37**
PDC, CH_2Cl_2, powdered MS	7.90 (d)	6	**37**
Swern Oxidation (DMSO, oxalyl chloride, Et_3N)	–	–	–
TPAP, NMO	8.10 (s)	–	–

Finally, direct oxidation of **31c** with 2.2 eq of selenium dioxide in refluxing dioxane[15] gave dihydrooxazinone **37** in 22% yield, but no aldehyde.



31c **37**

2.5 Conclusion

In summary, none of the oxidants investigated gave an aldehyde, but some produced the novel dihydrooxazinone **37**. The formation and chemical properties of this compound will be discussed further in Chapter 3. None of the methods used to synthesize the 2-formyloxazoline (**25**) were successful indicating that a retooling of the synthetic scheme for the synthesis of bengazole A (**7**) was required. This will be discussed in Chapter 4.

2.6 References

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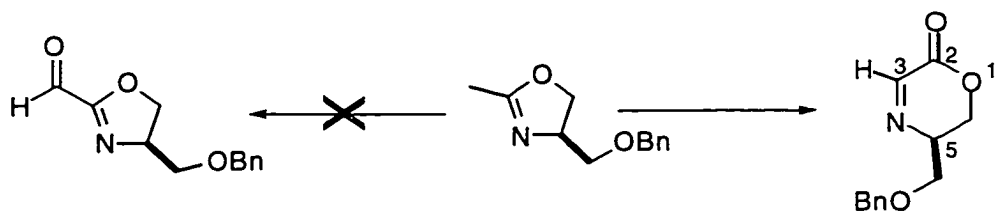
CHAPTER 3. OXIDATIVE REARRANGEMENT OF 2-SUBSTITUTED OXAZOLINES TO 5,6-DIHYDRO-2*H*-1,4-OXAZIN-2-ONES

3.1 Introduction

In the endeavor to synthesize 2-formyloxazolines **25**, an unprecedented oxidative rearrangement of an oxazoline was discovered (**31**→**37**). The significance of this finding is that it provides the first general method for preparation of 3-unsubstituted dihydrooxazinones.



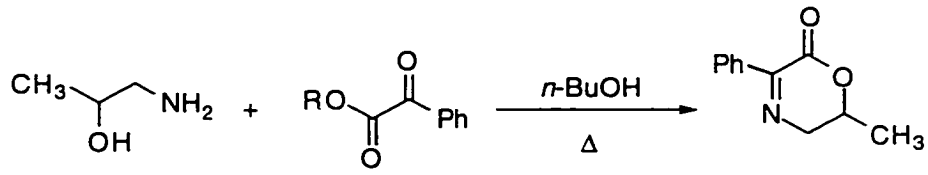
25 **31c** **37c**

5,6-Dihydro-2*H*-1,4-oxazin-2-ones (henceforth referred to as dihydrooxazinones) **37** have found a variety of uses. Koch discovered that dihydrooxazinones form captodative 2-oxomorpholin-3-yl radicals when treated with ultraviolet light in 2-propanol.[1] In addition, since the radicals serve as mild one-electron donors, electrons from two 2-oxomorpholin-3-yl radicals cause reductive cleavage of daunomycin, a potent anthracycline antibiotic used in the treatment of solid tumors.[2]

Dihydrooxazinones **37** have also served as precursors for the synthesis of morpholin-2-ones **38** which are then transformed into enantiomerically pure chiral amino acids.[3] Lastly, dihydrooxazinones have been used in a novel retro-aza-ene reaction to form protected amino acids in an enantiospecific manner *via* vacuum flash pyrolysis.[4]

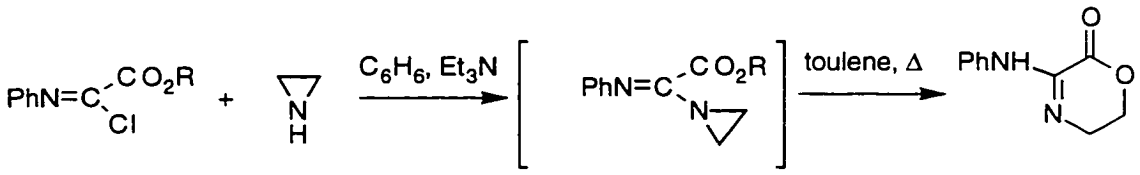
3.1.1 Preparative Methodology for Dihydrooxazinones

Very few syntheses for dihydrooxazinones **37** are available. The most common preparation is the one-step condensation and cyclization of an amino alcohol **39** with an α-ketoester **40** in alcoholic solution at reflux.[4-6] Yields range from 40-60% under these conditions and are plagued by formation of several byproducts.[6,7]



39 **40** **37**

Harwood modified this procedure by sequentially coupling an *N*-protected amino alcohol with an α-ketoester, deprotecting the nitrogen and cyclizing with concomitant dehydration giving the dihydrooxazinone (62% yield for 4 steps).[3] A more unusual method coupled aziridine (**41**) and chloroiminoacetates **42** to give aziridinyliminoacetates **43** which rearranged to 3-arylaminodihydrooxazinones at reflux in toluene (62% for 2 steps).[8]



41 **42** **43** **37**

Notably lacking is a general method for preparation of 3-unsubstituted dihydrooxazinones. The latter would find utility as an electrophilic "chiral glycine equivalent" for the preparation of α-amino acids. The first half of this chapter will illustrate a new route for preparing dihydrooxazinones while the second part will delve into the mechanistic details of the reaction. Both aspects of this work have been published.[9,10]

3.1.2 Spectroscopic Data for Dihydooxazinones

Heating a solution of oxazoline **31a**, $C_7H_{13}NO$, in dioxane with selenium dioxide (2.2 eq) at reflux resulted in efficient conversion to a single, less polar product (TLC) which was isolated after non-aqueous work-up. The product formula, $C_7H_{11}NO_2$ (HREIMS, *m/z* 141.0785, Δmmu 0.5), clearly showed oxidation of **31a** had taken place; however, the structure was that of dihydrooxazinone **37a** (75%) and not the anticipated isomeric 2-formyloxazoline **25**. The C2 methyl signal of **31a** had been replaced in the ^1H NMR spectrum of **37a** by a vinyl proton signal (δ 7.87, d, J = 2.8 Hz) which was now allylically coupled to the *N*-CH (δ 3.48, ^4J = 2.8 Hz). The IR spectrum revealed the presence of an ester carbonyl (ν 1748 cm^{-1}) and an imine double bond (1631 cm^{-1}) which were further corroborated by ^{13}C NMR (δ 154.5, s, C=O; 152.2, d, $^1J_{CH}$ 193 Hz, CH=N). The exceptionally high-field ^{13}C signal for the α,β-unsaturated azalactone carbonyl is characteristic of dihydrooxazinones.[4] Catalytic hydrogenation of **37a** (1 atm, H_2, Pd-C, Figure 5) gave morpholin-2-one **38a** ((5*S*)-5-isopropyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one, *m/z* 143.0944, Δmmu 0.2) as a ninhydrin-positive secondary amine. The spectroscopic data of **38a** (^1H NMR, ^{13}C NMR) compared well with literature values for related morpholin-2-ones.[3,11] In summary, the product of oxidation of oxazoline **31a** was shown to be the rearranged heterocycle **37a**.

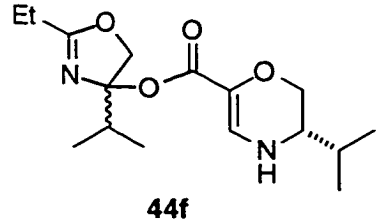
Conversion of **31i** to **37i** was achieved without detectable racemization at C5 as shown by chiral lanthanide reagent induced shifts in the ^1H NMR spectrum of (-)-**37i**. Resolution of the ^1H NMR signals of (±)-**37i** was achieved with (+)-Eu(hfc)$_3$; however, only one set of signals were detected in the reaction product (-)-**37i** (>99% ee).

3.2 Scope of Oxidative Rearrangement

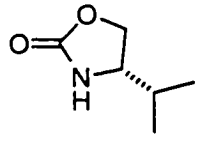
Because the known methods for preparing dihydrooxazinones **37** are low yielding or lack generality, the SeO_2-promoted oxidative rearrangement of oxazolines was explored

further. Table 2 summarizes the results of this investigation. The yields of **37** were highest when R was aryl or *tert*-alkyl [e.g. **31i** (94%), the naphthyl isomers **31k** (83%) and **31l** (93%), and the 2-neopentyl derivative **31h** (84%)]. The yield was lower for tertiary R (**31g**, 33%), and 2-ethyl oxazolines (R = Me) did not undergo the reaction at all but gave oxidized by-products which were tentatively assigned structures **44f** and *epi*-**44f** (~40% combined, entry 8).

The best yields of **37** from 2-methyloxazolines were obtained for compounds substituted at C4 with secondary alkyl or aryl groups (**31a**, 75%, **31b**, 72%). The C4 methyleneoxy-substituted oxazolines **31c-d** (entries 5 and 6) were also converted to the corresponding dihydrooxazinones **37c-d**, respectively, albeit in lower yields (22% and 53%), possibly due to competing side chain oxidation. The 'parent' oxazoline **31e** (entry 7) was oxidized with difficulty by SeO_2 to the simple, undescribed dihydrooxazinone **37e** (*m/z* 99) and in lower yield (60% by GC). Reaction of **31a** in refluxing THF (67°C) also gave **37a**; however, the reaction proceeded sluggishly with diminished yield (58%, entry 2). Oxidation of **31a** with SeO_2 in refluxing pyridine (entry 3) gave only traces of dihydrooxazinone **37a** with the other product being the known 2-oxazolidinone **45**,[12] arising from competitive oxidative carbon-carbon bond cleavage of the putative formyl intermediate **25a**.

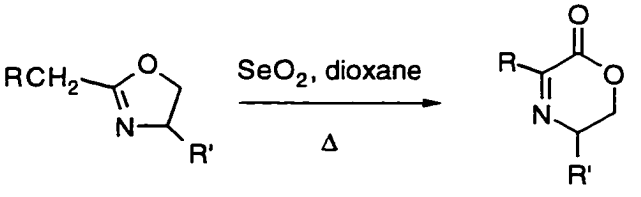


44f

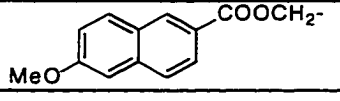


45

Table 2. SeO_2-promoted oxidative rearrangement of 2-substituted oxazolines



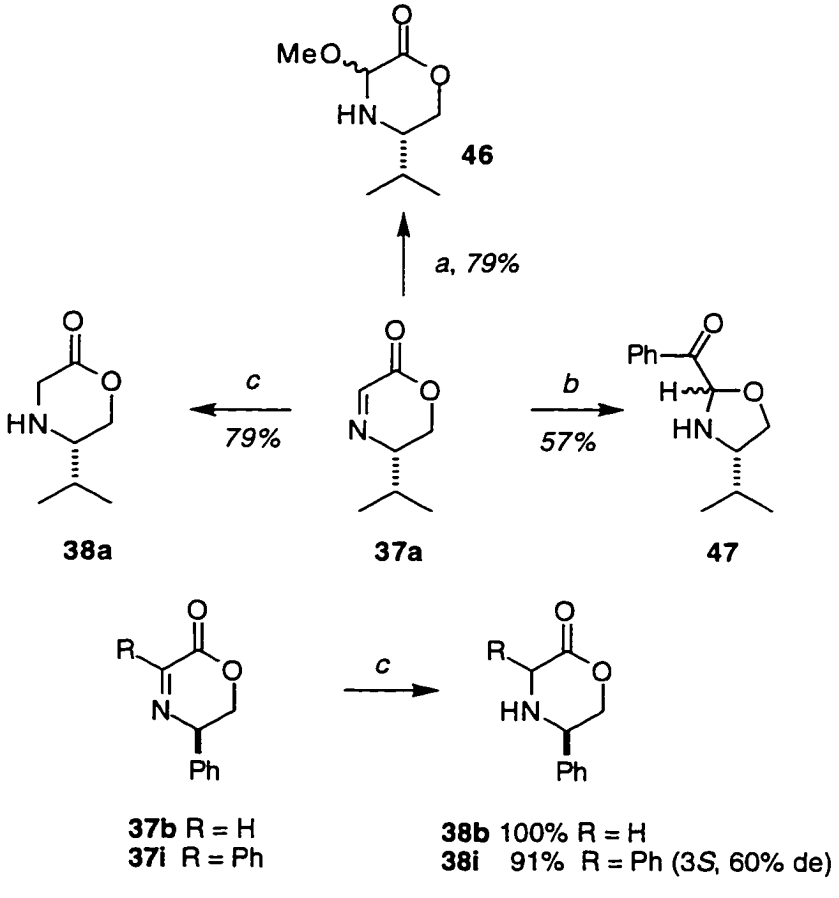
31 **37**

Entry	Oxazoline (**31**)	C4 of **31**	R	R'	Yield (%)	Product (**37**)
1	**31a**	*S*	H	*i*-Pr	75	**37a**
2	**31a**	*S*	H	*i*-Pr	58[a]	**37a**
3	**31a**	*S*	H	*i*-Pr	0[b, c]	-
4	**31b**	*R*	H	Ph	72	**37b**
5	**31c**	*R*	H	$BnOCH_2$-	22	**37c**
6	**31d**	*S*	H		53	**37d**
7	**31e**	-	H	H	60[d]	**37e**
8	**31f**	*S*	Me	*i*-Pr	0[e]	**37f**
9	**31g**	*S*	*i*-Pr	*i*-Pr	33	**37g**
10	**31h**	*R*	*t*-Bu	Ph	84	**37h**
11	**31i**	*R*	Ph	Ph	94	**37i**
12	**31j**	*S*	Ph	*i*-Pr	74	**37j**
13	**31k**	*R*	1-naphthyl	Ph	83	**37k**
14	**31l**	*R*	2-naphthyl	Ph	93	**37l**

(a) solvent was THF; (b) isolated product was 4-isopropyloxazolidinone (**45**); (c) carried out in pyridine; (d) GC yield. Product **37e** was detected by GCMS (*m/z* 99, M^+) and ^1H NMR (δ 7.88, t, 1H, CH=N, *J*= 2.3 Hz); (e) Only dimeric products **44f** and *epi*-**44f** were isolated in low yield (*ca.* 40%).

3.3 Reactivity of 3-Unsubstituted 5,6-Dihydro-2*H*-1,4-oxazin-2-ones

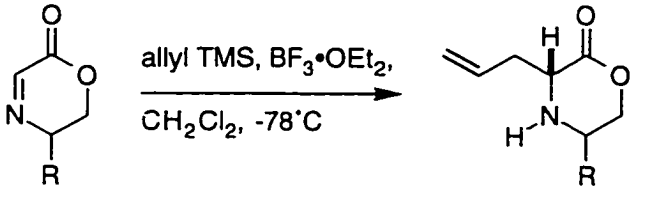
3-*Unsubstituted* dihydrooxazinones were unknown in the literature so their chemical properties were investigated (Figure 5). Heating dihydrooxazinone **37a** with methanol at reflux gave a 1:1 ratio of epimeric 3-methoxymorpholin-2-ones, **46** (96% yield). Addition of phenylmagnesium bromide to **37a** (-78 °C, THF, 20 min) gave the substituted epimeric 2-benzoyl-1,3-oxazolidines **47** by nucleophilic attack at the carbonyl group and subsequent ring closure by intramolecular addition of the liberated alkoxide to the 3,4-imine double bond. Brief catalytic hydrogenation of the imine bond (1 atm, H_2, Pd-C) in derivatives **37a**, **37b** and **37i** was quantitative and proceeded without hydrogenolysis of the benzylic carbon in **37b**.



a. MeOH, 60°C; *b.* PhMgBr, THF, -78°C; *c* H_2, Pd-C

Figure 5. Reactivity of 3-unsubstituted dihydrooxazinone nucleus

The electrophilic addition of allyltrimethyl silane to 3-unsubstituted dihydro-oxazinones **37a-b** (BF_3•OEt_2, CH_2Cl_2, -78°C) gave **48a-b**. The major diastereomer of **48b** showed a 10% nOe enhancement of H3 upon irradiation of the *ortho* phenyl proton signals indicating that the allyl group added from the opposite face of the phenyl ring. The diastereomeric ratio was determined by ^{13}C NMR to be 8:1.

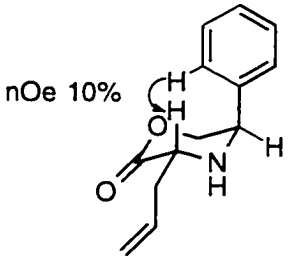


37a R = (*S*)-*i*-Pr

37b R = (*R*)-Ph

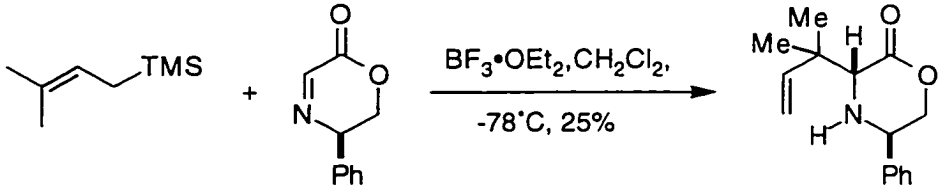
48a R = *i*-Pr, 78% (NMR yield)

48b R = Ph, 58%, 8:1 epimers



48b

Substituted silanes could also be used in this reaction. Reacting **37b** with trimethyl (3-methyl-2-butenyl)silane and BF_3•OEt_2 in CH_2Cl_2 at -78°C gave **48c** as a 4.5:1 mixture of diastereomers (25%) and exclusive addition at the more substituted allylic terminus.



37b **48c**

3.4 Synthesis of Chiral Amino Acids *via* Morpholin-2-ones

SeO_2-promoted oxidative rearrangement of **31** to **37** is useful in the synthesis of optically active α-amino acids. Although 3-substituted dihydrooxazinones have been utilized in the synthesis of chiral amino acids,[3] the previously unknown 3-*unsubstituted* analogs of **37** represent potentially useful chiral glycine synthons. The more familiar

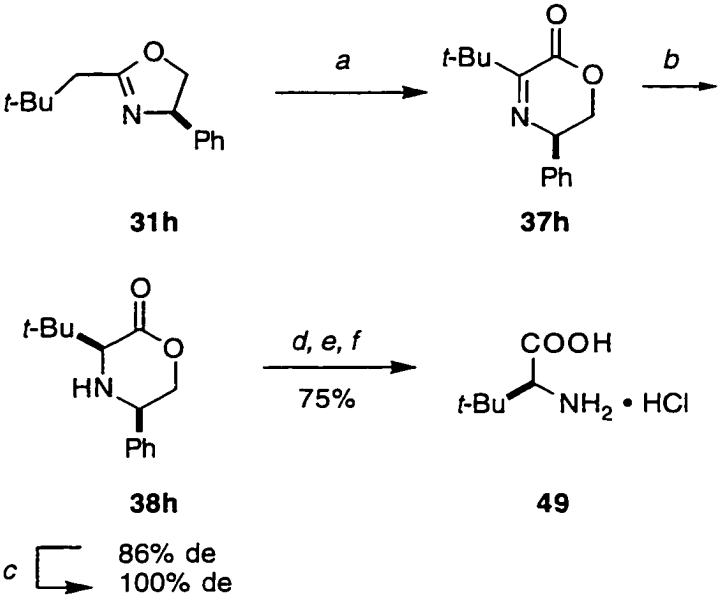
morpholin-2-one **38b** has been utilized in synthesis of α-amino acids by stereoselective alkylation[11,13,14] and the synthesis of β-hydroxy substituted amino acids *via* azomethine ylids[15] while the 6-phenyl derivative of **38b** has been employed in α-amino acid synthesis as an "electrophilic glycinate."[16]

Only a few syntheses for 3-unsubstituted morpholin-2-ones **38** are described. Condensation of an amino alcohol with phenyl α-bromoacetate[11,14,16] gives variable yields (40-83%), and the product must be immediately protected to prevent product dimerization. *N*-Protected morpholin-2-ones are made by heating ethylene bromide and an amino acid with K_2CO_3 in DMF for 12h (44%).[17] Hegedus synthesized 3-substituted morpholin-2-ones **38** from chromium-carbene complexes and amino alcohols under photolytic conditions (63% for two steps).[18]

Because dihydrooxazinones **37** are readily converted to **38**, the SeO_2 oxidative rearrangement makes 3-unsubstituted morpholin-2-ones **38** conveniently accessible from oxazolines, which in turn are easily prepared from the corresponding 2-amino alcohols.[19] Thus, oxazoline **31b** prepared by condensation of *R*-(-)-phenylglycinol with ethyl acetimidate hydrochloride (Et_3N, CH_2Cl_2, 91%), was smoothly converted to **37b** (SeO_2, reflux, 1.5 h, dioxane, 72%, Table 2, entry 4). Hydrogenation of **37b** (H_2, 1 atm, Pd-C, 3 h, quantitative, Figure 5) afforded optically pure (-)-morpholinone **38b** in an overall *reproducible* yield of 66% in three steps from phenylglycinol. By an analogous sequence, **37i** was hydrogenated to the known (3*S*, 5*R*)-3,5-diphenylmorpholinone **38i** (91%, 60% de) in 74% overall yield from α-phenylacetimidate hydrochloride and (*R*)-(-)-phenylglycinol.

The utility of this novel reaction was demonstrated by an asymmetric synthesis of the amino acid (*S*)-*tert*-leucine (*tert*-butylglycine, **49**, Figure 6), a component of natural product peptides isolated from marine sponges of the genus *Theonella* and from other sources.[20,21] The chiral auxiliary, (*R*)-2-phenylglycinol, was readily condensed with *tert*-butylacetyl chloride in two steps to provide oxazoline **31h**.[22] Oxazoline **31h** was

smoothly converted to **37h** with SeO_2 in refluxing dioxane (84%, Table 2, entry 10). Hydrogenation of **37h** using Harwood's conditions (PtO_2, CH_2Cl_2, 1 atm H_2),[3] gave the desired (2*S*, 4*R*)-morpholinone diastereomer **38h** (97%, 86% de) which was improved to 100% de (82% yield) after one crystallization from ethyl acetate-hexane. Ethanolysis of diasteromerically pure **38h** (HCl, EtOH) followed by sequential hydrogenolysis of the benzylic C-N bond[11] and acid hydrolysis (6N HCl aq) provided (*S*)-(-)-**49** (75% from **38h**) which was identical with an authentic sample by ^1H NMR, $[\alpha]_D$ and TLC. HPLC analysis of chiral derivatives of **49** (Marfey's method)[23] indicated that **49** was optically pure.



a. SeO_2, diox, Δ; *b*. H_2, 1 atm, PtO_2, CH_2Cl_2; *c*. recryst. EA/hex; *d*. EtOH, HCl; *e*. H_2, 1 atm, Pd-C, EtOH; *f*. 6M HCl (aq)

Figure 6. Synthesis of (*S*)-*tert*-leucine (**49**)

This method provides entry to the synthesis of heavily β-branched α-amino acids in high optical purity and complements recently reported catalytic methods, such as the catalytic asymmetric Strecker synthesis[24] and supercritical homogeneous catalytic hydrogenation of α-enamides.[25]

3.5 Investigation of Oxidative Rearrangement Mechanism

Because of the synthetic utility of this reaction, a greater understanding of the mechanism was desired. The reaction proceeded smoothly and in high yield for 2-methyl- (**31a-b**, R = H), benzyl- (**31i-j**, R = Ph) and neopentyl-oxazolines (**31h**, R = *t*-Bu) but failed with 2-ethyloxazoline (**31f**, R = Me). The latter observations suggested a possible mechanism involving carbon-carbon bond migration and correlation of reaction efficiency with migratory aptitude of the group attached at the α-position of the 2-oxazoline. A mechanism was advanced to explain the events leading to heterocyclic product **37** which involved oxidation to the putative acyl intermediate **50** followed by ring opening and a 'nitrilium-acylium' ion rearrangement (Figure 7, *path a*). High migratory aptitude of R in the nitrilium ion *i* would promote rearrangement to the acylium ion *ii*.

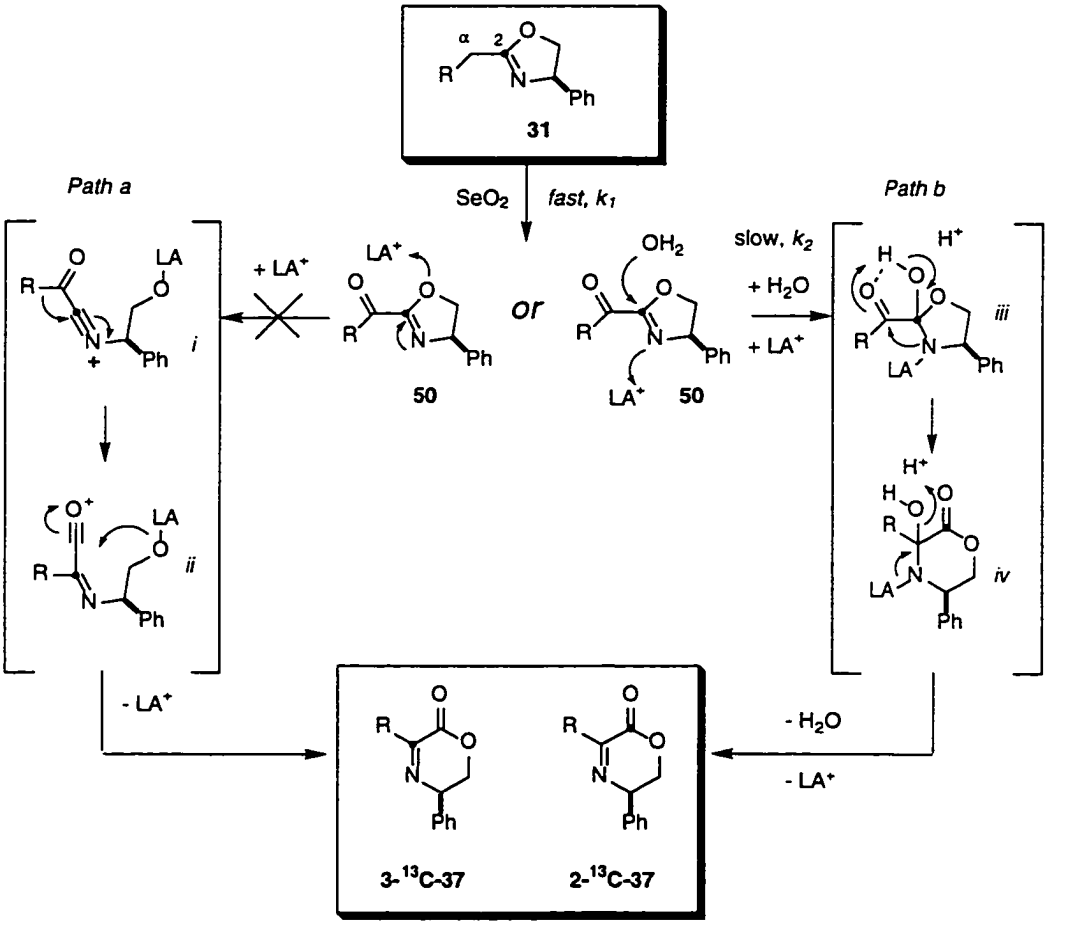
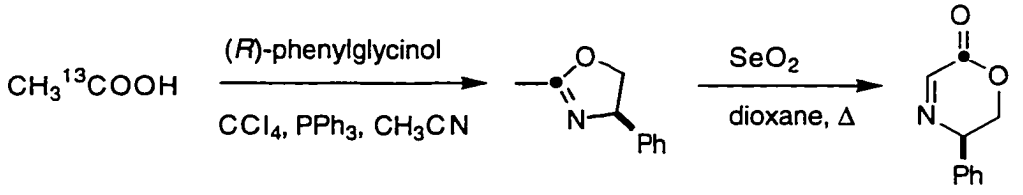


Figure 7. Proposed mechanistic pathways for oxidative rearrangement

3.5.1 ^{13}C Isotopic Labeling of 31b

The mechanism shown in Figure 7 *path a* predicts that the oxidation state of C2 will be exchanged with that of the α-carbon (the 2-acyl group) in the putative oxazoline intermediate **50**. The latter hypothesis was easily tested by ^{13}C labeling. [2-^{13}C]-Oxazoline 2-^{13}C-**31b** (50 atom %) was synthesized by condensation of acetic acid-1-^{13}C with (*R*)-(-)-phenylglycinol using the one step procedure of Vorbrüggen and Krolikiewicz (CCl_4, Ph_3P, CH_3CN, 17%).[26]



2-^{13}C-**31b** 2-^{13}C-**37b**

Treatment of 2-^{13}C-**31b** with 2.2 eq SeO_2 under standard conditions gave 2-^{13}C-**37b** (61%) after chromatography. A unimolecular rearrangement was evident because EIMS analysis of 2-^{13}C-**37b** showed retention of label (44±5 atom %, no inter-molecular exchange of label). Examination of the ^{13}C NMR spectrum of 2-^{13}C-**37b** revealed that the enhanced signal was C2 (carboxyl), instead of C3 as expected from the mechanism in Figure 7, *path a*. The chemical shift of the C2 signal was unambiguously assigned in earlier work from DEPT and 2D heteronuclear correlation spectroscopy. This labeling pattern is consistent, not with C-C bond fission and migration but with retention of ^{13}C label at the carboxylate and preservation of the oxidation state of oxazoline C2. A mechanism that is congruent with this finding must invoke fission of the C=N bond in oxazoline **31b**, and subsequent migration of N to the acyl carbon in presumed intermediate **50**.

3.5.2 Isolation of 2-Acyloxazoline Intermediate 50i

In order to further elucidate details of the mechanism, the kinetics of the oxidative rearrangement were studied. Oxazoline **31i** was chosen for the kinetics studies because it gave consistently high yields (94%) under the standard conditions (100°C, 2.2 eq SeO_2, anhydrous dioxane) and because both the starting material and product could be followed with UV detection (λ 254 nm). The temperature for the kinetic studies was lowered to 40°C to allow convenient monitoring at several time points. When oxidation of **31i** was carried out with SeO_2 at 40°C, a less polar intermediate appeared rapidly and increased in concentration at the expense of **31i**. Over the time course of the reaction, the concentration of the intermediate decreased as **37i** increased (Figure 8).

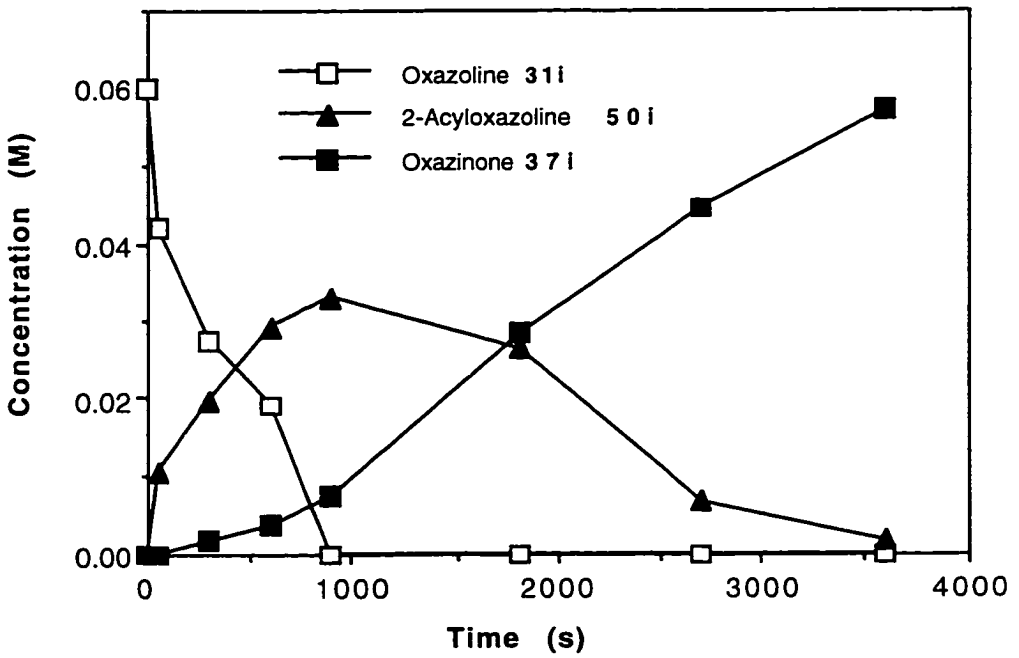
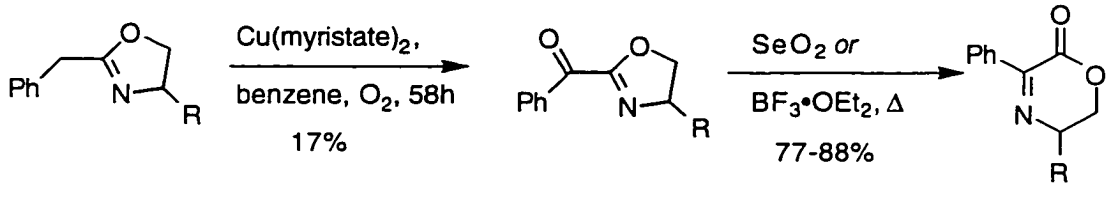


Figure 8. Time course of SeO_2 promoted oxidation rearrangement of oxazoline **31i** to dihydrooxazinone **37i** in 1,4-dioxane. Initial [SeO_2] ~ 0.11 M, T = 40°C

When the reaction was run again on larger scale and quenched before completion, an intermediate was found which was isolated by HPLC (9%) and determined to be the 2-acyloxazoline **50i** by interpretation of spectroscopic data. The formula of **50i** ($C_{16}H_{13}NO_2$) was isomeric with product **37i**. The UV spectrum of **50i** showed a strong chromophore (λ_{max} 258, ε 10,200) associated with a substituted acetophenone. The ^{13}C NMR spectrum revealed that the α-methylene carbon found in **31i** was replaced in **50i** by a signal due to a conjugated C=O (δ 183.4 ppm, s). Finally, the structure was confirmed by independent synthesis of **50i** by autoxidation of **31i** (O_2, Cu(myristate)$_2$, benzene, 17%).



31i R = Ph
31j R = *i*-Pr

50i R = Ph
50j R = *i*-Pr

37i R = Ph
37j R = *i*-Pr

Heating **50i** in dioxane at reflux (100°C) in the absence of SeO_2 for 19 hours produced no change; however, when the reaction was repeated with 2 eq SeO_2, rapid conversion to **37i** was observed. While SeO_2 is required for the oxidation of **31i** to **50i**, the function of SeO_2 in the rearrangement of **50i** to **37i** appears to be that of a Lewis acid catalyst. Efficient conversion of **50i** to **37i** was catalyzed by the presence of 2 eq or less of SeO_2, while 2-acyloxazoline **50j**, prepared by autoxidation of oxazoline **31j** (38%), could be smoothly converted to **37j** by 0.15 eq of either SeO_2 (77%) or freshly distilled BF_3•OEt_2 (88%) in refluxing dioxane.

Selenium dioxide therefore serves the dual roles of oxidant and Lewis acid catalyst in the oxazoline-oxazinone conversion. While BF_3•OEt_2 catalyzed rearrangement was most intriguing, further kinetic studies were restricted to the SeO_2 catalyzed reaction because it was most relevant to the rearrangement step in **31**→**37**.

3.5.3 Kinetic Rate Studies

Assuming other 2-acyloxazolines **50** (R = alkyl, aryl, etc.) behaved the same in the presence of SeO_2, the mechanism was examined in more detail by measuring kinetics of both the oxidation and rearrangement steps using **50i**. Reactions were initiated under inert atmosphere at controlled temperature (oil bath, 40°C) by adding solutions of **31i** in anhydrous dioxane to rapidly stirred mixtures of SeO_2 in the same solvent (final concentration of **31i**, 0.060-0.061 M). Aliquots of the reaction mixture were sampled at various time intervals after initiation and analyzed by HPLC (Dynamax 8μ silica, EtOAc:*n*-hexane). Concentrations of **31i**, **37i** and **50i** in each sample were determined by integration of peak areas in the respective chromatograms and comparison with standard curves or by standards addition to individual samples. Both analytical methods gave comparable results. Calculations of initial rates were done using only the first four time points (≤10 min), and rate constants k were calculated from integrated rate equations (Table 3).[27]

Appreciable conversion of **31i** to **50i** was observed within the first minute of the reaction at 40°C with little or no apparent induction period (Figure 8). Prolonged reaction was accompanied by a decline in the concentration of **31i**, followed by an initial rise in **50i**, the appearance of **37i** and a concomitant decrease in the concentration of **50i** as **31i** was depleted. Consumption of **31i** was shown to be second order with respect to SeO_2 and **31i**, and the second order rate constant k_1 of the first step (oxidation of **31i**→**50i**) was estimated from the rate of consumption of **31i** to be $k_1 = 2.85 \times 10^{-2}\ M^{-1}\cdot s^{-1}$ at 40°C. Because of the heterogeneous nature of the reaction, the reaction may in fact be *pseudo* second order.

The rate constant for conversion of **50i**→**37i** could not be reliably measured from this time course data for two reasons. First, the rate of appearance of **37i** was dependent upon the concentration of **50i**, which in turn was dependent upon the amount of

conversion of **31i**→**50i**. Second, since the rearrangement step (**50i**→**37i**, rate constant k_2) was found to be catalyzed by SeO_2, the concentration of the catalyst also varied with time. The rate constant k_2 was determined by carrying out separate experiments in which pure **50i** was subjected to the same reaction conditions but in the presence of a fixed SeO_2 concentration (2.0 eq, ~0.11 M).

Starting Material & initial conc. (M)		Product	Equiv H_2O	Equiv SeO_2	Temp (°C)	Initial Rate, ($M \cdot s^{-1}$)	Rate constants k (± uncert.) (s^{-1})
31i	0.060	**37i**, **50i**	-	2.2	40	9.6×10^{-5}	2.85^a $(0.62) \times 10^{-2}$
50i	0.053	**37i**	-	1.0	40	2.2×10^{-5}	7.70 $(0.93) \times 10^{-4}$
50i	0.053	**37i**	-	2.0	26	2.9×10^{-5}	1.10 $(0.12) \times 10^{-3}$
50i	0.053	**37i**	-	2.0	40	3.3×10^{-5}	1.15 $(0.09) \times 10^{-3}$
50i	0.053	**37i**	-	2.0	58	4.8×10^{-5}	1.60 $(0.26) \times 10^{-3}$
50i	0.053	**37i**	-	2.0	79	8.1×10^{-5}	3.21 $(0.31) \times 10^{-3}$
50i	0.053	**37i**	-	2.0	100	8.1×10^{-5}	3.90 $(0.24) \times 10^{-3}$
50i	0.055	**37i**	1.0	2.0	40	6.9×10^{-5}	3.40 $(0.78) \times 10^{-3}$
31i	0.061	**37i**, **50i**	1.0	2.2	40	2.2×10^{-4}	8.13^a $(-)^b \times 10^{-2}$

Table 3. Compilation of initial rates of reaction and rate constants for SeO_2 promoted reactions of **31i** or **50i** in anhydrous dioxane. Rates were calculated based on consumption of **31** or **50**. Initial rates were *estimated* from slope (d[**x**]/dt where **x** is **31i** or **50i**) over the first 10 minutes of reaction. Rate constants are first order for **50i**→**37i** and second order for **31i**→**50i**. Rate constants and uncertainties were determined as described in the Experimental. ^{a} k_1 second order rate constant, units $M^{-1} \cdot s^{-1}$; ^{b} estimate only, N=3 data points.

The *first order* rate constant of the rearrangement step **50i**→**37i** was calculated as $k_2 = 1.15 \times 10^{-3}$ s^{-1} (40°C and 0.11 M SeO_2) and, therefore, must be the slower, rate

limiting step of oxidation rearrangement. As no other intermediates could be detected under these reactions conditions, the simplest sequence of events is rapid SeO_2 promoted oxidation of **31** to 2-acyloxazoline **50** followed by a slower rearrangement of **50** to dihydrooxazinone **37**.

SeO_2 functions as a Lewis acid and catalyzes the conversion of **50i** to **37i**. The dependence of k_2 upon [SeO_2] was examined in reaction time courses conducted in the presence of varying amounts of SeO_2. Rearrangement of **50i** was promoted by 1.0 eq of SeO_2 ($k_2 = 7.7 \times 10^{-4}$ s^{-1} at 40°C) while 2.0 eq SeO_2 almost doubled the rate ($k_2 = 1.15 \times 10^{-3}$ s^{-1}) under otherwise identical conditions.

The effect of temperature of the rearrangement of **50i** to **37i** was investigated by carrying out the reaction at different temperatures. Predictably, the reaction was slowest at room temperature 26°C ($k_2 = 1.1 \times 10^{-3}$ s^{-1}) and fastest at 100°C ($k_2 = 3.9 \times 10^{-3}$ s^{-1}). An Arrhenius plot[27] of rate constants, k_2 measured at different temperatures provided an *apparent* Arrhenius activation energy of $E_A = 4.2 \pm 1.6$ kcal·mol^{-1} for the rearrangement step in the presence of 2.0 eq SeO_2 (Figure 9).

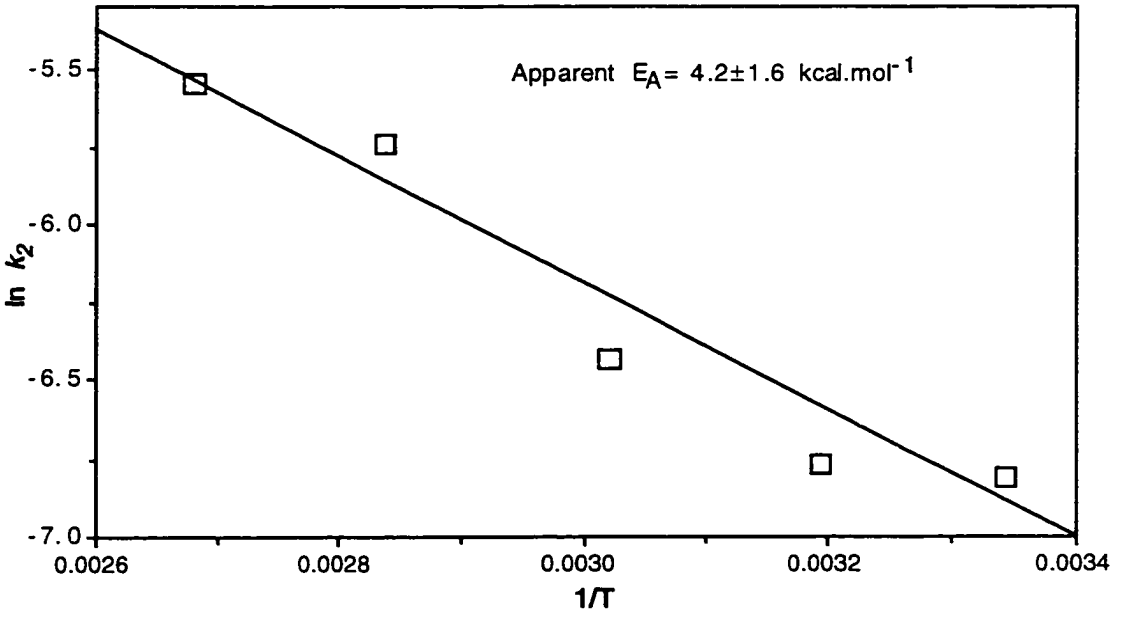


Figure 9. Temperature dependence of the first order rate constant k_2 for rearrangement **50i**→**37i** in 1,4-dioxane in the presence of 2.0 eq of SeO_2

In the absence of evidence for the involvement of an incipient nitrilium ion *i* (Figure 7, *path a*), the possibility was considered that H_2O or a nucleophilic selenium byproduct might be involved in an addition-elimination at the same time as ring opening. Although the reaction conditions made use of anhydrous solvent and inert atmosphere, water most likely may be generated by disproportionation or elimination of the 'H_2SeO' equivalent formed during the oxidation step. The effect of small amounts of added water would be expected to accelerate the reaction, and, indeed, the rate constant increased when the rearrangement of **50i→37i** was carried out in the presence of 2.0 equivalents of SeO_2 and 1.0 eq of added H_2O ($k_2 = 3.4 \times 10^{-3}$ s^{-1}). Nucleophilic catalysis with H_2O is necessary and sufficient to account for this rate increase; however, SeO_2 may also undergo hydration in the presence of H_2O. The product, H_2SeO_3, is an appreciable Brønsted acid (pKa_1 2.62, pKa_2 8.32)[28] and may also participate in general acid catalysis of the reaction. While the initial rate of appearance of **37** was enhanced by added H_2O, prolonged reaction times resulted in loss of product and starting material, presumably due to competing irreversible hydrolytic ring opening of the H_2O-sensitive oxazoline and dihydrooxazinone.

The mechanism of SeO_2 promoted oxidative rearrangement of 2-oxazolines involves oxidation of the α-carbon to carbonyl followed by Lewis acid catalyzed ring opening and migration of the nitrogen to the newly formed α-carbonyl. Formally, this must involve fragmentation of the oxazoline ring to an ester by departure of an amino group rather than conventional leaving group OR. The relatively low *apparent* activation energy of $E_A = 4.2$ kcal·mol^{-1} (Figure 9) strongly suggests a mechanism limited by one or more transport processes (diffusion, chemiadsorption, desorption, etc.) as is typically found in some heterogeneous catalytic reactions.[29,30] However, at 40°C the rate constants (Figure 7 and Table 3) show the rate limiting step under these conditions is intramolecular rearrangement **50i→37i**, but the observed rate enhancement with H_2O also militates for simultaneous nucleophilic catalysis.

A possible sequence of elementary reactions for the rearrangement that is consistent with these observations is presented in Figure 7, *path b*. Some or all of these reactions may occur at the surface of solid phase SeO_2. Activation of the nitrogen on the oxazoline ring by Lewis acid (SeO_2) is followed by addition of trace H_2O (for example, adsorbed on hygroscopic SeO_2) at C2 of oxazoline, generating a tetrahedral intermediate, *ortho*-amide *iii* that collapses by protonation of the α-carbonyl and migration of N to the α-carbonyl giving aminal *iv*. The latter intermediate eliminates H_2O to provide the final product **37**.

Essentially the proposed sequence in Figure 7 *path b* is Schiff base formation between the newly created carbonyl group and an amino group liberated by cleavage of the oxazoline ring. The latter appears to be initiated by nucleophilic attack by trace H_2O. Displacement of the amino group rather than hydroxyl is the usual path for cleavage of oxazolines by aqueous acid (55 M H_2O)[31] or under certain conditions with strong nucleophiles[32] although this may not be so under anhydrous conditions with other Lewis acids. In the conversion of **50i** to **37i**, under *almost* anhydrous conditions the weak nucleophile H_2O apparently still prevails, again with displacement of the amino group. Several factors probably contribute to this preference, for example preferential Lewis acid activation of the more basic nitrogen, ring-strain relief by opening of the oxazoline and facile 1,2 nitrogen migration-elimination, assisted by intramolecular H-bonding in *iii* to produce the stable conjugated heterocycle **37**.

3.6 Conclusion

The discovery of the novel oxidative rearrangement of oxazolines to dihydrooxazinones has led to useful methodology for preparation of α-amino acids, in particular the synthesis of chiral β-branched α-amino acids. The isolation of an intermediate and the labeling and kinetic studies have allowed refinement of a possible mechanism of reaction.

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CHAPTER 4. REVISED SYNTHESIS FOR BENGAZOLE A AND SYNTHESIS OF C1-C6 SIDE CHAIN

4.1 Introduction and Revised Synthetic Scheme

Chapter 2 illustrated the initial retrosynthetic strategy towards the synthesis of bengazole A (**7**). Because of the inability to prepare 2-formyloxazoline **25** (Figure 3, Chapter 2), the synthesis of bengazole A (**7**) was revised taking advantage of the ambident nucleophilicity of 2-lithiooxazole (Figure 10, *i*). Prior work has shown that addition of electrophiles can occur at C2, C4, or at the oxygen in the ring-opened isonitrile-enolate *ii*.[1] For instance, D_2O and TMSCl quench *ii* giving the *O*-substituted isonitriles. Ketones add to *i* giving C2 substituted oxazoles, but aldehydes couple only at C4 giving **51**.[2]

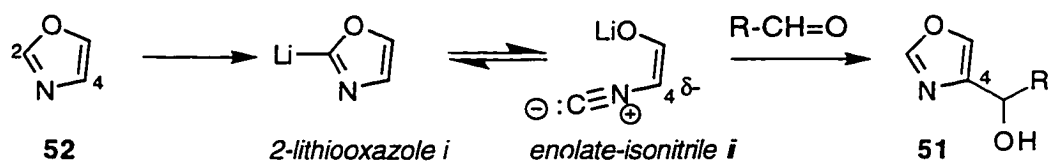


Figure 10. Ambident nucleophilicity of oxazole anion

The reaction of *ii* with aldehydes was applied to the synthesis of bengazole A (**7**, Figure 11). Ring B of bengazole A would be built from oxazole (**52**). The side chain **53** would be synthesized from the inexpensive sugar, D-galactose (**54**), and then coupled to **52** giving the key intermediate **55**.

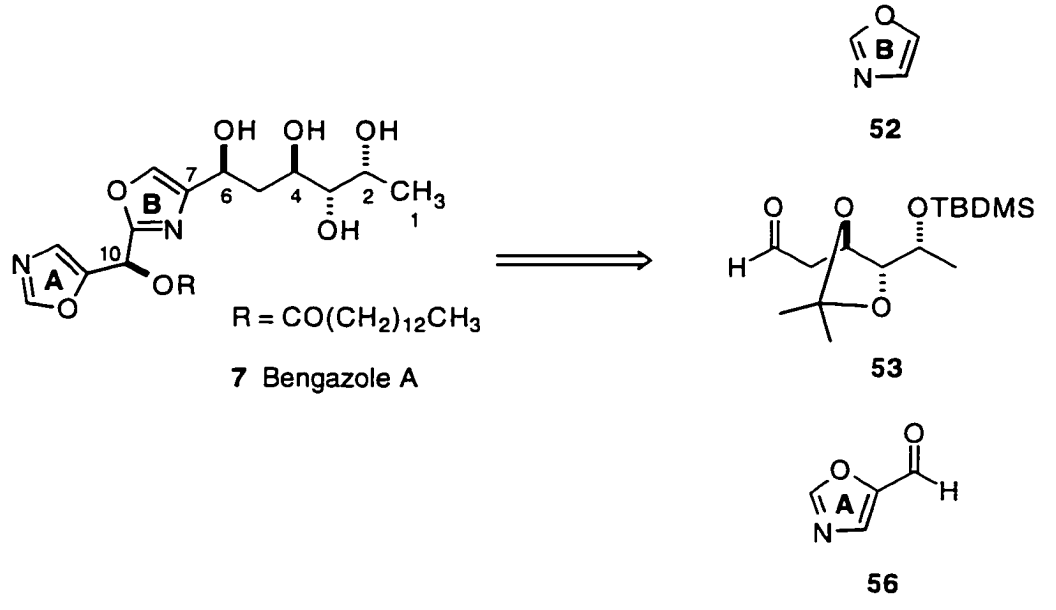
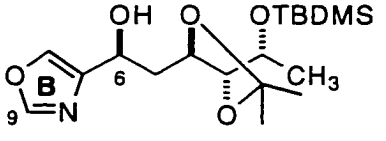


Figure 11. Revised retrosynthetic analysis of bengazole A (**7**)



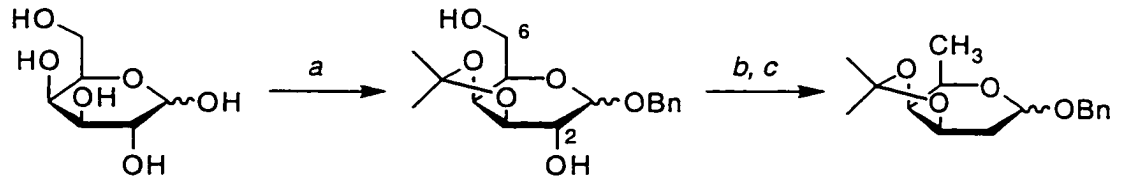
After protection of the C6 hydroxyl, **55** can be deprotonated at C9 (bengazole numbering) and coupled with 5-formyloxazole[3] (**56**) to give the complete bengazole A carbon skeleton as a mixture of diastereomers. Following separation of the diastereomers, the C10 hydroxyl would be esterified with myristic acid, and the hydroxyls on the side chain deprotected to give the natural product bengazole A (**7**).

4.2 Synthesis of Side Chain from D-Galactose (54)

Several methods are available for the synthesis of oxazole (**52**).[4-6] Aldehyde **53** was not known, so a novel preparation from D-Galactose (**54**) was devised taking advantage of the *lyxo* configuration found at C3,4,5 in both **54**, fucose and the derived relationship of **7** to D-sugars.[7] Thus, a convenient transformation of **54** to D-2-

deoxyfucose (D-2,6-dideoxy-*lyxo*-hexose, **57**) was developed involving C2,C6 deoxygenation.

The anomeric hydroxyl of D-galactose (**54**) was protected as the benzyl ether,[8] and the C3,C4 hydroxyls were selectively protected as the acetonide with 2,2-dimethoxypropane and *p*-TSA giving **58** (69% for two steps, Figure 12).[9]



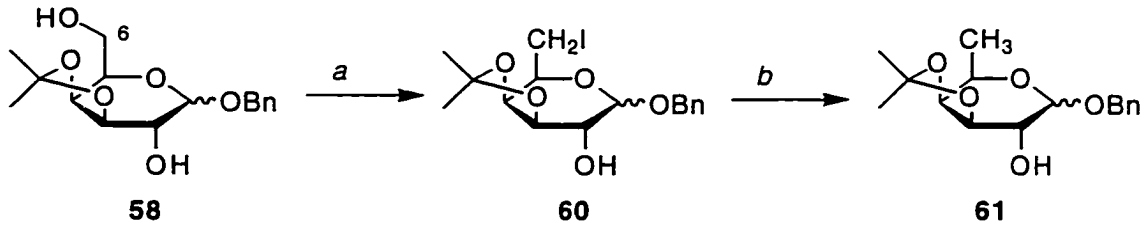
D-Galactose **54** **58** **59**

a. i BnOH, HCl, 4°, 72%, *ii* 2,2-dimethoxypropane, *p*-TSA, then Et_3N, MeOH: H_2O, 98%; *b.* NaH, CS_2, CH_3I, imidazole, THF, *96%*; *c.* H_3PO_2, Et_3N, AIBN, Δ, dioxane, 9%

Figure 12. Synthesis of **59**

Formation of the C2,6 *bis*-xanthate and double Barton-McCombie deoxygenation[10,11] on the β-anomer of **58** worked well (**59**, 76%) on small scale but failed on a larger scale with an 8:1 mixture of α and β anomers (9%, Figure 12). Removal of the C2,C6 hydroxyls was attempted by double displacement with iodide followed by hydrogenolysis (H_2, Pd/C, K_2CO_3, MeOH).[12,13] Attempted iodide displacement of **58** (I_2, PPh_3, imidazole, toluene, Δ) gave low yield of the 6-iodo-6-deoxygalactose (7%) but none of the 2,6-diiodo-2,6-dideoxygalactose.

Double Barton-McCombie deoxygentation, although achieved in very good yield in one instance, was unreliable, so methods for stepwise deoxygenation were investigated (Figure 13). Displacement of the primary hydroxyl of **58** by iodide gave variable yields of **60** (0-70%, I_2, PPh_3, imidazole, toluene, Δ) while the hydrogenolysis (H_2, Pd/C, K_2CO_3, MeOH) proceeded in good yields (76%) to give **61**.[12,13]



58 60 61

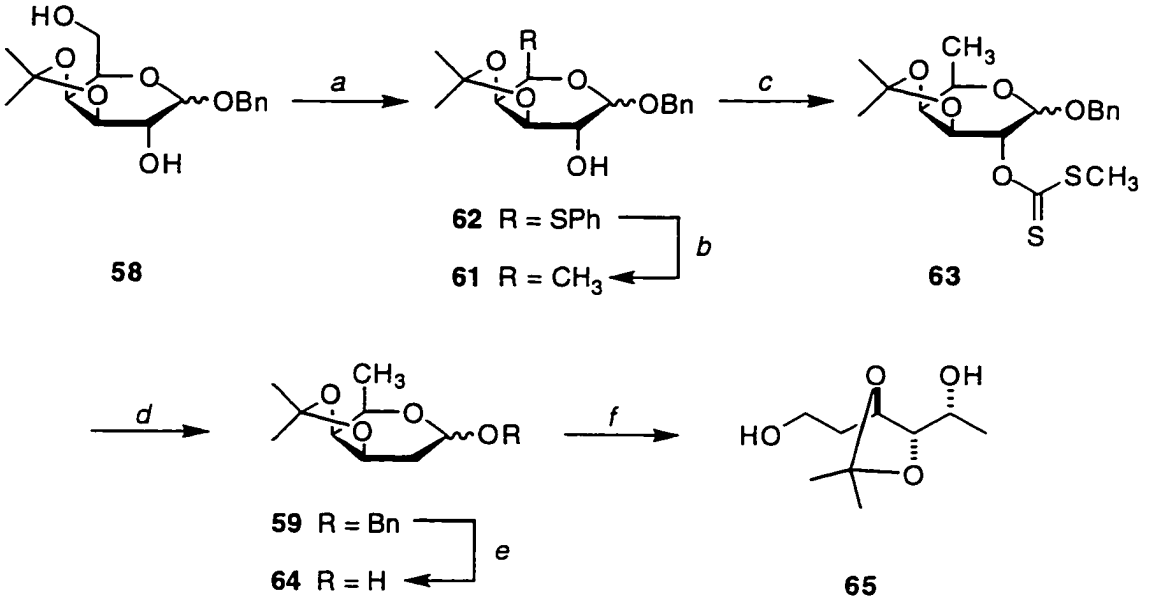
a. I_2, PPh_3, imidazole, toluene, Δ, 0-70%; *b.* H_2, Pd/C, K_2CO_3, MeOH, 76%

Figure 13. Formation of **61**

Mono-tosylation of the C6 hydroxyl in **58** followed by displacement with iodide was also explored.[14] Formation of the 6-*O*-tosylate from **58** with *N*-tosylimidazole in CH_2Cl_2[15] was unsuccessful while TsCl in pyridine gave a low yield (35%). Displacement of the 6-*O*-tosylate group with NaI in acetone[16] was difficult but gave an acceptable yield of **60** (62%); however, the long reaction time (40 h) and harsh conditions (sealed tube, 50°C) made this method unsuitable for large scale reactions.

The method that proved to be the most efficient and amenable to large scale synthesis was conversion of **58** to the C6 thiophenyl ether **62** (PhSSPh, *n*-Bu_3P, THF, 86%) followed by desulfurization with Raney Ni in refluxing EtOH (91%) to give **61** (Figure 14).[17]

2-*O*-Xanthate ester formation (**63**, 96%) from **61** and deoxygenation under Barton-McCombie conditions[10,11] gave **59** in good yield (76%, Figure 14). The use of the inexpensive, aqueous soluble hydrogen donor H_3PO_2 gave improved yield over standard reducing conditions (*n*-Bu_3SnH, toluene, 110°C) and avoided the difficult and often tedious removal of Sn byproducts associated with stannane reductions.[11]

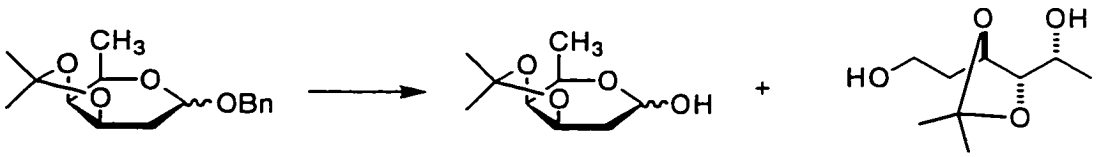


a. PhSSPh, *n*-Bu_3P, THF, Δ, 86%; *b.* Ra-Ni, EtOH, Δ, *91%* ; *c.* NaH, CS_2, CH_3I, imidazole, THF, *96%*; *d.* H_3PO_2, Et_3N, AIBN, Δ, dioxane, *77%*; *e.* Ca^*, NH_3 (*l*), THF, -33°C, *70%*; *f.* Li^*, NH_3 (*l*), THF, -33°C, *92%*

Figure 14. Synthesis of alditol **65**

Catalytic hydrogenolysis[8,18,19] to effect debenzylation of **59** (Pd/C, $Pd(OH)_2/C$ or Pd/C and NH_4HCO_2) was unexpectedly slow and gave mixtures of starting material **59**, aldose **64**, and over-reduced alditol **65** (Table 4). Sulfur poisoning of the catalyst was suspected, but pretreating **59** with Pd/C (entry 3) or Raney Ni (entry 4) did not improve yields or reaction times. Changing the solvent from ethanol to 2,2,2-trifluoroethanol (TFE) accelerated the reaction rate but yielded a product that had lost the acetonide group. It was initially thought that the product was 2-deoxyfucose (**57**); however, its solubilty in $CDCl_3$ and its anomalous optical rotation ($[\alpha]_D$ +74.3, *c* 0.52, H_2O; D-2-deoxyfucose $[\alpha]_D$ +48.8, *c* 1.0, H_2O, equilibrated[20]) were inconsistent with expected properties (entry 5). Catalytic hydrogenolysis in the presence of a small amount of TFE gave a good yield of **64** on small scale (entry 6).

Table 4. Results of attempted debenzylation of **59**



59 **64** **65**

Entry	Reagent	Solvent	Reaction Time (h)	Product	Yield (%)
1	Ammonium formate, Pd/C	MeOH	72	**NR**	0[a]
2	$Pd(OH)_2/C$, H_2	EtOH	15	**64**	17
3	a. Pd/C, H_2, EtOAc; b. $Pd(OH)_2/C$, H_2	EtOH (abs)	a. 2 b. 120	**64**	16[b]
4	a. Raney Ni b. $Pd(OH)_2/C$, H_2	EtOH (abs)	a. 1.5 h b. 7 h	-	0[c]
5	$Pd(OH)_2/C$, H_2	CF_3CH_2OH	6	-	-[d]
6	$Pd(OH)_2/C$, H_2	1:20 TFE: EtOH (abs)	1.5	**64**	91[e]
7	Raney Ni (W-2)	EtOH (abs)	66	**65**	46[f]
8	Raney Ni (W-4), 40 psi	EtOH (abs)	101	**65**	45
9	Na°, NH_3 (*l*)	THF	0.2	**64**	9[g]
10	Na°, NH_3 (*l*)	THF	0.4	**65**	69[f]
11	Ca°, NH_3 (*l*)	THF	0.75	**64**	70
12	Li°, NH_3 (*l*)	THF	0.75	**65**	92

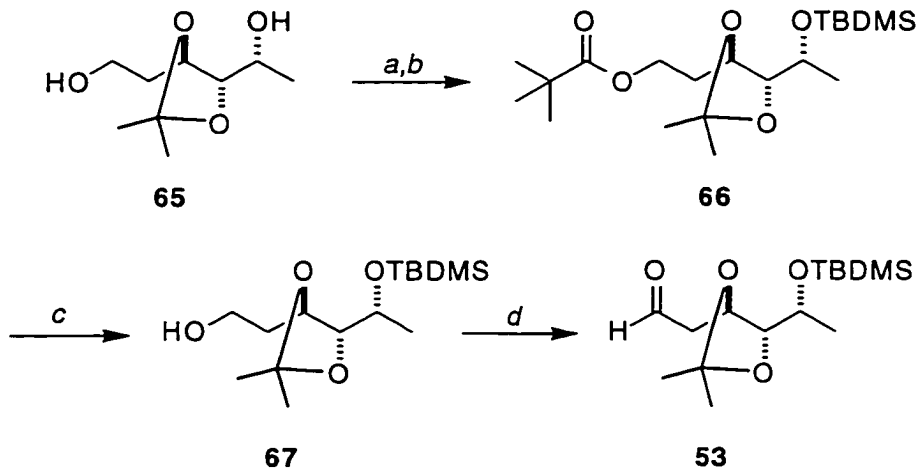
(a) sealed tube at 80°C; (b) 11% of **59** isolated; (c) unidentified mixture; (d) unidentified product; (e) 28% yield on larger scale (0.54 g); (f) crude yield; (g) 4% of **59** isolated.

Raney nickel in EtOH gave exclusively the alditol **65** but required long reaction times and gave mediocre yields (entries 7 and 8). Dissolving metal reductions with Na° or

Li° in NH_3 (*l*) were difficult to control and generally resulted in the alditol **65** instead of the expected **64** (entries 9-10, 12).[21] Ca° in NH_3 (*l*); however, gave exclusively aldose **64** in good yield (70%, entry 11).

Attempted coupling of aldose **64** with lithiooxazole (see Section 4.4) was unsuccessful. Alditol **65** was refunctionalized to **53** which was anticipated to reduce undesirable influences of the free C5 hydroxyl. Full reduction of **59** to **65** was achieved in 92% using Li° in NH_3 (*l*, -33°C, 45 min, entry 11).

With alditol **65** in hand, selective protection of the secondary hydroxyl at C5 was needed (Figure 15). Pivaloyl chloride (1 eq) with DMAP in pyridine gave the mono-ester at the primary OH (77%)[22] which was followed by silylation of the C5 OH (**66**, 94%).



a. Piv-Cl, DMAP, pyridine, 77%; *b.* TBDMSCl, imidazole, DMF, 94%;
c. LiOH, THF, H_2O, quant; *d.* $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%

Figure 15. Synthesis of aldehyde **53**

The pivaloyl ester was saponified (**67**, quant.), and the liberated primary alcohol oxidized to the aldehyde **53** under Swern's conditions ($(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%).[23] The workup for this oxidation proved to be critical. When an acidic workup was carried out (NH_4Cl, aq, satd), only low yields of **53** (15%) were obtained, presumably due to partial hydrolysis of the acetonide. A mildly basic workup ($NaHCO_3$, aq, satd)

preserved the acetonide, and the yield improved to 96%. Catalytic oxidation (TEMPO, bleach, KBr, CH_2Cl_2),[24] worked adequately on small scale (49%) but over oxidation to the carboxylic acid could not be prevented on larger scale (51%, ~1g).

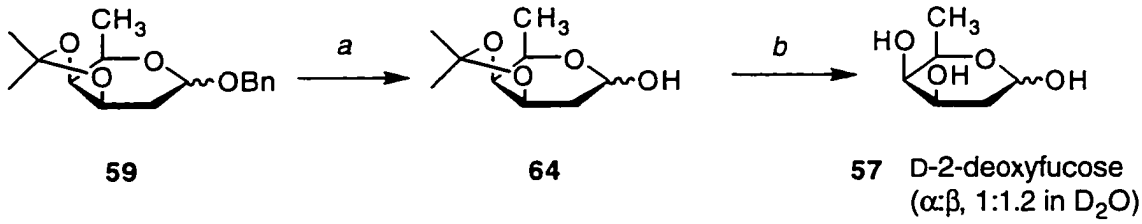
Despite a number of difficult reactions, a high yielding, efficient synthesis of **53** was achieved (11 steps, 24%) which also proved amenable to the synthesis of the rare sugar D-2-deoxyfucose (D-2,6-dideoxy-*lyxo*-hexose, **57**).

4.3 Synthesis of D-2-Deoxyfucose (57) from D-Galactose (54)

D-(+)-2-Deoxyfucose (**57**, oliose) and its *O*-Me ethers occur as glycosides in natural products; for example the olivomycin antitumor-antibiotics,[25-29] the cardenolide glycoside adigoside[30] and polyketide glycosides, phenelfamycins.[31] Sugar **57** is not commercially available despite the desirability for its incorporation into natural product syntheses. Syntheses have been reported for DL-**57**,[32] and **57**,[20,33,34] but in general they involve starting materials or reagents that are not amenable to large-scale preparation. For example, the Roush synthesis, beginning with 6-hepten-3-yn-2-ol, required kinetic resolution by Sharpless asymmetric epoxidation and gave **57** in seven steps (overall yield 18-20%).[20] Molinski *et al.* reported a short synthesis of the 2-deoxy-L-fucose derivative, *ent*-**64**, from L-fucose (3 steps, 59% yield).[7] While the common naturally occurring form of fucose is L- (derived from kelp polysaccharide),[35] D-fucose is rare and prohibitively expensive (L- and D-fucose are priced at $350 /500 g and $4,500 /100 g, respectively; Pfanstiehl Laboratories, Inc.) as a starting material for preparation of **64**. Because D-galactose (**54**, ~$80/kg) is inexpensive, it would serve as a suitable precursor for the synthesis of D-2-deoxyfucose (**57**). The procedure described below for the synthesis of **57** is economical and amenable to multigram scale-up.

2-Deoxyfucose (**57**) was conveniently accessible from precusor **59**. As described in Section 4.2, deprotection of the anomeric *O*-benzyl group was carried out with Ca° in NH_3 (*l*) at -33°C. The acetonide was removed by hydrolysis in the presence of cation exchange

resin (Dowex 50X2-400, H^+ form) giving a good yield (90%) of D-2-deoxyfucose (**57**). The overall yield for the synthesis of **57** from D-galactose (**54**) was 25% for eight steps.



59 **64** **57** D-2-deoxyfucose (α:β, 1:1.2 in D_2O)

a. Ca^*, NH_3 (*l*),THF, -33°C, *70%*; *b.* Dowex 50X2-400 (H^+), THF-H_2O, *90%*

Figure 16. Synthesis of 2-deoxy-D-fucose (**57**)

4.4 Synthesis of C1-C9 Fragment of Bengazole A

Aldose **64** embodies a masked carbonyl (C6 of bengazole A) for coupling to **52**. Earlier model studies confirmed that opening of the pyranose ring takes place in the presence of excess organolithium reagent, followed by 1,2-addition to the unmasked aldehyde.[7] Unfortunately, 2-lithiooxazole (8 equiv each of **52** and *n*-BuLi, 20 min, -78°C, THF-hex, add **64**, 1 equiv, warm to 23°C, 16 h) failed to add to **64** to give the C1-C9 fragment of bengazole A (**7**). The liberated C5-alkoxide somehow interfered with 2-lithiooxazole addition to the carbonyl group which indicated the need for protection at C5.

Coupling of lithiooxazole (10 eq, -78°C→-33°C, THF, 16 h) with side chain **53** gave a 1:1 mixture of epimers, **55a** and **55b** in 25% yield (Figure 17). Attempts to increase the yield or improve the diastereoselectivity with the following were unsuccessful: Et_2O; TMEDA, THF, -78°C; $ZnCl_2$, THF, -78°C; $MgBr_2$-OEt_2, THF, -78°C. Using the polar, aprotic base DMPU led to an improved yield (62%); however, the diastereoselectivity was in favor of **55b** (1:3.4 **55a**:**55b**). The C4 regioselectivity of substitution in **55a,b** was confirmed by comparison of $^1J_{CH}$ of the remaining oxazole protons (H8,9) with that of **7** and other 2,4-disubstituted oxazoles (**55a**: H9-C9 $^1J_{CH}$ =

234.4 Hz; **7**: H8-C8 $^1J_{CH}$ = 233.6 Hz; **52**: H2-C2 $^1J_{CH}$.= 231.1 Hz, Table 6, Chapter 5).[36] No 2-substituted oxazole by-products were detected.

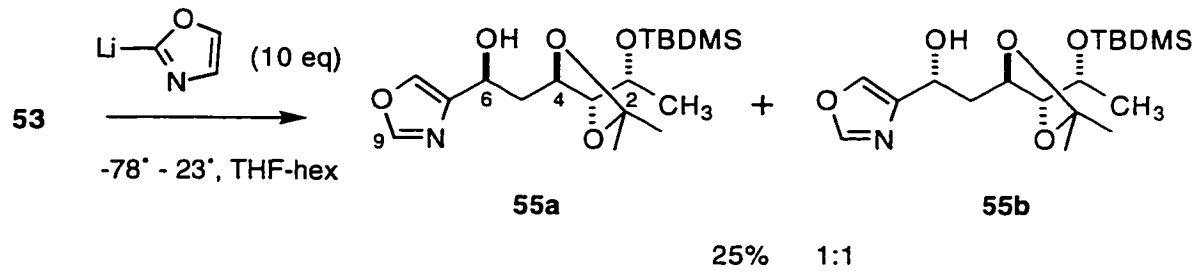
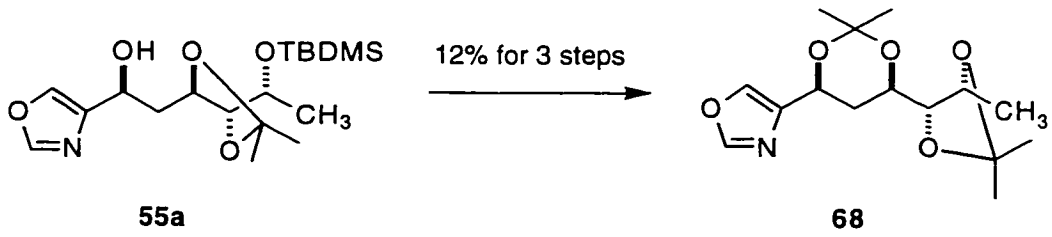


Figure 17. Synthesis of monooxazole intermediate **55a**

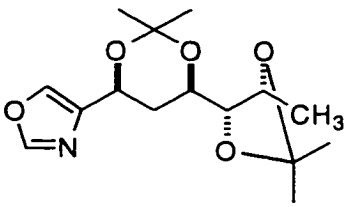
The diastereomers were separated by HPLC, and the faster-migrating epimer (retention time = 16 min) was identified as **55a** by refunctionalization to the *bis*-acetonide **68** (Figure 18) and direct stereochemical comparison with the known *bis*-acetonide **69**[7] by ^{1}H NMR (500 MHz, Table 5). The ^{1}H chemical shifts and vicinal coupling constants of H1-H6 in **68** and **69** ($CDCl_3$) were essentially identical.



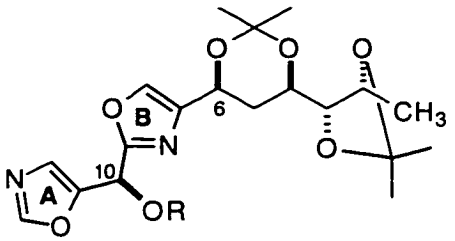
a. *n*-Bu_4NF, THF, 50°; *b.* Dowex (H^+), MeOH, 23° C, 2 h; *c.* 2,2-dimethoxypropane, acetone, *p*-TSA

Figure 18. Synthesis of *bis*-acetonide **68**

Table 5. Comparison of bengazole *bis*-acetonide (**69**) and synthetic intermediate **68**



68



69 R = $CO(CH_2)_{12}CH_3$

Proton	Compound 68			Compound 69[7]		
	δ	multiplicity	*J* (Hz)	δ	multiplicity	*J* (Hz)
1	1.34	d	6.0	1.34	d	6.1
2	4.02	dq	7.0, 6.0	4.00	dq	7.6, 6.1
3	3.46	dd	7.5, 7.0	3.44	dd	7.6, 7.2
4	3.96	ddd	12.0, 7.5, 2.5	3.94	ddd	11.4, 7.2, 2.5
5	2.10	ddd	13.0, 2.5, 1.5	2.10	ddd	13.0, 2.5, 2.1
5	1.70	ddd	13.0, 12.0, 11.5	1.69	ddd	13.0, 11.8, 11.4
6	5.00	dd	11.5, 1.5	4.97	dd	11.8, 2.1

Antifungal testing on **55a** and **55b** showed moderate antifungal activity (Chapter 5, Table 10). Compound **55a** was active against *Candida albicans* (ATCC 14053) and *C. krusei* (10 mm and 9 mm zones of inhibition respectively) while **55b** was only active against *C. albicans* (ATCC 14053, 8 mm zone of inhibition).

4.5 Conclusion

In summary, an advanced intermediate **55a** towards the synthesis of bengazole A (**7**) has been prepared which takes advantage of the ambident nucleophilicity of 2-lithiooxazole

with preferential C4 addition to aldehydes. Compound **55a** can now be extended at C9 (bengazole numbering) for completion of the *bis*-oxazole nucleus of bengazole A. The introduction of ring 'A' requires appropriate elaboration of a C5 monosubstituted oxazole. The synthetic plan will utilize 5-formyloxazole[3] (**56**) and C5-protected **55a** (Figure 19).

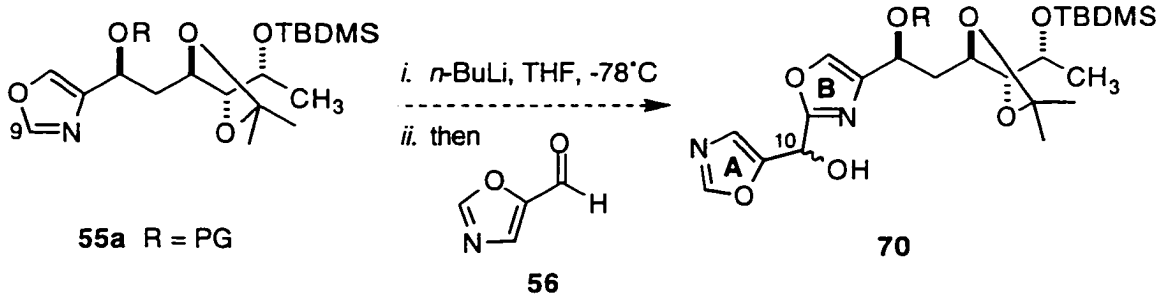


Figure 19. Anticipated completion of bengazole A carbon skeleton **70**

An alternate plan to the synthesis which will be discussed in Chapter 5 involves 'protection' of the C2 position of oxazole (**52**) and anion formation of C5 followed by C-C bond construction by electrophilic addition. To this end, new methodology was developed to allow construction of a suitable C5 oxazole anion equivalent.

4.6 References

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CHAPTER 5. SYNTHESIS OF 5-MONOSUBSTITUTED OXAZOLES BY DIRECTED ALKYLATION

5.1 Introduction

Two general methods for synthesis of C5 monosubstituted oxazoles are known. One method developed by Schöllkopf condenses lithiated CH_3NC with carboxylic acid esters[1,2] while the other method utilizes triethylformate and phenacyl amines for heterocyclic construction.[3] Both methods have limitations for the synthesis of bengazole A (**7**). The selected synthetic strategy for completing bengazole A (**7**) links ring B to ring A by coupling the anion of **55a** to 5-formyloxazole (**56**, Figure 19). This strategy may suffer from competitive deprotonation at C2 of **56** from the anion of **55a**. The relative acidities of the three protons on oxazole (**52**) decrease in the order of H2, H5, and H4, and the pK_a of H2 is estimated to be 20±2.[4] As is shown in Figure 20, the 2-lithiooxazole *i* is kinetically labile and opens to the enolate-isonitrile *ii*. The enolate-isonitrile reacts with electrophiles at either C2 or C4 depending on the nature of the electrophile. Generally deprotonation-addition at C5 is not possible. Kinetic deprotonation at C5 can occur only if a carboxyl group is present at C4; however, the resulting anions are poor nucleophiles.[5,6] In an effort to circumnavigate forseen difficulties in the synthetic strategy shown in Figure 19, an alternate synthesis of C5 monosubstituted oxazoles was developed.[7]

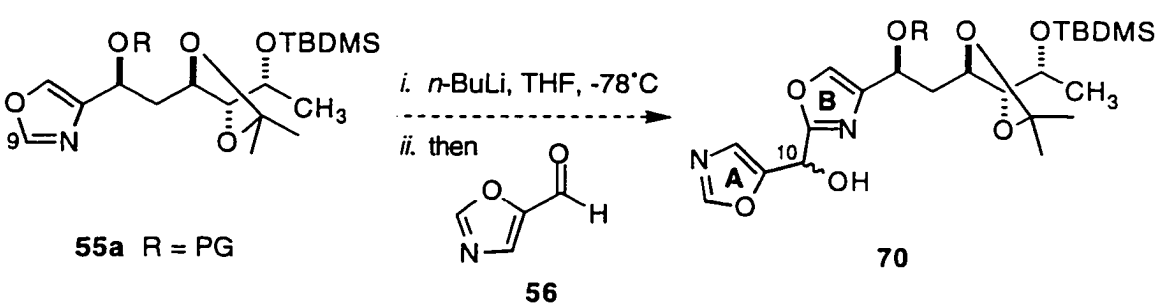


Figure 19. Anticipated completion of bengazole A carbon skeleton **70**

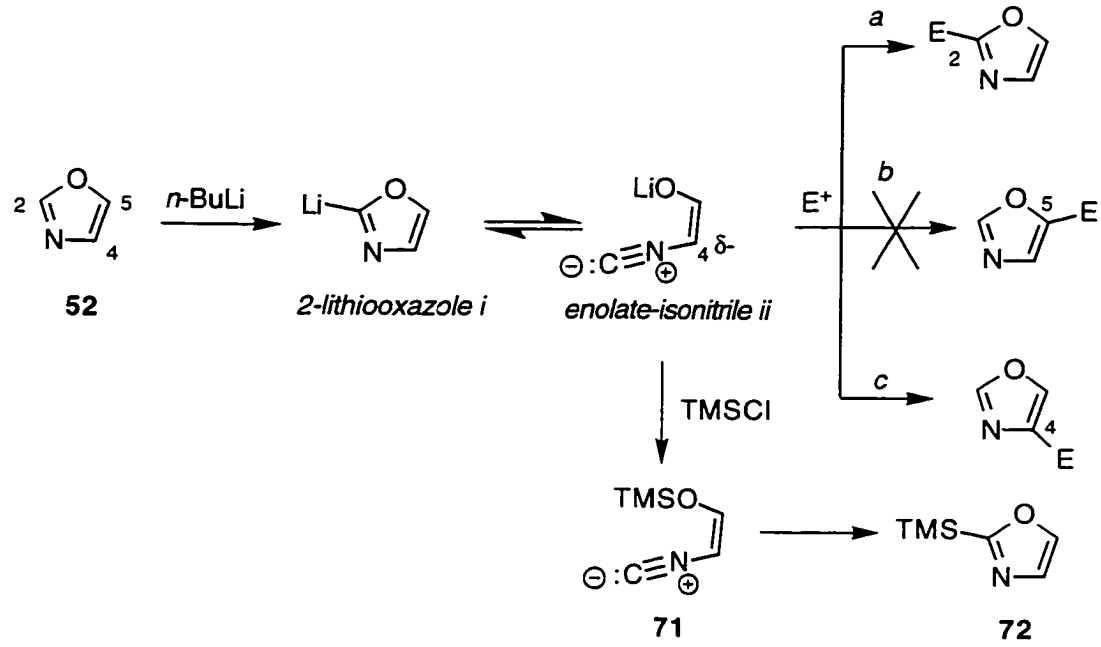


Figure 20. Oxazole reactivity

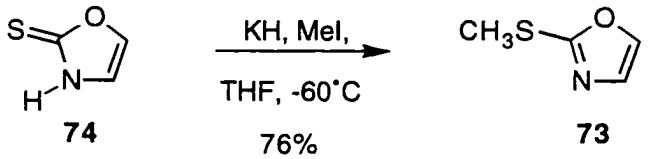
Placement of a TMS group at C2 was considered as a means to direct deprotonation to C5. When Dondoni attempted the synthesis of 2-TMS oxazole (**72**), the initial product was the TMS ether **71** (Figure 20). Distillation of **71** from KOH effected ring closure-rearrangement to give 2-TMS oxazole (**72**).[8] Attempts by Rickborn[4] and this author were unsuccessful in reproducing Dondoni's work. Another drawback of the 2-TMS oxazole approach to C5 activation is the requirement for oxazole (**52**) as the starting material. Oxazole is no longer commercially available which necessitates a lengthy synthesis of **52**. Finally, oxazole is volatile (bp 69°C) and hygroscopic, so careful handling would be needed.

2-Methylthiooxazole (**73**) seemed to be a promising alternate precursor to C5 substituted oxazoles. The methylthio substituent is a more robust surrogate group than TMS, and a synthesis beginning from the readily available oxazole-2-thione (**74**) would eliminate problems associated with **52**, in particular, the acidity of H2. Once the desired

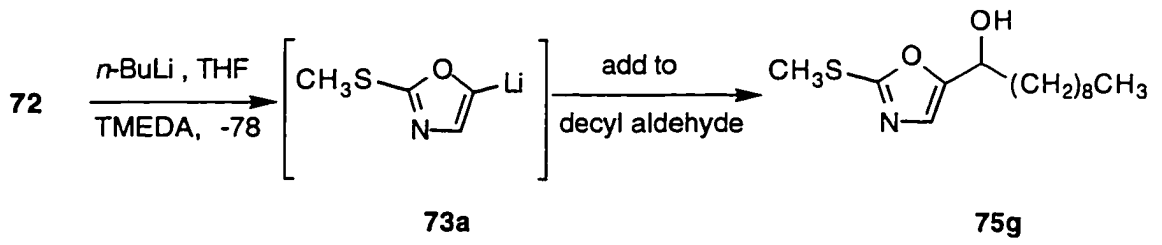
C5 alkyl- or acylation was complete, the MeS group could be easily removed by reductive desulfurization with Raney nickel.

5.2 Optimization of Reaction Conditions

Oxazole 2-thione (**74**) was prepared from dihydroxyfumaric acid and hydrogen thiocyanate according to Lacasse and Muchowski.[9] Methylation of **74** (KH, then MeI, -60°C) gave **73** in good yield (76%) after bulb to bulb distillation (bp 70-100°C, 28 mm Hg). Sodium hydride gave lower yields, and ethanolic alkali[10] produced mixtures of *S*- and *N*- methylated products.



Deprotonation of **73** with *n*-BuLi in hexanes-THF followed by addition of decyl aldehyde failed to produce the 5-oxazolyl carbinol **75g**. Instead, a dialkylation product was isolated (e.g. Figure 21). Reversing the order of addition by adding the carbanion **73a** *to* a solution of aldehyde at -78° C improved the yield of **75g** to 58%. In an attempt to suppress potential enolization of the aldehyde, $CeCl_3$[11] was incorporated into the reaction; however, the yield was poor (37%). Addition of TMEDA (10 eq) to the mixture prior to deprotonation at -78°C and addition to aldehyde dramatically improved the yield (73%, Table 7, entry 7).



The deprotonation-aldehyde addition was critically dependent on equivalency of base. Use of excess *n*-BuLi (1.4 eq) produced significant amounts of **76d** (44%, Figure 21) caused by double deprotonation-addition at both C5 and the MeS group.

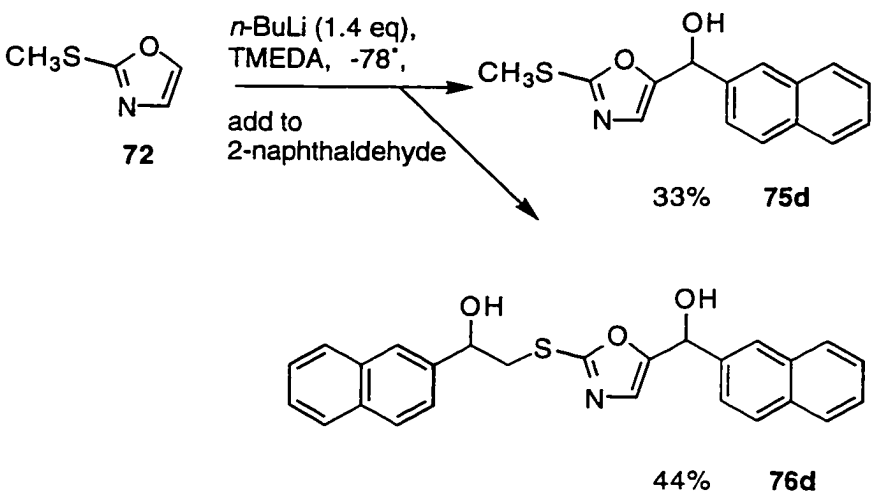


Figure 21. Double alkylation product **76d**

Conditions for the reaction were optimized as follows: addition of a solution of **73** in TMEDA-THF to *n*-BuLi (1.05 eq) in THF-hexanes at -78°C was followed after 20 min by cannulation of the anion **73a** to a solution of the aldehyde at -78°C. Work up of the mixture followed by column chromatography gave pure **75g** in 73% yield.

5.3 Verification of C5 Substitution

The location of the substituent in the oxazole ring of the addition product **75a** was confirmed by measurement of heteronuclear coupling constants ($^1J_{CH}$) and deuterium quench experiments (Section 5.6). The product **75a** showed one aromatic singlet (δ 6.62 ppm) with a heteronuclear coupling constant of $^1J_{CH}$ = 195.8 Hz, measured from ^{13}C satellites peaks in the ^1H NMR spectrum (Table 6).

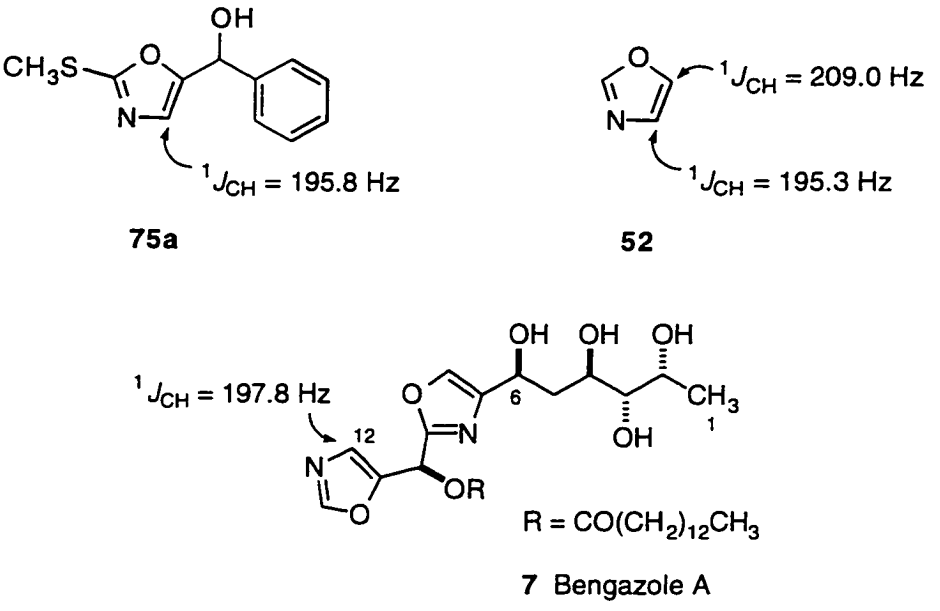


Table 6. $^1J_{CH}$ of oxazole containing compounds

Compound	$^1J_{CH}$ Coupling for Oxazole Protons		
	C2-H2	C4-H4	C5-H5
oxazole (**52**)	231.1	195.3	209.0
bengazole A (**7**)	233.6	197.8	211.7
55a	234.4	–	–[a]
75a	–	198.5	–
81a	229.3	–[a]	–

(a) Not determined.

It has been shown that magnitudes of coupling constants, $^1J_{CH}$, in the oxazole ring vary considerably with the electronic environment at different positions around the ring (C2, C4 or C5) but are essentially invariant with respect to alkyl substitution.[12,13] The relatively low value of $^1J_{CH}$ of the remaining oxazole ring proton signal in **75a** is

consistent with substitution at C5 and not C4 (c.f. oxazole, C4, $^1J_{CH}$ =195.2 Hz, C5, $^1J_{CH}$ = 209.0 Hz, Table 6).[13] In addition, the data fits well with the value measured for the C12-H12 heteronuclear coupling constant of bengazole A (**7**, $^1J_{CH}$ = 197.8 Hz).[12]

5.4 Scope of Reaction

Following optimization of the reaction conditions, a survey of electrophiles was conducted. Aldehydes gave consistently high yields, and the reactions involving aldehydes were normally complete in less than 10 minutes (Table 7, entries 1-9). Ketones reacted more slowly (45 min to several hours) and gave lower yields (entries 10 and 11). Reactions involving ketones often did not go to completion, possibly due to competitive ketone enolization of the α-protons.

Two examples of additions to acid chlorides were investigated. In both cases (Table 7, entries 12 and 13), large equivalencies of the acid chloride were required to prevent a second molecule of **73a** from adding to the first formed ketone product **75m**. For example, deprotonation of **73** (1.05 eq base) followed by addition to pivaloyl chloride (1.1 eq) gave substantial amounts of **77** (43%).

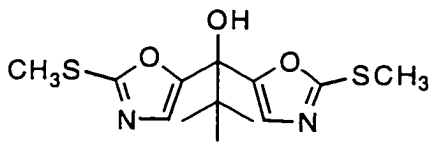


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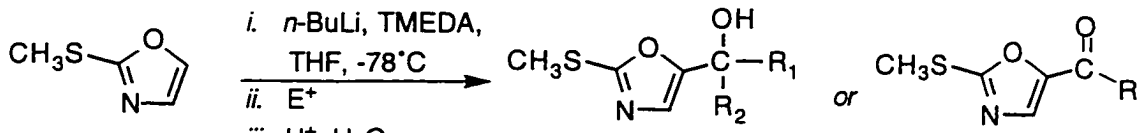
Table 7. Formation of 5-substituted oxazoles



73 **75**

Entry	Electrophile (E^+)	Eq. of **73**	Eq. of E^+	Eq. of TMEDA	Product	Yield (%)[a]
1	benzaldehyde	1.0	2.3	10.4	**75a**	84
2	*p*-anisaldehyde	1.0	2.2	10.0	**75b**	85
3	*p*-bromobenzaldehyde	1.0	2.2	10.4	**75c**	84
4	2-naphthaldehyde	1.0	2.0	10.3	**75d**	77
5	2-furaldehyde	2.0	1.0	16.2	**75e**	72
6	citral	1.0	2.2	10.5	**75f**	83[b]
7	decyl aldehyde	1.0	2.2	12.2	**75g**	73
8	pivaldehyde	1.0	2.1	10.4	**75h**	69
9	2,3-*O*-isopropylidene-D-glyceraldehyde	1.0	1.4	14.0	**75i**	60[c]
10	3-methyl-2-butanone	1.0	2.2	10.4	**75j**	39[d]
11	cyclohexanone	2.0	1.0	16.0	**75k**	53
12	benzoyl chloride	1.0	19.9	9.9	**75l**	38
13	pivaloyl chloride	1.0	15.9	9.9	**75m**	71
14	isovaleronitrile	1.0	2.2	9.9	**78**	33[e]
15	1-iodobutane	1.0	1.7	-	**79**	23[f]

(a) Yield of isolated product. Each new compound gave satisfactory HRMS and/or elemental analysis, IR, ^{1}H NMR and ^{13}C NMR; (b) Δ^2 *E/Z* ratio was 2:1 from 1.3:1*E/Z* -citral; (c) 2:1 diastereomeric ratio; (d) based on recovered starting material, 24% yield; (e) 3-methyl-2-(2'-oxazolyl)-butanenitrile (**78**); (f) addition of **73a** to 1-iodobutane (unoptimized) gave 23% 5-butyl-2-pentylthiooxazole (**79**) and 8% 2-pentyloxazole (**80**).

One example of addition to an alkanenitrile was explored (Table 7, entry 14). At the standard temperature (-78° C), no reaction with isovaleronitrile was observed (TLC), but upon allowing the mixture to warm to 25° C over 16 hours a new product (33%, unoptimized) could be isolated after work-up and chromatography. The ^{1}H NMR spectrum of the product showed loss of the MeS group from **73** and addition of alkyl proton signals corresponding to isovaleronitrile. Two diastereotopic methyl signals were now evident (δ 1.11, d, J = 6.7 Hz; 1.12, d, J = 6.7 Hz), and the α-methylene protons were replaced by a one-proton doublet (δ 3.98, d, J = 6.7 Hz). The IR and ^{13}C NMR spectra showed that the nitrile group had been retained (ν 2250 cm^{-1}; δ_{13C} 115.7 ppm), and thus the structure of the product is **78**.

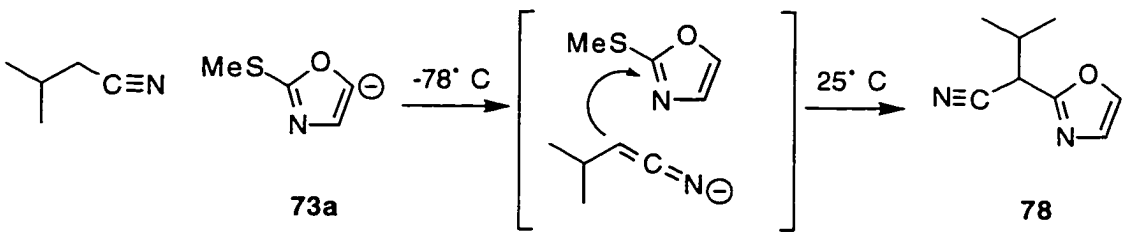


Figure 22. Formation of nitrile **78**

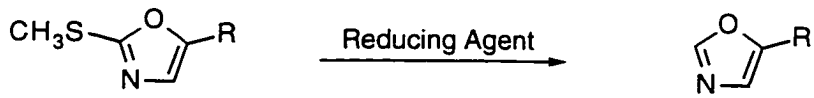
The differential reactivity of **73a** towards electrophiles indicates synthetic utility in selective addition reactions. Slower reaction of **73a** with ketones and poor reactivity with isovaleronitrile suggests that **73a** may add selectively at low temperature to aldehydes in the presence of ketones, nitriles and perhaps esters. On the other hand, the formation of **78** with **73a** and isovaleronitrile indicates the α-nitrile carbanion is preferentially formed by intermolecular proton transfer. The electrophilic nature of C2 is then revealed by addition-elimination of the α-nitrile carbanion to **73** and displacement of the MeS group to provide a moderate (unoptimized) yield of **78**. Thus, the MeS group, conveniently introduced in **73** as a robust surrogate group to direct electrophilic C-C bond formation at C5 by reaction with hard electrophiles (aldehydes) may also function as a leaving group for

C-C bond formation at C2 under another set of conditions. This carbon-carbon bond forming reaction complements the successful Vedejs modification for metallation-addition to 2-unsubstituted oxazoles.[14]

5.5 Desulfurization Procedure and Yields

Completion of the C5 monosubstituted oxazole synthesis required removal of the 2-MeS group. This was done using Raney nickel or nickel boride, "Ni_2B" (created *in situ* from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$).[15,16] Table 8 shows the results.

Table 8. Reductive desulfurization of **75** to 5-substituted oxazoles, **81**

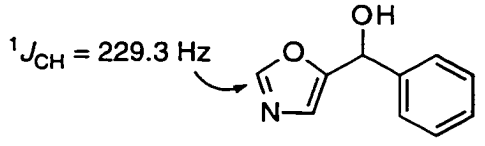


75 **81**

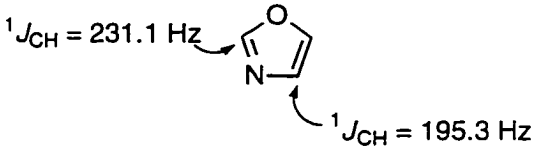
Entry	Starting Material (**75**)	Reducing Agent	Temperature (°C)	Product (**81**)	Yield (%)
1	**75a**	Ni_2B	0-25	**81a**	18
2	**75a**	Raney nickel	78	**81a**	68
3	**75d**	Raney nickel	78	**81d**	60
4	**75g**	Ni_2B	0-25	**81g**	41
5	**75g**	Raney nickel	78	**81g**	60
6	**75h**	Raney nickel	78	**81h**	59
7	**75k**	Raney nickel	78	**81k**	60

Removal of the 2-methylthio group with Raney nickel in refluxing EtOH (entries 2-3, 5-7) gave consistently higher yields than with Ni_2B (MeOH, 0-25°C, entries 1 and 4). While the Ni_2B method has the advantage of rapid completion (< 15 min), large excesses of $NiCl_2 \cdot 6H_2O$ (7 eq) and $NaBH_4$ (21 eq) were required, and poor mass recovery was observed, presumably from adsorption of the product to the nickel surface.

The heteronuclear coupling constant of C2-H2 for **81a**, $^1J_{CH}$ = 229.3 Hz, compared well with the C2-H2 coupling constant for oxazole ($^1J_{CH}$ = 231.1 Hz), and the C13-H13 coupling constant for bengazole A (**7**), $^1J_{CH}$ = 233.6 Hz (see also, Table 6, Section 5.3).



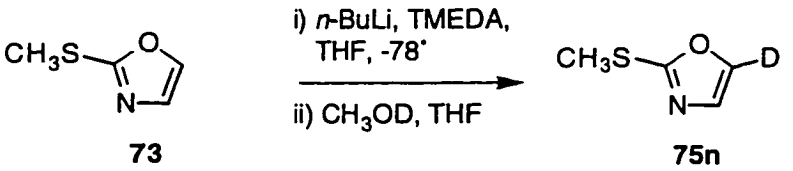
81a



52

5.6 Deuteration Studies and Electrostatic Calculations of 2-Methylthiooxazole (73)

The anion formed by deprotonation of **73** under optimized conditions added smoothly to aldehydes, but when an excess of *n*-BuLi (1.4 eq) was used or the aldehyde was added to the preformed oxazole anion (inverse addition), significant amounts of side-product due to 'double alkylation' were observed. The second alkylation always occurred by deprotonation-addition to the MeS group (e.g. product **76d**, Section 5.2). Although standard conditions gave no products from addition to MeS group, the low acidity of the methylthio hydrogens raised the possibility that in the presence of excess lithioanion **73a** proton exchange with **73** may rearrange the anion at C5 with the α-anion of the methylthio group, perhaps *via* a doubly charged anionic intermediate. In order to examine the lability of the C5 anion, deuterium quench experiments were conducted.



73 **75n**

The anion was prepared under standard conditions from **73** (1.0 eq *n*-BuLi, THF-TMEDA, -78° C), and after 20 minutes a portion of this mixture was cannulated into a solution of CH_3OD in -78° C. The remaining solution of anion was raised to -40°C, and two additional aliquots were quenched with CH_3OD after a further 15 minutes and 100 minutes. For each sample, ^1H NMR integration and GCMS showed >90% deuterium incorporation at C5, but <5% incorporation at the MeS group (EIMS, *m/z* 100, M^+-Me). This confirms that metallation occurred exclusively at C5 within the limits of detection, and no deuterium incorporation in the MeS group was observed. Thus, the C5 carbanion **73a** does not appear to rearrange under the conditions of the addition reaction.

The behavior of anion **73a** with various electrophiles (rapid with aldehydes, slower with ketones) suggested a nucleophilicity similar to that of 2-lithiofuran. To compare charge densities at C5, molecular orbital calculations of the α-anions of **73**, 2-ethyloxazole, 2-ethylfuran, 2-methylthiofuran and oxazole (PM3 level, MacSpartan Plus, Table 9) were conducted. Each heterocyclic anion molecule was optimized by molecular mechanics (Sybyl) prior to PM3 calculations.

Examination of fractional electrostatic charge at each ring atom revealed that >80% of the fractional charge resided at the anionic carbon (C5 of **73**). The formal carbanion corresponding to **73a** has charge localized in an sp^2 orbital orthogonal to the π system and is not expected to be stabilized by classical resonance. All oxazole anions examined gave comparable charge densities (range, -0.86 to -0.88) and were slightly higher than the corresponding furans (~ -0.81), suggesting a negligible inductive electron withdrawing effect of the MeS group on C5.

Parent heterocycle	δ^- at C5
oxazole	-0.86
2-methylthiooxazole	-0.88
2-ethyloxazole	-0.87
furan	-0.81
2-methylthiofuran	-0.82
2-ethylfuran	-0.81

Table 9. Calculated electrostatic charges at C5 of heterocyclic carbanions (PM3, MacSpartan Plus)

While these calculations do not allow for solvent effects, stabilization by counterion or coordination to the adjacent heteroatom, it supports the hypothesis that C5 lithiated 2-methylthiooxazole is at least as nucleophilic as lithiofuran in contrast with the poor nucleophilicity observed with 5-lithio-4-carboxylates.[17]

5.7 Biological Activity

Because bengazole A (**7**) has such potent antifungal activity, it was anticipated that oxazole compounds prepared in the course of this study might also exhibit antifungal properties. Each oxazole compound discussed in this chapter (with the exception of **73**) was tested against the five human pathogenic fungi using a standard disk diffusion assay[18] or broth dilution assay. The five fungal strains used were *Candida albicans* (ATCC 14053), *C. glabrata* (M6820, 0942738), *C. krusei* (BC10746, 1255044), and two strains of fluconazole-resistant *C. albicans*. Fluconazole-resistant *C. albicans* (96-489) was obtained from a clinical isolate (University of Texas medical center) while the UCDFR1 strain of *C. albicans* was sub-cultured from *C. albicans* (ATCC 14053) by passage through agar medium containing a sub-fungistatic concentration of Fluconazole™ (Dr. Matthew

Sage). Table 10 displays the data for compounds that tested positive for antifungal activity in the disk diffusion assay.

Table 10. Disk diffusion assay for antifungal activity of oxazole containing compounds (zones of inhibition in mm, a value of "0" indicates a response of ≤ 6.5 mm)

Compound	**Antifungal Activity (mm) at 300μg/disk**				
	Candida albicans	*Candida glabrata*	*Candida krusei*	F.R. *Candida albicans* 96-489	F.R. *C. albicans* UCDFR1
75a	8	8	7	8	NT
75b	8	7.5	0	0	7.5
75c	10	**11**	9	**14**	10
75i	8	7	0	0	7
75d	7.5	0	6.5	8	9
75e	8	7.5	7.5	0	8
75l	8	7	**11**	10	**12**
76c	7	0	0	0	7.5
79	8	0	7	0	NT
81a	8.5	7	6.5	0	7
81d	10	0	7.5	8	8
81g	9	10	8	**12**	NT
55a	10	0	9	0	0
55b	8	0	0	0	0

The most active compound was **75c** and the least active **76c**. The 'hit' rates of each set of compounds were similar - 47% for sulfur containing compounds versus 40%

for non-sulfur containing compounds. Comparing the results of **75a** and **81a** showed similar activity with the exception of fluconazole-resistant *C. albicans* (96-489) indicating that the C2 methylthio moiety does not play a critical role in antifungal activity. The presence of the *p*-bromobenzyl substituent in **75c** significantly increases the antifungal activity compared to the benzyl (**75a**) and *p*-methoxybenzyl (**75b**) analogs.

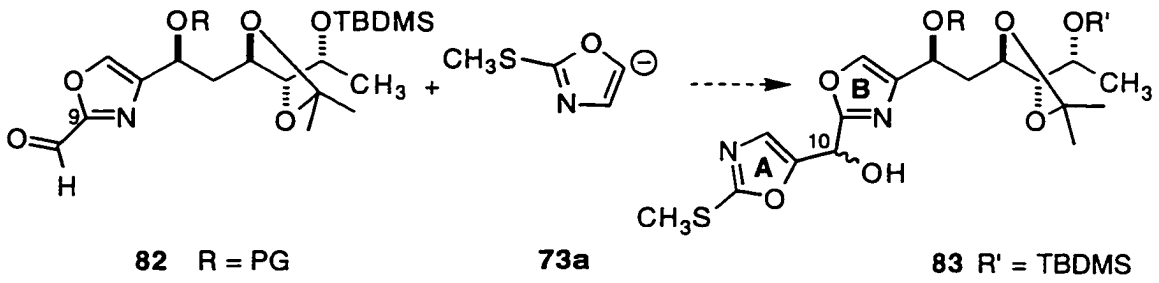
Several of the compounds that showed impressive zones of inhibition (**75c**, **75l**, **81d** and **81g**) were further tested in the broth dilution assay to determine the minimum inhibitory concentration (Table 11). The results from the MIC testing was unimpressive - only two of the compounds, **75c** and **81g**, were active and only at the highest concentration tested (5000 μg/mL).

Table 11. Broth dilution assay for determination of minimum inhibitory concentration (MIC) for antifungal activity

Compound	**Antifungal Activity (μg/mL)**				
	Candida albicans	*Candida glabrata*	*Candida krusei*	F.R. *Candida albicans* 96-489	F.R. *C. albicans* UCDFR1
75c	-	5000	-	-	-
75l	-	-	-	-	-
81d	-	-	-	-	-
81g	5000	5000	-	5000	NT

5.8 Conclusion

A synthetically useful preparation of C5 monosubstituted oxazoles was developed which encompasses a wide range of substituents at C5. This methodology can be used in an alternative approach to the synthesis of bengazole A (**7**, Figure 23).



82 R = PG **73a** **83** R' = TBDMS

Figure 23. Alternative synthesis of bengazole A (**7**) using the new oxazole methodology

In addition, the C2 methylthio group undergoes displacement with stabilized anions (e.g. isovaleronitrile) to provide a 2-monosubstituted oxazole **65**. Thus, **73a** can be activated under nucleophilic or electrophilic conditions for the preparation of 5- or 2-monosubstituted oxazoles.

5.9 References

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CHAPTER 6. EXPERIMENTAL

General Experimental: All solvents were dried and distilled from glass prior to use. THF and 1,4-dioxane were purified by distillation from sodium-benzophenone ketyl. Silica chromatography was carried out using 43-60 μ silica (EM Merck); TLC was conducted on 0.2 mm plates coated with silica impregnated with a fluorescent indicator. Melting points are uncorrected. Optical rotations were measured on a JASCO DIP 370 polarimeter. Class A analytical volumetric flasks were used in the kinetic studies. ^{1}H NMR and ^{13}C NMR spectra were recorded on a General Electric QE 300 (300 MHz and 75 MHz, respectively) or GE Omega 500 NMR spectrometers (500 MHz and 125 MHz respectively). Unless otherwise stated, chemical shifts are referenced as follows. ^{1}H; δ 0.00 ppm, (Me_4Si in $CDCl_3$ or DSS in D_2O), and ^{13}C; δ 77.00 ppm for the center peak of $CDCl_3$ or δ 66.5 ppm for dioxane in D_2O. Homonuclear *J* couplings were confirmed by COSY or single-frequency decoupling experiments. ^{13}C NMR signal chemical shift and multiplicity assignments (CH_3, methyl; CH_2, methylene; CH, methine; C, quaternary) were made from DEPT and HETCOR and HMBC spectra. GCMS was carried out on a capillary column (silicone coating) coupled to an ion-trap mass detector. High resolution mass spectra were provided by the University of Minnesota Mass Spectrometry Laboratory and the University of California, Riverside, Mass Spectrometry facility. Elemental analyses were provided by Midwest Microlabs (Indianapolis, IN).

(4*R*)-4-(Benzoxymethyl)-2-methyl-4,5-dihydrooxazole (31c). (4*R*)-4-(hydroxymethy)-2-methyl-4,5-dihydrooxazole (0.5020 g, 4.37 mmol) in 8 mL of dry THF was added dropwise to a hexane-washed suspension of NaH (0.1593 g, 6.64 mmol) in 8 mL of THF. After two hours, benzyl bromide (0.525 mL, 4.41 mmol) was added in 8 mL of THF. Tetrabutylammonium iodide (0.1623 g, 0.43 mmol) was then added. The

reaction was monitored by TLC. After 18 hours at 23°C, the reaction was heated to reflux for one hour, cooled, and Florisil® was added. The THF was evaporated, and the Florisil® containing the adsorbed compound was placed on the top on a Florisil® column. (4*R*)-4-(benzoxymethyl)-2-methyl-4,5-dihydrooxazole was eluted from the column with a gradient of 1:19 EtOAc in hexane to 100% EtOAc. It was then purified by bulb to bulb distillation to yield a clear, colorless oil (125°C, 3 mm Hg) in 73% yield (0.6504 g). R_f (EtOAc) = 0.23; $[\alpha]_D$ +19.2° (*c* 2.95, $CHCl_3$); UV (MeOH) 207 (ε 9083); IR (NaCl, neat) 1672 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3 H), 3.40 (m, 1 H), 3.64 (m, 1 H), 4.11 (bs, 1 H), 4.27 (2 H), 4.55 (s, 2 H), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 65.9 (CH), 70.4 (CH_2), 72.0 (CH_2), 73.2 (CH_2), 127.5 (CH), 128.2 (CH), 137.9 (C), 165.8 (C); HREIMS found 205.1082 (M^+), $C_{12}H_{15}NO_2$ requires 205.1103.

(4*R*)-4-(Benzoxymethyl)-2-(styryl)-4,5-dihydrooxazole (29). THF (10 mL) was cooled to -65°C, and *t*-BuLi (1.6 mL, 2.72 mmol) was added. A solution of **31c** (0.5088 g, 2.48 mmol) in THF (8mL) was added dropwise to the cooled solution. After 15 minutes, a solution of distilled benzaldehyde (0.40 mL, 3.94 mmol) in THF (5 mL) was added dropwise to the cooled solution. After 10 minutes, TLC indicated that the starting material had been consumed. The reaction was quenched at -72°C with NH_4Cl (saturated, aqueous) and warmed to 0°C. The mixture was poured into EtOAc, and the solvent was evaporated. The mixture was diluted with EtOAc (200 mL) and NH_4Cl (50 mL, saturated, aqueous). The aqueous layer was extracted 3 times with EtOAc. The organic layers were combined, washed with NaCl (saturated, aqueous), dried through a plug of $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (2.5 × 20 cm, 1:19 EtOAc:hexane to 100% EtOAc). (4*R*)-4-(benzoxymethyl)-2-(2-hydroxy-2-phenylethyl)-4,5-dihydrooxazole was obtained in 75% yield (0.58 g) as a yellow oil. R_f (EtOAc) = 0.70; $[\alpha]_D$ +14.1° (*c* 5.00, $CHCl_3$); UV (MeOH) 209 nm (ε 17230); IR (NaCl, neat) 3353-3247 (OH), 1661 cm^{-1} (C=N); ^1H

NMR (300 MHz, $CDCl_3$) δ 2.62 (m, 2 H), 3.40 (m, 1 H), 3.60 (m, 1 H), 4.15 (m, 1 H), 4.28 (m, 2 H), 4.54 (d, 2 H), 5.05 (m, 1 H), 7.31 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 37.2 (CH_2), 65.4 (CH), 70.0 (CH_2), 70.1 (CH), 71.6 (CH_2), 73.1 (CH_2), 125.6 (CH), 127.3 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 137.8 (C), 142.9 (C), 167.3 (C); HREIMS found 311.1502 (M^+), $C_{19}H_{21}NO_3$ requires 311.1521.

Triethylamine (0.77 mL, 5.52 mmol) was added to a solution of (4*R*)-4-(benzoxymethyl)-2-(2-hydroxy-2-phenylethyl)-4,5-dihydrooxazole (0.8694 g, 2.80 mmol) and CH_2Cl_2 (14 mL). DMAP (0.3384 g, 2.77 mmol) was added, and the mixture was cooled to 0°C. Methanesulfonyl chloride (0.45 mL, 5.81 mmol) was added dropwise to the mixture. The ice bath was removed, and, after 30 minutes, TLC indicated that the starting material had been consumed. The reaction was quenched by pouring into 40 mL of cold $NaHCO_3$ (saturated, aqueous), and the aqueous layer was extracted 3 times with CH_2Cl_2. The organic layers were combined, washed with 50 mL of 0.01 M HCl and then $NaHCO_3$ (saturated, aqueous), dried through a plug of $MgSO_4$, and concentrated under reduced pressure. The NMR of the crude material indicated that the mesylated alcohol had eliminated entirely to **29**. The crude material was first passed through a plug of alumina with 1% MeOH in CH_2Cl_2 and then purified by flash chromatography on TLC grade silica gel (5 × 5 cm, 3:1 EtOAc:hexane) to give **29** in 88% yield (0.7427g). R_f (EtOAc) = 0.45; mp 63-66°C; $[\alpha]_D$ +31.3° (*c* 2.87, $CHCl_3$); UV ($CHCl_3$) 284 nm (ε 22138); IR (NaCl, neat) 1652 (C=N), 1608 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 3.48 (m, 1 H), 3.72 (m, 1 H), 4.24 (m, 1 H), 4.41 (m, 3 H), 4.58 (s, 2 H), 6.63 (d, 1 H, *J* = 16.3 Hz), 7.40 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 66.2 (CH), 70.2 (CH_2), 72.0 (CH_2), 73.3 (CH_2), 114.9 (CH), 127.3 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 129.4 (CH), 135.0 (C), 137.9 (C), 140.1 (CH), 164.4 (C); HREIMS found 293.1440 (M^+), $C_{19}H_{19}NO_2$ requires 293.1416.

(4*R*)-4-(Benzoxymethyl)-2-oxazolidinone (32). Compound **29** (0.3138 g, 1.07 mmol) was dissolved in THF (2.5 mL), and H_2O (2.5 mL) added. $NaIO_4$ (0.5768 g, 2.70

mmol) and then OsO_4 (2.5 wt % in *t*-butanol, 1.34 mL, 0.11 mmol) were added. After 8 h, additional $NaIO_4$ (0.3000 g, 1.40 mmol) was added. After 18 h, mixture filtered through a fritted funnel and then through $MgSO_4$. The liquid was concentrated *in vacuo* to give a black oil which was purified by column chromatography (1.0 cm × 8.0 cm, EtOAc/hexane) to afford oxazolidinone **32** (71.7 mg, 32%). IR (NaCl, neat) 3310 (NH), 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.70 (m, 5 H), 4.58 (s, 2 H), 6.55 (bs, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 49.6 (CH), 62.9 (CH_2), 69.8 (CH_2), 73.4 (CH_2), 127.7 (CH), 127.9 (CH), 128.5 (CH), 137.4 (C), 161.7 (C).

(4*R*)-4-(Benzoxymethyl)-2-(dibromomethyl)-4,5-dihydrooxazole (33). *N*-bromosuccinimide (1.02 g, 5.70 mmol) was added to a solution of **31c** (1.0365 g, 5.10 mmol) in CCl_4 (25 mL). After 3 h, additional NBS (0.80 g, 4.50 mmol) was added. After 4 h, the reaction was stopped by filtration through a fritted funnel. The solution was concentrated under reduced pressure to give a clear yellow oil (1.6545 g). Flash chromatography on silica gel (6 × 18 cm; 1:19 EtOAc:hexane to EtOAc) gave (4*R*)-4-(benzoxymethyl)-2-(dibromomethyl)-4,5-dihydrooxazole (**33**, 0.3489 g, 19%) and (4*R*)-4-benzoxymethyl)-2-(tribromomethyl)-4,5-dihydrooxazole (0.5138 g, 23%). **33**: R_f (1:1 EtOAc:hexane) = 0.56; $[\alpha]_D$ +30.2° (*c* 1.44, $CHCl_3$); UV (CH_3CN) 212 nm (ε 13137); IR (NaCl, neat) 1656 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ 3.50 (m, 1 H), 3.67 (m, 1 H), 4.46 (m, 3 H), 4.56 (s, 2 H), 6.11 (s, 1 H), 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 27.1 (CH), 66.5 (CH), 71.0 (CH_2), 72.3 (CH_2), 73.4 (CH_2), 127.6 (CH), 127.7 (CH), 128.4 (CH), 137.8 (C), 163.6 (C).

(4*R*)-4-benzoxymethyl)-2-(tribromomethyl)-4,5-dihydrooxazole: R_f (1:1 EtOAc:hexane) = 0.50; mp 72-78°C; $[\alpha]_D$ +52.0° (*c* 0.49, $CHCl_3$); UV (CH_3CN) 212 nm (ε 9434); IR (NaCl, neat) 1648 cm^{-1} (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (dd, 1 H), 3.70 (dd, H), 4.58 (m, 5 H), 7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.0 (C), 67.0 (CH), 70.8 (CH_2), 73.5 (CH_2), 74.5 (CH_2), 127.6 (CH), 127.7 (CH), 128.4 (CH),

137.8 (C), 164.2 (C); HRCIMS found 439.8499 (MH^+), $C_{12}H_{13}NO_2Br_3$ requires 439.8496.

***N*-(1-Hydroxymethyl-2-benzoxyethyl)-1,1-dibromoethanamide (34).** (4*R*)-4-(benzoxymethyl)-2-(dibromomethyl)-4,5-dihydrooxazole (**33**, 0.2994 g, 0.82 mmol) was dissolved in THF (3.8 mL), and H_2O (0.5 mL) and $CaCO_3$ (0.43 g, 4.3 mmol) were added. The solution was refluxed for 7 h. The reaction was stopped by filtering the reaction mixture through $MgSO_4$ and evaporating the solvent to a clear yellow oil (0.3126 g). The crude material was purified by column chromatography on silica gel (2.5 × 14 cm, 1:9 EtOAc:hexane) to give **34** (0.1687 g, 54%) of a pale yellow oil which crystallized upon standing. mp 88.5-90.5°C; $[\alpha]_D$ -8.57° (*c* 5.90, $CHCl_3$); UV (CH_3CN) 210 nm (ε 12302); IR (NaCl, neat) 3273 (OH, NH), 1661 (amide I band), 1554 cm^{-1} (amide II band); ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (bs, 1 H), 3.70 (m, 3 H), 3.87 (bs, 1 H), 4.08 (m, 1 H), 4.59 (s, 2 H), 5.90 (s, 1 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 35.9 (CH), 50.9 (CH), 62.0 (CH_2), 69.0 (CH_2), 73.0 (CH_2), 127.2 (CH), 127.5 (CH), 128.1 (CH), 136.8 (C), 164.2 (C); HREIMS found 300.0223 ($M-Br^+$), $C_{12}H_{15}NBrO_3$ requires 300.0235.

(4*R*)-4-(Benzoxymethyl)-2-(2-hydroxy-2-methyl-propyl)-4, 5-dihydrooxazole (35). *t*-BuLi (1.7 M, 0.3 mL, 0.51 mmol) was added to THF (1 mL) at -78°C. After 5 minutes, **31c** (0.1005 g, 0.49 mmol) was added dropwise in THF (1.5 mL). Fifteen minutes later, this solution was transfered *via* cannula to a solution of dimethyldioxirane solution in acetone (0.116 M, 6 mL, 0.70 mmol) at -78°C. After several hours, no reaction had occurred so the solution was allowed to warm up to rt. After 3 h at 23°C, the starting material was consumed so the reaction was quenched by the addition of pH 7 buffer (1 mL, Na_2HPO_4/NaH_2PO_4). The solvent was removed under vacuum, and the residue was mixed with CH_2Cl_2 and water. The aqueous layer was extracted with

CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried through Na_2SO_4 and concentrated under vacuum to give a yellow oil. The crude material was purified on silica gel (1 × 0.6 cm; 1:9 MeOH:$CHCl_3$) to yield 59.8 mg (51%) of **35**. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.27 (s, 3 H), 2.41 (s, 2 H), 3.45 (dd, 1 H), 3.60 (dd, 1 H), 4.15 (dd, 1 H), 4.25 (m, 2H), 4.57 (s, 2 H), 7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.2, 40.4, 65.6, 68.7, 69.6, 71.8, 73.3, 127.6, 128.3, 137.8, 167.2.

(4*R*)-4-(Benzoxymethyl)-2-(hydroxymethyl)-4, 5-dihydrooxazole (36). A solution of **31c** (0.4889 g, 2.38 mmol) in THF (6 mL) was added dropwise to a stirred solution of *t*-BuLi (1.4 M, 2.60 mmol) in THF-hexane (7.9 mL) at -78°C. After 30 minutes, the flask was purged with N_2, and then oxygen was bubbled into the solution for 3 h at -78°C. Triethylphosphite (0.48 mL, 2.80 mmol) was added to the solution, and the reaction mixture was warmed to rt over 20 minutes. The solution was diluted with EtOAc (50 mL) and washed with cold HCl (0.01 M, 5 mL). The aqueous layer was extracted 3 times with EtOAc (15 mL). The organic layer was washed twice with cold, saturated $NaHCO_3$ (8 mL), dried through Na_2SO_4 and concentrated under vacuum to yield yellow oil (0.5328 g). The crude oil was purified on silica gel (5 × 20 cm; 1:9 MeOH:$CHCl_3$) to give **36** as a yellow oil (0.2725 g, 51% yield). IR (NaCl, neat) 3227 (OH stretch), 1673 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 (dd, 1 H, J = 6.1 Hz), 3.63 (dd, 1 H, J = 4.0 Hz), 4.21 (s, 2 H), 4.35 (m, 2 H), 4.53 (s, 2 H), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 57.0 (CH_2), 65.1 (CH), 71.3 (CH_2), 71.6 (CH_2), 73.4 (CH_2), 127.6 (CH), 127.7 (CH), 128.3 (CH), 137.8 (C), 169.5 (C); HREIMS found 222.1122 (MH^+), $C_{12}H_{16}NO_3$ requires 222.1130.

General Preparation of Oxazolines: 2-Methyloxazoline and ethyl acetimidate hydrochloride were purchased from the Aldrich Chemical Company. Oxazolines were prepared according to one of three methods. Method A: Condensation of ethyl acetimidate

hydrochloride with (*S*)-(+)-valinol (**31a**, 78%[1]) or (*R*)-(-)-phenylglycinol (**31b**, 91%) according to Meyers.[2] Method B: Condensation of (*S*)-valinol or (*R*)-(-)-phenylglycinol with ethyl propionimidate hydrochloride (**31f**),[3] or ethyl α–phenylacetimidate hydrochloride (**31i**, 87%;[4] **31j**, 78%), or 1-naphthylacetimidate (**31k**, 91%) or 2-naphthylacetimidate hydrochloride (**31l**, 49%). Arylacetimidate hydrochlorides were prepared by bubbling dry HCl into cold ethanolic solutions of the corresponding arylacetonitriles.[3] Method C: Condensation of acid chloride with (*R*)-valinol or (*R*)-(-)-phenylglycinol followed by dehydration of the product amide with $SOCl_2$ and Et_3N in CH_2Cl_2.[5] Other oxazolines were prepared by alkylation (**31c**, NaH, $ArCH_2Br$, THF) or acylation (**31d**, $ArCO_2H$, DCC, Et_3N, THF) of (*R*)-4-hydroxymethyl-2-methyloxazoline, obtained from (*S*)-serine ethyl ester hydrochloride.[6]

(4*S*)-4-Isopropyl-2-(2-methylpropyl)-4,5-dihydrooxazole (31g). Method C. A solution of *S*-valinol (3.00 g, 29.1 mmol) in CH_2Cl_2 (20 mL) was added to solution of isovaleroyl chloride (3.4 mL, 32.5 mmol) in CH_2Cl_2 (50 mL) was added . Triethylamine (4.6 mL, 33.0 mmol) was added, and the solution was stirred overnight. The reaction mixture was poured into NH_4Cl (15 mL, aq, satd) and H_2O (30 mL). The aqueous layer was extracted 2 × 300 mL of Et_2O. The Et_2O was dried through $MgSO_4$ and reduced to a clear colorless oil (5.49 g) which crystallized upon standing. The amide alcohol (5.49 g, 29.0 mmol) was then dissolved in CH_2Cl_2 (150 mL) to which thionyl chloride (8.6 mL, 118 mmol) was added at 0°C. After 3.5 h, the solvent and excess thionyl chloride was removed *in vacuo*. The crude material was dissolved in Et_2O (400 mL), and $NaHCO_3$ (35 mL, satd), H_2O (35 mL), and 3 M NaOH (23 mL) were added. This mixture stirred for 0.5 h. The layers were separated, and the aqueous layer was extracted with Et_2O (400 mL). The Et_2O layers were dried through $MgSO_4$ and reduced to a yellow oil (5.51 g) The crude mixture was purified by bulb-to-bulb distillation (125°C, 0.9 torr) to give 2.44 g (50%) of a clear, colorless oil. $[\alpha]_D$ -56.0° (*c* 5.42, CH_3CN); IR (NaCl, neat) 1643 cm^{-1}

(C=N); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.81 (d, 3 H, *J* = 6.8 Hz), 0.892 (d, 3 H, *J* = 6.8 Hz), 0.895 (d, 3 H, *J* = 6.6 Hz), 0.90 (d, 3 H, *J* = 6.6 Hz), 1.68 (ddq, 1 H, *J* = 6.8 Hz), 1.96 (dq, 1 H, *J* = 6.6 Hz), 2.10 (d, 2 H, *J* = 6.8 Hz), 3.84 (m, 2 H), 4.13 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.0 (CH_3), 18.6 (CH_3), 22.3 (2 × CH_3), 26.2 (CH), 32.4 (CH), 37.0 (CH_2), 69.5 (CH_2), 71.9 (CH), 166.6 (C); HREIMS found *m/z* 169.1462 (M^+), $C_{10}H_{19}NO$ requires 169.1467.

(4*R*)-2-(2,2-Dimethylpropyl)-4-phenyl-4,5-dihydrooxazole (31h). Method C, oil, 51%. $[\alpha]_D$ +34.0° (*c* 4.46, $CHCl_3$); IR (NaCl, neat) 1661 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 9 H), 2.32 (s, 2 H), 4.05 (dd, 1 H, *J* = 8.5, 8.5 Hz), 4.60 (dd, 1 H, *J* = 10.2, 8.5 Hz), 5.19 (dd, 1 H, *J* = 10.2, 8.5 Hz), 7.27 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.6 (CH_3), 30.7 (C), 41.6 (CH_2), 69.4 (CH), 74.1 (CH_2), 126.4 (2 × CH), 127.2 (CH), 128.4 (2 × CH), 142.4 (C), 167.4 (C); HREIMS found *m/z* 217.1464 (M^+), $C_{14}H_{19}NO$ requires 217.1467.

(4*S*)-2-Benzyl-4-(1-isopropyl)-4,5-dihydrooxazole (31j). Clear oil, 78%; R_f = 0.26, 3:7 EtOAc:hexane. IR (NaCl, neat) 1669 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$) δ 0.85 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 1.72 (dq, 1 H, *J* = 6.8 Hz), 3.60 (s, 2 H), 3.87 (m, 2 H), 4.14 (m, 1 H), 7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 17.8 (CH_3), 18.4 (CH_3), 32.3 (CH), 34.6 (CH_2), 69.9 (CH_2), 71.8 (CH), 126.6 (CH), 128.2 (2 × CH), 128.6 (2 × CH), 135.1 (C), 165.3 (C); HREIMS found *m/z* 203.1311 (M^+), $C_{13}H_{17}NO$ requires 203.1310.

(4*R*)-2-(1-Naphthylmethyl)-4-phenyl-4,5-dihydrooxazole (31k). Triethylamine (5.2 mL, 37.3 mmol) was added dropwise to a stirred mixture of (*R*)-(-)-2-phenylglycinol (3.94 g, 28.7 mmol), ethyl 1-naphthylacetimidate hydrochloride (8.60 g, 34.5 mmol) and CH_2Cl_2 (144 mL). After stirring at room temperature overnight, the

reaction mixture was poured into ice water, and the aqueous layer was extracted three times with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and reduced *in vacuo* to a opaque, viscous oil (8.58 g). Baseline impurities were removed by column chromatography (silica gel, 3:7 EtOAc:hexane) to give **31k** as a yellow solid (5.94 g, 91%; R_f = 0.18, 3:7 EtOAc:hexane). mp 57-59°C; $[\alpha]_D$ +62.6° (*c* 4.65, $CHCl_3$); UV (CH_3CN) 225 (ε 44670), 271 (5870), 281 (6970), 288 (4700), 291 (4680), 313 nm (220); IR (NaCl, neat) 1662 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 3.93 (dd, 1 H, *J* = 8.5, 8.1 Hz), 4.14 (s, 2 H), 4.43 (dd, 1 H, *J* = 10.1, 8.5 Hz), 5.10 (dd, 1 H, *J* = 10.1, 8.1 Hz), 7.19 (m, 5 H), 7.43 (m, 4 H), 7.74 (d, 1 H, *J* = 8.1), 7.80 (dd, 1 H, *J* = 7.6, 1.3 Hz), 8.22 (d, 1 H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 32.6 (CH_2), 69.5 (CH), 74.7 (CH_2), 124.0 (CH), 125.3 (CH), 125.6 (CH), 126.0 (CH), 126.4 (CH), 127.3 (CH), 127.5 (CH), 127.8 (CH), 128.4 (2 × CH), 128.5 (CH), 131.2 (C), 131.9 (C), 133.7 (C), 142.1 (C), 157.2 (C), 166.9 (C); HREIMS found *m/z* 287.1308 (M^+), $C_{20}H_{17}NO$ requires 287.1310.

(4*R*)-2-(2-Naphthylmethyl)-4-phenyl-4,5-dihydrooxazole (31l). Oxazoline **31l** was prepared (49%) from ethyl 2-naphthylacetimidate hydrochloride in a similar fashion to **31k**. Yellow solid, R_f = 0.14, 3:7 EtOAc:hexane. mp 50-50.5°C; $[\alpha]_D$ +86.1° (*c*4.92, $CHCl_3$); UV (CH_3CN) 224 (ε 111,000), 267 (6750), 276 (6970), 286 (5250), 366 nm (1950); IR (NaCl, neat) 1666 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 3.82 (s, 2 H), 4.09 (dd, 1 H, *J* = 8.5, 8.2 Hz), 4.60 (dd, 1 H, *J* = 10.0, 8.5 Hz), 5.21 (dd, 1 H, *J* = 10.0, 8.2 Hz), 7.28 (m, 5 H), 7.48 (m, 3 H), 7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 34.8 (CH_2), 69.4 (CH), 74.7 (CH_2), 125.6 (CH), 125.9 (CH), 126.4 (3 × CH), 126.9 (CH), 127.3 (CH), 127.5 (2 × CH), 128.1 (CH), 128.5 (2 × CH), 132.3 (C), 132.5 (C), 133.3 (C), 142.1 (C), 166.9 (C); HREIMS found *m/z* 287.1308 (M^+), $C_{20}H_{17}NO$ requires 287.1310.

General Procedure for SeO_2 Promoted Oxidative Rearrangement:

(5*S*)-5-Isopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37a). A solution of (4*S*)-oxazoline **31a** (0.101 g, 0.82 mmol)[1] in dry dioxane (2 mL) was added to a suspension of selenium dioxide (0.196 g, 1.77 mmol) in dioxane (2 mL), and the mixture heated at reflux for 2 h. The mixture was cooled and purified by direct application to a column of silica gel and elution with EtOAc to give **37a** as a light-tan oil, essentially pure by ^{1}H NMR (0.0849g, 75 %), R_f (EtOAc) = 0.58. Crystallization of **37a** from *n*-hexane at -20°C gave an analytical sample as long colorless needles, mp 2-3°C; $[\alpha]_D$ +97.4° (*c* 0.83, $CHCl_3$); CD (hexane) λ 197 nm (Δ ε -7.5), 243 (7.8), 291 (-0.1), 335 (0.5); UV (hexane) λ 202 nm (ε 13800), 348 (298); IR (NaCl, neat) 1748 (C=O), 1631 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3 H, *J* = 6.8 Hz, *i*-Pr), 1.06 (d, 3 H, *J* = 6.8 Hz, *i*-Pr), 1.93 (dq, 1 H, *J* = 6.8, 6.8 Hz, *i*-Pr), 3.48 (dddd, 1 H, *J* = 9.5, 6.8, 4.4, 2.8 Hz, H5), 4.24 (dd, 1 H, *J* = 11.7, 9.5 Hz, H6a), 4.45 (dd, 1 H, *J* = 11.7, 4.4 Hz, H6b), 7.87 (d, 1 H, *J* = 2.8 Hz, H3); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_3), 19.2 (CH_3), 30.4 (CH), 61.5 (CH), 68.3 (CH_2), 152.2 (CH, $^1J_{C-H}$ = 193 Hz, C3), 154.5 (C, C2); HREIMS found *m/z* 141.0785 (M^+), $C_7H_{11}NO_2$ requires 141.0790; Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.21; H, 7.89; N, 9.83.

(5*R*)-5-Phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37b). Yellow oil (72%); $[\alpha]_D$ -252° (*c* 5.23, $CHCl_3$); UV (CH_3CN) λ 212 (ε 11200), 240 (1420), 338 (150); IR (NaCl, neat) 1762 (C=O), 1631 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.28 (dd, 1 H, *J* = 11.7, 10.8 Hz, H6a), 4.61 (dd, 1 H, *J* = 11.7, 4.7 Hz, H6b), 4.91 (ddd, 1 H, *J* = 10.8, 4.7, 3.1 Hz, H5), 7.37 (m, 5 H), 8.06 (d, 1 H, *J* = 3.1 Hz, H3); ^{13}C NMR ($CDCl_3$) δ 59.5 (CH), 70.6 (CH_2), 126.8 (CH), 128.1 (CH), 128.6 (CH), 136.0 (C), 152.9 (CH, C-3), 153.8 (C); HREIMS found *m/z* 175.0634 (M^+), $C_{10}H_9NO_2$ requires 175.0633.

(5*R*)-5-(Benzyloxymethyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (37c). Colorless oil (22%); R_f = 0.62 (EtOAc); $[\alpha]_D$ -23.8° (*c*0.913, $CHCl_3$); IR (NaCl, neat)

1746 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.62 (dd, 1 H, *J* = 9.6, 7.3 Hz), 3.87 (dd, 1 H, *J* = 9.6, 4.2 Hz), 4.00 (m, 1 H), 4.42 (dd, 1 H, *J* = 11.7, 8.4 Hz), 4.57 (dd, 1 H, *J* = 11.7, 4.4 Hz), 4.59 (s, 2 H), 7.35 (m, 5 H), 7.90 (d, 1 H, *J* = 2.6 Hz, H3); ^{13}C NMR ($CDCl_3$) δ 56.1 (CH), 68.0 (CH_2), 69.0 (CH_2), 73.6 (CH_2), 127.6 (CH), 127.9 (CH), 128.5 (CH), 137.3 (C), 153.5 (CH, $^1J_{C-H}$ = 194 Hz, C-3), 154.3 (C); HRCIMS found *m/z* 220.0982 (MH^+), $C_{12}H_{14}NO_3$ requires 220.0974.

(5*S*)-5-(6'-Methoxy-2'-naphthoyloxymethyl)-5,6-dihydro-2*H*-1,4-oxazin-2-one (37d). Colorless solid (53%); R_f = 0.56 (EtOAc); ^1H NMR ($CDCl_3$) δ 3.95 (s, 3 H), 4.26 (m, 1 H), 4.50 (dd, 1 H, *J* = 11.8, 8.6 Hz), 4.57 (dd, 1 H, *J* = 11.6, 6.4 Hz), 4.68 (dd, 1 H, *J* = 11.8, 4.4 Hz), 4.77 (dd, 1 H, *J* = 11.6, 4.5 Hz), 7.15 (d, 1 H, *J* = 2.5 Hz), 7.21 (dd, 1 H, *J* = 8.9, 2.5 Hz), 7.76 (d, 1 H, 8.6 Hz), 7.85 (d, 1 H, 8.9 Hz), 7.97 (dd, 1 H, *J* = 8.6, 1.7 Hz), 7.98 (d, 1 H, *J* = 2.8, H3), 8.49 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 55.3 (CH_3), 55.4 (CH), 63.3 (CH_2), 67.7 (CH_2), 105.7 (CH), 119.8 (CH), 124.0 (C), 125.7 (CH), 127.0 (CH), 127.8 (C), 130.9 (CH), 131.2 (CH), 137.4 (C), 154.0 (CH, C-3), 159.8 (C), 166.3 (C); HREIMS found *m/z* 313.0956 (M^+), $C_{17}H_{15}NO_5$ requires 313.0950.

5,6-Dihydro-2*H*-1,4-oxazin-2-one (37e). A solution of 2-methyloxazoline (**31e**, 0.1037 g, 1.22 mmole) and *n*-nonane (10 mol%, internal standard) in dry THF (6 mL) was heated under reflux with SeO_2 (0.2875 g, 2.59 mmol), and the reaction monitored by GCMS. After 1.5 h, the crude mixture was filtered through silica gel and eluted with diethyl ether. Careful evaporation of the eluate under a stream of nitrogen gave a yellow oil (11 mg) containing **37e** that was analyzed by NMR and GCMS. 60% yield by GC; ^1H NMR ($CDCl_3$) δ 3.87, (m, 2H), 4.47 (t, 2H, *J* = 5.5 Hz), 7.88 (t, 1H, CH=N, *J*= 2.3 Hz), ; GCMS, *m/z* 99 (M^+), Rt 7.29 min, 50-150°C @ 4°/min, 30 m × 0.32 mm, DB5.

(5*S*)-2,5-Diisopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37g). 33%; R_f = 0.47, 3:7 EtOAc:hexane. $[\alpha]_D$ +89.4° (*c*3.76, CH_3CN); IR (NaCl, neat) 1738 (C=O), 1637 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, *J* = 7.0 Hz), 1.05 (d, 3 H, *J* = 7.0 Hz), 1.13 (d, 3 H, *J* = 6.8 Hz), 1.16 (d, 3 H, *J* = 6.8 Hz), 1.86 (dq, 1 H, *J* = 6.8 Hz), 3.20 (dq, 1 H, *J* = 7.0, 1.3 Hz), 3.40 (dddd, 1 H, *J* = 9.2, 6.8, 4.1, 1.3 Hz), 4.14 (dd, 1 H, *J* = 11.3, 9.2 Hz), 4.39 (dd, 1 H, *J* = 11.3, 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6 (CH_3), 19.1 (CH_3), 19.3 (CH_3), 20.0 (CH_3), 30.4 (CH), 31.8 (CH), 60.8 (CH), 68.2 (CH_2), 155.6 (C), 165.6 (C); HREIMS found *m/z* 183.1255 (M^+), $C_{10}H_{17}NO_2$ requires 183.1259.

(5*R*)-3-*tert*-Butyl-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37h). Yellow solid, 84%. mp 63-65.5°C; $[\alpha]_D$ -191.1° (*c* 5.37, $CHCl_3$); IR (NaCl, neat) 1742 (C=O), 1628 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 9 H), 4.00 (dd, 1 H, *J* = 11.3, 11.0 Hz), 4.45 (dd, 1 H, *J* = 11.3, 4.3 Hz), 4.76 (dd, 1 H, *J* = 11.0, 4.3 Hz), 7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 27.9 (CH_3), 39.1 (C), 59.2 (CH), 71.0 (CH_2), 126.8 (2 × CH), 127.9 (CH), 128.6 (2 × CH), 137.0 (C), 154.0 (C), 168.5 (C); HREIMS found *m/z* 231.1257 (M^+), $C_{14}H_{17}NO_2$ requires 231.1259.

(5*R*)-3,5-Diphenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37i). Yellow oil (94 %); R_f 0.68 (EtOAc); $[\alpha]_D$ -351° (*c* 3.96, $CHCl_3$); UV (CH_3CN) λ 210 (ε 20700), 265 (7500), 366 (210); IR (NaCl, neat) 1746 (C=O), 1609 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.25 (dd, 1 H, *J* = 11.3, 10.8 Hz), 4.59 (dd, 1 H, *J* = 11.3, 4.4 Hz), 4.98 (dd, 1 H, *J* = 10.8, 4.4 Hz), 7.40 (m, 8 H), 8.08 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 60.1 (CH), 71.2 (CH_2), 127.1 (CH), 128.1 (CH), 128.2 (CH), 128.8 (2 × CH), 131.2 (CH), 133.9 (C), 136.8 (C), 154.8 (C), 158.2 (C); HREIMS found *m/z* (M^+) 251.0955, $C_{16}H_{13}NO_2$ requires 251.0946. Lanthanide shifts induced by titration of both (-)-**37i** and (±)-**37i**

(prepared from (±)-phenylglycinol) with a $CDCl_3$ solution of (+)-Eu(hfc)$_3$ (20 mol%) gave only one set of ^1H NMR signals for the optically active product (ee >99%).

(5*S*)-5-Isopropyl-2-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37j). Yellow oil, 74%. $[\alpha]_D$ +151.3° (*c* 1.08, $CHCl_3$); UV (CH_3CN) 264 (ε 6290), 328 nm (640); IR (NaCl, neat) 1738 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (d, 3 H, *J* = 6.8 Hz), 1.15 (d, 3 H, *J* = 6.8 Hz), 2.01 (dq, 1 H, *J* = 6.8 Hz), 3.58 (ddd, 1 H, *J* = 9.7, 6.8, 4.0 Hz), 4.27 (dd, 1 H, *J* = 11.2, 9.7 Hz), 4.53 (dd, 1 H, *J* = 11.2, 4.0 Hz), 7.43 (m, 3 H), 8.00 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (CH_3), 19.5 (CH_3), 30.6 (CH), 62.0 (CH), 68.5 (CH_2), 128.2 (CH), 128.6 (CH), 130.9 (CH), 134.2 (C), 155.4 (C), 157.4 (C); HREIMS found *m/z* 217.1103 (M^+), $C_{13}H_{15}NO_2$ requires 217.1103.

(5*R*)-3-(1-Naphthyl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37k). Yellow solid (93%). mp 155.5-156° C; $[\alpha]_D$ -276.2° (*c* 2.54, $CHCl_3$); UV (CH_3CN) 220 (ε 78220), 273 (5980), 278 nm (ε 5840); IR (NaCl, neat) 1739 (C=O), 1610 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (dd, 1 H, *J* = 11.5, 10.6 Hz), 4.71 (dd, 1 H, *J* = 11.5, 4.4 Hz), 5.14 (dd, 1 H, *J* = 10.6, 4.4 Hz), 7.36 (m, 4 H), 7.50 (m, 3 H), 7.69 (d, 1 H, *J* = 7.1 Hz), 7.87 (m, 1 H), 7.93 (d, 1 H, *J* = 8.2 Hz), 8.04 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 60.6 (CH), 71.5 (CH_2), 124.6 (CH), 124.8 (CH), 126.1 (CH), 126.8 (CH), 127.1 (2 × CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 128.9 (2 × CH), 130.8 (CH), 130.9 (C), 132.0 (C), 133.6 (C), 136.4 (C), 155.2 (C), 161.1 (C); HREIMS found *m/z* 301.1105 (M^+), $C_{20}H_{15}NO_2$ requires 301.1103; Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.81; H, 5.06; N, 4.86.

(5*R*)-3-(2-naphthyl)-5-phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (37l). Yellow solid, (83% ; R_f = 0.34, 3:7 EtOAc:hexane). mp 108-108.5° C; $[\alpha]_D$ -336° (*c* 4.96, $CHCl_3$); UV (CH_3CN) 221 (ε 61600), 261 (17200), 299 (12200), 343 nm (3100);

IR (NaCl, neat) 1739 (C=O), 1603 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.21 (dd, 1 H, *J* = 11.3, 10.8 Hz), 4.55 (dd, 1 H, *J* = 11.3, 4.4 Hz), 4.95 (dd, 1 H, *J* = 10.8, 4.4 Hz), 7.34 (m, 5 H), 7.47 (m, 2 H), 7.84 (m, 3 H), 8.16 (dd, 1 H, *J* = 8.7, 1.7 Hz), 8.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 60.2 (CH), 71.1 (CH_2), 124.6 (CH), 126.4 (CH), 127.1 (2 × CH), 127.5 (CH), 127.6 (CH), 127.9 (CH), 128.1 (CH), 128.7 (2 × CH), 129.2 (CH), 130.3 (C), 131.1 (C), 132.5 (C), 134.4 (C), 136.8 (C), 154.9 (C), 157.8 (C); HREIMS found *m/z* 301.1103 (M^+), $C_{20}H_{15}NO_2$ requires 301.1103; Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.71; H, 5.02; N, 4.65. Found: C, 79.60; H, 5.11; N, 4.69.

(5*S*)-5-Isopropyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (38a). A solution of **37a** (0.100 g, 0.709 mmol) in EtOAc (4 mL) was hydrogenated (Pd-C, 10% w/w, 10 mg, 1 atm H_2) at room temperature for 4 h. Additional Pd-C (32.3 mg) was added and hydrogenation continued for another 3 h. The mixture was filtered through diatomaceous earth, and the filter pad washed with EtOAc. Solvent was removed from the combined filtrate and washings to give morpholin-2-one **38a** as a yellow oil (80.4 mg; 79%; R_f = 0.18, EtOAc), pure by TLC and ^1H NMR. $[\alpha]_D$ +15.5° (*c* 1.73, $CHCl_3$); UV (MeOH) λ 204 (ε 3290), 252 (330); IR (NaCl, neat) 3312 (NH), 1741 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (d, 3 H, *J* = 6.8 Hz), 0.94 (d, 3 H, *J* = 6.8 Hz), 1.62 (dq, 1 H, *J* = 6.8, 6.8 Hz), 1.74 (bs, 1 H), 2.69 (ddd, 1 H, *J* = 10.7, 6.8, 3.7 Hz), 3.56 (d, 1 H, *J* = 18.0 Hz), 3.72 (d, 1 H, *J* = 18.0 Hz), 4.10 (dd, 1 H, *J* = 11.0, 10.7 Hz), 4.36 (dd, 1 H, *J* = 11.0, 3.7 Hz); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_3), 18.6 (CH_3), 29.6 (CH), 47.7 (CH_2), 56.6 (CH), 72.5 (CH_2), 168.5 (C); HREIMS found *m/z* 143.0944 (M^+), $C_7H_{13}NO_2$ requires 143.0946.

(5*R*)-5-Phenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (38b).[7] Compound **37b** was hydrogenated as above to obtain **38b** as yellow oil (quantitative); R_f = 0.39 (EtOAc); $[\alpha]_D$ -91.6° (*c* 4.81, $CHCl_3$); UV (CH_3CN) λ 205 (ε 9090); IR (NaCl, neat) 3239 (NH),

1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (d, 1 H, *J* = 17.8 Hz), 3.95 (d, 1 H, *J* = 17.8 Hz), 4.18 (dd, 1 H, *J* = 10.3, 3.7 Hz), 4.29 (dd, 1 H, *J* = 10.6, 10.3 Hz), 4.40 (dd, 1 H, *J* = 10.6, 3.7 Hz), 7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 48.1 (CH_2), 55.9 (CH), 74.1 (CH_2), 126.7 (CH), 128.2 (CH), 128.6 (CH), 137.4 (C), 167.6 (C); HREIMS found *m/z* 177.0785 (M^+), $C_{10}H_{11}NO_2$ requires 177.0790; Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.77; H, 6.26; N, 7.91. Found: C, 67.55; H, 6.25; N, 7.90.

(5*R*)-3-*tert*-Butyl-5-phenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (38h). Compound **37h** (0.0214 g, 0.093 mmol) was dissolved in CH_2Cl_2 (1 mL). The flask was purged with N_2, and platinum (IV) oxide (14.7 mg) was added. The stirred mixture was hydrogenated for 3 h. After purging with N_2, the mixture was filtered through diatomaceous earth. Removal of the solvent gave **38h** as a white solid (21.4 mg, 99%; R_f = 0.32, 3:7 EtOAc:hexane). ^1H NMR showed a 13:1 mixture of diastereomers. mp 111-112°C; $[\alpha]_D$ -76.4° (*c* 2.00, $CHCl_3$); IR (NaCl, neat) 3330 (NH), 1728 (C=O) cm^{-1}. Crystallization from EtOAc-hexane provided *a single diastereomer* (82%, de >99%). ^1H NMR (C_6D_6) δ 1.04 (s, 9 H), 3.13 (s, 1 H), 3.54 (dd, 1 H, *J* = 10.3, 3.0 Hz), 3.72 (dd, 1 H, *J* = 10.3, 3.0 Hz), 3.85 (dd, 1 H, *J* = 10.3, 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 26.6 (CH_3), 36.3 (C), 56.6 (CH), 67.2 (CH), 74.3 (CH_2), 127.2 (CH), 128.6 (CH), 128.8 (CH), 138.3 (C), 168.9 (C); HREIMS found *m/z* 233.1416 (M^+), $C_{14}H_{19}NO_2$ requires 233.1416; Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.16; H, 8.22; N, 6.00.

(3*S*,5*R*)-3,5-Diphenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (38i). Compound **37i** was hydrogenated as described above for **38b** to obtain a mixture of diastereoisomers **38i** (4:1, ^1H NMR), oil (91%); R_f = 0.53 (1:1 EtOAc:hexane); UV (CH_3CN) 207 (ε 11900), 252 (350), 257 (370), 263 (290); IR (NaCl, neat) 3315 (NH), 1743 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (bs, 1 H), 4.36 (m, 3 H), 4.79/4.91 (s, 1 H),

7.36 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 52.0/57.4 (CH), 60.3/64.0 (CH), 73.8/74.8 (CH_2), 126.8/127.0 (CH), 127.2/128.1 (CH), 128.3/128.4 (CH), 128.6 (CH), 128.8 (2 × CH), 137.4/137.9 (C), 138.0/138.1 (C), 168.3/168.9 (C); HREIMS found *m/z* (M^+) 253.1109, $C_{16}H_{15}NO_2$ requires 253.1103.

Dimeric Products, 44f and *epi*-44f, from SeO_2 Oxidation of 31f.

A solution of **31f** (0.400 g, 2.84 mmol) in dioxane (7 mL) was added to selenium dioxide (0.70 g, 6.3 mmol) suspended in dioxane (7 mL). The mixture was stirred and heated under reflux (1h), cooled and filtered through silica gel with 1:1 EtOAc:hexane. Removal of solvent under reduced pressure gave a reddish-brown oil (0.250 g) which was separated by chromatography (silica gel, 1:4 to 3:1 EtOAc:hexane) to afford of **44f** (86.5 mg, 20%) and *epi*-**44f** (91.6 mg, 21%).

44f. solid; $[\alpha]_D$ +33.0° (*c* 1.09, $CHCl_3$); UV (CH_3CN) λ 286 (ε 12700), 314 nm (13500); IR (NaCl, neat) 3293 (weak), 1742, 1685, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, 3 H, *J* = 6.8 Hz), 0.97 (d, 3 H, *J* = 6.7 Hz), 1.12 [m (overlapped d and t), 6 H], 1.89 (dq, 1 H, *J* = 6.7 Hz), 2.34 (q, 2 H, *J* = 7.5 Hz), 2.44 (septet, 1 H, *J* = 6.9 Hz), 3.12 (m, 1 H), 4.08 (dd, 1 H, *J* = 11.4, 7.4 Hz), 4.20 (dd, 1 H, *J* = 11.4, 4.1 Hz), 4.80 (s, 2 H), 7.11 (d, 1 H, *J* = 13.4 Hz), 7.99 (bt, 1 H, *J* = 9.7 Hz); ^{13}C NMR ($CDCl_3$) δ 9.0 (CH_3), 18.1 (CH_3), 19.4 (2 × CH_3), 19.5 (CH_3), 27.4 (CH_2), 30.1 (CH), 34.0 (CH), 64.1 (CH), 65.0 (CH_2), 66.8 (CH_2), 104.6 (C), 152.2 (CH), 155.8 (C), 163.5 (C), 174.1 (C); HREIMS found *m/z* 310.1885 (M^+), $C_{16}H_{26}N_2O_4$ requires 310.1893.

epi-**44f**. solid; $[\alpha]_D$ +6.0° (*c* 0.58, $CHCl_3$); UV (CH_3CN) λ 312 nm (ε 19800); IR (NaCl, neat) 3318 (weak), 1739, 1702, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, 3 H, *J* = 6.8 Hz), 0.99 (d, 3 H, *J* = 6.8 Hz), 1.14 [m, (overlapped d and t), 6 H], 1.92 (dq, 1 H, *J* = 6.7 Hz), 2.36 (q, 2 H, *J* = 7.6 Hz), 2.50 (septet, 1 H, *J* = 6.9 Hz), 3.26 (m , 1H), 4.18

(m, 2H), 4.83 (s, 2 H), 5.80 (bt, 1 H, J = 11.5 Hz), 7.39 (d, 1 H, J = 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 9.0 (CH_3), 18.2 (CH_3), 19.4 (CH_3), 19.5 (2 × CH_3), 27.5 (CH_2), 30.3 (CH), 34.0 (CH), 63.1 (CH), 65.0 (CH_2), 67.2 (CH_2), 104.9 (C), 144.5 (CH), 158.9 (C), 162.0 (C), 174.2 (C); HREIMS found *m/z* 310.1882 (M^+), $C_{16}H_{26}N_2O_4$ requires 310.1893.

(4*S*)-4-Isopropyl-2-oxazolidinone (45). A solution of **31a** (0.298 g, 2.35 mmol) in dry pyridine (6 mL) was added to SeO_2 (0.576 g, 5.20 mmol) in pyridine (6 mL) and the mixture heated at reflux (1h), cooled and eluted through silica gel with 1:1 EtOAc:hexane. The brown residue (0.1094 g) obtained by removal of solvent under vacuum was purified by chromatography (silica, 1:9 EtOAc:hexane to EtOAc) to afford the known oxazolidinone **45** as a yellow oil (32.8 mg, 11%).[8] IR (NaCl, neat) 3275 (NH), 1748 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 3 H, J = 6.8 Hz), 0.94 (d, 3 H, J = 6.8 Hz), 1.71 (dq, 1 H, J = 6.8, 6.8 Hz), 3.59 (m, 1 H), 4.08 (dd, 1 H, J = 8.7, 6.3 Hz), 4.42 (dd, 1 H, J = 8.7, 8.7 Hz), 6.85 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 17.6 (CH_3), 17.9 (CH_3), 32.6 (CH), 58.4 (CH), 68.6 (CH_2), 160.5 (C).

(3*S*,5*S*) and (3*R*,5*S*)-5-Isopropyl-3-methoxy-3,4,5,6-tetrahydro-1,4-oxazin-2-one (46). 5,6-Dihydro-2*H*-oxazin-2-one **37a** (0.0422 g, 0.299 mmol) was heated in methanol (1.5 mL, 37.0 mmol) at reflux (6 h). Removal of the solvent under reduced pressure afforded **46** as a 1:1 mixture of C3 epimers (yellow oil, 0.0497 g, 96%; R_f = 0.48, EtOAc). UV (hexane) λ 202 (ε 1520), 220 (540); IR (NaCl, neat) 3311 (NH), 1750 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (d, 3 H, J = 6.7 Hz), 0.93 (d, 3 H, J = 6.7 Hz), 1.04 (d, 3H, J = 6.7 Hz), 1.08 (d, 3 H, J = 6.7 Hz), 1.64 (dq, 2 × 1 H, J = 6.7, 6.7 Hz), 2.20 (bs, 1 H), 3.00 (m, 1 H), 3.18 (ddd, 1 H, J = 7.5, 7.5, 7.5 Hz), 3.32 (m, 1 H), 3.42 (t, 1 H, J = 7.5, 7.5 Hz), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.95 (m, 1 H), 4.05 (t, 1 H, J = 7.5, 7.5 Hz), 4.87 (s, 1 H), 5.04 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4/19.6 (CH_3),

20.0/20.3 (CH_3), 31.2/31.4 (CH), 52.0/52.2 (CH_3), 63.8/65.5 (CH), 69.7/69.8 (CH_2), 88.0/88.2 (CH), 169.9/170.3 (C); HREIMS found *m/z* 173.1042 (M^+), $C_8H_{15}NO_3$ requires 173.1052.

(4*S*)-2-Benzoyl-4-isopropyl-3*H*-1,3-oxazolidine (47). A solution of phenylmagnesium bromide in THF (1M, 3.0 mL, 3.0 mmol) was added dropwise to a stirred solution of **37a** (0.401 g, 2.85 mmol) in THF (15 mL) at -78°C. The reaction was quenched at -78°C after twenty minutes by the addition of $NaHCO_3$ (aq, satd, 2.5 mL). The reaction mixture was diluted with EtOAc (50 mL) and H_2O (10 mL), and the layers separated. The aqueous layer was extracted with EtOAc (3 × 75 mL). The combined organic layers were dried ($MgSO_4$), and the solvent removed to give a yellow oil (0.567g) consisting of a 1:1 epimeric mixture of the sensitive product **47** (57%, by NMR); R_f = 0.74 (1:1 EtOAc:hexane). Silica gel chromatography provided pure **47** (colorless oil) accompanied by substantial loss of material through decomposition. UV (MeOH) λ 247 (ε 8360), 287 (2170); IR (NaCl, neat) 3305 (NH, weak), 1692 (PhC=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, 3 H, *J* = 6.7 Hz), 0.95 (d, 3 H, *J* = 6.7 Hz), 1.04 (d, 3 H, *J* = 6.6 Hz), 1.13 (d, 3 H, *J* = 6.6 Hz), 1.68/1.70 (dq, 1 H, *J* = 6.6 Hz), 2.90 (bs, 1 H), 3.13 (m, 3 H), 3.62 (dd, 1 H, *J* = 7.9, 6.2 Hz), 3.92 (dd, 1 H, *J* = 7.9, 6.8 Hz)/3.98 (dd, 1 H, *J* = 6.8, 5.9 Hz), 5.60/5.62 (s, 1 H, H2), 7.53 (m, 3 H), 8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 19.4/19.9(CH_3), 20.0/20.6 (CH_3), 31.3 /31.9 (CH), 64.1/65.8 (CH), 69.9/70.0 (CH_2), 89.2/89.4 (CH), 128.5 /128.6 (2 × CH), 129.3 /129.4 (2 × CH), 133.6 /133.9 (CH), 134.2/134.3 (C), 193.6/194.3 (C=O); HREIMS found *m/z* 219.1252 (M^+), $C_{13}H_{17}NO_2$ requires 219.1259.

(3*S*,5*S*)-5-Isopropyl-3-(prop-2-enyl)-3,4,5,6-tetrahydro-1,4-oxazin-2-one (48a). Allyl trimethylsilane (0.085 mL, 0.54 mmol) was added to a solution of **37a** (0.0565 g, 0.40 mmol) in CH_2Cl_2 (3 mL) at -78°C. After 15 minutes, BF_3•OEt_2 (0.1 mL,

0.813 mmol) was added. After 30 minutes, the reaction was quenched with satd $NaHCO_3$ (0.5 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the organic layer was dried through $MgSO_4$ and reduced *in vacuo* to a brown oil (0.1789 g). The crude material was purified by column chromatography (2.5 × 17 cm; 3:7 EtOAc:hexane to EtOAc to1:9 MeOH:$CHCl_3$) to give the product which still contained minor contaminants (0.0659 g, 78% based on NMR). IR (NaCl, neat) 3345 (NH), 1741 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3 H, J = 6.8 Hz), 0.91 (d, 3 H, J = 6.8 Hz), 1.61 (dq, 1 H, J = 6.8 Hz), 1.81 (bs, 1 H, NH), 2.50 (m, 2 H), 2.76 (ddd, 1 H, J = 10.1, 6.8, 4.0 Hz), 3.61 (dd, 1 H, J = 8.5, 4.3 Hz), 4.10 (dd, 1 H, J = 11.0, 10.1 Hz), 4.30 (dd, 1 H, J = 11.0, 4.0 Hz), 5.12 (m, 2 H), 5.82 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 18.7 (CH_3), 19.0 (CH_3), 29.8 (CH), 36.1 (CH_2), 54.1 (CH), 54.2 (CH), 71.2 (CH_2), 119.2 (CH_2), 133.9 (CH), 171.4 (C); HREIMS found *m/z* 183.1263 (M^+), $C_{10}H_{17}NO_2$ requires 183.1259.

(3*R*,5*R*)-5-Phenyl-3-(prop-2-enyl)-3,4,5,6-tetrahydro-1,4-oxazin-2-one (48b). Yellow oil (58%, 8:1 mixture of diastereomers). The major diasteomer shows a 10% nOe between H3 and the *ortho* protons on the phenyl ring. IR (NaCl, neat) 3335 (NH), 1743 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (m, 2 H), 3.93 (dd, 1 H, J = 8.1, 4.8 Hz, H3), 4.42 (m, 3 H, H5, H6), 5.25 (m, 2 H), 5.94 (m, 1 H), 7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 36.1 (CH_2), 52.9 (CH), 54.3 (CH), 72.8 (CH_2), 119.2 (CH_2), 126.8 (2 × CH), 128.1 (CH), 128.7 (2 × CH), 133.5 (CH), 138.3 (C), 170.8 (C); HREIMS found *m/z* 217.1103 (M^+), $C_{13}H_{15}NO_2$ requires 217.1103.

(3*R*,5*R*)-3-(1,1-Dimethylprop-2-enyl)-5-phenyl-3,4,5,6-tetrahydro-1,4-oxazin-2-one (48c). Yellow oil (25%, 4.5:1 mixture of diastereomers). IR (NaCl, neat) 3342 (NH), 1741 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 6 H), 3.62 (s, 1 H, H3), 4.48 (m, 1 H), 4.61 (m, 2 H), 5.20 (m, 2 H), 5.39 (bs, 1H), 6.06 (dd, 1 H,

J = 17.4, 10.5 Hz), 7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ major diastereomer 24.3 (CH_3), 24.9 (CH_3), 40.8 (C), 53.9 (CH), 61.7 (CH), 70.3 (CH_2), 115.3 (CH_2), 127.1 (2 × CH), 128.7 (CH), 129.1 (2 × CH), 136.0 (CH), 142.8 (C), 167.6 (C); δ minor diastereomer 22.6 (CH_3), 42.0 (C), 56.6 (CH), 66.2 (CH), 74.1 (CH_2), 113.8 (CH_2), 126.5 (CH), 128.7 (CH), 128.9 (CH), 137.7 (CH), 144.5 (C), 168.0 (C); HREIMS found *m/z* 246.1502 (M^+), $C_{15}H_{19}NO_2$ requires 246.1494.

(*S*)-*tert*-Leucine hydrochloride (49). A solution of morphilinone **38h** (0.0195 g) in ethanol (10 mL) was saturated with dry HCl then heated at reflux for 16 h, cooled and concentrated under vacuum to a yellow oil (35.8 mg). The residue was dissolved in $CHCl_3$, evaporated and dissolved in ethanol (10 mL). Pd-C (10% w/w, 13.1 mg) was added, and the mixture hydrogenated (25°C, 1 atm H_2) for 5 h. After filtering the mixture through diatomaceous earth, the filtrate was concentrated to an off-white solid which was dissolved in water and extracted once with ether.[7] The ether layer was back-extracted with water, and the combined aqueous layers were diluted with ethanol and concentrated under vacuum to give of an off-white solid (11.7 mg). The residue was dissolved in 6M HCl (2 mL, aq) and heated in a sealed tube (110°C) for 26 h. After cooling to room temperature, the volatiles were removed from the mixture to give a pale-yellow solid (11.2 mg) which was eluted through a short charcoal column with water. Removal of water gave pure (*S*)-*tert*-leucine hydrochloride (**49**, white solid, 10.5 mg, 75% for three steps), which was identical with an authentic sample by ^1H NMR, $[\alpha]_D$ and TLC (R_f = 0.43, 3:1:1 *n*-BuOH: AcOH: H_2O). A portion of the product (*ca.* 0.5 mg) was treated with 1-fluoro-2,4-dinitrophenyl-5-(*S*)-alanine amide (FDAA) according to Marfey[9] as were authentic (*S*)-(-)-**49** and (±)-**49**, and the FDAA adducts analyzed by diode array HPLC (4.6 mm × 150 mm RP18 column, 1.5 mL·min^{-1}, elution with a linear gradient; buffer A, 90% 0.05 M triethylamine phosphate, B, 10% CH_3CN, to 10% buffer A over 30 min) and UV

monitoring at λ 340 nm. (*S*)-*tert*-Leucine FDAA adduct eluted at 18.1 min, and no adduct was detected from (*R*)-*tert*-leucine.

(4*R*)-2-Methyl-4-phenyl-4,5-dihydrooxazole-2-^{13}C (2-^{13}C-**31b**). Triphenylphosphine (2.58 g, 9.84 mmol) was added to a solution of acetic acid (0.1 ml, 1.75 mmol), [1-^{13}C]acetic acid (99 atom%, 0.1 ml, 1.72 mmol) and acetonitrile (7.5 ml). The reaction solution was cooled to 0°C, and CCl_4 (3.2 ml, 33.2 mmol) was added dropwise. After stirring for 2h at 0°C, a solution of (*R*)-(-)-2-phenylglycinol (0.4019 g, 2.93 mmol), Et_3N (1.6 ml, 11.5 mmol) and acetonitrile (12.5 ml) was added dropwise. After 20 min, the ice bath was removed, and the reaction stirred at room temperature for 14 h. The reaction mixture was filtered, and the filter pad washed with EtOAc. The solvent was removed under reduced pressure leaving a brown solid which was purified by column chromatography (2.5 × 30 cm; 1:5 EtOAc:*n*-hexane to 2:3 EtOAc:*n*-hexane) to give 2-^{13}C-**31b** as a yellow oil (0.0812 g, 17%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (s, 3 H), 4.07 (m, 1 H), 4.59 (m, 1 H), 5.16 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3, $^1J_{C\text{-}C}$ = 58.6 Hz), 69.6 (CH), 74.5 (CH_2), 126.4 (CH), 127.4 (CH), 128.6 (CH), 142.3 (C), 165.6 (C × 68 times enhanced intensity). The nominal isotopic purity, determined from dilution of acetic acid-^{13}C was ~50 atom % [2-^{13}C].

(5*R*)-5-Phenyl-5,6-dihydro-2*H*-1,4-oxazin-2-one-2-^{13}C (2-^{13}C-**37b**). A solution of (4*R*)-2-methyl-4-phenyl-4,5-dihydrooxazole-2-^{13}C (2-^{13}C-**31b**, 0.0379 g) in dioxane (3 ml) was added to SeO_2 (0.0623 g, 0.56 mmol) in 2 ml of dioxane. The mixture was stirred under reflux for 45 min, cooled, and filtered through silica gel with 1:1 EtOAc:*n*-hexane. The solvent was removed under reduced pressure to give a red oil (0.0340 g) with some red precipitate. The crude material was purified by HPLC (silica, Dynamax, 3:7 EtOAc:*n*-hexane; 3 ml·min^{-1}) to provide pure 2-^{13}C-**37b** (61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (m, 1 H), 4.59 (m, 1 H), 4.92 (m, 1 H), 7.37 (m, 5 H), 8.06

(dd, 1 H, J = 3.0 Hz, $^2J_{C\text{-}H}$ = 14.6 Hz); ^{13}C NMR ($CDCl_3$) δ 59.9 (CH, $^3J_{C\text{-}C}$ = 10.0 Hz), 71.0 (CH_2), 127.0 (CH), 128.5 (CH), 129.0 (CH), 136.0 (C), 153.2 (CH, $^1J_{C\text{-}C}$ = 59.1 Hz), 154.0 (C × 21 enhanced intensity, $^1J_{C\text{-}C}$ = 59.1 Hz, C2); LRCIMS found *m/z* 177.15 (MH+1, 53%), 176.20 (MH^+, 47%) $C_{10}H_{10}NO_2$, $^{13}C_1C_9H_{10}NO_2$. ^{13}C isotopic purity estimated from MS (44±5 atom %).

(±)-2-Benzoyl-4-phenyl-4,5-dihydrooxazole (50i). Method A: A solution of (±)-2-benzyl-4-phenyl-4,5-dihydrooxazole (**31i**, 0.5001 g, 2.14 mmol) in dioxane (5 ml) was added to SeO_2 (0.5157 g, 4.65 mmol) in 16 ml of dioxane. The mixture was heated at 40°C for 26 min, cooled, and filtered through silica gel with 1:1 EtOAc:hexane. The solvent was removed under reduced pressure to give 0.3649 g of a yellow oil with red precipitate. The crude material was dissolved in EtOAc:*n*-hexane, centrifuged and the supernatant separated by HPLC (silica Dynamax 3:7 EtOAc:*n*-hexane, 3.0 ml·min^{-1}) to obtain **50i** (9%), recovered starting material **31i** and oxazinone **37i**.

Method B: To a rapidly stirred solution of oxazoline **31i** (0.5000 g, 2.22 mmol) in benzene (50 ml) was added copper (II) myristate (0.0462 g, 0.089 mmol). The flask was repetitively evacuated and purged with O_2 and left under one atmosphere of O_2 for 58 h with continuous stirring. Removal of the solvent under reduced pressure and purification of the crude product by column chromatography (silica gel; 1:4 methyl *t*-butyl ether:*n*-hexane) provided **50i** (oil, 93.8 mg, 17%, 25% based on recovered starting material) and starting material. UV (CH_3CN) λ 258 (ε 10,200); IR (NaCl, neat) 1737 (PhC=O), 1668 (C=N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (dd, 1 H, J = 8.8, 8.5 Hz), 4.83 (dd, 1 H, J = 10.5, 8.8 Hz), 5.53 (dd, 1 H, J = 10.5, 8.5 Hz), 7.40 (m, 7 H), 7.61 (m, 1 H), 8.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 70.9 (CH), 74.4 (CH_2), 126.7 (2 × CH), 128.4 (CH), 128.9 (2 × CH), 130.6 (2 × CH), 134.3 (2 × CH), 134.7 (C), 140.7 (C), 160.1 (C), 183.4 (C); HREIMS found *m/z* 251.0940 (M^+), $C_{16}H_{13}NO_2$ requires 251.0946.

(4*S*)-2-(Benzoyl)-4-(1-isopropyl)-4,5-dihydrooxazole (50j). Compound **50j** was prepared by autoxidation (Method B, above) of **31j** (38%). $[\alpha]_D$ -57.1° (*c* 1.89, $CHCl_3$); UV (CH_3CN) λ 221 (ε 2420), 257 (ε 11100), 339 (ε 110); IR (NaCl, neat) 1678 (PhC=O), 1634 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, 3 H, *J* = 6.7 Hz), 1.06 (d, 3 H, *J* = 6.7 Hz), 1.94 (dq, 1 H, *J* = 6.7 Hz), 4.21 (m, 2 H), 4.46 (dd, 1 H, *J* = 9.2, 7.8 Hz), 7.48 (m, 2 H), 7.62 (m, 1 H), 8.30 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 18.3 (CH_3), 18.9 (CH_3), 32.6 (CH), 70.1 (CH_2), 73.6 (CH), 128.4 (CH), 130.6 (CH), 134.1 (CH), 134.8 (C), 159.1 (C); HREIMS found *m/z* 217.1101 (M^+), $C_{13}H_{15}NO_2$ requires 217.1103.

Preparative Synthesis of 37j by Rearrangement of 50j with Catalytic Lewis Acid.

Method A: A solution of **50j** (26.5 mg, 0.122 mmol) in dioxane (1 ml) was added to SeO_2 (2.0 mg, 0.018 mmol, 0.15 equiv) in dioxane (1 ml). The mixture heated to reflux for 1 h, cooled and centrifuged. The yellow supernatant was filtered through a plug of silica gel, and concentrated under reduced pressure to a yellow oil of pure **37j** (20.5 mg, 77%), identical by ^1H and ^{13}C NMR with authentic material.

Method B: A solution prepared by diluting BF_3•Et_2O in anhydrous dioxane (final conc. BF_3 1.63 M, 13 μl) was added to a stirred solution of **50j** (30.4 mg, 0.140 mmol) in dioxane (1.5 ml). The mixture was heated to reflux for 1.5 h, cooled, and treated with pyridine (5 μl). After stirring for 15 min, the mixture was filtered through silica gel and concentrated under reduced pressure to give a yellow oil of **37j** (26.8 mg, 88%).

Copper (II) myristate, $Cu(C_{13}H_{27}COO)_2$. Potassium hydroxide (10 mmol) was added to a solution of myristic acid (tetradecanoic acid, 10 mmol) in ethanol (50 ml) and poured slowly into an aqueous solution of $CuSO_4$ (20 mmol) in H_2O with constant stirring. The resultant gelatinous precipitate was filtered, air dried under suction then dried

under high vacuum at 56°C overnight, and the product $Cu(C_{13}H_{27}COO)_2$, a light blue powder, was used without further purification.

Kinetic Studies: Standard Reaction Conditions and Analytical Methods

Concentrations of **31i**, **37i**, and **50i** were assayed using HPLC with UV detection using a Rainin Rabbit HP pump (25 ml·min^{-1} pump head) coupled to a Dynamax silica column (8μ, 250 × 10 mm), EtOAc:*n*-hexane mobile phase (3.0 ml·min^{-1}) and an ISCO UA-5 detector (λ 254 nm filter). For analysis of **37i** and **50i**, solvent A (3:7 EtOAc:*n*-hexane) was used, while analysis of **31i** was carried out using solvent B (1:1 EtOAc:*n*-hexane). Peak areas were measured using a Hewlett Packard HP 3394 integrator. HPLC injections (50 μL) were made with a Hamilton 100 μL syringe such that the maximum absorbance was ≤ 1.0 AU. Retention times of the relevant compounds are listed as follows: Compound (retention time in solvent A, min ; retention time in solvent B, min): **31i** (18.52; 10.62), **37i** (8.47; 6.81), **50i** (9.58; 7.28). The following control experiment is representative of standard reaction conditions and analysis of the reaction time course. A dry 15 ml two neck round bottom flask, fitted with a reflux condensor and a rubber septum, was purged with dry nitrogen and charged with anhydrous dioxane (6.0 ml) and SeO_2 (0.1035 g, 0.933 mmol). The mixture was equilibrated with stirring for 10 min at 40°C (oil bath) followed by addition of a standard solution of 2-benzyl-4-phenyl-4,5-dihydrooxazole (**31i**, 0.423 M, 1.00 ml, 0.423 mmol, final conc. 0.060 M) in dioxane. The color of the reaction mixture immediately change to an opaque orange. Aliquots (0.100 ml) of the mixture were removed with a calibrated syringe at the following time points: t = 1, 5, 10, 15, 30, 45 and 60 min. Each aliquot was immediately eluted through a small pipet column containing silica gel (height ~ 1 cm) with dioxane, and the eluate made up to 2.00 ml in a volumetric flask. The samples were analyzed by HPLC as described above. The initial concentration of **31i** (0.060 M, t = 0) was calculated from dilution of the standard solution at initiation of reaction. Concentrations in the reaction mixture at

subsequent time points were determined by comparison of peak areas from sample HPLC chromatograms with those of standard curves prepared for **31i-50i** and corrected for dilution. In one run, use of the standards addition method to monitor oxidation of **31i** at 40° C gave essentially the same results.

Assignment of second and first reaction orders were made by linear fit to plots of $0.5\times$ [**31i**]$^{-1}$ *vs.* t (factor of 0.5 accomodates 1:2 stoichiometry of **31i**:SeO_2) and ln [**50i**] *vs.* t, respectively (N = 6-7 sample points, correlation coefficient $R \geq 0.95$).[10] Rate constants were calculated from the slopes of the corresponding linear regression plots and uncertainties were derived from standard deviations of linear regression[11] (1.94-2.0 σ, student t distribution,[12] 90% confidence).

***i.* Rearrangement of 50i to 37i. Standard Conditions, T° Dependence and E_A.**

Reaction time course was followed as above, only the starting materials were 2-benzoyl-4-phenyl-4,5-dihydrooxazole (**50i**, 0.0399 g, 0.159 mmol) in 1,4 dioxane (total 3.00 ml, initial concentration of **50i**, 0.053 M) and SeO_2 at 40°C (oil bath). The reaction mixture remained clear throughout the time course and aliquots (0.100 ml) were sampled as described above. Kinetic measurements were repeated at 26°, 58°, 79° and 100°C (see Table 3), and the *apparent* Arrhenius activation energy $E_A = 4.2 \pm 1.6$ kcal·mol^{-1} calculated from the slope of ln k_2 vs T^{-1}.

***ii.* Effect of H_2O**

A stirred mixture of dioxane (2.00 ml) and SeO_2 (0.0368 g, 0.332 mmol, 2.2 equ) was equilibrated in an oil bath at 40°C under N_2. After 10 min, **31i** (0.0417 g, 0.1661 mmol) in dioxane (1.00 ml) and 3.0 µl of H_2O (0.17 mmol) were added simultaneously (initial concentration of **31i**, 0.055 M). The reaction mixture remained clear throughout the reaction. Aliquots (0.100 ml) of the reaction mixture were sampled and measured as described above (see Table 3).

iii. Effect of SeO_2 Concentration

Reaction time course of **50i→37i** was monitored under the same conditions as before, only with the addition of 1.0 or 2.0 equivalents of SeO_2.

Benzyl 3,4-*O*-isopropylidene-6-deoxy-6-iodo-D-galactopyranoside (60). Method A: Triphenylphosphine (0.88 g, 3.4 mmol), imidazole (0.23 g, 3.4 mmol), and iodine (0.47 g, 1.9 mmol) were added to a solution of **58** in toluene (15 mL). The reaction mixture was heated to reflux for 2 h and then cooled to room temperature. Saturated sodium bicarbonate (8 mL) was added and stirred for 5 min. Iodine was added and stirred for 10 min. Finally $Na_2S_2O_4$ (0.1 M, 10 mL) was added and stirred for 20 min. The mixture was diluted with an additional 100 mL of toluene. The layers were separated, and the organic layer was washed with H_2O (20 mL), dried through $MgSO_4$, and reduced *in vacuo* to give a yellow solid (1.49 g). The crude material was purified by column chromatography (2.5 × 22 cm; 1:19 to 2:3 EtOAc:hexane) to give **60** as a white crystals (0.3300 g, 47%). α anomer: R_f (2:3 EtOAc:hexane) = 0.38; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3 H), 1.40 (s, 3 H), 2.50 (bs, 1 H, OH), 3.24 (m, 2 H, H6), 3.80 (m, 1 H), 4.12 (m, 1 H), 4.23 (m, 2 H), 4.54 (d, 1 H, J = 11.5 Hz, CH_2Ph), 4.85 (d, 1 H, J = 11.5 Hz, CH_2Ph), 4.88 (d, 1 H, J = 4.1 Hz, H1), 7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 3.0, 25.6, 27.2, 68.3, 69.5, 69.6, 73.5, 75.5, 96.0, 109.7, 128.0, 128.2, 128.4, 136.8; HRCIMS found *m/z* 421.0512 (MH^+), $C_{16}H_{22}O_5I$ requires 421.0512. β anomer: R_f (2:3 EtOAc:hexane) = 0.30; ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.52 (s, 3 H), 2.55 (bs, 1 H, OH), 3.45 (d, 2 H, J = 7.0 Hz, H6), 3.60 (dd, 1 H, J = 8.3, 7.4 Hz, H2), 3.89 (dt, 1 H, J = 7.0, 2.2 Hz, H5), 4.06 (dd, 1 H, J = 7.4, 5.5 Hz, H3), 4.23 (d, 1 H, J = 8.7 Hz, H1), 4.27 (dd, 1 H, J = 5.5, 2.2 Hz, H4), 4.67 (d, 1 H, J = 11.7 Hz, CH_2Ph), 4.97 (d, 1 H, J = 11.7 Hz, CH_2Ph), 7.38 (m, 5 H).

Method B: Toulensulfonyl chloride (1.40 g, 7.34 mmol) added to **58** (2.1337 g, 6.88 mmol) in pyridine (20 mL). After stirring for 20h, the reaction was diluted with EtOAc (80

mL) and washed with $NaHCO_3$ (satd, 20 mL) and H_2O (10 mL). The organic layer was dried through $MgSO_4$ and reduced to a yellow oil (2.8387 g). The crude material was purified by column chromatography (4.5 × 25 cm, 1:4 to 3:1 EtOAc:hexane) to give 1.6001 g (50%) of the monotosylated product as a yellow solid. α anomer: R_f (1:1 EtOAc:hexane) = 0.27, ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3 H), 1.40 (s, 3 H), 2.43 (s, 3 H), 2.65 (bs, 1 H, OH), 3.82 (dd, 1 H, *J* = 5.8, 3.9 Hz, H2), 4.13 (dd, 1 H, *J* = 6.4, 1.8 Hz), 4.25 (m, 4 H), 4.51 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 4.75 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 4.90 (d, 1 H, *J* = 3.9 Hz, H1), 7.33 (m, 7 H), 7.81 (d, 2 H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 25.6, 27.2, 66.8, 68.3, 69.1, 69.5, 72.4, 75.3, 95.7, 109.9, 127.9, 128.0, 128.2, 128.5, 129.7, 133.0, 136.7, 144.7; HREIMS found *m/z* 449.1227 ($M-15^+$), $C_{23}H_{28}O_8S$ requires 464.1505. β anomer: R_f (1:1 EtOAc:hexane) = 0.22; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3 H), 1.42 (s, 3 H), 2.42 (s, 3 H), 2.70 (bs, 1 H, OH), 3.52 (dd, 1 H, *J* = 8.0, 6.6 Hz), 4.02 (m, 3 H), 4.19 (d, 1 H, *J* = 8.2 Hz, H1), 4.28 (m, 2 H), 4.54 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 4.83 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 7.33 (m, 7 H), 7.81 (d, 2 H, *J* = 8.3 Hz).

The monotosylated product (0.1013 g, 0.22 mmol) was dissolved in acetone (5 mL), and NaI (0.3259 g, 2.17 mmol) was added. The reaction mixture was heated at 50°C for 22 h, and then heated at 125°C in a sealed tube for 17 h. The reaction mixture was dissolved in EtOAc and extracted with $NaHCO_3$ (2 mL, aq, satd) and then H_2O (5 mL). The organic layer was dried through $MgSO_4$ and concentrated to a yellow oil (0.1150 g). The crude material was purified by column chromatography (1.5 cm × 12 cm; 1:4 to 3:1 EtOAc:hexane) to give **60** (56.5 mg, 62%).

Benzyl 3,4-*O*-isopropylidene-6-phenylthio-6-deoxy-α-D-galactopyranoside (62). Compound **58**[13,14] (31.43 g, 0.10 mol) in THF (300 mL) was added to a solution of *n*-Bu_3P (64 mL, 0.26 mol) and phenyl sulfide (48.03 g, 0.26 mol) in THF at 0°C. After stirring at room temperature for 27.5 h, the solvent was remove *in vacuo* to give a

yellow oil and purified by vacuum flash chromatography (silica gel; hexane to 3:7 EtOAc:hexane) to give a white solid (35.17 g, 86%). The α anomer **62** was purified by crystallization (EtOAc-hexane) and silica gel chromatography (73%). α anomer: mp 103-104°C; $[\alpha]_D$ +80.6° (*c* 5.03, $CHCl_3$); R_f = 0.35 (1:1 EtOAc:hexane); UV (CH_3CN) 257 (ε 8767), 328 nm (ε 49); ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (s, 3 H), 1.49 (s, 3 H), 2.45 (bs, 1 H), 3.24 (m, 2 H, H6), 3.83 (m, 1 H), 4.15 (m, 1 H), 4.23 (m, 2 H), 4.48 (d, 1 H, *J* = 11.5 Hz, CH_2Ph), 4.74 (d, 1 H, *J* = 11.5 Hz, CH_2Ph), 4.94 (d, 1 H, *J* = 3.8 Hz, H1), 7.29 (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_3), 27.5 (CH_3), 34.2 (CH_2), 67.3 (CH), 69.0 (CH), 69.4 (CH_2), 73.6 (CH), 75.8 (CH), 96.4 (CH), 109.5 (C), 126.1 (CH), 127.9 (CH), 128.2 (2 × CH), 128.4 (2 × CH), 129.0 (2 × CH), 129.1 (2 × CH), 136.0 (C), 136.8 (C); HREIMS found *m/z* 402.1505 (M^+), $C_{22}H_{26}O_5S$ requires 402.1501; Anal. Calcd for $C_{22}H_{26}O_5S$: C, 65.65; H, 6.52; S, 7.95. Found: C, 65.57; H, 6.42; S, 7.97; β anomer: R_f = 0.31 (1:1 EtOAc:hexane); ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 3 H), 1.51 (s, 3 H), 2.24 (bs, 1 H, OH), 3.34 (dd, 1 H, *J* = 13.4, 6.7 Hz, H6), 3.38 (dd, 1 H, *J* = 13.4, 6.7 Hz, H6), 3.60 (dd, 1 H, *J* = 8.5, 7.2 Hz, H2), 3.79 (ddd, 1 H, *J* = 6.7, 6.7, 2.1 Hz, H5), 4.00 (dd, 1 H, *J* = 7.2, 5.5 Hz, H3), 4.16 (d, 1 H, *J* = 8.5 Hz, H1), 4.19 (dd, 1 H, *J* = 5.5, 2.1 Hz, H4), 4.58 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 4.88 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 7.34 (m, 10 H).

Benzyl 3,4-O-isopropylidene-α-D-fucose (61). Method A: Potassium carbonate (3.24 g, 23.4 mmol) and 10% Pd/C (1.99 g) were added to a solution of **60** (6.541 g, 15.6 mmol) in MeOH (80 mL). The flask was evacuated and purged with H_2 three times. After 21 h, the reaction was complete by TLC so the reaction mixture was filtered through Celite and reduced to a yellow solid *in vacuo*. The solid was titurated with $CHCl_3$, and the entire contents were filtered and then centrifuged. The $CHCl_3$ layer was removed and concentrated *in vacuo* to give **61** as a clear yellow oil (3.493 g, 76%).

Method B: Raney nickel (W-2, Acros, aqueous suspension) was resuspended and decanted from absolute EtOH (3 ×) before use. Portions of the Raney Ni-EtOH suspension were added to a stirred solution of **62** (23.78 g, 59.2 mmol) in absolute EtOH (200 mL) at reflux over a period of 7 h until the reduction was complete (TLC). The suspension was cooled, filtered through Celite, the filter pad washed with EtOH and combined filtrates concentrated *in vacuo* to a yellow oil (17.2 g). The crude material was purified by column chromatography (4.5 cm × 15 cm, 2:3 to 3:7 EtOAc:hexane) to give **61** as a clear oil (15.79 g, 91%). R_f = 0.62 (EtOAc); HRCIMS found *m/z* 295.1546 (MH^+), $C_{16}H_{22}O_5$ requires 295.1545; α anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (d, 3 H, *J* = 6.7 Hz, H6), 1.36 (s, 3 H), 1.52 (s, 3 H), 2.31 (d, 1 H, *J* = 7.0 Hz, OH), 3.82 (ddd, 1 H, *J* = 7.0, 6.5, 3.9 Hz, H2), 4.06 (dd, 1 H, *J* = 6.0, 2.2 Hz, H4), 4.16 (dq, 1 H, *J* = 6.7, 2.2 Hz, H5), 4.23 (dd, 1 H, *J* = 6.5, 6.0 Hz, H3), 4.57 (d, 1 H, *J* = 11.8 Hz, CH_2Ph), 4.79 (d, 1 H, *J* = 11.8 Hz, CH_2Ph), 4.94 (d, 1 H, *J* = 3.9 Hz, H1), 7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.0 (CH_3), 25.7 (CH_3), 27.5 (CH_3), 64.0 (CH), 69.2 (CH), 69.5 (CH_2), 75.5 (CH), 75.9 (CH), 96.9 (CH), 108.9 (C), 127.7 (CH), 128.2 (CH), 137.3 (C); β anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.44 (d, 3 H, *J* = 6.6 Hz, H6), 1.53 (s, 3 H), 2.65 (bs, 1 H, OH), 3.59 (dd, 1 H, *J* = 8.3, 6.9 Hz, H2), 3.83 (dq, 1 H, *J* = 6.6, 2.0 Hz, H5), 3.99 (m, 2 H), 4.22 (d, 1 H, *J* = 8.3 Hz, H1), 4.58 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 4.93 (d, 1 H, *J* = 11.6 Hz, CH_2Ph), 7.34 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.5 (CH_3), 26.3 (CH_3), 28.2 (CH_3), 69.3 (CH), 70.7 (CH_2), 73.7 (CH), 76.4 (CH), 79.0 (CH), 101.2 (CH), 109.8 (C), 127.9 (CH), 128.2 (CH), 128.4 (CH), 137.2 (C).

Benzyl 3,4-*O*-isopropylidene-2-*O*-((*S*-methylthio)thiocarbonyl)-α-D-fucoside (63). Benzyl 3,4-*O*-isopropylidene-α-D-fucose (**61**, 3.493 g, 11.9 mmol) was dissolved in THF (30 mL) and added to hexane-washed NaH (0.53 g-80% dispersion in oil, 17.7 mmol) in THF (30 mL). Imidazole (0.0122 g, 0.18 mmol) was added, and then

after 2 h, carbon disulfide (3.0 mL, 49.9 mmol) was added. After another 2 h, methyl iodide (3.0 mL, 48.2 mmol) was added. Forty-five minutes later the reaction was poured into 10 mL of H_2O. The aqueous layer was extracted three times with CH_2Cl_2, dried through $MgSO_4$, and reduced *in vacuo* to give **63** as a yellow oil (4.3774 g, 96%). α anomer: mp 67-68°C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.37 (d, 3 H, J = 6.6 Hz, H6), 1.54 (s, 3 H), 2.56 (s, 3 H), 4.13 (dd, 1 H, J = 5.2, 2.5 Hz, H4), 4.21 (dq, 1 H, J = 6.6, 2.5 Hz, H5), 4.53 (d, 1 H, J = 12.3 Hz, CH_2Ph), 4.55 (dd, 1 H, J = 8.1, 5.2 Hz, H3), 4.71 (d, 1 H, J = 12.3 Hz, CH_2Ph), 5.17 (d, 1 H, J = 3.6 Hz, H1), 5.76 (dd, 1 H, J = 8.1, 3.6 Hz, H2), 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.0 (CH_3), 18.7 (CH_3), 26.3 (CH_3), 27.8 (CH_3), 63.6 (CH), 69.8 (CH_2), 73.2 (CH), 76.3 (CH), 80.0 (CH), 94.7 (CH), 109.2 (C), 127.4 (2 × CH), 127.6 (CH), 128.2 (2 × CH), 137.2 (C), 215.8 (C); HRCIMS found *m/z* 385.1150 (MH^+), $C_{18}H_{25}O_5S_2$ requires 385.1177; Anal. Calcd for $C_{18}H_{24}O_5S_2$: C, 56.23; H, 6.29; S, 16.68. Found: C, 55.92; H, 6.25; S, 16.51; β anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.45 (d, 3 H, J = 6.6 Hz, H6), 1.61 (s, 3 H), 2.56 (s, 3 H), 3.85 (dq, 1 H, J = 6.6, 2.0 Hz, H5), 4.03 (dd, 1 H, J = 5.3, 2.0 Hz, H4), 4.23 (dd, 1 H, J = 7.3, 5.3 Hz, H3), 4.43 (d, 1 H, J = 8.1 Hz, H1), 4.63 (d, 1 H, J = 12.8 Hz, CH_2Ph), 4.89 (d, 1 H, J = 12.8 Hz, CH_2Ph), 6.05 (dd, 1 H, J = 8.1, 7.3 Hz, H2), 7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.4, 19.2, 26.3, 27.5, 68.8, 69.7, 76.5, 76.9, 80.9, 98.4, 110.2, 127.3, 127.5, 128.2, 137.0, 215.7.

Benzyl 3,4-*O*-isopropylidene-2-deoxy-α-D-fucoside (59). Method A: Benzyl 3,4-*O*-isopropylidene-D-galactopyranoside (**58**, 8.313 g, 26.7 mmol) was dissolved in THF (135 mL) and added to hexane-washed NaH (2.65 g-80% dispersion in oil, 88.3 mmol). Imidazole (0.020 g, 0.294 mmol) was added, and then after 2 h, carbon disulfide (12.5 mL, 213.4 mmol) was added. After 2 h, methyl iodide (13.5 mL, 216.3 mmol) was added. Forty-five minutes later the reaction was poured into 10 mL of H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL), dried through $MgSO_4$, and reduced *in*

vacuo to a yellow oil (12.1824 g, 93%). α-anomer: UV (CH_3CN) 225 (ε 11879), 279 nm (ε 19374); IR (NaCl, neat) 1208 cm^{-1} (C=S), 1072 cm^{-1} (C=S); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3 H), 1.54 (s, 3 H), 2.57 (s, 3 H), 2.60 (s, 3 H), 4.31 (dd, 1 H, *J* = 5.5, 2.4 Hz, H4), 4.49 (ddd, 1 H, *J* = 7.8, 4.3, 2.4 Hz), 4.53 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 4.59 (dd, 1 H, *J* = 8.0, 5.5 Hz, H3), 4.73 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 4.84 (dd, 1 H, *J* = 11.5, 7.8 Hz, C-6), 4.95 (dd, 1 H, *J* = 11.5, 4.3 Hz, H6), 5.23 (d, 1 H, *J* = 3.6 Hz, H1), 5.77 (dd, 1 H, *J* = 8.0, 3.6 Hz, H2), 7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.0 (2 × CH_3), 26.3 (CH_3), 27.8 (CH_3), 65.4 (CH), 69.7 (CH_2), 71.9 (CH_2), 73.1 (CH), 73.5 (CH), 79.4 (CH), 94.2 (CH), 110.2 (C, CMe_2), 127.7 (2 × CH), 127.9 (CH), 128.4 (2 × CH), 136.6 (C), 215.5 (C), 216.0 (C); HRCIMS found *m/z* 491.0654 (MH^+), $C_{20}H_{27}O_6S_4$ requires 491.0691. β-anomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.60 (s, 3 H), 2.58 (s, 3 H), 2.61 (s, 3 H), 4.16 (ddd, 1 H, *J* = 7.4, 4.4, 2.1 Hz, H5), 4.22 (dd, 1 H, *J* = 5.5, 2.1 Hz, H4), 4.31 (dd, 1 H, *J* = 6.8, 5.5 Hz, H3), 4.46 (d, 1 H, *J* = 7.8 Hz, H1), 4.67 (d, 1 H, *J* = 12.6 Hz, CH_2Ph), 4.87 (dd, 1 H, *J* = 11.6, 7.4 Hz, H6), 4.88 (d, 1 H, *J* = 12.6 Hz, CH_2Ph), 4.96 (dd, 1 H, *J* = 11.6, 4.4 Hz, H6), 6.07 (dd, 1 H, *J* = 7.8, 6.8 Hz, H2), 7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.1, 19.3, 26.3, 27.3, 70.0, 70.4, 71.7, 73.6, 80.3, 98.3, 111.1, 127.7, 127.8, 128.4, 136.6, 215.6.

The *bis*-xanthate (β anomer, 0.0754 g, 0.154 mmol) was dissolved in dioxane (2 mL). To this solution, triethylamine (0.32 mL, 2.30 mmol) and hypophosphorous acid (0.04 mL of a 50% aqueous solution, 0.772 mmol) were added in that order. This solution was deoxygenated by bubbling nitrogen through it for 10 min. An aliquot of degassed AIBN/dioxane solution (0.1 eq) was added to the solution, and the solution was heated to reflux for 40 min. The reaction was cooled and quenched with H_2O (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The organic layer was dried through $MgSO_4$ and reduced *in vacuo* to a yellow oil (58.2 mg). The crude material was purified

by column chromatography (1 cm × 12 cm; 3:7 EtOAc:hexane) to give **59** (β anomer) as a yellow oil (32.6 mg, 76%; R_f = 0.39, 3:7 EtOAc:hexane).

Method B: Benzyl 3,4-*O*-isopropylidene-2-*O*-((*S*-methylthio)thiocarbonyl)-α-D-fucoside (**63**, 1.5160 g, 3.95 mmol) was dissolved in 1,4-dioxane (20 mL). Freshly distilled triethylamine (5.4 mL, 38.7 mmol) was added, and the solution was deoxygenated by passage of a fine stream of N_2 for 10 min. Hypophosphorous acid (2.0 mL of a 50% aqueous solution, 19.3 mmol) was deoxygenated separately and then added to the above solution. An aliquot of degassed AIBN (0.1 eq, in 1,4-dioxane) was added to the solution, and the flask was immersed in a 100°C oil bath. After 1 h, TLC indicated that the starting material had been consumed. The reaction was cooled, and H_2O (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2, dried over $MgSO_4$, and reduced *in vacuo* to a yellow oil. The crude material was purified by column chromatography (silica gel; 4.5 cm × 25 cm; 1:19 to 2:3 EtOAc:hexane) to give the product **59** as a yellow oil (0.8501 g, 77%). α anomer: $[\alpha]_D$ +80.2° (*c* 1.0, $CHCl_3$); R_f = 0.45 (3:7 EtOAc:hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 3 H, *J* = 6.5 Hz, H6), 1.34 (s, 3 H), 1.49 (s, 3 H), 1.80 (ddd, 1 H, *J* = 14.9, 6.3, 4.0 Hz, H2), 2.22 (ddd, 1 H, *J* = 14.9, 5.1, 4.9 Hz, H2), 3.92 (dq, 1 H, *J* = 6.5, 2.0 Hz, H5), 3.98 (dd, 1 H, *J* = 7.1, 2.0 Hz, H4), 4.48 (ddd, 1 H, *J* = 7.1, 4.9, 4.0 Hz, H3), 4.51 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 4.77 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 5.02 (dd, 1 H, *J* = 6.3, 5.1 Hz, H1), 7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 16.0 (CH_3), 25.3 (CH_3), 26.7 (CH_3), 30.5 (CH_2), 64.5 (CH), 68.9 (CH_2), 70.6 (CH), 75.1 (CH), 95.7 (CH), 108.6 (C), 127.4 (CH), 127.6 (2 × CH), 128.3 (2 × CH), 138.2 (C); HREIMS found *m/z* 278.1524 (M^+), $C_{16}H_{22}O_4$ requires 278.1518. β anomer: $[\alpha]_D$ = -41.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3 H), 1.44 (d, 3 H, *J* = 6.6 Hz, H6), 1.52 (s, 3 H), 1.69 (ddd, 1 H, *J* = 12.9, 9.8, 9.8 Hz, H2), 2.08 (ddd, 1 H, *J* = 12.9, 7.0, 2.0 Hz, H2), 3.74 (dq, 1 H, *J* = 6.6, 2.0 Hz, H5), 3.81 (dd, 1 H, *J* = 5.1, 2.0 Hz, H4), 4.21 (ddd, 1 H, *J* = 9.8, 7.0, 5.1 Hz, H3), 4.37 (dd, 1 H, *J* = 9.8, 2.0 Hz, H1), 4.57 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 4.90 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 7.33 (m, 5

H); ^{13}C NMR ($CDCl_3$) δ 16.9 (CH_3), 26.4 (CH_3), 28.2 (CH_3), 35.3 (CH_2), 68.8 (CH), 69.9 (CH_2), 72.3 (CH), 74.0 (CH), 98.0 (CH), 109.1 (C), 127.6 (CH), 127.9 (CH), 128.2 (CH), 137.4 (C).

3,4-*O*-Isopropylidene-2-deoxy-D-fucose (64). Calcium turnings (0.0806 g, 2.01 mmol) were added to predried liquid NH_3 (200 mL, distilled from $NaNH_2$). A solution of benzyl 3,4-*O*-isopropylidene-2-deoxy-α-D-fucose (**59**, 0.1121 g, 0.40 mmol) in THF (10 mL) was added to the blue solution. After 40 min, reaction quenched by addition of solid NH_4Cl. The mixture was diluted with THF and stirred while immersed in a warm water bath until the NH_3 had evaporated. Filtration through $MgSO_4$ and concentration *in vacuo* gave a yellow oil (0.1135 g). Column chromatography (1.5 × 15 cm; 3:7 EtOAc:hexane) gave **8** as a clear oil (52.5 mg; 70%) consisting of a mixture of anomers (4.5:1 α:β). $[\alpha]_D$ +10.3° (*c* 3.5, $CHCl_3$); R_f = 0.20 (1:1 EtOAc:hexane); IR (NaCl, neat) 3440 (OH), 1460 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (d, 3 H, *J* = 6.3 Hz, H6), 1.35 (s, 3 H), 1.48 (s, 3 H), 1.72 (ddd, 1 H, *J* = 15.1, 7.1, 3.5 Hz, H2), 2.25 (ddd, 1 H, *J* = 15.1, 5.3, 4.4 Hz, H2), 2.55 (d, 1 H, *J* = 3.2 Hz, OH), 3.99 (m, 2 H), 4.50 (m, 1 H), 5.34 (ddd, 1 H, *J* = 7.1, 5.3, 3.2 Hz, H1); ^{13}C NMR ($CDCl_3$) α anomer δ 16.1 (CH_3), 25.1 (CH_3), 26.5 (CH_3), 30.8 (CH_2), 64.9 (CH), 70.6 (CH), 75.1 (CH), 90.4 (CH), 108.7 (C), β anomer δ 16.5 (CH_3), 25.1 (CH_3), 26.5 (CH_3), 33.8 (CH_2), 68.3 (CH), 72.0 (CH), 74.9 (CH), 93.2 (CH), 108.7 (C); HRCIMS found *m/z* 188.1284 [$(M+NH_4^+-H_2O)^+$], $C_9H_{18}O_3N$ requires 188.1287.

(+)-2-Deoxy-D-fucose (57). Dowex 50X2-400 resin (acid washed, H^+ form) was added to a solution of 3,4-*O*-isopropylidene-2-deoxy-D-fucose (**63**, 40 mg) in THF/H_2O (1:5, 24 mL). After stirring for 1.5 h at 23°C, the suspension was filtered, and the resin washed with hot deionized-water. Volatile solvent was removed by rotary evaporation and the remaining aqueous solution was lyophilized. The residue was dissolved in H_2O and

filtered through a syringe filter (Nalgene, 0.2 μm, 25 mm cellulose acetate) followed by removal of water to afford **57** as clear glass (31.2 mg, 90%). $[\alpha]_D$ +55° (*c* 0.61, H_2O, equil); R_f = 0.05 (1:9 EtOH:CH_2Cl_2); ^1H NMR (500 MHz, D_2O) Mixture of isomeric forms: pyranose (90%, α:β 1:1.2) and furanose (10%), δ were identical with literature values.[15,16] α pyranose, δ 1.19 (d, 3 H, *J* = 6.5 Hz, H6), 1.84 (m, 1 H, H2), 1.96 (ddd, 1 H, *J* = 12.1, 4.8, 2.2 Hz, H2), 3.68 (d, 1 H, *J* = 3.5 Hz, H4), 4.07 (ddd, 1 H, *J* = 12.0, 5.5, 3.5 Hz, H3), 4.12 (q, 1 H, *J* = 6.5 Hz, H5), 5.34 (d, 1 H, *J* = 3.5 Hz, H1); β pyranose δ 1.23 (d, 3 H, *J* = 6.5 Hz, H6), 1.60 (dt, 1 H, *J* = 12.1, 9.9 Hz, H2), 1.84 (m, 1 H, H2), 3.58 (d, 1 H, *J* = 3.0 Hz, H4), 3.65 (dq, 1 H, *J* = 6.5, 1.0 Hz, H5), 3.86 (ddd, 1 H, *J* = 12.0, 4.5, 3.0 Hz, H3), 4.80 (dd, 1 H, *J* = 10.0, 2.5 Hz, H1); ^{13}C NMR (D_2O) δ 15.8/16.0 (CH_3), 31.6/34.5 (CH_2), 64.7/66.4 (CH), 68.0/69.4 (CH), 70.4/70.8 (CH), 91.3/93.5 (CH); α/β furanose δ 1.21 (d, 3 H, *J* = 7.0 Hz, H6)/1.22 (d, 3 H, *J* = 6.5 Hz, H6), 2.14 (dd, 1 H, *J* = 6.0, 4.5 Hz), 2.39 (ddd, 1 H, *J* = 14.3, 7.3, 5.5 Hz), 3.80 (m, 2 H), 3.92 (dd, 1 H, *J* = 5.0, 3.5 Hz), 4.26 (ddd, 1 H, *J* = 7.0, 3.5, 3.5 Hz), 4.37 (dt, 1 H, *J* = 6.5, 4.5 Hz), 5.55 (dd, 1 H, *J* = 5.5, 2.0 Hz, H1)/5.59 (t, 1 H, *J* = 4.5 Hz, H1); ^{13}C NMR (D_2O) δ 18.2/18.4, 41.3/41.4, 67.3/68.4, 71.4/71.5, 88.9/89.3, 97.8/98.0; HRCIMS found *m/z* 166.1084 (MNH_4^+), $C_6H_{16}NO_4$ requires 166.1079.

(3*R*, 4*S*, 5*R*)-3,4-*O*-Isopropylidene-1,3,4,5-hexanetetraol (65). Hexane-washed lithium (0.270 g, 38.9 mmol) was added to liquid NH_3 (300 mL, distilled from $NaNH_2$). A solution of benzyl 3,4-*O*-isopropylidene-2-deoxy-α-D-fucose (**59**, 0.9707 g, 3.48 mmol) in 20 mL THF was added, and after 40 min the reaction was quenched by addition of solid NH_4Cl. The mixture was diluted with THF and stirred while immersed in a warm water bath until the NH_3 had evaporated. Filtration of the mixture through $MgSO_4$ and concentration *in vacuo* gave a yellow oil (0.8303 g). Column chromatography (4.5 × 18 cm; 1:1 EtOAc:hexane to EtOAc) gave **65** as a clear oil (0.6077 g; 92%). $[\alpha]_D$ +16.9° (*c* 0.55, $CHCl_3$); R_f = 0.09 (1:1 EtOAc:hexane); IR (NaCl, neat) 3420 (OH) cm^{-1}; ^1H

NMR (300 MHz, $CDCl_3$) δ 1.20 (d, 3 H, J = 6.2 Hz, H6), 1.38 (s, 3 H), 1.50 (s, 3 H), 1.69 (m, 1 H, H2), 1.90 (m, 1 H, H2), 2.59 (bs, 2 H, OH), 3.82 (m, 3 H), 3.90 (dd, 1 H, J = 6.3, 5.9 Hz), 4.33 (ddd, 1 H, J = 10.9, 5.9, 2.8 Hz); ^{13}C NMR ($CDCl_3$) δ 19.6 (CH_3), 25.4 (CH_3), 27.8 (CH_3), 31.9 (CH_2), 60.6 (CH_2), 65.6 (CH), 75.5 (CH), 81.6 (CH), 108.3 (C); HRCIMS found *m/z* 191.1287 (MH^+), $C_9H_{19}O_4$ requires 191.1283.

5-*tert*-Butyldimethylsilylhydroxyl-3,4-*O*-isopropylidene-1-pivaloylhexane (66). (3*R*, 4*S*, 5*R*)-3,4-*O*-Isopropylidene-1,3,4,5-hexanetetraol (**65**, 0.0506 g, 0.27 mmol) dissolved in pyridine (4 mL), and DMAP (0.0327 g, 0.27 mmol) added. Reaction solution cooled to 0°C and pivoyl chloride (0.04 mL, 0.32 mmol) added dropwise. After 17 h, an additional Piv-Cl (0.06 mL, 0.49 mmol) added. After 22 h total, reaction quenched with NH_4Cl (1.5 mL, aq, satd) and NaCl (1.5 mL, aq, satd). The aqueous layer was extracted with EtOAc (3 × 25 mL). The organic layer was dried through $MgSO_4$ and reduced *in vacuo* to an oil. Crude material purified by column chromatography (2.5 cm × 20 cm, 1:4 to 3:7 ethyl acetate:hexane) to give a clear oil (0.0563 mg, 77%, R_f = 0.39, 1:1 ethyl acetate:hexane). $[\alpha]_D$ +35.3° (*c* 5.37, $CHCl_3$); IR (NaCl, neat) 3530 (OH), 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 9 H), 1.14 (d, 3 H, J = 4.2 Hz), 1.29 (s, 3 H), 1.41 (s, 3H), 1.80 (m, 2 H), 3.75 (dq, 1 H, J = 6.1, 6.1 Hz), 3.83 (dt, 1 H, J = 6.1 Hz), 4.14 (m, 3 H); ^{13}C NMR ($CDCl_3$) 19.7 (CH_3), 25.2 (CH_3), 27.1 (CH_3), 27.7 (CH_3), 29.0 (CH_2), 38.6 (C), 61.5 (CH_2), 65.6 (CH), 73.6 (CH), 81.4 (CH), 108.1 (C), 178.2 (C); HRCIMS found *m/z* 275.1863 (MH^+), $C_{14}H_{27}O_5$ requires 275.1858.

3,4-*O*-Isopropylidene-1-pivaloylhexan-5-ol (0.0563 g, 0.21 mmol) was dissolved in DMF (3 mL), and *tert*-butyldimethylsilyl chloride (0.0621 g, 0.41 mmol) and imidazole (0.0420 g, 0.62 mmol) were added. After 15 h, additional *tert*-butyldimethylsilyl chloride (0.1184 g, 0.79 mmol) was added. After 18 h total, reaction worked up by pouring into ice water and extracting with Et_2O (3 × 25 mL). The organic layer was dried through $MgSO_4$ and

reduced *in vacuo* to an oil. The crude material was purified by column chromatography (1.5 cm × 15 cm, 1:19 ethyl acetate:hexane) to give **66** as a clear oil (0.0750 g, 94%, R_f = 0.59, 3:7 ethyl acetate:hexane). $[\alpha]_D$ +44.7° (*c* 5.68, $CHCl_3$); IR (NaCl, neat) 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 1.13 (d, 3 H, *J* = 5.9 Hz), 1.31 (s, 3 H), 1.43 (s, 3 H), 1.76 (m, 2 H), 3.86 (m, 2 H), 4.11 (m, 2 H), 4.28 (m, 1 H); ^{13}C NMR ($CDCl_3$) -4.5 (CH_3), -4.6 (CH_3), 18.2 (C), 20.2 (CH_3), 25.8 (CH_3), 27.2 (CH_3), 28.2 (CH_3), 29.1 (CH_2), 38.7 (C), 61.5 (CH_2), 67.3 (CH), 73.7 (CH), 82.0 (CH), 108.2 (C), 178.4 (C); HRCIMS found *m/z* 389.2724 (MH^+), $C_{20}H_{41}O_5Si$ requires 389.2723.

5-*tert*-Butyldimethylsilylhydroxyl-3,4-*O*-isopropylidene-hexanol (67). 5-*tert*-Butyldimethylsilylhydroxyl-3,4-*O*-isopropylidene-1-pivaloylhexane (**66**, 15.43 g, 39.8 mmol) dissolved in EtOH (700 mL, 95%). LiOH (400 mL, 1.51 M) added, and reaction heated to 35°C for 25 h. Reaction worked up by pouring into NaCl (aq, satd) and extracting with EtOAc (3 × 800 mL). The organic layer was dried through $MgSO_4$ and reduced *in vacuo*. The crude meaterial was purified by column chromatography (4.5 cm × 20 cm, 3:7 ethyl acetate:hexane) to give **67** as a clear oil (12.09 g, quant., R_f = 0.22, 3:7 ethyl acetate:hexane). $[\alpha]_D$ +42.3° (*c* 5.34, $CHCl_3$); IR (NaCl, neat) 3430 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.14 (d, 3 H, *J* = 5.9 Hz), 1.33 (s, 3 H), 1.47 (s, 3 H), 1.61 (dddd, 1 H, *J* = 12.5, 7.6, 4.9, 2.7 Hz), 1.83 (dddd, 1 H, *J* = 12.9, 12.5, 6.7, 5.3 Hz), 3.82 (m, 2 H), 3.90 (m, 2 H), 4.21 (ddd, 1 H, *J* = 11.2, 5.3, 2.7 Hz); ^{13}C NMR ($CDCl_3$) -4.7 (CH_3), -4.6 (CH_3), 18.2 (C), 20.2 (CH_3), 25.8 (CH_3), 27.0 (CH_3), 28.0 (CH_3), 31.8 (CH_2), 60.6 (CH_2), 67.2 (CH), 75.9 (CH), 82.1 (CH), 108.2 (C); HRCIMS found *m/z* 322.2407 (MNH_4^+), $C_{15}H_{36}NO_4Si$ requires 322.2414.

5-*tert*-Butyldimethylsilylhydroxyl-3,4-*O*-isopropylidene-hexan-1-al (53). DMSO (3.6 mL, 50.7 mmol) added to $(COCl)_2$ (2.2 mL, 25.2 mmol) in CH_2Cl_2 (20 mL) at -78°C. After 15 min, **67** (0.5081 g, 1.67 mmol) dissolved in CH_2Cl_2 (20 mL) was slowly added. Et_3N was added after 1.5 h. After 15 min, reaction warmed to rt, and $NaHCO_3$ (20 mL, aq, satd). The aqueous layer was extracted with CH_2Cl_2 (3 × 125 mL). The organic layer was dried through $MgSO_4$ and reduced *in vacuo* to a white solid. The crude material was purified by column chromatography (2.5 cm × 22 cm, 1:9 to 1:4 ethyl acetate:hexane) to give a yellow oil (0.4834 g, 96%, R_f = 0.47, 3:7 ethyl acetate:hexane). $[\alpha]_D$ +37.1° (*c* 0.38, $CHCl_3$); IR (NaCl, neat) 1720 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.17 (d, 3 H, *J* = 6.3 Hz), 1.35 (s, 3 H), 1.46 (s, 3 H), 2.63 (ddd, 1 H, *J* = 16.2, 4.4, 1.4 Hz), 2.77 (ddd, 1 H, *J* = 16.2, 9.3, 2.5 Hz), 3.83 (dq, 1 H,*J* = 6.7, 6.3 Hz), 4.00 (t, 1 H, *J* = 6.7, 5.7 Hz), 4.60 (ddd, 1 H, *J* = 9.3, 5.7, 4.4 Hz), 9.80 (dd, 1 H, *J* = 2.5, 1.4 Hz); ^{13}C NMR ($CDCl_3$) -4.6 (CH_3), -4.5 (CH_3), 18.2 (C), 20.1 (CH_3), 25.5 (CH_3), 25.6 (CH_3), 27.7 (CH_3), 44.5 (CH_2), 67.5 (CH), 71.9 (CH), 81.1 (CH), 108.6 (C), 200.6 (CH); HRCIMS found *m/z* 320.2254 (MNH_4^+), $C_{15}H_{34}NO_4Si$ requires 320.2257.

5-*tert*-Butyldimethylsilylhydroxyl-3,4-*O*-isopropylidene-1-oxazolylhexan-1-ol (55a/55b). *n*-BuLi (1.3 mL, 3.21 mmol) added to oxazole (0.21 mL, 3.20 mmol) in THF (2 mL) at -78°C. The mixture turned an opaque, dark red color. After 20 min, **53** (0.927 g, 0.31 mmol) in THF (3 mL) was added dropwise. Reaction mixture warmed slowly to rt overnight. The reaction was quenched with NH_4Cl (aq, satd), and the aqueous layer was extracted with EtOAc (3 × 125 mL). The organic layer was dried through $MgSO_4$ and reduced *in vacuo* to a dark yellow oil (0.1122 g). The crude material was purified by column chromatography (2.5 cm × 25 cm, 1:9 to 3:1 EtOAc:hexane) to give the product as a 1:1.1 mixture of diastereomers (0.0286 g, 25%). The diastereomers were separated by HPLC (Dynamax 60-A silica, 2:3 EtOAc:hexane, flow rate 3 mL/min) to give

two pure compounds: **55a**: 8.1 mg (7.1%, retention time 16 min), and **55b**: 8.6 mg (7.6%, retention time 18 min).

55a. (1*S*, 3*R*, 4*S*, 5*R*), $[\alpha]_D$ +10.9° (*c* 0.34, $CHCl_3$); IR (NaCl, neat) 3440 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 1.15 (d, 3 H, *J* = 5.9 Hz), 1.35 (s, 3 H), 1.54 (s, 3 H), 1.97 (m, 2 H), 3.88 (m, 2 H), 4.27 (ddd, 1 H, *J* = 10.1, 5.3, 3.5 Hz), 4.96 (dd, 1 H, *J* = 8.6, 4.3 Hz, H1), 7.65 (d, 1 H, *J* = 0.8 Hz), 7.84 (d, 1 H, *J* = 0.8 Hz; $^1J_{CH}$.= 234.4 Hz); ^{13}C NMR ($CDCl_3$) -4.6 (CH_3), -4.5 (CH_3), 18.3 (C), 20.4 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 28.0 (CH_3), 36.2 (CH_2), 67.0 (CH), 68.1 (CH), 78.0 (CH), 82.4 (CH), 108.8 (C), 135.0 (CH), 143.0 (C), 151.0 (CH); HRCIMS found *m/z* 372.2211 (MH^+), $C_{18}H_{34}NO_5Si$ requires 372.2206.

55b. (1*R*, 3*R*, 4*S*, 5*R*) $[\alpha]_D$ +37.7° (*c* 0.56, $CHCl_3$); IR (NaCl, neat) 3430 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.15 (d, 3 H, *J* = 5.8 Hz, H6), 1.32 (s, 3 H), 1.50 (s, 3 H), 1.92 (ddd, 1 H, *J* = 14.2, 7.1, 2.5 Hz, H2), 2.08 (ddd, 1 H, *J* = 14.2, 11.2, 3.3 Hz, H2), 3.41 (d, 1 H, *J* = 6.3 Hz, OH), 3.88 (m, 2 H, H4/H5), 4.24 (ddd, 1 H, *J* = 11.2, 5.2, 2.5 Hz, H3), 5.0 (ddd, 1 H, *J* = 7.1, 6.3, 3.3 Hz, H1), 7.64 (d, 1 H, *J* = 1.0 Hz), 7.85 (d, 1 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$) -4.6 (CH_3), -4.5 (CH_3), 18.3 (C), 20.3 (CH_3), 25.9 (CH_3), 28.2 (CH_3), 34.5 (CH_2), 65.7 (CH), 67.2 (CH), 74.1 (CH), 82.3 (CH), 108.5 (C), 135.1 (CH), 143.6 (C), 151.3 (CH); HRCIMS found *m/z* 372.2185 (MH^+), $C_{18}H_{34}NO_5Si$ requires 372.2206.

(1*S*, 3*R*, 4*S*, 5*R*)-1,3:4:5-*O*-Diisopropylidene-1-oxazolylhexane-1,3,4,5-tetraol (68). TBAF (0.030 mL, 0.03 mmol) was added to **55a** (3.2 mg, 0.09 mmol) in THF (2 mL) at 0°C. Starting material consumed after 3 h. Two drops $NaHCO_3$ (aq, satd) added to reaction mixture and mixed with a pipet. The mixture was dried through a pipet column of $MgSO_4$ and concentrated to a film (12.4 mg). The crude material was partially

purified by pipet column chromatography (1:19 MeOH:$CHCl_3$) to give 2.2 mg of a yellow film. This material was then dissolved in MeOH and Dowex 50x2-400 (washed with 2 M HCl, H_2O, 4:1 THF:H_2O, and finally MeOH) was added. After 1h, starting material was consumed. The resin was filtered and washed with MeOH. The methanol layer was dried *in vacuo* to give a yellow oil (4.5 mg). The oil was dissolved in acetone (dried over molecular sieves), and 2,2-dimethoxypropane (1 mL) and *p*-TSA (@ 0.5 mg) was added. After 2 h, reaction mixture concentrated to give 5.0 mg of crude material which was passed through a plug of silica gel with EtOAc to give 2.9 mg of a yellow oil. This material further purified by HPLC (Dynamax 60-A silica, 6:4 EtOAc:hexane, flow rate 3 mL/min) to give **68** (0.3 mg, 12%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (d, 3 H, J = 6.0 Hz, H6), 1.37 (s, 3 H), 1.41 (s, 3 H), 1.45 (s, 3 H), 1.55 (s, 3 H), 1.70 (ddd, 1 H, J = 13.0, 12.0, 11.5 Hz, H2β), 2.10 (ddd, 1 H, J = 13.0, 2.5, 1.5 Hz, H2α), 3.46 (dd, 1 H, J = 7.5, 7.0 Hz, H4), 3.96 (ddd, 1 H, J = 12.0, 7.5, 2.5 Hz, H3), 4.02 (dq, 1 H, J = 7.0, 6.0 Hz, H5), 5.00 (dd, 1 H, J = 11.5, 1.5 Hz, H1), 7.62 (s, 1 H), 7.84 (s, 1 H); HRCIMS found *m/z* 298.1658 (MH^+), $C_{15}H_{24}NO_5$ requires 298.1654.

2-Methylthiooxazole (73). Oxazole-2-thione[17] (**74**, 4.98 g, 49.3 mmol) in THF (125 mL) was added to hexane-washed KH (35% dispersion in oil, 6.38 g, 55.7 mmol) in THF (125 mL) at -60°C, and, after 30 min, MeI was added. The reaction was stirred for 3.25 h and was quenched with NH_4Cl (aq, satd, 50 mL) and then diluted with H_2O (40 mL). The aqueous layer was extracted with Et_2O (3 × 800 mL), and the combined organic layers were dried ($MgSO_4$) and reduced to a yellow oil (6.6067 g). The crude material was purified by bulb-to-bulb distillation (70-100°C, 28 mm Hg) to give **73** as a colorless oil (4.315 g; 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 3 H), 7.10 (s, 1 H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 128.1 (CH), 139.8 (CH), 161.1 (C); HREIMS found *m/z* 115.0090 (M^+), C_4H_5NOS requires 115.0092.

General Procedure for C-5 Alkylation:

1-(2'-Methylthiooxazol-5'-yl)-1-phenyl-methanol (75a). 2-Methylthiooxazole (**73**, 0.2496 g, 2.17 mmol), TMEDA (3.4 mL, 22.5 mmol) and THF (5 mL) were added to a solution of *n*-BuLi (0.88 mL, 2.31 mmol) in THF (5 mL) at -78°C. In a separate flask, benzaldehyde (0.50 mL, 4.92 mmol) was dissolved in THF (7 mL) and cooled to -78°C. After 20 min, the oxazole anion of **73** was added to the aldehyde over 10 min *via* an insulated cannula. The mixture was stirred for an additional 12 min, quenched with $NaHCO_3$ (aq, satd, 3 mL), diluted with 10 mL H_2O and extracted with EtOAc (3 × 125 mL). The organic layer was dried ($MgSO_4$) and reduced to a yellow oil which was purified by column chromatography (silica, 3:7 to 1:1 EtOAc:hexane) to give **75a** as a colorless oil (0.4008 g, 84%). IR (NaCl, neat) 3304 (OH), 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 5.76 (s, 1 H), 6.62 (s, 1H, $J_{C4\text{-}H4}$ = 195.8 Hz), 7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 68.04 (CH), 125.3 (CH), 126.5 (CH), 128.3 (CH), 128.5 (CH), 139.6 (C), 154.5 (C), 161.7 (C); HREIMS found *m/z* 221.0517 (M^+), $C_{11}H_{11}NO_2S$ requires 221.0511.

1-(4'-Methoxyphenyl)-1-(2"-methylthiooxazol-5"-yl)methanol (75b). Yellow oil (85%); IR (NaCl, neat) 3332 (OH), 1614 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.79 (s, 3 H), 5.70 (s, 1 H), 6.62 (s, 1H), 6.87 (d, 2 H, J = 8.6 Hz), 7.31 (d, 2 H, J = 8.6 Hz) ; ^{13}C NMR ($CDCl_3$) δ 14.5 (CH_3), 55.2 (CH_3), 67.7 (CH), 113.8 (CH), 125.1 (CH), 127.8 (CH), 131.8 (C), 154.8 (C), 159.5 (C), 161.4 (C); HREIMS found *m/z* 251.0604 (M^+), $C_{12}H_{13}NO_3S$ requires 251.0616.

1-(4'-Bromophenyl)-1-(2"-methylthiooxazol-5"-yl)methanol (75c). Yellow oil (84%) which crystallized from EtOAc and hexane, mp 96-97°C; IR (NaCl, neat) 3270 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (s, 3 H), 5.58 (s, 1 H), 6.46 (s, 1H), 7.37 (d, 2 H, J = 8.3 Hz), 7.37 (d, 2 H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3),

67.0 (CH), 122.0 (C), 124.9 (CH), 128.1 (CH), 131.5 (CH), 138.6 (C), 154.1 (C), 161.8 (C); HREIMS found *m/z* 298.9607 (M^+), $C_{11}H_{10}BrNO_2S$ requires 298.9616; Anal. Calcd for $C_{11}H_{10}BrNO_2S$: C, 44.02; H, 3.36; N, 4.67; S, 10.68. Found: C, 44.30; H, 3.41; N, 4.49; S, 10.59.

"Double alkylation" of 73a. Bi-*p*-bromobenzyl diol 76c. The above reaction was repeated with 1.3 eq of BuLi and addition of metallated **73** to aldehyde (2.2 eq) at -70°C. Silica gel chromatography gave **75c** (54%) in addition to a new compound **76c** (33%). IR (NaCl, neat) 3353 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.19 (m, 2 H), 4.76 (1 H, 1 H), 5.56 (s, 1 H), 6.49 (s, 1H), 7.09 (m, 4 H), 7.34 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 40.8 (CH_2), 67.1 (CH), 72.6 (CH), 121.7 (C), 122.3 (C), 124.8 (CH), 127.5 (CH), 128.1 (CH), 131.5 (CH), 131.6 (CH), 138.3 (C), 141.0 (C), 154.6 (C), 161.3 (C); HRCIMS found *m/z* 483.9213 (MH^+), $C_{18}H_{16}Br_2NO_3S$ requires 483.9218.

1-(2'-Methylthiooxazol-5'-yl)-1-(2"-naphthyl)methanol (75d). Yellow oil (77%) which crystallized from EtOAc/hexane, mp 106-107°C; IR (NaCl, neat) 3284 (OH), 1603 (C=C), 1487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (s, 3 H), 5.29 (bs, 1 H), 5.85 (s, 1 H), 6.62 (s, 1H), 7.48 (m, 3 H), 7.84 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 67.6 (CH), 124.1 (CH), 124.9 (CH), 125.2 (CH), 125.9 (CH), 126.0 (CH), 127.4 (CH), 127.8 (CH), 128.1 (CH), 132.8 (C), 132.9 (C), 137.0 (C), 154.6 (C), 161.5 (C); HREIMS found *m/z* 271.0656 (M^+), $C_{15}H_{13}NO_2S$ requires 271.0667; Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.50; H, 4.91; N, 5.07; S, 11.64.

"Double alkylation" of 73a. Binaphthyl diol 76d. The above reaction was repeated with 1.4 eq of BuLi and addition of metallated **73** to aldehyde (2.2 eq) at -40°C. Silica gel chromatography gave **75d** (33%) in addition to a new compound **76d** (44%)

which crystallized from EtOAc/hexane, mp 145-146°C; IR (NaCl, neat) 3369 (OH), 1734, 1484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.37 (dd, 1 H, *J* = 13.7, 8.2 Hz), 3.57 (dd, 1 H, *J* = 13.7, 3.3 Hz), 5.10 (dd, 1 H, *J* = 8.2, 3.3 Hz), 5.55 (bs, 2 H), 5.90 (s, 1 H), 6.76 (s, 1H), 7.44 (m, 6 H), 7.82 (m, 8 H); ^{13}C NMR ($CDCl_3$) δ 40.7 (CH_2), 67.2 (CH), 72.0 (CH), 123.6 (CH), 124.1 (CH), 124.4 (CH), 124.5 (CH), 124.9 (CH), 125.3 (CH), 125.6 (CH), 125.7 (CH), 127.0 (CH), 127.1 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 132.4 (C), 132.5 (C), 132.6 (C), 137.7 (C), 155.1 (C), 160.0 (C); HRCIMS (NH_3) found *m/z* 428.1332 (MH^+), $C_{26}H_{21}NO_3S$ requires 428.1320.

1-(2'-Furyl)-1-(2"-methylthiooxazol-5"-yl)methanol (75e). Yellow oil (72%); IR (NaCl, neat) 3269 (OH), 1487 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.53 (s, 3 H), 5.75 (s, 1 H), 6.30 (m, 2 H), 6.80 (s, 1 H), 7.35 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 61.7 (CH), 107.8 (CH), 110.3 (CH), 125.3 (CH), 142.5 (CH), 152.2 (C), 161.6 (C); HREIMS found *m/z* 211.0299 (M^+), $C_9H_9NO_3S$ requires 211.0303.

3,7-Dimethyl-1-(2'-methylthiooxazol-5'-yl)-octa-2,6-dien-1-ol (75f). Clear oil (83%, 2:1 *E*:*Z*); IR (NaCl, neat) 3336 (OH), 1726, 1668 (C=C), 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 3 H), 1.59 (s, 3 H), 1.61 (s, 3 H), 2.00 (m, 4 H), 2.52 (s, 3 H), 4.99 (m, 1 H), 5.34 (m, 2 H), 6.72 (s, 1 H; *E*), 6.75 (s, 1 H, *Z*); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 16.5/17.5 (CH_3), 22.4/23.2 (CH_3), 25.4/25.5 (CH_3), 26.0/26.2 (CH_2), 32.2/ 39.2 (*Z*/*E*, CH_2), 62.0/62.4 (CH), 122.6 (CH), 123.4 (CH), 123.8 (CH), 131.7/132.3 (C), 140.6/140.9 (C), 154.6/154.7 (C), 160.9 (C); HRCIMS (NH_3) found *m/z* 268.1368 (MH^+), $C_{14}H_{22}NO_2S$ requires 268.1371.

1-(2'-Methylthiooxazol-5'-yl)-*n*-decanol (75g). Colorless solid (73%); IR (NaCl, neat) 3338 (OH), 1491 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80 (m, 3 H), 1.19 (s, 12 H), 1.36 (m, 2 H), 1.71 (m, 2 H), 2.52 (s, 3 H), 4.05 (bs, 1 H), 4.56 (t, 1 H, *J* =

6.8 Hz), 6.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 14.3 (CH_3), 22.5 (CH_2), 25.3 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 34.9 (CH_2), 65.3 (CH), 123.5 (CH), 155.6 (C), 160.6 (C); HRCIMS (NH_3) found *m/z* 272.1679 (MH^+), $C_{14}H_{26}NO_2S$ requires 272.1684.

2,2-Dimethyl-1-(2'-methylthiooxazol-5'-yl)propanol (75h). Colorless solid (69%); mp 71-73°C (recrystallized from EtOAc/hexane); IR (NaCl, neat) 3285 (OH), 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (s, 9 H), 2.53 (s, 3 H), 4.28 (s, 1 H), 6.76 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 25.6 (CH_3), 35.3 (C), 74.0 (CH), 125.0 (CH), 154.5 (C), 160.1 (C); HRCIMS (NH_3) found *m/z* 202.0901 (MH^+), $C_9H_{16}NO_2S$ requires 202.0902.

(2*R*)-2,3-*O*-Isopropylidene-1-(2'-methylthiooxazol-5'-yl)propanol (75i). Yellow oil (60%, 2:1 ratio of diastereomers); IR (NaCl, neat) 3412 (OH), 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36/1.39 (s, 3 H), 1.42/1.46 (s, 3 H), 2.63 (s, 3 H), 3.43 (bs, 1 H), 3.80 (m, 2 H), 4.02 (m, 1 H), 4.08 (m, 1 H), 4.34 (m, 1 H)/ 4.38 (m, 1 H), 4.63 (d, 1 H, *J* = 6.5 Hz)/4.75 (d, 1 H, *J* = 5.9 Hz), 6.99/7.01 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 24.9 (CH_3), 26.3 (CH_3), 65.6/65.8 (CH_2), 66.7 (CH), 76.4/76.8 (CH), 109.5/109.9 (C), 125.1/125.4 (CH), 151.7/152.4 (C), 161.2/161.4 (C); HRCIMS (CH_4) found *m/z* 246.0796 (MH^+), $C_{10}H_{16}NO_4S$ requires 246.0800.

2,3-Dimethyl-1-(2'-methylthiooxazol-5'-yl)propanol (75j). Colorless solid (27%, 39% based on consumed starting material), recrystallized from EtOAc/hexane, mp 76-77°C; IR (NaCl, neat) 3385 (OH), 1492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (d, 3 H, *J* = 6.8 Hz), 0.87 (d, 3 H, *J* = 6.8 Hz), 1.36 (s, 3 H), 2.01 (2 overlapping q, 1 H, *J* = 6.8 Hz), 2.52 (s, 3 H), 3.12 (bs, 1 H), 6.73 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 16.7 (CH_3), 17.3 (CH_3), 22.1 (CH_3), 36.6 (CH), 72.9 (C), 123.4 (CH), 158.1 (C),

159.9 (C); HREIMS found *m/z* 201.0816 (M^+), $C_9H_{15}NO_2S$ requires 201.0824; Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.70; H, 7.51; N, 6.96; S, 15.93. Found: C, 53.88; H, 7.62; N, 6.82; S, 15.99.

1-(2'-Methylthiooxazol-5'-yl)cyclohexanol (75k). Colorless oil (53%) which crystallized from EtOAc/hexane, mp 85-86°C; IR (NaCl, neat) 3314 (OH), 1492 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (m, 5 H), 1.79 (m, 5 H), 2.60 (s, 3 H), 3.31 (bs, 1 H), 6.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 21.8 (CH_2), 25.2 (CH_2), 36.1 (CH_2), 68.7 (C), 122.7 (CH), 158.7 (C), 160.1 (C); HREIMS found *m/z* 213.0826 (M^+), $C_{10}H_{15}NO_2S$ requires 213.0824; Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03. Found: C, 56.59; H, 7.17; N, 6.49; S, 14.90.

5-Benzoyl-2-methylthiooxazole (75l). Orange oil (38%) which crystallized from *t*-butylmethyl ether/hexane, mp 62-63°C; UV ($CHCl_3$) λ_{max} 258 (ε 7085), 311 (17810); IR (NaCl, neat) 1718 (C=O), 1653 (C=C), 1454 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 3 H), 7.53 (m, 3 H), 7.73 (s, 1 H), 7.91 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 128.4 (CH), 128.5 (CH), 132.9 (CH), 136.4 (C), 137.3 (CH), 150.6 (C), 167.2 (C), 180.2 (C); HREIMS found *m/z* 219.0363 (M^+), $C_{11}H_9NO_2S$ requires 219.0354; Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39; S, 14.62. Found: C, 59.92; H, 4.14; N, 6.35; S, 14.77.

2,2-Dimethyl-1-(2'-methylthiooxazol-5'-yl)propanone (75m). Yellow oil (71%) which crystallized from *n*-hexane, mp 58-59°C; UV ($CHCl_3$) 292 (ε 13026); IR (NaCl, neat) 1669, 1552, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (s, 9 H), 2.63 (s, 3 H), 7.66 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 26.4 (CH_3), 43.0 (C), 135.2 (CH), 150.6 (C), 165.0 (C), 192.9 (C); HREIMS found *m/z* 199.0668 (M^+),

$C_9H_{13}NO_2S$ requires 199.0667; Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03; S, 16.09. Found: C, 54.32; H, 6.46; N, 6.94; S, 16.02.

1,1-Di(2'-methylthiooxazol-5'-yl)-2,2-dimethylpropanol (77). Yellow oil (43%); IR (NaCl, neat) 3337, 1482 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9 H), 2.56 (s, 3 H), 6.86 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.8 (CH_3), 25.0 (CH_3), 28.5 (C), 40.0 (C), 126.5 (CH), 154.0 (C), 161.0 (C); HREIMS found *m/z* 315.0835 (MH^+), $C_{13}H_{19}N_2O_3S_2$ requires 315.0837; Anal. Calcd for $C_9H_{13}NO_2S$: C, 54.25; H, 6.58; N, 7.03; S, 16.09. Found: C, 54.32; H, 6.46; N, 6.94; S, 16.02.

Addition-Elimination of Isovaleronitrile to 2-Methylthiooxazole. 3-Methyl-2-(2-oxazolyl)-butanenitrile (78). The reaction was carried out as for addition to aldehydes, but the reaction mixture was allowed to warm to 25° C over 16 h. Work-up and chromatography of the product gave **78** as a yellow oil (33%). IR (NaCl, neat) 2250 (CN), 1571, 1467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (d, 3 H, J = 6.7 Hz), 1.12 (d, 3 H, J = 6.7 Hz), 2.47 (dq, 1 H, J = 6.7 Hz), 3.98 (d, 1 H, J = 6.1 Hz), 7.14 (d, 1 H, J = 0.8 Hz), 7.71 (d, 1 H, J = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 19.0 (CH_3), 20.1 (CH_3), 31.5 (CH), 38.8 (CH), 115.7 (C), 127.6 (CH), 139.8 (CH), 157.2 (C); HRCIMS (NH_3) found *m/z* 151.0866 (MH^+), $C_8H_{11}N_2O$ requires 151.0871.

2-Pentylthiooxazole (79) and 5-Butyl-2-pentylthiooxazole (80). 2-Methylthiooxazole (**73**, 0.0870 g, 0.76 mmol) in 2.5 mL THF was added to a solution of *n*-BuLi (0.60 mL, 0.97 mmol) in THF (2.5 mL) at -78°C. After 1/2 h, 1-iodobutane (0.15 mL, 1.32 mmol) was added dropwise. The reaction was quenched after 4 h at -60°C with NH_4Cl (aq, satd, 1.5 mL). The mixture was diluted with H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 125 mL). The organic layer was dried through $MgSO_4$ and reduced to a brown oil (0.1115 g). The crude material was purified by column

chromatography (1:19 EtOAc:hexane) to give 2 compounds as a 1:3 mixture (**79**, 39.9 mg, clear oil; **80**, 10.3 mg, clear oil). **79**. IR (NaCl, neat) 1497, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (m, 6 H), 1.38 (m, 6 H), 1.60 (m, 2 H), 1.74 (m, 2 H), 2.61 (t, 2 H, J = 7.4 Hz), 3.12 (t, 2 H J = 7.5 Hz), 6.70 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 13.8 (CH_3), 22.0 (CH_2), 22.1 (CH_2), 25.2 (CH_2), 29.2 (CH_2), 29.5 (CH_2), 30.7 (CH_2), 32.5 (CH_2), 123.1 (CH), 154.4 (C), 158.6 (C); HREIMS found *m/z* 227.1347 (M^+), $C_{12}H_{21}NOS$ requires 227.1344.

80. IR (NaCl, neat) 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 7.1 Hz), 1.38 (m, 4 H), 1.75 (quin, 2 H), 3.16 (t, 2 H, J = 7.4 Hz), 7.10 (d, 1 H, J = 0.8 Hz), 7.65 (d, 1 H, J = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.2, 29.2, 30.8, 32.5, 128.2, 139.8; HREIMS found *m/z* 171.0715 (M^+), $C_8H_{13}NOS$ requires 171.0718.

General Procedure for Reductive Displacement of the Methylthio Group: 1-(Oxazol-5'-yl)-1-phenylmethanol (81a). Compound **75a** (0.1071 g, 0.48 mmol) was dissolved in absolute EtOH. Raney nickel in EtOH was added, and the reaction mixture was refluxed for 1.5 h. The hot reaction mixture was filtered through Celite which was washed with hot absolute EtOH (500 mL). The solvent was removed to give a cloudy oil which was purified by column chromatography (1:1 EtOAc:hexane) to give **81a** (0.0575 g, 68%). IR (NaCl, neat) 3295 (OH), 1507, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.94 (bs, 1 H), 5.83 (s, 1 H), 6.75 (s, 1 H), 7.30 (m, 5 H), 7.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 68.2 (CH), 123.5 (CH), 126.5 (CH), 128.5 (CH), 128.6 (CH), 139.8 (C), 151.1 (C), 153.5 (C); HREIMS found *m/z* 174.0565 (M^+), $C_{10}H_9NO_2$ requires 174.0555.

1-(2-Naphthyl)-1-(oxazol-5'-yl)methanol (81d). Offwhite solid (60%); mp 102-103°C (recrystallized from chloroform/hexane); IR (NaCl, neat) 3270 (OH), 1603 (C=C), 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (bs, 1 H), 5.99 (s, 1 H), 6.80 (s, 1 H),

7.47 (m, 3 H), 7.74 (s, 1 H), 7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 67.9 (CH), 123.1 (CH), 124.1 (CH), 125.3 (CH), 126.1 (CH), 126.2 (CH), 127.7 (CH), 127.9 (CH), 128.2 (CH), 132.9 (C), 133.0 (C), 137.2 (C), 151.0 (CH), 153.6 (C); HREIMS found *m/z* 225.0800 (M^+), $C_{14}H_{11}NO_2$ requires 225.0790; Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.12; H, 4.99; N, 6.06.

1-(Oxazol-5'-yl)-decanol (81g). Yellow oil (60%); mp 62-64°C (recrystallized from EtOAc/hexane); IR (NaCl, neat) 3364 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3 H), 1.25 (m, 12 H), 1.46 (m, 2 H), 1.84 (m, 2 H), 2.65 (bs, 1 H), 4.76 (t, 1 H, J = 6.8 Hz), 6.97 (s, 1 H), 7.84 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 25.3, 29.3, 29.5, 31.8, 35.3, 65.9, 122.5, 150.6, 154.2; HRCIMS found *m/z* 226.1808 (MH^+), $C_{13}H_{24}NO_2$ requires 226.1807; Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 69.56; H, 10.03; N, 6.20.

2,2-Dimethyl-1-(oxazol-5'-yl)propanol (81h). Yellow oil (59%); mp 57-58°C (recrystallized from EtOAc/hexane); IR (NaCl, neat) 3330 (OH), 1508, 1479 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 9 H), 3.50 (bs, 1 H), 4.41 (s, 1 H), 6.87 (s, 1 H), 7.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_3), 35.5 (C), 74.2 (CH), 123.4 (CH), 150.2 (C), 153.3 (C); HRCIMS (*i*-C_4H_9) found *m/z* 156.1025 (MH^+), $C_8H_{14}NO_2$ requires 156.1025; Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.00; H, 8.43; N, 9.08.

1-(Oxazol-5'-yl)-cyclohexanol (81k). White solid (60%); mp 76-77°C (recrystallized from EtOAc/hexane); IR (NaCl, neat) 3355 (OH), 1648, 1505, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (m, 4 H), 1.74 (m, 2 H), 1.91 (m, 4 H), 2.89 (bs, 1 H), 6.91 (s, 1 H), 7.79 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8 (CH_2), 25.2 (CH_2), 36.3 (CH_2), 68.9 (CH), 121.2 (CH), 150.2 (CH), 157.5 (C); HRCIMS (*i*-C_4H_9) found *m/z*

168.1025 (MH^+), $C_9H_{14}NO_2$ requires 168.1024; Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.61; H, 7.82; N, 8.28.

Deuterium Incorporation Experiment:

2-Methylthiooxazole-5-*d* (75o). Compound **72** (0.2984 g, 2.59 mmol), TMEDA (4.0 mL, 26.5 mmol), and THF (8 mL) were added to *n*-BuLi (1.0 mL, 2.62 mmol) and THF (7 mL) at -78°C. After 15 min, approximately one third of the reaction mixture was transferred *via* an insulated cannula to CH_3OD (1 mL) in Et_2O (5 mL) at -78°C (Sample 1). The temperature of the remaining reaction mixture was raised to -40°C, and after another 15 min, approximately one third of the reaction mixture was transferred to a mixture of CH_3OD (1 mL) and Et_2O (5 mL) at -78°C using an insulated cannula (Sample 2). The remaining reaction mixture was stirred for an additional 1.7 h at -40°C after which it was quenched by addition of CH_3OD (1 mL, Sample 3). Each of the three samples was dried ($MgSO_4$), concentrated under vacuum and purified by column chromatography (silica, elution with Et_2O). The ^1H NMR signal of H5 was integrated and compared to the H4 integral. Comparison of the integrations of H5 to H4 gave the following results (atom % deuterium). Sample 1 (96%); Sample 2 (94%); Sample 3 (90%). Comparison of NMR integrations of H4 to the MeS group indicated that in each case the ratio was 1:3 (~ ± 5% error). GC/MS (column DB-5, 30 m; T_i 50°C, t_i 1 min, ramp 10°C/min, T_f 280°C, t_f 5 min) gave % deuteration. Sample 1 (89%); Sample 2 (95%); Sample 3 (86%) error ± 2%.

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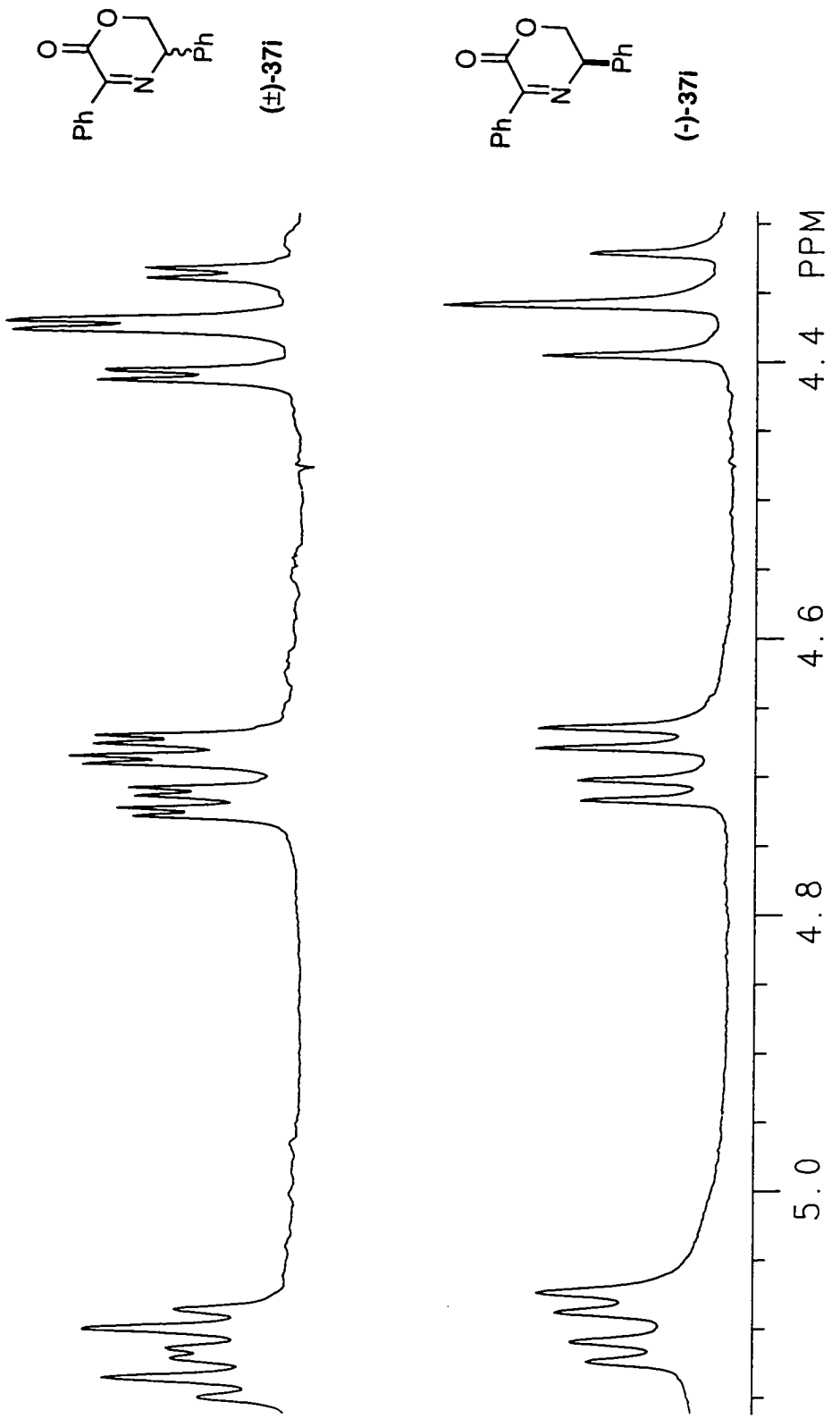
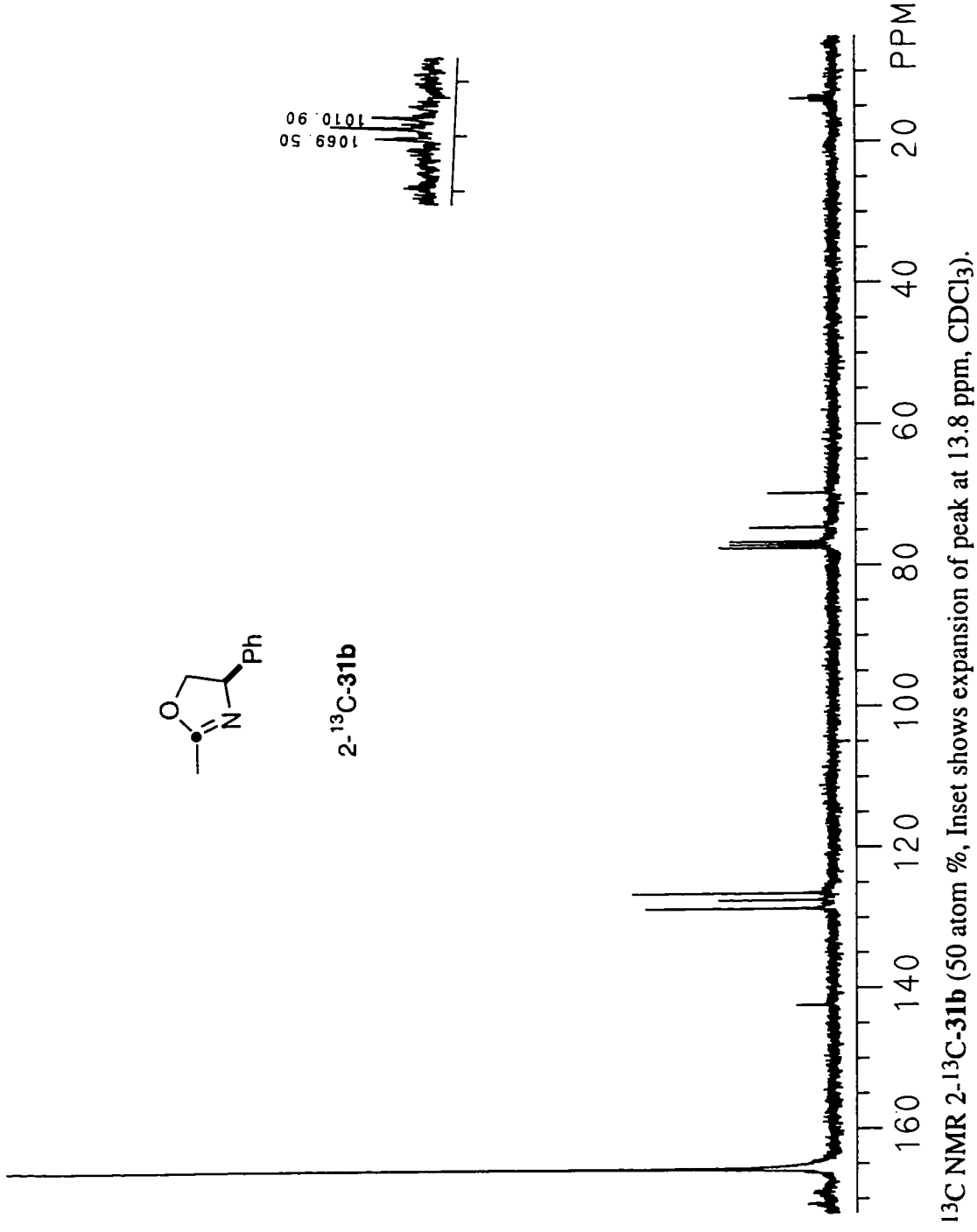
Appendix

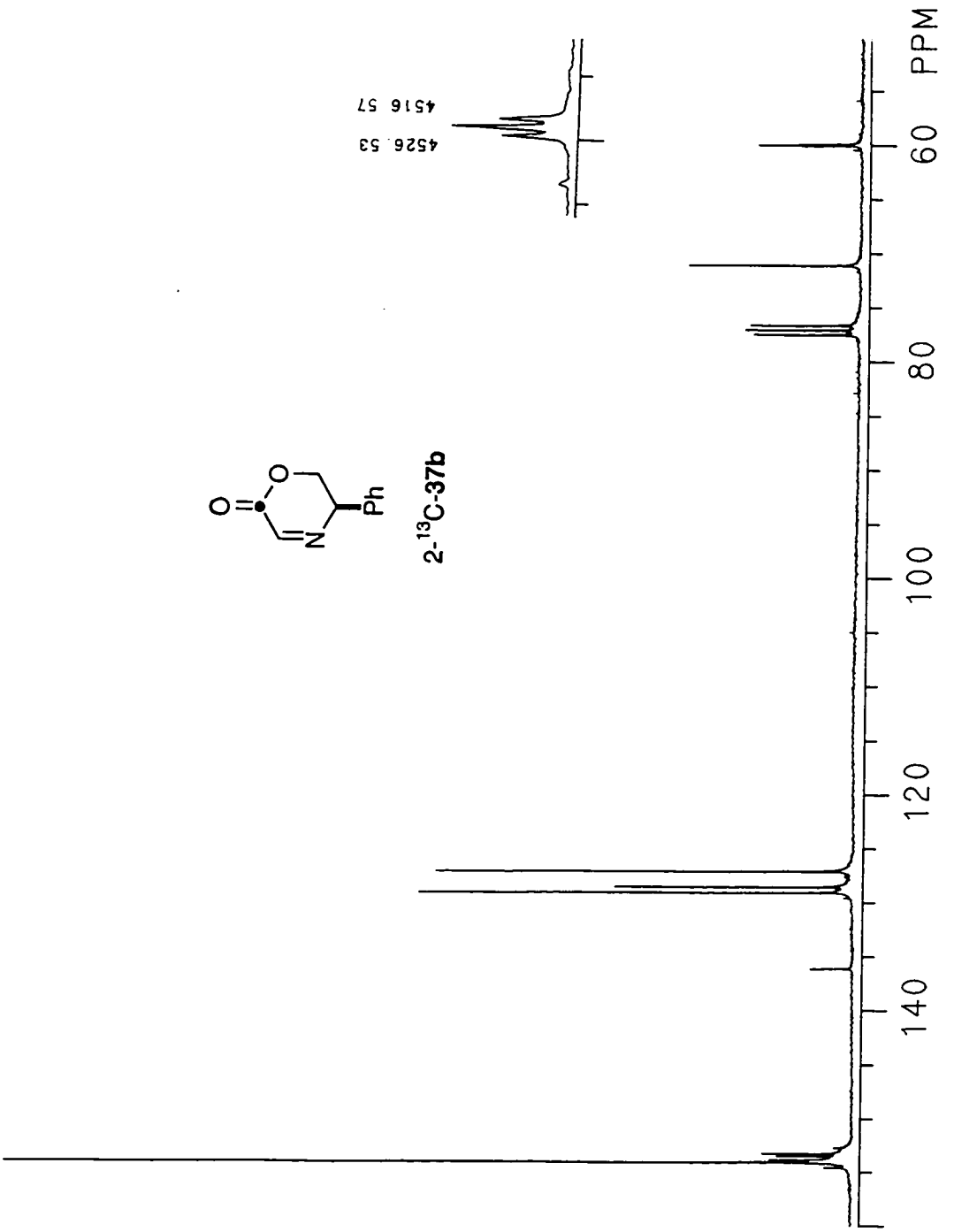
1. ^{1}H NMR signals of (-)-**37i** and (±)-**37i** with 20 mol% (+)-Eu(hfc)$_3$ ($CDCl_3$).
2. ^{13}C NMR 2-^{13}C-**31b** (50 atom %, Inset shows expansion of peak at 13.8 ppm, $CDCl_3$).
3. ^{13}C NMR 2-^{13}C-**37b** (50 atom %, Inset shows expansion of peak at 59.9 ppm, $CDCl_3$).
4. ^{13}C NMR expansion of **37b** and 2-^{13}C-**37b** (50 atom %, $CDCl_3$).
5. ^{1}H NMR of **55** ($CDCl_3$).
6. ^{1}H NMR of **75a** ($CDCl_3$). Expansion shows H4 δ 6.62 and "^{13}C satellites" representing $^{1}J_{CH}$ of C4-H4.



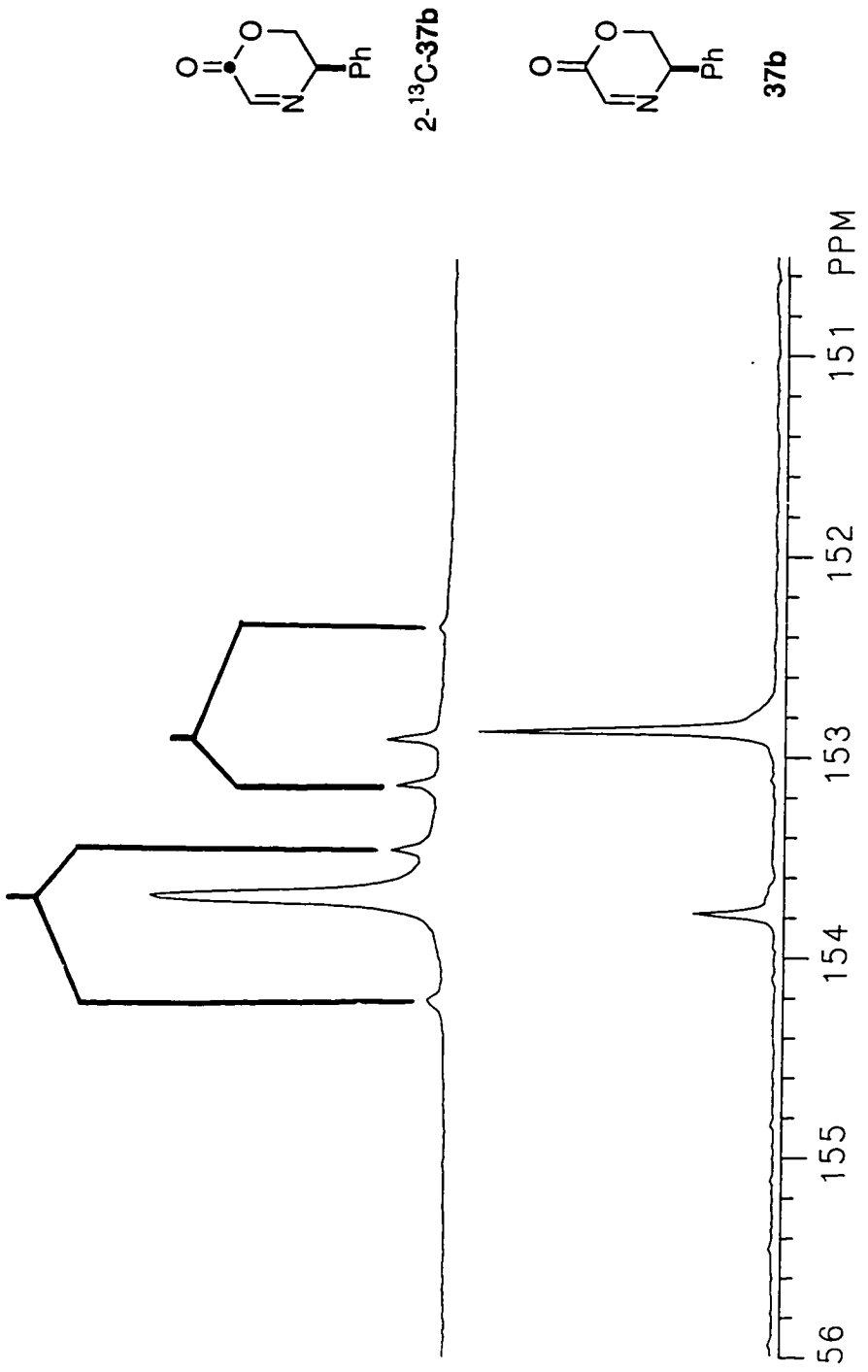
1. ^{1}H NMR signals of (-)-**37i** and (±)-**37i** with 20 mol% (+)-Eu(hfc)$_3$ ($CDCl_3$).



2. ^{13}C NMR 2-^{13}C-**31b** (50 atom %, Inset shows expansion of peak at 13.8 ppm, $CDCl_3$).

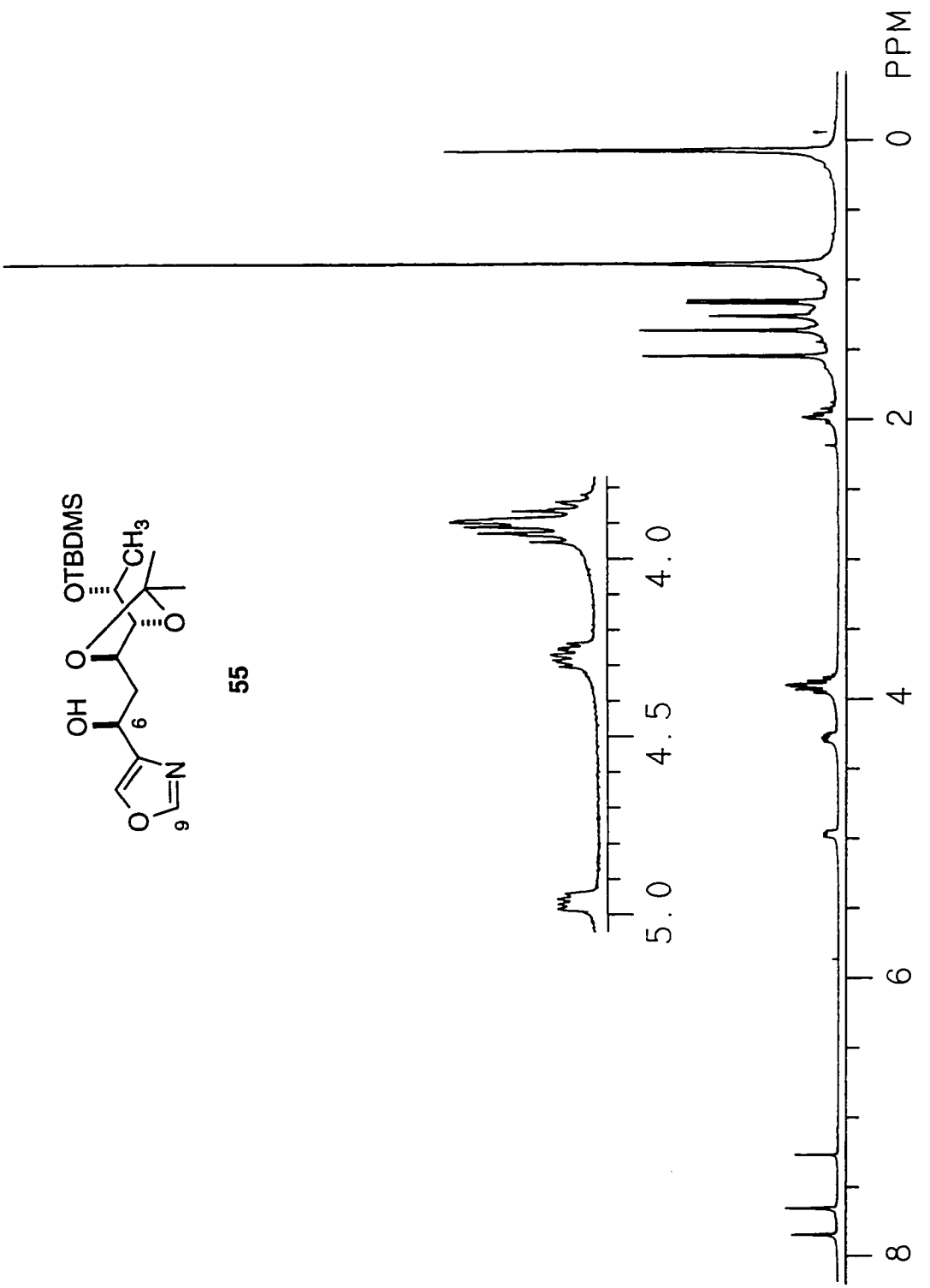


3. ^{13}C NMR 2-^{13}C-**37b** (50 atom %, Inset shows expansion of peak at 59.9 ppm, $CDCl_3$).

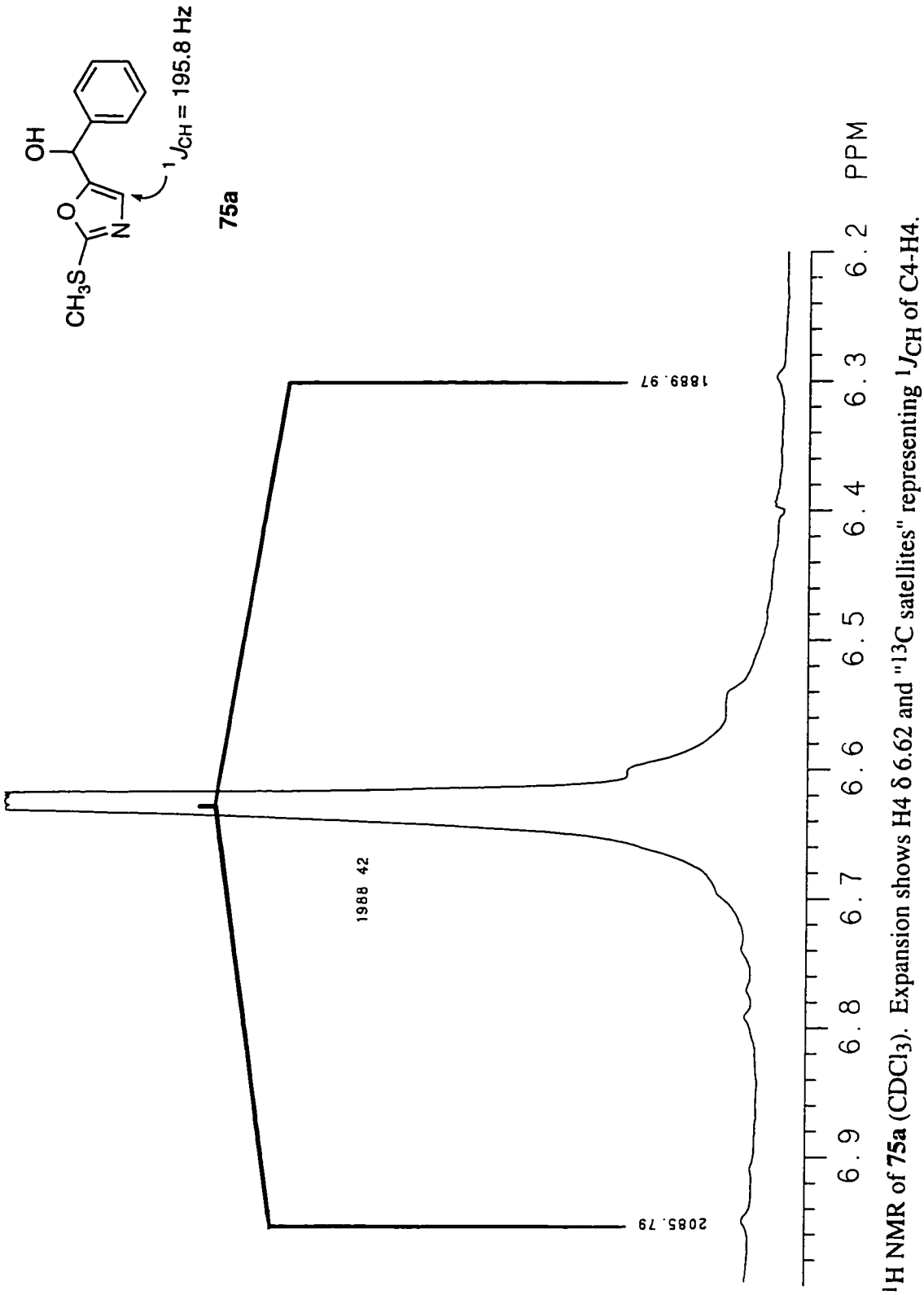


4. ^{13}C NMR expansion of **37b** and 2-^{13}C-**37b** (50 atom %, $CDCl_3$).

C2 and C3 of 2-^{13}C-**37b** are each split into a doublet giving an AB quartet. (Silverstein, R. M.; Bassler, G. C.; T.C.Morrill *Spectrometric Identification of Organic Compounds*; 5th ed.; John Wiley: New York, 1991)

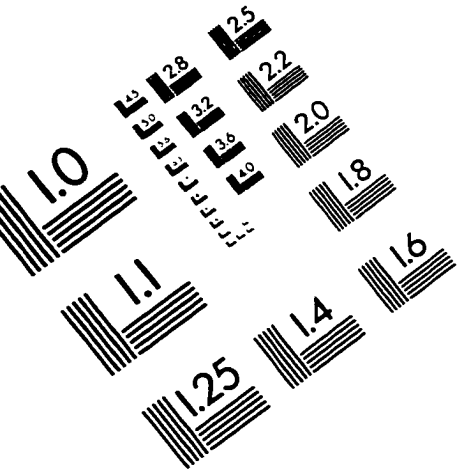


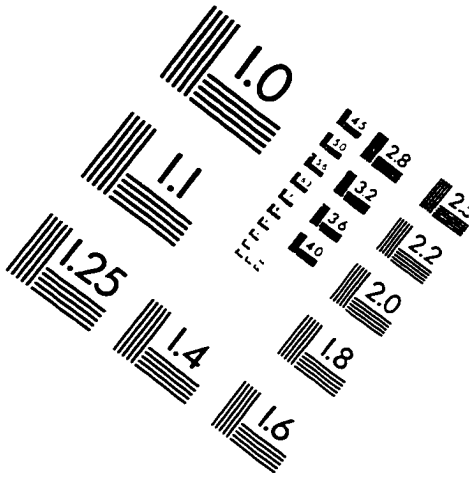
5. ^{1}H NMR of **55** ($CDCl_3$).

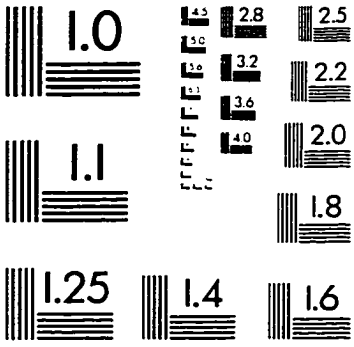


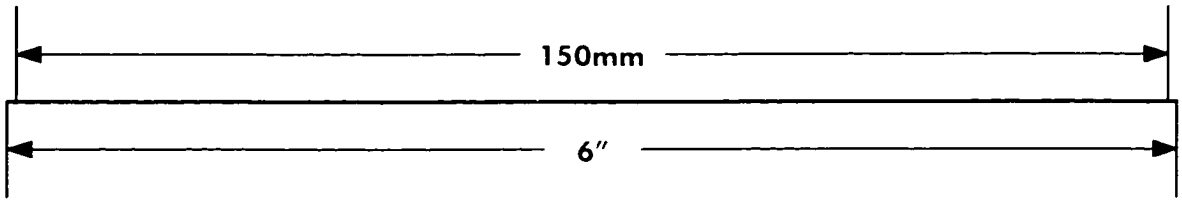
6. ^{1}H NMR of **75a** ($CDCl_3$). Expansion shows H4 δ 6.62 and "^{13}C satellites" representing $^1J_{CH}$ of C4-H4.

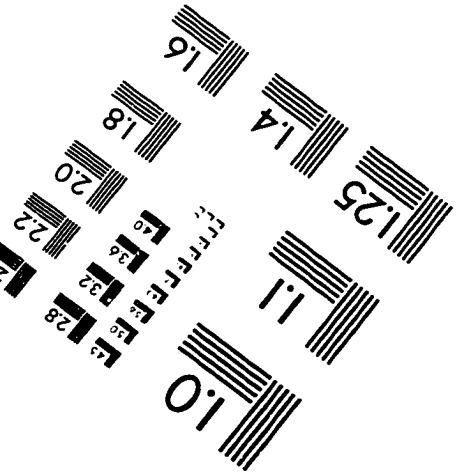
IMAGE EVALUATION
TEST TARGET (QA-3)











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