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Synthesis of Angiotensin-converting Enzyme (ACE) Inhibitors Using Dynamic Kinetic Resolution

Synthesis of the Highly Methylated Tryptophan Residue of Hemiasterlin Using Glycidic Ester Ring Opening Reactions

Synthesis of Benz(o)indenes

A thesis submitted to the
School of Graduate Studies and Research
University of Ottawa
in partial fulfillment of the requirements for
Doctor of Philosophy in the
Ottawa-Carleton Chemistry Institute
Department of Chemistry

University of Ottawa, Ottawa, Ontario, Canada, 1999.

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Abstract

This thesis consists of four separate chapters. The first three chapters contain a common theme; the diastereoselective synthesis of medicinally relevant compounds using Dynamic Kinetic Resolution (DKR). Unfortunately, in chapter three DKR could not be applied to our desired target, and an alternate route was found. This chemistry allowed for the preparation of two novel classes of *bis*-indole compounds. Chapter four is unrelated to the first three chapters and describes the synthesis of two tricyclic chiral ligand precursors, using known ring annulation techniques.

Chapter One:

DKR was applied to the preparation of the core structures of several Angiotensin-converting Enzyme (ACE) inhibitors. High levels of diastereoselectivity were observed in the DKR of [*R*]-pantolactone 2-iodo-4-phenylbutanoate with benyl and dibenzylamine, several chiral α-amino esters, and [*S*]-2-aminocaprolactam. The benzolactam core of benazepril was prepared by the DKR of [*R*]-pantolactone 2-iodo-4-(2-nitrophenyl)butanoate with benzylamine, and reductive cyclization of the resultant DKR product.

Chapter Two:

The treatment of α-halo [*R*]-pantolactone esters with various diamines resulted in the formation of optically active 6 membered heterocycles, via DKR mediated displacement of the halide followed by transamidation. Alternately, this reaction yielded diastereomerically enriched *bis*-α-amino esters when the chain length between the amines was greater than 3 carbon atoms. Similarly, α-halo [*R*]-pantolactone acrylates provided 6 membered heterocyclic esters, via a 1,4-Michael addition of one amine to the acrylate, followed by DKR mediated halide displacement by the second amine. Moderate to high levels of diastereoselectivity were observed in these reactions.

Chapter Three:

β,β-Disubstituted and β-monosubstituted glyoxylate esters reacted with substituted indoles and $SnCl_4$, to provide highly substituted tryptol derivatives in 45 to 70% yield. Conversion of these trytols to the corresponding azides was facilitated by the Mitsunobu reaction, however, it proved difficult to reduce these azides to the corresponding tryptophan derivatives. Ringing opening reaction using ZnI_2 as the Lewis acid provided access to α,α-*bis*(indolyl) esters. Modifications to this chemistry provided access to α,β-*bis*(indolyl) esters.

Chapter Four:

4,5-Benz-1-indene was prepared regioselectively, in 45-50% yield, after 5 steps, via a modified ring annulation/dehydration process. This new synthetic strategy dramatically increased the overall yield while simplifying the synthetic manipulations required for its preparation. A similar procedure was used in the preparation of a new ligand precursor 8,9,10,11-tetrahydro-4,5-benz(o)indene, in 22% overall yield, after 7 steps.

For my wife Jennifer, and my two sons,
Justin and Simon.

Acknowledgements

I would like to express my deepest thanks to Professor Tony Durst for his continuing support, guidance, and understanding. I truly appreciate the personal interest you have taken in my family. While allowing me to pursue my own ideas, you always managed to keep me focused on the goals we had set together.

Special thanks go to R. Capoor and Dr. G. Facey for NMR services, C. Kazakoff for mass spectral services, and Dr. G. Yap for the X-ray crystal structure of [*R*,*R*]-**23a**.

Thanks must also go to Chris Vanderwal and the rest of the Durst group for their continuing support and encouragement.

Most importantly, I wish to thank my wife Jennifer for supporting me through my studies, and for giving me two sons, Justin and Simon. I love you with all my heart. My only hope is to make you proud.

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Abbreviations

Å – angstroms

AgOTf – silver triflate

Bn – benzyl

Bn_2NH - dibenzylamine

$BnNH_2$ – benzylamine

br – broad

Bu – butyl

n-Bu4NI – tetra(*n*-butyl)ammonium iodide

^{t}Bu – *tert*-butyl

ca. – circa, about

cal'd – calculated

CH_2Cl_2 – methylene chloride

CH_3NO_2 – nitromethane

Cp – cyclopentadienyl

$(COCl)_2$ – oxalyl chloride

m-CPBA – *meta*-chloroperbenzoic acid

d – doublet

dd – doublet of doublets

ddd – doublet of doublet of doublets

DCC – 1,3-dicyclohexylcarboximide

DEAD – diethyl azodicarboxylate

DMF – dimethylformamide

DMSO – dimethylsulfoxide

DPPA – diphenylphosphorylazide

dt – doublet of triplets

Et - ethyl

Et_3N - triethylamine

equiv. – equivalent

HOBt – 1-hydroxybenzotriazole hydrate

hrs - hours

Me – methyl

MeOH - methanol

MHz – megahertz

NaI – sodium iodide

NaHMDS – sodium *bis*(trimethylsilyl)amine

NMR – Nuclear Magnetic Resonance

N_3 - azide

NOE – Nuclear Overhauser Effect

Nuc - nucleophile

OTf – trifluoromethanesulfonate; triflate

rac – racemic

pent – pentet

Ph – phenyl

Ph_3P - triphenylphosphine

ppm – parts per million

s – singlet

sept – septet

$SOCl_2$ – thionyl chloride

t – triplet

THF – tetrahydrofuran

TMEDA – tetramethylethylenediamine

TMSCl - chlorotrimethylsilane

TMSOTf – trimethylsilyl triflate

TsOH H_20 – *para*-toluenesulfonic acid, monohydrate

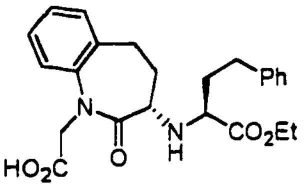
q - quartet

Chapter One

Synthetic Studies Towards the Synthesis of Benazepril

1.0 Introduction

Captopril, Enalapril, Lizinapril, and Benazepril (**1**) comprise a series of potent Angiotensin-converting Enzyme (ACE) inhibitors used in the clinical treatment of hypertension related diseases.[1] Despite the fact that these ACE inhibitors are all patented compounds with highly refined syntheses, we thought that they would make interesting synthetic targets to demonstrate the versatility of our Dynamic Kinetic Resolution (DKR) strategies.

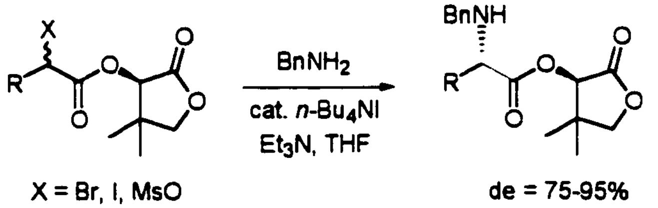


1

These compounds all contain the unnatural α-amino ester residue [*S*]-2-amino-4-phenylbutanoate (the right hand portion of **1**). The central benzolactam core of benazepril also displays (*S*)- stereochemistry. We envisioned the introduction of both of these chiral centres using DKR.

The DKR of α-bromo [*R*]-pantolactone esters (**2**) was first reported by Durst and Koh.[2] Treatment of a THF solution of **2** with benzylamine, triethylamine, and a catalytic quantity of *n*-Bu_4NI or NaI preferentially yielded [*S*,*R*]-**3** in >50% yield and 75 to 95% de. This resolution stratedy is termed Dynamic Kinetic Resolution.

2



[S, *R*]-**3**

This chapter outlines our synthetic route to benazepril and other ACE inhibitors using DKR. The mechanism of DKR is briefly discussed. Additionally, a brief description of the physiological mechanism of the Renin-Angiotensin system and the development of the above ACE inhibitors will be presented.

1.1 The Renin-Angiotensin System

The physiological importance of the renin-angiotensin system has been known for well over 50 years.[3] In the last 20 years concerted efforts have been made to target this system in the therapeutic treatment of hypertension and related diseases. The importance of this system stems from its various humoral vasoconstrictor and vasodilator mechanisms that have been implicated in blood pressure regulation and electrolyte homeostasis. The octapeptide angiotensin II has been identified as the end product of the renin-angiotensin system. One of the most potent vasoconstrictor agents known, angiotensin II plays a critical role in controlling blood pressure and aldosterone levels in mammals; aldosterone is known to act on the kidneys and is involved in electrolyte homeostasis.[3]

The renin-angiotensin system is depicted below in Figure 1.1.

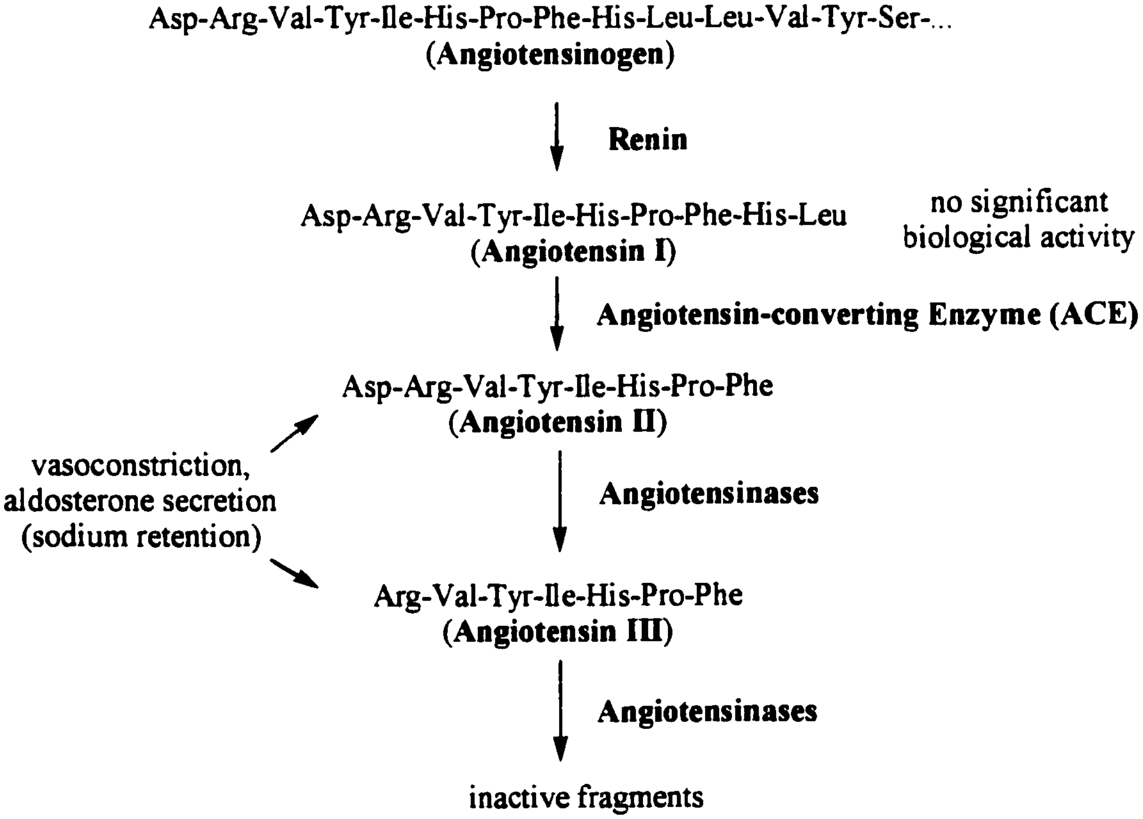


Figure 1.1: The Renin-Angiotensin System

The first step in the renin-angiotensin system involves the formation of angiotensin I, a decapeptide fragment, which displays no significant biological activity. Angiotensin I is derived from the cleavage of the Leu-Leu peptide bond of the α-globulin angiotensinogen, by low molecular weight renin.[3] Angiotensin II is derived from angiotensin I by the hydrolysis of the Phe-His peptide bond, by the COOH-terminal dipeptidyl peptididase, Angiotensin-converting Enzyme (ACE). Upon binding to receptors found in various smooth muscle tissues, angiotensin II produces one of the strongest vasoconstriction responses known for naturally occurring substrates.[3]

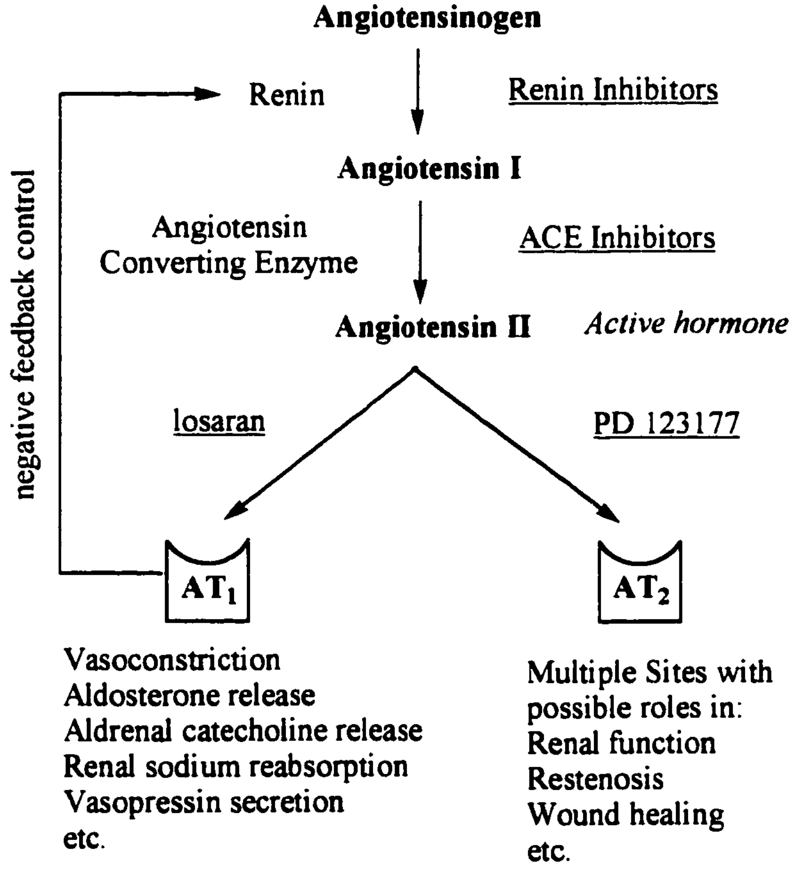


Figure 1.2: Angiotensin II Receptors in the Renin-Angiotensin System

Two angiotensin II receptor subtypes have been identified and these have been designated as AT_1 and AT_2.[4] The AT_1 receptor mediates most of the known angiotensin II physiological functions, such as vasoconstriction and aldosterone release. The functions associated to AT_2 are less well known, but AT_2 has been implicated in renal-free water clearance, restenosis following vascular injury, collagen synthesis in cardiac fibroblasts, and the depressor response to angiotensin II in rats.[4]

Angiotensin II is degraded to angiotensin III by a variety of angiotensinases. Angiotensin III has been linked to increased aldosterone secretion, however, it displays diminished vasoconstrictive properties as compared to angiosensin II. Subsequent angiotensinase mediated degradation of angiotensin II and III, to biologically inactive fragments, completes the renin-angiotensin sequence.[3]

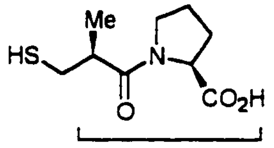
ACE has also been shown to degrade brandykinin, a vasodilator and natriuretic peptide, to an inactive heptapeptide, further demonstrating the central role this enzyme plays in blood pressure regulation and electrolyte homeostasis.[3]

Control of the renin-angiotensin system has been pursued at several key points in the system, as shown in Figure 1.2. Despite its high binding specificity, renin inhibitors have been developed which 'tie-up' the renin, preventing the formation of angiotensin I.[5] Similarly, ACE inhibitors have been developed which mimic angiotensin I, suppressing the formation of the vasoconstrictor octapeptide, angiotensin II.[1] More recently, increased attention has been turned to angiotensin II receptor antagonists, as fewer known side effects (such as ACE inhibitor induced rashes and 'ACE induced cough') are related to these medications.[1,4,5]

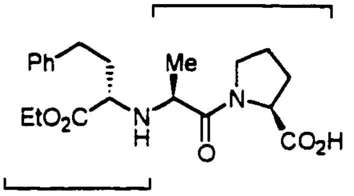
Inhibition of ACE has been the focus of a variety of research efforts, with benazepril being the latest of these ACE inhibitors to be commercialized. ACE is a plasma soluble enzyme which has been isolated from most mammalian species; human, hoarse, bovine, pig, rat, mouse etc. This enzyme has been found in most organ tissues, with the highest concentrations being found in the lung plasma membrane.[1] To our knowledge no X-ray crystal structure has been obtained, but from structure activity relationships, much has been inferred about the active site structure. ACE has been shown to be a Zn^{2+} containing enzyme. A terminal carboxylate binding site, one amide hydrogen bonding site, and three hyrdophobic regions have been identified. From this knowledge a 'hypothetical active site' has been proposed, as seen in Figure 1.3 (Section 1.2.1).[7]

1.2 Angiotensin-converting Enzyme (ACE) Inhibitors

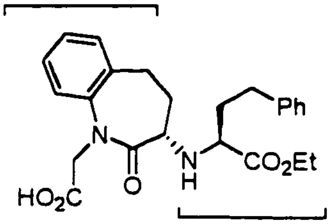
Several ACE inhibitors have been developed and commercialized in the past 20 years. The most notable of these compounds include captopril(**4**),[7] enalapril (**5**),[8] and benazepril (**1**).[9] More recently, compounds based around the caprolactam core similar to **1** have also been reported and advanced to clinical trials.[1a, 10] Some of these compounds are shown below.



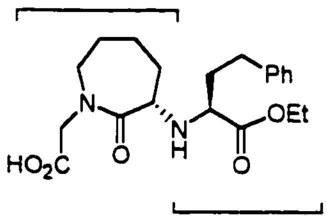
Captopril (Capoten)
4; IC$_{50}$ = 23 nm



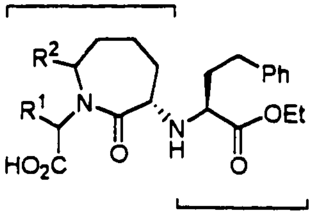
Enalapril (Vasotec)
5;IC$_{50}$ = 3.8 nm



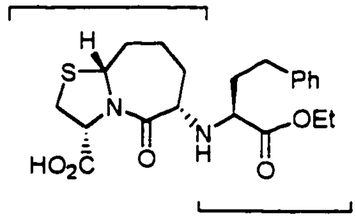
Benazepril (Lotensin)
1; IC$_{50}$ = 1.7 nm



IC$_{50}$ = 19 nm



IC$_{50}$= 7 to 8 nm



IC$_{50}$ = 0.6 nm

The structural similarities between these compounds can be readily observed and are highlighted in brackets. These similarities are a direct result of the chronological development of these drugs.

The ACE inhibitor captopril was one of the first class of pharmacologically active drugs developed as a 'by product analog'. The importance of this approach in the design of modern pharmaceuticals can not be overlooked. For this reason the history of the ACE inhibitors will be briefly outlined in the next section.

1.2.1 Captopril

Bayer and Wolfenden reported in 1973 that enzyme specific substrates could be developed that closely mimicked the hydrolysis products of enzymatic reactions. Benzylsuccinic acid was found to be a successful 'by-product analogue' in the inhibition of pancreatic carboxypeptidase A.[11] ACE and carboxypeptidase A were believed to be similar in function and structure. With this in mind, Cushman and Ondetti pursued "active-site-directed inhibitors" which would mimic the binding modes of angiotensin I, in a manner similar to the 'by-product analogues' developed for the inhibition of carboxypeptidase A.[7a]

Succinyl-*L*-proline (9) resembled the ACE hydrolysis products of angiotensin I (as seen in Figure 1.3) and was found to be a weak, but specific ACE inhibitor.[7]

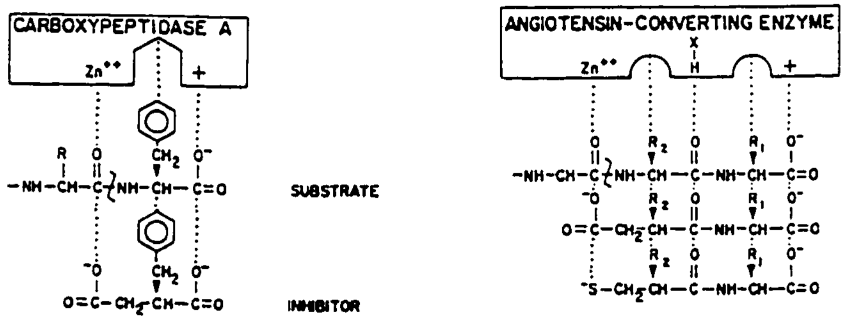
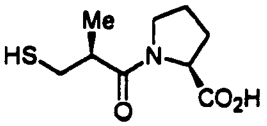


Figure 1.3: Hypothetical Active Site of ACE (adapted from reference 7b)

Succinyl-*L*-proline displayed low levels of ACE inhibition and poor intestinal uptake, after oral administration. A large number of variations were made to the general structure of succinyl-*L*-proline, before the mercapto side chain of captopril was tested. Inclusion of a [*R*]-methyl group α to the amine carbonyl greatly increased the *in vitro* IC_{50} to 1.7 x 10^{-8} M^{-1}, to yield captopril (4) as a highly active, orally available ACE inhibitor.[7]



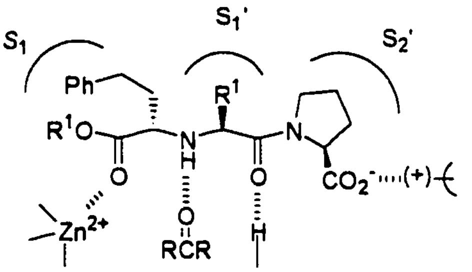
4

Captopril, like succinyl-*L*-proline, fit the hypothetical active site model as shown in Figure 1.3. At physiological pH the mercapto moiety acts as a weakly binding Zn^{2+} ligand, the amide carbonyl allows for hydrogen bonding within the active site, and the proline carboxylate interacts with a positively charged binding site. Removal or inversion of stereochemistry of any of these groups resulted in decreased inhibition and enzymatic specificity.

Clinical trials showed captopril to be very effective in the treatment of hypertension with the most common side effects involving rashes, loss of taste and 'captopril induced cough.' These side effects were attributed to the mercapto functionality of captopril.[12] Despite these side effects, captopril was the first compound in this class to come to market for the treatment of hypertension in humans, under the trade name Capoten.

1.2.2 Enalapril (MK-421) and Lisinopril

Enalapril (**5**) and lisinopril (**10**) were both developed in the early 1980's, and displayed similar structures and ACE activities as captopril.[8] Enalapril and lisinopril were developed in accord with the active site-inhibitor binding modes of captopril, as illustrated below.



5; $R^1 = CH_3$, $R^2 = C_2H_5$
10: $R^1 = (CH_2)_4NH_2$, $R^2 = H$

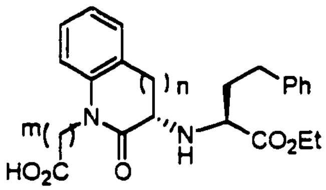
Figure 1.4: Binding of enalapril and lisinopril to the hypothetical ACE active site

Three hydrophobic pockets were identified in the hypothetical active site of ACE, S1, S1' and S2. These pockets are occupied by the phenethyl, R^1, and proline methylene functionalities, respectively. The ester carbonyl acts as a Zn^{2+} ligand, the amide carbonyl and amine allow for hydrogen bonding within the active site, and the proline carboxylate interacts with positively charged residues in the active site.[8]

These compounds still retain the peptide backbone of captopril, but lack the troublesome mercapto functionality. Clinical trials showed that enalapril and lisinopril both displayed ACE inhibition levels comparable to those observed for captopril. Enalapril was shown to be orally active and was marketed under the trade name Vasotec. Lisinopril showed poor oral activity, but is in use as an intervenous cardiac drug.

1.2.3 Benazepril

The search for more structurally ridged compounds which would display increased hydrophobic binding at the S_2' pocket, centred upon modification of the proline ring. The most successful of these variations involved the insertion of fused 6, 7, and 8 membered benzolactams, into the enalapril backbone. The benzolactam core acted as a conformationally restricted proline/alanine peptidomimetic.



n = 1-3, m = 1,3

Parson and coworkers[9] found that compounds containing 7 and 8 membered benzolactams (n = 2 and 3), and short terminal carboxylic acid chains (m=1), demonstrated high levels of ACE inhibition, with benazepril (**1**) (n = 2, m = 1, *in vitro* $IC_{50} = 2.8 \times 10^{-9}$M) entering clinical trails.

As predicted, benazepril re-enforced the hypothetical active site scheme first proposed for captopril. The fused benzolactam was accommodated by the S1'/S2' hydrophobic pocket, while the phenethyl, ethyl ester and terminal carboxylate moieties closely resembled the binding modes of Enalapril.

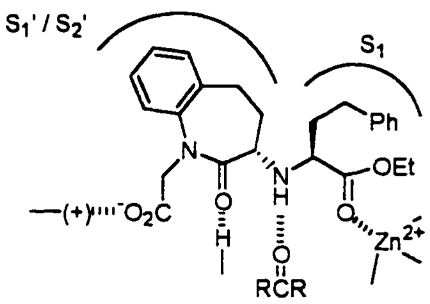


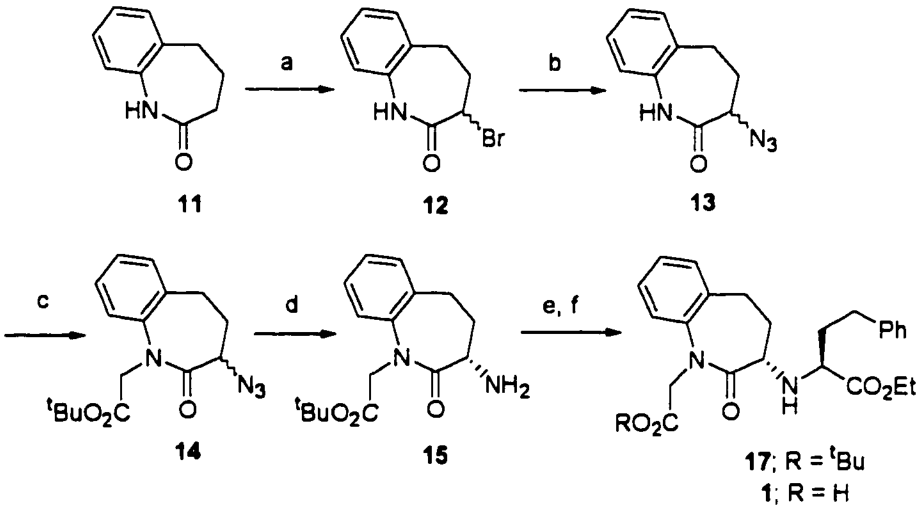
Figure 1.5: Binding Modes of Benazepril to the Hypothetical ACE Active Site

Benazepril displayed better oral activity that either captopril or enalapril, and during the course of clinical trials was shown to be active over a 24 hr period. This made benazepril the only 'once a day' treatment for hypertension, known at that time. Benazepril is currently available under the trade name Lotensin.

1.3 Synthesis of Benazepril

The first synthesis of benazepril was reported by Parson and began with benzolactam **11** (see Scheme 1.1).[9] α-Bromination of **11** with phosphorus pentachloride and molecular bromine, was followed by bromine displacement with sodium azide to provide compound **13**.

Scheme 1.1 : Parson's Synthesis of Benazepril[9]

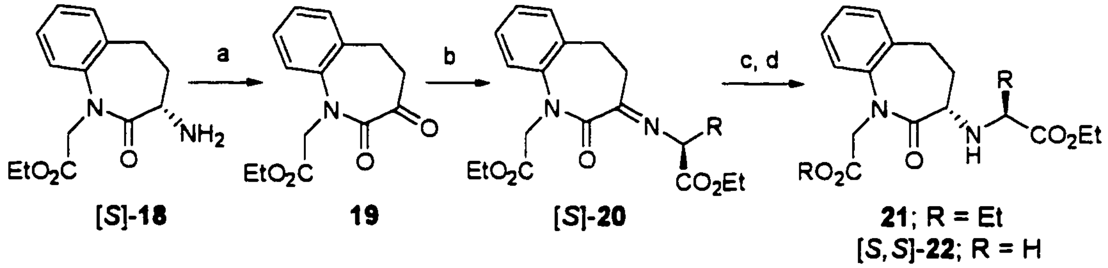


a) i) PCl_5, ii) Br_2, b) NaN_3, DMF, c) i) NaH, THF, ii) $ICH_2CO_2{}^tBu$, d) H_2, Pd/C; chromatographic separation, e) i) $C_6H_5(CH_2)_2COCO_2C_2H_5$ (**16**), $NaCNBH_3$, C_2H_5OH, f) CF_3CO_3H.

The terminal carboxylic moiety was inserted as the ^{t}butyl protected ester by treatment of compound **13** with NaH in THF, followed by ^{t}butyl 2-iodoacetate. Reduction of azide **14** with hydrogen, over Pd/C, provided compound **15**. Separation of [*R*]-**15** and [*S*]-**15** was performed by silica gel chromatography. The 4-phenylbutanoate side chain was inserted by treating [*R*]-**15** with ethyl 2-oxo-4-phenylbutanoate (**16**) and $Na(CN)BH_3$ in ethanol, to provide [*S*,*S*]-**17** as the major product. Deprotection of the *tert*-butyl protecting group with trifluoroacetic acid, provided access to benazepril, [*S*,*S*]-**1**.

Stanton, Watthey and coworkers developed a variation on this synthetic route,[13] in order to prepare a wide range of Benazepril derivatives. High *in vivo* activities, similar to those observed for enalapril and benazepril, were observed with oral doses of compound, where $R=CH_2CH_2NH_2$, $R'=H$ (lisinopril side chain).

Scheme 1.2 : Stanton's Synthesis of Various Benazepril Analogues[13]

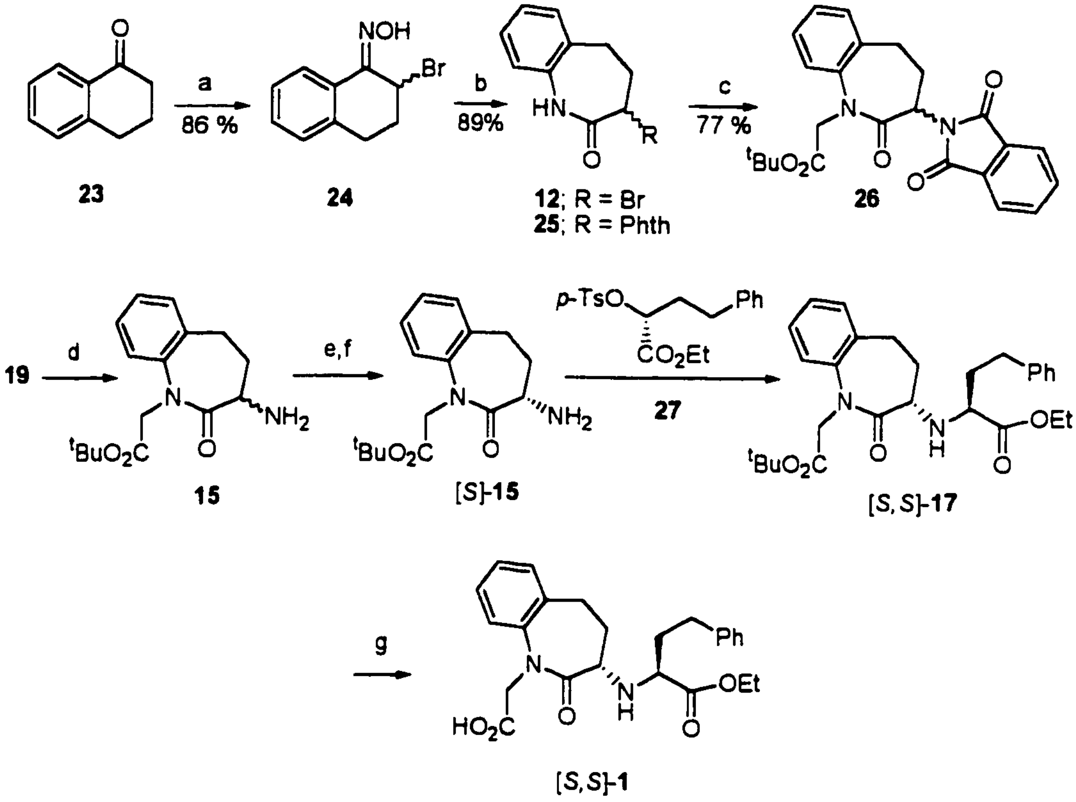


a) i) ^{t}BuONO, $CHCl_3$, ii) *m*-chloroperbenzoic acid, b) i) L amino ester, (n-Bu)$_2$SnCl, c) $NaBH_3CN$, AcOH, d) NaOH, MeOH

Oxidation of [*S*]-3-amino-1-[(ethoxycarbonyl)methyl]-2,3,4,5,-tetrahydro-1*H*-1-benzazepin-2-one (**18**) with *tert*-butylnitrite, followed by *m*-chloroperbenzoic acid, yielded the α-ketoamide **19**. Imine [*S*]-**20** was prepared by the condensation of the α-ketoamide **19** with the appropriate L-amino ester, in the presence of di-*n*-butyltin chloride. Reduction of [*S*]-**20** with $NaBH_3CN$ provided diastereomeric mixtures of the amino diesters **21**. Separation of diastereomers was performed using silica gel chromatography or preparative HPLC. Finally, selective hydrolysis of the amino diesters was performed using one equivalent of NaOH in methanol, to yield the benazepril analogues [*S*,*S*]-**22**.

Wetter and coworkers reported a third, related synthesis of benazepril.[14] α-Bromination of α-tetralone (**23**) with bromine was followed by oxime formation with hydroxylamine hydrochloride, to provide the 2-bromooxime **24**. Treatment of **24** with polyphosphoric acid resulted in ring expansion to the 2-bromobenzolactam **12**. Displacement of bromine with potassium phthalimide yielded intermediate **25**.

Scheme 1.3 : Wetter's Synthesis of Benazepril[14]

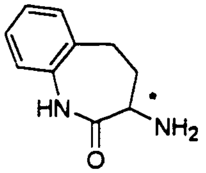


a) Br_2, $NH_2OH{\cdot}H_2O$, b) polyphosphoric acid, c) i) K-phthalimide, ii) ^tBuOK, $BrCH_2CO_2{}^tBu$, d) $NH_2CH_2CH_2OH$, e) *L*-tartaric acid, f) NaOH, g) HCl.

Again, *tert*-butyl bromoacetate was used to install the acetic acid side chain, to provide ester **26**. Treatment of **26** with ethanolamine yielded the racemic amine **15**. Separation of diastereomers was accomplished by treating racemic **15** with (+)-*L*-tartaric acid, and selectively recrystallizing the corresponding (+)-L-tartaric acid/[*S*]-**15** salt from ethanol. The free amine [*S*]-**15** was provided by treating the (+)-L-tartaric acid/[*S*]-**15** salt with NaOH. Treatment of [*S*]-**27** with [*S*]-**15** allowed for insertion of the 2-amino-4-phenylbutanoate side chain, yielding [*S*,*S*]-**17**. Deprotection of the acetic acid side chain with HCl provided benazepril (**1**) in diastereomerically pure form.

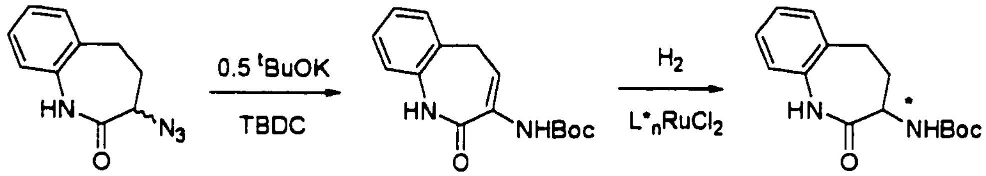
These three syntheses display several distinct similarities; the use of racemic bicyclic starting materials, similar intermediates, insertion of the carboxylic acid moiety via the amide anion of compound **12** and $XCH_2CO_2{}^tBu$, and the need to separate diastereomers at some point in the synthesis. Although the yields at each of the individual steps are generally quite reasonable, the need to separate diastereomers severely limited the quantities of benazepril available from these synthetic routes.

Several research groups have turned their attention to the synthesis of optically active 3-amino-2,3,4,5-tetrahydro-1*H*-[1]benzazepin-2-one, benzolactam **27**.[15] The more successful of these approaches are described below.



27

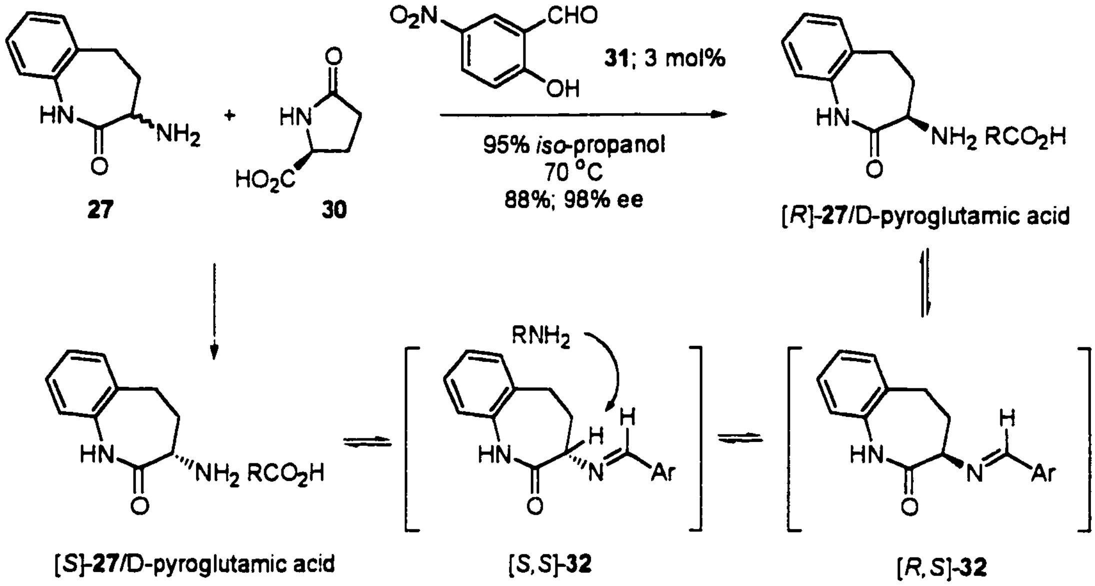
Researchers at Merck recently reported the enantioselective reduction of enamine **28**, using chiral ruthenium based hydrogenation catalysts.[16]



(*S*)-BINAP $RuCl_2$; 9:91 *R/S*; 80%
(*R*)-BINAP $RuCl_2$; 82:18 *R/S*; 56%

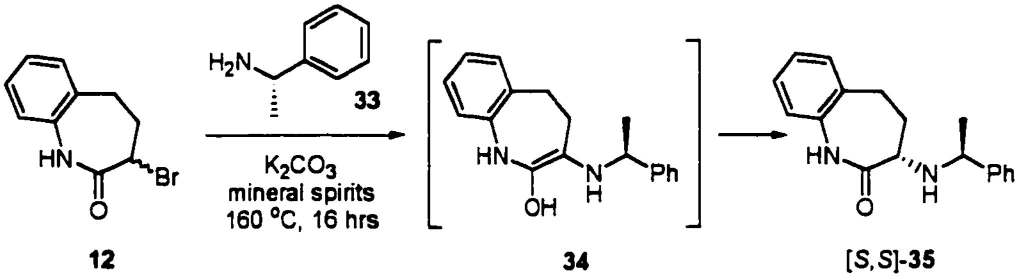
The Boc protected benzolactam **29** was obtained as either the [*R*]- or [*S*]-enantiomer, depending on the ligand system used. These reductions displayed high levels of enantioselectivity, however, the yields were poor.

In the same paper, this group described the resolution of *rac*-**27**, using an unprecedented racemization/resolution reaction. The optimal reaction conditions were found to involve treating *rac*-**27** with D-pyroglutamic acid (**30**) and a catalytic quantity of 5-nitrosalicylaldehyde (**31**; 3 mol%). When aqueous *iso*-propanol was used as the solvent, the mixture of diastereomeric pyroglutamic acid salts was observed to epimerize if a catalytic quantity of aldehyde was added.



The observed epimerization must have been the result of the increased acidity of the methylene proton at C3 of the benzaldimines **32**. After refluxing these salts for 48 hours, in the presence of **31**, the [*R*]-**27**/D-pyroglutamic acid salt was obtained in 88% and 98% ee from a racemic mixture of **27**.

By heating **12** with (*S*)-α-methylbenzylamine and K_2CO_3, in odourless mineral spirits, Shiel and co-workers at Novartis have prepared [*S*,*S*]-**35** in 88% and >98% ee.[17]



The diastereoselectivity was shown to be highly dependent on both the temperature and the duration of heating. Epimerization was believed to be the result of thermally induced formation of enol **34**.

Clearly, these new methodologies greatly reduce the cost of preparing large quantities of optically active **27**.

1.4 Retrosynthetic Synthesis of Benazepril From [*R*]-Pantolactone 2-Iodo-4-(2-nitrophenyl)butanoate

We thought that benazepril (**1**) could be synthesized using simple extensions of previously developed DKR strategies (see Section 1.5). The synthesis of **1** would feature two DKR steps and one reductive cyclization. The following retro-synthetic analysis summarizes our approach.

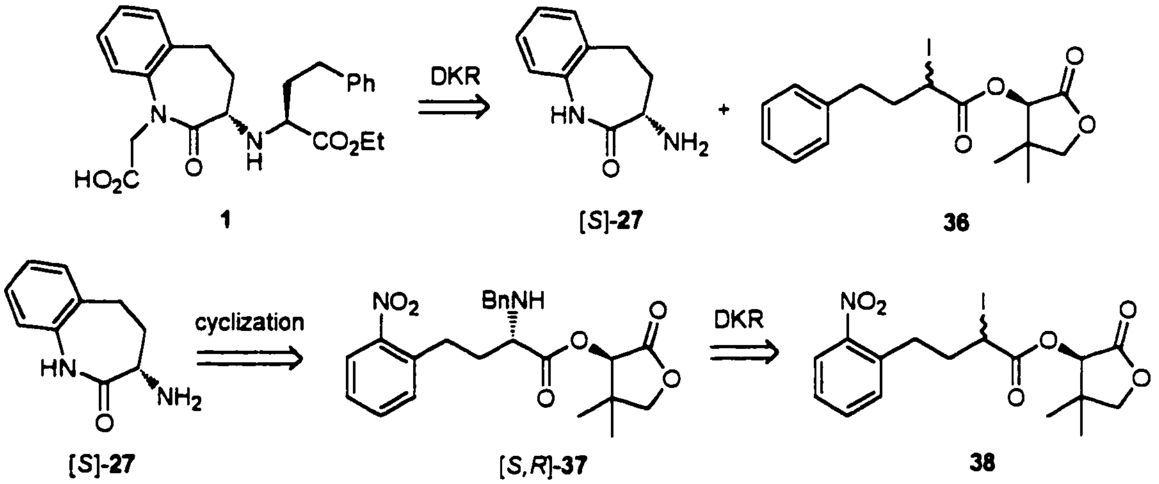
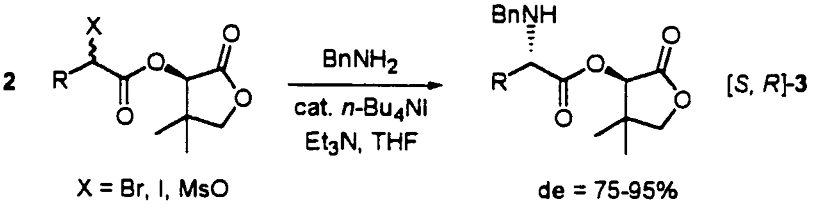


Figure 1.6: Retro-synthetic Approach to the Synthesis of Benazepril Using DKR

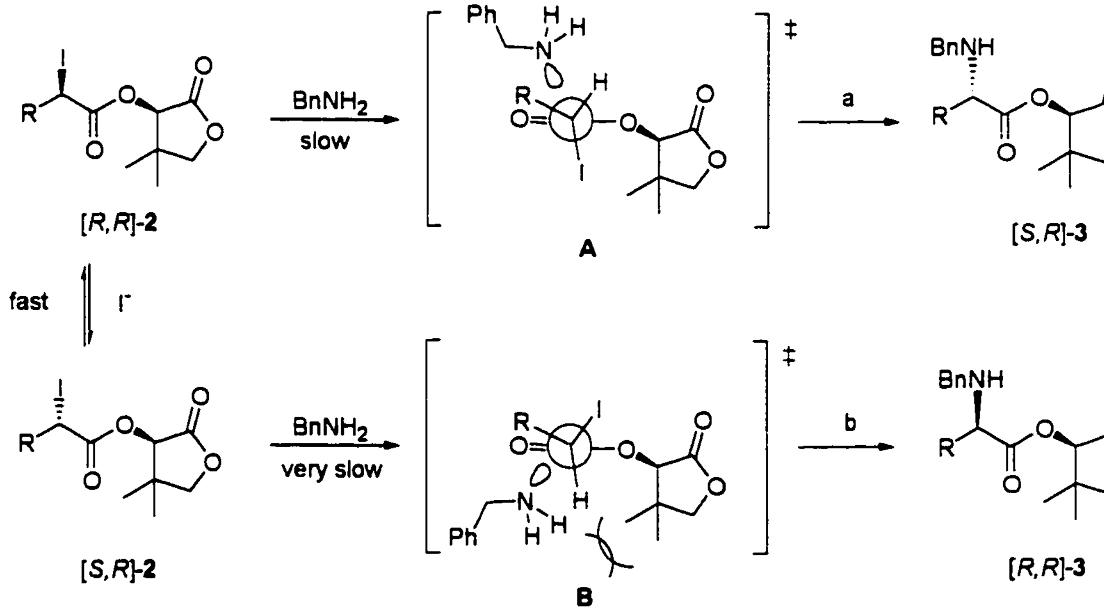
Treatment of the [*R*]-pantolactone ester **36** with [*S*]-**27**, under DKR conditions, will allow for diastereoselective insertion of the [*S*]-2-amino-4-phenylbutanoate side chain. The benzolactam core, [*S*]-**27**, will be prepared by reductive cyclization of [*S*,*R*]-**37**. Ester [*S*,*R*]-**37** will be prepared with high levels of diastereoselectivity by the DKR resolution of the [*R*]-pantolactone ester **38** with benzylamine, or dibenzylamine, under DKR conditions. In this way we will have demonstrated the application of DKR to a pharmaceutically important target. We were not attempting to compete with the current commercial processes, but simply to illustrate the utility of this method, which clearly differs from the various known preparations of chiral α-amino acids and their derivatives.

1.5 Dynamic Kinetic Resolution

Dynamic Kinetic Resolution (DKR) has been shown to be a highly effective and selective means of introducing chirality into organic compounds.[18] Durst *et al.* investigated the S_N2 displacement of bromine from [*R*]-pantolactone α-bromo esters by benzylamine.[2] High levels of diastereoselectivity were observed when the reactions were run in THF solvent, using one to two equivalents of Et_3N, and catalytic quantities of either NaI or *n*-Bu_4NI.



The mechanism by which this reaction occurs is depicted below.

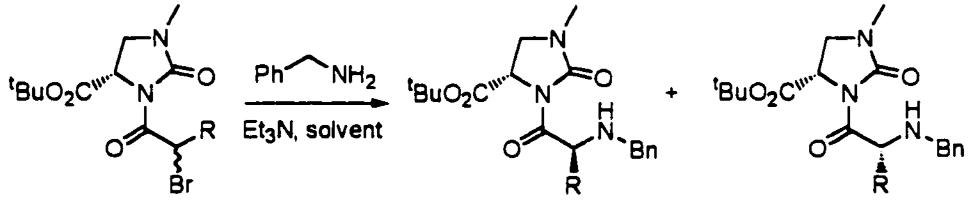


Rapid halide induced epimerization between [*S*,*R*]-**2** and [*R*,*R*]-**2**, is followed by slow halide displacement by benzylamine. The *gem*-dimethyl moiety of [*R*]-pantolactone hinders the S_N2 approach of benzylamine to [*S*,*R*]-**2**, transition state **B**, thereby making the formation of [*R*,*R*]-**3** energetically unfavorable. No such hindrance is evident in the

S_N2 displacement of halide by benzylamine when going from [*R*,*R*]-**2** to [*S*,*R*]-**3**, transition state **A**. The different rates of halide displacement, coupled with the rapid epimerization of **2** allows for the majority of starting material to be 'funneled' into path **a**, yielding [*R*,*S*]-**3** as the major reaction product.[19]

Computer modeling of the ground state conformations adopted by both [*R*,*R*]- and [*R*,*S*]-**2**, suggested that the ester carbonyl preferred to lie perpendicular to the carbonyl group of [*R*]-pantolactone, as depicted in transition states **A** and **B**. Additionally, the bromine was found to lie perpendicular to the ester carbonyl, while the R group eclipsed the ester carbonyl. These early calculations by Durst and O'Meara[20] were confirmed by myself using Semi-Empirical (AM1 and PM3) calculations and by the X-ray crystal structure of [*R*,*R*]-**2**, where R = ^{t}Bu (see Chapter 3, Section 3.3).[21]

Nunami and coworkers reported that 2-oxoimidazolidine-4-carboxylate was an effective chiral auxiliary for the 'Kinetic Resolution' of α-haloamides.[22]

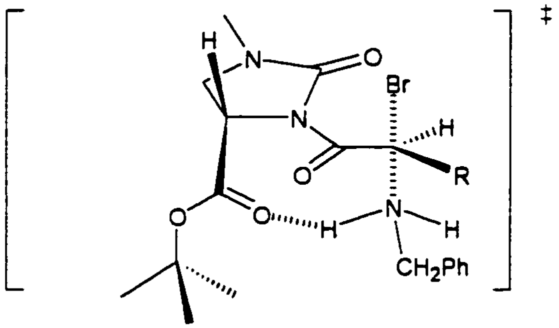


39 **[*S*,*S*]-40** **[*S*,*R*]-40**

Durst and co-workers demonstrated that in THF solvent, *n*-Bu_4NI or NaI acted as effective epimerizing agents for **39**, allowing for the DKR of **39** with benzylamine.[23] Under standard DKR conditions [*S*,*R*]-**40** was obtained as the sole product. In subsequent reports, Nunami and coworkers[24] have used more polar solvents such as DMSO and HMPA. Under these conditions Et_3N was basic enough to act as the epimerizing agent. Again, [*S*,*R*]-**40** was obtained (R=Me, HMPA, 98% de) as the sole product. DKR was implicated in both reports, with the only significant difference being the solvent polarity, and the choice of epimerizing agents.

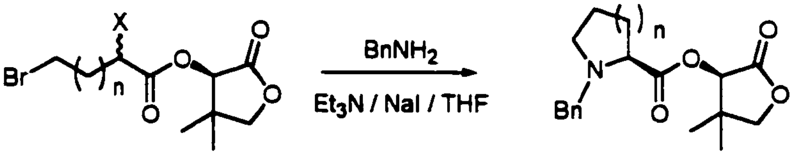
These results seem to be counter intuitive. One would expected that the bulky ^{t}butyl ester would act to shield one face of **39** from attack by benzylamine, providing

[*S*,*S*]-**40** as the major product. Clearly, this is not the case. Nunami suggested that the polar nature of the solvents used in his studies allowed for hydrogen bonding between the incoming benzylamine and the $^tBuO_2C$ carbonyl (shown below).[24] This 'coordination' of the benzylamine allowed for the S_N2 attack to occur from the same side of the molecule as the $^tBuO_2C$ moiety, yielding [*S*,*R*]-**40** as the major diastereomer.



If this hypothesis is correct, a similar mechanism should be at work in the less polar THF solvent. Molecular modeling studies performed on this system provided inconsistent results.[21] The multiple ground state rotamers of both [*S*,*S*]- and [*S*,*R*]-**39** differ by only 1-2 kcal/mol. All of these conformations should be accessible at room temperature, making predictions about the ground state structure of **39** meaningless. The accuracy, implications, and significance of these calculations are currently in question and will not be discussed further.

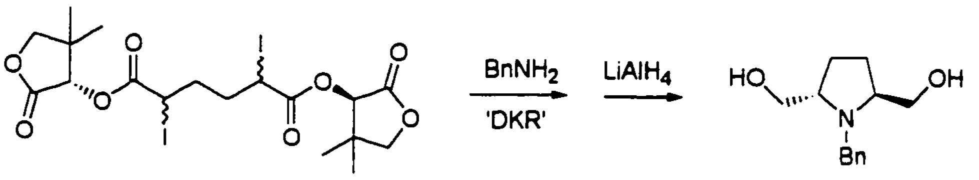
DKR has been applied to the synthesis of a variety of natural and unnatural α-amino acids and their derivatives. Several variations on this theme have been made, allowing for access to structurally interesting compounds. Treatment of the dibromo [*R*]-pantolactone esters **41** or **42**, with benzylamine, under DKR conditions, provided N-substituted prolines (**43**) and pipecolinic acids (**44**), respectively.[2b]



41; n = 1
42; n = 2

43; n = 1, 70%, 5:1 [*S,R*]/[*R,R*]
44; n = 2, 68%, 10: 1 [*S,R*]/[*R,R*]

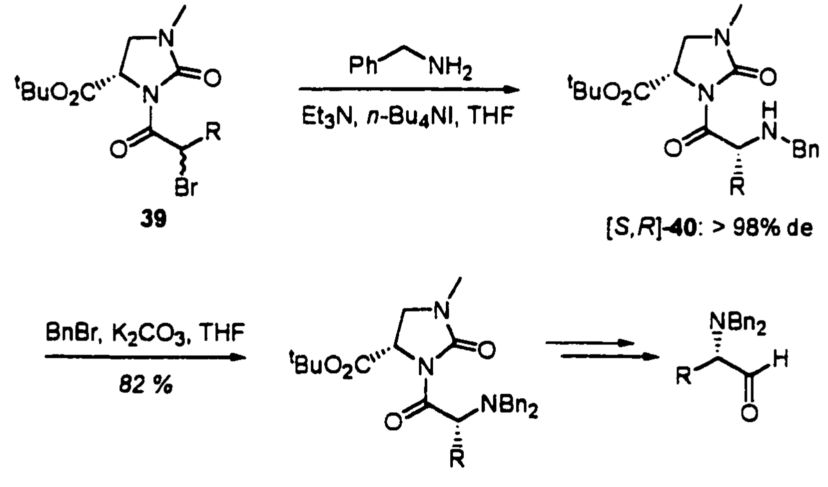
In a related reaction, the double DKR of the *bis*-α-iodo [*R*]-pantolactone ester **45** provided access to the C2 symmetric diol **46**.[2b]



45

46; 35 % - single isomer

More recently, Durst and O'Meara have demonstrated the utility of DKR in the diastereoselective synthesis of Reetz aldehydes from α-halo amides.[25] As before, the DKR of **39** provided [*S*,*R*]-**40** as a single diastereomer. Benzylation of [*S*,*R*]-**40** provided [*S*,*R*,]-**47**, which was converted to the Reetz aldehyde [*S*]-**48**.



39

[*S*,*R*]-**40**: > 98% de

[*S*,*R*]-**47**

[*S*]-**48**

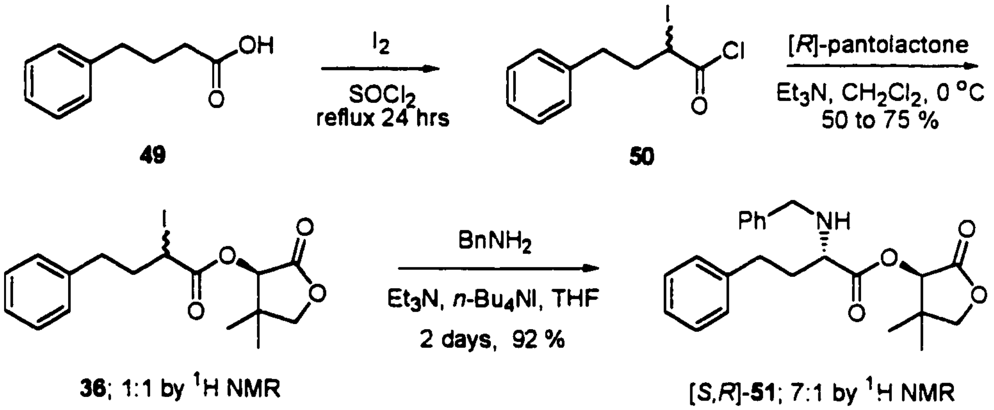
Clearly, DKR is a very powerful route into α-amino acids, esters, and aldehydes. This methodology should be applicable to a wider range of molecular structures and motifs. This chapter addresses several investigations in this area.

1.6 Results

The following section summarizes recent work dealing with the application of DKR to the synthesis of several well known ACE inhibitors. Initial studies focused on the synthesis of the (*S*)-2-amino-4-phenylbutanoate side chain of these compounds, using benzylamines as nucleophiles. Subsequent work dealt with the use of α-amino esters and (*S*)-2-aminocaprolactam as nucleophiles. The remaining discussion deals with the synthesis of the benzolactam core of benazepril, using DKR.

1.6.1 Synthesis of the (*S*)-2-Amino-4-phenylbutanoate Side Chain

The first step in our approach to the synthesis of various ACE inhibitors involved the synthesis of the 2-amino-4-phenylbutanoate side chain, common to the ACE inhibitors discussed in Sections 1.2. We were pleased to find that this moiety was readily prepared in good yield and moderate diastereoselectivity using our DKR methodology.



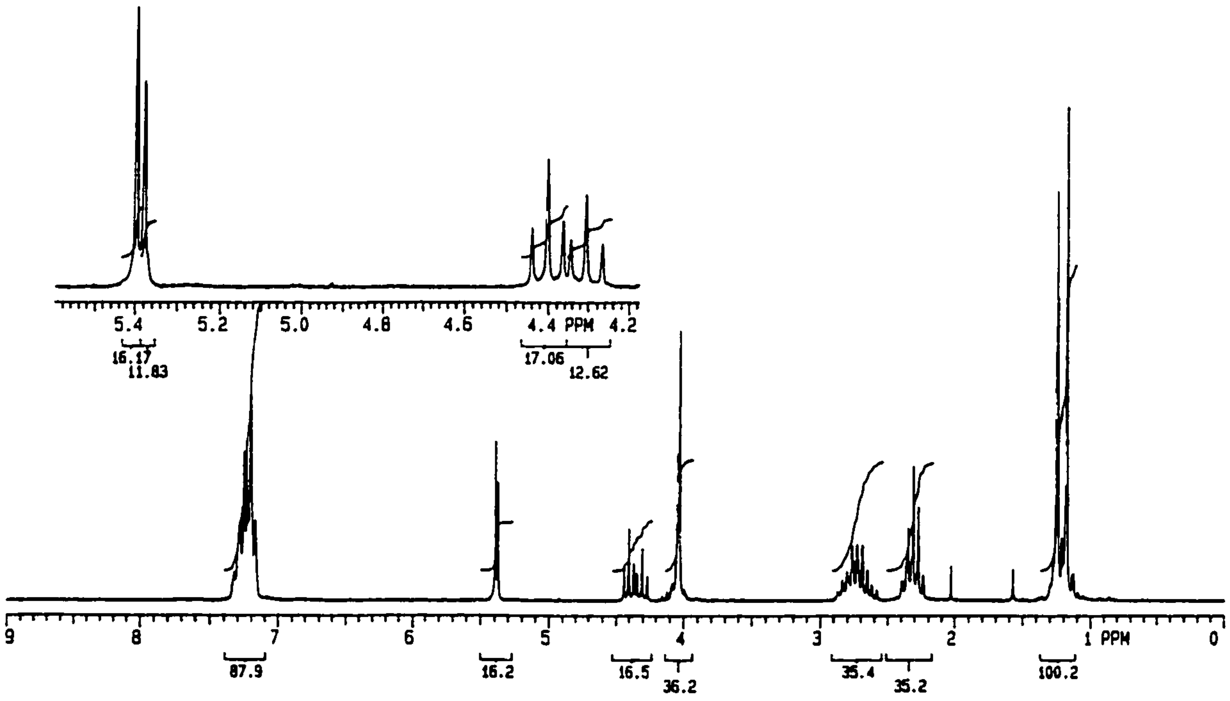
49

50

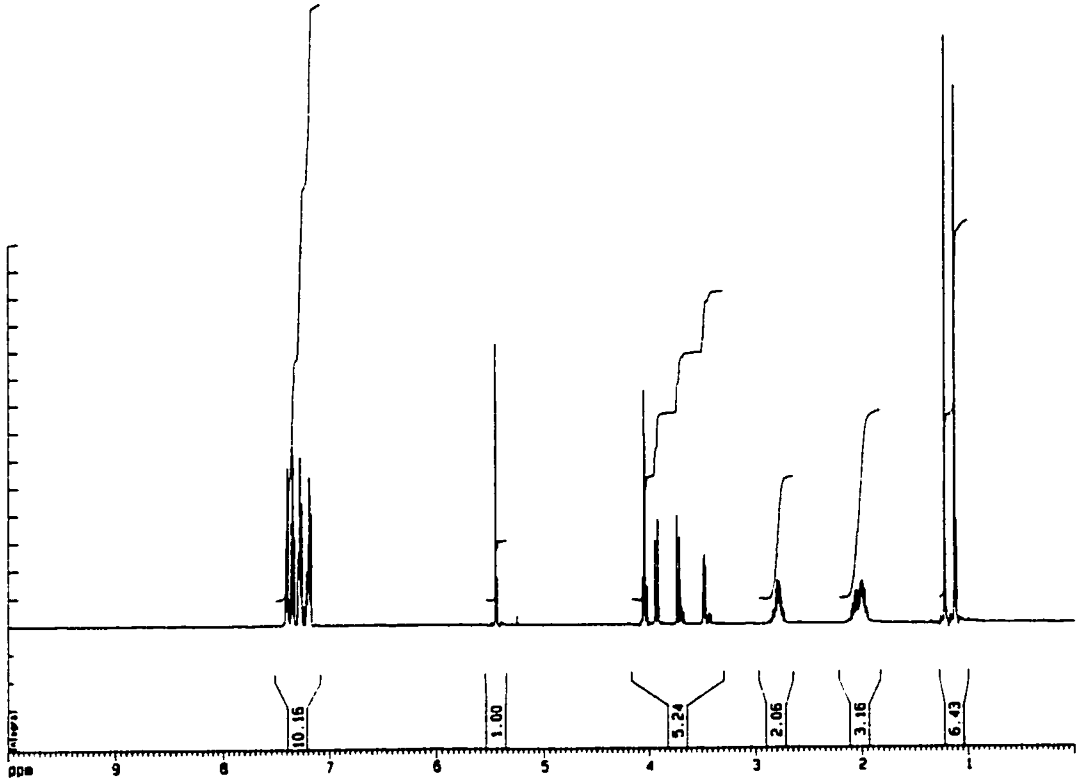
36; 1:1 by ^1H NMR

[*S*,*R*]-**51**; 7:1 by ^1H NMR

The α-iodo [*R*]-pantolactone ester **36** was prepared via a two step sequence. Commercially available 4-phenylbutanoic acid (**49**) was dissolved in neat $SOCl_2$. After refluxing this solution for 30 minutes, iodine (0.6 equiv.) was added in one portion.[26] The resulting purple solution was refluxed for an additional 12 hours, before excess $SOCl_2$ was removed *in vacuo* to provide crude **50**. After being 'pumped on' (0.1 torr) for 1 to 2 hours, this crude oil was taken up in CH_2Cl_2 and added, via cannula, to a cold (0 °C) CH_2Cl_2 solution of [*R*]-pantolactone (1 equiv.) and Et_3N (2 equiv.). After stirring at room temperature over night the crude ester was treated to an aqueous work up and



Spectrum 1.1 : 200 MHz ^{1}H NMR Spectrum of Ester **36**



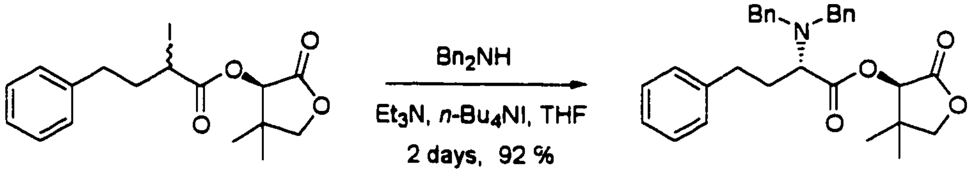
Spectrum 1.2 : 500 MHz ^{1}H NMR Spectrum of [*S*,*R*]-**51**

purified by silica gel chromatography, eluting with 3:1 hexanes/ethyl acetate, to provide pure ester **36** as a 1:1 mixture of diastereomers, in 50 to 75% yield.

The 2:3 diastereomeric ratio observed for **36** was clearly visible using standard 200 or 500 MHz ^{1}H NMR spectroscopy. Both the α-protons and the *gem*-dimethyl protons of these two diastereomers displayed separate resonances, with *good* base line separation, even at 200 MHz (see Spectrum 1.1). This resonance shift is characteristic of α-substituted [*R*]-pantolactone esters, and unless stated other wise, was the method used to determine the diastereoselectivity of the following reactions (see Spectrum 1.2).

Treatment of a 0.5 M solution of **36**, in THF, with benzylamine (1 equiv.), Et_3N (1 equiv.), and *n*-Bu_4NI (0.05 equiv.), provided the desired displacement product [*S*,*R*]-**51**, after stirring at room temperature for 48 hrs. The diastereoselectivity was observed to be approximately 7:1, by 500 MHz ^{1}H NMR spectroscopy. The absolute stereochemistry of the [*S*,*R*]-**51** was not independently confirmed, but is based on previous experience in our lab. The moderate yield (50%) and diastereoselectivity (72% de) that was observed in this reaction was disappointing.

Fortunately, when the above reaction was run using dibenzylamine in place of benzylamine, the diastereoselectivity increased significantly.



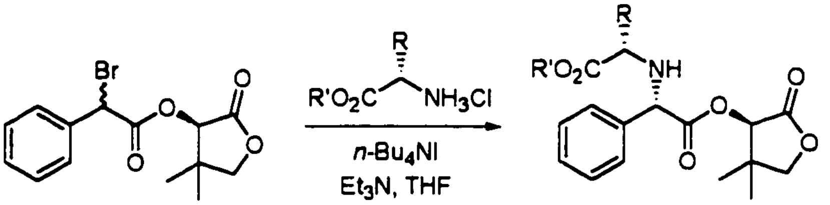
36

[S,*R*]-**52**; 20:1 by ^{1}H NMR

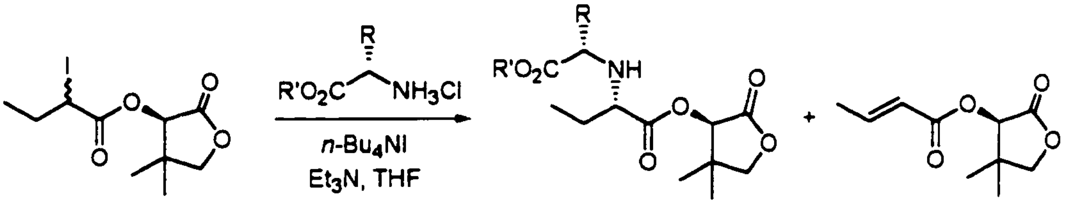
Ester [*S*,*R*]-**52** was obtained in 89% yield as a 20:1 mixture of diastereomers, making this a highly effective method of preparing (*S*)-2-amino-4-phenylbutanoate esters.

1.6.2 DKR of Ester 36 with α-Amino Esters

In earlier work, Koh and Durst showed that α–amino esters could be used in the DKR of [*R*]-pantolactone α-bromophenylacetate (**53**), providing [*S*,*S*,*R*]-**54** in high yields and high diastereomeric excess. When similar reactions were performed on aliphatic substrates such as **55**, the desired product, [*S*,*S*,*R*]-**56**, was isolated in low yields but high levels of diastereoselectivity. The major product isolated was identified as [*R*]-**57**, the result of halide elimination from compound **55**.[2b]

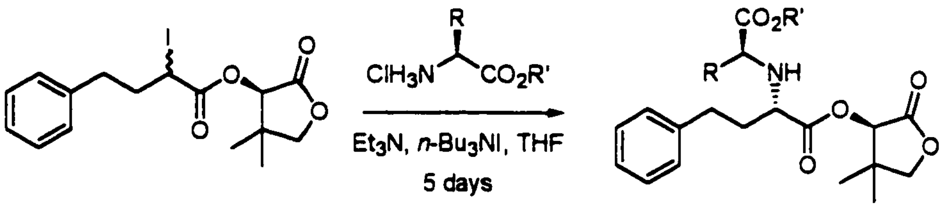


53 [*S*,*S*,*R*]-**54**



55 [*S*,*S*,*R*]-**56** [*R*]-**57**

Undaunted by this elimination process, we decided to investigate the use of α-amino esters in the DKR of compound **36**. Although the observed diastereoselectivities were very good, the yields were fair to poor, and only two α-amino ester substrates were tolerated.



36

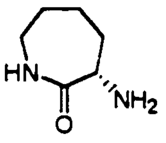
[*S*,*S*,*R*]-**58**; R = H, R' = Et; 50 %, 98% d.e.
[*S*,*S*,*R*]-**59**; R = CH_2Ph, R' = ^tBu; 25 %, 98 % d.e.

The above reactions were run in THF solvent (0.5M in **36**), using equamolar quantities of **36** and the α-amino ester, 2 equiv. of Et_3N, and 10 mol% of *n*-Bu_4NI. After stirring at room temperature for 5 days the reactions were subjected to an aqueous work-up and purified by silica gel chromatography. L-Glycine ethyl ester provided [*S,S,R*]-**58** as a clear oil in 50% yield, and as a single diastereomer, as seen by 500 MHz ^1H NMR spectroscopy. L-Phenyl alanine butyl ester provided [*S,S,R*]-**59** in 25% and 98% de. Reactions involving L-alanine, L-valine, and L-serine provided none of the desired products.

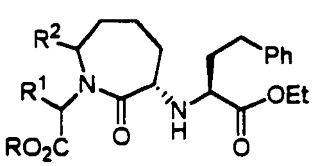
Interestingly, the crude reaction mixtures contained no starting material, and generally less than 5% of elimination products, as seen by the ^1H NMR spectrum of the crude reaction mixture. We are uncertain as to why the yields never exceeded those listed above. The low yields may be a result of unfavourable steric interactions or be the result of a match/mismatch phenomenon. Additional study is required to fully understand this system.

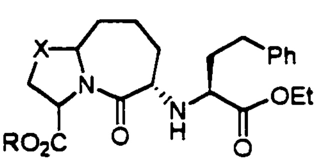
1.6.3 DKR of Ester 36 with (*S*)-2-Aminocaprolactam

Several groups have investigated the use of cyclic lactam peptidomimetics, for the replacement of the proline-valine portion of enalapril (**5**).[1,10] Freidinger's lactam[27] (**60**) has received considerable attention, as seen by the following structures:



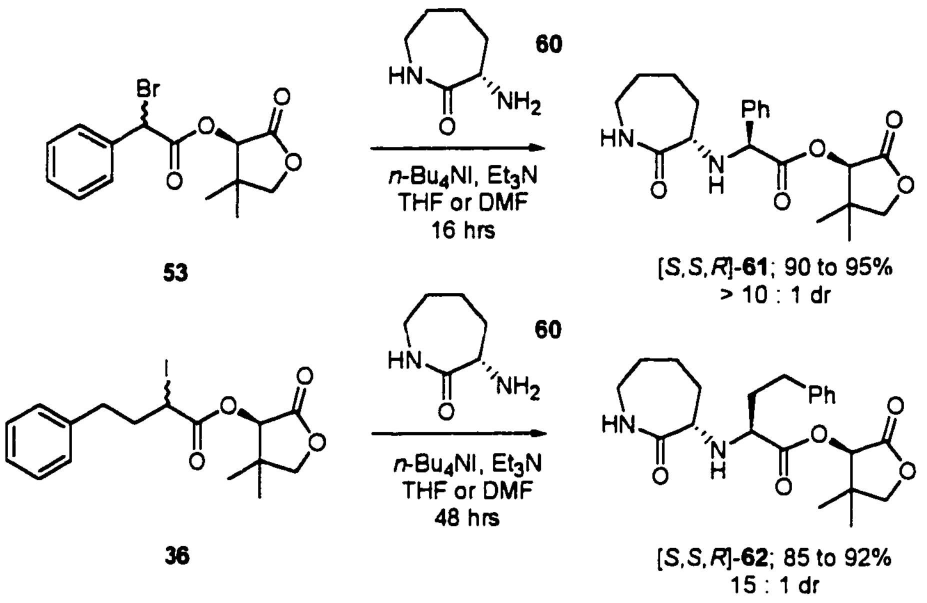
60





X = S, CH_2

(*S*)-2-Aminocaprolactam (**60**, Freidinger's lactam) was found to be an effective nucleophile for the DKR reaction, providing the corresponding amino acid derivatives in high yield, and high diastereomeric excess.



[*S*,*S*,*R*]-**61**; 90 to 95%
> 10 : 1 dr

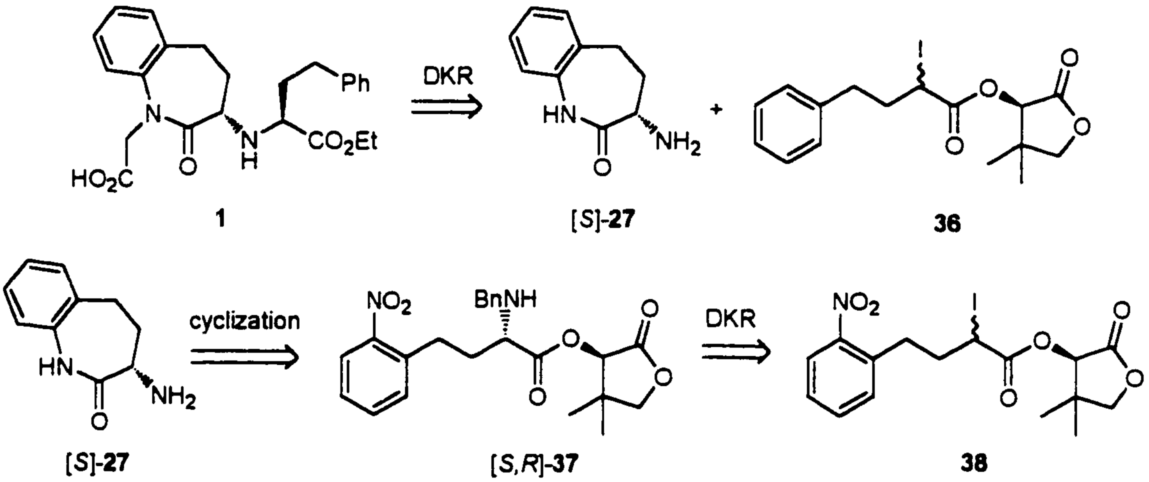
[*S*,*S*,*R*]-**62**; 85 to 92%
15 : 1 dr

Equimolar quantities of either ester **53** or **36** were stirred in THF solvent (0.5 M in the ester), with 1 equiv. of **60**, 1 equiv. of Et_3N, and 10 mol% *n*-Bu_4NI; DRK conditions. As was expected, the reaction involving ester **53** provided [*S*,*S*,*R*]-**61** in high yield and with a diastereomeric ratio of approximately 10:1. Surprisingly, when ester **36** was used, the desired product, [*S*,*S*,*R*]-**62** was obtained in 85 to 92% yield, as a 15:1 mixture of diastereomers. Both compounds were obtained optically pure, as seen by their ^{1}H NMR spectra, in >75% yield after a single recrystallization from methylene chloride/hexane solutions. No elimination product was observed in the ^{1}H NMR spectrum of the crude product.

The above reactions displayed similar yields and diastereoselectivities whether they were run in THF or DMF solvent. The reactions were finished in 16 to 48 hrs, with yields generally exceeding 85%. The speed of these reactions and the high yields obtained, were in sharp contrast to the reactions involving α-amino esters (see Section 1.6.2). We currently do not understand why lactam **60** was an effective nucleophile, while simple α-amino esters were not. These questions are currently being addressed.

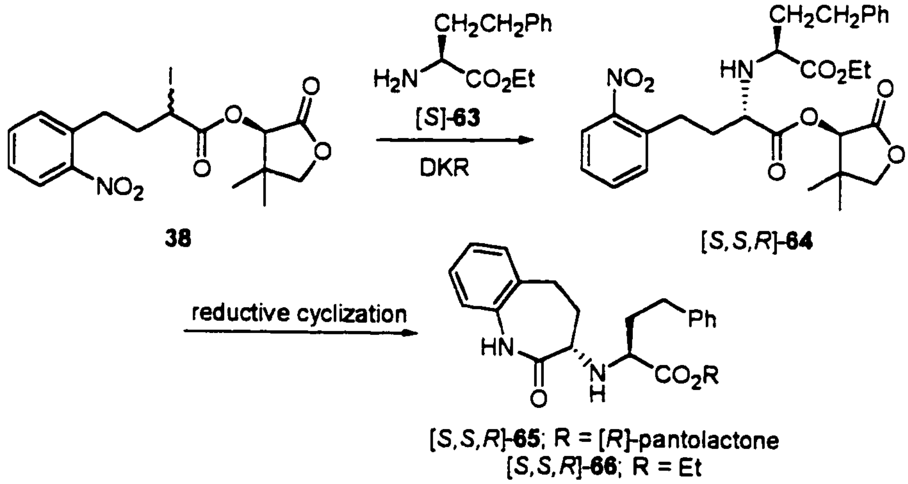
1.6.4 Synthesis of Benazepril Via Dynamic Kinetic Resolution

Revisiting the retrosynthetic analysis of benazepril (**1**) one finds two *S*-stereocentres, both of which we intended to install using DKR. The (*S*)-2-aminobutanoate side chain will be constructed by the treatment of the [*R*]-pantolactone ester **36** with (*S*)-[**27**].



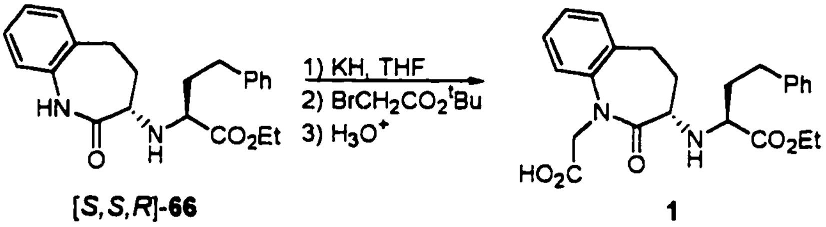
DKR of **38** with benzylamine, provided [*S*,*R*]-**37** in high diastereomeric purity. Reductive cyclization of [*S*,*R*]-**37** provided the benzolactam core [*S*]-**27**

A second approach was also considered. Again, this method would involve two DKR steps and one reductive cyclization. This route is presented in Scheme 1.5. The α-amino ester [*S*]-**63** would be prepared via DKR, as described earlier. Treatment of ester **38** with [*S*]-**63**, under DKR conditions, would provide [*S*,*S*,*R*]-**64**.



Scheme 1.5 : Alternate approach to Benazepril

Reductive cyclization of [*S*,*S*,*R*]-**64** would allow for access to the benzolactam core and the 4-phenylbutanoate side chain of benazepril in one step. Insertion of the acetic acid side chain, as described in the literature will complete the synthesis.



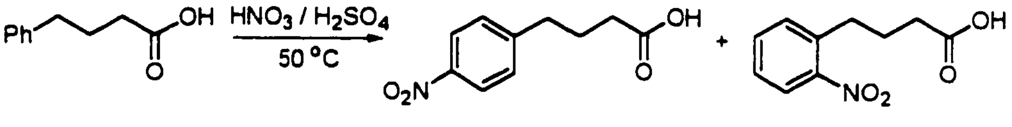
We chose to pursue the first of these synthetic routes and results of this study are presented in the following pages.

1.6.5 Synthesis of 4-(2-Nitrophenyl)butanoic Acid

In order to prepare the benzolactam core of benazepril significant quantities of 4-(2-nitrophenyl)butanoic acid, **67**, would be required in order to prepare the α-iodo ester **38**. Several different routes to this compound were explored. The results from these studies are summarized below.

1.6.5.1 Direct Nitration of 4-Phenylbutanoic Acid

The most direct route to this material involved nitration of the aromatic ring of commercially available 4-phenylbutyric acid. Nitration was carried out in concentrated nitric acid, pre-warmed to 50 °C, by the drop wise addition of concentrated sulfuric acid (1 equiv.) over a period of five minutes. After stirring at 50 °C for 2 hours, the addition of ice water resulted in the formation of a white precipitate. Filtration of the solid yielded a 2:1 ratio of the *para* and *ortho* substituted acid **67**, in 95% yield.



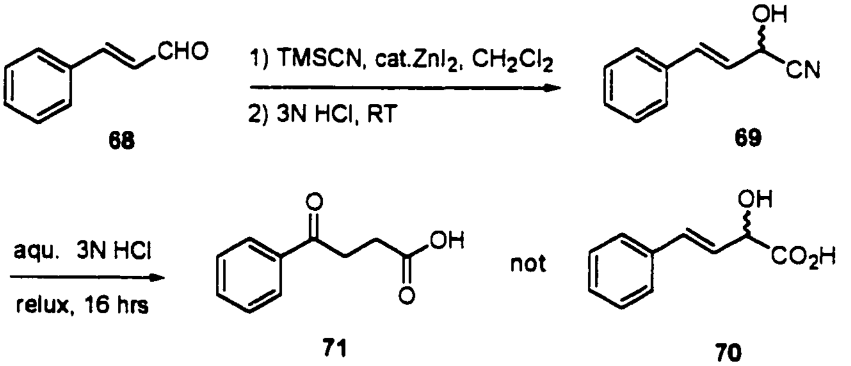
para-**67** *ortho*-**67**

The *para* isomer was found to crystallize preferentially from cold diethyl ether. In this way fractional recrystallization allowed for the removal to the undesired *para* isomer as a solid, yielding *ortho* enriched filtrates. A single recrystallization improved the isomer ratio from 2:1 *para/ortho* to approximately 2:1 *ortho/para*. Subsequent recrystallizations gave varied degrees of improvement in the *ortho/para* ratio. In one instance *ortho*-**67** was obtained 95% pure. Unfortunately, this was not a reproducible result. Additionally, this pure material only amounted to approximately 1 g of *ortho*-**67** from 25 g of the original 2:1 *para/ortho* mixture. Attempts to separate the methyl esters of **67** by silica gel chromatography also failed. Clearly, a more efficient route was required.

1.6.5.2 4-Phenylbutanoic Acids From Cinnamaldehydes and TMSCN

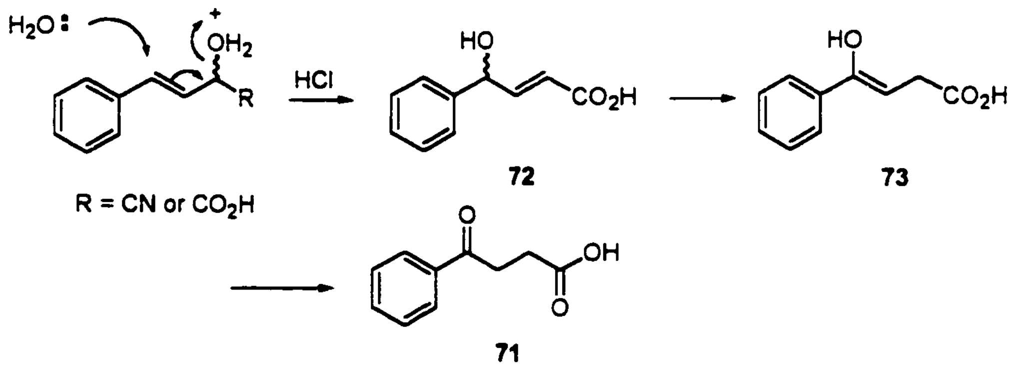
A second route that was explored involved the treatment of cinnamaldehydes with TMSCN, to provide the corresponding cyanohydrins. We had hoped that this route would provide quick access to 2-hydroxy-4-phenylbutanoic acids, which would be converted to the desired [*R*]-pantolactone ester **38**. Unfortunately, this was not the case.

Treatment of *trans*-cinnamaldehyde (**68**) with TMSCN, followed by aqueous 3N HCl, provided cyanohydrin **69**, in near quantitative yield.[28] Attempts to hydrolyze the cyano group by refluxing **69** in aqueous 3N HCl did not yield the expected α-hydroxy acid **70**. Instead, compound **71** was obtained in greater than 90% yield.



68 **69** **71** **70**

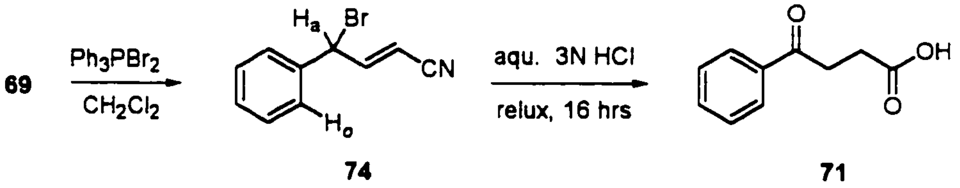
This was a surprising result, but may be explained if one considers the following mechanism:



72 **73** **71**

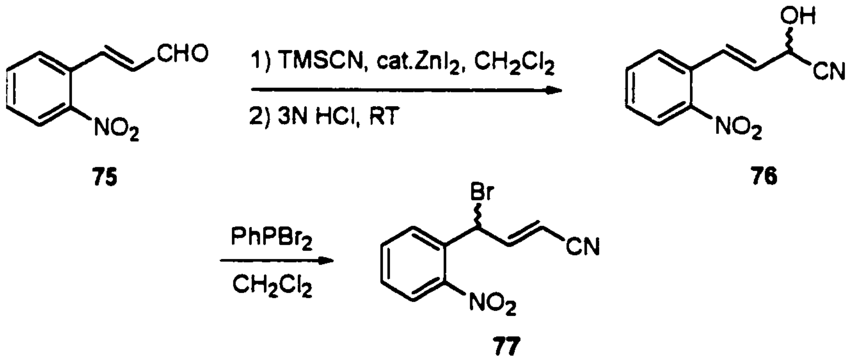
Protonation of the cyanohydrin hydroxyl group of **69** allowed water to attack the double bond via an S_N2' mechanism, giving rise to intermediate **72**. Deconjugation of the double bond provided enol **73**, which tautomerized to yield the observed product, compound **71.**

Similar reactivity was observed during attempts to convert **69** to the corresponding α-halo cyanide. Addition of **69** to a CH_2Cl_2 solution of Ph_3PBr_2,[31] provided compound **74** in 78% yield.

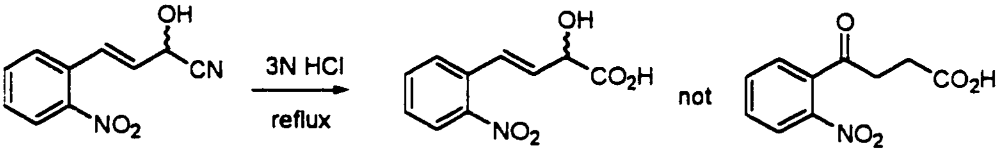


The structure of **74** was confirmed by NOE difference ^1H NMR spectroscopy, as a positive NOE was observed between H_a and the *ortho* protons of the aromatic ring, H_o. When **74** was refluxed in 3N HCl, compound **71** was obtained as the sole product

When *trans*-2-nitrocinnamaldehyde (**75**) was used, slightly different chemistry was observed. Again, treatment of **75** with TMSCN provided quantitative yields of **76**.



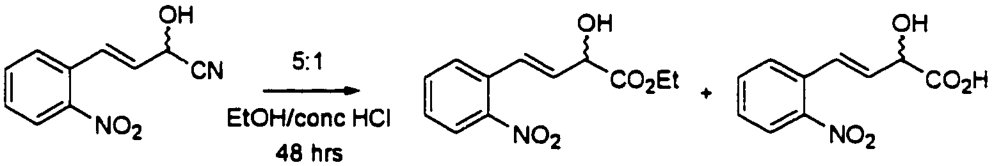
Bromination of **76** with Ph_3PBr_2 provided compound **77**, the regiochemistry of which was confirmed by NOE difference ^1H NMR spectroscopy, as above. Hydrolysis of **76** in 3N HCl provided the desired α-hydroxy acid **78** in 82% yield. No trace of the γ-keto acid **79** was observed in the crude reaction mixture.



76 **78** **79**

Prior to performing this reaction it was postulated that the nitro group would act to block access to the double bond, preventing the formation of 79. This apparently was the case. Our intention was to convert **78** into the corresponding [*R*]-pantolactone ester, in order to investigate the DKR of these compounds. Unfortunately, compound **78** could not be esterified using DCC or acidic media. Unidentified reaction mixtures were observed when **78** was treated with thionyl chloride, oxalyl chloride, or acetic anhydride.

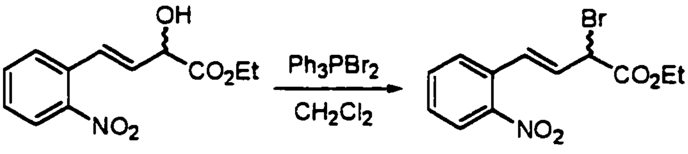
The α-hydroxy ester **80** was prepared from **76**, albeit in poor yield. Compound **76** was suspended in a 5:1 mixture of 99% ethanol and concentrated hydrochloric acid. After refluxing this solution for 48 hrs (until no starting material was observed in the ^{1}H NMR spectra of samples taken during the course of the reaction), compound **80** was obtained in 53% yield after purification by silica gel chromatography. Compound **78** was also isolated in 23% yield during the aqueous work-up with saturated $NaHCO_3$.



76 **80** **78**

Compound **78** was the result of aqueous hydrolysis. In an effort to minimize the amount of water in solution, gaseous HCl was bubbled through an ethanol solution of **76** for 1 hour. Unfortunately, no reaction was observed even when this solution was refluxed overnight. Similarly, no reaction was observed when THF solutions of **76** and [*R*]-pantolactone were treated with gaseous HCl.

Compound **80** was converted to bromide **81** by treatment with Ph_3PBr_2. The regiochemistry of this reaction was confirmed by NOE difference ^{1}H NMR spectroscopy.

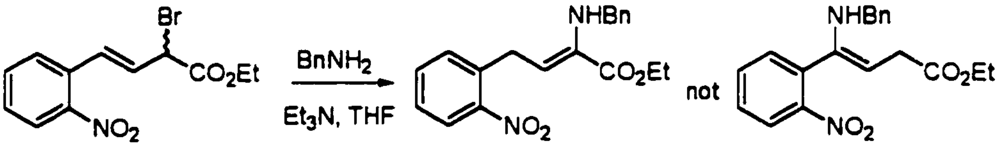


80 **81**

Irradiation of the α-methine proton (4.99 ppm) resulted in a positive NOE to the β-methine proton (7.16 ppm), but no NOE was seen to the aromatic protons. This result implied structure **81** represents the correct regiochemistry (see Spectra 1.3 and 1.4).

Treatment of **81** with NaOH or LiOH did not provide the desired α-bromo acid. The products of these reactions were not fully characterized.

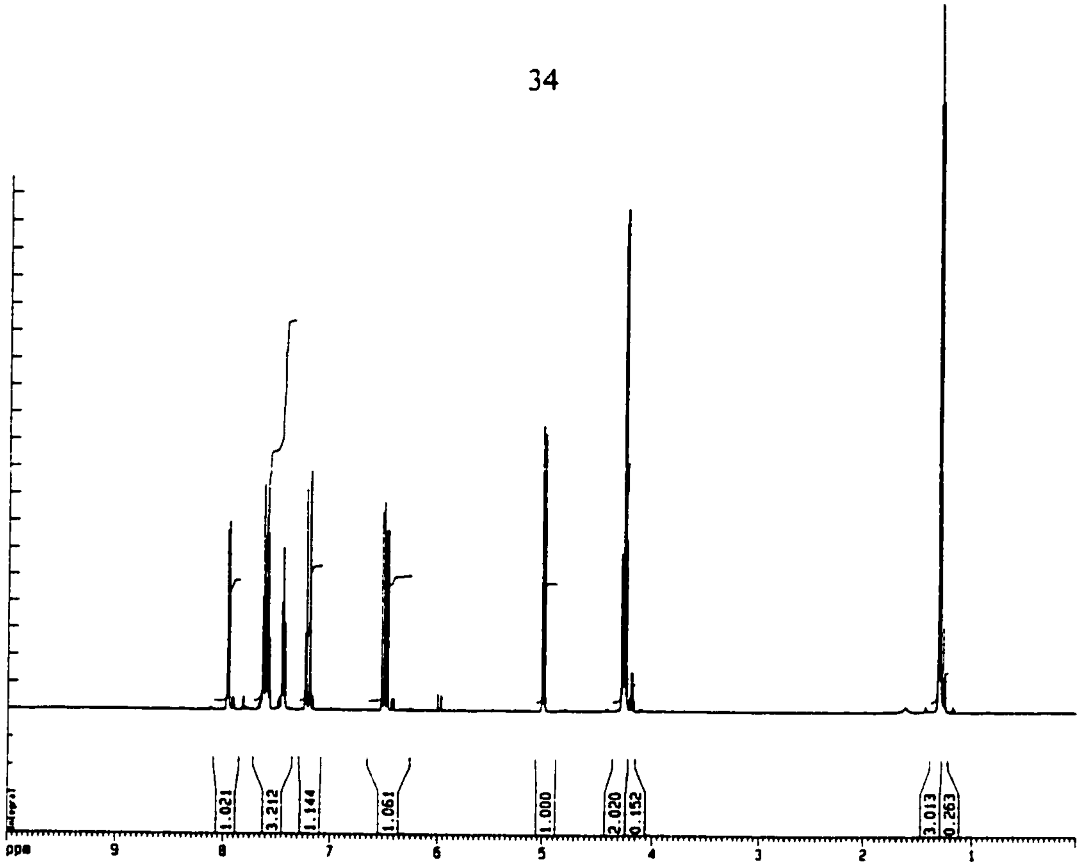
Displacement of the bromine with BnNH$_2$ did not provide the desired α-amino ester. Instead, enamine **82** was isolated in 82% yield. Again, this structure was confirmed by NOE difference ^{1}H NMR spectroscopy. Irradiation of the methylene protons (resulted in a positive NOE to both the β-methylene proton (5.82 ppm) and to the aromatic proton *ortho* to the alkyl substituent found at 7.21 ppm (see Spectra 1.5 and 1.6).



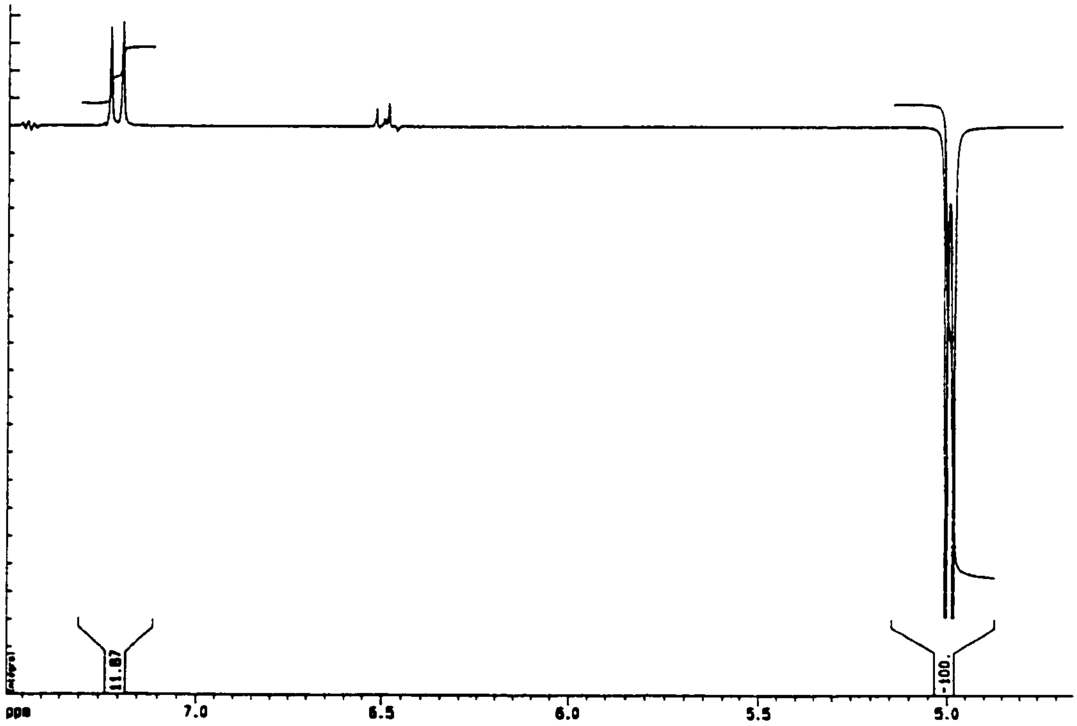
81 **82** **83**

Our primary interests lay in the DKR of [*R*]-pantolactone esters. Since we were not able to prepare the [*R*]-pantolactone ester of **81**, and due to the above enamine formation, we decided to pursue a different route to *ortho*-**67**.

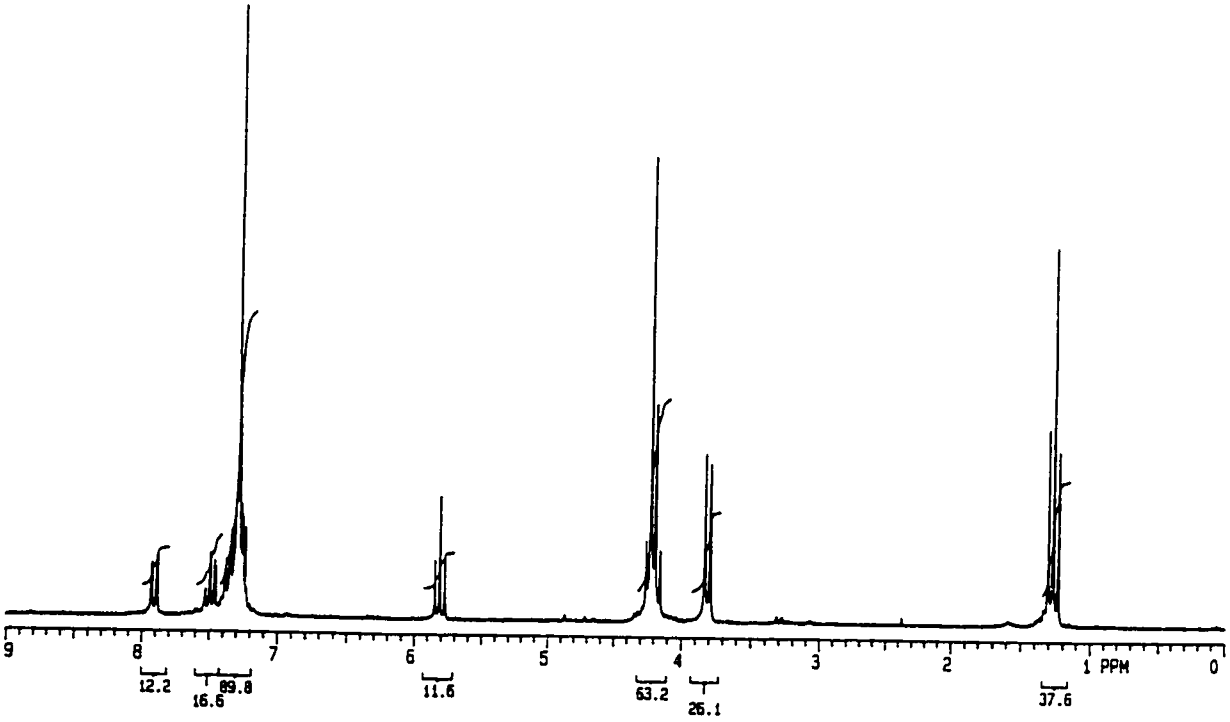
This decision was slightly premature, as this chemistry may still lead to an alternate entry into these benzolactam systems. One possible route involves the reductive cyclization of **82** using chiral catalysts. Based on the reduction of enamine **28** (see Section 1.3), the intermediate enamine **84** should also be reduced with some degree of enantioselectivity.



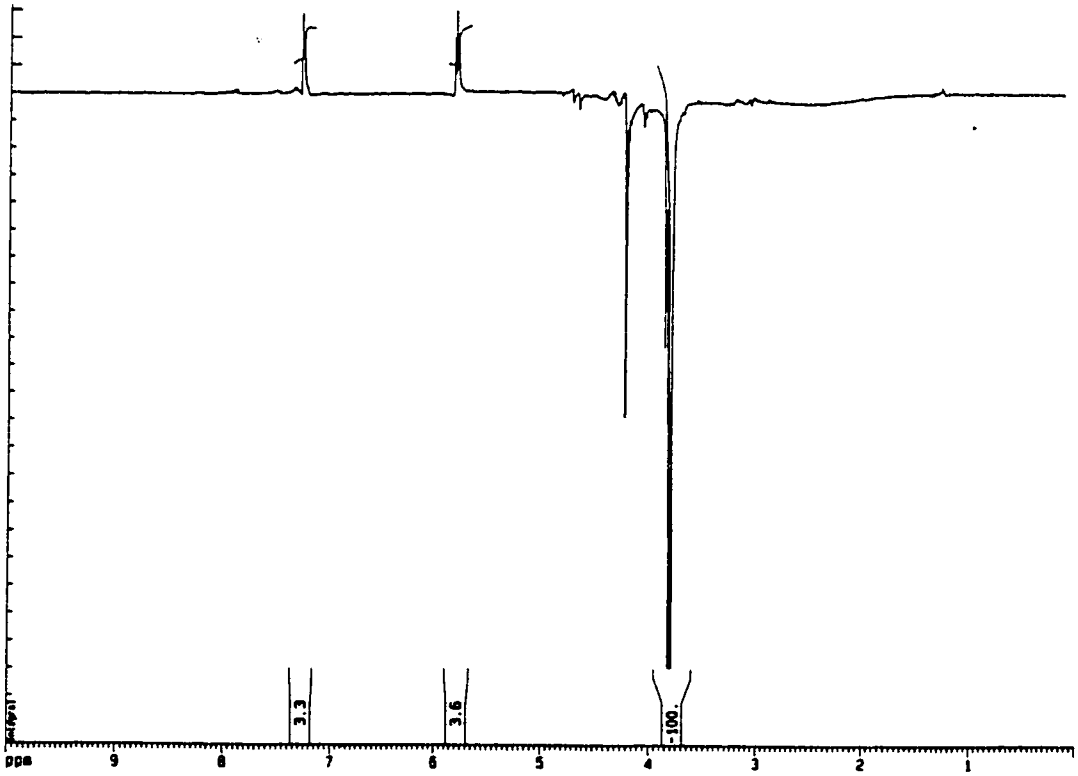
Spectrum 1.3 : ^{1}H NMR Spectrum of Compound **81**



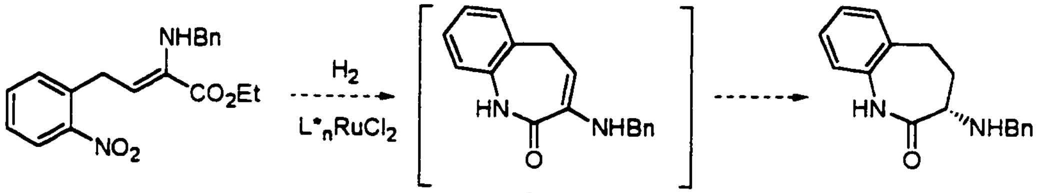
Spectrum 1.4: NOE Difference ^{1}H NMR Spectrum of **81** Irradiating at 4.99 ppm.



Spectrum 1.5 : ^{1}H NMR Spectrum of Compound **82**

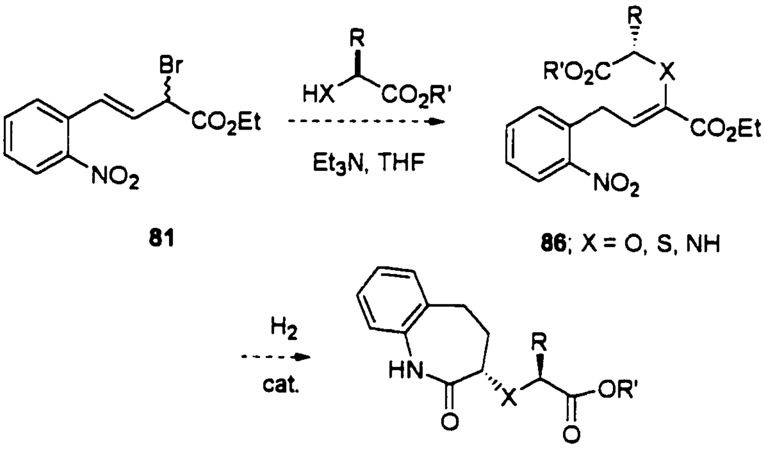


Spectrum 1.6: NOE Difference ^{1}H NMR Spectrum of **81** Irradiating at 3.81 ppm.



82 **84** **85**

An alternate route, which will allows for the direct insertion of the desired side chain, involves treating **81** with a chiral nucleophile, such as α-amino or α-hydroxy esters to provide **86**.



81

86; X = O, S, NH

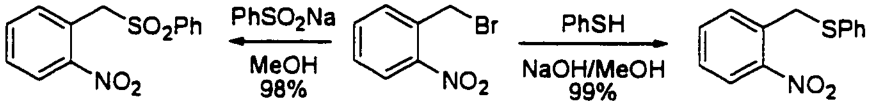
87; X = O, S, NH

The inherent chirality of **86** will allow for the diastereoselective reduction of **86** to provide a variety of optically active benzolactams such as **87**. The degree of chiral induction will be the result of steric shielding of one face enamine **86**. These studies are currently under way.

1.6.5.3 Anions of *ortho*-Nitrobenzyl Phenyl Thioethers and Sulfones

A second route involved the 1,4-addition of sulfur stabilized *o*-nitrobenzyl anions to acrylates. Although this route did allow for the synthesis is 4-(*o*-nitrophenyl)butanoic acids, it did not provide access to ester **38**. Some interesting and unpredicted chemistry did come from this work. These results are briefly summarized below.

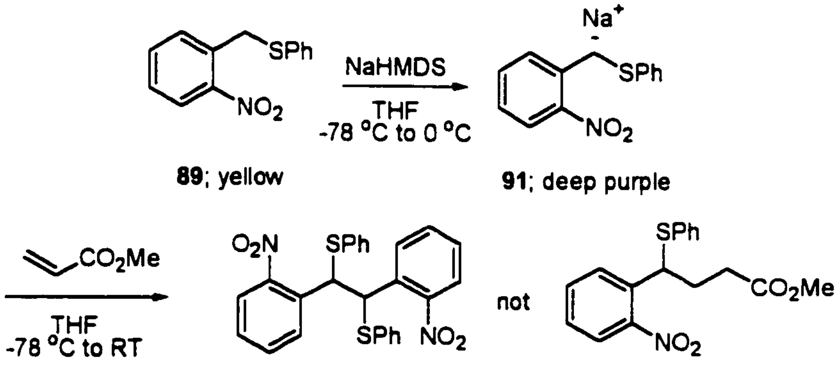
Commercially available *o*-nitrobenzyl bromide (**88**) was readily converted to either sulfide **89** or to sulfone **90**, using the one step procedures illustrated below.



90 **88** **89**

The yields were quantitative, and both **89** and **90** were used without further purification.

Treatment of a THF solution of **89** with NaHMDS, at –78 °C, resulted in the immediate formation of a deep purple colour, characteristic of anion **91**. Initially these solutions were allowed to warm to 0 °C for 30 minutes, before being cooled back down to –78 °C. The addition of methyl acrylate at this point did not result in the formation of the desired butanoate **93**. Instead, compound **92** was isolated in greater than 80% yield, with no trace of **93**.



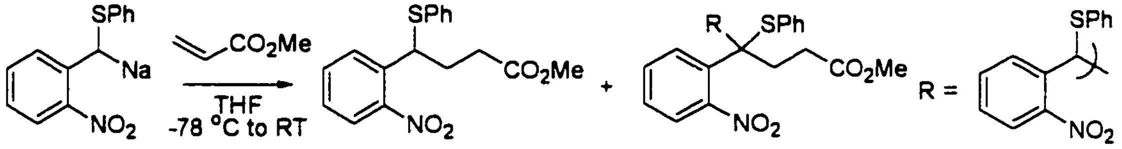
89; yellow **91**; deep purple

92 **93**

ortho-Nitrobenzyl anions are known to undergo single electron transfer (SET) reactions; one of the 'anion electrons' is transferred to the nitro group, while the other is transferred to the metal. The formation of **92** may therefore be attributed to the free radical coupling of two molecules of **91**, which had undergone single electron transfer during the course of warming. The disappearance of the purple anion colour during this warming period also supports this idea. When a solution of **91** was allowed to warm from

−78 °C to 0 °C and then quenched with water, the only products observed by ^{1}H NMR spectroscopy, besides a small amount of **89** (5 to10%), was compound **92**.

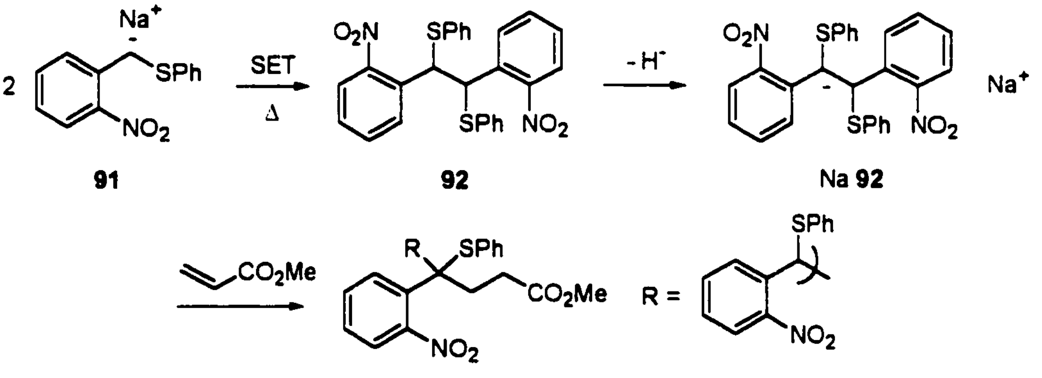
When methyl acrylate was added at −78 °C, immediately after the addition of NaHMDS, and the solution was warmed to room temperature over a 3 to 4 hour period, an even more intriguing result was obtained.



91; deep purple **94** **95**

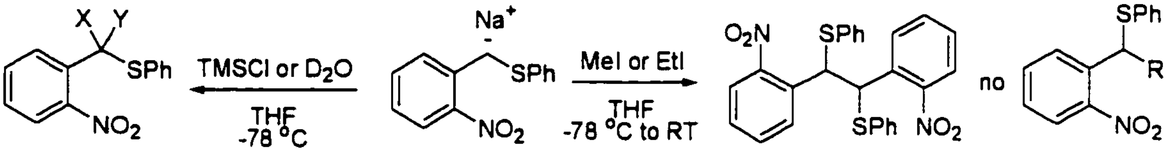
The ^{1}H NMR spectrum of the crude reaction mixture showed that in addition to a small quantity of starting material, two new products were present in the reaction mixture. The desired butanoate **94** was isolated in 43% yield by silica gel chromatography. An additional product, identified as compound **95**, was isolated in 23% yield.

Compound **95** may originate from the deprotonation of **92** by unreacted **91**, to provide the anion Na **92**. This species may then react with methyl acrylate either via anionic 1,4-addition, or by a similar free radical process.



95

In an effort to better understand this reaction sequence, anion **91** was treated with a variety of electrophiles. After stirring at −78 °C for 5 minutes, anion **91** was quenched with D_2O. This resulted in 89% deuterium incorporation, as seen by ^1H and ^{13}C NMR spectra of the crude reaction product, compound **98**.



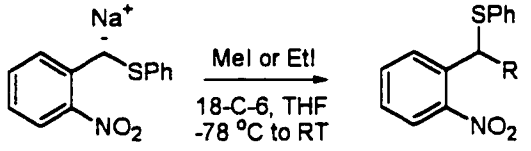
98; X=D, Y=H
99; X=Y=O
91
92
100; R = Me
101; R = Et

The addition of TMSCl to **91** at –78 °C, resulted in an instantaneous loss of colour. This suggests that the TMS adduct (where X=TMS and Y=H) was formed. However, after warming to room temperature and aqueous work up, no TMS incorporation was observed. No benzylic hydrogens were observed in the ^1H NMR spectrum of the isolated material, however, a peak at 159.6 ppm was observing in the ^{13}C NMR spectrum of this material. These results suggest that thio ester **99** was formed during the aqueous workup.

When anion **91** was treated with either MeI or EtI, and allowed to warm to room temperature, the major product observed was compound **92**. None of the desired products, **100** and **101** respectively, were observed by ^1H NMR spectra of the crude reaction mixtures.

The presence of the Na cation was believed to be the source of the SET process. Use of LDA as a base provided the lithium carbanion (light orange solution). The corresponding potassium carbanion was available by using KHMDS as the base (deep purple solution). Unfortunately, similar results were obtained for these carbanions, as were observed for the sodium carbanion **91**. No reaction was observed using triethylamine in refluxing THF solvent, or when the phase transfer catalysts 18-crown-6 and *n*-Et_3BnNI were used with methylene chloride/15% NaOH solutions.

In an effort to alter this SET process, 18-crown-6 was added to the reaction mixtures. This would result in complexation of the Na cation with 18-crown-6, preventing any SET processes. When NaHMDS was added to a THF solution of **89** and 18-crown-6, at –78 °C, a deep purple solution was obtained. This indicated that anion **89** had formed. After stirring for at –78 $^{\circ}$C for 5 minutes MeI and EtI were added to separate reactions. The solutions were allowed to warm to room temperature overnight.



91

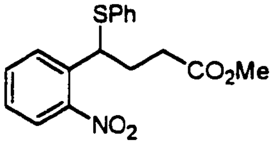
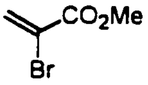
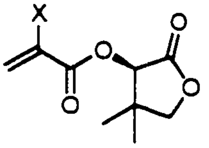
100; R = Me
101; R = Et

Compounds **100** and **101** were isolated in 82% and 78% yield, respectively. Only small quantities of **92** were observed in the ^{1}H NMR spectra of the crude reaction mixtures (less than 5%).

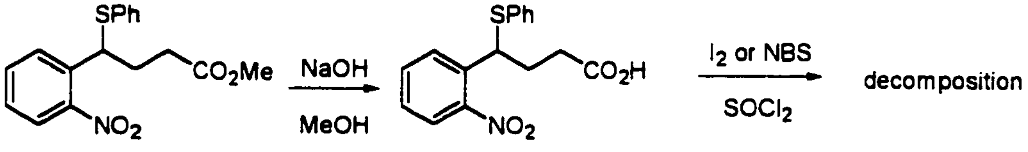
When these reaction conditions were applied to the coupling of **91** with methyl acrylate, the desired butanoate **94** was obtained in 78% yield (see entry 1, Table 1.1). A small quantity of **95** was observed in the ^{1}H NMR spectrum of the crude reaction mixture (again less than 5%), however it was not isolated.

If this coupling reaction could be applied to α-bromoacrylates, then we would have direct access to α-bromobutanoate esters. Unfortunately, methyl α-bromoacrylate (**102**), [*R*]-pantolactone acrylate (**103**), and [*R*]-pantolactone α-bromoacrylate (**104**) were all observed to decompose under the above reaction conditions (see Chapter 2 for the synthesis of these compounds).

Table 1.1 : Acrylate Coupling reactions Using Anion **91**/18-Crown-6 Complexes

Entry	Acrylate	Product	Yield (%)
1		 **94**	78
2	 **102**	decomposition	
3,4	 **103**; X = H **104**; X = Br	decomposition	

Saponification of **94** yielded the acid **105**. Unfortunately, attempts to introduce a halide α- to the carbonyl group, using Hell-Volhard-Zelinskii reaction conditions, resulted in the formation of complex product mixtures.

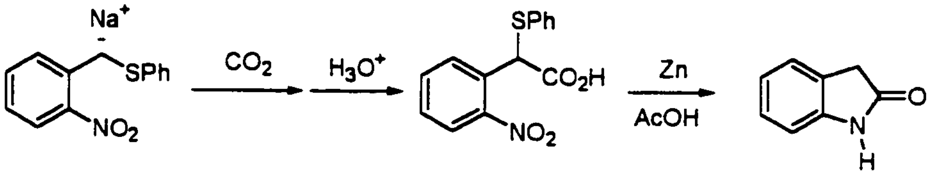


94 **105**

This was not surprising, as the thio ether may also react with the thionyl chloride, to yield a variety of different products.

The chemistry of sulfone **90** was similar to that of compound **89**, and will not be discussed in detail. This route did not provide ready access to ester **38**, and was abandoned at this point.

One interesting reaction sequence that did emerge from this chemistry is illustrated below.

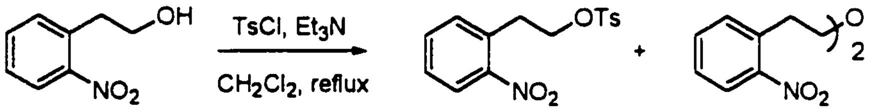


91 **106** **107**

When CO_2 was bubbled through a solution of Na **91** at −78 °C, the characteristic purple anion colour was observed to fade to a milky brown colour after approximately one hour. Acid work up provided acid **106** in 85% yield. When **106** was refluxed in AcOH with 2 equiv. of Zn powder, oxindole (**107**) was obtained in 70% yield. This reaction was interesting in that both reductive cyclization and desulfurization occurred in a single step. This may be a useful method for the preparation of functionalized oxindole systems.

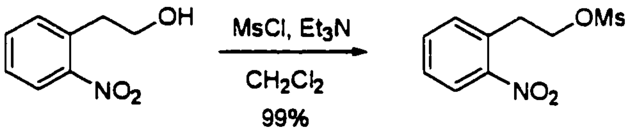
1.6.5.4 Chain Extension of *o*-Nitrophenethyl Alcohol With Diethylmalonate

A more general synthetic route was developed, which provided 4-(2-nitrophenyl)butanoic acid (**67**), in 50 to 60 % overall yield, after 5 steps. Treatment of commercially available *o*-nitrophenethyl alcohol (**108**) with TsCl (2 equiv.) and Et_3N (2 equiv.), in refluxing CH_2Cl_2 (1M in **108**), provided a 1:1.1 mixture of the desired tosylate **109** and ether **110**. No improvement in the product ratio was observed when the reaction was repeated at higher dilution (0.1 M).



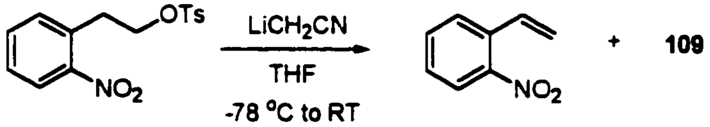
108 **109** **110**

These two compounds were readily separated by silica gel chromatography (eluting with 3:1 hexane/diethyl ether), with **110** eluting first, followed by **109**. The addition of DMAP to this reaction may have allowed for the reaction to be performed at lower temperature, thereby preventing ether formation. This reaction was not attempted as mesylation of **108** cleanly provided mesylate **111**, in quantitative yield.



108 **111**

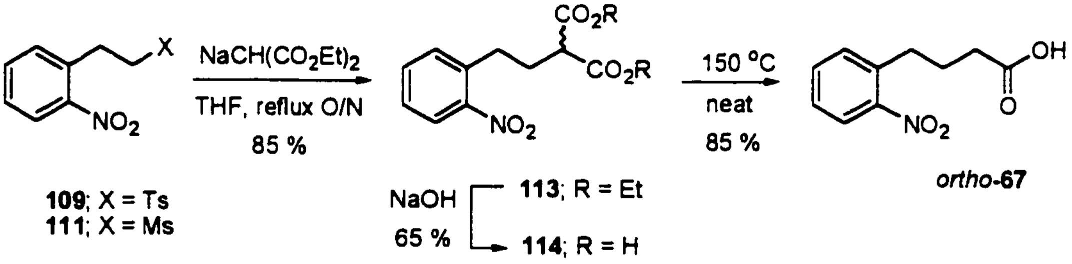
In order to effect the desired two carbon chain extension, **109** was treated of with $BrZnCH_2CO_2Et$, formed under standard Reformantsky reaction conditions. No reaction was observed, even after refluxing in THF for 16 hrs. Addition of lithiated acetonitrile to compound **109** did not provide the desired cyanide.



109 **112**

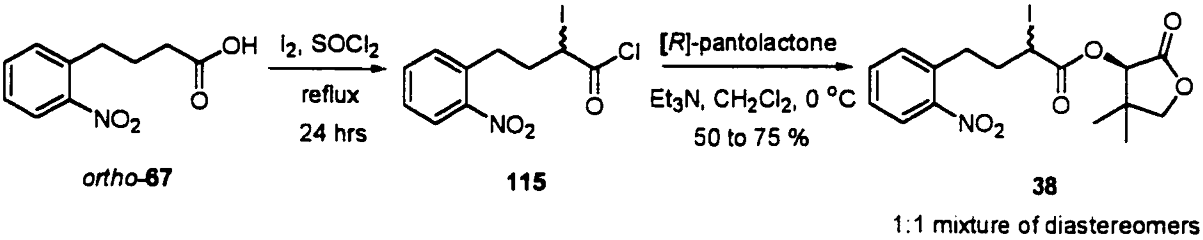
The major products from this reaction were *ortho*-nitrostyrene (**112**) and unreacted **109**. This was not surprising. In fact, we had been concerned about using compounds **109** and **111** as precursors to **67**, as benzylic protons adjacent to a nitro group are known to be relatively acidic. This increased acidity may, and did, allow for elimination of the tosyl or mesyl groups, respectively, to yield *o*-nitrostyrene.

However, treatment of either **109** or **111** with diethyl sodium malonate for 16 hours in refluxing THF, yielded the diester **113** in 85% yield. No reaction was observed at room temperature. Additionally, no elimination product was observed in the ^1H NMR spectrum of the crude reaction mixture.

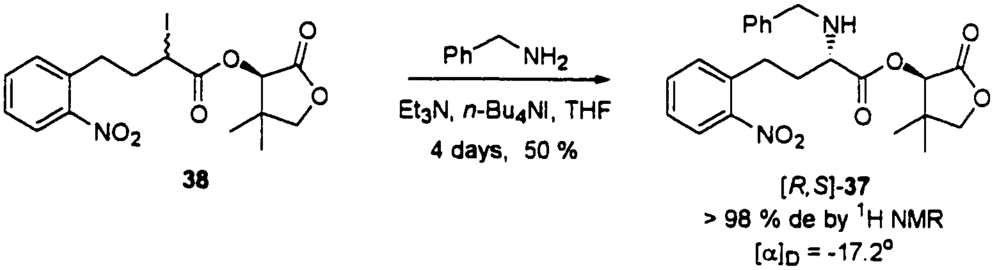


The crude diester **113** was not purified, but treated directly with NaOH in 3:2:1 THF/MeOH/H_2O, to provide the diacid **114**, in 65% yield. The diacid **114** was obtained directly from the crude reaction mixture in >95% purity by aqueous extraction; dilution the of saponification reaction mixture with water, washing the aqueous layer with several portions of diethyl ether, and acidifying the resulting aqueous phase. Ethyl acetate extraction of the now acidic aqueous phase yielded the desired diacid **114**. Finally, decarboxylation was preformed by heating solid **114** to 150 °C, under nitrogen. After the solid had melted and no more frothing was observed (approximately 30 minutes) the dark brown oil was allowed to cool to room temperature, to provide *ortho*-**67** as a light brown solid.

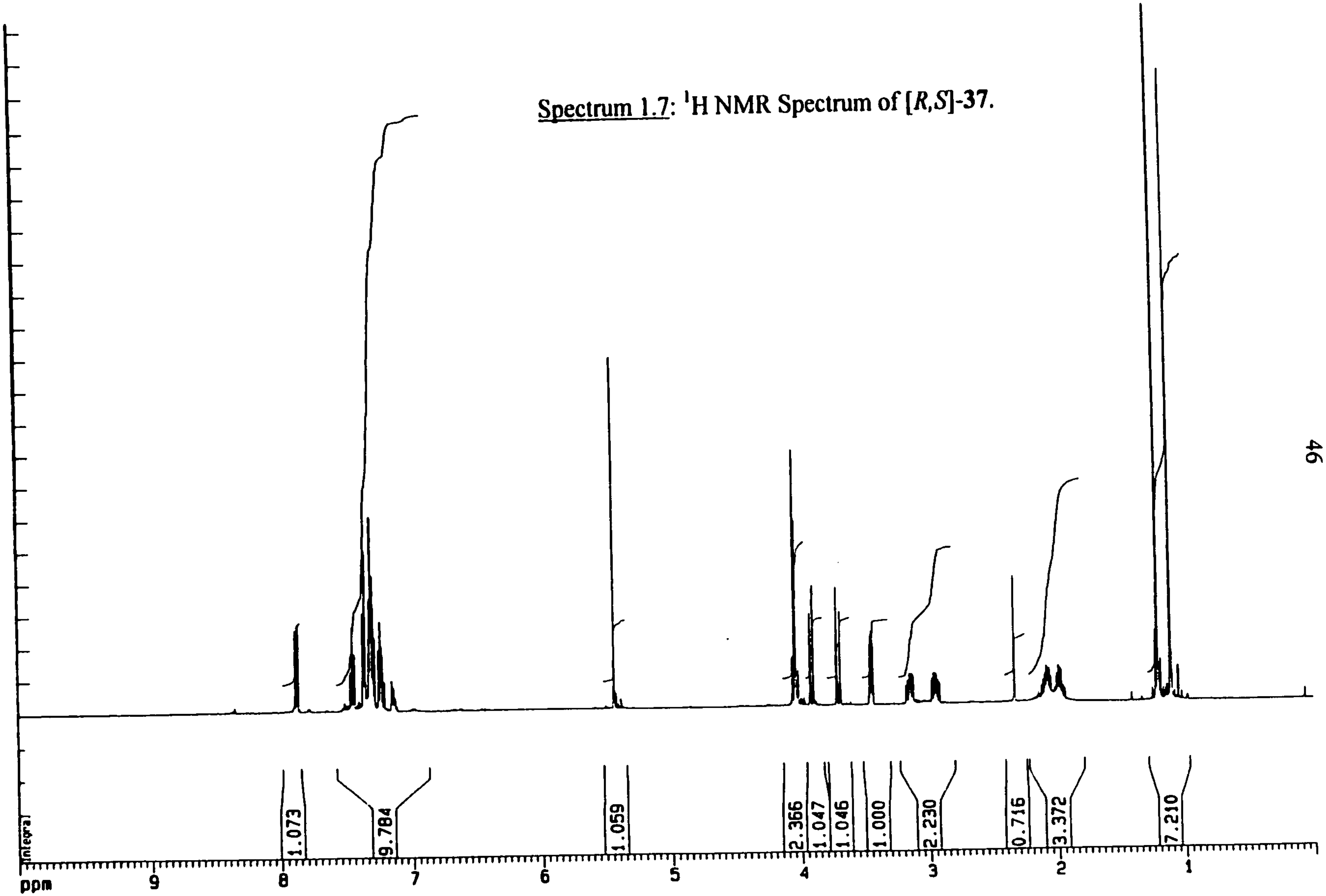
With pure *ortho*-**67** in hand, the α-iodo [*R*]-pantolactone ester **38** was prepared as described previously for compound **36**. When *ortho*-**67** was refluxed in thionyl chloride with 0.6 equiv. of I_2, the α-iodo acid chloride **115** was obtained. Crude **115** was dissolved in CH_2Cl_2 and added to a CH_2Cl_2 solution of [*R*]-pantolactone and Et_3N. After aqueous work up and purification by silica gel chromatography, ester **38** was obtained in 50 to 75% yield, as a 1:1 mixture of diastereomers.



The first DKR step involved the treatment of **38** with benzylamine, under standard DKR conditions. All of the starting material was consumed after a period of 5 days. After purification by silica gel chromatography, [*S*,*R*]-**37** was obtained in 50% yield, as a single diastereomer, as shown by 500 MHz ^1H NMR spectroscopy (see Spectrum 1.7).

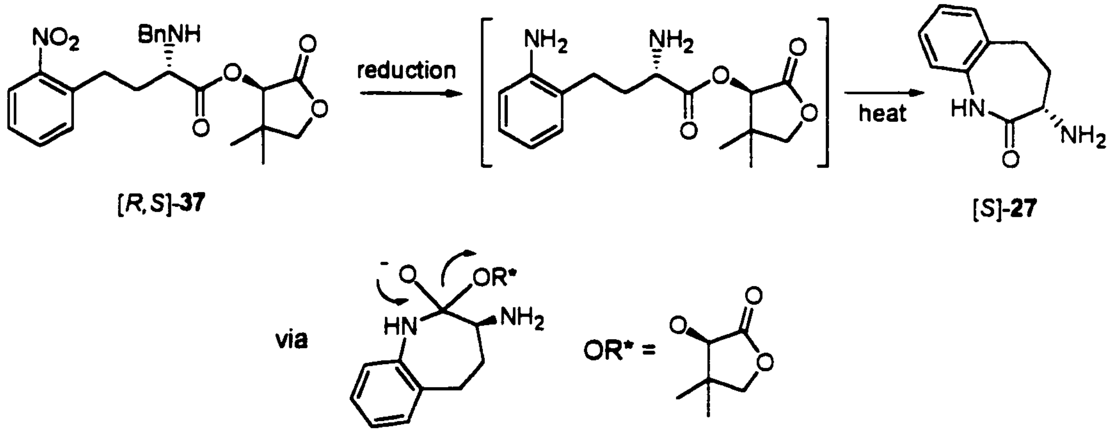


The remaining step in the synthesis of the benzolactam core of benazepril, [*S*]-**27**, involved the reductive cyclization of [*S*,*R*]-**37**. Reduction of the aromatic nitro group would allow for the formation of the seven membered benzolactam ring, via transamidation with [*R*]-pantolactone. Ideally, the benzyl protecting group would also be reduced to the free amine, to provide unprotected [*S*]-**27** in one step (Figure 1.7). Unfortunately, under the optimal cyclization conditions the benzyl group was not reduced.



Spectrum 1.7: ^{1}H NMR Spectrum of [*R*,*S*]-**37**.

Figure 1.7: Proposed Reductive Cyclization of [*S*,*R*]-**37** to [*S*]-**27**



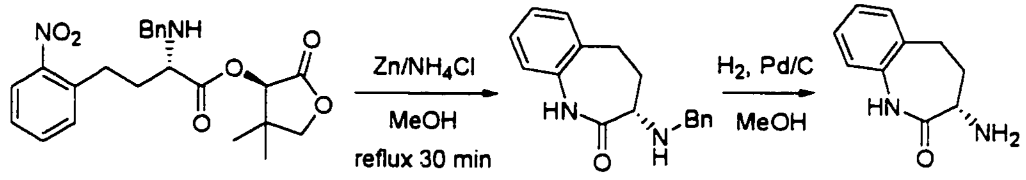
Several reaction conditions were investigated for the reductive cyclization of [*R*,*S*]-**37**. Cyclization to the benzolactam would produce free [*R*]-pantolactone, and this would be observed in the ^{1}H NMR spectrum. When [*S*,*R*]-**37** was refluxed in toluene with 5 equiv. of cyclohexene and 5% Pd/C, [*R*]-pantolactone was observed in the ^{1}H NMR spectrum of the crude reaction mixtures. Unfortunately, it proved difficult to isolate pure [*S*,*R*]-**37** from these reactions.

Stirring [*S*,*R*]-**37** under 1 atmosphere of H_2 (10 wt% Pd/C in methanol) resulted in complete reduction of the aromatic nitro group to the corresponding aniline (2 hours at room temperature) as seen by the ^{1}H NMR spectra of several aliquots removed during the course of the reaction. Reduction of the benzyl group was slow at best; approximately 20% reduction was observed after 3 days at room temperature. No free [*R*]-pantolactone was observed, even after refluxing overnight, suggesting that no cyclization had occurred. The addition of various acids, including TsOH•H_2O, acetic acid, 10% HCl, in both catalytic and stoichiometric amounts, did not catalyze the cyclization.

Refluxing [*S*,*R*]-**37** with 5 equiv. of Zn metal in acetic acid resulted in complete decomposition of the starting material.

The optimal conditions for the reductive cyclization of [*R*,*S*]-**37** involved refluxing [*S*,*R*]-**37** in MeOH with 5 equiv. of Zn powder and 10 equiv. of solid NH_4Cl (30 minutes).

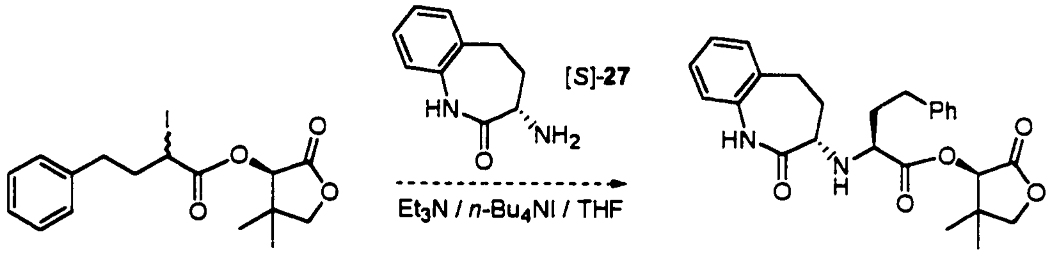
Reduction of the *o*-nitro group was accompanied by cyclization to the benzyl protected benzolactam [*S*]-**116**.



[*R*,*S*]-**37** [*S*]-**116** [*S*]-**27**

After cooling to room temperature the solids were filtered off. The solvent was removed under reduced pressure to provide a mixture of [*S*]-**116** and [*R*]-pantolactone. These two products were readily separated by silica gel chromatography, eluting with 5:1 hexane/diethyl ether. The benzyl group was removed in a subsequent step by stirring [*S*]-**116** under 1 atm of H_2, with 5% Pd/C, in MeOH solvent, to provide [*S*]-**27**.

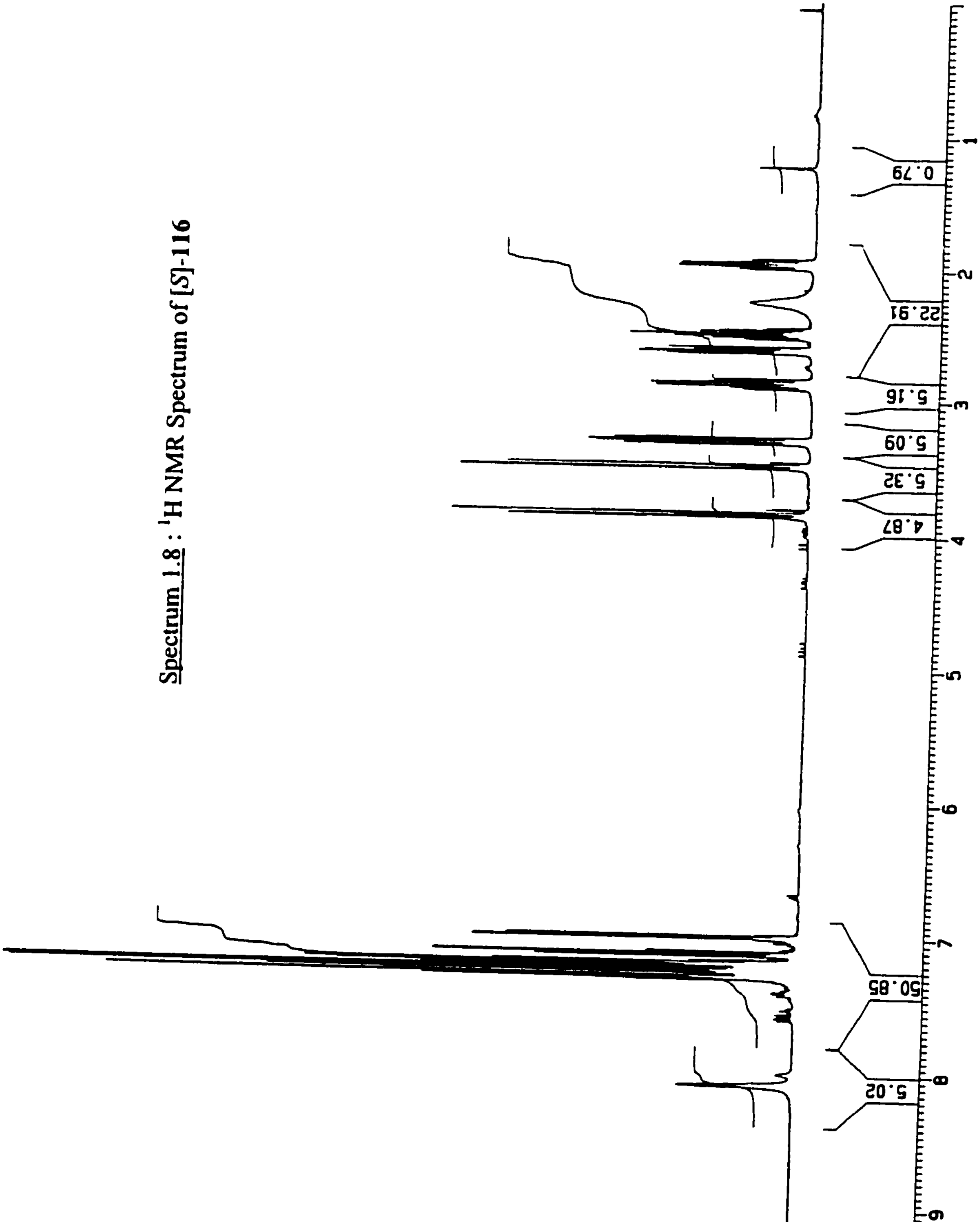
The final DKR step has not been yet been performed, however, based on the reactivity of (*S*)-2-aminocaprolactam (see Section 1.6.2), we expect to obtain the desired benazepril intermediate [*S*,*S*,*R*]-**65** in high diastereomeric excess.



38 [*R*,*S*,*S*]-**65**

Removal of [*R*]-pantolactone, and insertion of the acetic acid side chain, should be straight forward, and provide enantiomerically pure benazepril.

Spectrum 1.8 : ^{1}H NMR Spectrum of [*S*]-116



1.7 Summary

Dynamic Kinetic Resolution has been successfully applied to the partial synthesis of various Angiotensin-converting Enzyme inhibitors. The (*S*)-2-amino-4-phenylbutanoate side chain of enalapril and benazepril was prepared in high yield, and high diastereoselectivity, using either benzylamine or dibenzylamine as nucleophiles for the displacement of bromine from ester **36**. Attempts to employ α-amino esters as nucleophiles with ester **36** provided thc corresponding dipeptide fragments in low yields. (*S*)-2-Aminocaprolactam, however, was an ideal nucleophile for these displacement reactions, providing the desired fragments in high yields and optical purity. Finally, the benzolactam core of benazepril was prepared in four steps from *ortho*-**67**, involving one DKR and one reductive cyclization step.

Clearly DKR is a powerful tool. Continued exploration of this area should bring improvements in both the level of chiral induction observed as well as the general utility of this method for the synthesis of biologically active compounds.

1.8 References

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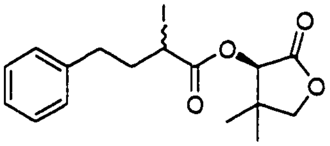
1.9 Experimental

1.9.1 General

All reaction, unless stated otherwise, were run under a nitrogen atmosphere using dry solvents. THF was dried over sodium benzophenone ketyl, and distilled prior to use. Methylene chloride, acetonitrile, triethylamine, benzylamine, dibenzylamine, and methyl acrylate were dried over NaH, and distilled prior to use. DMSO and DMF were dried over NaH, and distilled under reduced pressure. The [*R*]-pantolactone esters **53** and **55** were prepared according to published procedures.[2] All chemical reagents were obtained from Aldrich Chemical Company and used as received, unless stated otherwise.

1.9.2 Ester 36



4-Phenylbutanoic acid (2.0 g, 12.2 mmol) was dissolved in neat thionyl chloride (10 mL) and refluxed for 30 minutes. After cooling to room temperature iodine (1.86 g, 7.32 mmol) was added and the resulting solution was refluxed for an additional 3 hrs. After cooling to room temperature the solution was concentrated using a roto-vap. The residue was taken up in chloroform (25 mL) and the remaining $SOCl_2$ and iodine was removed azeotropically, under reduced pressure. The resulting oil was further 'pumped on' for 1 hour (RT, 0.1 torr) to provide compound **50** as a dark brown oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.09 (m, 5H), 4.56 (t, J=7.5Hz, 1H), 2.85-2.60 (m, 2H), 2.48-2.22 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.3, 138.8, 128.7, 128.3, 126.7, 37.6, 34.7, 29 9.

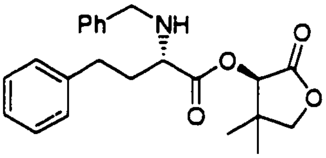
Crude **50** was dissolved in methylene chloride (25 mL) and added via cannula to an ice cold methylene chloride solution of [*R*]-pantolactone (1.59 g, 12.2 mmol) and triethylamine (1.70 mL, 12.2 mmol). The resulting solution was allowed to warm to room temperature and stirred over night. The reaction mixture was diluted with diethyl ether

(100 mL) and the organic layer was washed with water (3 x 50 mL) before being dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide a dark brown oil. Purification by silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, provided ester **36** as a brown oil in 56% yield. The diastereomeric ratio was shown to be 1.3:1 by ^{1}H NMR spectrum of the purified product.

Major diastereomer : IR (neat, cm^{-1}) 3027 (s), 2965 (s), 2933 (s), 2877 (s), 1795 (s), 1745 (s), 1603 (s), 1585 (m), 752 (s), 701 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 5.40 (s, 1H), 4.40 (t, J=7.5Hz, 1H), 4.03 (s, 2H), 2.78-2.49 (m, 2H), 2.31 (p, J=7.5Hz, 2H), 1.26 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 170.8, 139.4, 128.6, 128.5, 126.4, 76.2, 75.6, 40.8, 37.1, 34.9, 23.0, 19.8, 18.5. MS (FAB, m/z) M^+ = 401.5.

Minor diastereomer : ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 5.38 (s, 1H), 4.31 (t, J=7.5Hz, 1H), 4.05 (s, 2H), 2.89-2.41 (m, 2H), 2.31 (p, J=7.5Hz, 2H), 1.25 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 169.9, 139.4, 128.6, 128.5, 126.4, 76.1, 75.6, 40.5, 37.7, 35.0, 23.0, 19.8, 18.8.

1.9.3 [*S*,*R*]-51



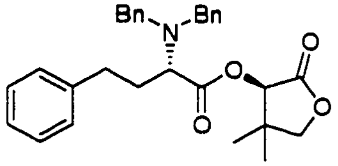
Ester **36** (370 mg, 1.0 mmol) and *n*-Bu_4NI (34 mg, 0.01 mmol) were dissolved in dry THF (10 mL) and treated with triethylamine (140 µL, 1.0 mmol) and benzylamine (109 µL, 1.0 mmol). The solution was sealed under nitrogen and allowed to stir at room temperature until no starting material was visible by TLC (48 hours). The resulting suspension was treated with ethyl acetate (50 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL) before being dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was further purified by silica gel chromatography, eluting with

3:1 hexanes/ethyl acetate, to provide [*S*,*R*]-**51** as a light brown oil in 92% yield, as a 7:1 mixture of diastereomers.

[*S*,*R*]-51 : IR (neat, cm^{-1}) 3338 (m), 3085 (m), 3028 (s), 2965 (s), 2931 (s), 2879 (m), 1795 (s), 1746 (s), 1603 (m), 1495 (s), 1450 (s), 1158 (s), 1080 (s), 743 (s), 701 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.34 (m, 2H), 7.28 (m, 3H), 7.20 (m, 3H), 5.46 (s, 1H), 4.05 (d, J=9.0Hz, 1H), 4.03 (d, J=9.0Hz, 1H), 3.93 (d, J=12.9Hz, 1H), 3.72 (d, J=12.9Hz, 1H), 3.48 (dd, J=5.7, 7.7Hz, 1H), 2.60 (overlapping ddd, 1H), 2.75 (overlapping ddd, 1H), 2.07 (overlapping dddd, 1H), 2.05 (overlapping dddd, 1H), 1.2197 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (68.3 MHz, $CDCl_3$) δ 174.1, 171.9, 141.0, 139.5, 128.4, 128.2, 127.0, 125.9, 125.8, 75.9, 75.1, 5.8, 51.7, 39.9, 35.0, 31.8, 22.8, 19.9. HRMS Cal'd for $C_{23}H_{27}NO_4$ 381.1940. Found 381.1911.

[*R*,*R*]-51 : ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.34 (m, 2H), 7.28 (m, 3H), 7.20 (m, 3H), 5.45 (s, 1H), 4.05 (d, J=9.0Hz, 1H), 4.03 (d, J=9.0Hz), 1H), 3.91 (d, J=12.7Hz, 1H), 3.68 (d, J=12.7Hz, 1H), 3.42 (dd, J=5.9, 7.3Hz, 1H), 2.60 (overlapping ddd, 1H), 2.75 (overlapping ddd, 1H), 2.07 (overlapping dddd, 1H), 2.05 (overlapping dddd, 1H), 1.224 (s, 3H), 1.11 (s, 3H).

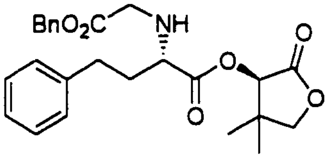
1.9.4 [*S*,*R*]-52



[*S*,*R*]-**52** was prepared according to the procedure described for [*S*,*R*]-**51**. Ester **36** (404 mg, 1.0 mmol) and *n*-Bu_4NI (36 mg, 0.01 mmol) were dissolved in dry THF (10 mL) and treated with triethylamine (140 μL, 1.0 mmol) and dibenzylamine (189 μL, 1.0 mmol). The solution was sealed under nitrogen and allowed to stir at room temperature until no starting material was visible by TLC (48 hours). Aqueous work up and silica gel chromatography, eluting with 3:1 hexanes/diethyl ether, provided [*S*,*R*]-**52** was a clear oil in 89% yield, as a 20:1 mixture of diastereomers.

^{1}H NMR (200 MHz, CDCl$_3$) δ 7.39-7.15 (m, 15H), 5.55 (s, 1H), 4.05 (d, J=9.0Hz, 1H), 4.03 (d, J=9.0Hz, 1H), 3.93 (d, J=12.9Hz, 1H), 3.84 (d, J=12.7Hz, 1H), 3.72 (d, J=12.9Hz, 1H), 3.69 (d, J=12.7Hz, 1H), 3.52 (dd, J=5.4, 7.8Hz, 1H), 2.94 (m, 2H), 2.15 (m, 2H), 1.13 (s, 3H), 0.97 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 174.5, 171., 141.0, 139.5, 138.5, 128.4, 128.2, 127.5, 127.0, 126.2, 126.1, 125.9, 125.8, 75.9, 75.1, 75.2, 51.8, 51.7, 39.9, 35.0, 31.8, 22.8, 19.9. MS (CI, m/z) M+1 = 472.

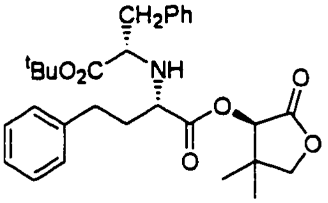
1.9.5 [*S*,*R*]-58



Ester **36** (370 mg, 1.0 mmol), L-glycine benzyl ester hydrochloride (200 mg, 1.0 mmol), and *n*-Bu$_4$NI (37 mg, 0.10 mmol) were dissolved in dry THF (10 mL). The solution was sealed under nitrogen and triethylamine (280 μL, 2.0 mmol) was added. The resulting suspension was stirred at room for 5 days before ethyl acetate (50 mL) and water (20 mL) was added. The organic layer was washed with water (3 x 10 mL) before being dried over anhydrous MgSO$_4$, filtered, and concentrated *in vacuo*. Further purification by silica gel chromatography, eluting with 3:1 hexanes/diethyl ether, provided [*S*,*R*]-**58** as a clear oil in 50% yield, as a single diastereomers.

IR (neat, cm^{-1}) 3344 (m), 3064 (m), 3029 (m), 2965 (s), 2936 (s), 2972 (m), 2796 (s), 1732 (s), 1604 (m), 1497 (m), 1455 (s), 1150 (s), 1013 (s), 751 (s), 700 (s). ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.34 (s, 5H), 7.27-7.16 (m, 5H), 5.39 (s, 1H), 5.16 (s, 2H), 4.02 (s, 2H), 3.51 (d, J=4.3Hz, 2H), 2.73 (t, J=8.0Hz, 2H), 2.07 (m, 2H), 1.19 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 173.3, 171.9, 171.5, 141.0, 135.5, 128.6, 128.5, 128.4 (2 peaks), 126.1, 126.0, 76.1, 75.4, 66.6, 65.8, 49.0, 34.9, 31.8, 22.9, 20.0. MS (FAB, m/z) M+1 = 440.2.

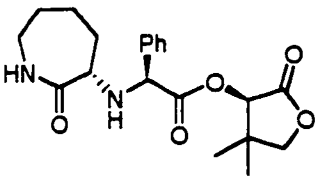
1.9.6 [*S*,*S*,*R*]-59



[*S*,*S*,*R*]-**59** was prepared according to the procedure described for [*S*,*S*,*R*]-**58**. Ester **36** (370 mg, 1.0 mmol), phenylalanine *tert*-butyl ester hydrochloride (258 mg, 1.0 mmol), and *n*-Bu_4NI (37 mg, 0.10 mmol) were dissolved in dry THF (10 mL). The solution was sealed under nitrogen and triethylamine (280 μL, 2.0 mmol) was added. The resulting suspension was stirred at room for 5 days before ethyl acetate (50 mL) and water (20 mL) was added. Aqueous work up and silica gel chromatography, eluting with 2:1 hexanes/diethyl ether, provided [*S*,*S*,*R*]-**59** as a white solid in 25% yield, as a 20:1 mixture of diastereomers. Recrystallization from hexane provide optically pure [*S*,*S*,*R*]-**59** as fine white needles.

m.p. 89.0-90.0 °C. IR (KBr, cm^{-1}) 3332 (s), 3030 (s), 2978 (s), 2922 (s) 2886 (s), 1789 (s), 1733 (s), 1605 (m), 1497 (s), 1444 (s), 1340 (s), 747 (s), 723 (s), 701 (s). ^1H NMR (200 MHz, $CDCl_3$) δ 7.30-7.15 (m, 10H), 5.33 (s, 1H), 3.98 (s, 2H), 3.57 (t, J=7.0Hz, 1H), 3.49 (t, J=6.8Hz, 1H), 2.71 (t, J=8.2Hz, 2H), 2.01-1.93 (m, 2H), 1.33 (2, 9H), 1.13 (s, 3H), 1.02 (s, 3H). ^{13}C NMR (58.3 MHz, $CDCl_3$) δ 173.0, 172.8, 171.7, 140.9, 136.8, 129.3, 129.2, 128.4, 128.3, 128.2, 128.0, 126.5, 125.9, 81.2, 75.87, 75.84, 75.03, 75.00, 61.2, 59.2, 39.9, 39.7, 35.1, 31.7, 27.7, 22.8, 19.7. MS (CI, m/z) M+1 = 496.

1.9.7 [*S*,*S*,*R*]-61

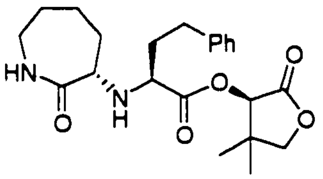


[*S*,*S*,*R*]-**61** was prepared according to the procedure described for [*S*,*R*]-**51**. Ester **53** (326 mg, 1.0 mmol), (*S*)-2-aminocaprolactam (128 mg, 1.0 mmol) and *n*-Bu_4NI (37 mg, 0.1

mmol) were dissolved in dry THF (10 mL). The solution was sealed under nitrogen and triethylamine (140 µL, 1.0 mmol) was added. The resulting suspension was stirred at room temperature until no starting material was visible by TLC (16 hours). Aqueous work up and silica gel chromatography, eluting with 3:1 hexanes/diethyl ether, provided [*S*,*S*,*R*]-**61** was a white solid in 90% yield, as a 20:1 mixture of diastereomers.

m.p. 181.0-182.0 °C. IR (KBr, cm^{-1}) 3290 (m), 3251 (m), 2975 (m), 2923 (m), 2839 (m), 1790 (s), 1738 (s), 1660 (s), 1467 (m), 1204 (s), 1008 (s), 740 (s), 705 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H), 7.32-7.25 (m, 3H), 6.77 (br t, J=5.9Hz, 1H), 5.33 (s, 1H), 4.60 (s, 1H), 3.88 (d, J=9.0Hz, 1H), 3.86 (d, J=9.0Hz, 1H), 3.11 (t, J=5.8Hz, 1H), 2.81 (br s, 1H), 1.97-1.89 (dd, J=5.0, 10.2Hz, 2H), 1.71-1.65 (m, 1H), 1.61-1.45 (m, 2H), 1.32-1.29 (m, 1H), 0.89 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (48.5 MHz, $CDCl_3$) δ 177.6, 172.10, 171.99, 137.9, 128.6, 128.3, 127.7, 76.0, 75.1, 63.7, 58.1, 41.7, 40.3, 31.8, 28.8, 27.9, 22.6, 19.1. MS (FAB, m/z) M+1 = 375.2.

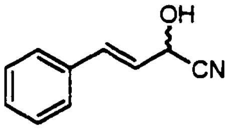
1.9.8 [*S*,*S*,*R*]-62



[*S*,*S*,*R*]-**62** was prepared according to the procedure described for [*S*,*S*,*R*]-**58**. Ester **36** (370 mg, 1.0 mmol), (S)-2-aminocaprolactam (128 mg, 1.0 mmol), and *n*-Bu_4NI (37 mg, 0.1 mmol) were dissolved in dry THF (10 mL). Triethylamine (140 µL, 1.0 mmol) was added and the solution was stirred at room temperature until no starting material was visible by TLC (12 hours). Aqueous work up and silica gel chromatography, eluting with 2:1 hexanes/diethyl ether, provided [*S*,*S*,*R*]-**62** as a single diastereomer in 95% yield.

m.p. 156.0-157.0 °C. IR (KBr, cm^{-1}) 3310 (m), 3214 (m), 3090 (m), 2937 (s), 1787 (s),, 1750 (s), 1656 (s), 743 (s), 670 (s). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, J=7.5Hz, 2H), 7.21-7.14 (m, 3H), 6.21 (br s, 1H), 5.42 (s, 1H), 4.04 (d, J=9.0Hz, 1H), 4.01 (d, J=9.0Hz, 1H), 3.59 (t, J=6.5Hz, 1H), 3.51 (d, J=10.5Hz, 1H), 3.32-3.26 (m, 1H), 3.21-3.18 (m, 1H), 2.79-2.69 (m, 1H), 2.15-2.01 (m, 2H), 1.94 (d, J=11.5Hz, 2H), 1.77-1.70 (m, 1H), 1.69-1.63 (m, 1H), 1.60-1.54 (m, 1H), 1.39-1.31 (m, 1H), 1.17 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.2, 173.5, 172.1, 141.0, 128.4, 128.4, 126.1, 76.2, 75.4, 60.3, 59.0, 41.7, 34.8, 32.3, 32.0, 28.9, 27.8, 23.0, 20.0. HRMS Cal'd for $C_{22}H_{30}N_2O_5$ 402.2155. Found 402.2155.

1.9.9 Compound 69



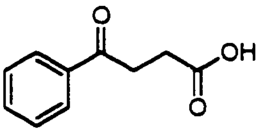
trans-Cinnamaldehyde (5.0 g, 37.8 mmol) and ZnI_2 (50 mg) were dissolved in dry methylene chloride (50 mL) and cooled to 0 °C. TMSCN (5.55 mL, 41.6 mmol) was added dropwise via syringe. The solution was warmed to room temperature and stirred for 1 hour. The solvent was removed under reduced pressure to yield the TMS protected cyanohydrin **69**, a light brown oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.43-7.30 (m, 5H), 6.80 (dd, J=1.2, 15.8Hz, 1H), 6.17 (dd, J=6.0, 15.8Hz, 1H), 5.10 (dd, J=1.3, 6.0Hz, 1H), 0.24 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.9, 133.8, 129.0, 128.6, 128.5, 126.8, 123.4, 118.3, 62.1, -0.2.

The crude oil was vigorously stirred with 3 N HCl (50 mL) for approximately 1 hour. The resulting solid was either extracted with ethyl acetate or filtered off, washing with several portions of water, to yield compound **69** as a light orange solid, in 92 to 98% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.28 (m, 5H), 6.86 (dd, J=1.3, 15.8Hz, 1H), 6.22 (dd, J=6.0, 15.8Hz, 1H), 5.13 (d, J= 6.0Hz, 1H), 3.93 (br s, 1H).

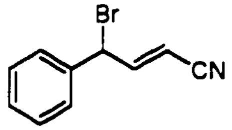
1.9.10 4-Keto-4-phenylbutanoic Acid (71)



Either **69** or TMS protected **69** were suspended in 3N HCl. The mixture was refluxed for 16 hours, yielding an orange solid, which was either extracted with ethyl acetate, or filtered off, washing with several portions of water, to provide **71** in 85 to 95% yield.

m.p. 110.0-112.0 °C. IR (KBr, cm^{-1}) 3300-2350 (br, m), 1681 (s), 1593 (m), 1398 (m), 1344 (m), 1237 (s), 1167 (m), 760 (m), 688 (m). ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.42 (br s, 1H), 7.94 (dd, J=1.5, 8.2Hz, 2H), 7.54 (t, J=7.1Hz, 1H), 4.43 (dd, J=7.1, 8.2Hz, 2H), 3.28 (t, J=6.7Hz, 2H), 2.78 (t, J=6.7Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.8, 179.1, 136.3, 133.3, 128.6, 128.0, 33.1, 28.0. HRMS Cal'd for $C_{10}H_{10}O_3$ 178.0630. Found 178.0621.

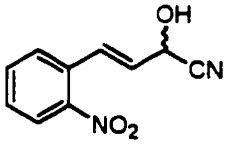
1.9.11 Compound 74



Triphenylphosphine (1.43 g, 5.46 mmol) was dissolved in a dry methylene chloride (25 mL). The solution was placed under nitrogen and cooled in an ice bath. Bromine was added drop wise until a faint red colour persisted. Several crystals of triphenylphosphine were added until the colour faded. Compound **69** (870 mg, 5.46 mmol) was dissolved in methylene chloride (5 mL) and added to the first solution, via cannula, over several minutes. The solution was warmed to room temperature and stirred for an additional 2 hours. The solvent was removed under reduced pressure, and compound **74** was isolated by silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, to provide **74** as a clear liquid in 54% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H), 6.98 (dd, J=7.6, 16.0Hz, 1H), 5.60 (dd, J=1.3, 7.5Hz, 1H), 5.49 (dd, J=1.1, 16.0Hz, 1H).

1.9.12 Compound 76



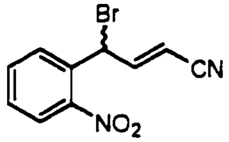
ortho-Nitrocinnamaldehyde (10.0 g, 68.0 mmol) and ZnI_2 (100 mg) were dissolved in dry methylene chloride (50 mL) and cooled to 0 °C. TMSCN (10.0 mL, 74.8 mmol) was added dropwise via syringe. The solution was warmed to room temperature and stirred for 1 hour. The solvent was removed under reduced pressure to yield TMS protected **76** a light brown oil.

IR (neat, cm^{-1}) 3071 (w), 2960 (m), 1607 (m), 1572 (m), 1526 (s), 1348 (s), 1258 (s), 1111 (m), 878 (s), 849 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (dd, J=1.5, 8.0Hz, 1H), 7.56 (dt, J=1.5, 8.0Hz, 2H), 7.43 (dd, J=3.1, 8.0Hz, 1H), 7.28 (dd, J=1.3, 15.5Hz, 1H), 6.17 (dd, J=5.7, 15.5Hz, 1H), 5.17 (dd, J=1.4, 5.7Hz, 1H), 0.22 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5, 133.4, 130.8, 129.5, 129.1, 128.8, 128.1, 124.6, 117.7, 61.7, -0.44.

This crude oil was vigorously stirred with 3 N HCl (50 mL) for approximately 1 hour. The resulting solid was filtered off, washing with several portions of water, to yield compound **69** as a light orange solid, in 92 to 98% yield.

m.p. 66.0-67.0 °C. IR (KBr, cm^{-1}) 3450 (w), 2960 (m), 2369 (w) 1606 (m), 1573 (m), 1525 (s), 1347 (s), 1256 (s), 1010 (m), 966 (m), 876 (s), 848 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.99 (dd, J=1.0, 8.0Hz, 1H), 7.58 (dt, J=1.2, 8.1Hz, 2H), 7.47 (dd, J=1.2, 8.1Hz, 1H), 6.18 (dd, J=5.7, 15.7Hz, 1H), 5.22 (dd, J=1.4, 5.7Hz, 1H), 3.57 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5, 133.7, 131.0, 130.6, 129.3, 129.2, 129.1, 127.4, 124.9, 124.8, 118.0, 61.3.

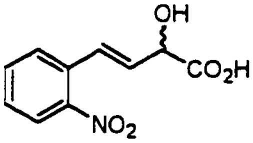
1.9.13 Compound 77



Compound 77 was prepared according to the procedure described for compound **74**. A methylene chloride solution of compound **76** was added to a methylene chloride solution of triphenylphosphine dibromide (prepared *in situ*) which had been pre-cooled in an ice bath. Purification was performed on silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, to yield compound 77 in 56% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (dd, J=1.0, 8.0Hz, 1H), 7.60 (dt, J=1.2, 8.1Hz, 1H) 7.55 (dt, J=1.2, 8.1Hz, 1H), 7.50 (dd, J=1.2, 8.1Hz, 1H), 7.01 (dd, J=7.5, 16.2Hz, 1H), 5.87 (dd, J=1.3, 7.5Hz, 1H), 5.52 (dd, J=1.2, 16.2Hz, 1H).

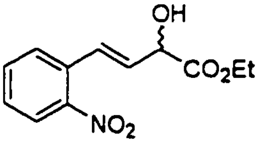
1.9.14 Compound 78



Compound **76** (500 mg) was suspended in 3N HCl and refluxed for 16 hrs. The resulting suspension was filtered and the resulting filter cake was washed with several portions of water. The solid was dried *in vacuo* for 48 hours, to provide compound **78** in 92% yield as a light yellow solid.

m.p. 195.0 °C. IR (KBr, cm^{-1}) 3415 (s), 2997 (m), 1743 (s), 1601 (w), 1570 (m), 1528 (s), 1338 (s), 1243 (s), 1102 (s), 1014 (s), 967 (s), 872 (s), 831 (m), 787 (m), 743 (s), 701 (s), 651 (m). ^{1}H NMR (200 MHz, acetone-d^6) δ 7.89 (d, J=8.0Hz, 1H), 7.79 (d, J=8.0Hz, 1H), 7.73 (t, J=8.0Hz, 1H0, 7.49 (t, J=8.0Hz, 1H), 7.21 (dd, J=1.7, 15.8Hz, 1H), 6.52 (dd, J=4.9, 15.8Hz, 1H), 4.98 (dd, J=2.0, 4.9Hz, 1H). ^{13}C NMR (74.8 MHz, acetone-d^6) δ 173.9, 149.2, 133.9, 133.1, 129.6, 129.3, 126.0, 124.9, 71.5.

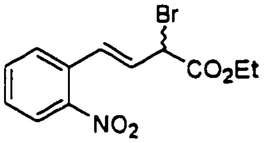
1.9.15 Compound 80



Compound **76** (8.0 g, 39.2 mmol) was suspended in absolute ethanol (50 mL). Concentrated HCl (10 mL) was added and the resulting solution was refluxed for 48 hours (until compound **76** was no longer visible in the ^{1}H NMR spectra of samples taken during the course of the reaction). After cooling to room temperature the solution was stirred with saturated $NaHCO_3$ (200 mL) and extracted with ethyl acetate (100 mL). The organic layer was washed with water (3 x 100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting brown oil was purified by silica gel chromatography, eluting with 3:1 hexanes/ethyl acetate, to provide compound **80** as an off white solid in 56% yield. Acidification of the aqueous NaH_2CO_3 layer, and extractive work-up with ethyl acetate provided compound **78** as a light brown solid in 23% yield.

m.p. 63.0-64.0 °C. IR (KBr, cm^{-1}) 3305-2358 (br, m), 1689 (m), 1594 (s), 1563 (m), 1451 (s), 1375 (s), 1114 (m), 930 (m), 805 (s), 774 (s), 749 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84 (d, J=8.1Hz, 1H), 7.49 (m, 2H), 7.34 (m, 1H), 7.20 (dd, J=1.4, 15.7Hz, 1H), 6.22 (dd, J=5.1, 15.6Hz, 1H), 4.83 (br d, J=5.1Hz, 1H), 4.22 (q, J=7.2Hz, 2H), 3.32 (br s, 1H), 1.25 (t, J=7.2Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5, 147.6, 133.0, 131.8, 130.8, 128.6, 128.3, 127.2, 124.3, 71.0, 62.2, 13.9. MS (FAB, m/z) M^+ = 252.13.

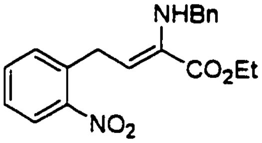
1.9.16 Compound 81



Compound **81** was prepared according to the procedure described for compound **74**. A methylene chloride solution of **80** was added to methylene chloride solution of triphenylphosphine dibromide (prepared *in situ*) which had been pre-cooled in an ice bath. Purification was performed on silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, to yield compound **81** as a clear yellow oil in 82% yield.

IR (neat, cm^{-1}) 3071 (m), 2984 (s), 2940 (m), 2905 (m), 1738 (s), 1609 (m), 1575 (m), 1220 (s), 1346 (s), 1262 (s), 1021 (s), 964 (s), 864 (s), 786 (s), 744 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.90 (d, J=8.6Hz, 1H), 7.62 (m, 2H), 7.38 (m, 1H), 7.47 (m, 1H), 7.21 (d, J=15.4Hz, 1H), 6.51 (dd, J=10.0Hz, 1H), 4.99 (d, J=10.0Hz, 1H), 4.26 (q, J=7.2Hz, 2H), 1.32 (t, J=7.2Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7, 147.5, 133.3, 130.8, 130.1, 129.1, 128.8, 128.5, 124.6, 62.3, 44.6, 14.0. HRMS for M^+-Br (m/z) Cal'd for $C_{12}H_{12}NO_4$. Found 234.0767.

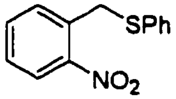
1.9.17 Compound 82



Triethylamine (140 µL, 1.0 mmol) and benzylamine (109 µL, 1.0 mmol) were added to a THF (10 mL) solution of **81** (313 mg, 1.0 mmol). The resulting solution as stirred at room temperature for 24 hours. Water and ethyl acetate were added and the organic layer was washed with water (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with 3:1 hexanes/ethyl acetate, to provide enamine **82** as a yellow oil, in 52% yield.

IR (neat, cm^{-1}) 3393 (m), 2981 (m), 1705 (s), 1645 (m), 1609 (w), 1525 (s), 1349 (s), 1256 (s), 860 (w), 788 (m), 741 (m), 699 (m). ^1H NMR (200 MHz, $CDCl_3$) δ 7.99 (dd, J=1.2, 8.0Hz, 1H), 7.48 (dt, J=1.2, 8.0Hz, 1H), 7.41-7.15 (m, 7H), 5.82 (t, J=7.4Hz, 1H), 4.19 (q, J=7.2Hz, 2H), 3.80 (d, J=7.4Hz, 2H), 1.26 (t, J=7.2Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.7, 139.7, 136.4, 135.1, 133.1, 131.5, 128.5, 128.4, 127.4, 127.3, 127.1, 124.6, 112.9, 61.4, 51.3, 30.3, 14.1. HRMS Cal'd for $C_{19}H_{20}N_2O_4$ 340.1432. Found 340.1405.

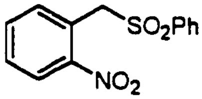
1.9.18 Compound 89



NaOH (1.04 g, 34.1 mmol) was stirred in methanol until the solid had dissolved. Benzenethiol (3.50 mL, 34.1 mmol) was added and the solution was allowed to stir for an additional 5 minutes before solid *o*-nitrobenzyl bromide (5.00 g, 23.1 mmol) was added in one portion. The mixture was stirred at room temperature for 1 hour before the methanol was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with several portions of water before being dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **89** was obtained as a bright yellow solid in 90 to 99% yield, and was used in subsequent steps without further purification.

m.p. 60.5-61.5 °C. IR (CH_2Cl_2, cm^{-1}) 2827 (w), 1609 (w), 1529 (s), 1481 (w), 1350 (m), 1025 (w), 859 (w). ^1H NMR (200 MHz, $CDCl_3$) δ 7.94 (dd, J=1.8, 7.4Hz, 1H), 7.41 (dt, J=1.8, 7.4Hz, 1H), 7.33 (dt, J=1.8, 7.4Hz, 1H), 7.27-7.19 (m, 7H), 4.41 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.2, 134.5, 133.3, 132.9, 131.8, 131.6, 128.9, 128.1, 127.3, 125.1, 37.1. HRMS Cal'd for $C_{13}H_{11}NO_2S$ 245.0510. Found 245.0495

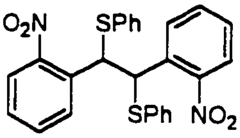
1.9.19 Compound 90



o-Nitrobenzyl bromide (5.00 g, 23.1 mmol) and benzenesulfinic acid, sodium salt (4.60 g, 34.1 mmol) were dissolved in methanol (25 mL). The solution was allowed to stir at room temperature for 1 hour before the methanol was removed under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was washed with several portions of water before being dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Compound **90** was obtained as a bright yellow solid in 98% yield, and was used in subsequent steps without further purification.

IR (KBr, cm^{-1}) 3014 (w), 2958 (w), 1725 (w), 1611 (w), 1581 (m), 1527 (s), 1444 (m), 1357 (s), 1319 (m), 1305 (m), 1150 (s), 1085 (m), 863 (m), 776 (m), 756 (m), 734 (s),, 678 (s). ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (dd, J=1.3, 8.0Hz, 1H), 7.61 (dd, J=1.4, 8.0Hz, 2H), 7.58 (dt, J=1.4, 7.4Hz, 1H), 7.51 (dt, J=1.4, 7.4Hz, 1H), 7.46 (dt, J=1.4, 8.0Hz, 1H), 7.42 (t, J=7.4Hz, 2H), 7.32 (dd, J=1.4, 7.4Hz, 1H), 4.89 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.1, 137.6, 134.1, 134.0, 133.2, 130.0, 129.1, 128.1, 125.3, 122.7, 58.3. MS (m/z) $M^+ = 277.0$.

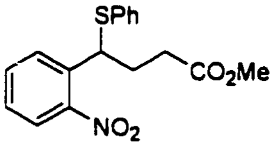
1.9.20 Compound 92



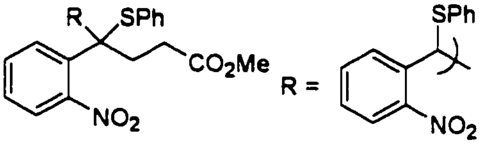
Compound **89** (125 mg, 0.5 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. NaHMDS (0.55 mL, 1M in THF, 0.55 mmol) was added drop wise over approximately 1 minute, resulting in the formation of a deep purple colour. This solution was allowed to warm to room temperature over 1 hour, during which time the solution turned a dark brown colour. Water (10 mL) was added and the solution was stirred for 5 minutes. Diethyl ether (10 mL) was added and the organic layer was washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was purified by silica gel chromatography to provide compound **92** in 78% yield, as a light yellow solid.

IR (KBr, cm^{-1}) 3071 (w), 3007 (w), 2871 (w), 1606 (m), 1576 (m), 1525 (s), 1480 (m), 1440 (m), 1349 (s), 746 (m). ^1H NMR (200 MHz, $CDCl_3$) δ 7.54 (dd, J=Hz, 2H), 7.49 (dd, J= Hz, 2H), 7.40-7.15 (m, 10H), 7.06 (dd, J=Hz, 2H), 5.78 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.5, 134.6, 132.8, 131.8, 130.3, 128.9, 128.8, 128.7, 127.9, 124.1, 51.1. MS (m/z) M^+ - SPh = 379.

1.9.21 Compounds 94 and 95



94



95

Compound **89** (245 mg, 1.0 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. NaHMDS (1.0 mL, 1.0M in THF, 1.0 mmol) was added drop wise over approximately 1 minute, resulting in the formation of a deep purple colour. Methyl acrylate (140 μL, 1.5 mmol) was added via syringe over approximately one minute and the solution was allowed to warm to room temperature over 1 hour. Saturated aqueous NH_4Cl (10 mL) was added and the solution was stirred for 5 minutes. Ethyl acetate (20 mL) was added and the organic layer was washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The ^1H NMR spectrum of the crude reaction mixture showed evidence of two compounds, which were separated by silica gel chromatography to provide compound **94** in 43% yield, as colourless oil, and compound **95** in 23% yield, as a yellow oil.

Compound **94**: IR (neat, cm^{-1}) 3065 (m), 3000 (m), 2952 (m), 1736 (s), 1652 (m), 1600 (m), 1576 (m), 1526 (s), 1439 (s), 1352 (s), 1209 (s), 1167 (s), 855(m), 784 (m), 746 (s), 693 (s). ^1H NMR (200 MHz, $CDCl_3$) δ 7.68 (d, J=8.2Hz, 1H), 7.65 (d, J=8.2Hz, 1H), 7.59 (t, J=7.4Hz, 1H), 7.34 (d, J=7.2Hz, 1H), 7.25 (t, J=7.4Hz, 1H), 7.18 (s, 3H), 4.93 (t, J=6.7Hz, 1H), 3.64 (s, 3H), 2.54-2.36 (m, 2H), 2.35-2.26 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.8, 149.4, 136.4, 132.89, 132.86, 132.7, 129.5, 128.99, 128.93, 128.87, 127.93. 128.87, 124.0, 51.7, 46.5, 31.8, 31.0. HRMS Cal'd for $C_{17}H_{17}NO_4S$; 331.0878. Found 331.0867.

Compound **95**: IR (neat, cm^{-1}) 3061 (m), 2950 (m), 1737 (s), 1605 (w), 1579 (m), 152 (s), 1477 (s), 1438 (s), 1352 (s), 1244 (m), 1217 (m), 1173 (m), 1023 (m), 784 (m), 743 (s), 692 (s). ^1H NMR (200 MHz, $CDCl_3$) δ 7.55-7.43 (m, 4H), 7.39-7.25 (m, 6H), 7.25-7.12 (m, 6H), 3.64 (s, 3H), 3.27 (t, J=7.8Hz, 2H), 2.62 (t, J=7.8Hz, 2H).

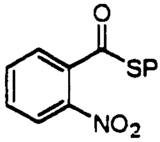
1.9.22 Compound 98

Compound **89** (125 mg, 0.5 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. NaHMDS (0.55 mL, 1.0M in THF, 0.55 mmol) was added drop wise over approximately 1 minute, resulting in the formation of a deep purple colour. A solution of D_2O (0.5 mL) in THF (2 mL) was added, and the solution was warmed to room temperature.

Anhydrous $MgSO_4$ was added. The solution was filtered and concentrated under reduced pressure to provide compound **98** as a light yellow solid, in 89% yield.

IR (KBr, cm-1) 3064 (m), 1608 (m), 1576 (m), 1480 (s), 1346 (s), 1304 (m), 1025 (m), 856 (m), 786 (m), 739 (s), 692 (s). ^1H NMR (200 MHz, $CDCl_3$) δ 7.95 (dd, J=2.0, 7.5Hz, 1H), 7.42 (dt, J=2.2, 7.0Hz, 1H), 7.36 (dd, J=2.0, 7.5Hz, 1H), 7.28-7.19 (m, 6H), 4.39 (s, 1H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 148.4, 134.6, 133.3, 132.9, 131.8, 131.7, 128.9, 128.2, 127.3, 125.2, 36.9 (t, J_{DC}=22.2Hz). HRMS Cal'd for $C_{13}H_{10}NO_2SD$ 246.0572. Found 246.0566.

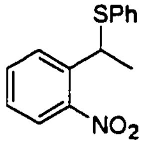
1.9.23 Compound 99



Compound **89** (125 mg, 0.50 mmol) was dissolved in THF (5 mL) and cooled to −78 °C. NaHMDS (0.55 mL, 1M in THF, 0.55 mmol) was added drop wise over approximately 1 minute, resulting in the formation of a deep purple colour. After stirring at −78 °C for 5 minutes TMSCl (65 μL , 0.50 mmol) was added, resulting in immediate colour loss. The solution was warmed to room temperature and diluted with water (10 mL) and diethyl ether (10 mL). The organic layer was washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide compound **99** as a yellow oil in 85% yield.

IR (neat, cm^{-1}) 3062 (m), 1632 (s), 1580 (m), 1450 (s), 1477 (s), 1412 (m), 1376 (s), 1123 (m), 1021 (s), 742 (s), 689 (s). ^1H NMR (200 MHz, $CDCl_3$) δ 7.53 (d, J=9.0Hz, 1H), 7.45-7.37 (m, 2H), 7.32-7.22 (m, 5H), 6.92 (t, J=0.9Hz, 1H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 159.6, 157.6, 131.5, 131.0, 129.5, 129.3,128.6, 124.4, 119.7, 115.4. HRMS Cal'd for $C_{13}H_9NO_3S$ 259.0303. Found 259.0685.

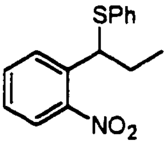
1.9.24 Compound 100



Compound **89** (125 mg, 0.50 mmol) and 18-crown-6 (147 mg, 0.55 mmol) were dissolved in THF (5 mL) and cooled to −78 °C. NaHMDS (0.55 mL, 1M in THF, 0.55 mmol) was added drop wise over approximately 1 minute, resulting in the formation of a deep purple colour. MeI (43 μL, 0.55 mmol) was added dropwise over 1 minute and the resulting solution was slowly warmed to room temperature (1 to 2 hours) and allowed to stir over night. The reaction mixture was treated with water (10 mL) and was stirred for 5 minutes. Diethyl ether (10 mL) was added and the organic layer was washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, provided compound **100** as a yellow oil in 75% yield.

IR (neat, cm^{-1}) 3073 (m), 2972 (m), 2868 (m), 1739 (m), 1606 (m), 1579 (m), 1527 (s), 1481 (m), 1439 (m), 1352 (s), 1298 (m), 855 (m), 784 (m), 745 (s), 693 (m). ^1H NMR (200 MHz, $CDCl_3$) δ 7.72 (dt, J=1.2, 8.0Hz, 1H), 7.69 (dd, J=1.2, 8.0Hz, 1H), 7.52 (dt, J=1.4, 8.0Hz, 1H), 7.31 (dd, J=1.4, 8.0Hz, 1H), 7.28-7.15 (m, 5H), 5.06 (q, J=7.0Hz, 1H), 1.66 (t, J=7.0Hz, 3H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 138.1, 133.9, 132.9, 132.6 (2 C's), 129.2, 128.9, 127.7, 124.0, 42.1, 22.1. HRMS Cal'd for $C_{14}H_{13}NO_2S$ 259.0667. Found 259.0685

1.9.25 Compound 101



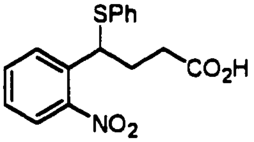
Compound **101** was prepared in a similar fashion as to that described for compound **100**, except that EtI (74 μL, 0.55 mmol) was used in place of MeI, to provided compound **101** as a light yellow oil in 78% yield.

IR (neat, cm^{-1}) 3073 (m), 2969 (m), 2932 (m), 2875 (m), 1606 (m), 1582 (m), 1526 (s), 1480 (m), 1440 (m), 1352 (s), 856 (m), 783 (m), 745 (s), 692 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (dt, J=1.4, 8.0Hz, 1H), 7.66 (dd, J=1.4, 8.0Hz, 1H), 7.51 (dt, J=1.4, 8.0Hz, 1H), 7.30 (dd, J=1.4, 8.0Hz, 1H), 7.24-7.14 (m, 5H), 4.87 (t, J=7.3Hz, 1H), 2.01 (p, J=7.3Hz, 2H), 1.01 (t, J=7.3Hz, 3H). ^{13}C NMR (74.5 MHz, $CDCl_3$) δ 137.1, 133.7, 132.6 (2 C's), 129.5, 128.9 (2 C's), 127.60, 127.56, 123.9, 48.7, 29.4, 12.1. HRMS Cal'd for $C_{15}H_{15}NO_2S$ 273.0823. Found 273.0810.

1.9.26 Compounds 102, 103, and 104

See Chapter 2, Section 2.1.2, for the synthesis of these compounds.

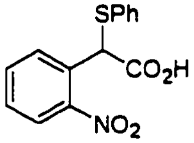
1.9.27 Compound 105



To a solution of 3:2:1 THF/MeOH/water (20 mL) was added NaOH (200 mg, 5.0 mmol) and compound **93** (350 mg, 1.0 mmol). The solution was allowed to stir over night before being concentrated under reduced pressure. The resulting slurry was partitioned between ethyl acetate and water. This solution was acidified using 6N HCl. The organic layer was washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide compound **105** as a light yellow solid, in 53% yield.

^{1}H NMR (200 MHz, $CDCl_3$) δ 10.68 (br s, 1H), 7.66 (dt, J=1.3, 8.0Hz, 1H), 7.52 (dt, J=1.3, 8.0Hz, 1H), 7.39-7.20 (m, 2H), 7.17 (s, 5H), 4.93 (t, J=7.2Hz, 1H), 2.65 (t, J=7.4Hz, 1H), 2.50 (m, 1H), 2.32 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.9, 149.4, 136.3, 133.0, 132.9, 132.8, 130.2, 129.4, 128.0, 127.9, 126.7, 124.1, 46.4, 31.9, 30.6.

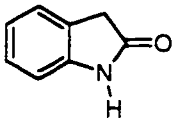
1.9.28 Compound 106



Compound **89** (500 mg, 2.0 mmol) was dissolved in THF (10 mL) and cooled to –78 °C. NaHMDS (2.0 mL, 1.0 M, 2.0 mmol) was added drop wise over approximately 1 minute, resulting in the formation of a deep purple colour. Carbon dioxide gas was bubbled through this solution until no purple colour was visible (approximately 1 hour). The solution was warmed to room temperature under a carbon dioxide atmosphere, before being treated saturated aqueous NaH_2CO_3 (5 mL). Ethyl acetate (10 mL) was added and the aqueous layer was separated, and acidified with 3N HCl. The resulting precipitate was extracted with ethyl acetate (10 mL) and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide compound **106** as an orange solid, in 53% yield.

IR (KBr, cm^{-1}) 3500-2350 (br m), 1715 (s), 1608 (m), 1578 (m), 1526 (s), 1348 (s), 746 (s), 713 (s), 692 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.34 (br s, 1H), 7.97 (dd, J=1.3, 8.0Hz, 1H), 7.70 (dd, J=1.3, 7.7Hz, 1H), 7.58 (dt, J=1.3, 7.7Hz, 1H), 7.54-7.36 (m, 3H), 7.27-7.24 (m, 3H), 5.53 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.2, 147.8, 133.5, 133.3, 132.6, 131.7, 131.0, 129.23, 129.20, 128.8, 125.0, 53.1. MS (m/z) M^+ = 289.

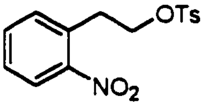
1.9.29 Compound 107



Zinc powder (207 mg, 3.0 mmol) was added to a solution of compound **106** (150 mg, 0.6 mmol) in glacial acetic acid (10 mL). The solution was refluxed for 30 minutes. After cooling to room temperature, the solution was filtered through celite, washing with several portions of acetic acid. The solvent was removed *in vacuo* to provide compound **107**, in 85% yield.

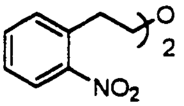
^{1}H NMR (200 MHz, acetone-d^6) δ 9.52 (br s, 1H), 7.21 (d, J=7.2Hz, 1H), 7.14 (d, J=7.6Hz, 1H), 6.93 (t, J=7.7Hz, 1H), 6.90 (t, J=7.6HZ, 1H), 3.44 (s, 2H). ^{13}C NMR (50 MHz, acetone-d^6) δ 175.9, 143.6, 127.1, 124.8, 121.8, 121.1, 108.8, 35.1.

1.9.30 Compound 109



109

+



110

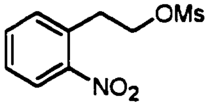
To a solution of *o*-nitrophenethyl alcohol (10.0 g, 66.2 mmol) in methylene chloride (66 mL) was added triethylamine (10.2 mL, 72.8 mmol) and *p*-toluenesulfonylchloride (13.9 g, 72.8 mmol). The solution was refluxed for 24 hours before being cooled to room temperature. Saturated aqueous Na_2HCO_3 (50 mL) was added, and the solution was stirred vigorously for 2 hours. Two compounds were identified in the ^{1}H NMR spectrum of the crude reaction mixture. These were separated using silica gel chromatography, eluting with 1:1 hexane/diethyl ether. Compound **110** eluted first and was isolated as a yellow oil, in 55% yield. Compound **109** eluted second and was isolated as a white solid in 43% yield.

Compound **109** : m.p. 60.5-61.5 °C. IR (KBr, cm^{-1}) 2848 (w), 2928 (w), 2863 (w), 1612 (m), 1598 (m), 1579 (m), 1356 (s), 1098 (s), 978 (s), 900 (s), 865 (m). ^{1}H NMR (200

MHz, $CDCl_3$) δ 7.91 (dd, J=1.5, 8.2Hz, 1H), 7.64 (d, J=9.3Hz, 2H), 7.53 (dd, J=1.5, 8.2Hz, 1H), 7.39 (t, J=8.2Hz, 2H), 7.26 (d, J=8.2Hz, 2H), 4.33 (t, J=6.2Hz, 2H), 3.24 (t, J=6.2Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 133.2, 133.1, 132.3, 131.3, 129.7, 128.1, 127.5, 127.4, 124.8, 69.2, 32.8, 21.4. MS (CI, m/z) M^+ = 321. Anal. Cal'd. for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.70; N, 4.36. Found C, 55.62; H, 4.62; N, 4.20.

Compound **110** : IR (KBr, cm^{-1}) 3070 (m), 2963 (m), 2864 (m), 1611 (m), 1579 (m), 1440 (s), 957 (m), 908 (m), 865 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, J=7.8Hz, 1H), 7.56 (dt, J=1.1, 7.7Hz, 1H), 7.45-7.37 (m, 2H), 3.81 (t, J=6.9Hz, 2H), 3.33 (t, J=6.9Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.1, 133.10, 133.07, 132.8, 128.1, 124.9, 43.7, 36.2.

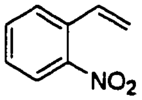
1.9.31 Compound 111



To a solution of *o*-nitrophenethyl alcohol (10.0 g, 66.2 mmol) and triethylamine (10.2 mL, 72.8 mmol) in methylene chloride (100 mL), pre-cooled to –78 °C, was added a methylene chloride (20 mL) solution of methanesulfonyl chloride (5.63 mL, 72.7 mmol). After warming to room temperature and the solvent was removed under reduced pressure. The residue was partitioned between diethyl ether and water. The organic layer was washed with several portions of water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, to provide **111** as a clear oil, in 98% yield. Compound **111** may be further purified by distillation under reduced pressure (60 °C, 0.1 torr).

IR (neat, cm^{-1}) 3029 (w), 2942 (w), 1611 (m), 1578 (w), 1526 (s), 1347 (s), 1173 (s), 967 (s), 908 (s), 856 (m), 798 (s), 744 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.98 (dd, J=1.1, 8.1Hz, 1H), 7.57 (d, J=8.1Hz, 1H), 7.43 (dt, J=1.1, 8.1Hz, 2H), 4.52 (t, J=6.4Hz, 2H), 3.34 (t, J=6.4Hz, 2H), 2.93 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.0, 133.2, 132.9, 131.2, 128.2, 124.8, 68.9, 36.9, 32.7.

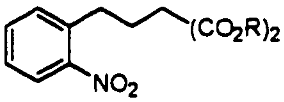
1.9.32 Compound 112



LiHMDS (2.0 mL, 1M in THF, 2.0 mmol) was added to a solution of THF containing acetonitrile (104 mL, 2.0 mmol), that had been cooled to –78 °C. In a separate flask, compound **109** (304 mg, 2.0 mmol) was dissolved in THF and cooled to –78 °C. The $LiCH_2CN$ solution was added to this second solution, via cannula. The resulting solution was warmed to room temperature before being quenched with saturated aqueous NH_4Cl. Ethyl acetate was added and the organic layer was washed with several portions of water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The ^1H NMR spectrum of the crude reaction product showed a 20:13 ratio of compounds **112** and **109**.

^1H NMR (200 MHz, $CDCl_3$) δ 7.91 (dd, J=1.5, 8.2Hz, 1H), 7.52 (dd, J=1.5, 8.2Hz, 1H), 7.35 (t, J=8.2Hz, 1H), 7.69 (d, J=8.2Hz, 1H), 7.11 (dd, J=11.0, 17.3Hz, 1H), 5.69 (dd, J=1.0, 17.3Hz, 1H), 5.43 (dd, J=1.0, 11.0Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.7, 133.0, 132.4, 132.2, 129.7, 128.3, 128.2, 124.2, 118.8.

1.9.33 Compounds 113 and 114



113; R = Et
114; R = H

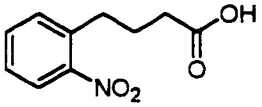
Neat diethyl malonate (5.0 g, 31.3 mmol) was added to a THF (50 mL) suspension of NaH, cooled to 0 °C. The solution was warmed to room temperature and allowed to stir for an additional 15 minutes, before being added, via cannula, to a THF (50 mL) solution of either **109** or **111** (28.5 mmol). The resulting solution was refluxed over night before being cooled to room temperature. Water (100 mL) was slowly added, followed by diethyl ether (200 mL). The organic layer was washed with several portions of water (2 x 100 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide compound **113** as a clear oil, in 85% yield. Compound **113** was advanced to the next step without further purification.

Compound **113** : IR (neat, cm-1) 2984 (m), 2940 (m), 1738 (s), 1610 (m), 1577 (m), 1527 (s), 1456 (m), 1350 (s), 1264 (m), 1224 (m), 1175 (m), 1158 (m), 1033 (m), 856 (m), 788 (m), 745 (m). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.60 (dd, J=1.1, 8.0Hz, 1H), 7.22 (dd, J=1.1, 8.0Hz, 1H), 7.08 (t, J=8.0Hz, 1H), 7.04 (t, J=8.0Hz, 1H), 3.88 (q, J=7.1Hz, 4H), 3.08 (t, J=8.2Hz, 1H), 2.62 (t, J=8.2Hz, 2H), 1.94 (m, 2H), 0.95 (t, J=7.1Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.8, 149.2, 135.7, 133.3, 133.0, 131.9, 127.3, 124.7, 61.4, 51.3, 30.3, 29.3, 13.9.

Crude **113** was dissolved in THF (60 mL). Methanol (20 mL) was added, followed by an aqueous 15% NaOH solution (10 mL). The mixture was allowed to stir overnight at room temperature. The resulting solution was diluted with water and ethyl acetate (100 mL). The aqueous layer was washed with ethyl acetate (2 x 50 mL) before being acidified by the addition of 3 N HCl. The aqueous phase was extracted with ethyl acetate (150 mL). The ethyl acetate was washed with several portions of water, dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide compound **113** as an orange solid in 65% yield.

Compound **114** : m.p. 133.0-134.0 °C (decomposition). IR (KBr, cm^{-1}) 3554-2427 (br s), 1695 (s), 1607 (w), 1596 (w), 1519 (s), 1412 (s), 1263 (s), 1219 (s), 1187 (m). ^{1}H NMR (200 MHz, acetone-d^6) δ 9.05 (br s, 2H), 7.92 (dd, J=1.3, 8.0Hz, 1H), 7.66 (dt, J=1.3, 7.3Hz, 1H), 7.53 (dd, J=1.5, 7.3Hz, 1H), 7.48 (dt, J=1.5, 7.3Hz, 1H), 3.47 (t, J=7.8Hz, 1H), 2.98 (t, J=7.8Hz, 2H), 2.22 (q, J=7.8Hz, 2H). ^{13}C NMR (50 MHz, acetone-d^6) δ 170.6, 136.5, 134.0, 132.8, 128.5, 125.2, 51.7, 30.8, 30.6.

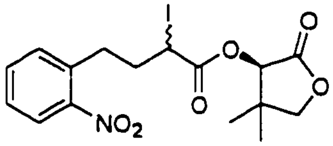
1.9.34 4-(*ortho*-Nitrophenyl)butanoic acid (67)



Compound **114** (5.0 g, 19.8 mmol) was placed in a round bottom flask and placed under a nitrogen atmosphere. The flask was heated in an oil bath set at 150 °C for 30 minutes (until no more gas was being released). The flask was cooled to room temperature to provide ortho-**67** as a light brown solid in 85% yield.

IR (KBr, cm-1) 3391-2490 (br m), 1708 (s), 1610 (w), 1567 (w), 1589 (w), 1524 (s), 1348 (s), 855 (w), 787 (w), 742 (w). ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.51 (br s, 1H), 7.80 (d, J=8.1Hz, 1H), 7.51 (t, J=8.1Hz, 1H), 7.31 (d, J=8.1Hz, 1H), 7.28 (t, J=8.1Hz, 1H), 2.95 (t, 7.3Hz, 2H), 2.49 (t, J=7.3Hz, 2H), 1.98 (p, J=7.3Hz, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.6, 149.3, 136.2, 133.0, 131.9, 127.3, 124.8, 33.4, 32.0, 25.8.

1.9.35 Ester 38



Compound **67** (3.0 g, 14.4 mmol) was dissolved in neat thionyl chloride (15 mL) and refluxed for 30 minutes. After cooling to room temperature iodine (2.02 g, 8.64 mmol) was added and the resulting solution was refluxed for an additional 24 hrs. After cooling to room temperature the solution was concentrated using a roto-vap to remove excess thionyl chloride and iodine. The resulting oil was further 'pumped on' for 1 hour (RT, 0.1 torr) to provide the α-iodo acid chloride **115** as a dark brown or purple oil.

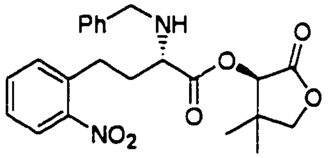
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.09 (m, 5H), 4.56 (t, J=7.5Hz, 1H), 2.85-2.60 (m, 2H), 2.48-2.22 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.0, 148.9, 134.3, 133.5, 132.1, 128.0, 125.2, 36.8, 32.6, 29.3.

Crude **115** was dissolved in methylene chloride (10 mL) and added via cannula to an ice cold methylene chloride (50 mL) solution of [*R*]-pantolactone (1.87 g, 14.4 mmol) and triethylamine (2.0 mL, 14.4 mmol). The resulting solution was warmed to room temperature and stirred overnight. The reaction mixture was diluted with diethyl ether (100 mL) and the organic layer was washed with water (3 x 50 mL) before being dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to provide a dark brown oil. Purification by silica gel chromatography provided ester **38** as a brown oil, in 56% yield.

Major diastereomer : IR (neat, cm^{-1}) 3030 (s), 2960 (s), 2931 (s), 1793 (s), 1741 (s), 1606 (s), 1585 (m), 760 (s), 705 (s). ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, J=8.0Hz, 1H), 7.51 (t, J=8.0Hz, 1H), 7.30 (d, J=8.0Hz, 1H), 7.31 (t, J=8.0Hz, 1H), 5.40 (s, 1H), 4.40 (t, J=7.5Hz, 1H), 4.03 (s, 2H), 2.78-2.49 (m, 2H), 2.31 (p, J=7.5Hz, 2H), 1.26 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8, 170.8, 139.4, 130.1, 128.6, 128.5, 126.4, 123.0, 76.2, 75.6, 40.8, 37.1, 34.9, 23.0, 19.8, 18.5. MS (m/z) M^+ - I = 320

Minor diastereomer : ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (d, J=8.0Hz, 1H), 7.51 (t, J=8.0Hz, 1H), 7.30 (d, J=8.0Hz, 1H), 7.31 (t, J=8.0Hz, 1H), 5.38 (s, 1H), 4.31 (t, J=7.5Hz, 1H), 4.05 (s, 2H), 2.89-2.41 (m, 2H), 2.31 (p, J=7.5Hz, 2H), 1.25 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.6, 169.9, 139.4, 130.0, 128.6, 128.5, 126.4, 123.0, 76.1, 75.6, 40.5, 37.7, 35.0, 23.0, 19.8, 18.8.

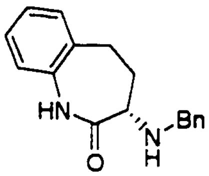
1.9.36 [*S*,*R*]-37



[*S*,*R*]-**37** was prepared according to the method described for [*S*,*R*]-**51**. Ester **36** (3.2 g, 7.22 mmol) and *n*-Bu_4NI (260 mg, 0.72 mmol) were dissolved in THF (70 mL) and treated with triethylamine (1.01 mL, 7.22 mmol) and benzylamine (0.79 mL, 7.22 mmol). The solution was allowed to stir at room temperature for 48 hours before aqueous workup and silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided [*S*,*R*]-**37** as a light brown oil, in 50% yield.

IR (neat, cm^{-1}) 3479 (br, m), 3063 (m), 3029 (m), 2965 (s), 2942 (s), 2874 (m), 1789 (s), 1745 (s), 1668 (s), 1603 (m), 1570 (m), 738 (m), 700 (s). ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.88 (dd, J=1.2, 8.3Hz, 1H), 7.45 (dt, J=1.3, 8.5Hz, 1H), 7.37 (dd, J=1.3, 8.4Hz, 1H), 7.34-7.28 (m, 4H), 7.26-7.21 (m, 2H), 5.44 (s, 1H), 4.05 (d, J=9.0Hz, 1H), 4.03 (d, J=9.0Hz, 1H), 3.91 (d, J=12.8Hz, 1H), 3.69 (d, J=12.8Hz, 1H), 3.44 (dd, J=5.3, 8.1Hz, 1H), 3.14 (overlapping dddd, 1H), 2.94 (overlapping dddd, 1H), 2.10 (overlapping dddd, 1H), 2.02 (br s, 1H), 1.97 (overlapping dddd, 1H), 1.21 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 173.8, 172.0, 149.1, 139.4, 136.1, 133.0, 132.1, 128.32, 128.28, 127.2, 127.1, 127.0, 125.6, 76.4, 76.1, 59.8, 51.6, 39.9, 33.9, 29.3, 22.7, 18.8. MS (CI, m/z) M+1 = 427.

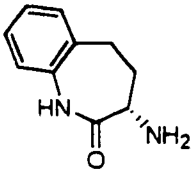
1.9.37 [*S*]-116



[*S*,*R*]-**37** (1.0 g, 2.42 mmol), zinc powder (760 mg, 12.1 mmol), and finely ground NH$_4$Cl (650 mg, 12.1 mmol) were suspending in methanol. This mixture was heated to reflux for 30 minutes before being cooled to room temperature. The solids were filtered off and the solvent removed under reduced pressure to provide a mixture of [*S*]-**116** and [*R*]-pantolactone. The two compounds were separated by silica gel chromatography, eluting with 1:1 hexanes/ethyl acetate, to provide [*S*]-**116** as an off white solid, in 70% yield.

m.p. 119.5-120.5 °C. IR (KBr, cm^{-1}) 3341 (m), 3193 (m), 3059 (w), 2940 (w), 2867 (w), 2853 (w), 1668 (s), 1624 (m), 1625 (m), 1583 (m), 1490 (m), 761 (m), 723 (m), 695 (m). ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.08 (br s, 1H), 7.30-7.17 (m, 7H), 7.12 (dt, J=1.2, 7.4Hz, 1H), 7.00 (d, J=7.8Hz, 1H), 3.85 (d, J=12.6Hz, 1H), 3.49 (d, J=12.6Hz, 1H), 3.30 (dd, J=7.9, 11.4Hz, 1H), 2.88 (dt, J=7.6, 13.5Hz, 1H), 2.62 (dd, J=6.8Hz, 1H), 2.49 (sept. J=6.8Hz, 1H), 2.25 (br s, 1H), 1.95 (m, 1H). ^{13}C NMR (125.5 MHz, CDCl$_3$) δ 175.4, 140.0, 136.6, 134.7, 129.7, 128.3, 128.2, 127.6, 126.9, 126.0, 122.1, 57.9, 52.6, 37.8, 29.1.

1.9.38 [*S*]-27



[*S*]-**116** was dissolved in methanol and stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd/C. After 24 hours the solution was filtered through celite and the methanol was removed under reduced pressure to provide [*S*]-**27** as a white solid in 98% yield.

m.p. 150.0-151.5 °C. IR (KBr, cm^{-1}) 3370 (s), 3297 (s), 3053 (s), 3029 (s), 2953 (s), 2856 (s), 1665 (s), 1620 (s), 158 (s), 1492 (s), 14040 (s), 1337 (s), 1233 (s), 1021 (m), 948 (s), 858 (s), 757 (s), 737 (s), 694 (m), 643 (m). ^{1}H NMR (500 MHz, DMSO-d^6) δ 9.31 (br s, 1H), 7.35 (dd, J=1.2, 7.8Hz, 1H), 7.29 (dt, J=1.2, 7.8Hz, 1H 7.12 (dt, J=1.2, 7.8Hz, 1H), 7.00 (dd, J=1.2, 7.8Hz, 1H), 3.40 (dd, J=7.6, 11.4Hz, 1H), 2.98 (dt, J=7.6, 13.5Hz, 1H), 2.65 (dd, J=6.8Hz, 1H), 2.70 (sept. J=6.8Hz, 1H), 2.65 (br s, 2H), 2.15 (m, 1H). ^{13}C NMR (125.5 MHz, DMSO-d^6) δ 177.0, 142.1, 134.7, 129.7, 128.3, 127.6, 126.0, 52.8, 40.0, 29.6. HRMS Cal'd for $C_{10}H_{12}ON_2$ 176.0950. Found 176.0929.

Chapter Two

Dynamic Kinetic Resolution of α-Halo [*R*]-Pantolactone Esters with Bifunctional Nucleophiles

2.0 Introduction

DKR had been applied to the synthesis of α-amino acids by using simple, monofunctional nucleophiles such as benzylamine,[1] dibenzylamine,[1] and potassium phthalimide.[2] Phenolates,[3] malonates,[4] and carboxylic acids[5] have also display varied degrees of DKR. Clearly, a wide range of relatively weak nucleophiles may be applied to this system.

In order to fully develop this methodology I thought it would be prudent to investigate the use of 'bifunctional nucleophiles' in our DKR process. From this study we would gain an appreciation for which nucleophilic species in a mixed system would react faster, and develop methods to control or reverse this selectivity. The reader should be advised that these are primary findings, and that due to time constraints, only a few functional group combinations have been investigated.

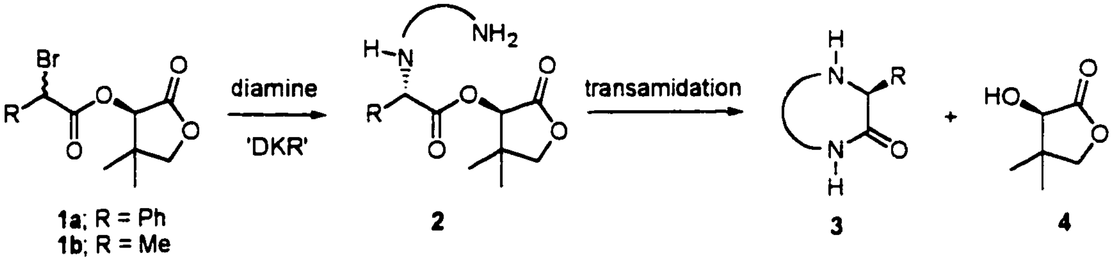
2.1 Results

To date, the only examples of bifunctional nucleophiles being applied to DKR involve the use of α-amino esters[6] and (*S*)-2-aminocaprolactam (see Sections 2.2.2 and 2.2.3). In this chapter the DKR of α-halo [*R*]-pantolactone esters and α-halo [*R*]-pantolactone acrylates with bifunctional nucleophiles will be discussed.

2.1.1 DKR of α-Halo [*R*]-Pantolactone Esters with Bifunctional Nucleophiles

In the previous chapter the synthesis of the benzolactam core of benazepril was discussed. The precursor to this 7 membered lactam was a linear α-amino ester prepared using DKR. The ring closure was facilitated by a reductive cyclization of an aromatic nitro group. This strategy has been extended to the synthesis of 6 membered heterocycles. The use of bifunctional nucleophiles has allowed for these cyclizations to occur *in situ*, thereby eliminating the need for a separate cyclization step. The following scheme depicts this idea using a tethered diamine.

Scheme 2.1: The Synthesis of Heterocycles using DKR of α-Halo [*R*]-Pantolactone Esters with Diamines



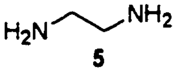
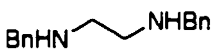
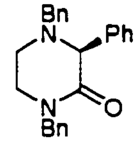
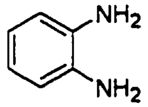
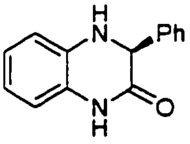
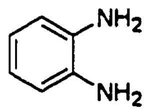
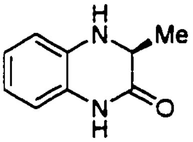
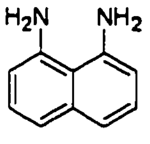
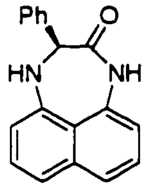
The first step involves bromine displacement by one of the amino groups of the diamine. If this step is performed under DKR conditions relatively high levels of chiral induction should be observed in ester **2**. Intramolecular transamidation will result in the formation of heterocyclic amide **3**, and free [*R*]-pantolactone (**4**).

The results form several diamine/α-halo [*R*]-pantolactone ester combinations are summarized in Table 2.1. These reactions were run in 0.5 M THF solutions, using equimolar quantities of [*R*]-pantolactone ester **1** and the diamine, 1 equiv. of Et_3N, and 10 mol% of *n*-Bu_4NI. After stirring for 4 to 24 hours at room temperature these reactions were subjected to an aqueous work-up, and the products were isolated by silica gél chromatography.

Addition of ethylenediamine (**5**) to **1a** resulted in the immediate precipitation of an unknown, and highly insoluble material (entry 1). When dibenzylethylenediamine (**6**) was used, compound **7** was obtained as a white solid in 86% yield (entry 2). Attempts to determine the diastereoselectivity of this reaction using chiral HPLC failed, as no separation was observed with a Chiralcel OD column, when eluting with solvent mixtures ranging from 90:10 to 99:1 hexanes/*iso*-PrOH.

When **1a** was treated with 1,2-phenylenediamine (**8**), compound **9** was obtained in 72% yield. The diastereomeric ratio was determined to be approximately 94:6 by HPLC, using a Chiralcel OD column, eluting with 95:5 hexanes/*iso*-PrOH. The same reaction, using ester **1b** provided compound **10** with a enantiomeric ration of 2.4:1, as seen by chiral HPLC (entry 4). The low diastereoselectivity observed for **1b** was disappointing, but not unexpected. Ester **1a** is generally a better substrate for DKR, as the rate of halide epimerization in this compound is faster than that of corresponding alkyl esters.

Table 2.1: Synthesis of Heterocycles using DKR of α-Halo [*R*]-Pantolactone Esters with Diamines

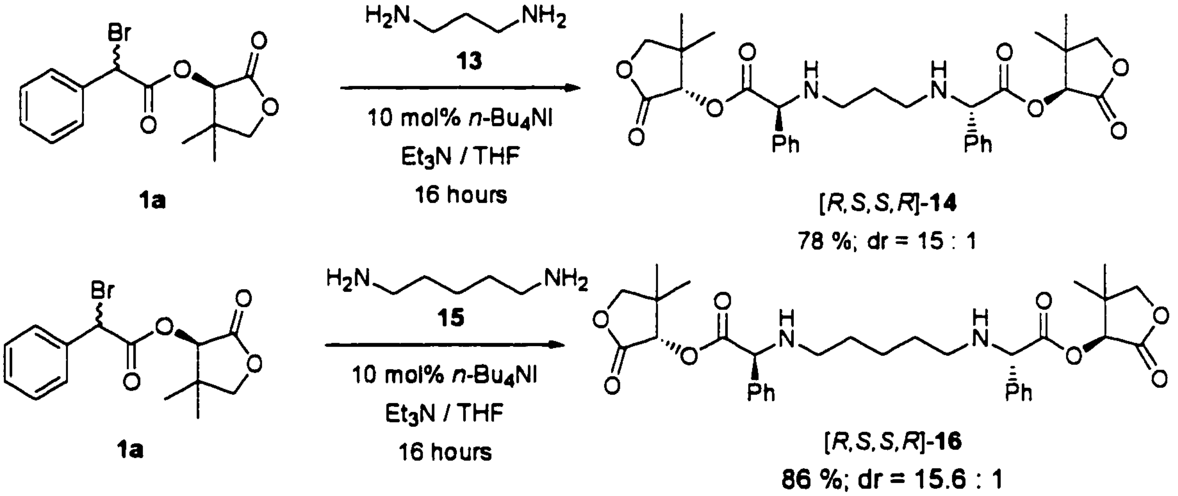
Entry	Ester	Diamine	Product	Yield	ee
1	**1a**	 **5**	insoluble material		
2	**1a**	 **6**	 **7**	84	na
3	**1a**	 **8**	 **9**	72	94 : 6
4	**1b**	 **8**	 **10**	58	2.4 : 1
5	**1a**	 **11**	 **12**	45	na

The reaction of ester **1a** with 1,8-diaminonaphthalene (**11**) was very quick (8 hrs), providing compound **12** as a red solid in 45% yield (entry 5). Again however, no separation of diastereomers was observed by chiral HPLC, and the diastereomeric ratio has yet to be determined.

The absolute stereochemistry of these compounds has not been independently confirmed. The major enantiomer is believed to be the (*S*)-enantiomer, based on previous experience. Initial work using 2-aminophenol and 2-aminothiophenol in place of 1,2-

phenylenediamine has been carried out. The results look promising, however, some problems have been encountered in cyclizing the initial DKR product, ester **2**. For this reason these results will not be disclosed at this time.

Treatment of ester **1a** with one half equivalent of either cadaverine hydrochloride (**13**) or with 1,5-diaminopentane hydrochloride (**15**), under DKR conditions, provided the corresponding *bis*-α-amino esters [*R*,*S*,*S*,*R*]-**14** and [*R*,*S*,*S*,*R*]-**16**, in high yields and high diastereomeric excesses, as seen by their 500 MHz ^{1}H NMR spectra.



1a

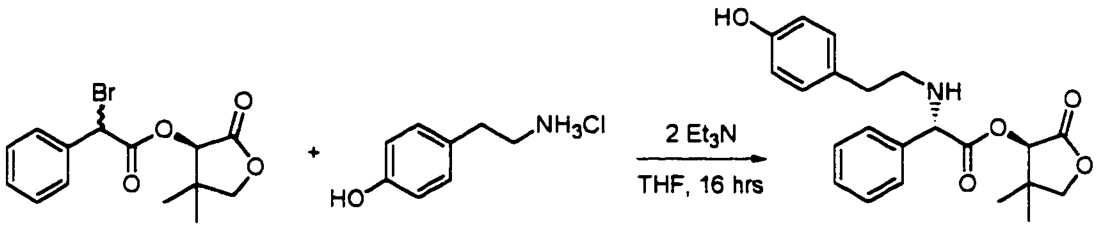
[*R*,*S*,*S*,*R*]-**14**
78 %; dr = 15 : 1

1a

[*R*,*S*,*S*,*R*]-**16**
86 %; dr = 15.6 : 1

No cyclized products were isolated or identified in the ^{1}H NMR spectra of the crude reaction mixtures. This was not surprising as cyclization of the initial DKR product would result in the formation of 7 and 9 membered rings, respectively. Esters [*R*,*S*,*S*,*R*]-**14** and [*R*,*S*,*S*,*R*]-**16** represent a structurally interesting class of tethered C2 symmetric *bis*-α-amino acids. These compounds may find applications as pharmacological agents. Additionally they may find use in the synthesis of chiral dendridic backbones.

The use of 'mixed' nucleophiles was investigate to determine which group would participate in the initial displacement reaction, and which would be involved in ring formation. The first of these systems involved the combination of a phenol with a primary amine. Tyramine hydrochloride (**17**) was stirred over night in THF with ester **1a** and two equivalents of triethylamine. The product was identified as [*S*,*R*]-**18**. The diastereomeric ratio was shown to be approximately 15:1 by its 500 MHz ^{1}H NMR spectrum.

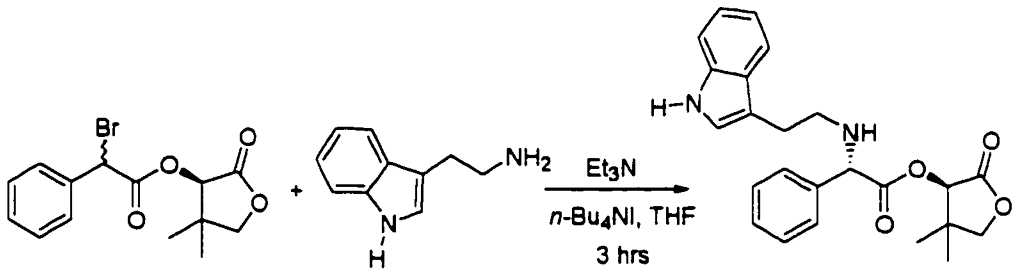


1a **17** [*R,S*]-**18**

92%; 15:1 dr

The primary amine was clearly more nucleophilic than the phenol. This result suggests that DKR using primary amines may be performed in the presence of unprotected phenols.

When tryptamine (**19**) was used as a nucleophile the tryptamine derivative [*S,R*]-**20** was obtained in 45% yield. The diastereomeric ratio was shown to be approximately 7:1 by 500 MHz ^1H NMR spectroscopy. The nucleophilic indole nitrogen was not expected to compete with the amine functionality. This was simply another example of a bifunctional system.



1a **19** [*R,S*]-**20**

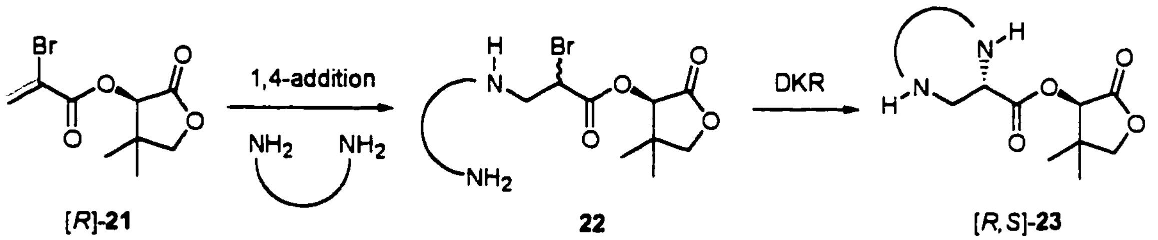
45%; 7:1 dr

This reaction was exceptionally fast, being completed in 3 hours. Attempts to improve the selectivity by adding **19** via a syringe pump over 1 hour failed to improve the selectivity, again yielding a 7:1 mixture of diastereomers. This result suggests that the rate of epimerization still exceeds the rate of halide displacement, but that the energy differences between the two possible S_N2 transition states are close enough in energy that the product ratio is independent of the substrate concentration.

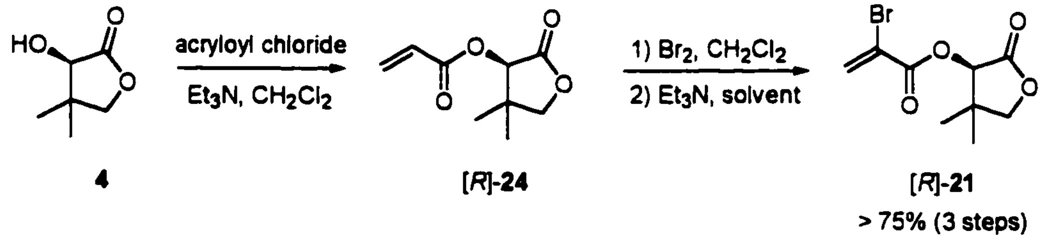
2.1.2 DKR of α-Halo [*R*]-Pantolactone Acrylates with Bifunctional Nucleophiles

A second bifunctional motif was investigated which involved the addition of bifunctional nucleophiles to [*R*]-pantolactone α-haloacrylates; as illustrated in Scheme 2.2. The initial 1,4-Michael addition of the diamine to [*R*]-pantolactone α-bromoacrylate (**21**) results in the *in situ* formation of the saturated α-bromo ester **22**. Ester **22** may now under go a DKR mediated halide displacement to provide compounds such as [*R*,*S*]-**23**.

Scheme 2.2 : DKR of [*R*]-Pantolactone α-Bromoacrylates with Bifunctional Nucleophiles

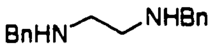
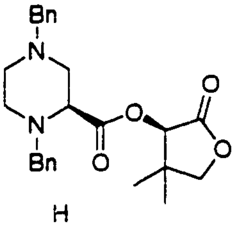
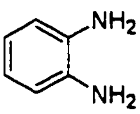
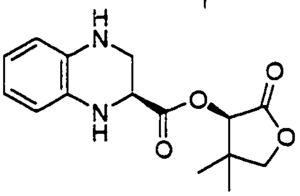
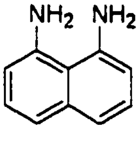
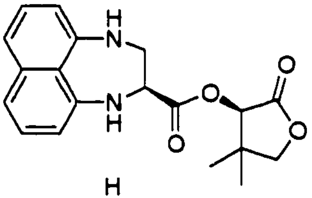
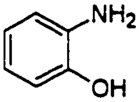
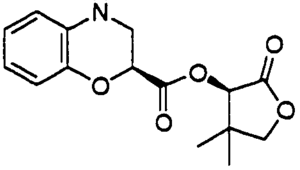


Acrylate **21** was prepared using the three step procedure outlined below. Neat acryloyl chloride (1.1 equiv.) was added to a cold CH_2Cl_2 solution containing equimolar quantities of [*R*]-pantolactone (**4**) and Et_3N. After warming to room temperature and aqueous work up, the crude [*R*]-pantolactone acrylate (**24**) was dissolved in CH_2Cl_2, cooled to 0 °C, and treated with an excess of Br_2. After stirring for 1 hour at RT, the solvent was removed *in vacuo* and the residue was dissolved in either CH_2Cl_2 or THF. Dropwise addition of Et_3N (3 equiv.), followed by aqueous work up, provided [*R*]-pantolactone α-bromoacrylate (**21**) as an off white solid in > 75% yield for the 3 steps. The resulting ester was used without further purification.



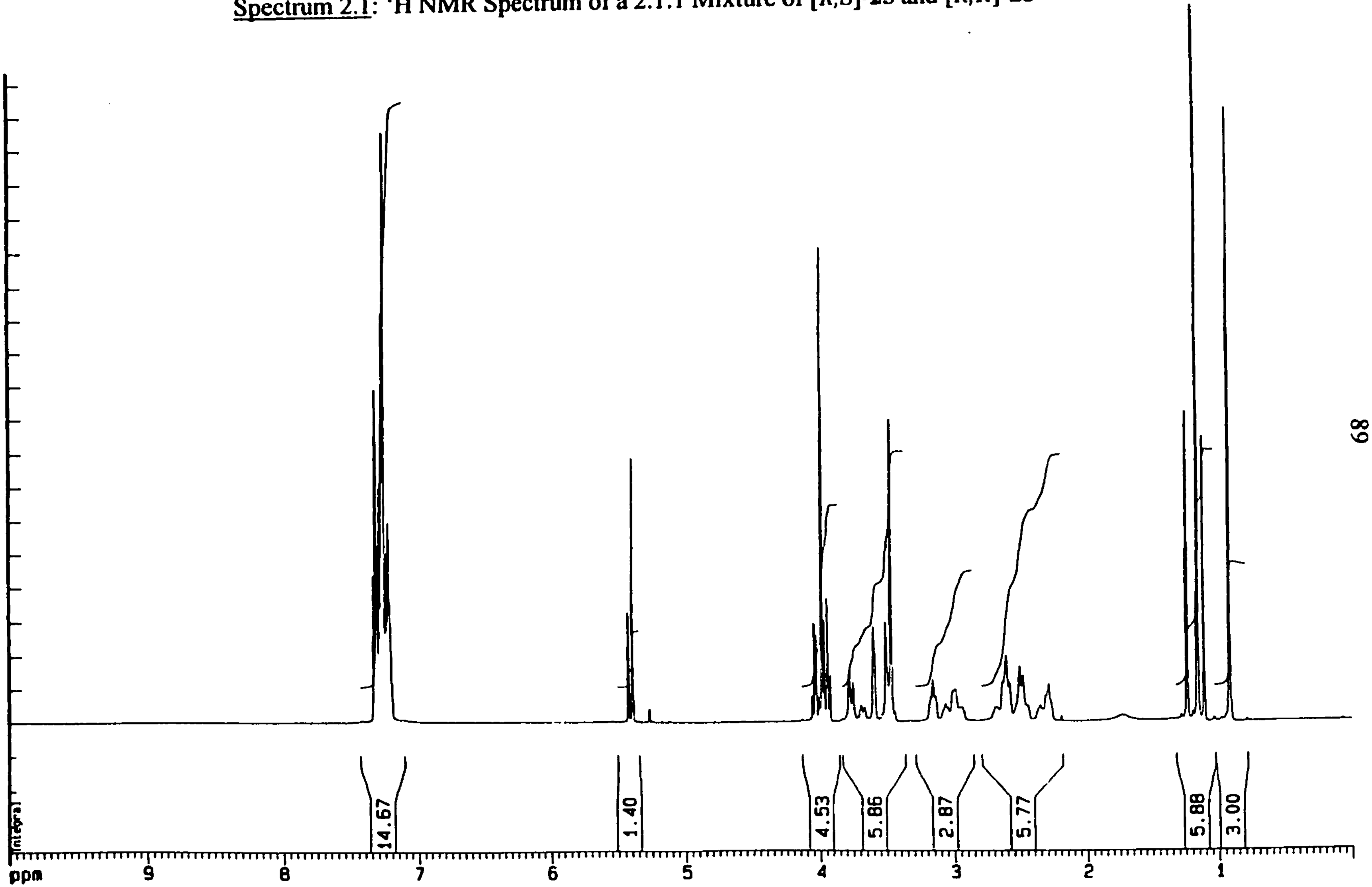
The reaction of several diamines with [*R*]-**21** is summarized in Table 2.2. Again, reactions were run under standard DKR conditions, in THF solvent. These reactions were surprisingly fast, all being complete in under 16 hrs.

Table 2.2: DKR Reaction of [*R*]-**21** With Bifunctional Nucleophiles

Entry	Diamine	Product	Yield(%)	dr
1	 **6**	 **25**	97	3 : 1
2	 **8**	 **26**	34	5 : 1
3	 **11**	 **27**	76	6 : 1
4	 **28**	 **29**	34	4 : 1

The reaction of [*R*]-**21** with dibenzylethylenediamine (**6**) was over in a little over an hour, to provide [*S,R*]-**25** in 97% yield (entry 1). The diastereoselectivity of this reaction was readily determined from the separate resonances observed for the hydrogens α- to the ester carbonyl (5.43 and 5.40 ppm, respectively), and from the distinctive [*R*]-pantolactone methyl resonances observed in the ^{1}H NMR spectrum of the crude and purified product (see Spectrum 2.1). Two diastereomers were clearly visible, in a ratio of 3:1.

Spectrum 2.1: ^{1}H NMR Spectrum of a 2.1:1 Mixture of [*R*,*S*]-**25** and [*R*,*R*]-**25**



A similar reaction with 1,2-phenylenediamine (**8**) provided [*S*,*R*]-**26** in 34% yield, as a single diastereomer (entry 2). Acrylate **21** was completely consumed in the reaction, but no other identifiable products were isolated by column chromatography.

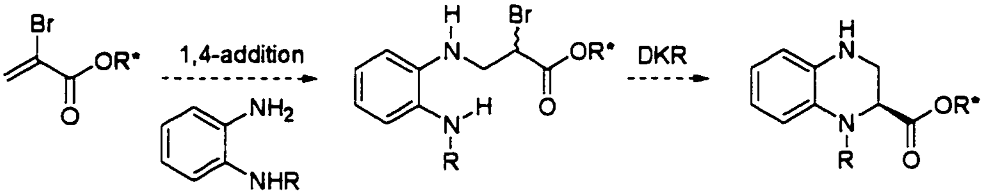
1,8-Diaminonaphthalene (**11**) provided [*S*,*R*]-**27** in 76% yield, as a 6:1 diastereomeric ratio. Again, separate resonances were clearly visible in the ^{1}H NMR spectrum of the isolated product.

2-Aminophenol (**28**) was also an effective nucleophile in this reaction, providing [*S*,*R*]-**29** in 36% isolated yield, with a diastereomeric ratio of 4:1. The amine reacted via 1,4-addition to leave the phenol in a position to perform the displacement. In previous work it was shown that the sodium salt of various phenols were effective in the DKR of [*R*]-pantolactone esters, providing the α-hydroxy compounds with good chiral induction.

We were disappointed, but not completely surprised, with the poor to moderate diastereoselectivities observed in entries 1, 3, and 4. The premise of DKR is that the epimerization reaction *must* be faster that the actual displacement reaction (see Section 1.3). This is likely the case in most intermolecular reactions. In the above situation, however, the displacement reactions are intramolecular. One would expect the intramolecular displacement reaction to be much faster than the corresponding intermolecular reaction, thereby lowering the overall diastereoselectivity of the displacement reaction.

In intermolecular DKR reactions, secondary, or bulky amines, display higher levels of chiral induction than do primary or unhindered amines. The diamines used in this study were all relatively hindered, in comparison to benzylamine. The *ortho*-aromatic diamines should be involved in some hydrogen bonding, lowering their nucleophilicity. One would therefore predict that these compounds would make ideal nucleophiles for DKR, providing the desired α-amino esters in high yield, and with high levels of diastereoselectivity. Unfortunately, this was not the case.

Recently a programme has been initiated to investigate the effect of using mono and/or disubstituted derivatives of 1,2-phenylenediamine and 1,8-diaminonaphthlene, in an effort to increase the diastereoselectivity of these reactions. An example of this is shown below for mono N-substituted 1,2-phenylenediamine **30**.

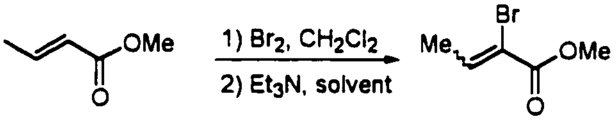


[*R*]-**21** **30** **31** [*R*,*S*]-**32**

The non-substituted amine should react first via a 1,4-Michael addition to yield the α-bromo ester **31**. The secondary amine should react slower than the corresponding non-substituted amine, allowing for epimerization to occur prior to the displacement reaction. An additional advantage of this type of system is that one of the nitrogens of [*R*,*S*]-**32** is already either protected, or it has been appropriately substituted.

The above reaction all involved the use of acrylate **21**, which was not substituted at the β-position. In order to determine the effect of substitution on the 1,4-Michael addition β-substituted α-bromoacrylates were to be tested.

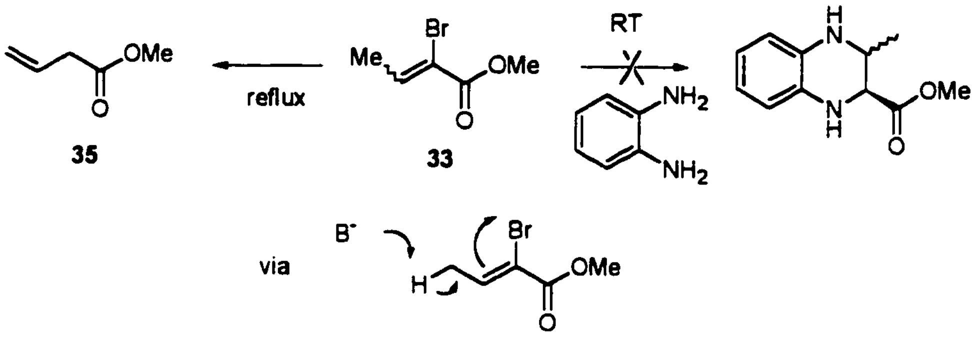
Before attempting these reactions using chiral acrylates, the reactions were attempted on methyl α-bromocrotonate (**33**). Compound **33** was prepared according to the method described for [*R*]-**21**, using methyl crotonate (**34**).



34 **33**

3:1 E/Z

Dehydrohalogenation of the dibromide of **34** with Et_3N provided a 3:1 mixture of (E)-**33** and (Z)-**33**. This meant that mixtures of diastereomers would be produced in the 1,4-addition, and the subsequent DKR reaction. Despite this the reaction between 1,2-phenylenediamine and **33** was attempted. Under standard DKR conditions (RT, 3 days), no reaction was observed. Upon refluxing over night, crotonate **33** was completely consumed.



The only isolated product from this reaction, compound **35**,[6] was the result of elimination of bromide, via deconjugative halo-dehydration of one of the crotyl methyl protons. This product was only isolated in 35% yield, suggesting the remaining crotonate was consumed via a different pathway.

No reaction was observed between **33** and 2-aminophenol, or with 2-aminothiophenol, under standard DKR conditions. Clearly these compounds are not nucleophilic enough to undergo 1,4-Michael additions with β-substituted α-bomoacrylates.

2.2 Summary

The addition of bifunctional nucleophiles to α-bromo [*R*]-pantolactone esters and to [*R*]-pantolactone α-bromoacrylates has been shown to proceed with moderate levels of diastereo- and enantioselective induction. Future studies, involving the use of mono-protected diamines, should yield increase the level of chiral induction.

2.3 References

1. a) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.*, **1993**, *34*, 4476. b) Koh, K.; Ben, R. N.; Durst, T. *Tetrahedron Lett.*, **1994**, *35*, 375. c) O'Meara, J. A.; Jung, M.; Durst, T. *Tetrahedron Lett.*, **1995**, *36*, 2559. d) Kubota, H.; Kubo, A.; Takahashi, M.; Shimizu, R.; Da-te, T.; Okamura, K.; Nunami, K. *J. Org. Chem.*, **1995**, *60*, 6776. e) O'Meara, J.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. *J. Org. Chem.*, **1998**, *63*, 3117.
2. Kubo, A.; Kubato, H.; Takahashi, M.; Nunami, K. *Tetrahedron Lett.*, **1996**, *37*, 4957.
3. Ben, R. in "The Synthesis of Optically Active α-Amino Esters Via Kinetic Dynamic Resolution", Ph.D. Thesis, University of Ottawa, Ottawa, Ontario, Canada, 1995.
4. Ben, R.; Durst, T. unpublished results.
5. Jaquith, J. B.; Durst, T. unpublished results.
6. The ^{1}H NMR spectrum of **35** agreed with that of commercially available methyl 3-butenoate (Aldrich 38,426-7).

2.4 Experimental

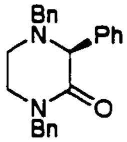
2.4.1 General

All reaction, unless stated otherwise, were run under a nitrogen atmosphere using dry solvents. THF was dried over sodium benzophenone ketyl, and distilled prior to use. Methylene chloride and triethylamine were dried over NaH, and distilled prior to use. DMF was dried over NaH, and distilled under reduced pressure. The [*R*]-pantolactone esters **1a** and **1b** were prepared according to published procedures.[1] All chemical reagents were obtained from Aldrich Chemical Company and used as received, unless stated otherwise.

2.4.2 General Procedure A : Addition of Bifunctional Nucleophiles to α-Bromo [*R*]-Pantolactone Esters

To a 1M THF solution of **1** (1 equiv.) was added *n*-Bu_4NI (10 mol%), triethylamine (1 equiv.), and the appropriate bifunctional nucleophile (1 equiv.). The solution was stirred at room temperature until no starting material was observed by TLC, or until the reaction was shown to be complete by ^1H NMR spectroscopy. Ethyl acetate and saturated aqueous Na_2HCO_3 were added, and the organic layer was washed with several portions of water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography.

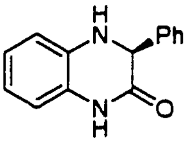
2.4.3 Compound 7



Compound 7 was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (5 mL) and treated with triethylamine (120 μL, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and *N*,*N*-dibenzylethylenediamine (210 μL, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided 7 as a white solid in 84% yield.

m.p. °C. IR (KBr, cm^{-1}) 3030 (w), 3000 (w), 1646 (s), 1491 (m), 1451 (m), 751 (s), 700 (s). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.56 (dd, J=1.4, 8.4Hz, 2H), 7.34 (t, J=8.4Hz, 2H), 7.32-7.28 (m, 4H), 7.26-7.19 (m, 6H), 4.63 (d, J=14.5Hz, 1H), 4.53 (d, J=14.5Hz, 1H), 4.14 (s, 1H), 3.74 (d, J=13.4Hz, 1H), 4.45 (dt, J=3.8, 11.0Hz, 1H), 3.15 (d, J=13.5Hz, 1H), 3.11 (dd, J=3.3, 11.8Hz, 1H), 2.95 (dd, J=3.5, 12.0Hz, 1H), 2.47 (J=3.4, 11.0Hz, 1H). ^{13}C NMR (50MHz, $CDCl_3$) δ 168.3, 139.4, 137.7, 136.8, 129.1, 128.8, 128.6, 128.4, 128.3, 127.9, 127.5, 127.2, 71.2, 58.8, 50.3, 46.6, 45.8. MS (m/z) M^+ = 359.

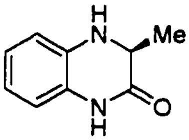
2.4.4 Compound 9



Compound **9** was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (5 mL) and treated with triethylamine (120 μL, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 1,2-phenylenediamine (108 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **9** as a yellow solid in 72% yield.

m.p. >250 °C. IR (KBr, cm^{-1}) 3310 (m) 2950 (m), 1669 (s), 1600 (m), 1503 (m), 1382 (m), 1309 (m), 739 (s), 698 (s). ^{1}H NMR (200MHz, DMSO-d^{6}) δ 12.56 br s, 1H), 7.34 (dd, J=1.8, 8.0Hz, 1H), 7.82 (dd, J=1.8, 8.0Hz, 1H), 7.81 (d, J=8.0Hz, 1H), 7.56-7.51 (m, 5H), 7.49-7.26 (m, 2H). ^{13}C NMR (50MHz, DMSO-d^{6}) δ 154.6, 135.7, 132.1, 130.19, 130.13, 129.2, 128.8, 127.8, 123.3, 115.1. HRMS Cal'd. for $C_{14}H_{12}N_2O$ 224.0950. Found 224.0950.

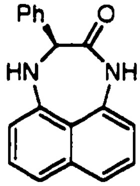
2.4.5 Compound 10



Compound **10** was prepared according to General Procedure A. Ester **1b** (153 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (120 mL, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 1,2-phenylenediamine (108 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided **9** as a red solid in 58% yield.

m.p. 136.0-137.0 °C. IR (KBr, cm^{-1}) 3329 (w), 3019 (w), 2974 (w), 2897 (w), 2839 (w), 1664 (s), 1568 (m), 1432 (m), 1380 (m), 829 (m). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.43 (br s, 1H), 6.93-6.91 (m, 2H), 6.85-6.72 (m, 2H), 4.07 (q, J=6.6Hz, 1H), 1.56 (d, J=6.6Hz, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 169.6, 133.4, 125.6, 123.8, 119.6, 115.5, 114.1, 52.0, 17.9. HRMS Cal'd. for $C_9H_{10}N_2O$ 162.0793. Found 162.0778.

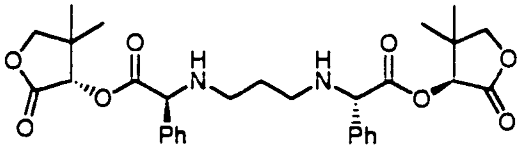
2.4.6 Compound 12



Compound **10** was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (120 μL, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 1,8-diaminonaphthylene (158 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided **9** as a red solid in 58% yield.

m.p. 77.0-95.0 °C (decomposed slowly). IR (KBr, cm^{-1}) 3341 (w), 3236 (w), 3056 (w), 1675 (s), 1579 (s), 1425 (m), 1381 (m), 1068 (w), 819 (m), 758 (m), 698 (w). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.41 (br s, 1H), 7.48 (d, J=8.2Hz, 1H) 7.40-7.16 (m, 8H), 6.85 (d, J=7.2Hz, 1H), 6.66 (d, J=7.2Hz, 1H), 5.08 (s, 1H). ^{13}C NMR (50MHz, $CDCl_3$) δ 171.6, 144.7, 137.0, 134.1, 128.8, 128.6, 128.3, 126.4, 126.0, 124.8, 121.1, 115.4, 112.2, 65.1.

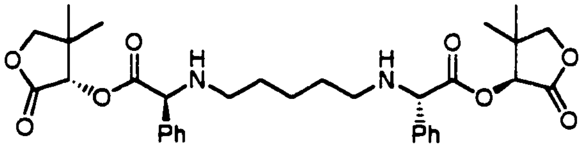
2.4.7 Preparation of [*R*,*S*,*S*,*R*]-14



[*R*,*S*,*S*,*R*]-**14** was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (120 μL, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and cadaverine hydrochloride (158 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided **14** as a yellow oil in 78% yield.

IR (neat, cm^{-1}) : 3350 (w), 2963 (m), 1790 (s), 1752 (s), 1692 (m). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.48-7.15 (m, 10H), 5.33 (s, 2H), 4.47 (s, 2H), 3.88 (s, 4H), 3.25 (br s, 2H), 2.79-2.52 (m, 4H), 1.78-1.53 (m, 2H), 0.91 (s, 6H), 0.62 (s 6H). ^{13}C NMR (50MHz, $CDCl_3$) δ 172.4, 171.3, 137.9, 128.2, 128.1, 127.3, 75.1, 75.0, 64.8, 41.2, 29.6, 24.5, 22.5, 19.0.

2.4.8 Preparation of [*R*,*S*,*S*,*R*]-16

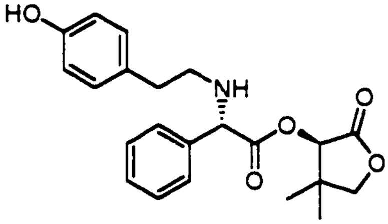


[*R*,*S*,*S*,*R*]-**16** was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (120 μL, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 1,5-diaminopentane (158 mg, 1.0 mmol). The resulting suspension was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided **16** as a clear oil in 86% yield, as a 15.6:1 mixture of diastereomers.

[*R*,*S*,*S*,*R*]-**16** (major) : IR (neat, cm^{-1}) 3326 (w), 2967 (m), 2929 (m), 1789 (s), 1767 (s), 1698 (m), 1651 (w), 1626 (w), 1457 (m), 1372 (m), 1209 (m), 1139 (s) 1072 (s), 1011 (s), 996 (s). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.34-7.29 (m, 4H), 7.28-7.24 (m, 4H), 7.23-7.22 (m, 2H), 5.30 (s, 2H), 4.47 (s, 2H), 3.87 (d, J=9.1Hz, 2H), 3.85 (d, J=9.1Hz, 2H), 2.55 (overlapping ddd, 2H), 2.45 (overlapping ddd, 2H), 1.44 (m, 4H), 1.29 (m, 2H), 0.87 (s, 3H), 0.60 (s, 3H). ^{13}C NMR (74.5MHz, $CDCl_3$) δ 172.1, 171.9, 137.9, 128.6, 128.1, 127.3, 75.8, 75.0, 65.0, 47.4, 40.2, 29.6, 24.5, 22.5, 19.0.

[*R*,*R*,*R*,*R*]-**16** (minor) : ^{1}H NMR (500MHz, $CDCl_3$) δ 7.34-7.29 (m, 4H), 7.28-7.24 (m, 4H), 7.23-7.22 (m, 2H), 5.27 (s, 2H), 4.45 (s, 2H), 3.94 (d, J=9.1Hz, 2H), 3.92 (d, J=9.1Hz, 2H), 2.55 (overlapping ddd, 2H), 2.45 (overlapping ddd, 2H), 1.44 (m, 4H), 1.29 (m, 2H), 1.09 (s, 3H), 0.96 (s, 3H).

2.4.9 Compound [*S*,*R*]-18

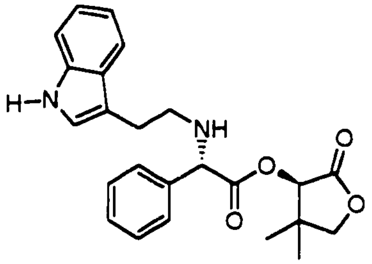


[*S*,*R*]-**18** was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with tyramine hydrochloride (174 mg, 1.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and triethylamine (240 μL, 2.0 mmol). The resulting suspension was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 2:1 hexane/ethyl acetate, provided **18** as a white solid in 92% yield, as an 11:1 mixture of diastereomers.

[*S*,*R*]-**18** : m.p. 125.5-126.5 °C. IR (KBr, cm^{-1}) 3289 (s), 3300-2500 (br s), 1813 (s), 1745 (s), 1615 (s), 1597 (s), 1517 (s), 1460 (s), 1372 (s), 839 (s), 724 (s), 934 (s). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.34-7.28 (m, 5H), 7.98 (d, J=8.4Hz, 2H), 6.68 (d, J=8.4Hz, 2H), 5.35 (s, 1H), 4.45 (s, 1H), 4.12 (s, 2H), 2.85-2.77 (m, 1H), 2.75-2.72 (m, 3H), 0.90 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (50MHz, CDCl$_3$) δ 172.5, 172.0, 154.5, 137.6, 130.9, 1129.7, 128.9, 128.3, 128.2, 115.5, 76.3, 65.1, 49.0, 40.5, 35.1, 22.7, 19.2.

[*R*,*R*]-**18** : ^{1}H NMR (200MHz, CDCl$_3$) δ 7.34-7.28 (m, 5H), 7.98 (d, J=8.4Hz, 2H), 6.68 (d, J=8.4Hz, 2H), 5.29 (s, 1H), 4.45 (s, 1H), 4.15 (s, 2H), 2.85-2.77 (m, 1H), 2.75-2.72 (m, 3H), 1.09 (s, 3H), 0.95 (s, 3H).

2.4.10 Compound [*S*,*R*]-20



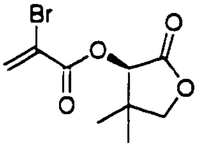
[*S*,*R*]-**20** was prepared according to General Procedure A. Ester **1a** (290 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with tryptamine (160 mg, 1.0 mmol), *n*-Bu$_4$NI (36 mg, 0.01 mmol), and triethylamine (240 μL, 2.0 mmol). The resulting suspension was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 2:1 ethyl acetate/hexane, provided **20** as a white solid in 92% yield, as a 7:1 mixture of diastereomers.

[*S*,*R*]-**20** : IR (KBr, cm^{-1}) 3414 (m), 3328 (sh), 2966 (m), 2929 (m), 1789 (s), 1750 (s), 1663 (w), 1456 (m), 1158 (s), 738 (s). ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.23 (br s, 1H), 7.55 (d, J=7.5Hz, 1H), 7.35-7.27 (m, 5H), 7.22 (d, J=7.1Hz, 1H), 7.20-7.07 (m, 2H), 6.99 (d, J=2.2Hz, 1H), 5.33 (s, 1H), 3.88 (s, 2H), 3.05-2.94 (m, 4H), 2.23 (br s, 1H), 0.87 (s, 3H), 0.61 (s, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 172.2, 137.5, 136.3, 128.7, 128.6, 128.3, 128.2, 127.5, 122.0, 121.8, 119.1, 118.7, 113.3, 111.1, 76.0, 75.1, 65.2, 47.5, 40.3, 25.6, 22.6, 19.1.

[*R*,*R*]-**20** : ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.23 (br s, 1H), 7.57 (d, J=7.5Hz, 1H), 7.35-7.27 (m, 5H), 7.22 (d, J=7.1Hz, 1H), 7.20-7.07 (m, 2H), 6.99 (d, J=2.2Hz, 1H), 5.27 (s, 1H), 3.92 (s, 2H), 2.91-2.80 (m, 4H), 2.23 (br s, 1H), 1.08 (s, 3H), 0.91 (s, 3H). ^{13}C

NMR (50 MHz, $CDCl_3$) δ 172.1, 137.5, 136.3, 128.7, 128.6, 128.3, 128.2, 127.5, 122.0, 121.8, 119.1, 118.7, 113.3, 111.1, 75.4, 75.1, 65.5, 47.7, 40.2, 25.6, 22.9, 19.6.

2.4.11 Preparation of [*R*]-Pantolactone α-bromoacetate, [*R*]-21



Acryloyl chloride (3.13 mL, 38.5 mmol) was added to a cold CH_2Cl_2 (100 mL) solution of [*R*]-pantolactone (5.00g, 38.5 mmol) and triethylamine (5.89 mL, 42.4 mmol). The solution was warmed to room temperature and allowed to stir for 2 hours. The solution was diluted with diethyl ether (200 mL) and water (100 mL). The organic layer was washed with several portions of water, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to provide [*R*]-**24** as clear oil in quantitative yield. This material was advanced to the next step without further purification.

[*R*]-**24** : ^{1}H NMR (200MHz, $CDCl_3$) δ 6.15 (dd, J=1.5, 17.2Hz, 1H), 6.20 (dd, J=10.3Hz, 1H), 5.95 (dd, J=1.5, 17.2Hz, 1H), 5.42 (s, 2H), 4.04 (s, 2H), 1.21 (s, 3H), 1.11 (s, 3H).

The crude oil was taken up in dry CH_2Cl_2 (50 mL) and cooled in an ice bath. Neat bromine was added until a deep red solution was obtained. The solution was allowed to stir at room temperature and the progress of the reaction was checked after 1 hour by ^{1}H NMR spectroscopy. If the reaction was not complete more bromine was added, and the solution was allowed to stir for an additional hour. The solvent and excess bromine were removed under reduced pressure to provide a 1:1.4 mixture of diastereomers. The crude oil was advanced to the next step without further purification.

Major diastereomer : ^{1}H NMR (200MHz, $CDCl_3$) δ 5.62 (s, 1H), 4.61 (dd, J=4.6, 10.8Hz, 1H), 4.05 (s, 2H), 3.90 (dd, J=1.8, 10.8Hz, 1H), 7.68 (dd, J=1.8, 10.8Hz, 1H), 1.25 (s, 3H), 1.18 (s, 3H).

Minor diastereomer : ^{1}H NMR (200MHz, CDCl$_3$) δ 5.40 (s, 1H), 4.53 (dd, J=4.6, 10.5Hz, 1H), 4.05 (s, 2H), 3.94 (dd, J=1.8, 10.8Hz, 1H), 3.73 (dd, J=1.8, 10.8Hz, 1H), 1.25 (s, 3H), 1.15 (s, 3H).

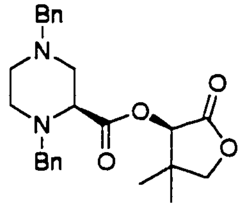
The crude oil obtained above was dissolved in dry THF (100 mL) and cooled on ice. Triethylamine (5.89 mL, 42.4 mmol) was added dropwise, and the solution was allowed to warm to room temperature. After stirring over night the solution was diluted with diethyl ether (200 mL) and treated with water (100 mL). The organic layer was washed with several portions of water, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure to provide [*R*]-**21** as an off white solid, 78% yield.

[*R*]-**21** : m.p. 66.0-67.0 °C. IR (KBr, cm-1) 3121 (w), 2978 (m), 2936 (m), 1791 (s), 1734 (s), 1603 (m), 1578 (w), 1250 (s), 1111(s). ^{1}H NMR (200MHz, CDCl$_3$) δ 6.98 (d, J=1.8Hz, 1H), 6.31 (d, J=1.8Hz, 1H), 5.33 (s, 1H), 3.99 (s, 2H), 1.14 (s, 3H), 1.06 (s, 3H). ^{13}C NMR (50MHz, CDCl$_3$) δ 171.6, 160.8, 132.7, 119.7, 77.1, 76.2, 40.4, 22.8, 19.9.

2.4.12 General Procedure B: Addition of Bifunctional Nucleophiles to [*R*]-Pantolactone α-Bromoacrylates

To a 1M THF solution of [*R*]-**21** (1 equiv.) was added *n*-Bu$_4$NI (10 mol%), triethylamine (2 equiv.), and the appropriate bifunctional nucleophile (1 equiv.). The solution was stirred at room temperature until no starting material was observed by TLC, or until the reaction was shown to be complete by ^{1}H NMR spectroscopy. Ethyl acetate and saturated aqueous NaH$_2$CO$_3$ were added, and the organic layer was washed with several portions of water, dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography.

2.4.13 Compound 25

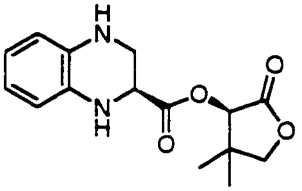


Compound **25** was prepared according to General Procedure B. Ester [*R*]-**21** (263 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (240 μL, 2.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and dibenzylethylenediamine (210 μL, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided **25** as a white solid in 97% yield. The diastereomeric ratio was shown to be 2.1:1 by 500 MHz ^1H NMR spectroscopy.

[*S*,*R*]-**25** : m.p. 105.5-107.5 °C. IR (KBr, cm^{-1}) 2972 (s), 2929 (s), 2856 (s), 2821 (s), 2775 (s), 1795 (s), 1755 (s), 1495 (m), 1452 (s), 1375 (s), 1257 (m), 1136 (s), 1029 (s), 996 (s), 748 (s), 701 (s). ^1H NMR (500MHz, $CDCl_3$) δ 7.32-7.21 (m, 10H), 5.40 (s, 1H), 4.03 (dd, J=9.0, 14.5Hz, 1H), 3.99 (s, 2H), 3.96 (d, J=9.0Hz, 1H), 3.59 (s, 1H), 3.51 (s, 1H), 3.47 (s, 2H), 3.16 (m, 1H), 3.03 (m, 1H), 2.62 (m, 1H), 2.51 (m, 1H), 2.27 (m, 1H), 1.15 (s, 3H), 0.91 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 172.3, 170.5, 138.3, 137.7, 129.12, 129.06, 128.9, 128.25, 127.11, 127.07, 76.1, 74.6, 62.9, 61.3, 59.2, 55.9, 53.1, 47.5, 40.2, 23.1, 19.8. HRMS Cal'd. for $C_{25}H_{30}N_2O_4$ 422.2206. Found 422.2222.

[*R*,*R*]-**25** : ^1H NMR (500MHz, $CDCl_3$) δ 7.32-7.21 (m, 10H), 5.43 (s, 1H), 4.03 (dd, J=9.0, 14.5Hz, 1H), 3.99 (s, 2H), 3.93 (d, J=9.0Hz, 1H), 3.73 (d, J=12.3Hz, 2H), 3. d, J=12.3Hz, 2H), 3.08 (m, 1H), 2.95 (m, 1H), 2.67 (m, 1H), 2.47 (m, 1H), 2.34 (m, 1H), 1.23 (s, 3H), 1.11 (s, 3H). . ^{13}C NMR (50MHz, $CDCl_3$) δ 172.0, 171.6, 138.2, 138.0, 129.12, 129.06, 128.9, 128.25, 127.11, 127.07, 76.1, 75.1, 62.7, 62.1, 59.3, 56.1, 52.4, 48.3, 40.2, 23.1, 20.3.

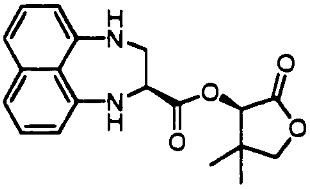
2.4.14 Compound 26



Compound **26** was prepared according to General Procedure B. Ester [*R*]-**21** (263 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (240 μL, 2.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 1,2-phenylenediamine (108 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided [*R*,*S*]-**26** as a light yellow solid in 34% yield. Compound **26** was shown to be a single diastereomer by 500 MHz ^1H NMR spectroscopy.

m.p. 134.0-135.0 °C. IR (KBr, cm^{-1}) 3420 (s), 3386 (s), 2981 (m), 2916 (m), 1795 (s), 1750 (s), 1603 (w), 1509 (m), 1463 (m), 1172 (s), 1136 (s), 997 (m), 743 (m). ^1H NMR (500MHz, $CDCl_3$) δ 6.65-6.61 (m, 3H), 6.51-6.49 (m, 1H), 5.30 (s, 1H), 4.33 (dd, J=3.2, 4.9Hz, 1H), 4.03 (d, J=9.1Hz, 1H), 4.00 (d, J=9.1Hz, 1H), 3.68 (dd, J=3.2, 11.1Hz, 1H), 3.59 (dd, J=4.9, 11.1Hz, 1H), 1.17 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 173.8, 172.5, 134.9,132.5, 121.0, 120.6, 116.9, 116.8, 79.1, 55.7, 45.1, 42.0, 24.4, 21.5. HRMS Cal'd. for $C_{15}H_{18}N_2O_4$ 290.1267. Found 290.1262.

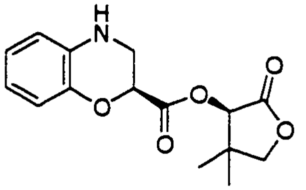
2.4.15 Compound 27



Compound **27** was prepared according to General Procedure B. Ester [*R*]-**21** (263 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (240 μL, 2.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 1,8-diaminonaphthylene (158 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided [*R*,*S*]-**26** as a light yellow solid in 34% yield. Compound **26** was shown o be a single diastereomer by 500 MHz ^1H NMR spectroscopy.

m.p. 65.0-70.0 °C (expands); 99.0-101.0 °C (melts). IR (KBr, cm^{-1}) 3380 (s), 3045 (m), 2971 (s), 2871 (m), 1785 (s), 1764 (s), 1582 (s), 1139 (s), 995, (s), 815 (s), 757 (s). ^1H NMR (200MHz, $CDCl_3$) δ 7.25 (d, J=7.3Hz, 1H), 7.26-7.16 (m, 2H), 7.19 (d, J=8.2Hz, 1H), 6.77 (dd, J=1.1, 7.3Hz, 1H), 6.59 (d, J=0.9. 7.1Hz, 1H), 5.38 (s, 1H), 4.47 (dd, J=5.6, 9.0Hz, 1H), 3.99 (s, 2H), 3.83 (dd, J=5.6, 13.4Hz, 1H), 3.63 (dd, J=9.0, 13.4Hz, 1H), 1.12 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (75.4MHz, $CDCl_3$) δ 172.7, 172.1, 147.8, 143.5, 138.0, 127.1, 126.3, 122.1, 121.3, 120.7, 114.9, 112.0, 76.8, 76.3, 61.5, 49.9, 40.8, 23.5, 20.6.

2.4.16 Compound 29



Compound **29** was prepared according to General Procedure B. Ester [*R*]-**21** (263 mg, 1.0 mmol) was dissolved in THF (10 mL) and treated with triethylamine (240 µL, 2.0 mmol), *n*-Bu_4NI (36 mg, 0.01 mmol), and 2-aminophenol (110 mg, 1.0 mmol). The resulting solution was stirred at room temperature for 16 hrs. Silica gel chromatography, eluting with 1:1 CH_2Cl_2/hexane, provided [*R*,*S*]-**29** as purple solid in 34% yield. The diastereomeric ratio was shown to be 4:1 by 500 MHz ^1H NMR spectroscopy.

[*S*,*R*]-**29**: m.p. 114.0-115.0 °C. IR (KBr, cm^{-1}) 3387 (s), 3361 (s), 2971 (m), 2929 (m), 2875 (m), 1782 (s), 1771 (s), 1611 (m), 1595 (m), 1502 (s), 1277 (s), 1078 (s). ^1H NMR (500MHz, $CDCl_3$) δ 6.88 (dd, J=1.5, 7.9Hz, 1H), 6.75 (dt, J=1.5, 7.6Hz, 1H), 6.70 (dt, J=1.5, 7.6Hz, 1H), 6.60 (dd, J=1.5, 7.7Hz, 1H), 5.37 (s, 1H), 5.00 (dd, J=3.4, 3.7Hz, 1H), 3.98 (s, 2H), 3.61 (dd, J=3.5, 6.5Hz, 2H), 1.15 (s, 3H), 1.00 (s, 3H). ^{13}C NMR

(50MHz, $CDCl_3$) δ 171.8, 168.5, 142.8, 132.5, 121.6, 119.9, 116.8, 116.2, 76.1, 75.7, 72.5, 42.6, 40.3, 22.8, 19.6. HRMS Cal'd. for $C_{15}H_{17}NO_5$ 291.1107. Found 291.1092.

Chapter Three

Studies Towards the Synthesis of Hemiasterlin And Hemiasterlin Analogues

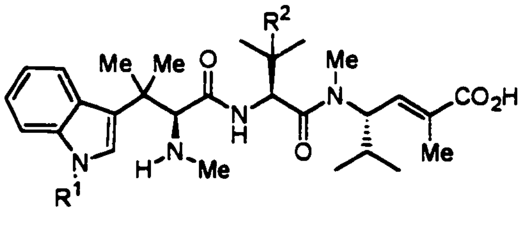
3.0 Introduction

In the search for new medicinal agents, many scientists have turned their attention to the isolation of structurally novel and biologically active compounds from marine organisms. The isolation and characterization of these compounds is an arduous task, generally yielding only milligram quantities of these substances. The novel molecular structures found in the marine environment have challenged organic chemists to prepare significant enough quantities of these compounds to allow for 'complete' biological testing.

One class of these compounds is known as the hemiasterlins.[1,2,3] These biologically and structurally novel compounds have received very little attention, despite their potential use as anti-cancer agents. The following chapter deals with the partial synthesis of hemiasterlin and various derivatives thereof.

3.1 The Hemiasterlins

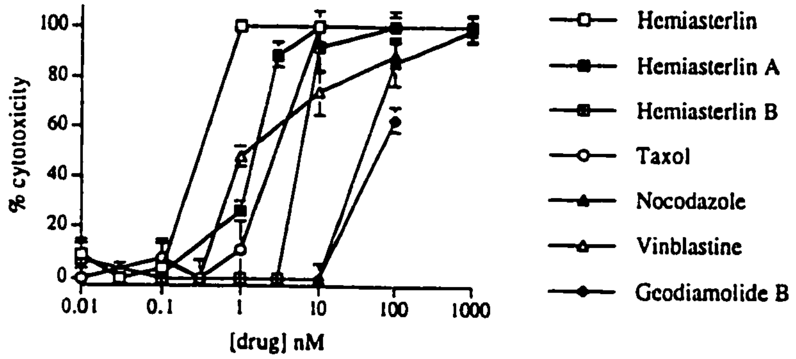
Hemiasterlin (**1**) was first isolated from the marine sponge *hemiasterella minor.*[1] More recently hemiasterlin (**1**), hemiasterlin A (**2**), and hemiasterlin B (**3**) have been isolated from the marine sponge *Cymbastela* sp., which is native to the waters of Papua New Guinea.[2] These tri- and tetrapeptides display high levels of *in vivo* cytotoxicity to murine leukemia P388 (IC_{50} = 4.57 μg/mL), human ovarian, colon, and lung cancer cell lines.[2]



1; Hemiasterlin; R^1 = R^2 = Me
2; Hemiasterlin A; R^1 = H, R^2 = Me
3; Hemiasterlin B; R^1 = R^2 = H

Anderson *et al.* have shown the hemiasterlins to be antimitotic agents.[3] The mode of action of hemiasterlin A and B involves the binding of hemiasterlin to tubulin, much like taxol, vincristin, and nocodazole. This results in the inhibition of regular microtubular formation and mitotic arrest. Unlike taxol, which promotes uncontrolled tubulin polymerization, hemiasterlin promotes tubulin depolymerization. However, unlike vincristin and nocodazole, which also promote tubulin depolymerization, hemiasterlin does not produce para-crystals or microtubule bundles.

The cytotoxicity of the hemiasterlins was compared to several well known microtubular inhibitors.[3] The hemiasterlins were shown to be more potent cytotoxins and mitotic blockers in MCF7 breast cancer cell lines than taxol, nocodazole or vinblastin, as shown below:



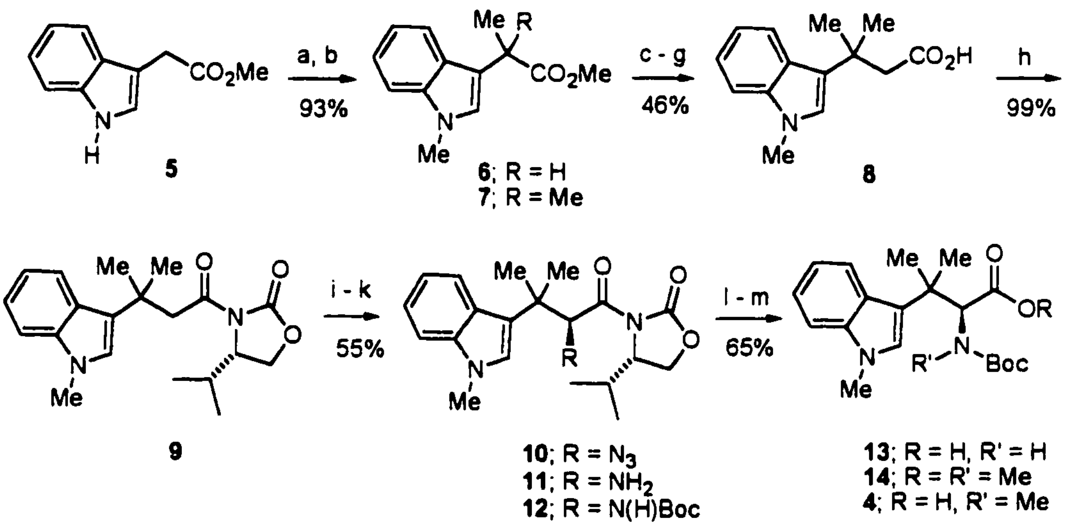
adapted from Anderson, H. J., *et. al.*, *Cancer Chemother. Pharma.*, **1997**, *39*, 223 (ref. 3)

In addition to their interesting cytotoxicity, these compounds display unique structures, containing two novel amino acids; a *tert*-butylglycine residue, and either a tri- or tetramethylated tryptophan residue. The first total synthesis of (-)-hemiasterlin was reported by Anderson and Piers *et al.*[4] This synthesis was quite lengthy, and is summarized in the following pages.

3.2 Synthesis of (-)-Hemiasterlin

Due to the presence of three unnatural α-amino acid residues, Piers and Anderson *et al.* chose to prepare each of the three unnatural α-amino acid residues of (-)-hemiasterlin separately. The final steps of their synthesis involved combining these residues, using standard peptide coupling reagents.

The synthesis of the methylated tryptophan moiety involved 16 steps, and yielded the Boc protected tryptophan **4** in 16% over all yield. The details of each step are summarized in Scheme 3.1. A two step methylation of methyl 3-indolylacetate (**5**), using $NaN(SiMe_3)_2$ and MeI, was followed by a one carbon chain extension, via a 5 step procedure, to provide acid **8**, in 46% yield from 7.

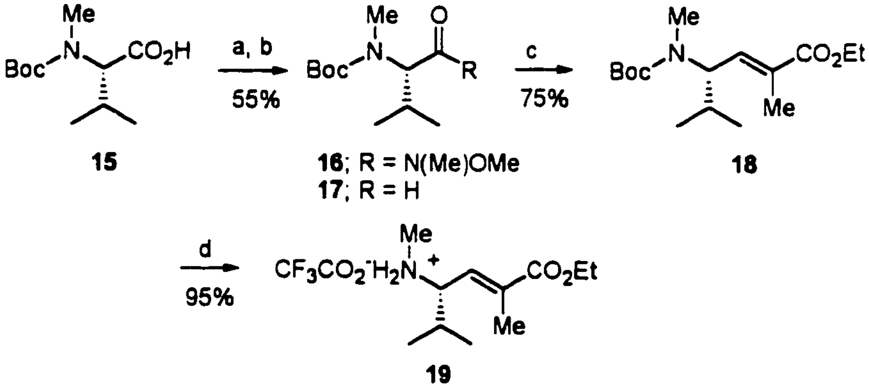


Scheme 3.1: Synthesis of the Tetramethyltryptophan Residue 4

a) $KN(SiMe_3)_2$ (3 equiv.), THF, -78 °C to RT, 3 hrs; MeI, -78 °C to RT, 2 hrs. b) $KN(SiMe_3)_2$ (1.5 equiv.), as in a. c) *i*-Bu_2AlH, Et_2O. d) TPAP, NMO, CH_2Cl_2, 4A mol. sieves. e) $Ph_3P{=}CHOMe$, THF, RT. f) *p*-TsOH, H_2O, dioxane, 60 °C, 16 hrs. g) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH, H_2O, 0 °C. h) Me_3CCOCl, Et_3N, THF, -78 °C; Li oxazolidinone, THF, -78 °C. i) $KN(SiMe_3)_2$, (1.1 equiv.), THF, -78 °C; 2,4,6-triisopropylbenzenesulfonyl azide, THF, -78 °C, 1 min; AcOH, 30-40 °C, 1 hr. j) $SnCl_2$, dioxane, H_2O, RT, 36 hrs. k) $(Me_3CO_2C)_2O$, dioxane, H_2O, RT, 16 hrs. l) LiOOH, THF, H_2O. m) NaH (6 equiv.), DMF; MeI, RT, 16 hrs. n) LiOH, MeOH, H_2O, 60 °C, 24 hrs; citric acid, H_2O.

Instillation of the Evan's auxiliary proceeded in near quantitative yield, which allowed for the diastereoselective azidation of **9**, to provide azide **10**. Reduction of the **10** with $SnCl_2$ and Boc protection of the resulting amine **11**, yielded compound **12**. Removal of the Evans auxiliary and methylation of the amine provided the desired tetramethyl tryptophan moiety **4**.

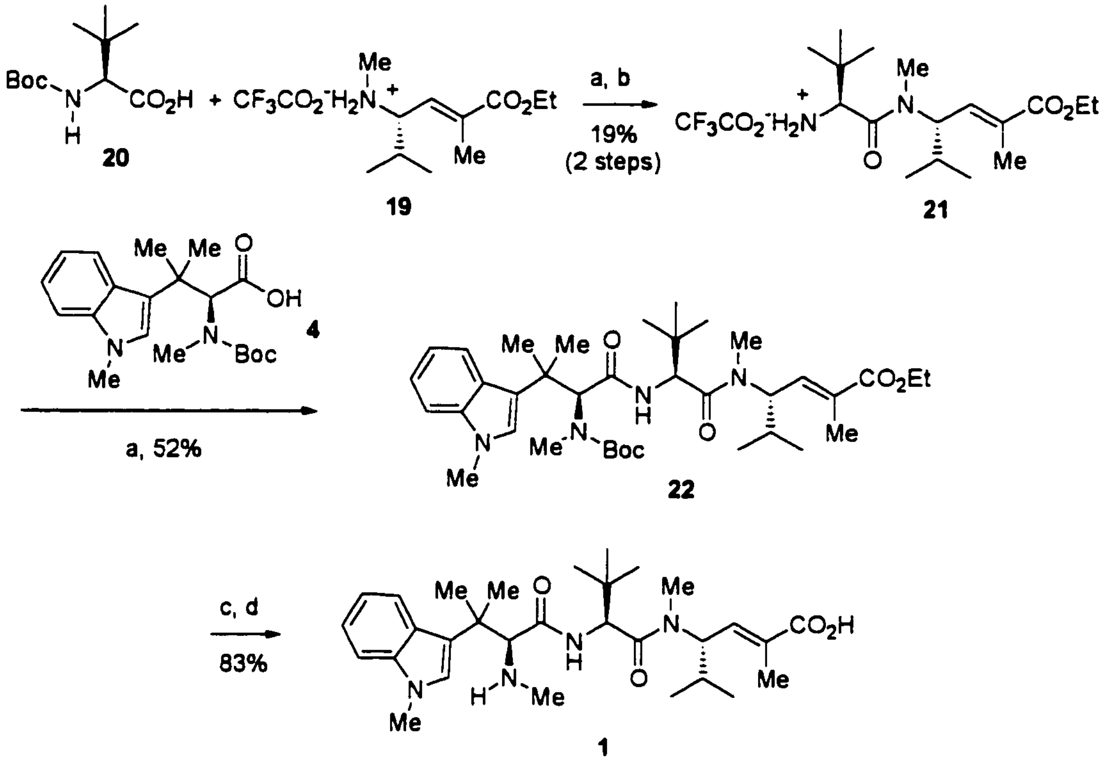
The right hand side of **1** was prepared from commercially available (*S*)-*N*-Boc-*N*-methylvaline (**15**). Lithium aluminum hydride reduction of the Weinreb amide **16** provided aldehyde **17** in 55% yield. Wittig olefination of **17** with $Ph_3P{=}C(Me)CO_2Et$, proceeded stereoselectively, to provide the *E*-2-alkenoate **18**. Deprotection of the amine with TFA provided the TFA ammonium salt **19** in 39% yield, from compound **15**.



Scheme 3.2: Synthesis of the *E*-alkenoate moiety **19**

a) $[H_2N(OMe)Me]Cl$, DCC, *i*-Pr_2NEt, MeCN, 0 °C to RT, 1 hr. b) $LiAlH_4$, THF, -78 °C, 30 min; $Na_2SO_4{\bullet}10H_2O$. c) $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2,. d) 1:1 TFA/CH_2Cl_2, RT, 30 min.

PyBroP-mediated coupling of **19** and (*S*)-*N*-Boc-*tert*-leucine (**20**), was followed by Boc deprotection to yield the TFA salt **21**, in approximately 19% yield. This coupling reaction only proceeded in 22% yield, even when 3 equiv. of DMAP was added to the reaction. Despite this low yield, enough material was available to couple **4** with **21**, to provide *N*-Boc (-)-hemiasterlin ethyl ester (**22**) in 52% yield. Saponification and removal of the Boc protecting group yielded (-)-hemiasterlin (**1**).



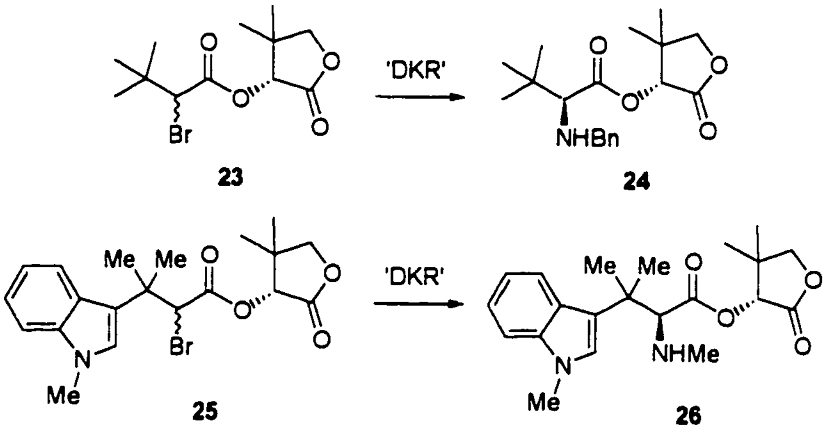
Scheme 3.3 : Coupling of residues **4**, **19**, and **20**.

a) PyBroP (1.1 equiv.), 4-(*N*,*N*-dimethylaminopyridine (3 equiv.), CH_2Cl_2, RT, 16 hrs. b) 1:1 TFA/CH_2Cl_2, RT, 30 min. c) LiOH, MeOH, H_2O, RT, 16 hrs; citric acid, H_2O. d) as in b, then reverse phase (C_{18}) HPLC, 45% H_2O (containing 0.05% TFA)/MeOH.

Clearly, the quantity of (-)-hemiasterlin available via this route is limited due to the poor yields observed throughout the synthesis. The synthesis of the tryptophan moiety **4** alone required a total of 16 steps. Due to the impressive cytotoxicity of these compounds more efficient synthetic approaches are required.

3.3 Proposed Synthesis of Hemiasterlin Via DKR

Recent work in the Durst lab has demonstrated the application of DKR to the synthesis of several unusual α-amino acids (see Chapters 1 and 2). We initially viewed the hemiasterlins as possible synthetic targets for our DKR methodology. More specifically, the synthesis of the *tert*-leucine and the tetramethyltryptophan residues. The DKR of ester **23** with $BnNH_2$ would provide access to the amino ester **24**. Similarly, ester **25** would yield compound **26**.



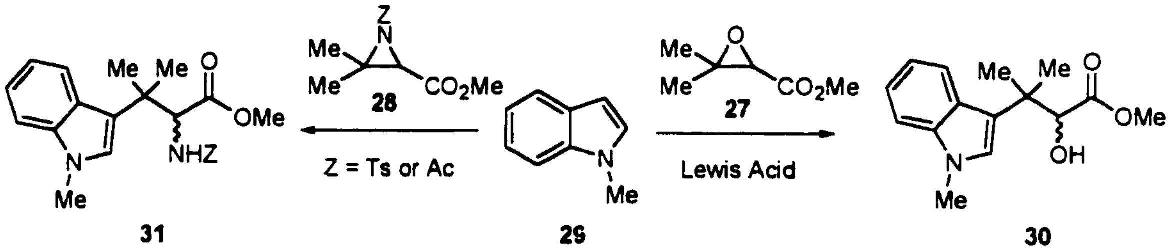
Previous work in our lab has shown that ester **23** can be prepared diastereoselectively, via ketene trapping reactions with [*R*]-pantolactone.[5] Displacement of the bromide using NaN_3 was investigated, but the DKR of ester **23** was not attempted. This chemistry was revisited, and some interesting new results were obtained. These will be discussed in Section 3.5.

The DKR of ester **25** was not attempted as this route presented few advantages over the route described by Piers and Anderson. Ester **25** would be derived from compound **8** (see Scheme 3.1) which we intended to prepare via Piers' method. Additionally, the preparation of **25** would require treating **8** with $SOCl_2$ and I_2 (see Chapter 1, Section 1.6.1). A variety of different products may be imagined from this reaction, including aromatic iodination and Friedel-Crafts acylation reactions. If compound **25** were successfully prepared via this route, displacement of bromine from the highly hindered, *pseudo*-neopentyl centre, might be a very unfavourable reaction.

Obviously compound **25** is not an 'ideal' candidate for DKR. Fortunately, an alternate and more convergent route to the tetramethyltryptophan **4** was found.

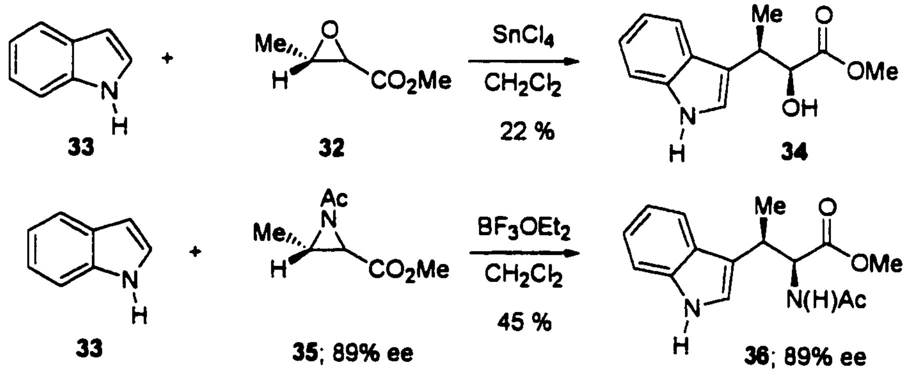
3.4 Proposed Synthesis of Tryptophan 4 Via Glycidic Ester Ring Opening

Several new routes to this unique α-amino acid residue were suggested. The most convergent of these involved the ring opening of either glycidic ester **27** or α,β-aziridinyl ester **28**, with 1-methylindole (**29**), in the presence of a Lewis acid.[6,7]



Ring opening of **27** would provide tryptol **30**, which could be converted to tryptophan **31** in a few steps. Tryptophan **31** would be prepared directly from **28**.

Since both of these reactions have been successfully applied to other systems, we were quite confident they would be applicable to the present case. It has been reported that glycidate **32** was opened with $SnCl_4$ and indole (**33**), to provide *syn*-**34** in 22% yield.[8]



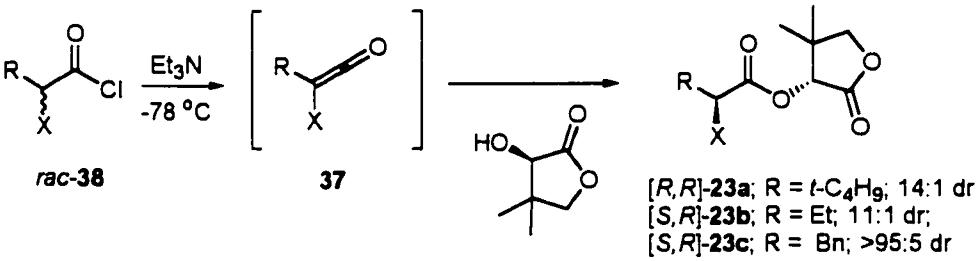
More recently, the chiral aziridine **35** (89% ee) was opened with indole and $BF_3{\bullet}Et_2O$, to provided compound **36** in 45% yield and 89% ee.[9] Based on the known mechanism of these Lewis acid promoted ring open reactions the chirality of the starting material was predictably translated into that of the product.

Due to the ease with which glycidic esters may be prepared, the Lewis acid mediated ring opening reactions of glycidic ester with indoles was pursued. The results from these studies will be discussed in Section 3.6.

3.5 Preparation of the *tert*-Butylvaline Residue of Hemiasterlin

3.5.1 Ketene Trapping Reactions with [*R*]-Pantolactone

Durst and Koh reported that various α-haloketenes (**37**), prepared by the treatment of *rac*-**38** with Et_3N at −78 °C, could be trapped with [*R*]-pantolactone, to provide the diastereomerically enriched α-halo [*R*]-pantolactone esters **23**.[5] The absolute configuration of the major diastereomer was determined to be [*R*,*S*]- when the R group was alkyl or benzyl.

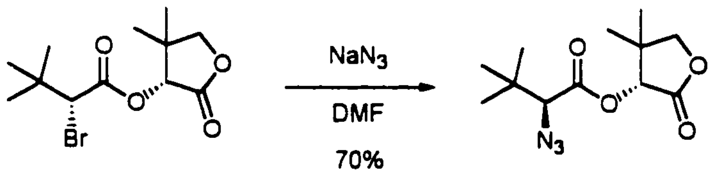


rac-**38**

37

[*R*,*R*]-**23a**; R = t-C_4H_9; 14:1 dr
[*S*,*R*]-**23b**; R = Et; 11:1 dr;
[*S*,*R*]-**23c**; R = Bn; >95:5 dr

When R was a *tert*-butyl group, [*R*,*R*]-**23a** was obtained in 86% yield, and 85% de (14:1 dr). The reason for this switch in selectivity remains unclear.



[*R*,*R*]-**23a**; 14:1 dr

[*S*,*R*]-**39**; 7:1 dr

When [*R*,*R*]-**23a** was treated with NaN_3 in DMF (60 °C, 40 hours) the corresponding azide, [*S*,*R*]-**39**, was obtained. Unfortunately, significant racemization was observed as [*S*,*R*]-**39** was obtained as a 7:1 mixture of diastereomers. Similar racemization has been observed for the conversion of α-halo carboximides (Evans auxiliaries) to α-azido acids.[10] The DKR of ester **23a** was not investigated.

3.5.2 DKR of [*R*]-Pantolactone 2-Bromo-3,3-Dimethylbutanoate (23a)

In order to obtain a 1:1 mixture of [*R*,*R*]- and [*R*,*S*]-**23a**, the ketene trapping reaction of α-bromo-*tert*-butylacetyl chloride with [*R*]-pantolactone was performed at 0 °C. Even at this temperature, [*R*,*R*]-**23a** was obtained as a 2:1 mixture of diastereomers.

The two diastereomers were readily separated by recrystallization from hexane. After a single recrystallization the diastereomeric purity was improved to 95:5. A subsequent recrystallization provided X-ray quality crystals of pure [*R*,*R*]-**23a**. These were the first X-ray quality crystals obtained in our lab for an α-halo [*R*]-pantolactone ester (see Figure 3.1).

In order to explain the diastereoselective nature of DKR (see Section 1.5), Durst and Ben considered the ground state structures of several α-bromo [*R*]-pantolactone esters.[11] Conclusions regarding the ground states were based on X-ray data derived from several [*R*]-pantolactone [*S*]-α-*N*-benzylamino esters which had been obtained as the major products of DKR reactions. Molecular modeling of α-bromo [*R*]-pantolactone esters suggested that similar ground state conformations were adopted by α-bromo [*R*]-pantolactone. The ester carbonyl preferred to lie perpendicular to the carbonyl group of [*R*]-pantolactone. Additionally, the bromine was found to lie perpendicular to the ester carbonyl. These early calculations were later confirmed by myself using Semi-Empirical (AM1 and PM3) calculations performed using the Spartan software for both [*R*,*R*]- and [*S*,*R*]-**23a,b,c**. The most stable rotamers only varied in energy by 1 to 2 kcal/mol.

We were gratified to see that the X-ray crystal structure of [*R*,*R*]-**23a** confirmed much of what we had predicted computationally (see Figure 3.1). Indeed, the two carbonyl groups do lie perpendicular to one another, and the *tert*-butyl group nearly eclipses the ester carbonyl (one must consider the steric bulk of the *tert*-butyl group – we predict that simple alkyl group would eclipse the ester carbonyl more closely). As we had predicted, the bromine was seen to lie at a 102° to the ester carbonyl.

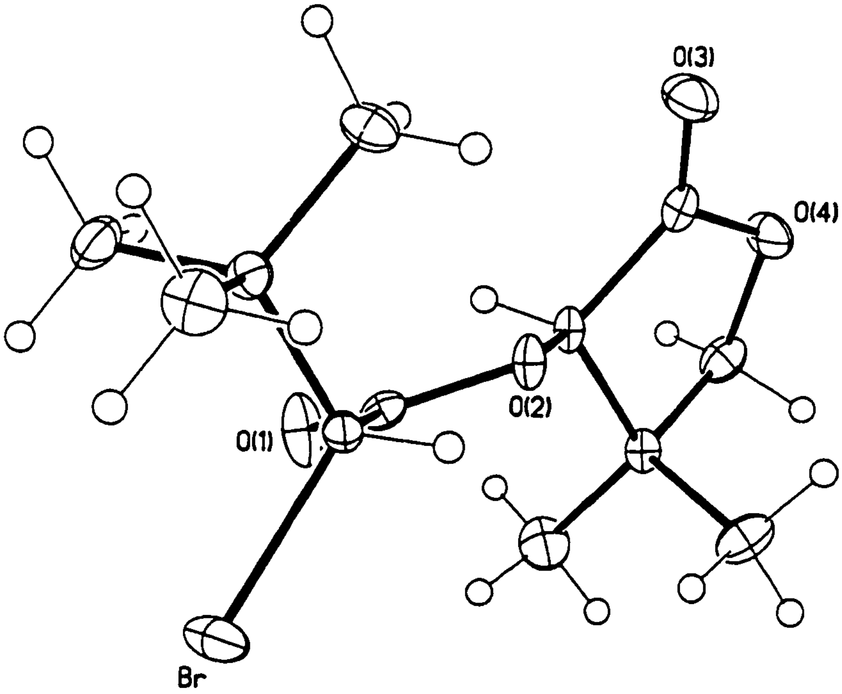
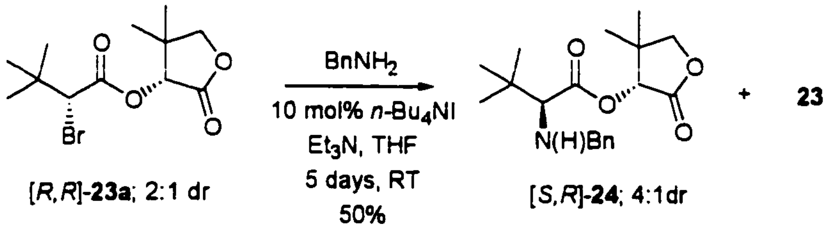


Figure 3.1: ORTEP Drawing of the X-ray Crystal Structure of [*R*,*R*]-**23a**

Unfortunately, the DKR of [*R*,*R*]-**23a** was not successful. Treatment of a 2:1 mixture of **23a** with benzylamine, under standard DKR conditions did not lead to impressive diastereoselectivities in **24**. After stirring the solution at RT for 5 days [*S*,*R*]-**24** was obtained in 50% yield, as a 4:1 mixture of diastereomers.



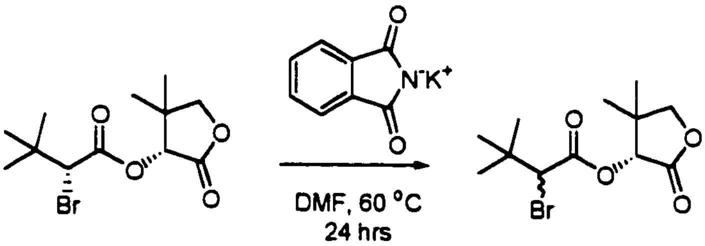
[*R*,*R*]-**23a**; 2:1 dr

[S,*R*]-**24**; 4:1dr

Starting material was recovered in 42% yield as a 1:1 mixture of diastereomers. The steric bulk of the *tert*-butyl group may have prevented rapid epimerization and/or rapid displacement reactions. This was not surprising based on earlier work by Evans.[10b]

Treatment of optically pure [*R*,*R*]-**23a** with NaN$_3$ in DMF (60 °C, 48 hrs) provided [*S*,*R*]-**39** as a 5:1 mixture of diastereomers. This result compares well with the 7:1 diastereomeric ratio obtained by Durst and Koh (see Section 3.5.1).[5]

Attempts to displace the bromine of optically pure [*R*,*R*]-**23a** with potassium phthalimide (DMF, 60 °C, 24 hrs) resulted in epimerization, providing **23a** as a 1:1 mixture of diastereomers.



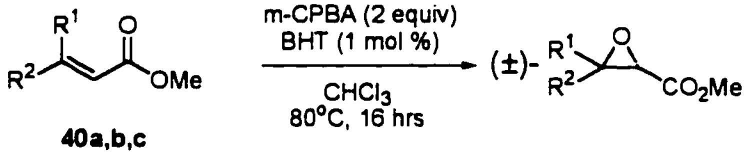
[*R*,*R*]-**23a**

23a; 1:1 dr

Due to the poor yield and poor chiral induction observed in the DKR reaction, the epimerization observed when NaN$_3$ or potassium phthalimide were used as nucleophiles, and the observations of Evans,[10b] no further attempts were made to improve the diastereoselectivity of these reactions.

3.6 Synthesis of Substituted Tryptophans Via Glycidic Ester Ring Opening and Mitsunobu Azidation

Although the primary target of this study was the synthesis of β,β-dimethyltryptophans, access to other β-mono and β,β-disubstituted tryptophans might become available by this method. In order to explore this chemistry a variety of racemic glycidic esters were prepared.

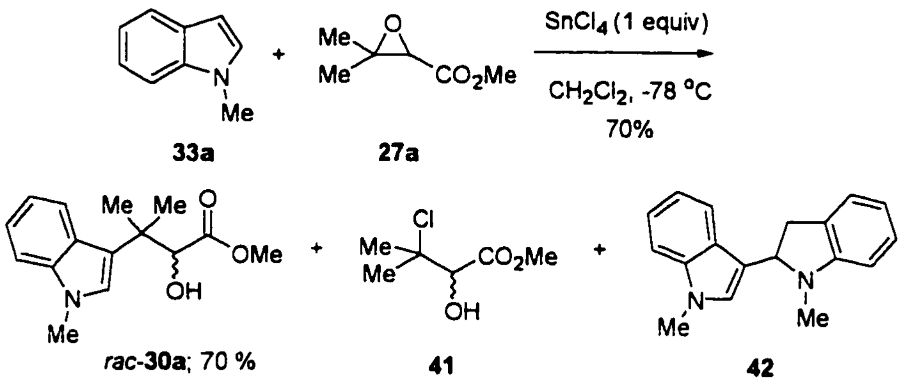


40a,b,c

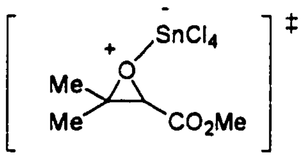
27a; $R_1 = R_2 = Me$; 92 %
27b; $R_1 = R_2 = -(CH_2)_5-$; 85 %
27c; $R_1 = Ph$, $R_2 = H$; 93 %

Treatment of the parent α,β-unsaturated esters (**40**) with 2 equiv. of 50-85% *m*-CPBA and a catalytic quantity of BHT (which acted as a free radical inhibitor), in refluxing $CHCl_3$, provided the desired glycidic esters (**27**) in good yields. The glycidic esters obtained from these reactions generally did not require further purification, but could be purified by distillation under reduced pressure (40 to 80 °C, 0.1 torr).

The next step involved ring opening of the glycidic esters with indole in the presence of a Lewis acid, to provide the corresponding tryptol. Initial experiments involved equamolar quantities of *rac*-**27a** and *N*-methylindole (**33a**). These two compounds were dissolved in CH_2Cl_2 and cooled to -78 °C. Dropwise addition of a 1M CH_2Cl_2 solution of $SnCl_4$ (over 2-3 minutes) yielded the racemic tryptol **30a**, in 70% yield, after aqueous work up and silica gel chromatography, eluting with 3:1 hexane/diethyl ether. Two other products were identified in the ^1H NMR spectrum of the crude reaction product; the chlorohydrin **41** and indolylindolane **42**. These two compounds were not isolated from the crude reaction mixture, but were prepared separately and their ^1H NMR spectra compared to that of the crude reaction mixture above.



We were pleased to obtain *rac*-**30a** in 70% yield, since it had been reported that tryptol **34** was only obtained in 22 % yield via a similar procedure (see Section 3.4). The presence of the *gem*-dimethyl group of **27a** may account for this increased yield. These methyl groups may act to partially stabilize the developing positive charge at the β-carbon, thus increasing the likely hood that this intermediate will be attacked by indole.

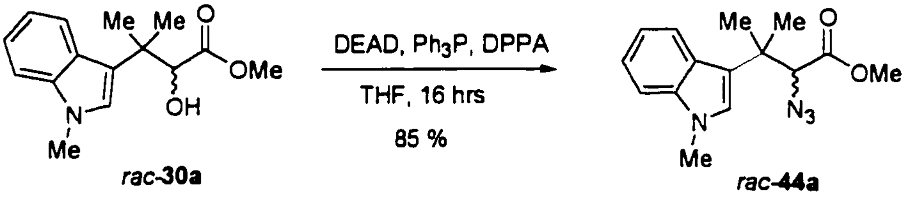


- stablized positive charge

The chlorohydrin **41** was the result of a competitive chloride transfer process. When $SnCl_4$ was added to **27a** in the absence of indole, compound **41** was the only product isolated. Indoles are known to dimerize under acid conditions to provide 3-indolylindolanes and indole dimers. The presence of indolylindolane **42**[12] indicates that either $SnCl_4$ or adventitious HCl catalyzed this 'dimerization'. Similar observations were made by a group at Pfizer.[13]

In an attempt to increase this yield, 2 equiv. of either *N*-methylindole or $SnCl_4$ were used. No improvements were observed, even when prolonged addition and/or reaction times were used. The yield of *rac*-**30a** was observed to decrease dramatically when $SnCl_4$ was added at higher temperatures or over shorted periods of time (less than 1 minute).

Azidation of tryptol *rac*-**30a**, under Mitsunobu conditions,[14] proceeded readily to provide the azide *rac*-**44a**. In order to obtain high yields in this azidation reaction, it was necessary to add the tryptol to the performed DEAD/Ph$_3$P/DPPA salt, in the presence of pyridine, to prevent decomposition of the tryptol (see Section 3.8 for a mechanistic consideration of the 'decomposition' of tryptol **30a**).

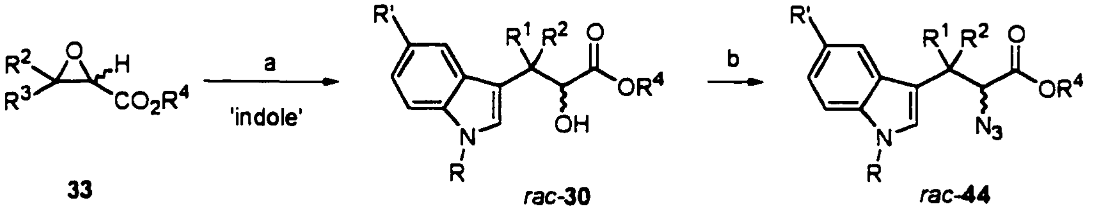


Azide **44a** is remarkably non-polar. Purification by silica gel chromatography, eluting with 9:1 hexanes/diethyl ether, provided the desired azide, but it was always contaminated with varied quantities of excess or unreacted DPPA. Changing the solvent system only slightly improved the separation. DPPA was found to oil out of most solvent systems, coating the crystals of *rac*-**44a**. An effective purification method has not yet been found.

In order to investigate the general utility of this reaction sequence, a variety of β-mono and β,β-disubstituted tryptols (**30**) were prepared by the treatment of the appropriate glycidic ester (**27**)/indole (**33**) combination with SnCl$_4$. After chromatographic purification, these tryptols were converted to the corresponding azides (**44**) via the Mitsunobu reactions with DEAD, Ph$_3$P, and DPPA. The results are summarized in Table 3.1.

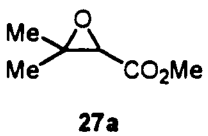
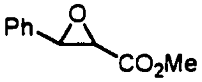
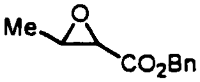
As mentioned earlier, *N*-methylindole (**33a**) and **27a** yielded tryptol **30a** in 70% yield. In contrast indole (**33b**) and **27a** provided tryptol **30b** in 50% yield, under identical reaction conditions. These yields were highly reproducible. In both reactions considerable quantities of the chlorohydrin **41** were observed. This suggests that the electron donating ability of the *N*-methyl group increased the nucleophilicity of the *N*-methylindole, resulting in an improved yield.

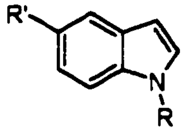
Substitution at the indole C5 position did not effect the yields substantially, when compared to reactions involving indole (**33b**). The reactions with 5-bromoindole (**33c**; electron withdrawing substituent) and 5-methoxylindole (**33e**; electron donating substituent) provided comparable yields of the corresponding tryptols **30c** and **30e**; 53% and 43% respectively.



a) $SnCl_4$, CH_2Cl_2, -78 °C, 30 min. b) DEAD, Ph_3P, DPPA, pyridine, THF, RT, 16 hrs.

Table 3.1 : Glycidic Ester Ring Openings and Mitsunobu Azidations

Entry	Indole	Glycidic Ester	Tryptol	Azide
1	**33a**; R = Me, R' = H	 **27a**	**30a**; 70 %	**44a**; 85 %
2	**33b**; R = R' = H		**30b**; 52 %	**44c**; 90 %
3	**33c**; R = H, R' = Br		**30c**; 52 %	
4	**33d**; R = H, R' = MeO		**30d**; 43 %	
5	**33a**	 **27b**	**30e**; 69 %	**44e**; 87 %
6	**33a**	 **27c**	**30f**; 50 %	**44f**; 75 %
7	**33a**	 **27d**	15 % - inseparable mixture of alcohols	
8	**33e**; R = Ts, R' = H	**27a**	chlorohydrin **41** + **33e**	



When treated with *N*-methylindole and $SnCl_4$ the β,β-cyclohexyl glycidate **27b** provided tryptol **30e** in 69% yield. This yield compares well with that observed for glycidate **27a** and *N*-methylindole. Again, one may invoke stabilization of the carbocation intermediate by the cyclohexyl methylene groups.

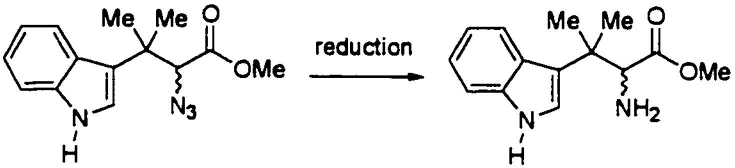
The β-phenyl glyoxylate **27c** and *N*-methylindole provided tryptol **30f** in 50% yield. A higher yield was expected due to the known stability of benzylic cations. This yield does exceed the 22% yield reported for unsubstituted glyoxylates (see Section 3.4). Therefore, some cation stabilization may still be invoked.

In an effort to qualitatively determine the amount of cation stabilization provided by the β-substituents, glycidate **27d** was treated with *N*-methylindole and $SnCl_4$. An inseparable mixture of two isomeric alcohols was obtained in 15% yield. The ^1H NMR spectrum of the crude reaction mixture showed the majority of the remaining material to be chlorohydrin **41** and the indole dimer **42**. This result is in contrast to earlier reports where tryptol **34** was the sole product isolated, albeit in 22% yield. Removal of one of the β-substituents reduced the stability of the proposed cationic intermediate, shifting the reaction path away from tryptol formation, to chloride transfer, to provide **41** as the major product.

Decreased electron density within the indole five membered ring greatly reduces its nucleophilicity. This was clearly observed in entry 8, when the indole nitrogen was protected with a tosyl group. The combination of **27a** and *N*-tosylindole (**33e**) provided none of the desired tryptol. Instead, **27a** was cleanly converted to the chlorohydrin **41**, while the *N*-tosylindole remained unreacted.

Conversion of tryptol **30a**, **30b**, **30e**, and **30f** to their corresponding azides proceeded with good yields. Again, purification of the *N*-methyl azides by silica gel chromatography was complicated by the tendency of the unreacted DPPA to travel at the same rate as the azides. The non-methylated azide **30b** was readily isolated by silica gel, free from DPPA, which eluted before **30b**.

Reduction of the *N*-methylated azides was complicated by the presence of DPPA. For this reason an attempt to optimize the reduction of *rac*-**30b** was under taken. The reduction of *rac*-**30a** with hydrogen (5 % Pd/C), Ph_3P/H_2O,[15] or $SnCl_2$/MeOH,[4] have given inconsistent yields of *rac*-**44b**, ranging from 35 to 65% (tryptophan **44b** represents the tryptophan moiety of hemiasterlin A and B).



rac-**44b** *rac*-**45b**

Piers and co-workers reported that the reduction of **10**, with $SnCl_2$ in methanol (3 days at room temperature), followed by *in situ* Boc protection of amine **11**, provided **12** in 55% (tryptophan **12** represents the tryptophan moiety of hemiasterin - see Section 3.1).[4] Our results, combined with those of Piers, suggest that this reduction is not straightforward. These azides are relatively hindered and this may be effecting the rate of reduction.

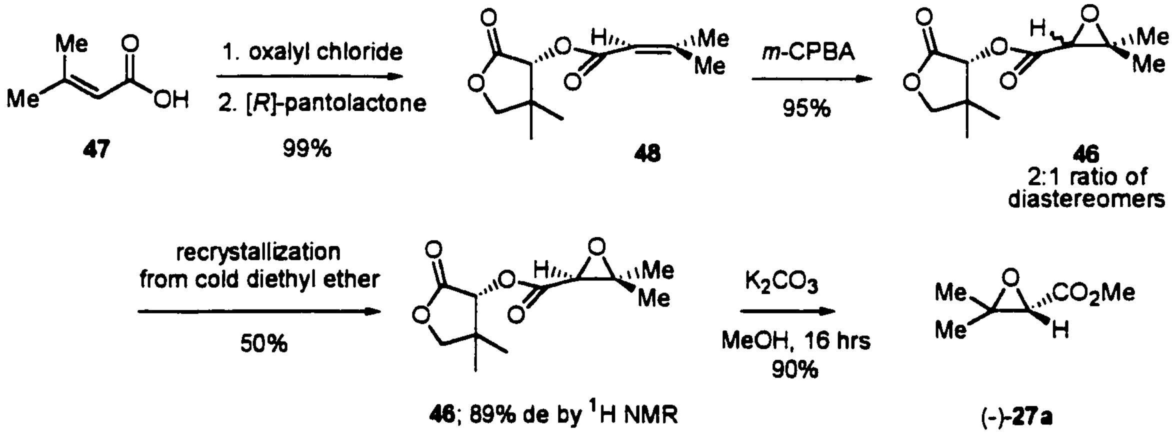
Reduction of azide **44b** with $SnCl_2$ in MeOH, or with 1 atm H_2 over Pd/C, was slow at best. After stirring with $SnCl_2$ for 78 hrs, the corresponding racemic tryptophan methyl ester **45b** was only obtained in 35% yield. The remaining azides were not reduced. Optimization of both the azidation and reduction reactions are required before this process becomes a viable route to the synthesis of β-mono and β,β-disubstituted tryptophans.

3.7 Preparation of Optically Active Tryptols

Akita and coworkers reported that the chirality of the glycidic ester may be conserved during the ring opening reaction.[8] For that reason the ring opening of optically active **27a** was investigated.

Although one may imagine preparing optically active **27a** using Sharpless epoxidation of the allylic alcohol 3-methyl-2-buten-1-ol, or Jacobsen epoxidation of the α,β-unsaturated ester **40a**, we pursued a different approach, involving the epoxidation of the [*R*]-pantolactone glycidate **46**.

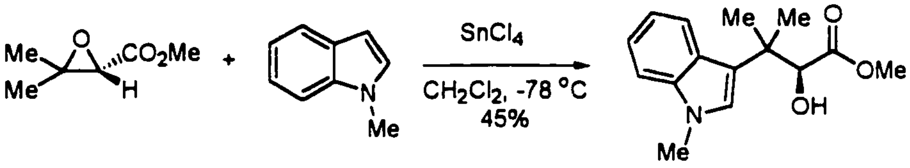
3,3-Dimethylacrylic acid (**47**) was converted to the corresponding acid chloride using oxalyl chloride and a catalytic quantity of DMF. Addition of this solution to a methylene chloride solution of [*R*]-pantolactone and triethylamine resulted in the preparation of ester **48**. Epoxidation of ester **48** with *m*-CPBA in refluxing $CHCl_3$, resulted in the formation of glycidate **46** as a 2:1 mixture of diastereomers, as seen by the ^1H NMR spectrum of the crude reaction mixture.



The major diastereomer was observed to crystallize preferentially from cold diethyl ether, providing **46** in 50% yield and 89% de after a single recrystallization. A second recrystallization generally provided optically pure material. Transesterification with K_2CO_3 in methanol provided (-)-**27a** in 90% isolated yield. One should note that the majority of the [*R*]-pantolactone released during this reaction was removed from the reaction mixture by washing with several portions of 1M HCl. Further purification by distillation under reduced pressure (50 °C, 0.1 torr) provided pure (-)-**27a**.

Although this may appear to be a long procedure, it is quite efficient, and compares favourably to the lipase catalyzed resolution used by Oishi to prepare optically active methyl 2,3-oxobutanoate (**32**) (see Section 3.4).[8]

Treatment of a 1:1 mixture of (-)-**27a** and **33a** with $SnCl_4$, under the standard conditions described above, provided (-)-**30a** in 45% yield.



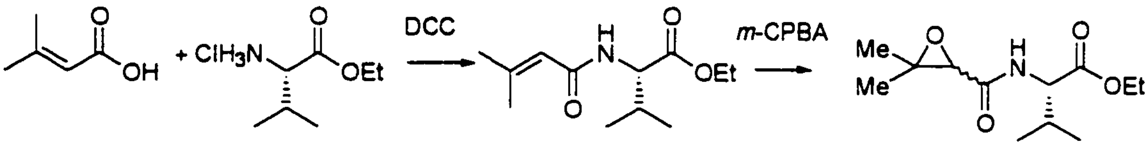
27a; 89% ee **33a** (-)-**30a**; 89% ee by HPLC

The yield of this reaction was conspicuously low, however, the product was shown to have an enantiomeric excess of 89%, as seen by chiral HPLC (ChiralCel OD column, eluting with 95:5 hexane/*iso*-propanol). This was an encouraging result as the chirality of glycidic ester (-)-**27a** was translated into the product, (-)-**30a**, with no racemization.

Due to the problems encountered with the reduction of azides **44**, (-)-**30a** was not converted to the corresponding azide. This will be performed once methods have been found which allow for the effective purification of **44a** and reliable reduction conditions have been found.

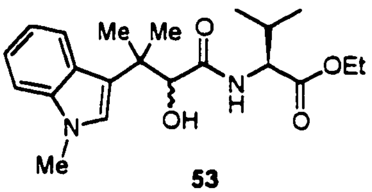
3.8 Ring Opening Reaction of Glycidic Amides With $SnCl_4$

In an effort to make the synthesis of hemiasterlin more convergent, it was hoped that a reaction sequence similar to that described for the reaction between indoles and glycidic esters could be applied to glycidic amides. Compound **49** was prepared by the DCC/HOBt mediated coupling of 3,3-dimethylacrylic acid (**50**) with valine ethyl ester hydrochloride (**51**). After silica gel chromatography, compound **49** was refluxed in $CHCl_3$ with 2 equiv. of *m*-CPBA and 1 mol% BHT, to provide glycidic amide **52** as a 1:1 mixture of diastereomers.



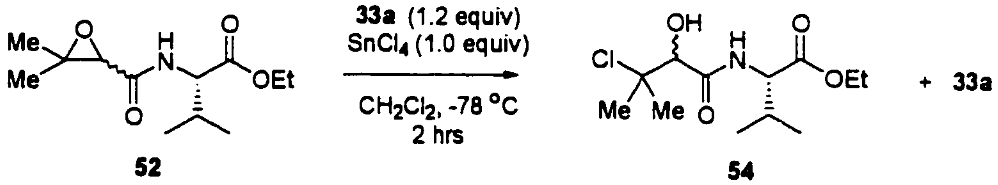
50 **51** **49** **52**; 1:1 dr

When **52** and *N*-methylindole (**33a**) were treated with $SnCl_4$ in CH_2Cl_2 solution, for 30 minutes at -78 °C, alcohol **53** was *not* observed.



53

Instead, the chlorohydrin **54** was obtained. The two diastereomers of **54** were separable by silica gel chromatography, eluting with 3:1 hexanes/diethyl ether, providing a 43% yield of one diastereomer and a 39% yield of the second diastereomer.



52 **54**

The identity of these two compounds was confirmed by MS, with both compounds displaying molecular ions M^{+}=279 m/z and M^{2+}=281 m/z. As we had no interest in these compounds no attempt was made to determine the absolute stereochemistry of the individual isomers.

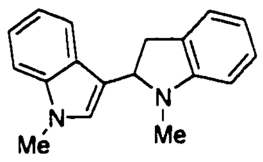
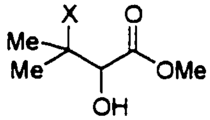
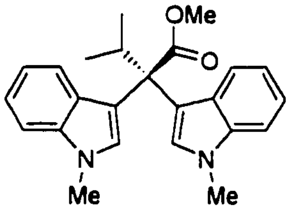
Sharpless reported that glycidic acids may be opened by a variety of nucleophiles using the Lewis acid $Ti(O^iPr)_4$.[16] When this reaction was attempted with **52** and **33a**, in CH_2Cl_2, no reaction was observed, even when the reaction was refluxed over night. Treatment of **27a** and **33a** with $Ti(O^iPr)_4$ resulted in the transesterification of **27a**, to provide the corresponding *iso*-propyl glyoxylate and unreacted **33a**.

These were both surprising and disappointing results. If a suitable Lewis acid may be found which mediates the ring open of the glycidic amide **52** by indole, this will represent a very significant improvement in the synthesis of hemiasterlin and its derivatives. We have not investigated the ring opening of suitably substituted aziridines with indoles, under Lewis acid catalyzed conditions.

3.9 Glycidic Ester Ring Opening Reactions with Other Lewis Acids

Due to the variable yields and various side products, several Lewis acids were screened for the glycidic ester ring opening reaction between **27a** and **33a**. Interestingly, *only* $SnCl_4$ yielded the desired tryptol, **30a**. Other Lewis acids either yielded indolylindolanes, halohydrins, or α,α-*bis*(indolyl) esters as the major product. These reactions are summarized below:

Table 3.2 : Reactions of **27a** and *N*-methylindole (**33a**) With Various Lewis Acids

Entry	Lewis Acid	Major Product(s) Observed
1 2 3 4	$BF_3 \cdot Et_2O$ TMSOTf $TiCl_4$ n-Bu_2BOTf	 **42**
5 6 7	Et_2AlCl (RT) $ZnCl_2$ (RT) $ZnBr_2$ (RT)	 **41a**; X =Cl **41b**; X = Br + **33a**
8 9 10	ZnI_2 (RT) $ZnCl_2$ (reflux) $ZnBr_2$ (felfux)	 **55a** α,α-bis(indolyl) ester
11 12 13	TMSCl $Zn(OTf)_2$ $Yb(OTf)_3$	no reaction

All of the above reaction were run in CH_2Cl_2 solvent. The appropriate Lewis acid was added to a mixture of **27a** and **33a** at -78 °C and the resulting solutions were stirred at room temperature until no starting material was observed by TLC (entries 1, 2, 3, 4, 5, and 11). Alternately, the Lewis acid was added as a solid, and the heterogeneous solution was stirred at the temperature indicated until all of the starting material had been consumed, as determined by TLC (entries 8 to 10).

The major product isolated from the reactions involving $BF_3{\bullet}Et_2O$, TMSOTf, $TiCl_4$, and *n*-Bu_2BOTf (entries 1 to 4) was identified as compound **42** after isolation by silica gel chromatography. Although resonances corresponding to methyl esters were observed in the crude ^1H NMR spectra of these reactions, they did not match any other compounds isolated during this study. These ester were not readily isolated by silica gel chromatography, and their exact composition remains unknown. Small quantities of compound **42** and the desired tryptol **30a** (less 1 to 5% each) were observed in the crude ^1H NMR spectra of the reactions involving TMSOTf and $TiCl_4$ (see Section 3.11 for a mechanistic consideration of these reactions).

When the mixtures of **27a** and *N*-methylindole were stirred in the presence of Et_2AlCl, $ZnCl_2$, or $ZnBr_2$, no tryptol formation was observed. The only materials isolated were to unreacted indole (> 90% recovery) and the corresponding halohydrins **41a** and **41b** (> 90% yield). This result suggested that these Lewis acids were strong enough to open the epoxide ring, however, halide transfer was faster than attack by indole.

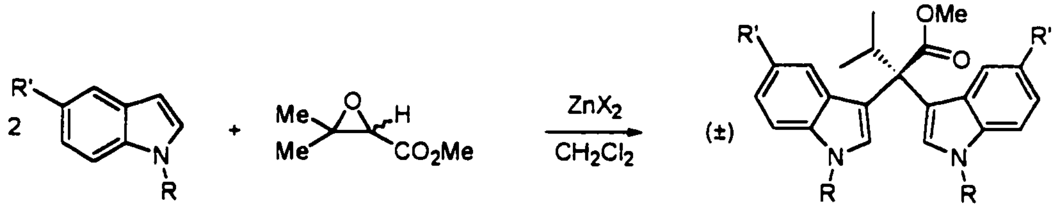
The most interesting and surprising result of this study came when a mixture of **30a** and *N*-methylindole was stirred overnight with ZnI_2. Compound **55a** was isolated in 92% yield. When this reaction was repeated using $ZnCl_2$ and $ZnBr_2$ in refluxing CH_2Cl_2, a small quantity of the corresponding halohydrin was observed, but compound **55a** was isolated in > 85% for both reactions. This appears to be a novel reaction and will be discussed further in Section 3.10.

No reaction was observed for the Lewis acids TMSCl, $Zn(OTf)_2$ (prepared *in situ* by the addition of AgOTf to a solution of $ZnCl_2$ in CH_2Cl_2), or $Yb(OTf)_3$ (entries 11 to 13).

Compound **41**, **42**, and **55a** have all been identified or isolated from the $SnCl_4$ reactions discussed earlier (in yields of 5 to 50% depending on the reaction conditions and substrates used). Therefore, a fine line exists between tryptol formation (**30**), halide transfer (**41**), indole condensation (**42**), and multiple indole additions (**55**).

3.10 Glycidic Ester Ring Opening Reactions with ZnI_2

As mentioned in the previous section, compound **55a** was obtained from the reaction between **27a**, **33a**, and ZnI_2. When equamolar quantities of **27a**, *N*-methylindole (**33a**), and ZnI_2, were stirred in CH_2Cl_2 over night, only a small quantity of the desired tryptol **30a** was obtained (approximately 3% based on *N*-methylindole). Instead, the α,α-*bis*(indolyl) ester **55a** was isolated in 42% yield along with a 33% yield of iodohydrin **41c** (X = I) (both yields are based on the initial quantity of **27a**). All of the *N*-methylindole added to the reaction had been consumed.



33a; R = Me, R' = H
33b; R = R' = H
33c; R = H, R' = Br
33d; R = H, R' = MeO

27a

X = Cl reflux 12 hrs
X = Br reflux 3 hrs
X = I RT 5 hrs

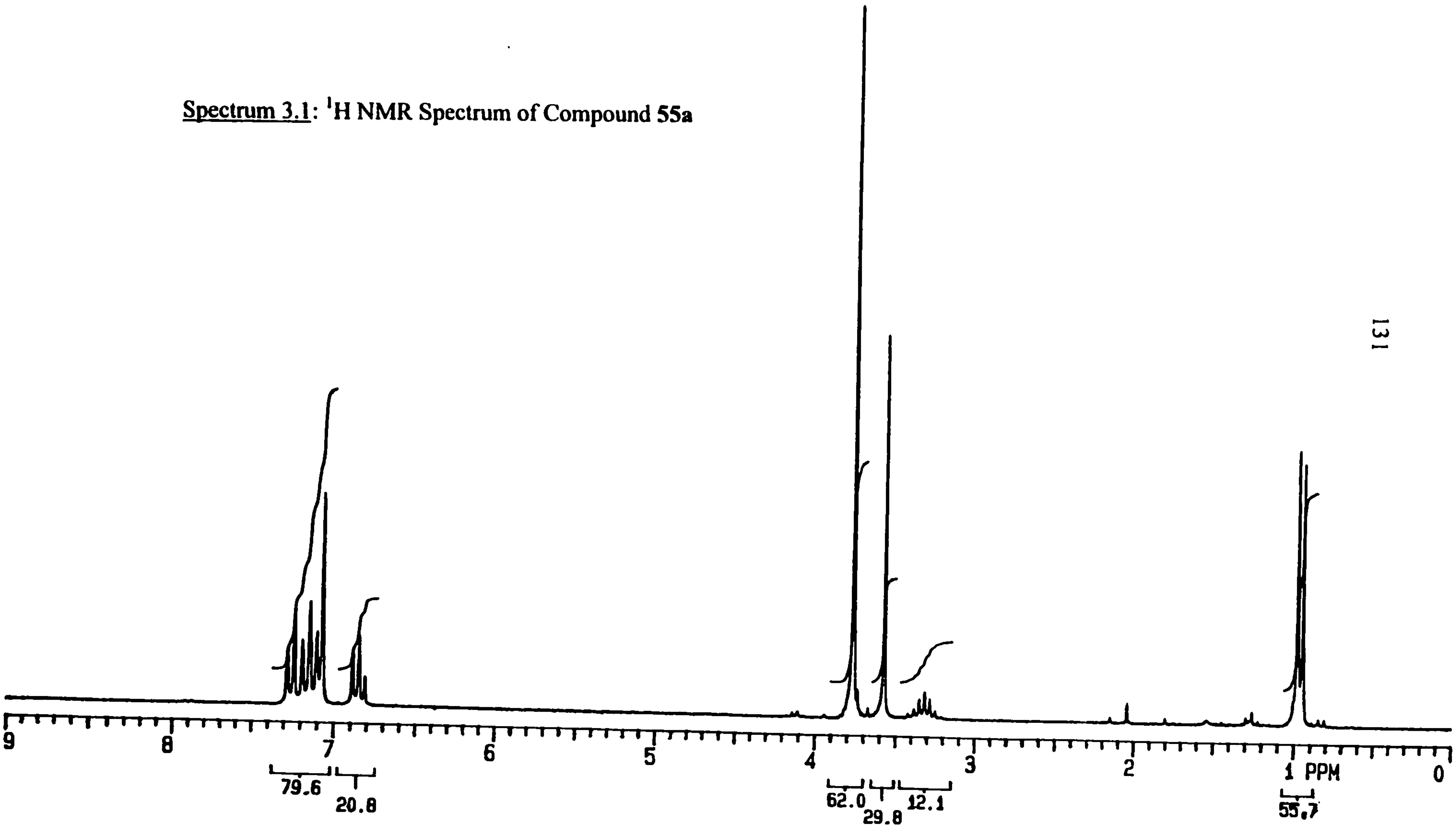
55a; 92 %
55b; 84 %
55c; 52 %
55d; 61 %

A ^1H NMR spectrum of **55a** is presented in Spectrum 3.1, and its structure has been confirmed by MS analysis (M^+ = 374.20 m/z). This was truly an intriguing and unexpected result. For this reason, a more indepth investigation of the generality of this reaction was under taken.

In subsequent reactions 1 equiv. of ZnI_2 was added to a CH_2Cl_2 solution containing 2 equiv. of indole **33a** and 1 equiv. of glyoxylate **27a**. These reactions were stirred over night at room temperature and the yields of **55a** generally exceeded 85%, based on the quantity of **27a** used. When $ZnCl_2$ or $ZnBr_2$ was used in place of ZnI_2 the only products observed were the corresponding halohydrins and unreacted indole (see Section 3.8). When the same reactions were run in refluxing CH_2Cl_2, compound **55a** was obtained in 85 to 92% yield, along with small quantities of the halohydrins **41a** and **41b**, respectively.

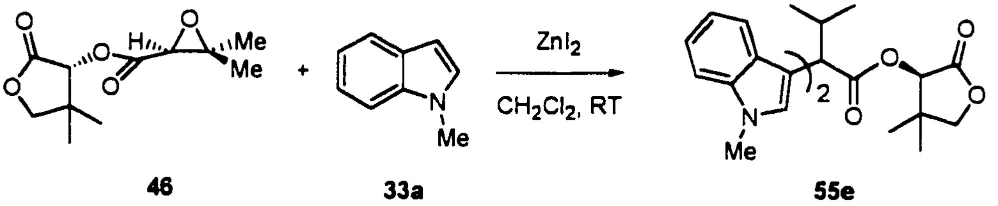
Similar reactivity was observed for unsubstituted indole. When **27a** was treated with 2 equiv. of **33b** and 1 equiv. of ZnI_2, compound **54b** was obtained in 91% yield.

Spectrum 3.1: ^{1}H NMR Spectrum of Compound 55a



The yields of **55** were dramatically decreased when 2 equiv. of 5-bromoindole (**33c**) or 5-methoxyindole (**33d**) were used in the above reaction, yielding compound **55c** in 52% yield, and compound **55d** in 61 % yield, respectively.

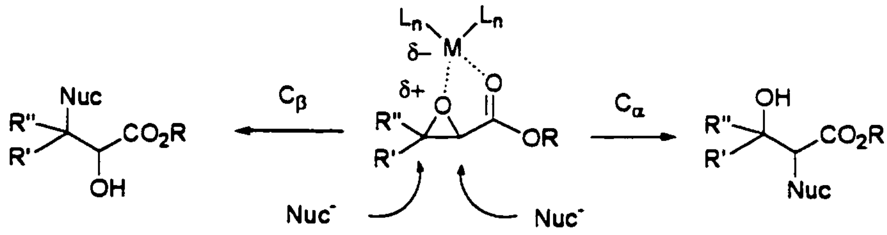
The [*R*]-pantolactone glycidic ester **46** also provided α,α-*bis*(indolyl) esters. Treatment of **46** with **33a** and ZnI_2 yielded compound **55e**.



This was disappointing as it was hoped that the steric bulk of the [*R*]-pantolactone group would hinder the attack of the second molecule of indole. Unfortunately, this was not the case.

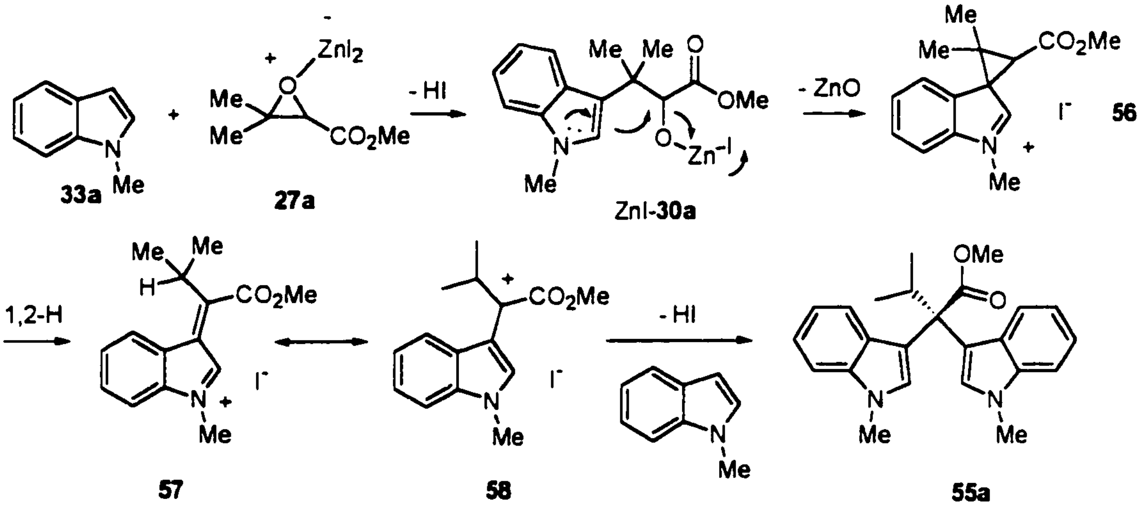
3.11 Mechanism of α,α-*bis*(Indolyl) Ester Formation

The mechanism for glycidic ester ring opening reactions with Lewis acids is well established, and involves co-ordination of the Lewis acid to both the epoxide and ester carbonyl oxygens. This co-ordination results in a loss of electron density on the epoxide oxygen, and the formation of a partial positive charge on the adjacent carbon atoms; C_α and C_β. Depending on the Lewis acid, the nature of nucleophile, and the substitution pattern around the nucleophile, nucleophilic attack is then directed to either C_α or C_β, to provide the corresponding β-hydroxy or α-hydroxy ester, respectively.



One mechanism that accounts for the formation of these α,α-*bis*(indolyl) esters involves initial formation of the *desired* tryptols by attack of indole at the β-carbon of glycidate

27a. This is what would be expected based on the results obtained for the reactions catalyzed by $SnCl_4$. Attack at the β-carbon should also be favoured due to the stabilizing effects of the *gem*-dimethyl group to cation formation at the β-carbon. Subsequent cation formation allows for a second equivalent of indole to attack, resulting in the formation of the observed α,α-*bis*(indolyl) esters. This is shown pictorially in Scheme 3.1.



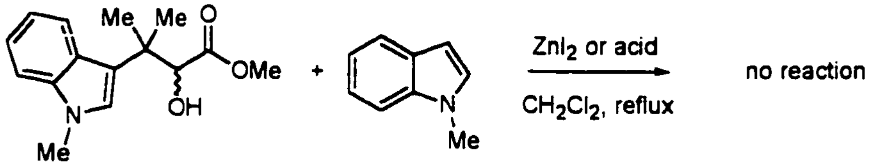
Scheme 3.4 : Formation of α,α-*bis*(indolyl) ester **37a**

Again, initial formation of ZnI-**30a** was followed by cation formation to yield intermediate **56**. Cation formation is the result of the high oxophilicity of zinc. The zinc alkoxide acts as a leaving group, being displaced intramolecularly, by attack of the lone pair of electrons found on the indole nitrogen on the tryptol C_α position, providing the imminium cyclopropane intermediate **56**. Similar intermediates have been proposed by other groups. Intermediate **56** may then undergo a 1,2-hydrogen shift to provide intermediate **57**, which also has the less favourable resonance structure **58**. Finally, **57** or **58** is attacked by indole, with loss of HI, to provide the observed α,α-*bis*(indolyl) ester **55a**.

One may argue that the ZnI anion of **30a** should be quenched by the presence of HI in solution, and that the cation formation was the result of a secondary reaction. For example acid promoted dehydration of the **30a** may also provide intermediate **56**.

Alternately, the interaction of **30a** with ZnI_2 itself may result in the formation of intermediate **56**.

In order to determine the effect of adventitious acid on cation formation, several reactions were performed. First, the above reaction was run in the presence of 2 equiv. of Na_2CO_3, in an effort to soak up any acid formed during the course of the reaction. This appeared to have little effect on the reaction as **54a** was obtained in 90% yield. The tryptol **30a** was treated with 1 equiv. each of *N*-methylindole and ZnI_2. Even after refluxing over night in CH_2Cl_2, no reaction was observed.



30a **33a**

Similarly, when equamolar quantities of tryptol and *N*-methylindole were refluxed with 1 equiv. or more of $TsOH{\bullet}H_2O$ (plus 4Å MS) or anhydrous TFA, no reaction was observed. This was not surprising as indole is basic enough that it resulted in protonation of indole at the C3 position. Interestingly, no indole dimerization was observed under these conditions. These observations support the idea that cation formation is an intramolecular process, involving displacement of ZnO from the tryptol ZnI anion.

Small quantities of **55a** (generally <5% yield as seen by ^1H NMR spectra of the crude reaction mixtures) were observed in the reactions between **27a**, **33a**, and the Lewis acids TMSOTf and $TiCl_4$. When one considers the mechanism proposed above, it appears that similar processes were at work. Both of these Lewis acids are highly oxophilic. The major product isolated was **42**, however, any tryptol that was formed may simply have undergone cation formation, and subsequent conversion to the corresponding α,α-*bis*(indolyl) ester.

3.12 Effect of Solvent Polarity and Additives on Product Composition

In an effort to further understand the dynamics of this reaction the effect of solvent polarity and various additives was investigated. In each of these reactions an equamolar quantities of **27a** and **33a** were dissolved in the appropriate solvent system and stirred for 3 to 16 hrs with ZnI_2 and the appropriate additive. The results of this study are presented in Table 3.3.

Table 3.3 : Effect of Solvent Polarity and Additives on ZnI_2 Mediated Reactions Between **27a** and *N*-Methylindole (**33a**)

Entry	Solvent	Additives	Time	Major Products (55a/30a)
1	CH_2Cl_2	none	3 hrs	92%; 5%
2	CH_2Cl_2	K_2CO_3 (2 equiv.)	5 hrs	90%; 3%
3	CH_2Cl_2	Et_3N (2 equiv.)	16 hrs	no reaction
4	CH_2Cl_2	TMEDA (1 equiv.)	16 hrs	no reaction
5	THF	none	16 hrs	no reaction
6	Et_2O	none	16 hrs	no reaction
7	ACN	none	16 hrs	no reaction
8	DMSO	none	16 hrs	no reaction
9	DMF	none	16 hrs	no reaction
10	1:1 CH_2Cl_2/CH_3NO_2	none	16 hrs	75%; 20%
11	CH_3NO_2	none	16 hrs	47%; 42%

As was mentioned earlier, ZnI_2 alone provided a 92% yield of **55a** and approximately 5% of **30a** was isolated after chromatographic separation. In order to determine whether the HI produced in this reaction was effecting cation formation, and promoted the second indole addition, Na_2CO_3 was added to the reaction mixture.

Although the reaction time was slightly longer, no dramatic effect was observed in the product ratio.

The addition of the soluble base Et_3N effectively killed the reaction, with no detectable product formation, as seen by ^1H NMR spectroscopy. This may have been a result of the Et_3N reacting directly with the ZnI_2, to form an unreactive species. With this in mind, TMEDA was used as an additive to prepare a TMEDA/ZnI_2 complex *in situ*, which may be less oxophilic than the parent ZnI_2. This was certainly the case, as no reaction was observed.

A variety of common solvents systems were investigated. No reaction was observed in THF or Et_2O. This may have been due to the insolubility of the ZnI_2 in these solvents. No reaction was observed in CH_3CN, DMF, or DMSO. The ZnI_2 was observed to dissolve in these solvents, however, these solvents may have interacted directly with the ZnI_2, decreasing its oxophilicity, and preventing co-ordination with glycidic ester oxygens.

The addition of CH_3NO_2 to the reaction mixture appeared to increase the quantities of **30a** that were isolated. When the reaction was run in a 1:1 mixture of CH_2Cl_2 and CH_3NO_2 the isolated yields of **55a** and **30a** shift to 70% and 23%, respectively. When the reaction was run in 100% CH_3NO_2, this product ratio shifted again to 47% and 32%, respectively.

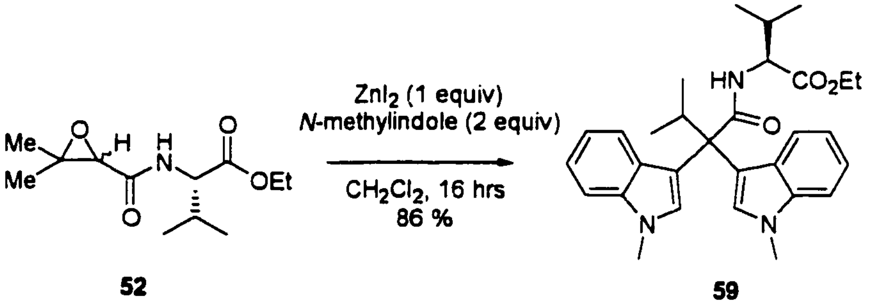
Increasing the polarity of the solvent did not increase the rate of cation formation. Instead, it appears to have either stabilized the ZnI-**30a** intermediate or increased the rate of protonation of ZnI-**30a**. Either way, increasing the solvent polarity appears to hinder the loss of ZnO and α,α-*bis*(indolyl) ester formation.

Control over this system appears to be a matter of finding the right solvent/catalyst system. When one compares the ease of adding solid ZnI_2 to a solution at RT vs. adding $SnCl_4$ to a solution at -78 °C, one can see a clear incentive for optimization of this system. Unfortunately, due to time constraints optimal conditions were not found that allowed for one to switch from α,α-*bis*(indolyl) ester formation to tryptol formation, simply by changing the solvent system.

3.13 Reactions of Other β-Mono and β,β-Disubstituted Glycidic Esters and Amides

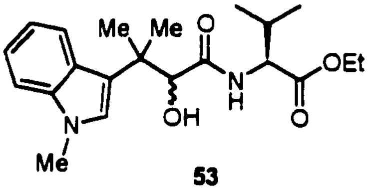
In an effort to prepare a series of these α,α-*bis*(indolyl) esters a variety of other β-mono and β,β-disubstituted glycidic esters and amides were treated with indole and ZnI_2 in CH_2Cl_2. Again, the results were quite surprising.

When the glycidic amide **52** was treated with N-methylindole (**33a**) and ZnI_2 the α,α-*bis*(indolyl) amide **59** was obtained in 86% yield.



52 **59**

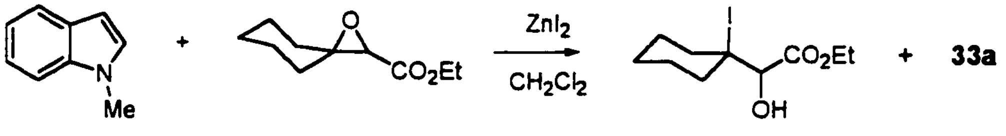
No trace of compound **53** was observed in the ^1H NMR spectrum of the crude reaction product. This was unfortunate as such a compound would provide rapid access to hemiasterlin and its derivatives.



53

Based on the observations that changing the solvent from CH_2Cl_2 to CH_3NO_2 altered the product ratio observed in the reaction of **27a** with **33a**, a CH_3NO_2 solution of **52** and **33a** was treated with ZnI_2, and stirred overnight at room temperature. Unfortunately, compound **59** was the only product isolated from this reaction.

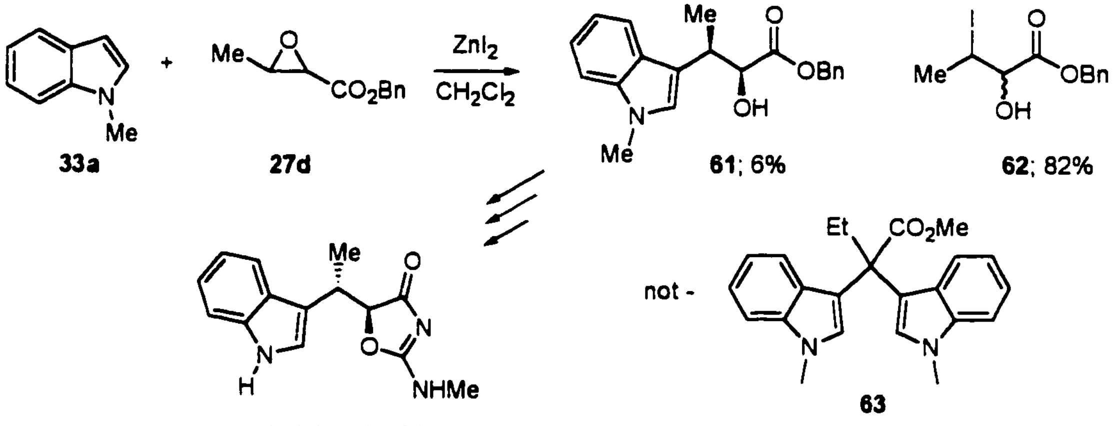
Treatment of several different substituted glycidic esters, under similar conditions, provided a variety of other products. Glycidic ester **27b** yielded the iodohydrin **41** and unreacted *N*-methylindole. No tryptol was observed even when 4 equiv. of *N*-methylindole was used and the reaction was refluxed.



33a **27b** **60** **33a**

Presumably ZnI$_2$ was strong enough to facilitate ring opening, however, the steric hindrance of the cyclohexyl ring system hindered attack of indole at the β-carbon. The only reaction possible was the result of halide transfer to provide **60**.

Under similar conditions, benzyl *trans*-2,3-epoxylbutyrate (**27d**) yielded 6% of the tryptol **61**, and 82 % of the iodohydrin **62**. Only *syn*-**61** was observed, as seen by the two methylene coupling constants of 5.6 Hz each. None of the corresponding α,α-*bis*(indolyl) ester **63** was isolated or observed in the ^{1}H NMR spectrum of the crude reaction mixture.

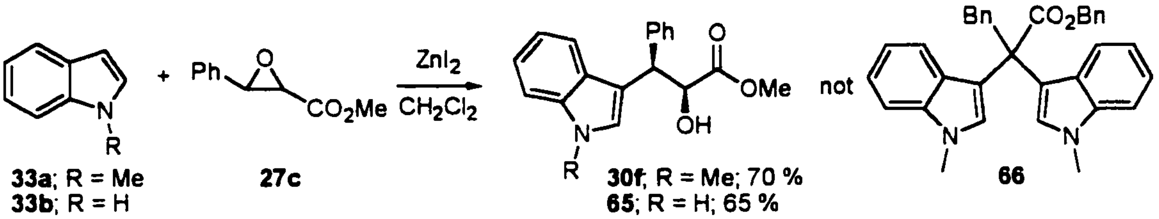


33a **27d** **61**; 6% **62**; 82% **63**

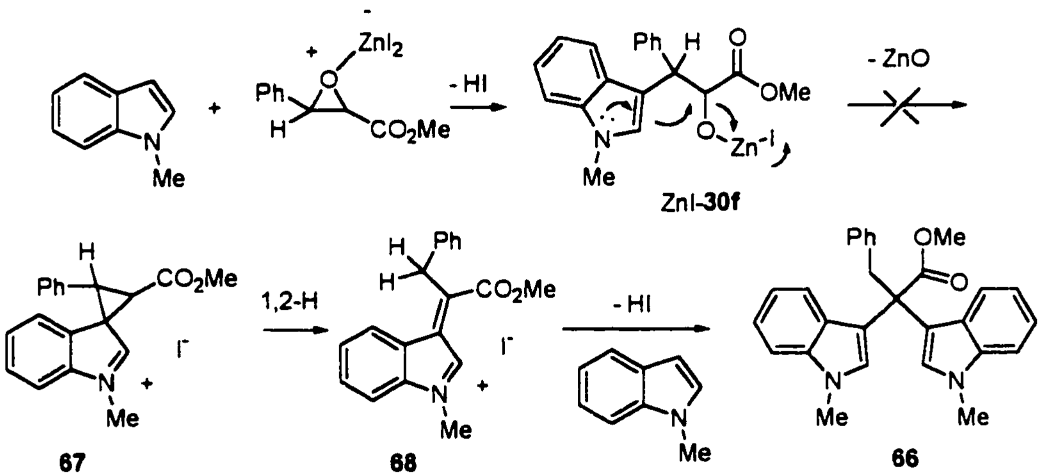
(-)-Indolmycin (**64**)

The small quantity of **61** was not surprising considering the previous results observed for the SnCl$_4$ reactions. The mild conditions of the ZnI$_2$ reaction suggests that optimization of this reaction may be useful in the synthesis of Indolmycin (**64**), a natural antibiotic which inhibits prokaryotic tryptophan tRNA synthetase and is active against drug resistant *Staphylococci*.[6,13,17]

Finally, racemic methyl *tran*-2,3-epoxycinnamate (**27c**) provided the *syn*-methyl β-phenyltryptols **30f** (R = H; J_{HaHb} = 5.3 Hz) and **65** (R = Me; J_{HaHb} = 5.6 Hz) in 70 and 65 % yield, respectively. These yields exceeded those of the SnCl$_4$ reactions making ZnI$_2$ the preferred Lewis acid for this ring opening reaction.



Again, none of the corresponding α,α-*bis*(indolyl) ester **66** was isolated or observed in the ^{1}H NMR spectrum of the crude reaction mixture, even after refluxing the reaction mixture overnight. The cation stabilization provided by the phenyl group would be expected to promote the 1,2-H shift to the *pseudo* doubly benzylic position in intermediate **67**.

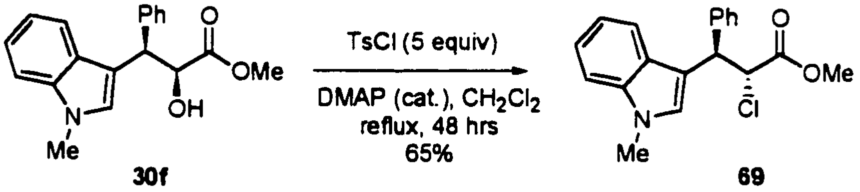


This was not the case, as the reaction stopped at the ZnI-**30f**, and ZnO was not displaced.

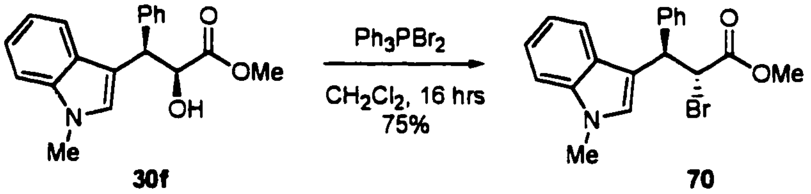
3.14 Preparation of α,β-*Bis*(indolyl) Esters

In an effort to prepare the α,α-*bis*(indolyl) ester **66** the α-hydroxy group of **30f** was converted into a leaving group. Intramolecular displacement of this group should provide access to the cyclopropyl cationic intermediate **67**, illustrated on the previous page. If the displacement reaction were carried out in the presence of excess indole, then this should lead to the formation of **66**.

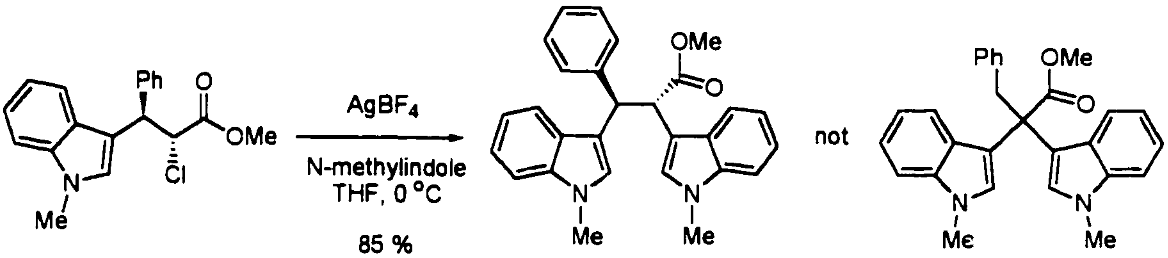
Conversion of **30f** to the corresponding tosylate was attempted, by treating **30f** with a 5 fold excess of tosyl chloride, and a catalytic quantity of DMAP. When this reaction was attempted in methylene chloride, at room temperature, no reaction was observed after 16 hours. Compound **30f** was completely consumed after refluxing this solution for 48 hours, however, the corresponding tosylate was not isolated. Instead, chloride **69** was obtained in 65% yield as a single diastereomer. A coupling constant of 11.0Hz was observed between the two methylene protons, suggesting these two protons were in an *anti* configuration.



Bromide **70** was also prepared by treating **30f** with Ph_3PBr_2, in CH_2Cl_2. Purification by silica gel chromatography provided *anti*-**70** (J=11.2Hz) in 75% yield, as a single diastereomer.



The first attempt at forming intermediate **67** involved cation formation by dehalogenation of *anti*-**69** with silver cation. Treatment of a THF solution of *anti*-**69** (1 equiv.) and *N*-methylindole (**33a**, 1 equiv.), with $AgBF_4$ (1.2 equiv.) provided a single compound which displayed two separate sets of indole resonances, and two methylene resonances (d, J=11.5Hz, 1H). Similarly, the ^{13}C NMR spectrum of this compound shows two sets of indole resonances and two methylene carbons (as seen by ^{13}C NMR JMOD experiments). From this spectral data the structure of this new compound was assigned as the α,β-*bis*(indolyl) ester **71**.

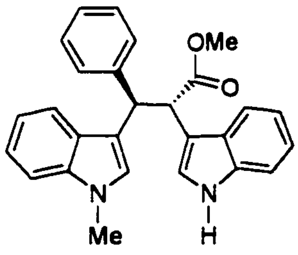


***anti*-69** **71**; J = 12.3 Hz **66**

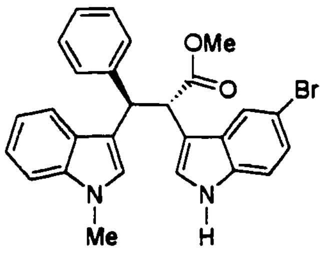
This result was quite surprising, as it was expected that the α,α-*bis*(indolyl) ester **66** would be formed as a result of a 1,2-hydride shift, and subsequent attack of indole. This result suggests that attack of indole on intermediate **67** is favoured over a 1,2-hydride shift.

Attempts were made to grow X-ray quality crystals of **71** in order to confirm the proposed structure. Unfortunately, compound **71** crystallized as a powder from all of solvent systems investigated.

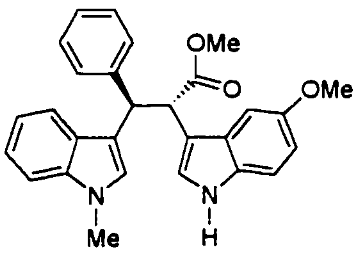
Based on the above reaction, several *mixed* indolyl systems were prepared, by treating THF solutions of *anti*-**69** and the appropriate indole, with $AgBF_4$. These compounds are illustrated below.



72; 79 %; J = 11.9 Hz

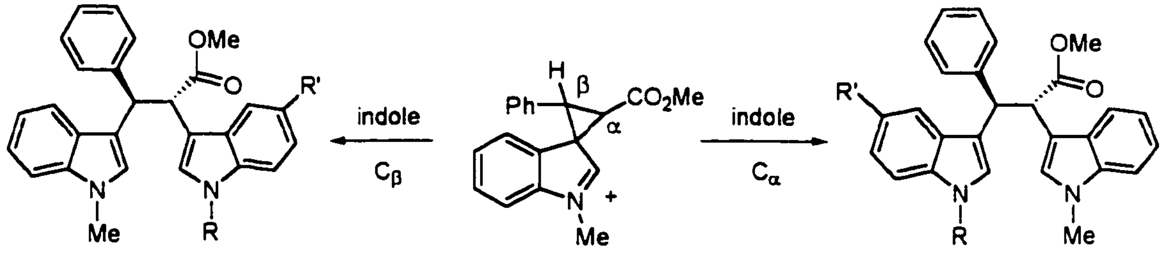


73; 70 %; J = 12.0 Hz



74; 34 %; J = 11.9 Hz

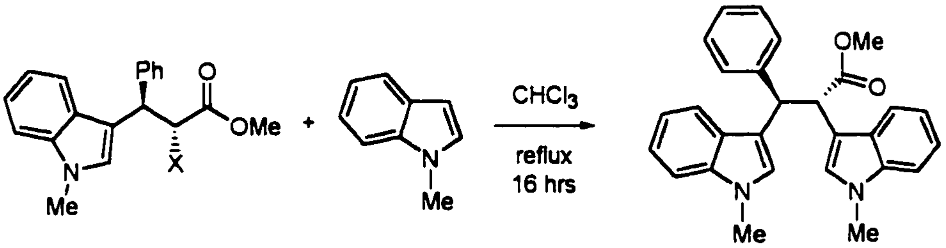
These structures are tentative assignments. At this time it is uncertain whether the second indole molecule attacked at the C_α or the C_β position of the cyclopropyl intermediate **67**, to provide isomer **A** or isomer **B**.



A **67** **B**

Several attempts have been made to grow X-ray quality crystals of these compounds. Unfortunately, no X-ray crystal structure is available at this time. The isomer **A** has been chosen to represent the structure of compounds **71** through **74**, based on the observations made during the preparation of various α,α-*bis*(indolyl) esters with ZnI_2.

Formation of the α,α-*bis*(indolyl) esters was proposed to be the result of an intramolecular displacement reaction (see Section 3.10). A similar displacement of the α-halogens of *anti*-**69** and *anti*-**70** may also provide access to the compounds described above. When either *anti*-**69** or *anti*-**70** and 1 equiv. of *N*-methylindole were heated in $CHCl_3$ for 16 hours, near quantitative yields of **71** were obtained. Interestingly, this reaction did not occur in $CDCl_3$, suggesting the residual acidity of $CDCl_3$ may inhibit this reaction.



69; X = Cl
70; X = Br

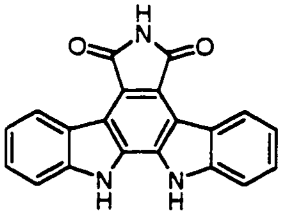
33a

71

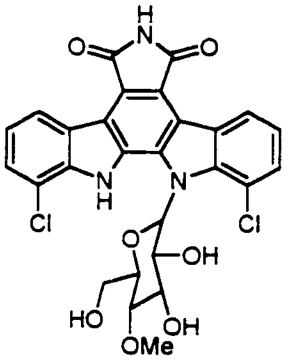
Similar reactions were observed for combinations of *anti*-**69** and the indoles **33b**, **33c**, **33d**, and 5-nitroindole (to provide compound **75**).

Clearly, one can see the potential for the synthesis of a large family of these compounds, either using standard or combinatorial synthetic methods.

Structurally, these compounds resemble the bisindolylmaleimides, a class of protein kinase C inhibitors.[18] One of these compounds, Rebeccamycin is currently in late stage clinical trials as an anticancer agent.



Bisindoylmaleimide

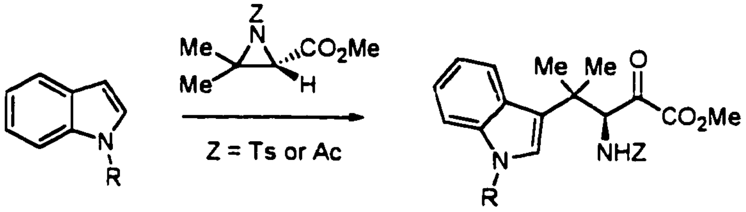


Rebeccamycin

Unfortunately, the mode of action of these compounds involves the binding of the maleimide functionality to the ATP binding site of various protein kinases. Sine the α,β-*bis*(indolyl) esters lack this maleimide functionality, it is not believed that they will share similar biological activity.

3.15 Future Work

As mentioned in the introduction, a more direct route to the tri- and tetramethyl tryptophans may involve the ring opening reactions of optically active aziridines.

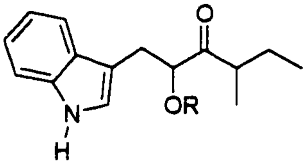


This route will provide direct access to the tetrasubstituted tryptophans. Unfortunately, synthesis of aziridine is more complicated than the synthesis of substituted glyoxylates, and the overall number of steps would increase from 4 to 7.

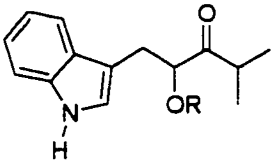
If the ring opening of glycidic amide **62** can be optimized to provide sufficient quantities of **53**, this would represent a novel and highly convergent route to the hemiasterlins. In order for this, or any route involving azide **44**, to be effective the azide reduction reaction must provide yields in excess of 50%.

Several biologically active natural products have been described which are synthetically accessible via these ring opening reactions. Optimization of the ring opening of glycidic ester will provide access to large quantities of substituted tryptols. Conversion of **61** to indolmycin (**64**) and indolmycin derivatives will be straight forward, following the procedure described in the literature.

Compounds **76** through **79** have been isolated from *Xenorhabdus bovienii*. The *iso*-butyl ketones **76** and **77**, have displayed antibiotic activity against *Cryptococcus neoformans*, while the *iso*-propyl derivatives, **78** and **79**, displayed activity against *Phytophthora* infestants.[19]

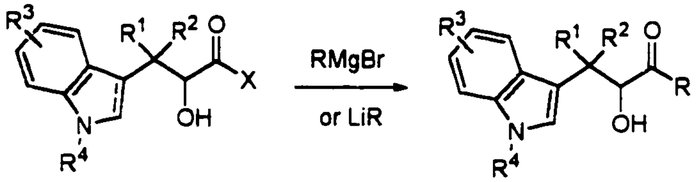


76; R = H
77; R = Ac



78; R = H
79; R = Ac

Direct treatment of **80** or **81** with Grignard or alkyl lithium reagents should provide direct access to a large family of highly substituted derivatives (**82**).



80; X = OMe
81; X = N(OMe)Me

82; R = alkyl

These compounds may display more diverse and higher levels of biological activity.

3.16 References

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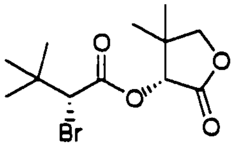
3.17 Experimental

3.17.1 General

All reaction, unless stated otherwise, were run under a nitrogen atmosphere using dry solvents. THF was dried over sodium benzophenone ketyl, and distilled prior to use. Methylene chloride, acetonitrile, triethylamine, and TMEDA were dried over NaH, and distilled prior to use. DMSO, DMF, and nitromethane were dried over NaH, and distilled under reduced pressure. All chemical reagents were obtained from Aldrich Chemical Company and used as received, unless stated otherwise. *tert*-Butyl bromoacetyl chloride was prepared according to the literature procedure.[5]

3.17.2 [*R*]-Pantolactone 2-Bromo-3,3-dimethylbutanoate (23c)



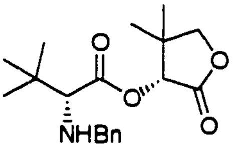
A methylene chloride (25 mL) solution of [*R*]-pantolactone and triethylamine was cooled to 0 °C and treated with a methylene chloride (10 mL) solution of *tert*-butyl bromoacetyl chloride. The solution was warmed to room temperature and stirred for 2 hours. The reaction mixture was diluted with diethyl ether (100 mL) and water (50 mL). The organic layer was washed with water (2 x 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant solid was purified by silica gel chromatagraphy, eluting with 5:1 hexane/ethyl acetate, to provide **23c** was a white solid in 89% yield, as a 2:1 mixture of diastereomers, as seen by a ^{1}H NMR spectrum of the purified product. Recrystallization from a minimum of cold (-10 °C) diethyl ether provided a [*R*,*R*]-**23c** in 89% de. A second recrystallization provided optically pure [*R*,*R*]-**23c** in 25% yield.

[*R*,*R*]-**23c** : IR (KBr, cm^{-1}) 2969 (s), 2937 (s), 2911 (s), 2876 (s), 1797 (s), 1756 (s), 1479 (s), 1465 (s), 1401 (s), 1371 (s), 1258 (s), 1141 (s), 1079 (s0, 1013 (s), 998 (s). ^{1}H NMR

(500MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.23 (s, 1H), 4.04 (d, J=9.0Hz, 1H), 4.01 (d, J=9.0Hz, 1H), 1.21 (s, 3H), 1.17 (s, 9H), 1.14 (s, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 171.6, 168.2, 56.9, 40.4, 34.6, 26.7, 22.9, 19.8. MS (CI, m/z) : M+1 = 307, M+2 = 309.

[*R*,*S*]-**23c** : ^1H NMR (500MHz, $CDCl_3$) δ 5.37 (s, 1H), 4.19 (s, 1H), 4.04 (d, J=9.0Hz, 1H), 4.01 (d, J=9.0Hz, 1H), 1.21 (s, 3H), 1.17 (s, 9H), 1.15 (s, 3H).

3.17.3 [*R*,*S*]-24



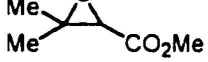
Ester **23a** (306 mg, 1.0 mmol) and *n*-Bu_4NI (36 mg, 0.01 mmol) were dissolved in dry THF (10 mL) and treated with triethyl amine (140 μL, 1.0 mmol) and benzylamine (109 μL, 1.0 mmol). The solution was sealed under nitrogen and allowed to stir at room temperature has 5 days. The resulting suspension was treated with diethyl ether (50 mL) and water (10 mL). The organic layer was washed with water (3 x 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting oil was further purified by silica gel chromatography, eluting with 5:1 hexanes/ethyl acetate, to provide [*R*,*S*]-**24** as a yellow oil in 50% yield, as a 4:1 mixture of diastereomers.

[*R*,*S*]-**24**: IR (neat, cm^{-1}) 3400 (s), 3089 (w), 3065 (w), 3032 (w), 2969 (s), 2937 (s), 2875 (m), 1748 (s), 1732 (s), 1660 (s). 1H NMR (200MHz, CDCl3) d 7.24-7.18 (m, 5H), 6.73 (br t, 1H), 5.18 (s, 1H), 4.46 (d, J=12.5Hz, 2H), 4.17 (s, 2H), 1.16 (s, 9H), 1.14 (s, 3H), 0.93 (s, 3H). 13C NMR (50 MHz, CDCl3) d 168.9, 167.6, 137.2, 128.6, 127.8, 127.6, 79.3, 69.4, 58.9, 43.3, 26.9, 22.7, 20.0.

3.17.4 General Procedure A: *m*-CPBA Preparation of Glycidic Esters

To a $CHCl_3$ solution of the appropriate acrylate (1 equiv.) was added 2,6-di-*tert*-butylphenol (1 mol%) and 85% *m*-CPBA (2 equiv.). The reaction mixture was refluxed for 16 to 28 hours before being allowed to cool to room tmeperature. The precipitated acid was filtered off and the $CHCl_3$ removed under reduced pressure. The resulting residue was taken up in diethyl ether and washed with 10% w/v sodium thiosulfate (2x), saturated $NaHCO_3$ (2x), and water (2x). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting gylcidic esters were purified either by distillation or by recrystallization.

3.17.5 *rac*-Methyl 2,3-epoxy-3-methylbutanoate (27a)



Compound **27a** was prepared according to General Procedure A, by treating methyl 3,3-dimethylacrylate (10.0 g, 87.7 mmol) with *m*-CPBA (30.2 g, 175 mmol) and 2,6-di-*tert*-butylphenol (500 mg), in $CHCl_3$ (500 mL). The reaction mixture was refluxed for 16 to 24 hours. After the standard work up the crude glycidic ester was further purified by Kruglhror distillation (50 to 60 °C, 0.1 torr), to provide racemic **27a** as a clear colourless liquid (10.30 g, 92% yield).

IR (neat) 2964 (m), 1751 (s), 1444 (m), 1206 (m) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.24 (s, 1H), 1.32 (s, 3H), 1.27 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 168.8, 60.0, 59.1, 52.0, 24.0, 18.1.

3.17.6 (-)-Methyl 2,3-epoxy-3-methylbutanoate (27a)

[*R*]-Pantolactone 2,3-epoxy-3-methylpropanoate (**46**) was dissolved in methanol (10 mL) and stirred overnight with K_2CO_3. Diethyl ether (50 mL) and water (50 mL) were added, and the organic layer was washed with water (2 x 25 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to provide (+)-**27a** in 90% yield.

$[\alpha]_D = -29.8°$ (c 0.040, $CHCl_3$).

3.17.7 Glycidate 27b

Compound **27b** was prepared from according to General Procedure A from Ethyl 3,3-cyclohexylacrylate.

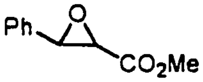
Ethyl 3,3-cyclohexylacrylate was prepared by treating cyclohexanone (10.0 g, 102 mmol) with (carbethoxymethylene)triphenylphosphorane (35.5 g, 102 mmol) in refluxing toluene (250 mL). After refluxing for 1 hour the solution was cooled and diluted with diethyl ether (500 mL). The organic layer was washed with water (3 x 150 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure, to provide as a clear oil. Further purification by distillation under reduced pressure (50 °C, 0.1 torr) provided pure in 95% yield.

IR (neat) 2981 (m), 2933 (s), 2857 (m), 1715 (s), 1649 (m), 1448 (m), 1379 (m), 1206 (s), 1158 (s). ^{1}H NMR (200MHz, $CDCl_3$) δ 5.56 (s, 1H), 4.09 (q, J=7.1Hz, 2H), 2.79 (m, 2H), 2.15 (m, 2H), 1.57 (m, 6H), 1.23 (t, J=7.1Hz, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 166.8, 163.5, 112.9, 59.4, 37.9, 29.8, 28., 27.8, 26.2, 14.3.

Ethyl 3,3-cyclohexylacrylate (5.0 g, 30.1 mmol) was dissolved in $CHCl_3$ (100 mL). *m*-CPBA (10.3 g, 60.2 mmol) and 2,6-di-*tert*-butylphenol (100 mg) were added and the reaction mixture was refluxed for 24 hours. After the standard work up the crude glycidic ester was further purified by Kruglhror distillation (50 to 60 ºC, 0.1 torr), to provide racemic **27b** as a clear colourless liquid in 85% yield.

IR (neat) 2980 (m), 2936 (s), 2860 (m), 1743 (s), 1465 (m), 1196 (s), 1032 (m) cm^{-1}. ^{1}H NMR (200MHz, $CDCl_3$) δ 4.21 (q, J=7.2Hz, 2H), 3.28 (s, 1H), 1.71-1.32 (m, 10H), 1.26 (t, J=7.2Hz, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 168.4, 64.8, 61.3, 59.4, 34.8, 28.6, 25.2, 25.0, 24.7, 14.2. HRMS Cal'd for $C_{10}H_{16}O_3$; 184.1100. Found 184.1084.

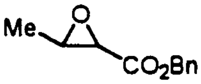
3.17.8 Methyl 2,3-epoxy-3-phenylpropanoate (27c)



Compound **27c** was prepared according to General Procedure A, by treating methyl *trans*-cinnamate (10.0 g, 61.7 mmol) with *m*-CPBA (21.7 g, 123.4 mmol) and 2,6-di-*tert*-butylphenol (500 mg), in $CHCl_3$ (500 mL). The reaction mixture was refluxed for 48 hours. After the standard work up the crude glycidic ester was further purified by Kruglhror distillation (50 to 60 °C, 0.1 torr), to provide compound as a yellow oil (9.75 g, 93% yield).

IR (neat) 3065 (w), 3030 (w), 2955 (m), 1746 (s), 1636 (w), 1560 (m), 1440 (s), 1416 (m), 1344 (m), 1292 (s), 1208 (s), 1022 (m), 1000 (m) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 7.33 (m, 3H), 7.26 (m, 2H), 4.08 (d, J=1.8Hz, 1H), 3.80 (s, 3H), 3.49 (d, J=1.8Hz, 1H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 168.6, 134.8, 128.9, 128.6, 125.7, 57.9, 56.5, 52.5. HRMS Cald for $C_{10}H_{10}O_3$; 178.0630. Found 178.0631.

3.17.9 *rac*-Benzyl 2,3-epoxybutanoate (27d)



Compound was prepared according to General Procedure A from benzyl crotanoate.

Benzyl crotanoate was prepared by the addition of crotonyl chloride (2.0 mL, 20.5 mmol) to a cold methylene chloride (25 mL) solution of benzyl alcohol (2.11 g, 19.5 mmol) and triethylamine (2.8 mL, 20.5 mmol). After stirring at room temperature for 2 hours the reaction was quenched by the addition of saturated NaH_2CO_3 (10 mL) and diethyl ether (100 mL). The organic layer was washed with water (2 x 50 mL), dried over anhyrous $MgSO_4$, filtered and concentrated under reduced pressure to provide benzyl crotonate in 75% yield.

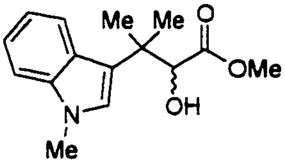
The crude benzyl crotanoate (2.34 g, 15.4 mmol) was dissolved in $CHCl_3$ (25 mL) with *m*-CPBA (5.40 g, 30.8 mmol) and 2,6-*tert*-butylphenol (200 mg). The reaction mixture was refluxed for 24 hours. After the standard work up the crude glycidic ester was further purified by Kruglhror distillation (70 °C, 0.1 torr), to provide compound as a colourless liquid in 80% yield.

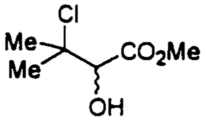
IR (neat) 3034 (m), 2972 (m), 1743 (s), 1457 (s), 1428 (s), 1334 (s), 1283 (s), 1251 (s), 1194 (s), 1146 (s), 1053 (s), 1032 (s), 1002 (s), 743 (s), 599 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.23 (d, J=12.3Hz, 1H), 5.14 (d, J=12.3Hz, 1H), 3.24 (m, 3H), 1.37 (d, J=5.3Hz, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 168.9, 134.9, 128.46, 128.38, 128.37, 67.0, 54.4, 53.7, 16.9.

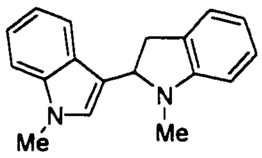
3.17.10 General Procedure B: Glycidic Ester Ring Opening Reactions with $SnCl_4$

A CH_2Cl_2 solution of the glycidic ester **27** (1 equiv.) and indole **33** (1 equiv.) was cooled to -78 °C. A 1.0 M CH_2Cl_2 solution of $SnCl_4$ (1 equiv.) was added drop wise over 5 to 10 minutes. After stirring at -78 °C for an additional 30 minutes the reaction was quenched by the drop wise addition of saturated $NaHCO_3$, and allowed to warm to room temperature. Additional saturated $NaHCO_3$ was added until frothing ceased. The resulting slurry was diluted with diethyl ether (5 to 10 times initial reaction volume) and the organic layer was washed with water, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting tryptols were purified by silica gel chromatography, and recrystallized form the appropriate solvent system.

3.17.11 Racemic Methyl 2-hydroxy-3-methyl-3-(N-methylindolyl)butanoate (30a)


rac-**30a**


41


42

Compound **30a** was prepared according to General Procedure B, by treating a 1M CH_2Cl_2 solution of methyl 3,3-dimethylglycidate and N-methylindole with $SnCl_4$. Compound **30** was obtained as a white solid after silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, in 70% yield. Further purification by recrystallization from cold diethyl ether provided **30** as fine white crystals.

rac-**30a** : m.p. 99.0-101.0 °C. IR (KBr) 3478 (br), 2957 (m), 1717 (s), 1615 (m), 1547 (m), 1230 (s), 1084 (s), 743 (s), 553 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 7.82 (d, J=8.0Hz, 1H), 7.31 (dd, J=1.6, 8.1Hz, 1H), 7.24 (t, J=8.1Hz, 1H), 7.11 (dt, J=1.4, 8.1Hz, 1H), 6.89 (s, 1H), 4.54 (d, J= 7.0Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 2.68 (d, J=7.0Hz, 1H), 1.56 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 173.8, 137.6, 126.7, 126.1, 121.3, 121.0, 118.7, 109.5, 77.5, 51.8, 39.9, 32.6, 25.3, 24.2. HRMS Cal'd for $C_{15}H_{19}NO_3$ 261.1365. Found 261.1347.

41 : IR (neat) 3475 (s), 2981 (m), 2956 (m), 1740 (s), 1446 (m), 1275 (m), 1205 (m), 1102 (m) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$) δ 4.04 (br d, J=7.7Hz, 1H), 3.76 (s, 3H), 3.38 (br s, 1H), 1.60 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 170.9, 77.1, 69.5, 51.0, 28.7, 28.3.

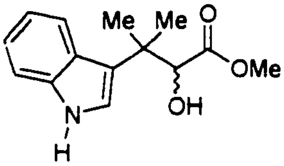
42 : ^1H NMR (200MHz, $CDCl_3$) δ 7.79 (dd, J=0.8, 7.9Hz, 1H), 7.40 (dd, J=0.8, 8.2Hz, 1H), 7.33 (t, J=7.9Hz, 1H), 7.25 (t, J=7.9Hz, 1H), 7.22 (d, J=8.2Hz, 1H), 7.16 (m, 1H), 7.14 (s, 1H), 6.81 (t, J=7.2Hz, 1H), 6.62 (d, J=7.9Hz, 1H), 4.70 (dd, J=9.8, 11.0Hz, 1H), 3.38 (s, 3H), 3.39 (dd, J=9.8, 11.0Hz, 1H), 3.30 (dd, J=9.8, 11.0Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 153.3, 137.4, 129.2, 127.5, 127.3, 126.7, 124.0, 121.7, 120.1, 118.9, 117.7, 115.0, 109.3, 107.1, 64.7, 37.8, 34.0, 32.6.

3.17.12 (-)-Methyl 2-hydroxy-3-methyl-3-(N-methylindolyl)butanoate (30a)

(-)-**30a** was prepared from (-)-**27a** (89% ee) and *N*-methylindole, in a similar manner as that described for *rac*-**30a**, to provide (-)-**30a** in 45% and 89% ee, as seen by chiral HPLC (ChiralCel OD column, eluting with 95:5 hexane/*iso*-propanol).

$[\alpha]_D$ = -46.9° (c 0.063, $CHCl_3$).

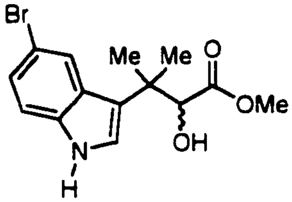
3.17.13 Methyl 2-hydroxy-3-methyl-3-(indolyl)butanoate (30b)



Compound **30b** was prepared according to General Procedure B, by treating a 1M CH_2Cl_2 solution of **27b** (260 mg, 2.0 mmol) and indole **33b** (230 mg, 2.0mmol) with $SnCl_4$ (2 mL, 1.0M in CH_2Cl_2, 2.0 mmol) at -78 °C. After the usual work up and silica gel chromatography, eluting with 2:1 hexane/ethyl acetate, compound **30b** was obtained as a white solid in 52% yield. An analytical sample was obtained by recrystallization from diethyl ether at -30 °C.

IR (KBr) 3397 (br s), 2966 (m), 1728 (s), 1618 (w), 1541 (w), 736 (s). ^1H NMR (200MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.80 (dd, J=1.2, 7.3Hz, 1H), 7.32 (dd, J=1.2, 7.4Hz, 1H), 7.17 (dt, J=1.3, 7.0Hz, 1H), 7.09 (dt, J=1.3, 7,0Hz, 1H), 6.95 (d, J=2.2Hz, 1H), 4.55 (s, 1H), 3.62 (s, 3H), 2.42 (br s, 1H), 1.53 (s, 6H). ^{13}C NMR (50MHz, $CDCl_3$) δ 174.0, 137.0, 125.7, 122.0, 121.7, 121.0, 120.3, 119.2, 11.5, 77.5, 51.9, 40.0, 25.1, 24.2.

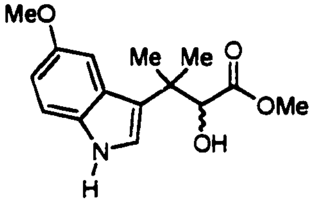
3.17.14 Methyl 2-hydroxy-3-methyl-3-(5-bromoindolyl)butanoate (30c)



Compound **30c** was prepared according to General Procedure B, by treating a 1M CH_2Cl_2 solution of **29a** and 5-bromoindole with $SnCl_4$ at -78 °C. After the usual work up and silica gel chromatography, compound **30c** was obtained as a light pink solid in 52% yield. Recrystallization from chloroform/hexane provided analytically pure material.

m.p. 138.0-140.0 °C. IR (KBr) 3501 (m), 3306 (br), 2953 (m), 1722 (s), 1649 (m), 1560 (m), 1436 (s), 1264 (s), 1144 (s), 1089 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) d 8.36 (br s, 1H), 7.90 (d, J=0.5Hz, 1H), 7.20 (dd, J=1.8, 8.7Hz, 1H), 7.09 (d, J=8.7Hz, 1H), 6.86 (d, J=2.5Hz, 1H), 4.45 (br d, J=3.3Hz, 1H), 3.64 (s, 3H), 2.82 (br d, J=3.3Hz, 1H), 1.48 (s, 6H). ^{13}C NMR (57.3Hz, $CDCl_3$) d 174.0, 135.5, 127.3, 124.4, 123.6, 123.5, 123.3, 119.8, 112.9, 112.3, 77.3, 52.1, 39.7, 25.2, 24.2. Anal Calc'd for $C_{14}H_{16}NO_3Br$ (326.17): C, 51.55; H, 4.94; N, 4.29. Found C, 51.19; H, 4.93; N, 4.22.

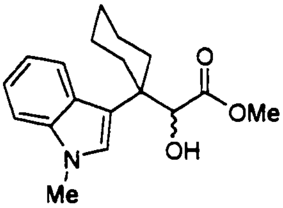
3.17.15 Methyl 2-hydroxy-3-methyl-3-(5-methoxyindolyl)butanoate (30d)



Compound **30d** was prepared according to General Procedure B, by treating a 1M CH_2Cl_2 solution of **27a** and 5-methoxylindole with $SnCl_4$, at -78 °C. After the usual work up and silica gel chromatography, compound was obtained as an off white solid in 43% yield.

m.p. 127.0 °C. IR (KBr, cm-1) 3438 (m), 3346 (m), 2985 (m), 2972 (m), 2902 (m), 1735 (s), 1623 (m), 1582 (s), 824 (s), 812 (s). ^{1}H NMR (200MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.25 (d, J=2.1Hz, 1H), 7.20 (d, J=8.8Hz, 1H), 6.92 (d, J=2.5Hz, 1H), 6.83 (dd, J=2.2, 8.8Hz, 1H), 4.52 (d, J=6.8Hz, 1H), 3.84 (s, 3H), 3.61 (s, 3H), 2.67 (d, J=6.8Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 173.9, 153.5, 132.3, 126.1, 122.8, 120.0, 112.0, 111.6, 103.6, 77.4, 56.0, 51.9, 39.9, 24.9, 24.2. HRMS Cal'd for $C_{15}H_{19}NO_4$ 277.1314. Found 277.1320.

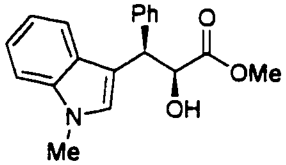
3.17.16 Tryptol 30e



Compound **30e** was prepared according to General Procedure B, by treating a 1M CH_2Cl_2 solution of **27a** and *N*-methylindole with $SnCl_4$, at -78 °C. After the usual work up and silica gel chromatography, compound **30e** was obtained as a light pink solid in 69% yield. Compound **30e** was further purified by recrystallization from hexane/chloroform.

m.p. 89.0-90.0 °C. IR (KBr) 3466 (br), 2915 (m), 1705 (s), 1617 (m), 1544 (m). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.74 (dd, J=0.9, 8.1Hz, 1H), 7.27 (dd, J=0.7, 8.2Hz, 1H), 7.17 (dt, J=1.0, 8.1Hz, 1H), 7.03 (dt, J=1.0, 8.1Hz, 1H), 6.85 (s, 1H), 4.18 (d, J=7.1Hz, 1H), 3.90 (q, J=7.1Hz, 2H), 3.75 (s, 3H), 2.58 (d, J=9.0Hz, 2H), 2.50 (m, 2H), 1.80-1.49 (m, 8H), 0.97 (t, J=7.1Hz, 1H). ^{13}C NMR (50MHz, $CDCl_3$) δ 173.2, 137.4, 128.7, 127.2, 121.3, 121.0, 118.7, 113.5, 109.3, 78.5, 60.9, 44.9, 33.2, 32.8, 32.7, 26.1, 22.1, 13.7.

3.17.17 *syn*-Methyl 2-hydroxy-3-(N-methylindolyl)-3-phenylpropanoate (30f)



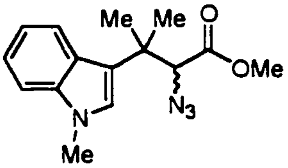
Compound **30f** was prepared according to General Procedure B, by treating a 1M CH_2Cl_2 solution of methyl 2,3-epoxy-3-phenylpropanoate and N-methyindole with $SnCl_4$, at -78 °C. After the usual work up and silica gel chromatography, eluting with 4:1 hexane/ethyl acetate, compound **30f** was obtained as a white solid in 50% yield.

m.p. 114.0-115.0 °C. IR (KBr) 3536 (s), 3028 (m), 2942 (m), 1740 (s), 1600 (w), 1547 (w), 1487 (m), 1446 (m), 1316 (m), 1280 (s), 1204 (s), 1090 (s), 748 9s), 701 (s) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$) δ 7.36 (td, J=0.9, 8.0Hz, 1H), 7.35 (d, J=0.7Hz, 1H), 7.34-7.22 (m, H), 7.20 (ddd, J=1.1, 7.1, 8.1Hz, 1H), 7.02 (ddd, J=1.0, 7.0, 8.0Hz, 1H), 4.97 (dd, J=3.1, 6.5Hz, 1H), 4.80 (d, J=3.1Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 2.85 (d, 7.1Hz, 1H). ^{13}C NMR (50MHz, $CDCl_3$) δ 174.0, 138.7, 136.7, 129.0, 128.2, 127.7, 127.3, 127.1, 119.0, 118.8, 114.3, 109.1, 74.0, 52.5, 46.2, 32.7. Anal Calcd for $C_{19}H_{19}NO_3$ (309.37): C, 73.75; H, 6.18; N, 4.53. Found C, 73.63; H, 6.24; N, 4.56.

3.17.18 General Procedure C : Mitsunobu Azidation of Tryptol 30

To a cold 1M THF solution of triphenylphosphine (1 equiv.) was added DEAD (1 equiv.), DPPA (1 equiv.), and pyridine (1 equiv.). The resulting slurry was stirred at 0 °C for 1 minute before a THF solution of tryptol **30** was added via cannula. The resulting solution was warmed to room temperature and stirred overnight. The solvent was removed under reduced pressure and azide **44** was purified by silica gel chromatography.

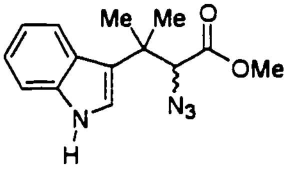
3.17.19 Methyl 2-azido-3-methyl-3-(*N*-methylindolyl)butanoate (44a)



Compound **44a** was prepared according to Genreal Procedure C using DEAD, Ph_3P, DPPA, pyridine, and **33a**. Purification of **44a** was performed by silica gel chromatography, eluting with 20:1 hexane/ethyl acetate, to provide an 18:1 mixture of **44a** and DPPA, in 85% yield (based on the quantity of **44a**).

IR (neat) 3050 (s), 2950 (s), 2867 (s), 2169 (s), 1725 (s), 1620 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, J=8.0Hz, 1H), 7.34 (s, 1H), 7.33 (t, J=8.0Hz, 1H), 7.27 (dd, J=0.9, 8.0Hz, 1H), 7.22 (dt, J=0.9, 8.0Hz, 1H), 4.15 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 1.52 (s, 3H), 1.48 (s, 3H).

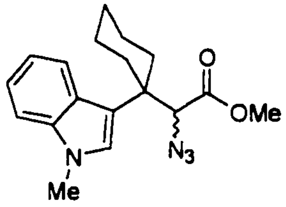
3.17.20 Methyl 2-azido-3-methyl-3-(indolyl)butanoate (44b)



Compound **44b** was prepared according to Genreal Procedure C using DEAD, Ph_3P, DPPA, pyridine, and **33b**. Purification of **44b** was performed by silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, to provide **44a** as a clear oil in 90% yield.

IR (neat) 3388 (s), 3058 (m), 2960 (s), 2872 (m), 2502 (w), 2098 (s), 1729 (s), 1619 (m), 1589 (m), 1542 (m), 744 (s) cm^{-1}. ^{1}H NMR (200MHz, $CDCl_3$) δ 8.53 (br s, 1H), 7.72 (d, J=9.0Hz, 1H), 7.35 (m, 2H), 7.24 (m, 3H), 4.19 (s, 1H), 3.74 (s, 3H), 1.50 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 172.7, 135.5, 127.3, 124.5, 122.0, 119.8, 118.5, 11.3, 108.5, 63.4, 51.8, 51.2, 25.1, 23.6. HRMS Cal'd for $C_{14}H_{16}N_4O_2$. Found 272.1249.

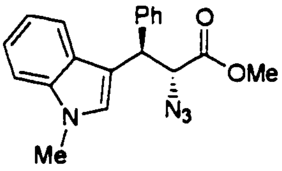
3.17.21 Azide 44e



Compound **44c** was prepared according to Genreal Procedure C using DEAD, Ph$_3$P, DPPA, pyridine, and **33c**. Purification of **44c** was performed by silica gel chromatography, eluting with 9:1 hexane/ethyl acetate, to provide a 10:1 mixture of **44c** and DPPA, in 87% yield (based on the quantity of **44c**).

IR (neat, cm-1) 3056 (m), 2940 (s), 2861 (s), 2170 (s), 1720 (s), 1614 (s), 1592 (s), 775 (s), 740 (s), 690 (s). ^{1}H NMR (200 MHz, CDCl$_3$) δ 7.68 (d, J=8.0Hz, 1H), 7.40 (s, 1H), 7.35 (t, J=8.0Hz, 1H), 7.29 (dd, J=0.9, 8.0Hz, 1H), 7.20 (dt, J=0.9, 8.0Hz, 1H), 4.05 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.43-2.31 (m, 4H), 1.52-1.39 (m, 6H).

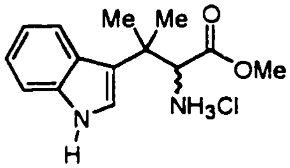
3.17.22 Methyl 2-azido-3-phenyl-3-(*N*-methylindolyl)propanoate (44f)



Compound **44f** was prepared according to Genreal Procedure C using DEAD, Ph$_3$P, DPPA, pyridine, and **33a**. Purification of **44f** was performed by silica gel chromatography, eluting with 9:1 hexane/ethyl acetate, to provide a 14:1 mixture of **44a** and DPPA, in 75% yield (based on the quantity of **44f**).

^{1}H NMR (200MHz, CDCl$_3$) δ 7.37 (d, J=8.0Hz, 1H), 7.31 (d, J=8.0Hz, 1H), 7.34-7.22 (m, H), 7.20 (dd, J= 7.1, 8.1Hz, 1H), 7.02 (ddd, J=1.0, 7.0, 8.0Hz, 1H), 5.02 (dd, J=10.8Hz, 1H), 4.85 (d, J=10.8Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H).

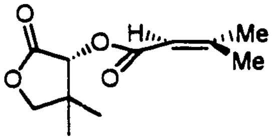
3.17.23 β,β-Dimethyltryptophan Methyl Ester Hydrochloride (45b)



Azide **44b** was stirred for 3 hours with 1 equiv. of Ph_3P in THF (10 mL). 3M HCl (1 mL) was added and the solution was refluxed overnight. Methylene chloride and 1M HCl were added and the aqueous phase was washed with methylene chloride (2 x 10 mL). The aqueous phase was dried under reduced pressure to provide compound **45b** as ab off white solid, in 70% yield.

m.p. >250 °C. IR (KBr) 3723-2577 (br s), 2007 (m), 1700 (s), 1632 (m), 1400 (s). ^1H NMR (200MHz, DMSO-d^6) δ 10.21 (br s, 1H), 7.80 (dd, J=1.2, 7.3Hz, 1H), 7.32 (dd, J=1.2, 7.4Hz, 1H), 7.17 (dt, J=1.3, 7.0Hz, 1H), 7.09 (dt, J=1.3, 7,0Hz, 1H), 6.95 (d, J=2.2Hz, 1H), 4.55 (s, 1H), 3.62 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (50MHz, DMSO-d^6) δ 174.0, 137.0, 125.7, 122.0, 121.7, 121.0, 120.3, 119.2, 11.5, 77.5, 51.9, 40.0, 25.1, 24.2.

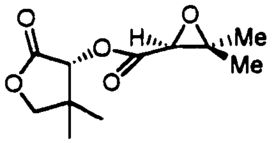
3.17.24 [*R*]-Pantolactone 3,3-dimethylacrylate (48)



Oxalyl chloride (4.36 mL, 50.0 mmol) was added to a cold (0 °C) CH_2Cl_2 (100 mL) solution of 3,3-dimethylacrylic acid (10.0 g, 50.0 mmol) and DMF (3 drops). The mixture was warmed to room temperature and stirred for 3 hours; an additional 30 minutes after no more gas evolution was observed. [*R*]-Pantolactone (6.50 g, 50.0 mmol), in CH_2Cl_2 (25 mL), was added via cannula, and the reaction mixture was allowed to stir overnight. The solvent was removed under reduced pressure to provide a white solid, which was used in the next step without further purification.

m.p. 95.0-96.0 °C. $[\alpha]_D$ -6.7° (0.126C, $CHCl_3$). IR (CH_2Cl_2) 2907 (m), 2878 (m), 1810 (s), 1778 (s), 1723 (s), 1649 (s), 1088 (s), 1021 (s), 1010 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 5.79 (t, J=1.2Hz, 1H), 5.39 (s, 1H), 4.04 (d, J=3.4Hz, 1H), 4.00 (d, J=3.4Hz, 1H), 2.18 (d, J=1.2Hz, 3H), 1.92 (d, J=1.3Hz, 3H), 1.19 (s, 3H), 1.09 (s, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 172.9, 164.8, 160.0, 114.5, 76.1, 74.1, 40.2, 27.5, 23.0, 20.5, 18.8. Anal Cal'd for $C_{11}H_{16}O_4$, C 62.25; H 7.60. Found C 62.25; H 7.46.

3.17.25 **[*R*]-Pantolactone 2,3-epoxy-3-methylbutanoate (46)**

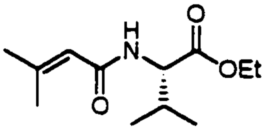


Compound **46** was prepared according to General Procedure A, by treating compound **48** with *m*-CPBA and 2,6-di-*tert*-butylphenol, in $CHCl_3$. The reaction mixture was refluxed for 48 hours to provide a 2.2:1 mixture of diastereomers. The resulting diastereomers were separated by fractional recrystallization with diethyl ether at -30 °C.

Major Diasteriomer: m.p. 95.0-96.0 °C. $[\alpha]_D$ +0.3° (0.06C, $CHCl_3$). ^1H NMR (500MHz, $CDCl_3$) δ 5.39 (s, 1H), 4.02 (d, J=9.0Hz, 1H), 3.99 (d, J=9.0Hz, 1H), 3.40 (s, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.18 (s, 3H), 1.11 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 171.6, 167.49, 76.1, 75.6, 61.0, 58.7, 40.1, 24.2, 22.8, 19.4, 18.0. Anal. Calcd for $C_{11}H_{16}O_5$ (228.25): C, 57.88; H, 7.07. Found C, 57.71; H, 6.96.

Minor Diastereomer: ^1H NMR (200MHz, $CDCl_3$) δ 5.39 (s, 1H), 4.02 (d, J=9.0Hz, 1H), 3.99 (d, J=9.0Hz, 1H), 3.43 (s, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 171.6, 167.55, 76.1, 75.6, 60.6, 58.8, 40.1, 24.2, 22.8, 19.8, 18.2.

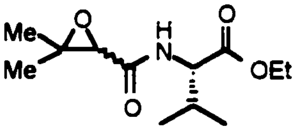
3.17.26 L-Valine 3,3-dimethylacrylamide (49)



To a CH_2Cl_2 (50 mL) solution of L-valine ethyl ester hydrochloride (5.0 g, 27.5 mmol), HOBt (3.72 g, 27.5 mmol), triethylamine (3.83 mL, 27.5 mmol), and DCC (5.65 g, 27.5 mmol), at 0 °C, was added a CH_2Cl_2 (10 mL) solution of 3,3-dimethylacrylic acid (3.49 g, 27.5 mmol). The solution was stirred over night. The resulting precipitate was filtered off, and the filtrate was washed with saturated $NaHCO_3$ (2 x 25 mL) and water (25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude acrylimide was further purified by silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, to provide compound **49** as a light yellow oil, in 78% yield.

^1H NMR (200MHz, $CDCl_3$) δ 6.97 (br d, J=8.4Hz, 1H), 5.91 (m, 1H), 4.01 (q, J=7.4Hz, 2H), 2.19 (sept, J=7.1Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.25 (t, J=7.4Hz, 3H), 0.90 (d, J=7.1Hz, 3H), 0.84 (d, J=7.1Hz, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 172.3, 166.5, 151.4, 118.1, 61.0, 56.5, 31.2, 27.0, 19.7, 18.8, 17.7, 14.1. HRMS Cal'd for $C_{12}H_{21}NO_3$ 227.1521. Found 227.1523.

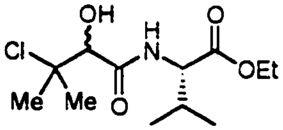
3.17.27 L-Valine 2,3-epoxy-3-methylbutanamide (52)



Compound was prepared according to General Procedure A, by treating methyl cinnamate with *m*-CPBA and 2,6-*tert*-butylphenol, in $CHCl_3$. The reaction mixture was refluxed for 48 hours. After the standard work up the crude glycidic ester was further purified by

Kruglrohr distillation (50 to 60 °C, 0.1 torr), to provide compound as a yellow oil in 90% yield.

3.17.28 L-Valine 2-hydroxy-3-chloro-3-methylbutanimide (54)

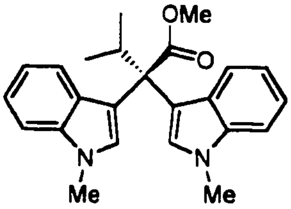


Compound **54** was prepared according to General Procedure C. Compound **52** and *N*-methylindole were dissolved in CH_2Cl_2 and cooled to −78 °C. A 1M CH_2Cl_2 solution of $SnCl_4$ was added dropwise. After the standard aqueous workup and silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, the two diastereomers of **54** were isolated in 43 and 39%, respectively.

Isomer A (least polar) : IR ($CHCl_3$) 3378 (s), 2972 (s), 2937 (s), 2877 (m), 1736 (s), 1668 (s), 1524 (s), 1463 (m) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 6.97 (br d, J=8.4Hz, 1H), 4.49 (dd, J=4.7, 8.8Hz, 1H), 4.16 (dq, J=1.1, 7.1Hz, 2H), 4.11 (d, J=4.5Hz, 1H), 3.82 (d, J=4.7Hz, 1H), 2.19 (dsept, J=4.7, 7.1Hz, 1H), 1.61 (s, 3H), 1.58 (s, 3H), 1.23 (t, J=7.1Hz, 3H), 0.93 (d, J=7.1Hz, 3H), 0.89 (d, J=7.1Hz, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 171.2, 169.5, 78.0, 72.4, 61.3, 57.4, 31.0, 28.4, 27.7, 19.0, 17.6, 14.1. HRMS (m/z) Cal'd for $C_{12}H_{22}O_4NCl$. Found 279.1160.

Isomer B (most polar) : IR ($CHCl_3$) : 3378 (s), 2973 (s), 2877 (m), 1735 (s), 1669 (s), 1524 (s), 914 (m), 869 (w), 735 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 7.29 (br d, J=8.4Hz, 1H), 4.44 (dd, J=4.6, 8.6Hz, 1H), 4.16 (dq, J=1.1, 7.3Hz, 2H), 4.10 (s, 1H), 4.03 (br s, 1H), 2.17 (sept, J=4.8, 6.8Hz, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.23 (t, J=7.1Hz, 3H), 0.91 (d, J=6.8Hz, 3H), 0.88 (d, J=6.8Hz, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 171.4, 169.9, 78.1, 73.2, 61.2, 57.3, 31.0, 28.5, 28.4, 19.0, 17.6, 14.1. MS (m/z) M^+=279, M^{+2}=281.

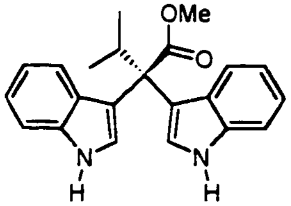
3.17.29 Methyl 2,2-*bis*(*N*-methylindolyl)-3-methylbutanoate (55a)



Glycidic ester **27a** (130 mg, 1.0 mmol) and N-methylindole (**33a**, 260 mg, 2.0 mmol) were dissolved in CH_2Cl_2 (5 mL). Solid ZnI_2, $ZnBr_2$, or $ZnCl_2$ (1 equiv.) was added in a single portion. The reaction containing ZnI_2 was stirred at room temperature for 16 hrs, while the reactions containing $ZnBr_2$ or $ZnCl_2$ were refluxed until no starting material was observed by TLC; 3 and 6 hrs respectively. The reaction mixture was diluted with diethyl ether (10 mL), and washed this saturated $NaHCO_3$ (10 mL) and water (2 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Products were purified by silica gel chromatography, eluting with 3:1 hexanes/diethyl ether, provided an off white solid in 85 to 93% yield.

m.p. 198.0-199.0 °C. IR (KBr, cm^{-1}) 3060 (w), 2964 (m), 2940 (m), 2872 (m), 1725 (s), 1618 (w), 1531 (m), 1465 (s), 1231 (s), 1214 (s), 745 (s). ^1H NMR (200MHz, $CDCl_3$) δ 7.26 (d, J=8.7Hz, 2H), 7.17 (d, J=8.9Hz, 2H), 7.11 (dt, J=1.1, 7.1Hz, 2H), 7.08 (s, 2H), 6.86 (dt, J=1.0, 7.0Hz, 2H), 3.77 (s, 6H), 3.58 (s, 3H), 3.32 (sept, J=6.6Hz, 1H), 0.97 (d, J=6.6Hz, 6H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 175.1, 136.9, 129.6, 127.8, 122.4, 120.8, 118.4, 113.6, 108.8, 55.6, 51.8, 33.5, 32.9, 19.4. HRMS Cal'd for $C_{24}H_{26}N_2O_2$ 374.1994. Found 374.1995.

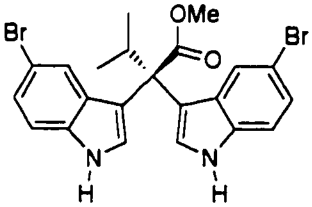
3.17.30 Methyl 2,2-*bis*(indolyl)-3-methylbutanoate (55b)



Compound **55b** was prepared in a similar manner as that described for compound **55a**. A mixture of **27b** (130 mg, 1.0 mmol), indole (**33b**, 220 mg, 2.0 mmol), and ZnI_2 (310 mg, 1.0 mmol), in CH_2Cl_2, was stirred at room for 16 hrs. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **55b** as an off white solid in 84% yield.

^{1}H NMR (200MHz, $CDCl_3$) δ 7.92 (br s, 2H), 7.30 (d, J=8.5Hz, 2H), 7.21 (d, J=8.5Hz, 2H), 7.11 (dt, J=1.1, 7.5Hz, 2H), 7.08 (s, 2H), 6.96 (dt, J=1.2, 7.4Hz, 2H), 6.94 (d, J=2.3Hz, 2H), 3.58 (s, 3H), 3.40 (sept, J=6.5Hz, 1H), 0.98 (d, J=6.5Hz, 6H).

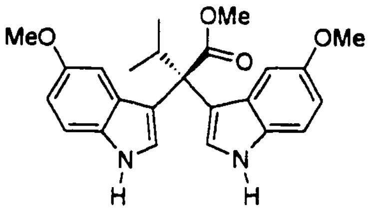
3.17.31 Methyl 2,2-*bis*(5-bromoindolyl-3-methylbutanoate (55c)



Compound **55c** was prepared in a similar manner as that described for compound **55a.** A mixture of **27a** (130 mg, 1.0 mmol), 5-bromoindole (**33c**, 392 mg, 2.0 mmol), and ZnI_2 (310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 hrs. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **55c** as an off white solid in 84% yield.

m.p. 131.0-132.0 °C, IR (KBr, cm^{-1}) 3435 (s), 3354 (sh), 2964 (m), 2872 (w), 1711 (s), 1560 (m), 1459 (s), 1222 (s), 1108 (s), 884 (s), 792 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (br s, 2H), 7.22 (s, 2H), 7.14 (d, J=4.0Hz, 4H), 3.62 (s, 3H), 3.22 (p, J=6.6Hz, 1H), 0.93 (d, J=6.6Hz, 6H). ^{13}C NMR (50MHz, CDCl$_3$) δ 175.1, 154.0, 135.5, 129.3, 126.5, 125.1, 124.7, 115.5, 113.1, 52.7, 34.2, 20.0. HRMS Cal'd for $C_{22}H_{20}N_2O_2Br_2$ 501.9892. Found 501.9874.

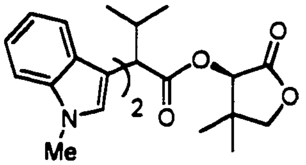
3.17.32 Methyl 2,2-*bis*(5-methoxyindolyl)-3-methylbutanoate (55d)



Compound **55d** was prepared in a similar manner as that described for compound **55b**. A mixture of **27a** (130 mg, 1.0 mmol), 5-methoxyindole (**33d**, 296 mg, 2.0 mmol), and ZnI_2 (310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 hrs. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **55c** as an off white solid in 61% yield.

m.p. 95.0-96.0 °C, IR (KBr, cm^{-1}) 3404 (br s), 2946 (m), 1719 (s), 1625 (m), 1578 (m), 1484 (s), 1212 (s), 1173 (s), 1032 (m), 925 (m), 798 (m). ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.18 (br s, 2H), 7.28 (s, 2H), 7.15 (d, J=4.0Hz, 4H), 6.71 (dd, J=1.0, 4.0Hz, 2H), 6.56 (d, J=1.0Hz, 2H), 3.70 (s, 3H), 3.52 (s, 6H), 3.27 (p, J=6.6Hz, 1H), 0.96 (d, J=6.6Hz, 6H). ^{13}C NMR (50MHz, CDCl$_3$) δ 175.5, 155.2, 131.8, 127.7, 125.8, 114.9, 111.7, 104.2, 55.7, 52.1, 33.9, 19.8. HRMS Cal'd for $C_{24}H_{26}N_2O_2$ 406.1893. Found 406.1888.

3.17.33 [*R*]-Pantolactone 2,2-*bis*(*N*-methylindolyl)-3-methylbutanoate (55e)

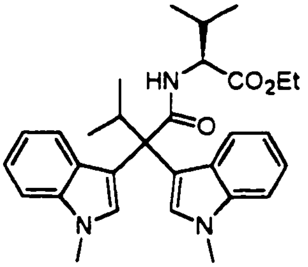


Compound **55e** was prepared in a similar manner as that described for compound **55b**. A mixture of **46** (130 mg, 1.0 mmol), *N*-methylindole (**33a**, 260 mg, 2.0 mmol), and ZnI_2

(310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL), was stirred at room temperature for 16 hours. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **55e** as a white solid in 84% yield.

m.p. >250 °C, IR (KBr, cm^{-1}) 3050 (m), 2969 (m), 2941 (m), 2952 (m), 2878 (m), 1789 (s), 1738 (s), 1620 (w), 1534 (m), 1465 (m), 1192 (s), 1135 (s), 1108 (s), 995 (s), 811 (m), 779 (m), 742 (s). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24 (m, 2H), 7.23 (s, 2H), 7.10 (d, J=7.9Hz, 2H), 7.08 (t, J=7.9Hz, 2H), 6.80 (t, J=7.9Hz, 2H), 5.30 (s, 1H), 3.82 (s, 3H), 3.80 (s, 2H), 3.76 (s, 3H), 3.39 (p, J=6.6Hz, 1H), 1.14 (d, J=6.6Hz, 3H), 0.97 (d, J=6.6Hz, 3H), 0.51 (s, 3H), 0.37 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 173.2, 172.6, 136.9, 136.7, 130.4, 128.8, 127.9, 127.5, 122.5, 122.1, 121.1, 120.8, 120.6, 118.6, 118.4, 114.2, 111.5, 108.7, 76.1, 74.7, 56.2, 40.1, 33.5, 32.9, 22.0, 19.4, 19.2, 18.7. HRMS Cal'd for $C_{29}H_{31}N_2O_4$ 472.2362. Found 472.2353.

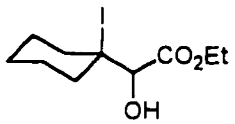
3.17.34 L-Valine 2,2-*bis*(*N*-methylindolyl)-3-methylbutanamide (59)



Compound **59** was prepared in a similar manner as that described for compound **55b**. A mixture of **52** (243 mg, 1.0 mmol), *N*-methylindole (**33a**, 260 mg, 2.0 mmol), and ZnI_2 (310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL), was stirred at room temperature for 16 hours. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **55e** as a brown oil in 86% yield.

IR (neat, cm^{-1}) 3420 (m), 3050 (m), 2957 (s), 2935 (s), 2877 (m), 1732 (s), 1661 (s), 1372 (s), 1019 (m), 910 (m), 739 (s). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.30 (s, 1H), 7.24-7.14 (m, 3H), 7.08-6.98 (m, 3H), 6.78 (dd, J=0.9, 7.5Hz, 1H), 6.69 (dd, J=0.9, 7.5Hz, 1H), 5.61 (d, J=5.3Hz, 1H), 4.37 (dd, J=5.0, 8.2Hz, 1H), 4.05 (q, J=7.1Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.23 (sept, J=6.8Hz, 1H), 1.87 (sept, J=6.9Hz, 1H), 1.16 (t, J=7.1Hz, 3H), 1.03 (d, J=6.8Hz, 3H), 0.98 (d, J=6.8Hz, 3H), 0.56 (d, J=6.9Hz, 3H), 0.46 (d, J=6.9Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.0, 171.8, 137.1, 129.2, 129.1, 127.6, 127.4, 122.3, 121.8, 121.1, 120.8, 118.5, 118.3, 114.8, 114.3, 108.8, 60.8, 57.5, 55.7, 34.5, 32.9, 32.8, 30.8, 19.8, 18.6, 17.4, 14.1.

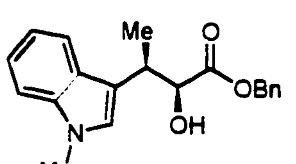
3.17.35 Ethyl 2-Hydroxy-2-(1-iodocyclohexyl)acetate (60)



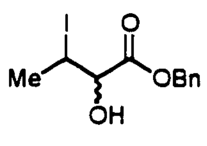
Compound **60** was prepared in a similar manner as that described for compound **55b**. A mixture of **27b** (184 mg, 1.0 mmol), *N*-methylindole (**33a**, 260 mg, 2.0 mmol), and ZnI_2 (310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL), was stirred at room temperature for 16 hours. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided unreacted **33a** in 92%, and **55e** as a yellow oil in 86% yield.

IR (3447 (m), 2981 (m), 2933 (s), 2859 (m), 1735 (s), 1450 (w), 1368 (w), 1255 (m), 1205 (m), 1157 (m), 1093 (m), 1056 (m), 1024 (m). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.78 (br s, 1H), 4.43 (br s, 1H), 4.20 (q, J=7.5Hz, 2H), 3.08 (m, 1H), 2.03 (m, 2H), 1.65-1.43 (m, 8H), 1.25 (t, J=7.5Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.2, 134.9, 127.3, 75.3, 61.8, 25.0, 23.6, 22.3, 22.0, 14.1. MS (FAB, m/z) $M^+ - H = 311$.

3.17.36 Benzyl *syn*-1-hydroxy-2-(*N*-methylindolyl)butanoate (61)



61



62

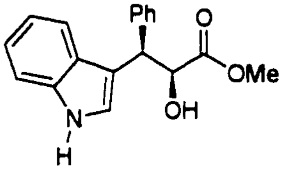
Compounds **61** and **62** were prepared in a similar manner as that described for compound **55a**. A mixture of **27d** (192 mg, 1.0 mmol), indole (**33a**, 260 mg, 2.0 mmol), and ZnI_2

(310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 hrs. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **61** as a yellow oil in 6% yield, **62** as a clear oil in 82% yield, and 75% recovered **33a**.

61 : IR (neat) : 3478 (br m), 3054 (m), 3033 (m), 2956 (m), 2934 (m), 1732 (s), 1615 (m), 1578 (w), 1549 (w), 1473 (s), 1435 (s), 1251 (s), 1204 (s), 1127 (s), 743 (s), 698 (s). ^{1}H NMR (200MHz, $CDCl_3$) δ 7.73 (d, J=8.8Hz, 1H), 7.42 (m, 2H), 7.37 (m, 4H), 7.24 (dt, J=1.0, 7.7Hz, 1H), 7.20 (dt, J=1.4, 7.7Hz, 1H), 6.99 (s, 1H), 5.23 (s, 2H), 4.51 (br t, 1H), 3.73 (s, 3H), 3.72 (m, 1H), 2.99 (br d, J=5.3Hz, 1H), 1.40 (d, J=7.1Hz, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 174.1, 136.7, 135.1, 128.4, 128.3, 126.9, 126.5, 121.5, 118.8, 115.5, 109.2, 74.3, 67.2, 34.7, 32.5, 15.6. HRMS Cal'd for $C_{20}H_{21}NO_3$ 323.1521. Found 323.1516.

62 : IR (neat) : 3468 (br s), 3064 (m), 3033 (m), 2967(m), 2915 (m), 2915 (m), 1736 (s), 1452 (s), 1259 (s), 1207 (s), 1132 (s), 1033 (s), 746 (s), 698 (s) cm^{-1}. ^{1}H NMR (200MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.26 (d, J=12.1Hz, 1H), 5.18 (d, J=12.1Hz, 1H), 4.41 (ddt, J=3.4, 7.3, 7.2Hz, 1H), 4.23 (dd, J=3.3, 5.7Hz, 1H), 3.46 (d, J=6.0Hz, 1H), 1.77 (d, J=7.2Hz, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 170.6, 134.4, 128.5, 75.8, 67.9, 26.9, 22.7. HRMS Cal'd for $C_{11}H_{13}OI$ 319.9909. Found 319.9900.

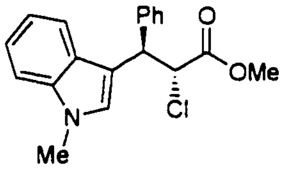
3.13.37 *syn*-Methyl 2-hydroxy-3-indolyl-3-phenylpropanoate (65)



Compound **65** was prepared in a similar manner as that described for compound **55a**. A mixture of **27c** (178 mg, 1.0 mmol), indole (**33b**, 220 mg, 2.0 mmol), and ZnI_2 (310 mg, 1.0 mmol), in CH_2Cl_2 (10 mL) was stirred at room temperature for 16 hrs. Purification by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, provided **55b** as an off white solid in 84% yield.

m.p. 132.0-133.0 °C. IR (KBr) 3503 (m), 3425 (s), 3045 (w), 2945 (w), 2878 (w), 1736 (s), 1454 (s), 1260 (s), 1100 (s), 744 (s), 705 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.47 (d, J=2.3Hz, 1H), 7.35-7.20 (m, 7H), 7.15 (t, J=8.0Hz, 1H), 7.00 (t, J=8.0Hz, 1H), 4.97 (dd, J=3.0, 6.7Hz, 1H), 4.78 (d, J=3.0Hz, 1H), 3.75 (s, 3H), 2.84 (d, J=3.0Hz, 1H). ^{13}C NMR (50MHz, $CDCl_3$) δ 174.0, 138.5, 136.0, 129.0, 128.3, 127.2, 126.8, 122.9, 119.4, 118.9, 155.9, 111.1, 73.9, 52.5, 46.3.

3.17.38 *rac*-Methyl *anti*-2-chloro-3-(N-methylindolyl)-3-phenylpropanoate (69)

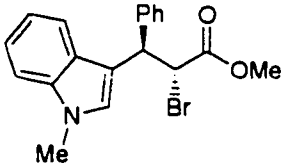


Compound **30f** (5.0 g, 16.2 mmol), triethylamine (11.2 mL, 80.9 mmol), DMAP (100 mg), and TsCl (10.2 g, 80.9 mmol) were dissolved in methylene chloride (100 mL). The solution was refluxed for 48 hours, or until no staring material was visible by TLC. After cooling to room temperature saturated aqueous NaH_2CO_3 was added, and mixture was stirred for 1 hour. Diethyl ether was added and the organic layer was washed with NaH_2CO_3 (2 x 50 mL) and water (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was purified by silica gel chromatography, eluting with 5:1 hexane/ethyl acetate, to provide **69** as a an off white solid in 65% yield

m.p. 187.5-189.0 °C. IR (KBr) 3045 (w), 2953 (w), 1730 (s), 1538 (w), 1465 (m), 1431 (s), 1331 (s), 1287 (s), 1163 (s), 743 (s), 718 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 7.50 (td, J=1.0, 8.1Hz, 1H), 7.19 (m, 2H), 7.14-7.06 (m, 5H), 7.00 (ddd, J=1.6, 6.5, 8.1Hz, 1H), 6.87 (s, 1H), 5.55 (d, J=11.2Hz, 1H), 4.52 (d, J=11.2Hz, 1H), 3.75 (s, 3H), 3.60 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (57.3MHz, $CDCl_3$) δ 172.6, 138.8, 136.5, 128.2, 127.9, 127.6, 126.5, 121.7, 119.4, 119.3, 119.1, 109.2, 106.2, 63.0, 52.5, 52.3, 32.7. Anal

Calc'd for $C_{19}H_{18}NO_2Cl$ (327.79): C, 69.62; H, 5.53; N, 4.27. Found C, 69.15; H, 5.55; N, 4.22.

3.17.39 *rac*-Methyl *anti*-2-Bromo-3-(N-methylindolyl)-3-phenylpropanoate (70)



Triphenylphosphine (1.43 g, 5.46 mmol) was dissolved in a dry methylene chloride (25 mL). The solution was placed under nitrogen and cooled in an ice bath. Bromine was added drop wise until a faint red colour persisted. Several crystals of triphenylphosphine were added until the colour faded. Compound **30f** (870 mg, 5.46 mmol) was dissolved in methylene chloride (10 mL) and added to the first solution, via cannula over several minutes. The solution was warmed to room temperature and stirred for an additional 2 hours. The solvent was removed under reduced pressure, and compound **70** was isolated by chromatography on a silica gel column, eluting with 5:1 hexane/ethyl acetate, to provide **70** as a white solid in 75% yield.

m.p. 176.0-177.0 °C. IR (KBr) : 3053 (w), 3035 (w), 2953 (m), 1729 (s), 1536 (m), 1430 (m), 1335 (m), 1160 (m), 759 (s), 749 (s), 699 (s). ^1H NMR (200MHz, $CDCl_3$) δ 7.62 (d, J=7.6Hz, 1H), 7.30-7.25 (m, 3H), 7.24-7.03 (m, 5H), 6.90 (s, 1H), 5.69 (d, J=11.5Hz, 1H), 4.77 (d, J=11.5Hz, 1H), 3.76 (s, 3H), 3.56 (s, 1H). ^{13}C NMR (50MHz, $CDCl_3$) δ 172.7, 139.2, 136.4, 128.2, 128.1, 128.0, 127.8, 127.7, 126.4, 126.3, 121.7, 119.4, 119.1, 109.2, 108.8, 53.8, 52.4, 52.2, 32.7. HRMS Cal'd for $C_{19}H_{18}NO_2Br$ 371.0521. Found 371.0559.

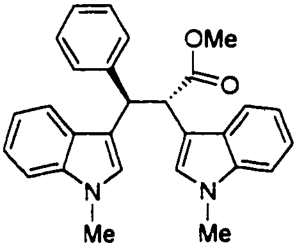
3.17.40 General Procedure D1 : Preparation of α,β-*Bis*(indolyl) Esters

A 1M THF solution of *anti*-**69** (1 equiv.) and indole **33** (1 equiv.) was cooled to 0 °C. To this was added a 5M THF solution of $AgBPh_4$ (1 equiv.). This mixture was allowed to warm to room temperature and stirred for 1 to 2 hours. The resulting slurry was filtered through celite and the filtrate was concentrated under reduced pressure. Purification by silica gel chromatography provided the desired the α,β-*bis*(indolyl) esters.

3.17.41 General Procedure D2 : Preparation of α,β-*Bis*(indolyl) Esters

A 1M $CHCl_3$ solution of *anti*-**69** (1 equiv.) and indole **33** (1 equiv.) was refluxed overnight. The solvent was removed *in vacuo* and the residue purififed by silica gel chromatography.

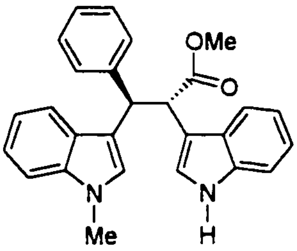
3.17.42 Methyl 2-(*N*-methylindolyl)-3-(*N*-methylindolyl)-3-phenylpropanoate (71)



Compound **71** was prepared in 85% yield by General Method D1, and in 87% yield by General Method D2.

m.p. 206.0-208.0 °C. IR (KBr) : 3060 (m), 3021 (m), 2947 (m), 1735 (s), 1601 (m), 1541 (m), 767 (s), 736 (s), 699 (s) cm^{-1}. ^1H NMR (200MHz, $CDCl_3$) δ 7.76 (d, J=7.7Hz, 1H), 7.62 (d, J=7.7Hz, 1H), 7.25-7.19 (m, 5H), 7.16-9.95 (m, 8H), 5.20 (d, J=12.0Hz, 1H), 4.74 (d, J=12.0Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H), 3.50 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 174.1, 142.8, 137.0, 136.6, 128.1, 128.0, 127.8, 127.3, 125.7, 125.4, 121.6, 121.3, 119.6, 119.5, 119.0, 118.7, 117.3, 110.6, 109.0, 108.9, 51.8, 49.2, 45.3, 32.7, 32.6. HRMS Cal'd for $C_{28}H_{26}N_2O_2$ 422.1994. Found 422.1995.

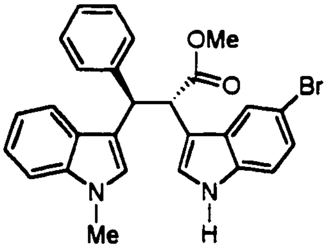
3.17.43 Methyl 2-(indolyl)-3-(*N*-methylindolyl)-3-phenylpropanoate (72)



Compound **72** was prepared in 79% yield by General Method D1, and in 83% yield by General Method D2.

^{1}H NMR (200MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.73 (dd, J=1.3, 7.8Hz, 1H), 7.68 (d, J=7.5Hz, 1H), 7.30-7.15 (m, 4H), 7.15-6.98 (m, 2H), 6.95 (s, 1H), 5.18 (d, J=11.9Hz, 1H), 4.72 (d, J=11.9Hz, 1H), 3.61 (s, 3H), 3.48 (s, 3H).

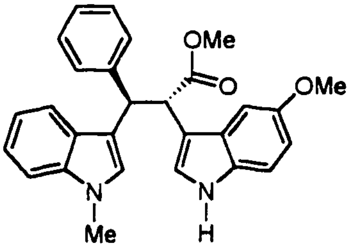
3.17.44 Methyl 2-(5-bromoindolyl)-3-(*N*-methylindolyl)-3-phenylpropanoate (73)



Compound **73** was prepared in 70% yield by General Method D1, and in 81% yield by General Method D2.

m.p. 238.0-239.0 °C. IR (KBr) : 3362 (br s), 3028 (w), 2953 (w), 1712 (s), 1607 (s), 1465 (s), 1434 (s), 1231 (s), 1200 (s), 1013 (s), 992 (s), 889 (s), 882 (s), 856 (s), 799 (s), 789 (s). ^{1}H NMR (200MHz, DMSO-d^6) δ 11.18 (br s, 1H), 7.87 (s, 1H), 7.80 (d, J=7.1Hz, 1H), 7.69 (s, 1H), 7.43-7.32 (m, 3H), 7.28-7.11 (m, 3H), 7.08-6.94 (m, 4H), 6.85 (m, 1H), 5.13 (d, J=12.4Hz, 1H), 4.95 (d, J=12.4Hz, 1H), 3.63 (s, 3H), 3.42 (s, 3H).). ^{13}C NMR (50MHz, DMSO-d^6) δ 173.6, 143.3, 136.2, 134.6, 128.6, 128.5, 128.2, 127.8, 127.0, 125.6, 123.6, 123.0, 121.0, 120.9, 119.3, 118.7, 118.1, 113.4, 111.1, 110.1, 109.6, 51.5, 47.6, 43.9, 32.4. HRMS Cal'd for $C_{27}H_{23}N_2O_2Br$ 486.0943. Found 486.0950.

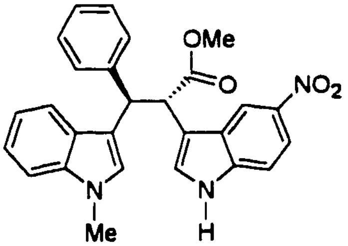
3.17.45 Methyl 2-(5-methoxyindolyl)-3-(*N*-methylindolyl)-3-phenylpropanoate (74)



Compound 74 was prepared in 34% yield by General Method D1 and in 75% yield by General Method D2.

m.p. 105.0-109.0 °C. IR (KBr) 4316 (m), 2953 (m), 1735 (s), 1619 (w), 1581 (w), 1486 (s), 1210 (s), 1162 (m), 1024 (m), 831 (m), 793(m), 742 (s), 700 (s) cm^{-1}. ^{1}H NMR (200MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.67 (d, J=7.7Hz, 1H), 7.32 (d, J=2.5Hz, 1H), 7.24 (s, 1H), 7.23-7.10 (m, 5H), 7.08-6.95 (m, 4H), 6.84 (d, J=6.3Hz, 1H), 5.05 (d, J=11.8Hz, 1H), 4.64 (d, J=11.8Hz, 1H), 3.75 (s, 3H), 3.63 (s, 3H), 3.48 (s, 3H). ^{13}C NMR (50MHz, $CDCl_3$) δ 174.3, 153.6, 142.4, 136.6, 131.4, 128.1, 128.0, 127.8, 127.3, 125.8, 121.5, 121.3, 119.5, 119.0, 118.3, 111.9, 111.6, 110.4, 109.1, 101.3, 55.7, 51.9, 49.1, 45.3, 32.5. HRMS Cal'd for $C_{28}H_{26}N_2O_3$ 438.1943. Found 438.1950.

3.17.46 Methyl 2-(5-nitroindolyl)-3-(*N*-methylindolyl)-3-phenylpropanoate (75)



Compound 75 was prepared in 77% yield by General Method D2.

IR (KBr) 3422 (br m), 3121 (w), 3060 (w), 2953 (w), 1729 (s), 1621 (m), 1578 (w), 1540 (w), 1511 (s), 1427 (s), 1322 (s), 1167 (s), 806 (m) 737 (s), 698 (s) cm^{-1}. ^{1}H NMR (200MHz, DMSO-d^6) δ 11.75 (br s, 1H), 8.71 (s, 1H), 7.97 (d, J=9.0Hz, 1H), 7.91 (s, 1H), 7.79 (d, J=7.3Hz, 1H), 7.51-7.44 (m, 3H), 7.25 (d, J=7.8Hz, 1H), 7.10-6.95 (m, 4H), 6.85 (d, J=7.3Hz, 1H), 5.27 (d, J=12.4Hz, 1H), 5.00 (d, J=12.4Hz, 1H), 3.63 (s, 3H), 3.40 (s, 3H). ^{13}C NMR (50MHz, DMSO-d^6) δ 173.6, 143.1, 140.4, 139.0, 136.2, 128.7, 128.2, 127.9, 127.1, 126.0, 125.8, 125.5, 121.2, 121.1, 119.2, 118.8, 116.7, 115.9, 112.0, 109.9, 109.8, 109.6, 51.5, 47.6, 43.6, 32.4. MS (m/z) M^+ = 435.1.

Chapter Four

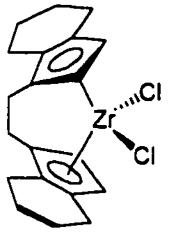
The Regioselective Synthesis of Benz(o)indene and Tetrahydrobenz(o)indene

4.0 Introduction

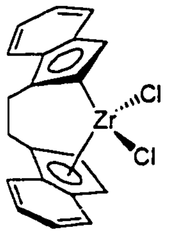
The first homogeneous catalyst systems developed for the polymerization of ethylene were discovered in the late 1950's and are generally referred to as Ziegler-Natta catalysts. These metallocene based systems, $Cp_2TiCl_2/AlMe_3$,[1] discovered by Ziegler and developed by Natta, and $Cp_2TiCl_2/EtAlCl_2$,[2] developed by Breslow and coworkers, initially caused much interest in the area of homogeneous polymerization catalysts.[3-8] Unfortunately, these systems did not find industrial application as they tended to produce low molecular weight polymers as a result of poor catalyst activity, short kinetic life-times, and a lack of stereospecificity.

Several workers discovered that the addition of water to their systems resulted in enhanced catalytic activity.[9-12] Kaminsky *et al.*[13] demonstrated that the addition of small amounts of water to trialkylaluminums resulted in the formation of oligomeric aluminoxanes. Once combined with titanocenes these aluminoxanes, generally referred to as co-catalysts, yielded highly active catalytic systems for the polymerization of ethylene. However, these systems provided *atactic* polymers once applied to the polymerization of propylene.[14]

This question of stereoregularity in propylene polymerization was not adequately addressed until stereo-ridged, racemic *ansa*-metallocene complexes (*ansa* meaning bridged) were utilized as catalysts for the polymerization of propylene. The first of these stereospecific systems was reported by Britzinger *et al.*[15-17] The combination of *rac*-ethylenebis(tetrahydroindenyl)$ZrCl_2$ (**1**) and methylaluminoxane was shown to be an efficient catalyst system for the production of highly isotactic polypropylene.[15]



1



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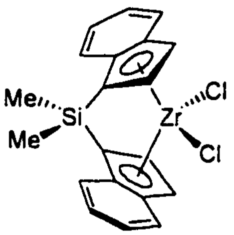

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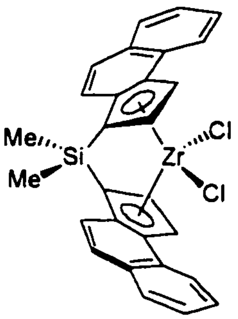
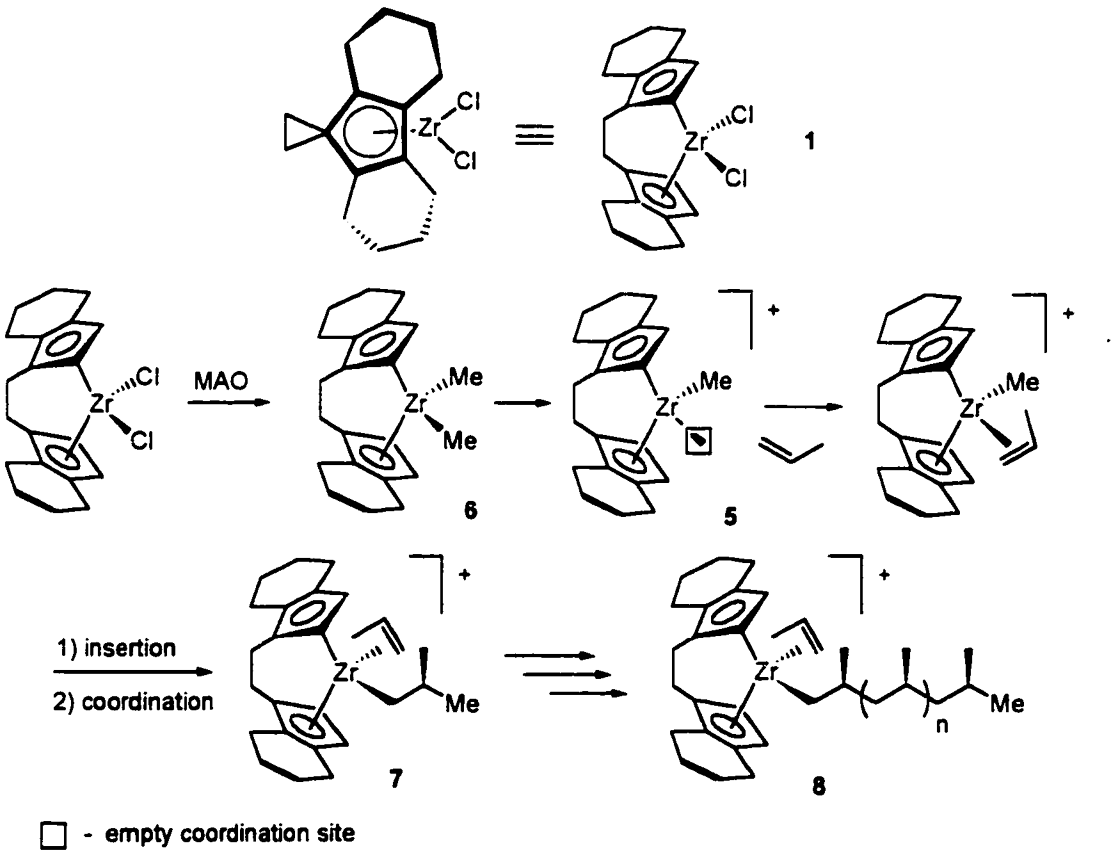


4

In recent years numerous effective catalyst systems have been developed based on the *ansa*-metallocene catalyst/MAO co-catalyst system. Complexes **1** through **4** represent several of the more successful metallocene catalysts.

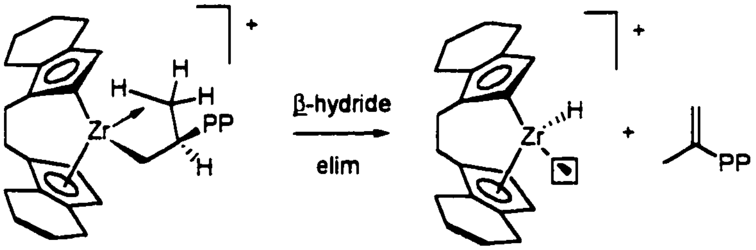
The mechanism of polymerization is reasonably well understood, and is depicted in Scheme 4.1 for complex **1**.



Scheme 4.1: Mechanism for the stereospecific polymerization of propylene by complex **1**

The active species of the metallocene/aluminoxane catalyst system is believed to be the electronically and coordinately unsaturated 14-electon cation racemic $[Et(Thindyl)_2MR]^+$ (**5**, M=Zr; R=Me - also implicated for M = Ti, Zr, Hf; R = H, alkyl), where the aluminoxane acts as a non-coordinating anion (*rac*-ethylenebis(tetrahydroindenyl)$ZrCl_2$ = *rac*-Et(Thindyl)$ZrCl_2$).[18-23] Treatment of *rac*-Et$(Thindyl)_2ZrCl_2$ with MAO results in the formation of *rac*-Et$(Thindyl)_2ZrMe_2$, **6**, which is subsequently converted to the unsaturated cation **5**. Coordination of one propylene unit is followed by insertion to provide cation **7**. Due to the steric environment around the metal, stereospecific insertion occurs, resulting in isotacticity in the growing polymer chain,[24] as shown in cation **8**. In most cases the overall tacticity of the resulting polymer is not the direct result of the chirality of the catalyst, but a result of the chiral environment which develops around the metal centre during the course of polymerization. When one considers the mechanism by which these catalysts operate, it is not surprising that non-bridged and meso *ansa*-metallocenes display little or no stereocontrol in the polymerization of propylene.

The over all molecular weight of the resulting polypropylene is governed by the relative rates of chain propagation and chain termination. Chain termination results from β-hydride elimination. Agostic interactions between the metal and the last polymer unit, shown below, can result in the formation of a metal hydride, freeing the polymer chain from the catalyst.



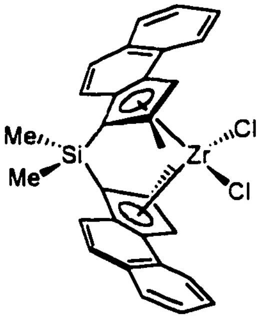
As a result of this β-elimination process metallocene catalyzed polypropylene may display unsaturation at their terminus, however, reactions are generally run in the presence of H_2 resulting in fully saturated polymers. Chain termination does not result in inactivation of the catalyst. The resulting metallocene hydrides are effective polymerization catalyst by themselves, which reinitiate polymerization. Unfortunately, this process of chain termination and polymerization reinitiation results in broadening of the molecular weight distribution.

Several groups have shown that increasing the steric bulk around the metal centre decreases the rate of chain termination, thereby dramatically increasing the molecular weight of the polymer. A comparison of the weight average molecular mass and melting temperatures of polypropylene prepared by various zirconocene catalysts is shown in Table 4.1. Silicon bridged metallocenes appear to out perform the corresponding ethylene bridged metallocenes, generally doubling the molecular weight of the resulting polypropylene. This is believed to be a result of increased rigidity and more favourable electronic characteristics of the silyl bridged metallocenes.

Table 4.1 : Comparison of *ansa*-metallocenes in propylene polymerization at 25 ^{o}C

Catalyst	M_w(x 10^{-3} g/mol)	T_m (^{o}C)
$Et(Ind)_2ZrCl_2$	42	138
$Me_2Si(Ind)_2ZrCl_2$	78	147
$Me_2Si(2\text{-}MeInd)_2ZrCl_2$	272	149
$Me_2Si(2\text{-}Me\text{-}4,5\text{-}benzoind)_2ZrCl_2$	413	153

Introduction of a methyl group at the indenyl 2- position and/or a fused benzo ring in the 4,5-indenyl positions results in dramatic increases in the weight average molecular mass. These observations have been explaining in terms of the increased steric hindrance and lower Lewis acidity of the catalyst, as a result of the electron donating substituents on the indenyl rings. These factors tend to disfavour β-hydride elimination and therefore the rate of chain termination.[25] Alternately, this effect may simply be a matter of the resulting polymer chain adopting conformations around these substituents, which make β-hydride elimination more difficult.[26]



9

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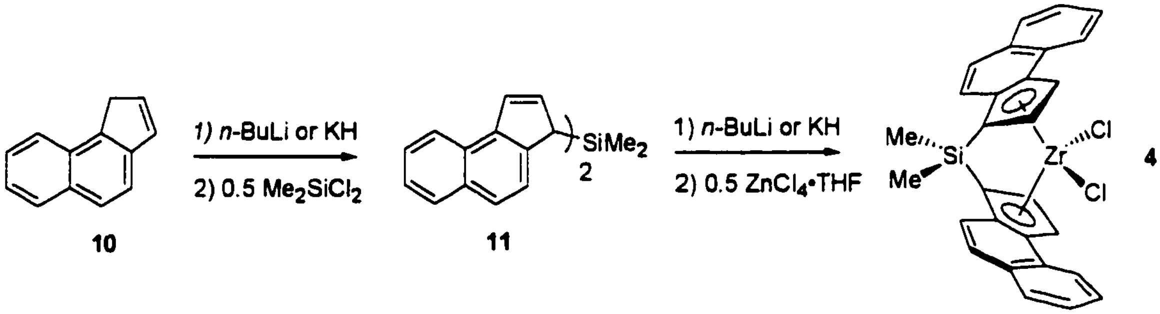
Recently several of the metallocene systems have been applied to the industrial production of isotactic polypropylene homopolymers as well as several polypropylene copolymers. One of these catalysts, complex **9**, is currently being used by BASF in Germany. This complex, once supported on silica, has been applied to TARGOR's Novolen gas phase polymerization process.[26] The details of this process and the physical properties of the resulting polymers have recently been reviewed.[28]

4.1 Synthesis of Benz(o)indene Based Metallocenes

The racemic *ansa*-bis(benz(o)indenyl) metallocenes have had a dramatic effect on the field of metallocene catalyzed Ziegler-Natta olefin polymerization. While completing my undergraduate thesis in the laboratory of Dr. Scott Collins, we began a programme to prepare these compounds, only to find that other workers in the field were thinking along the same lines. The synthesis of these metallocenes, and their effect on the catalysis of propylene, were reported in back to back papers by Spaleck[28] and Brintzinger.[29]

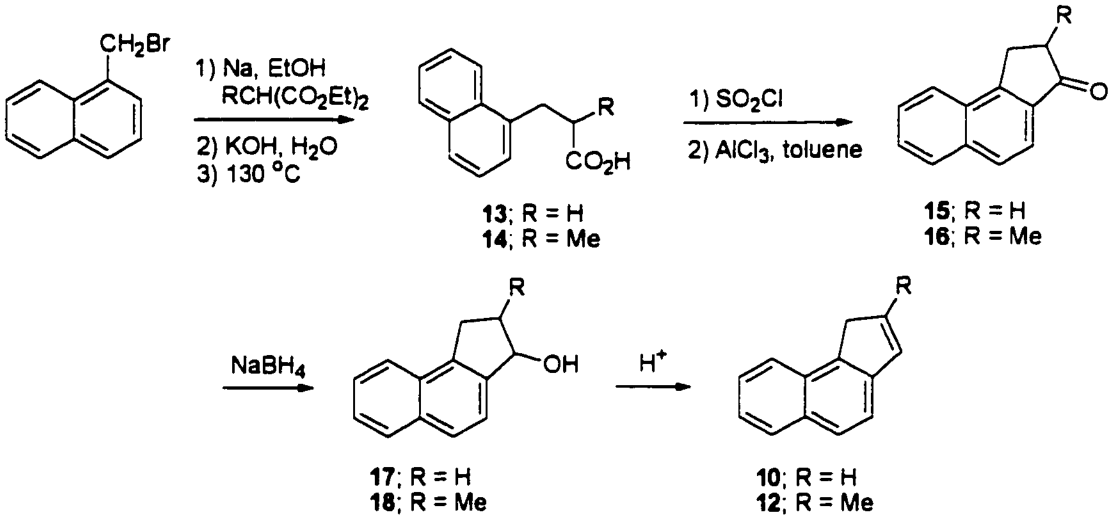
The actual metallocenes were prepared according to standard preparations.[30] For example, deprotonation of the 4,5-benz(o)indene, **10**, with *n*-BuLi or KH, in THF, provides the desired indenyl anion. Treatment of the indenyl anion with 0.5 equivalent of Me_2SiCl_2, yielded the silyl bridged bisindene **11**. Deprotonation of **11** with either *n*-BuLi or KH, was followed by addition of $ZrCl_4$•THF, in THF, under maximum dilution conditions, to provide metallocene **4**. Unfortunately, the yields of *rac*-metallocenes rarely exceed 50%.



Both Spaleck and Brintzinger used the above route for the preparation of their metallocenes. However, alternate routes were used in the preparation of indene **10**.

Although it is not implicitly stated, one might assume, based on the synthesis of several other substituted indenes featured in his paper, that Spaleck's[28] syntheses of 4,5-benz(o)indene, **10**, and 2-methyl-4,5-benz(o)indene, **12**, started with the treatment of commercially available 2-(bromomethyl)naphthalene with sodium malonate (R=H and Me, respectively). The resulting diesters were saponificated and decarboxylated to yield the corresponding carboxylic acids **13** and **14**. Conversion of the acids to their acid chlorides and intramolecular Freidel-Crafts acylation with $AlCl_3$ yielded the ketones **15** and **16**. Reduction of the ketones with $NaBH_4$ provided the alcohols **17** and **18**. Acid catalyzed dehydration yielded the desired indenes **10** and **12**. No mention of the yields of these reactions was made.

Scheme 4.2 : Spaleck's Synthesis of 4,5-Benz(o)indene and 2-Methyl-4,5-benz(o)indene



13; R = H
14; R = Me

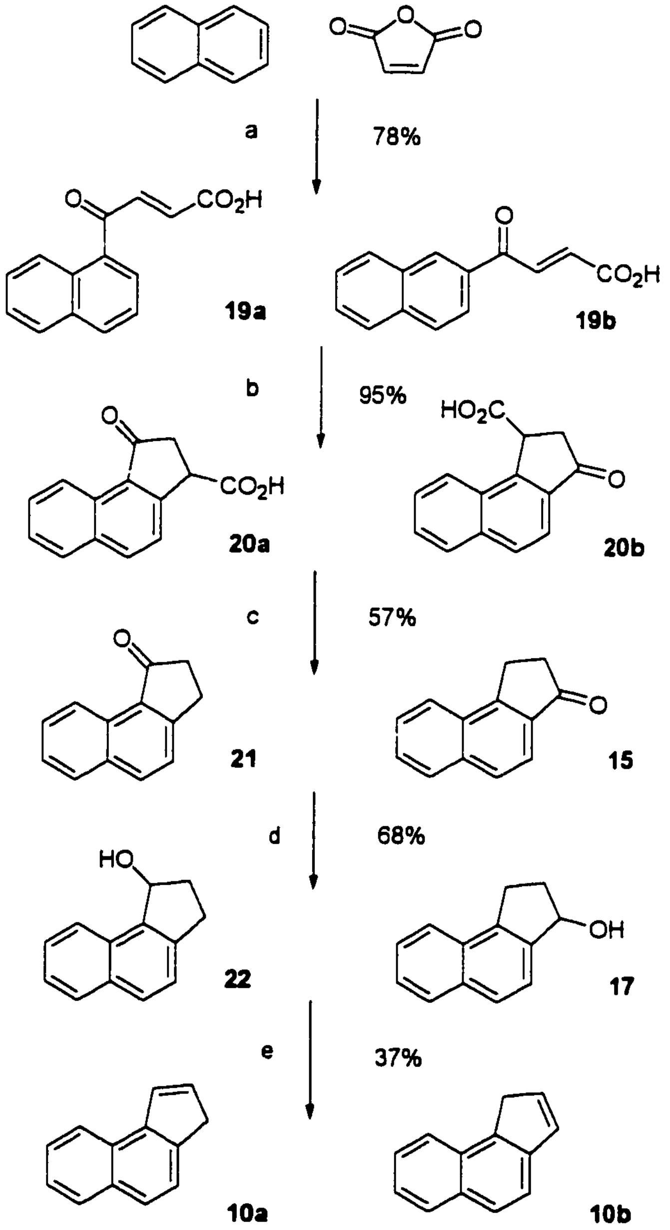
15; R = H
16; R = Me

17; R = H
18; R = Me

10; R = H
12; R = Me

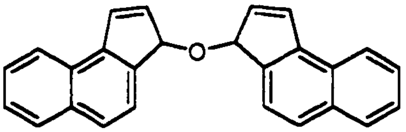
Brintzinger[29] prepared **10** via the literature procedure described by Marechal and Chaintron.[31] Naphthalene was treated with maleic anhydride and $AlCl_3$, to provide a mixture of the unsaturated acids **19a** and **19b**. This mixture of acids was added as a solid to a molten $AlCl_3/NaCl$ (130 °C). The resulting tricyclic acids, **20a** and **20b**, were decarboxylated by heating them to 150 °C, under a nitrogen atmosphere to provide ketones **21** and **15**. Lithium aluminum hydride reduction of the ketones to the corresponding alcohols **22** and **17**, proceeded in 95% yield.

Scheme 4.3 : Marechal and Chaintron's Synthesis of 4,5-Benz(o)indene[31]



a) $AlCl_3$, CH_2Cl_2, b) $AlCl_3/NaCl$, 130 °C c) neat, 150 °C, d) $LiAlH_4$, THF, e) 1M aqueous oxalic acid.

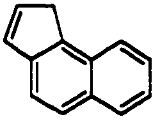
Dehydration of **17** and **22**, by heating the alcohols in aqueous 1M oxalic acid, was reported to provide the desired indenes **10a** and **10b**, in 37% combined yield. During our studies on the synthesis of complex **4** we obtained a 30% yield of indene **10** for this reaction. We also isolated significant quantities of the bis(benzoindenyl) ether **23** (50 to 68% yield) when using this and other acid catalyzed dehydration methods.[32]



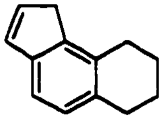
23

Clearly, the low yields and extreme reaction conditions used above make this a very inefficient synthetic route. Although Spaleck's[28] synthesis of **1** appears more efficient, his synthesis employed 2-(bromomethyl)naphthalene as the starting material. The high cost of this material precludes large scale synthesis. We therefore required a more direct route to **10**.

During my studies with Dr. Collins I began to work on a new route to compound **10**. Due to time constraints this approach was never completed. Upon moving to the University of Ottawa, with the approval of Dr. Durst and Dr. Collins, I decided to pursue this synthesis as a side project.



10



24

The well documented difference in activities of indenyl and tetrahydroindenyl *ansa*-metallocenes, also prompted us to explore the synthesis of the tetrahydro equivalent of **10**. In the following section I describe a modified, and regioselective, synthesis of **10**, and the synthesis of 8,9,10,11-tetrahydro-4,5-benz(o)indene (**24**).

4.2 Results

4.2.1 The Regioselective Synthesis of 4,5-Benz(o)-1-indene (10)

We desired a simple and inexpensive route to compound **10**, which would be amenable to large-scale synthesis. In order to simplify product characterization and purification, we desired a route which was regiospecific, providing only one of the regioisomers of **10**. The two main areas that required attention were the method of ring annulation, and the dehydration of compounds **17** and **22**. Both of these matters have been successfully addressed, and the results are summarized below (see Figure 4.4).

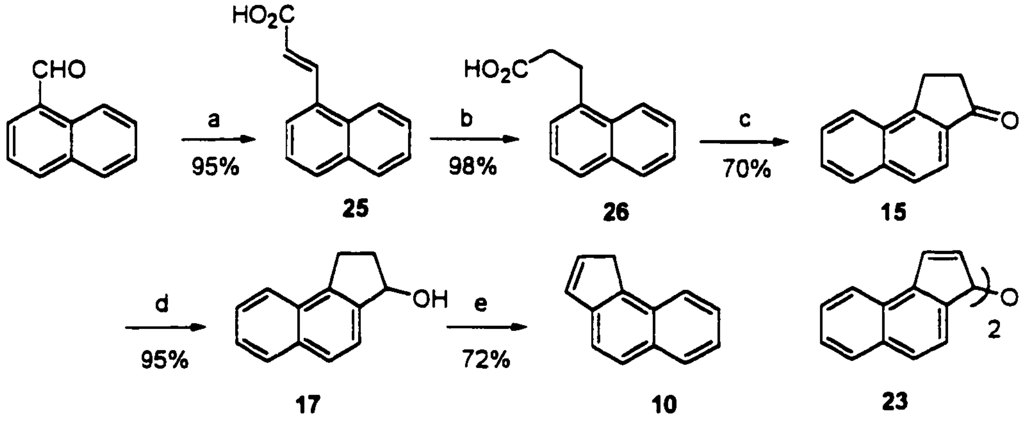
Commercially available 1-naphthaldehyde was treated with malonic acid and catalytic piperidine, in refluxing pyridine, to afford the α,β-unsaturated acid **25** in 95% yield.[32] Hydrogenation of the α,β-unsaturated double bond under standard conditions (100 PSI H_2, 5% Pd/C, MeOH or THF, 24 hrs) only resulted in partial hydrogenation.[32] Very mild reaction conditions were obtained, however, upon switching to acetic acid as the solvent system (1 atm H_2, 10% Pd/C, acetic acid, 3 days, RT) to provide 3-naphthylpropionic acid (**26**) in 98% yield.

Treatment of **26** with 1 equiv. of $SOCl_2$ (reflux 30 minutes) provided the corresponding acid chloride. Excess $SOCl_2$ was removed under reduced pressure and the crude acid chloride was taken up in CH_2Cl_2. This solution was added directly to a suspension of $AlCl_3$ (1.5 equiv.) in CH_2Cl_2, at 0 °C, resulting in intramolecular cyclization to ketone **15**, in 70% yield.

Alternately, compound **26** was stirred with 1 equiv. of oxalyl chloride and a catalytic quantity of DMF (RT, 2 hrs), in CH_2Cl_2, to provide the acid chloride of **26**. The acid chloride was not isolate, instead this solution was added directly to the $AlCl_3$ suspension, as described above. Similar yields were obtained for the two processes, however, the use of oxalyl chloride greatly simplifies this procedure.

As in the previous syntheses of **10**, reduction of **15** with $LiAlH_4$, in THF, provided alcohol **16** in near quantitative yield. This reaction, however, does not require the prescribed 30 minute reflux,[28] which can result in over reduction to the corresponding alkane.[32] Addition of a THF solution of **15** to a suspension of LAH in THF, followed by stirring at RT for 30 minutes was sufficient.

Scheme 4.4 : Synthesis of 4,5-Benz-1-indene (**10**)



a) 2 $(HO_2C)_2CH_2$, piperidine (cat.), pyridine, b) H_2, 10% Pd/C, AcOH, c) i) $SOCl_2$, ii) $AlCl_3$, CH_2Cl_2, d) $LiAlH_4$, THF, e) Phthalic anhydride, MeOH, reflux 1hr.

Acid promoted dehydration of **17** invariably led to significant quantities of bis(benz(o)indenyl) ether **23** and/or uncharacterized 'polymeric' material. When treated with aqueous 1M oxalic acid, as in the procedure described by Marechal and Chaintron,[31] we obtained a 30:70 mixture of **10** and **23**.[32] Changing the acid molarity, adding dioxane or THF to solublize the alcohol, working under maximum dilution conditions (ie. slow addition of to acidic solutions), or treating with 1M HCl or 1M H_2SO_4, again provided mixtures of **10** and **23**. When alcohol **17** was stirred in the presence of catalytic $TsOH•H_2O$ and 4Å MS, in CH_2Cl_2, ether **23** was the sole product observed. When refluxed in toluene, again in the presence of $TsOH•H_2O$, removing water azeotropically, an insoluble blue 'polymeric' material was obtained. Despite the formation of these mixtures, the desired indene was readily separated from the ether by column chromatography, eluting with hexanes.

These results suggest that the lifetime of the indenyl cation formed under the above conditions was long enough to allow for competition between proton elimination and nucleophilic attack by another molecule of **17**. One solution to this problem would be to convert the alcohol to a group that was either be a better leaving group than water (ie. a halide, tosylate, or mesylate), or to convert the alcohol to a group which would facilitate elimination (ie. an acetate).

Treatment of **17** with intrinsically acidic reagents such as $SOCl_2$, $(COCl)_2$, or PBr_3 lead to complex mixtures of products. Addition of $SOCl_2$ to a CH_2Cl_2 solution of **17** containing 2-5 equiv. of either pyridine or triethylamine, at –20 °C, and warming to RT, again provided complex mixtures. Both compound **10** and **23** could be identified by ^1H NMR spectroscopy, but their isolation was complicated by the presence of unidentified side products.

In order to avoid the formation of **23**, compound **17** was either mesylated with MsCl (1 equiv.), or brominated with Ph_3PBr_2 (1 equiv.), in CH_2Cl_2 at –20 °C, in the presence of Et_3N (2.5 equiv.). Subsequent warming of these solutions to RT and stirring overnight, provided compound **10**, free from **23**. Unfortunately the isolated yields of **10** never exceeded 50%.

Acylation of **17** with Ac_2O, pyridine, and catalytic DMAP, in CH_2Cl_2, provided the corresponding acetate in 95% yield. I had hoped to avoid the use of traditional 'flash thermolysis' (0.1 torr, 600-900 ^oC) as this method is not amenable to large scale synthesis. For this reason initial attempts at thermolysis were made using a Krugolrohr apparatus, at 250 ^oC and 10 torr. Some indene was found in the collection pot, however, most of the remaining material was simply distilled acetate. We did not attempt 'flash thermolysis', although it appears that it probably would provide compound **10**, as milder reaction conditions were found, as seen below.

Optimal dehydration conditions were found to involve the treatment of **17** with phthalic anhydride and catalytic TsOH, in refluxing benzene, to provide **10**, free from **23**, in 72% yield. As was mentioned earlier, purification of **10** was readily carried out by silica gel chromatography, eluting with hexanes.

This last step is the only step requiring column chromatography. Compounds **25** and **26** were obtained in >95% yield, and were recrystallized from toluene when necessary. Compounds **15** and **17** generally did not require purification, as they generally contained no more than 5% of unidentified impurities. These impurities could been carried through to the next step, without dramatically effecting the final yield. Analytically pure samples of **15** and **17** were obtained by silica gel column chromatography, eluting with hexanes and diethyl ether. The final product was not obtained analytically pure as it tended to decompose (turning from a light yellow to a red/brown colour) even when stored under nitrogen at –30 °C. This slow decomposition accounted for a 25% loss in material after one month at –30 °C. Again, purification via silica gel chromatography removed most or all of these impurities. A satisfactory HRMS as obtained for **10**. Compounds **15** and **17** also decomposed slowly at room temperature, however, they could still be used without the need for purification.

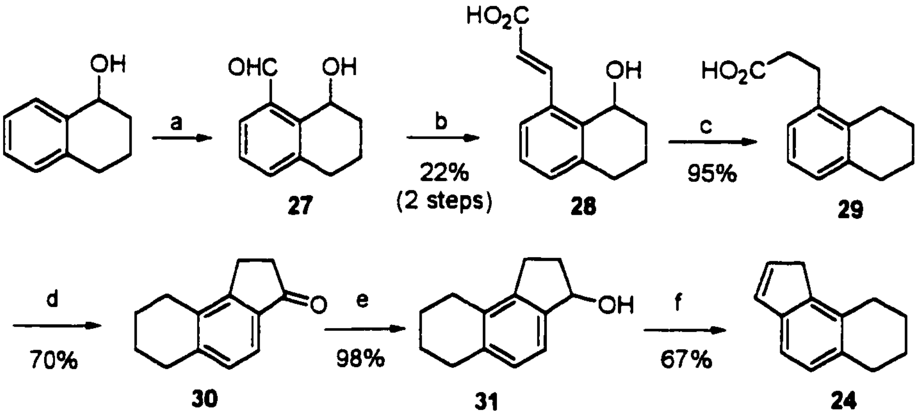
Compound **10** is therefore available from 1-naphthaldehyde, in *ca.* 45% overall yield, after 5 steps, and only requiring one chromatographic purification.

4.2.2 Regioselective Synthesis of 7,8,9,10-Tetrahydro-4,5-Benz(o)-1-indene (24)

As the above method proved to be an acceptable route to **10**, I hoped to apply a similar strategy to the synthesis of **24**. Since 5,6,7,8-tetrahydronaphthyl carboxaldehyde was not commercially available, aldehyde **27** seemed to be an appropriate starting point (see Scheme 4.5). Aldehyde **27** was available from 1,2,3,4-tetrahydro-1-naphthol via a lateral metallation, and quenching of the dianion with DMF.

Treatment of commercially available 1,2,3,4-tetrahydro-1-naphthol[33] with *n*-BuLi (2.2 equiv.) and TMEDA (2.2 equiv.),[6] followed by quenching with DMF, provided the relatively unstable aldehyde **25** and starting material, in a 60:40 ratio. Purification of the oily hydroxy aldehyde was complicated as it tended to decompose on silica and during fractional distillation. The crude reaction mixture was therefore advanced to the next step without further purification. Treatment of the crude mixture with malonic acid, as before, yielded the desired α,β-unsaturated acid **28**, albeit in low yield. Compound **28** was readily isolated from the complex reaction mixture by recrystallization from hot toluene, to provide analytically pure **28**, in 22% yield for the two steps. The material that remained in the filtrate was a mixture of several different compounds, none of which were isolated or characterized. None of these compounds displayed α,β-unsaturation, or an aldehyde proton, as seen by ^{1}H NMR spectroscopy.

Scheme 4.5 : Synthesis of Compound **24**



a) 2.2 *n*-BuLi, 2.2 TMEDA, hexane; 5 DMF, b) 2 $(HO_2C)_2CH_2$, piperidine (cat.), pyridine, c) H_2, 10% Pd/C, AcOH, 60 °C, 24 hrs. d) i) $SOCl_2$, ii) $AlCl_3$, CH_2Cl_2, e) $LiAlH_4$, THF, f) Phthalic anhydride, MeOH, reflux.

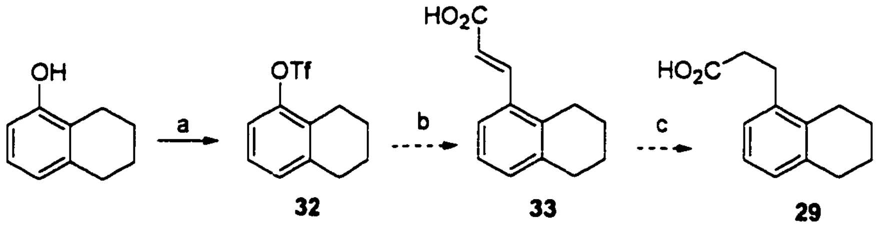
Reduction of the α,β-unsaturated double bond and the benzylic alcohol of **28** with H_2 (1 atm, 5% Pd/C, acetic acid, 60 °C, 24 hrs), provided the saturated acid **29** in 95% yield. Interestingly, the double bond was reduced faster than the benzylic alcohol, as seen by ^{1}H NMR spectra taken during the course of the reaction. Very little reduction was observed if the reduction was run at room temperature, as compared to the reduction of **25**. This may have been a matter of poor solubility of **28** in acetic acid. Compound **29** was subsequently transformed to **30** in a similar manner as that described for the conversion of **25** to **10**; treatment of the acid with oxalyl chloride, followed by intramolecular Friedel-Craft acylation with $AlCl_3$, to provide ketone **30** in 70% yield. Reduction of **30** with $LiAlH_4$ provided alcohol **31**, in 98% yield. Finally, alcohol **31** was converted into the desired indene **24** either by refluxing **31** with phthalic anhydride, in benzene for 30 minutes, or by treating **31** with MsCl and Et_3N. Again, purification using silica gel column chromatography, eluting with hexane, yielded **24** as a clear oil in 67% and 45% yield, respectively.

The above route provided the desired indene **24**, in *ca.* 10% overall yield, after six consecutive steps. The poor overall yield was a direct result of the instability of aldehyde **27** to purification and to the reaction conditions for the chain extension. In an effort to improve this synthesis an alternative route to compound **24** was investigated.

This new route is depicted in Scheme 4.6. Conversion of commercially available 5,6,7,8-tetrahydro-1-naphthol into the corresponding triflate, would be followed by a Heck reaction using Pd° and methyl acrylate. Saponification and hydrogenation would hopefully provide compound in greater than 20% yield over the four steps.

Treatment of 5,6,7,8-tetrahydro-1-naphthol with triflic anhydride and pyridine, in CH_2Cl_2, provided the desired triflate **32**, in 85% yield. When triflic chloride was used instead of triflic anhydride, a mixture of triflated compounds was obtained, presumably the result of Friedel-Crafts type reactions. Unfortunately, initial attempts to convert **32** to **33** have failed. Treatment of **32** with methyl acrylate (5 equiv.), K_3PO_4, (2.5 equiv.), and $Pd(PPh_3)_4$ (10 mol%), in refluxing THF or DMF, provided a number of uncharacterized compounds, with no evidence of an α,β-unsaturated ester.

Scheme 4.6 : Synthesis of **24** Via Triflate **32**



a) Tf_2O, pyridine, CH_2Cl_2, 80%, b) i) methyl acrylate, $Pd(PPh_3)_4$, K_2CO_4, toluene, ii) NaOH, $MeOH/H_2O$, c) H_2, 10% Pd/C, AcOH, RT.

Clearly, more work needs to be done to get this reaction to work. Various combinations of solvent, base, catalyst, and additives have been reported in the literature for optimizing yields in the Heck reaction. Some, as of yet, unknown combination of these will provide the desired ester.

4.3 Summary

In this section I have described an improved synthesis of indene **10**. The reaction sequence is simple and provided the desired indene in *ca.* 45% overall yield after five steps. Purification by column chromatography was only required in the final step of this reaction sequence.

The synthesis of **24** has also been described. The overall yield was *ca.* 10% yield after six steps. This low yield was a direct result of the instability of aldehyde **25** to purification and to the malonic acid/pyridine reaction conditions. An attempt was made to shorten this route by avoiding the *ortho*-metallation step and the unstable aldehyde **25**. This involved conversion of 5,6,7,8-tetrahydro-1-naphthol to its corresponding triflalte and coupling with methyl acrylate, using palladium catalyzed Heck reaction conditions. Unfortunately, the key Heck coupling reaction was not successful, and requires further study.

4.4 References

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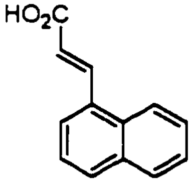
33. 1,2,3,4-Tetrahydro-1-naphthol is commercially available, but is rather expensive. Alternately, it may be prepared in large quantities by the reduction of inexpensive α-tetralone, with $LiAlH_4$.

4.5 Experimental

4.5.1 General

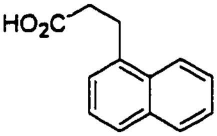
All reaction, unless stated otherwise, were run under a nitrogen atmosphere using dry solvents. THF was dried over sodium benzophenone ketyl, and distilled prior to use. Methylene chloride, triethylamine, pyridine, piperidine, methansulfonyl chloride, and methyl acrylate were dried over NaH, and distilled prior to use. All chemical reagents were obtained from Aldrich Chemical Company and used as received, unless stated otherwise.

4.5.2 Compound 25



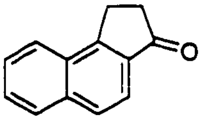
1-Naphthaldehyde (14.0 mL, 0.10 mol) was added under nitrogen to a stirring solution of malonic acid (20.8 g, 0.20 mol) in dry pyridine (40 mL). The solution was warmed to 35 °C before piperidine (1.5 mL, 15 mmol) was added. After refluxing for 3 hours the mixture was poured onto ice water (300 mL). Acidification with concentrated HCl (50 mL) resulted in the formation of a white precipitate. The precipitate was filtered off, washed with water (3 x 50 mL) and dried over night under reduced pressure to yield 17.7 g of white solid (95 % yield). Crude **3** was essentially pure, but may be recrystallized from toluene. m.p. 213.0-214.0 °C. IR (KBr, cm^{-1}) 3360-2200 (br), 1684 (s), 1618 (s), 1509 (w), 1423 (m), 1286 (s), 975 (m), 941 (m), 769 (s). ^1H NMR (200MHz, DMSO-d^6) δ 8.49 (d, J=15.7Hz, 1H), 8.28 (d, J=9.1Hz,1H), 8.11-8.02 (m, 3H), 7.75-7.60 (m, 3H), 6.69 (d, J=15.7Hz, 1H). ^{13}C NMR (50MHz , DMSO-d^6) δ 167.5, 140.2, 133.3, 131.0, 130.8, 130.4, 128.8, 127.2, 126.3, 125.8, 125.3, 123.0, 122.0. MS (m/z); M^+=198. Anal. Calcd. for $C_{13}H_{10}O_2$ (198.22): C, 78.77; H, 5.08. Found C, 79.08; H, 4.70.

4.5.3 Compound 26



Compound **25** (4.60 g) and 10% Pd/C (200 mg) were suspended in acetic acid (50 mL). The slurry was stirred under H_2 (1 atm) and stirred for 3 days. The solution remained heterogeneous, but the complete conversion from **25** to **26** was observed by ^1H NMR spectra of the crude solution. The crude acetic acid solution was heated until all of compound **26** had dissolved. The solution was filtered through celite, washing with warm acetic acid (3 x 20 mL). The acetic acid was evaporated under reduced pressure to provide 4.52 g of compound **26** as a white solid (98% yield) which was used in the next step without further purification. m.p. 153.5 °C. IR (KBr, cm^{-i}) 3360-2100 (br), 1701 (s), 1597 (w), 1508 (w), 1435 (m), 1402 (m), 1304 (m), 1224 (s), 1171 (m), 942 (m), 800 (s), 782 (s), 763 (m). ^1H NMR (200MHz, acetone-d^6) δ 8.12 (dd, J=1.3, 7.6Hz, 1H), 7.89 (dd, J=1.7, 8.5Hz, 1H), 7.77 (dd, J=4.8, 6.6Hz, 1H), 7.73-7.46 (m, 2H), 7.45-7.40 (m, 2H), 3.40 (t, J=7.8Hz, 2H), 2.74 (t, J=7.8Hz, 2H). ^{13}C NMR (57.4MHz, acetone-d^6) δ 174.0, 137.8, 134.8, 132.6, 129.6, 127.7, 126.9, 126.8, 125.7, 126.4, 124.3, 35.2, 28.6. Anal. Calcd. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found C 77.66; H, 6.01.

4.5.4 Compound 15

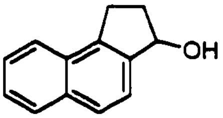


Compound **26** (5.67 g, 27.7 mmol) was refluxed in neat thionyl chloride (20 mL) for 30 minutes. After cooling to room temperature volitiles were removed *in vacuo* to provide a brown oil. The oil was pumped on for 1 hr (0.1 torr) before being dissolved in dry CH_2Cl_2 (50 mL). The acid chloride solution was then added via cannula to a flask containing $AlCl_3$ (7.34 g, 55.5 mmol) and CH_2Cl_2 (50 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for an additional hour before being poured over ice water (200 mL). The mixture was acidified with 6 N HCl (20 mL) and stirred for 1 hour. The organic layer was washed with water (3 x 100 mL) before being dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting brown solid was taken up in hot hexane (100 mL) and filtered through celite. Removal of the hexane, under reduced pressure, provided **15** as an off white solid (4.75 g, 94% yield). An analytically pure sample was obtained by recrystallization from hexane.

For a slightly altered preparation, using oxalyl chloride, instead of thionyl chloride, see compound **30**.

m.p. 78.5- 79.5 °C. IR (cm^{-1}, KBr) 2935 (w), 1674 (s), 1616 (m), 1582 (m), 1504 (m), 820 (s), 767 (s). ^1H NMR (200MHz, $CDCl_3$) : δ 8.18 (dd, J=1.3, 7.1Hz, 1H), 8.08 (dd, J=1.3, 8.2Hz, 1H), 7.78 (dd, J=1.3, 7.1Hz, 1H), 7.58 (dd, J=7.2, 8.2Hz, 1H), 7.49 (t, J=7.6Hz, 2H), 3.43 (t, J=7.6Hz, 2H), 2.97 (t, J=7.6Hz, 2H). ^{13}C NMR (57.3Hz, $CDCl_3$) : δ 198.2, 133.8, 133.1, 132.9, 131.3, 129.5, 126.0 (2 C's), 125.4, 125.3, 124.7, 38.2, 28.2. Anal. Calcd. for $C_{13}H_{10}O$: C, 85.69; H, 5.53. Found C 85.20; H, 5.68.

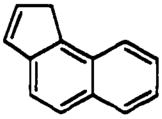
4.5.5 Compound 17



Lithium aluminum hydride (1.71 g, 20.2 mmol) was added in one portion to a THF (50 mL) solution of compound **15** (3.68 g, 20.2 mmol) at 0 °C. After stirring at 0 °C for 30 minutes the solution was stirred at room temperature for 2 hours. The reaction was quenched by the drop wise addition of water (50 mL) and 6 N HCl (5 mL). The solution was extracted with ethyl acetate (100 mL) and the organic layer was washed with water (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and dried *in vacuo* to provide 3.60 g of an off white crystalline solid (95% yield) which was used in the next step without further purification. m.p. °C. IR (KBr, cm^{-1}) 3190 (m, br), 2929 (m), 1597 (m), 1496 (m), 1091 (s), 817 (s), 769 (s). ^1H NMR (200MHz, $CDCl_3$) : δ ^{13}C NMR (57.3MHz, $CHCl_3$) : δ

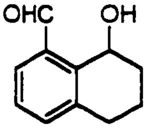
137.3, 135.0, 133.5, 128.6, 127.8, 125.7, 125.5, 125.4, 124.2, 123.3, 69.1, 31.1, 26.2. Anal. Calcd. for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found C 84.70; H, 6.51.

4.5.6 Compound 10



Compound **17** (1.32 g, 7.00 mmol) and phthalic anhydride (1.14 g, 7.70 mmol) were dissolved in methanol (20 mL) and refluxed for 30 minutes. After cooling to room temperature the mixture was taken up in diethyl ether (20 mL) and saturated $NaHCO_3$ (50 mL). The organic layer washed with water (2 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and dried *in vacuo*. The crude material was loaded onto a column of silica gel (30 x 4.5 cm), pretreated with hexane, and eluted with 500 mL of hexane. The hexane was dried down under reduced pressure to provide 0.61 g of white solid (70% yield). m.p °C. IR ($CHCl_3$, cm^{-1}) 3030 (w), 2860 (w), 1926-1710 (w aromatic overtones), 1648 (w), 1608 (w), 1585 (m), 155 (m), 820 (s), 769 (s), 713 (m). ^1H NMR (200MHz, $CDCl_3$) : δ 7.98 (dd, J=0.7, 6.9Hz, 1H), 6.59 (dt, J=2.2, 9.9Hz, 1H), 6.05 (dt, J=4.2, 9.9Hz, 1H), 4.07 (br s, 2H). ^{13}C NMR (57.3MHz, $CHCl_3$) : δ 134.2, 133.5, 132.0, 129.4, 127.74, 127.56, 126.6, 126.2, 126.0, 125.0, 124.9, 122.1, 32.0. HRMS Cal'd for $C_{13}H_{10}$ 166.0783. Found 166.0786.

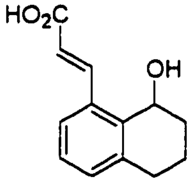
4.5.7 Compound 27



1,2,3,4-Tetrahydronaphthol (5.30 g, 36.0 mmol) and TMEDA (11.3 mL, 75.0 mmol) were dissolved in dry pentane (50 mL) and cooled to 0 °C. After the dropwise addition of *n*-butyl lithium (32.0 mL, 2.30 M, 75.0 mmol) the solution was warmed to room temperature and stirred for 3 hours before being treated with dry DMF (4.20 mL, 54.0

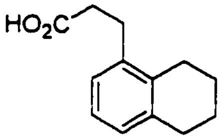
mmol). The solution was stirred for 30 minutes before being quenched with water (50 mL) and acidified to pH 1 with 6 N HCl. The mixture was extracted with ethyl acetate (100 mL) and the organic layer washed with water (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and dried *in vacuo* to provide 6.44 g of yellow oil as a 60:40 mixture of compound **1** and starting material as seen by the ^1H NMR spectum of the crude product. Compound **1** was not easily purified by silica gel chromatography or by recrystallization and was used in the next reaction without further purification. ^1H NMR (200 MHz, $CDCl_3$) : δ 10.02 (s, 1H), 7.61 (t, J=5.2Hz, 1H), 7.33 (d, J=5.2Hz, 2H), 5.06 (t, J=3.8Hz, 1H), 4.25 (br s, 1H), 2.82-2.69 (m, 3H), 2.10-2.05 (m, 1H), 1.92-1.70(m, 2H). ^{13}C NMR (57.3MHz, $CDCl_3$) : δ 195.3, 139.4, 138.6, 135.7, 134.9, 133.4, 127.3, 62.8, 30.7, 29.9, 17.2. HRMS M^+ (m/z) calcd for $C_{11}H_{12}O_2$ 176.0838. Found 176.0830.

4.5.8 Compound 27



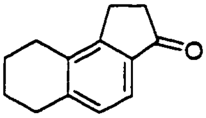
Compound **27** (6.64 g, 36.0 mmol) and malonic acid (7.80 g, 76.0 mmol) were dissolved in dry pyridine (40 mL). The solution was warmed to 35 °C before piperidine (0.56 mL, 5.7 mmol) was added. After refluxing for 3 hours the mixture was poured onto ice water (100 mL). Acidification with concentrated HCl (10 mL) was followed by extration with ethyl acetate (200 mL). The ethyl acetate layer was washed with water (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered, and dried *in vacuo*. Compound **28** was isolated from the complex mixture by crystalization from toluene to provide 1.64 g of white crystaline solid (22% yield). m.p. 190.5-191.5°C. IR (KBr, cm^{-1}) 3360-2100 (br), 1680 (s), 1619 (s), 1600 (m), 1450 (s), 1390 (s), 1271 (s), 680 (s). ^1H NMR (200 MHz, acetone-d^6) δ 8.33 (d, J=15.9Hz, 1H), 7.54 (d, J=7.1Hz, 1H), 7.22 (t, J=7.5Hz, 1H), 7.13 (d, J=7.2Hz, 1H), 6.39 (d, J=15.9Hz, 1H), 4.99 (t, J=2.9Hz, 1H), 2.78-2.68 (m, 2H), 2.14-1.91 (m, 2H), 1.86-1.66 (m, 2H). ^{13}C NMR (57.3MHz, DMSO-d^6) δ 168.1, 142.7, 137.8, 137.4, 134.6, 131.0, 127.5, 124.5, 120.0, 62.1, 32.2, 29.6, 16.8. MS (m/z) : M^+=218.

4.5.9 Compound 28



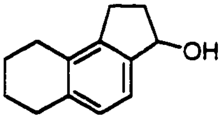
Compound **27** (2.40 g) and 10% Pd/C (0.25 g) were suspended in acetic acid (50 mL) and placed under H_2 gas (1 atm). The reaction mixture was heated to 60 °C and stirred for 24 hours. Compound **27** was observed to dissolve as it reacted; reduction of the double bond was followed by reduction of the alcohol as observed by ^1H NMR spectra. This solution was filtered hot through celite and the filter cake was washed with acetic acid (3 x 20 mL). The filtrate was concentrated under reduced pressure to provide 2.35 g of white crystals (95% yield), which were used in the next step without further purification. m.p. 134.5-135.5 °C. IR (KBr, cm^{-1}) 3360-2350 (br), 1693 (s), 1589 (m), 1435 (s), 1406 (s), 1310 (m), 1222 (s), 945 (m), 791 (m). ^1H NMR (500 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 7.09 (t, J=7.5Hz, 1H), 7.00 (d, J=7.5Hz, 1H), 6.99 (d, J=7.5Hz, 1H), 2.94 (t, J=7.5Hz, 2H), 2.81 (t, J=6.4Hz, 2H), 2.74 (t, J=6.4Hz, 2H), 2.66 (t, J=7.5Hz, 2H), 1.89-1.84 (m, 2H), 1.82-1.78 (m, 2H). ^{13}C NMR (50MHz, $CDCl_3$) δ 179.7, 138.2, 137.6, 135.0, 127.7, 125.7, 125.4, 36.3, 30.1, 27.4, 26.0, 23.3, 22.8. HRMS calcd for $C_{13}H_{16}O_2$ 204.1511. Found 204.1180.

4.5.10 Compound 30



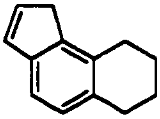
A cold methylene chloride (20 mL) solution of **29** (2.00 g, 9.80 mmol) was treated with DMF (3 drops) and oxalyl chloride (0.93 mL, 9.80 mmol). This solution was allowed to stir at room temperature for 1 hour (until gas evolution had ceased). The acid chloride solution was then added via cannula to a flask containing $AlCl_3$ (1.45 g, 12.5 mmol) and CH_2Cl_2 (10 mL) at 0 °C. The resulting solution was warmed to room temperature and stirred for an additional hour before water was carefully added (20 mL). The mixture was acidified with 6 N HCl (20 mL) and stirred for 1 hour. Diethyl ether (100 mL) was added and organic layer was washed with water (50 mL), saturated NaH_2CO_3 (50 mL), water (50 mL), and brine (50 mL), before being dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was purified by silica gel chromatography (eluting with 3:1 hexane/ethylacetate) to yield 0.83 g of compound **14** as an off white solid (0.83 g, 90% yield). m.p. 61.0-63.0 ^{o}C. IR (KBr, cm^{-1}) 2907 (m), 1692 (s), 1590 (s), 835 (s), 802 (s). ^{1}H NMR (200MHz, $CDCl_3$) : δ 7.48 (d, J=7.8Hz, 1H), 7.08 (d, J=7.8Hz, 1H), 2.93 (t, J=5.5Hz, 2H), 2.83 (J=5.5Hz, 2H), 2.66 (m, 2H), 1.84 (m, 2H). ^{13}C NMR (50MHz, $CDCl_3$): δ 206.5, 154.5, 143.9, 134.3, 134.1, 128.4, 119.8, 35.9, 29.7, 25.0, 23.9, 22.3, 22.2. HRMS M$^+$ (m/z) calcd for $C_{13}H_{14}O$ 186.1045. Found 186.1038. Anal. Calcd. for $C_{13}H_{14}O$ (186.26): C, 83.83; H, 7.58. Found C, 83.49, H, 7.48.

4.5.11 Compound 31



Lithium aluminum hydride (250 mg, 6.55 mmol) was added in one portion to a THF (25 mL) solution of compound **30** (1.22 g, 6.55 mmol) at 0 °C. After stirring at 0 °C for 30 minutes the solution was stirred at room temperature for 2 hours. The reaction was quenched by the drop wise addition of water (10 mL) and 6 N HCl (5 mL). The solution was extracted with ethyl acetate (50 mL) and the organic layer was washed with water (3 x 20 mL), dried over anhydrous $MgSO_4$, filtered, and dried *invacuo* to provide 1.20 g of a white crystalline solid (95% yield) which was used in the next step without further purification. m.p. 81.0 °C. IR (KBr, cm^{-1}) 3382 (br), 3000 (s), 2899 (s), 1696 (s), 1593 (s), 1478 (s), 1437 (s), 1320 (s), 1067 (s), 829 (m), 804 (m). ^1H NMR (500MHz, $CDCl_3$) : δ 7.21 (d, J=7.2Hz, 1H), 7.05 (d, J=7.1Hz, 1H), 5.22 (dd, J=5.1, 6.6Hz, 1H), 2.96 (overlapping dddd, 1H), 2.87 (t, J=6.0Hz, 2H), 2.72 (m, 2H), 2.49 (m, 1H), 1.99 (m, 1H), 1.90 (m, 2H). ^{13}C NMR (50MHz, $CDCl_3$) : δ 141.9, 141.8, 136.8, 133.0, 127.8, 121.0, 76.1, 35.2, 29.4, 27.9, 26.4, 23.0, 22.9. HRMS M+ (m/z) calcd for $C_{13}H_{16}O$ 188.1202. Found 188.1194. Anal. Calcd. for $C_{13}H_{16}O$ (188.27): C, 82.94; H, 8.57. Found C, 83.6, H, 8.39.

4.5.12 Compound 24



Compound **3** was prepared in a similar manner as described for compound **1**. Phthalic anhydride and **15** were refluxed in methanol overnight, and purified, after aqueous workup, by silica gel chromatography, eluting with hexanes, to provide a clear oil (72%). ^1H NMR (200 MHz, $CDCl_3$) δ 7.19 (d, J=7.1Hz, 1H), 7.00 (d, J=7.1Hz, 1H), 6.85 (dt, J=2.2, 5.4Hz, 1H), 6.53 (dt, J=4.2, 5.4Hz, 1H), 3.21 (br s, 2H), 3.95-3.70 (m, 4H), 1.97-1.74 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.6, 132.6, 132.0, 129.7, 127.3, 125.6, 120.7, 118.3, 37.4, 29.5, 26.4, 23.5, 23.2. HRMS Calc'd. for $C_{13}H_{14}$ 170.1096. Found 170.1096.