National Library
of Canada

Acquisitions and
Bibliographic Services Branch

395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale
du Canada

Direction des acquisitions et
des services bibliographiques

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file Votre référence

Our file Notre référence

NOTICE

The quality of this microform is heavily dependent upon the quality of the original thesis submitted for microfilming. Every effort has been made to ensure the highest quality of reproduction possible.

If pages are missing, contact the university which granted the degree.

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us an inferior photocopy.

Reproduction in full or in part of this microform is governed by the Canadian Copyright Act, R.S.C. 1970, c. C-30, and subsequent amendments.

AVIS

La qualité de cette microforme dépend grandement de la qualité de la thèse soumise au microfilmage. Nous avons tout fait pour assurer une qualité supérieure de reproduction.

S'il manque des pages, veuillez communiquer avec l'université qui a conféré le grade.

La qualité d'impression de certaines pages peut laisser à désirer, surtout si les pages originales ont été dactylographiées à l'aide d'un ruban usé ou si l'université nous a fait parvenir une photocopie de qualité inférieure.

La reproduction, même partielle, de cette microforme est soumise à la Loi canadienne sur le droit d'auteur, SRC 1970, c. C-30, et ses amendements subséquents.

Canada

National Library
of Canada

Acquisitions and
Bibliographic Services Branch

395 Wellington Street
Ottawa, Ontario
K1A 0N4

Bibliothèque nationale
du Canada

Direction des acquisitions et
des services bibliographiques

395, rue Wellington
Ottawa (Ontario)
K1A 0N4

Your file   Votre référence

Our file   Notre référence

ISBN 0-612-11586-0

Canada

To Mom, Dad,

Mike, Jenny,

and all of my friends,

especially Todd and Shelley

ACKNOWLEDGEMENTS

I wish to give my sincerest thanks to my supervisor, Dr. Tony Durst. His leadership, advice and confidence in my abilities have been inexplicably important to my young career as an organic chemist.

Terry Connolly, Yvonne Lear, Dr. Manfred Jung, Dr. Rob Ben, Dr. Fraser, Dr. Roy and Dr. Fallis are all graciously thanked for many enlightening discussions which have furthered my knowledge and understanding of organic chemistry.

I would also like to thank C. Bensimon for X-Ray services, Dr. Glen Facey and Raj Capoor for their high resolution NMR contributions to this work and C. Kazakoff for mass spectral analyses.

TABLE OF CONTENTS

List of Figures

List of Schemes

List of Tables

List of Abbreviations and Symbols

Ac	acetyl
AIBN	azabis(isobutyronitrile)
Ar	aryl
Bu	butyl
°C	degrees Celsius
CI	chemical ionization
cm	centimeters
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DKR	dynamic kinetic resolution
DMSO	dimethyl sufoxide
DMF	dimethyl formamide
EI	electron impact
eq.	equivalents
GC	gas chromatograph
h	hours
Hz	Hertz
HRMS	high resolution mass spectrum
HPLC	high pressure liquid chromatography
HMPA	hexamethyl phosphoramide
int	integration
IR	infrared
J	coupling constant
m	multiplet

M	molar
M^+	parent molecular ion
m/e	mass over elementary charge
min	minutes
mmole	millimoles
mp	melting point
Pr	propyl
MS	mass spectroscopy
NMR	nuclear magnetic resonance
p	page
q	quarted
rxn	reaction
s	seconds or singlet
t	triplet
tert-Bu	tertiary butyl
THF	tetrahydrofuran

*** note:**

The term "methodology" is used in this thesis to represent an established protocol for synthesizing a particular group, type of molecule or funtionality.

Abstract

The synthesis of optically active N-protected α-amino esters and α-amino imidazolidinones via a dynamic kinetic resolution protocol will be discussed. The methodology is based on fundamental reactivity differences between diastereomeric α-halo esters and α-halo imidazolidinones. The process involves nucleophillic displacement of the diastereomeric α-halogenated esters and imidazolidinones with benzylamine. The corresponding displacement products are obtained with 70 - > 98% de. Both absolute configurations are possible at the aminated postion by appropriate choice of the chiral auxiliary. The application of this methodology towards the synthesis of several optically active α-amino esters was investigated. A five step sequence, starting from commercially available acid chlorides, was developed for synthesizing α-amino esters in ~ 40 % overall yield.

By utilizing dibenzylamine as the nucleophile, the DKR process has been effectively utilized in an approach to Reetz aldehydes (α-dibenzylamino aldehydes). The increased bulk of dibenzylamine provides increased diastereoselectivity relative to benzylamine and the Reetz aldehyde precursors are obtained with a high degree of optical purity. Mechanistic aspects of the reaction will also be discussed.

1.0 Amino Acids: A Brief Introduction

α-Amino acids are an important class of molecule which have significance in virtually all disciplines of biology, medicine, biochemistry and chemistry. Optically active α-amino acids are the basic building blocks of all the proteins and enzymes found in living organisms. Moreover, α-amino acids are finding increasing use in the synthesis of pharmaceuticals, agricultural products, food additives and cosmetics. While many methodologies exist for synthesizing these important compounds, the developement of efficient and enantioselective methods for the synthesis of α-amino acids continues to present a challenge to the synthetic chemist.

From a synthetic organic chemists perspective, the twenty proteinogenic α-amino acids represent a pool of versatile chiral starting materials. The inherent optical activity of α-amino acids has been utilized efficiently and imaginatively to induce chirality in a large number of reaction products. The use of derivatized α-amino acids as chiral auxiliaries further expands the synthetic utility of these compounds. As a result of the obvious demand for these compounds, optically pure proteinogenic amino acids are now relatively inexpensive and are commercially available.

Non-proteinogenic α-amino acids and their analogues, in both the (L) and (D) form, have recently been demonstrated to posess interesting pharmacological properties. The possibility for creating new enzymes, hormones or drugs with these non-proteinogenic amino acids is particularily attractive because of the structural possibilities available when synthesizing these compounds. The diverse types of side chains that can be attached onto a glycine template permits the number of non-proteinogenic amino acids possible to be essentially infinite. This structural variability should allow the preparation of compounds which are highly specific in their task and function.

Progress in the enantioselective synthesis of these compounds has been relatively fast and a number of efficient methodologies have been developed. Excellent reviews are available which summarize this information[1]; however, several of the more successful methodologies will be discussed in section 1.1.

1.1. Asymmetric Synthesis of α-Amino Acids

A successful synthetic route to amino acids should focus on methods that provide equally facile access to both the L and D forms with high levels of optical purity. The literature of amino acid syntheses can be divided into approximately seven categories.

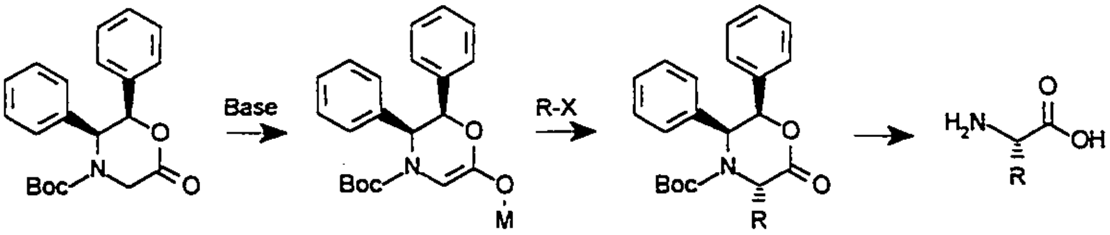
- asymmetric glycine enolate alkylation
- homologation of the β-carbon of already chiral amino acids
- electrophillic amination of enolates
- nucleophilic amination of α-substituted acids
- asymmetric Strecker synthesis
- asymmetric hydrogenation of dehydroamino acids
- enzymatic and/or cell based syntheses

Each of these routes has its own merit and its own limitations. Several recent methodologies displaying a high degree of enantioselectivity are outlined below:

William's group at Colorado State University have recently reported the asymmetric synthesis of mono subsituted α-amino acids, with > 95% diastereoselectivity, via a diastereoselective glycine enolate alkylation[2].

The enolates derived from the optically active and suitably protected 5,6 diphenyl -2,3,5,6-tetrahydro-4H-1,4 oxazin-2-ones couple efficiently with alkyl halides to afford the correseponding anti α–substituted-oxazinones.

Figure 1: Diastereoselective Glycine Enolate Alkylations



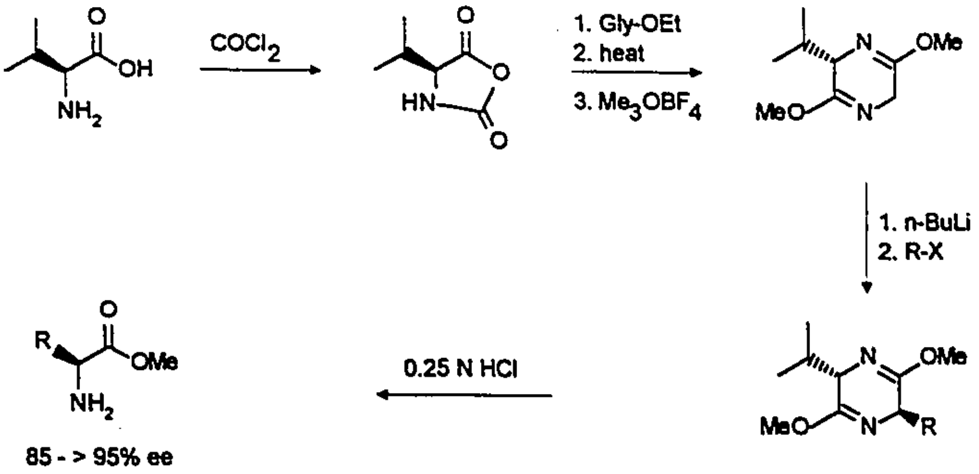
The diastereoselectivity in this reaction can be explained easily. The bulky phenyl groups block attack of the top face of the enolate, thereby restricting the incoming electrophile to anti attack. This bias provides the alkylated product with a very high degree of diastereoselectivity.

The N-BOC lactones can then be directly converted into the corresponding N-BOC-α–amino acids by dissolving metal reduction. Alternatively, deprotection of the amine, followed by catalytic hydrogenation furnished the α–amino acids in good yield with >95% diastereoselectivity in all cases. Further enolisation and alkylation also proceeds stereoselectively and provides access to the synthetically challenging α,α-disubstituted α-amino acids. A major drawback of this approach is that the chiral auxiliary is lost while freeing the α-amino acid by catalytic hydrogenation.

Schollkopf and his associates have developed a versatile and efficient method for the preparation of a wide variety of amino acids, based on the metallation and subsequent alkylation of bis-lactim ethers.[3] The general protocol involves peptide coupling of two amino acids, piperazinedione formation and bis-lactim ether formation with trimethyloxonium tetrafluoroborate. This is illustrated in **Figure 2** for the most popular and most extensively studied bis-lactim ether which is derived from L-valine and glycine. This reagent has become the most widely used glycine template and is commercially available in both enantiomeric forms. Metallation of the bis lactim ether with butyllithium in THF at low temperature followed by alkylation with a large variety of electrophiles proceeds with a high degree of stereoselectivity providing the anti substitution product.

The amino acids from this bis-lactim protocol may be obtained as either the free zwitterions or as the corresponding methyl esters. Hydrolysis of the alkylated bis-lactim compounds to the free zwitterions requires relatively vigorous conditions (refluxing 6N HCl, 1h); the methyl esters are obtained under much milder conditions (0.25 N HCl, RT, 1h).

Figure 2: Schollkopf's Bis Lactim Ether Methodology



In general, the levels of chiral induction in this process are excellent with typical values ranging from 85 - > 95% ee. A variety of synthetically challenging α-amino acids have been prepared using the Schollkopf methodology. For example, Hopkins and collaborators prepared the unusual histidine derivatives ovothiol A and C,[4] and Hartwig and Born[5] have employed a Micheal addition strategy to prepare the hepatoprotective agent clausenamide (**Figure 3**).

Figure 3: Ovothiol A and C ; Clausenamide

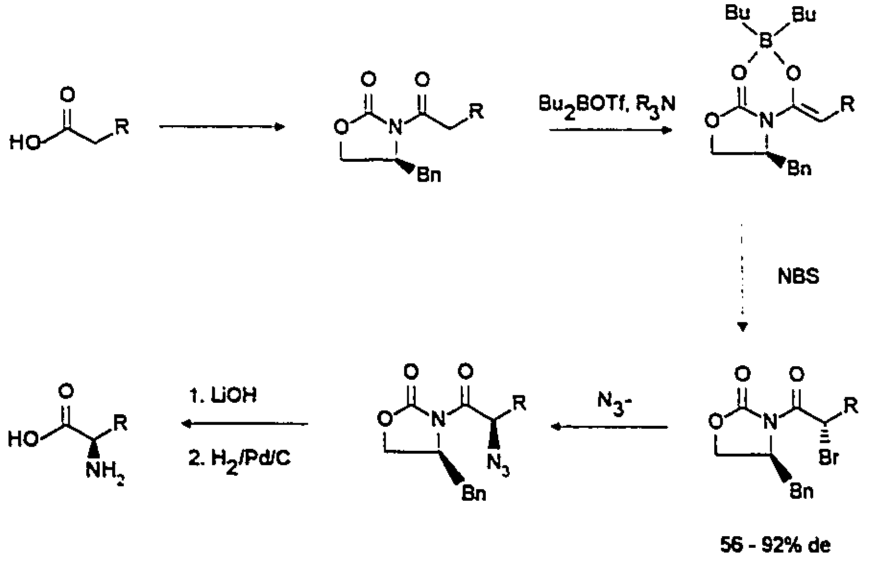
R=H, Ovothiol A
R=Me, Ovothiol C

(+)-Clausenamide

Evans and his research group have developed an efficient methodology based on his chiral auxiliary modified aldol reactions.[6] This process and subtle variations of it has been utilized for the preparation of a wide variety of functionalized and non-functionalized α-amino acids. The starting carboxylic acids are converted to the chiral carboximides, formation of the di-n-butylboron enolate is carried out with the corresponding triflate and the resulting enolate is trapped by electrophillic bromine supplied by NBS. This bromination step proceeds with high levels of diastereoselectivity (~ 95:5) and, upon isolation, provides essentially optically pure α-bromo derivatives.

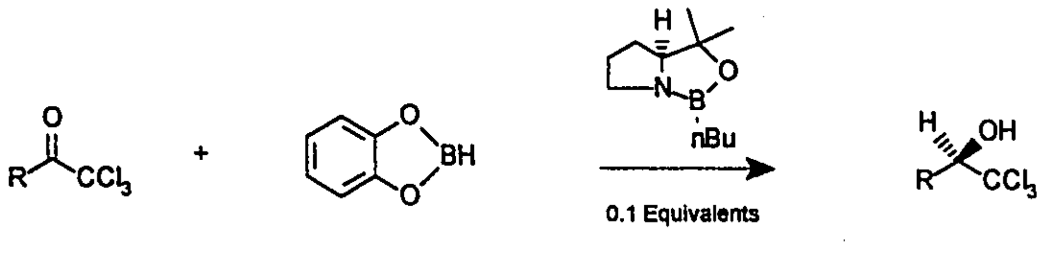
Azide displacement allows small amounts of epimerization (2-5%) under standard azidination protocols (NaN_3, DMF, 0^{o}C), however it is cleanly affected by utilizing tetramethylguanidinium azide as the nucleophillic source[6]. Following azidination the chiral auxiliary can then be removed (and recycled) and the resulting α-azido compounds can be reduced to provide the α-amino acids in high optical purity. This process has also been utilized extensively and has provided access to several natural products.

Figure 4: Evans Diastereoselective Bromination Route to α-Amino Acids



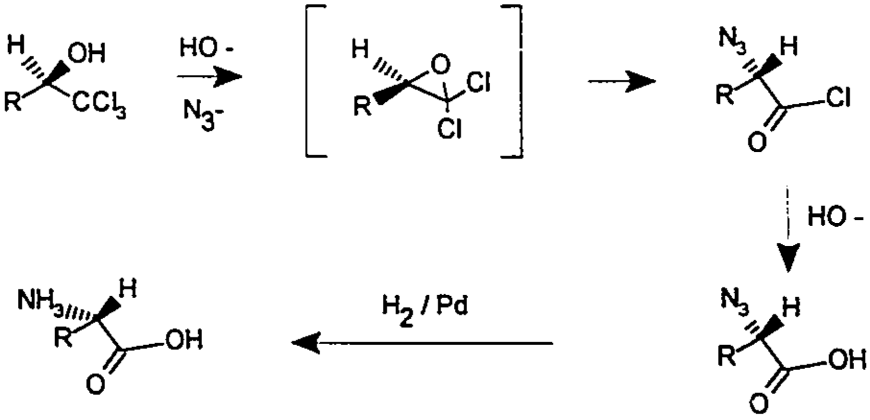
A methodology developed by Corey and researchers at Harvard has the advantage of being a general catalytic and enantioselective synthesis of α-amino acids involving an asymmetric reduction of trichloromethyl ketones with an S-oxazaborolidine catalyst to the corresponding R-trichloromethylcarbinols[7].

Figure 5: Enantioselective Reduction of Trichloromethyl Ketones



These R-trichloromethyl carbinols are converted to the S-azido acids and upon catalytic hydrogenation furnish the S-amino acids.

Figure 6: Conversion of R-Trichloromethyl Carbinols to S-α-Amino Acids



The forementioned synthetic routes, as well as several others, all provide access to the highly desireable optically pure α-amino acids. The major downfall of many of these routes however, is that they require fairly sensitive and complex reaction conditions such as enolate generation at low temperatures. These limitations may proclude the use of these methodologies on an industrial scale.

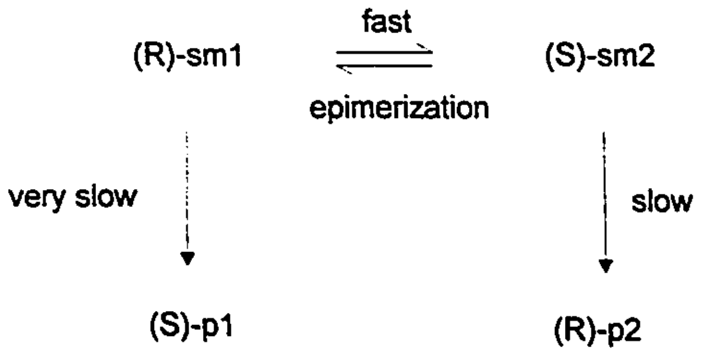
This thesis will focus on a methodology for producing α-amino esters , based on dynamic kinetic resolution, which combines high levels of chiral induction with relatively simple reaction conditions. Essentially optically pure materials can be produced under mildly basic conditions in THF at 0-25° C.

1.2 Dynamic Kinetic Resolution

Dynamic kinetic resolution (DKR), relies heavily on the Curtin Hammet principle and, by definition, involves two epimeric starting materials which are interconvertable under the reaction conditions. If one epimer reacts faster with a particular substrate than the other, optically enriched products are obtained. Its advantages over simple kinetic resolution are obvious, since kinetic resolution offers at most 50% chemical yield. In the

DKR process, internal recycling of the unreactive to reactive diastereomer allows quantitative conversion to product and the theoretical yield jumps to 100%. This process is depicted in **Figure 7** in which (S)-sm2 reacts faster than (R)-sm1 resulting in the preferential production of (R)-p2 over (S)-p1 (assuming inversion of stereochemistry upon reaction).

Figure 7: Dynamic Kinetic Resolution



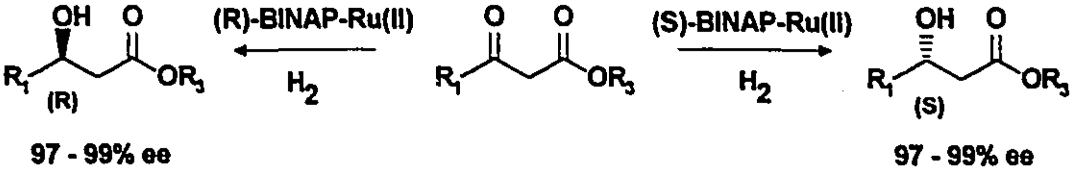
Examples of DKR in the literature are relatively sparse,[8] however the potential of this technique as a viable alternative is gradually being discovered and explored.

A large amount of work involving DKR has been done by Noyori. The focus of his research involves the transition metal catalysed hydrogenation of α-substituted and unsubstituted β-keto esters.[10] These chiral substrates undergo facile racemization through the enol form and are converted to a variety of synthetically useful β-hydroxy esters. This transformation can be affected, with high levels of stereochemical control, by a variety of microorganisms and enzymes including Bakers yeast,[11] and Oxidoreductase from *Geotrichum candidum.*[12]

Noyori's group has provided operational simplicity to this process by using homogeneous hydrogenation catalyzed by chiral BINAP-Ru(II) complexes (BINAP = 2,2'-bis(diarylphosphino)-1,1'-binaphthyl).[13]

This process is quite general for prochiral unsubstituted β-keto esters and provides the corresponding β-hydroxy esters with excellent levels of chiral induction (> 98% ee). The reaction probably proceeds through the Ru-monohydride produced by the reaction of the Ru(II) complex and hydrogen. The absolute stereochemistry of the products is easily predictable in that the (R)-BINAP-Ru(II) complex induces the (R) configuration in the β-hydroxy esters, whereas the (S)-catalyst induces the (S) stereochemisty in the products. The overall process is shown in **Figure 8**.

Figure 8: Noyori's BINAP-Ru(II) Catalyzed Asymmetric Reduction of β-Keto Esters

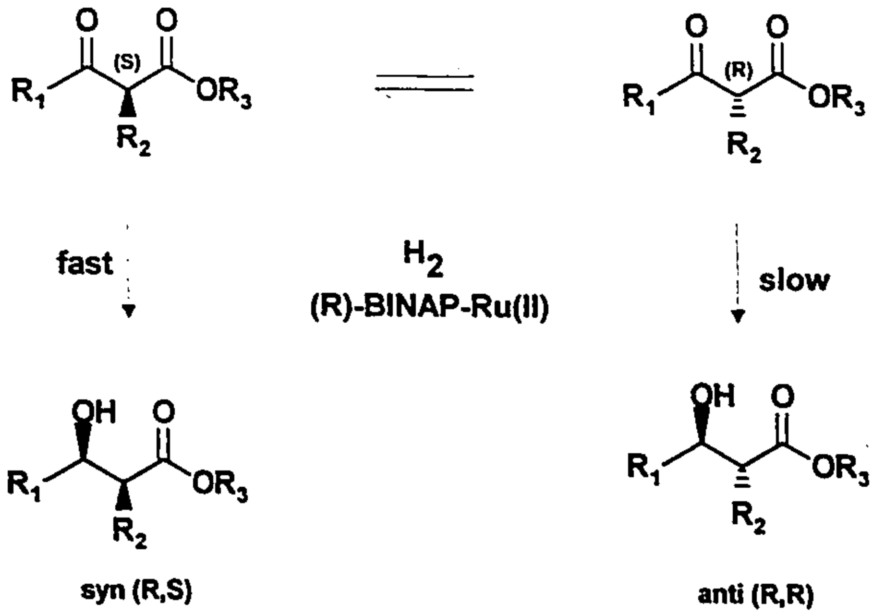


This asymmetric hydrogenation can also be carried out on labile α-substituted β-keto esters. The stereochemistry obtained at the β-position is still determined by the particular enantiomer of the BINAP-Ru(II) catalyst used. The second stereogenic center at the α-postion produces syn and anti diastereomers in these reactions. If one were to start with a racemic mixture of α-substituted-β-keto ester, a 1:1 mixture of syn/anti diastereomers might be expected, however, since these compounds are easily epimerizable and one enantiomer undergoes reduction significantly faster than the other, the syn/anti ratio can also be controlled in these reactions. The DKR control of the syn/anti diastereomer ratio is dependent on a number of factors including solvent, and nature of the α-substituent. An excellent review has recently been published by Noyori which addresses the factors controlling the diastereomeric ratios.[14]

The key aspect, however, is to notice that DKR is taking place in these reactions as is demonstrated in **Figure 9**.

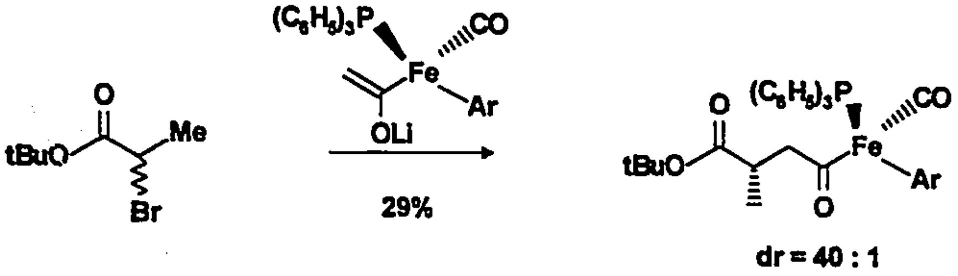
Figure 9:

DKR in BINAP-Ru(II) Catalyzed Reduction of 2-Substituted β-Keto Esters



Several more recent examples of DKR, many of which involve highly labile esters with electron withdrawing β-substituents, have demonstrated the synthetic value of this process. For example, Dr. S. G. Davies of Oxford University, has reported the DKR of α-halo esters by utilizing a chiral iron species as a nucleophile, **Figure 10** .Similar to our observations, Davies observes increased selectivity when an external bromide source is utilized to induce epimerization.[15]

Figure 10: S.G. Davies DKR of α-Halo Esters



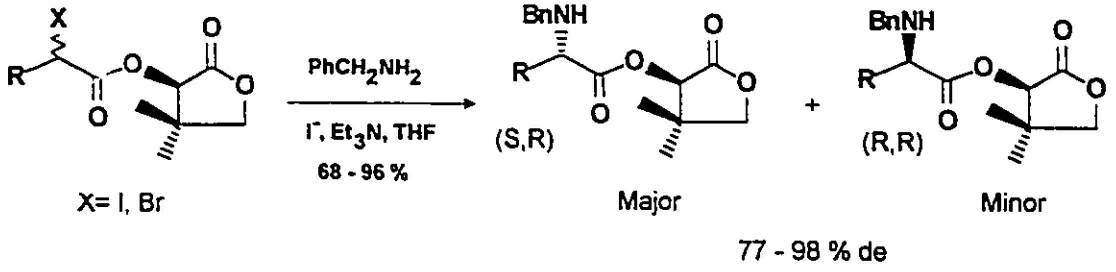
1.3 Background

The concept of controlling the stereochemistry at the α–position of a carboxylic acid derivative by utilizing a chiral auxiliary is certainly not a new one. This methodology has enjoyed much success, particularily in enolate chemistry. To a large extent, this success has been attributed to structural rigidity in the metal coordinated transition state complex. This structural rigidity provides facial biases during electrophillic quench thus permitting product formation with high levels of chiral induction.

In late 1992 K. Koh discovered that if racemic α-halo (R)-pantolactone esters were treated with benzylamine, the corresponding displacement products were obtained in a diastereomerically enriched form, in which the (S,R) product predominated. When optically enriched starting materials were used in which the (S,R)-α-bromo (R)-pantolactone ester predominated, the major displacement product obtained still posessed the (S,R) absolute stereochemistry. This result was intriguing in that, the typical inversion of stereochemistry which is inherent with an S_N2 process was obviously disrupted. A study was undertaken to understand this deviation from the simple inversion expected from this S_N2 process.

Optimization studies by K. Koh and R.N. Ben revealed that if the reaction were carried out in basic THF, in the presence of a catalytic amount of iodide ion, higher, and truly synthetically useful levels of diastereoselectivity were obtained. The displacement products were obtained as 7:1 to >25:1 ratios of diastereomers as demonstrated in **Figure 11.**

Figure 11: Diastereoselective Amination of α-Halo Esters



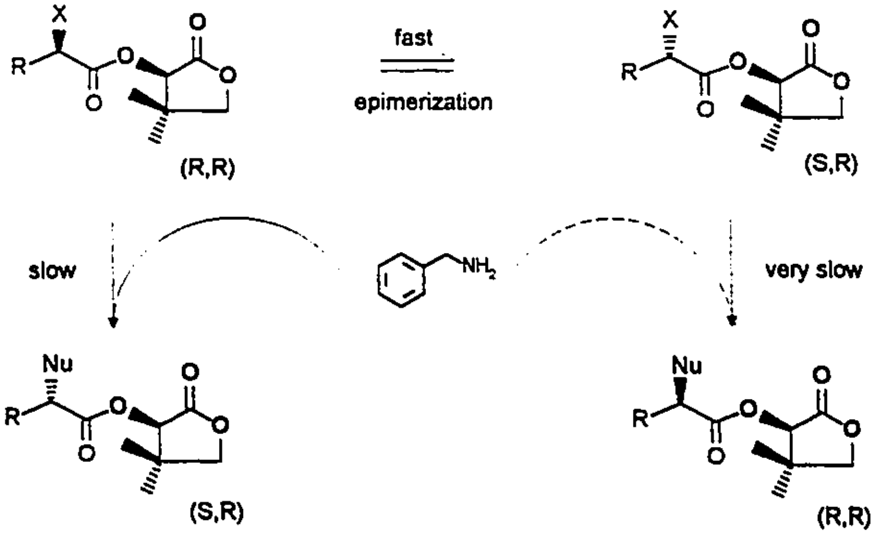
R = alkyl, aryl

Further studies revealed that the α-amino substituted products are configurationally stable under these reaction conditions. This eliminated the possibility that a simple, thermodynamically controlled, diastereoselective reprotonation of the ester's enol was responsible for the DKR selectiviity.

The observed optical activity in the displacement products could therefore only be rationalized if a version of Noyori's dynamic kinetic resolution was taking place. The proposed explanation requires that one diastereomer of the starting material react significantly faster than other. The major product obtained from this process was proven to posess the (S,R) absolute stereochemistry, it could therefore be reasoned the (R,R)-α-halo diastereomer undergoes displacement significantly faster than the (S,R)-α-halo isomer. The epimerization at the halogenated center, it was rationalized, was facilitated by the addition of catalytic amounts iodide ion. This epimerization serves to replenish the faster reacting diastereomer, at the expense of the slower reacting isomer. The equilibrium is forced in one direction, one product is formed in preference to the other and diastereomerically enriched displacement products are isolated.

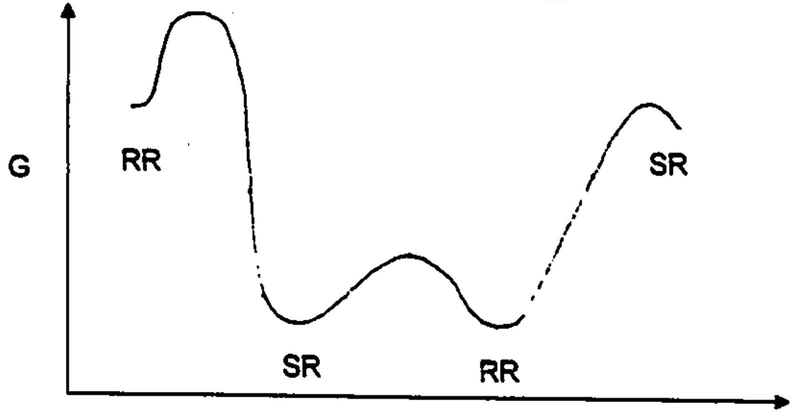
The process is depicted in **Figure 12.**

Figure 12: Dynamic Kinetic Resolution of α-Halo (R)-Pantolactone Esters



This can be represented by a free energy diagram in which the activation energy of the (S,R) α-halo compound is greater than that for the (R,R) isomer. The Curtin-Hammett Postulate requires that the conformation leading to the transition state of lowest energy be the reactive conformation. Since the (R,R) α-halo ester reacts quicker than the (S,R) diastereomer, inversion upon displacement by benzylamine leads to enhanced (S,R) α-amino ester formation. Since the two starting diastereomers are approximately of equal energy the diastereomer ratio provides an estimation of the energy difference between the two transition states as approximately 0.8-1.3 kcal/mole (based on 7:1-10:1 diastereomer ratio observed at room temperature).

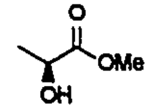
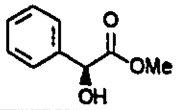
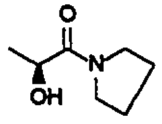
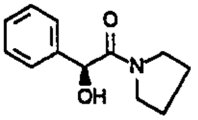
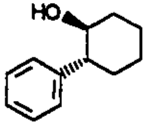
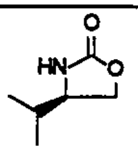
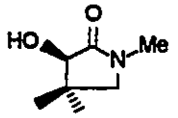
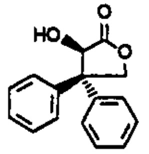
Figure 13: Energy diagram for the displacement reaction



This work was published as a new simple synthetic route to optically active α-amino esters.[16]

A comparison of several optically active α-hydroxy esters, amides and alcohols revealed that (R)-pantolactone is a superior chiral auxiliary for the DKR process. (R)-pantolactone gave displacement products with 75-92 % de whereas (S)-methyl lactate, (R)-methyl mandelate and (R,R)-trans-2-phenylcyclohexanol and several others resulted in severely diminished levels of diastereoselectivity (see **Table 1**). (R)-pantolactone, it was postulated, must provide unique interactions which increase the activation energy requirements of the slow reacting diastereomer relative to its faster reacting epimer, thus providing the basis for effective DKR.

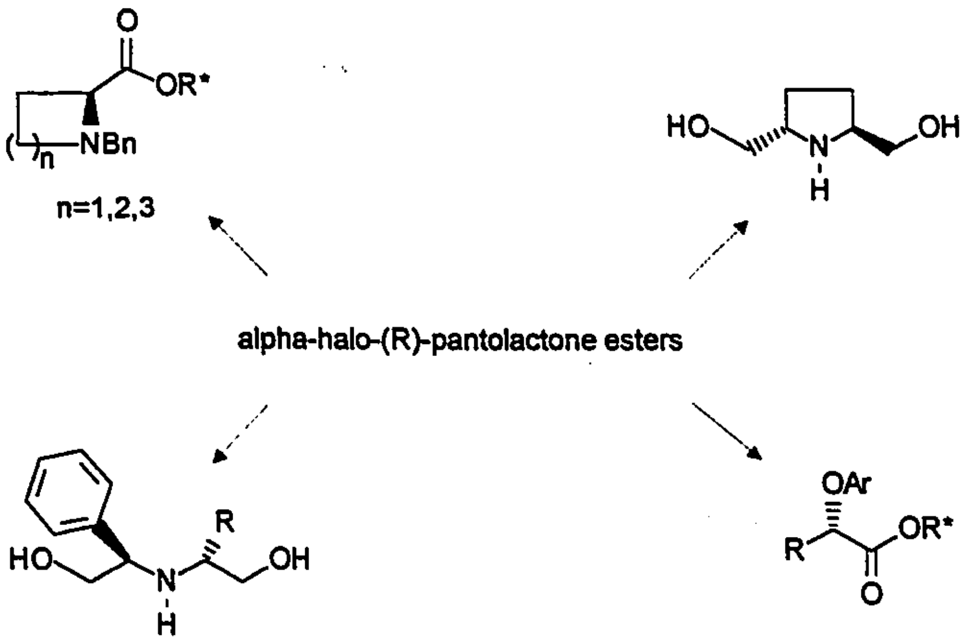
Table 1 : Other Chiral Auxiliaries in the DKR Process

AUXILIARY	RATIO (SR : RR)*	YIELD	AUXILIARY	RATIO (SR : RR)*	YIELD
	2 : 1	76		2 :1	60
	4 : 1	82		4 : 1	82
	2 : 1	92		5 : 1	85
	9 : 1	64		3 : 1	93

*- Absolute configuration of major product in some cases has not been verified

Research has shown that this process is versatile and provides access to a wide variety of α–amino esters. A number of proteinogenic and non-proteinogenic α-amino acids have been prepared including, a variety of N-substituted (S,R)-proline and pipecolinic acid derivatives, optically active C_2-symmetric 2,5-disubstituted pyrollidine derivatives and β,β–dihydroxy amines.[17] α-Hydroxy precursors are also available with approximately the same levels of diastereoselectivity by using sodium phenolates as the nucleophile.[18] The more reactive potassium phenolates provided significantly less diastereoselectivity, whereas the lithium phenolates failed to react. This demonstrates that there is a narrow margin of nucleophilicity in which DKR is effective and that the rate of epimerization of the starting material must be faster than the rate of displacement. While the rate of displacement for very reactive nucleophiles (like metallorganics, enolates or Grignard reagents) may be fast enough to proclude their use in DKR, the use of stabilized carbanions such as malonic esters or malononitrile as the nucleophile provides a diastereoselective carbon-carbon forming methodology.[19]

Figure 14: Compounds Available from the DKR process



1.3.1 Explanation Behind the Observed DKR Selectivity

The Curtin-Hammett Principle requires that reactants capable of existing in several conformations undergo transformation predominantly through a single conformation which gives rise to the lowest energy transition state.[20] In other words, the molecular conformation in the transition state will be the reactive conformation and all other orientations of a particular molecule can be ignored. This principle applies as long as the barrier to conformational alteration is significantly lower than the transition state energy. Cases in which products result from two or more different conformations, the energy difference between the transition states of each conformer is not large and is relected in the product distribution.

In order to understand and explain the differences in reactivity of the individual diastereomeric α-halo (R)pantolactone esters, several structural characteristics of the transition state must be known. Molecular modelling, X-ray crystallography and literature precedent have combined to lead to the following rationalization for the observed diastereoselectivity.

1. The ester functionality exists in its cisoid conformation. This is a reasonable suggestion since Houk has shown that the cisoid conformation of esters is ~7 Kcal/mole more stable than its transoid rotamer.[21]

2. The ester and pantolactone carbonyls lie perpendicular to each other as evidenced by molecular modelling and X-ray analysis of the displacement products.

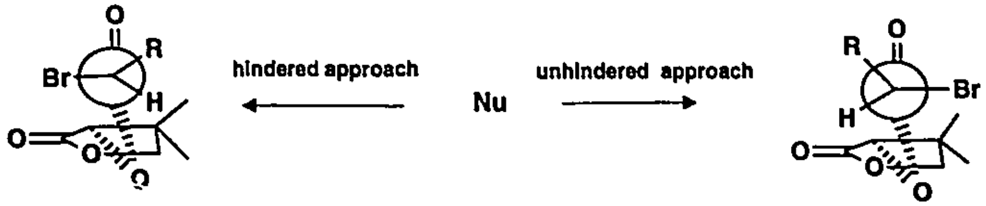
3. The α-halogen is perpendicular to the ester carbonyl oxygen. This is predicted on the basis of work done by many researchers including Streitweiser, which demonstrates that halogens which lie perpendicular and adjacent to an sp2 hybridized center undergo

displacement much quicker than in any other orientation.[22] The explanation resides in what is termed "neighbouring orbital overlap effect", and involves a non-bonding interaction between the incoming nucleophile and the p-orbital of the carbonyl carbon. This HOMO-LUMO interaction is maximized when the halogen and sp2 center lie perpendicular to one another. The result is maximum stabilization of the transition state and higer reactivity.

4. Lastly, the R group (side chain residue) should prefer to eclipse the ester carbonyl oxygen in the transition state, rather than eclipse the alkoxy oxygen of the chiral auxiliary. This is based on steric effects which have been studied by Allinger,[23] and once again lead to an energy minimized transition state.

R. Ben combined all of the above structural constraints and considered two possible transition states, one for each diastereomer. The electrophillic site in the slow reacting diastereomer is sterically shielded to attack by the gem dimethyl functionality. The fast reacting isomer not only has no such steric shielding, but also may allow hydrogen bond facilitated delivery of the nucleophile. The situation is depicted below in **Figure 15.**

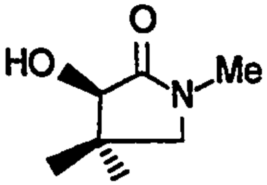
Figure 15: Two Possible Transition States For Racemic α-Halo (R)-Pantolactone Esters



The situation depicted above is extremely sensitive and tolerates no significant structural modifications. For example, removing the gem dimethyl functionality in (R)-pantolactone or replacing it with a gem diphenyl analog severely detracts from the selectivity observed in the DKR process.

Evidence for the possible hydrogen bond augmented delivery of the nucleophile is observed when one utilizes the lactam equivalent of (R)-pantolactone (**Figure 16**). This auxiliary is a superior hydrogen bond acceptor and leads to slightly higher levels of diastereoselectivity in the DKR process (see **Table 1**).

Figure 16: Lactam Equivalent of (R)-Pantolactone

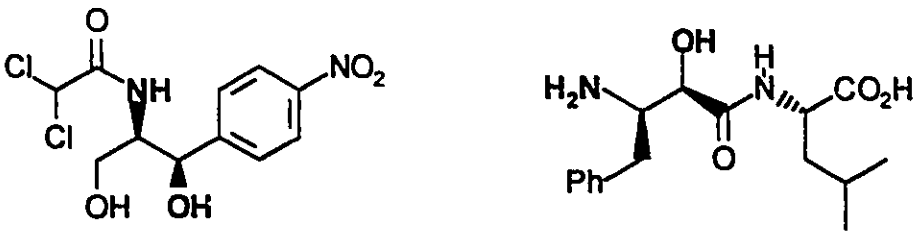


2.0 Diastereoselective Synthesis of Reetz Aldehydes Using Dynamic Kinetic Resolution

2.1 Introduction

β-Amino alcohols are versatile synthetic intermediates. Compounds containing this functionality typically exhibit high physiological activity and have been identified as antibiotics (chlorampheniciel),[24] renin inhibitors (pepstatin), aminopetidase-B inhibitors (bestatin), alkaloids as well as numerous other bio-active compounds[25] (**Figure 17**).

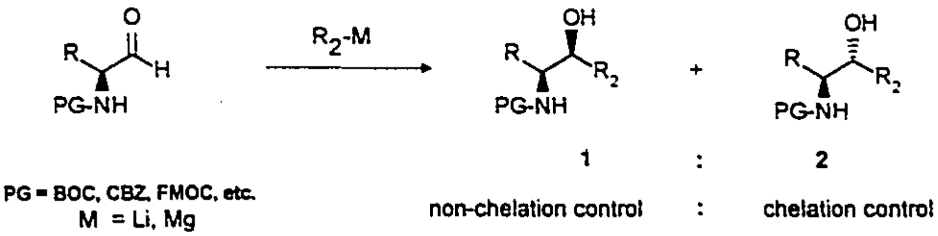
Figure 17: Biologically Active β-amino alchols



chloramphenicol **bestatin**

The physiological activity of this class of compound, has led to the developement of several methods for their preparation. The obvious route, via α-aminoaldehydes, suffers from several key drawbacks which have limitted its success. The problem lies in the fact that Grignard reagents and lithium enolates usually add to α-amino aldehydes bearing BOC or CBz protecting groups in an unselective fashion yielding 1:1 or 2:1 mixtures of diastereomers.[26] Exceptions to this poor selectivity are known, however success is very rare. A further complication is the fact that many N-protected α-amino aldehydes undergo facile racemization under weakly acidic or basic conditions and therefore, need to be handled very carefully.[27] The FMOC protecting group confers configurational stability to α-amino aldehydes, but Grignard and aldol additions result in poor selectivity, providing 2:1 mixtures of diastereomers favoring the chelation controlled adduct.[28]

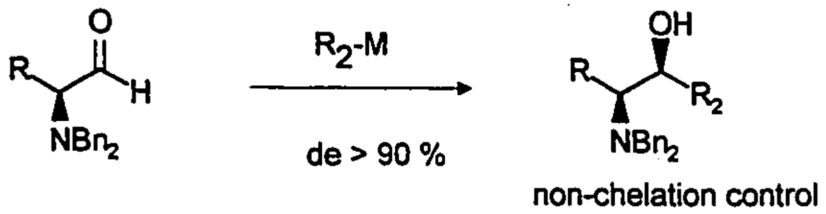
Figure 18: Poor Selectivity on Nucleophillic Addition to α-Amino Aldehydes



The demand for optically pure pharmaceuticals has led to several attempts to solve these obviously severe problems. Most notably, Reetz has reported that N,N-dibenzyl protected α-amino aldehydes not only preserve the stereochemical integrity of the starting amino acid but also impart high levels of diastereoselectivity upon addition of nucleophiles to the electrophillic carbonyl.[29] These compounds have been extensively studied and have become known as Reetz aldehydes.

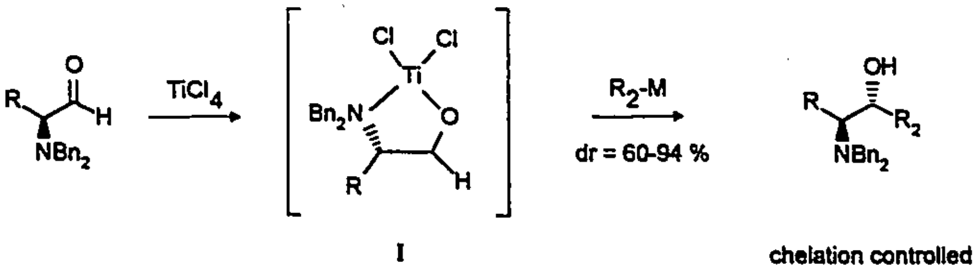
Tuning of the reaction conditions, involving transmetallation (titanation) of the nucleophillic species has led to impressive levels of selectivity in the synthesis of the desired β-amino alcohols. The major diastereomer obtained from these reactions is the "non-chelation controlled" or anti adduct predicted by the Felkin-Ahn model.[30]

Figure 19: Non Chelation Controlled addition to Reetz Aldehydes



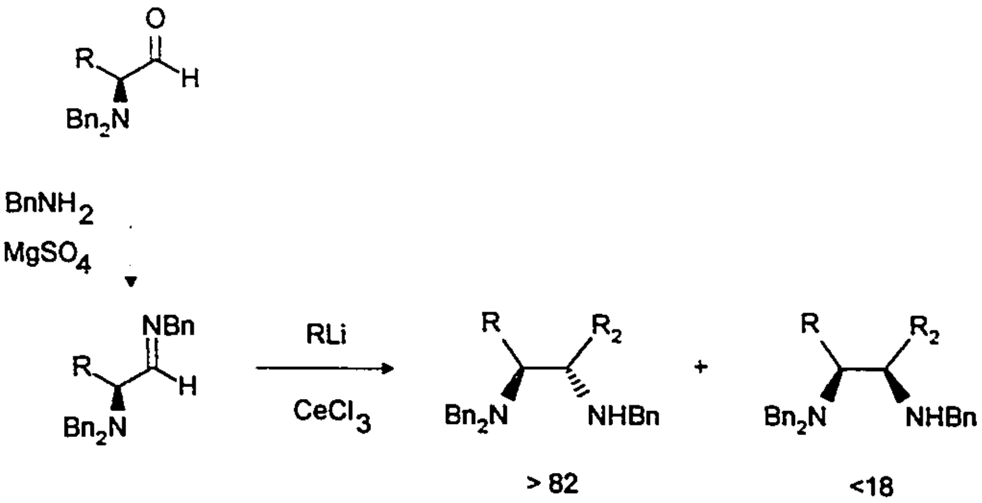
The observed Felkin-Ahn selectivity can be reversed under Lewis acidic ($TiCl_4$) conditions so that the chelation controlled products are obtained.[31] The selectivity in this case is somewhat lower due to, what Reetz has called, steric inhibition of chelation. As a result of relatively weak N-Ti bonding and steric interactions between the chlorine ligands, benzyl groups and other residues on the five membered ring, complex **I** (**Figure 20**) opens rather easily. Consequently the coordinated complex, which provides a cyclic transition state, may not be the reactive conformation. It probably opens to relieve the steric strain to provide an acyclic transition state. Typically acyclic transtion states provide much less stereochemical control over the product distribution.

Figure 20: Lewis Acid Catalyzed Chelation Controlled Addition To Reetz Aldehydes



α-N,N-Dibenzyamino ketones have also been prepared and have demonstrated the same diastereomeric control trends discussed for the aldehyde.[32] The Reetz aldehydes (and ketones) have been converted to their corresponding α-amino aldimines (and ketimines). Organocerium reagents are capable of adding to these compounds and they do so with moderate levels of chelation control (**Figure 21**).[33] The vicinal diamines prepared by this approach are encountered as ligands in metal induced stereoselective reactions, in various chemotherapeutic agents (cis-platin analogues), as well as in a variety of natural products.

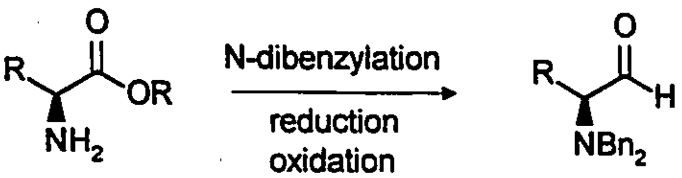
Figure 21. Vicinal Diamines Prepared From Reetz Aldehydes



2.2 Proposed Synthesis

Reetz aldehydes are obviously interesting and versatile synthetic intermediates. The standard methodology for preparing these compounds involves simple protection of commercial α-amino acids followed by reduction, either directly to the aldehyde or completely to the alcohol (**Figure 22**). The alcohol can be subsequently oxidized to the corresponding aldehyde. While it is true that these compounds are easily prepared from commercially available amino acids, a problem arises when non-proteinogenic amino acids are required. Ineffecient and often lengthy procedures are required to acquire the desired compound.

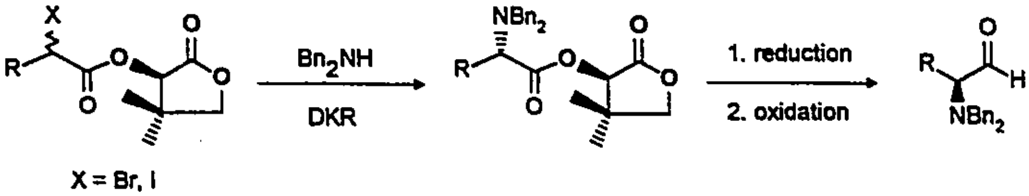
Figure 22: Standard Methodolgy for the Preparation of Reetz Aldehydes



During the course of the investigation of the DKR process, it became obvious that steric factors were very important contributors to the diastereoselectivity. Thus, when the nucleophile was changed to the sterically more demanding dibenzylamine, appreciably enhanced selectivity favoring the (S,R) diastereomer was observed. We therefore postulated that an efficient, diastereoselective, general synthesis of Reetz aldehydes could be accomplished using DKR.

The proposed route based on DKR is shown in **Figure 23** and involves the synthesis of the α-halo (R)-pantolactone esters, nucleophillic addition of dibenzylamine under DKR conditions, followed by reduction of the pantolactone ester and subsequent oxidation. This protocol, it was predicted, would provide the corresponding Reetz aldehydes with both high yield and high levels of chiral induction.

Figure 23.: Proposed DKR Route to Reetz Aldehydes



2.3 Results

In order to test this hypothesis, a number of α-halo acids were either purchased or prepared via the procedure of Harpp.[34] That is, the commercially available carboxylic acids were refluxed in thionyl choride containing NBS until the reaction was judged complete by ^1H NMR. Hydrolysis of the resulting acid chlorides and subsequent purification provided the α-halo acids in good overall yield. These compounds were coupled to the (R)-pantolactone auxiliary by utilizing the DCC peptide coupling methodology.[35] A solution of (R)-pantolactone was added to a CH_2Cl_2 solution containing the α-halo acid, DCC and a catalytic amount of DMAP. The resulting mixture was stirred overnight, filtered and submitted to extractive workup. The crude product was then purified by silica gel chromatography. The resulting α-halo (R)-pantolactone esters were isolated as approximately 1:1 mixtures of diastereomers in good to excellent chemical yield. The diastereomer ratio for these compounds is easily determined by accurate electronic integration of the singlets arising from the (R)-pantolactone methine proton at 5.2 - 5.4 ppm in the ^1H NMR spectrum.

Scheme 1: Preparation of the α-Halo (R)-pantolactone Esters

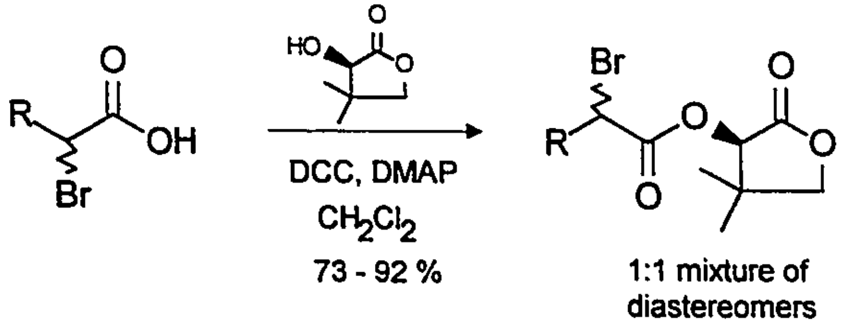


Table 2: Preparation of Racemic α-Halo (R)-Pantolactone Esters

R	Et	Ph	p-Br-Ph	c-hex-$(CH_2)_2$	Ph$(CH_2)_2$
YIELD (%)	86	91	89	78	80

Nucleophillic attack by dibenzylamine on the appropriate α-halo (R)-pantolactone ester under the optimized DKR conditions, provided the desired products in good yield and with good to excellent selectivity (**Table 3**). Optimized DKR conditions imply a 0.1 M solution of the α-halo (R)-pantolactone ester in THF. 1.1 equivalents of the nucleophile, 0.2 equivalents of $nBu_4N^+I^-$ and 2.0 equivalents of Et_3N are added and the resulting mixture is stirred at room temperature for 24 - 72 hours. Aqueous work-up, extraction and silica gel chromatography of the crude product provided the desired displacement products. The diastereomer ratio was once again determined by ^{1}H NMR analysis of the (R)-pantolactone methine signal at ~ 5.22 ppm. In each case, baseline separation existed between the individual singlets corresponding to each diastereomer and accurate integration of each singlet displayed (S,R):(R,R) ratios of 11:1 - 99:1. This is illustrated in **Figure 24**:

Scheme 2: DKR Using Dibenzylamine as the Nucleophile

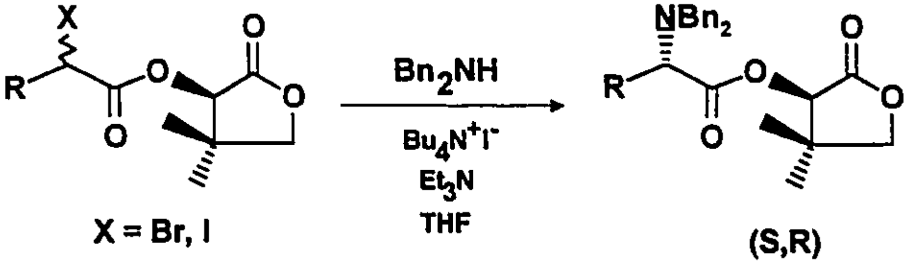
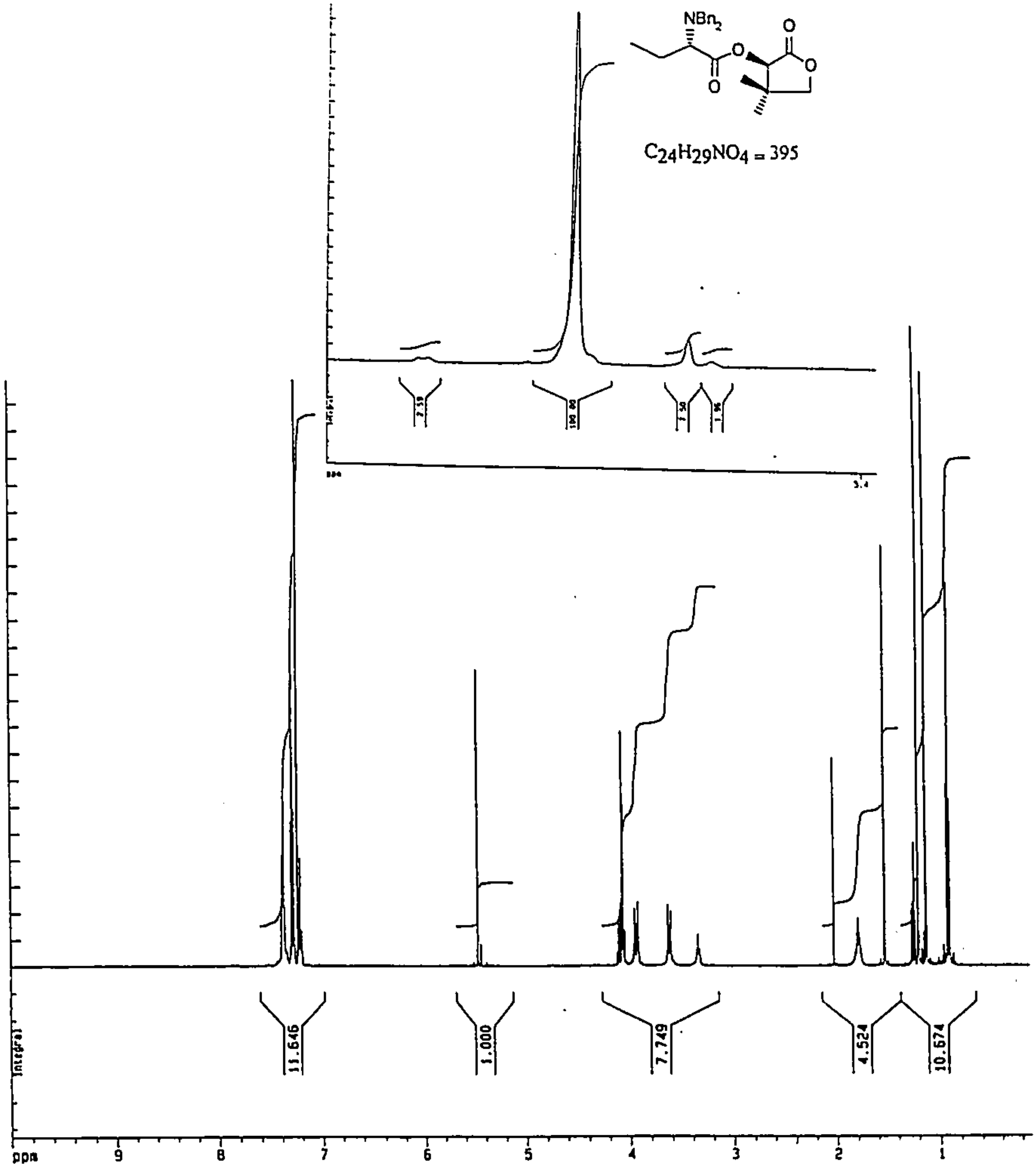


Table 3: Preparation of α-dibenzylamino-(R)-pantolactone Esters via DKR

R	yield	ratio (S,R):(R,R)	de
Et	66	93:7	86
Ph	82	94:6	88
$PhCH_2CH_2$	56	91:9	82
cyclohexyl-CH_2CH_2	64	94:6	88
p-Br-Ph	76	99:1	98

Figure 24: NMR Determination of Diastereomer Ratios of DKR Displacement Products

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-butanoate



The major byproduct (10 -20 %) observed in these reactions corresponded to the α,β unsaturated elimination product (see **Figure 25**). For example, when (±)-(R)-pantolactone 2-bromo butanoate was used as the substrate, 12 % yield of what appeared to be a mixture of 1:1 cis:trans (R)-pantolactone 2-butenoate was isolated. Higher yields of the displacement product are therefore obtained for substrates in which this elimination is not possible. A small amount (5 -10 %) of acyl transfer product, in which the nucleophile displaces the chiral auxiliary, is also observed in some cases.

Figure 25: Observed Byproducts in the DKR Process

elimination

acyl transfer

The seemingly anomalous result in which the p-bromophenyl derivative provided essentially only one diastereomer can be rationalized if the reaction takes place under non-Curtin Hammett conditions. That is, in the unsubstituted phenyl derivative, displacement of the fast reacting diastereomer occurs at a rate which is superior to the rate of epimerization. When the fast reacting diastereomer has completely reacted, only the slow reacting diastereomer remains in solution and epimerization becomes the rate limitting step. The high concentration of slow reacting diastereomer must undergo a small amount of displacement while waiting to be epimerized. In the p-bromophenyl derivative this situation is avoided, owing to the increased acidity of the α-proton caused by the bromines' electronic influence, which is transmitted through the polarizable pi-electron system. This increased acidity allows base catalyzed epimerization to take place, so that the build up of slow reacting diastereomer is avoided.

Simultaneous removal of the chiral auxiliary and reduction to the β-amino alcohols was accomplished by reduction of the α-dibenzylamino (R)-pantolactone esters with $LiAlH_4$ in THF (**Scheme 3**). Thus the α-dibenzylamino (R)-pantolactone esters were dissolved in THF and cooled to 0°C, 2.0 equivalents of $LiAlH_4$ were added portionwise and the resulting slurry was allowed to warm to room temperature over a six hour period. Analysis of the reaction mixture by TLC demonstrated the replacement of the starting material by two more polar materials. After the reaction was judged complete, excess $LiAlH_4$ was quenched with MeOH and a saturated solution of sodium potassium tartrate, which serves to complex the aluminum and release the desired amino alcohol, was added. The tartrate solution was stirred for 16 hours during which time the white sludge produced in the reaction became solubilized. Extractive workup with CH_2Cl_2, followed by silica gel chromatography provided slightly yellow oils which gave characteristic broad IR absorptions at 3360 cm^{-1}. Under these reduction conditions, the (R)-pantolactone auxiliary was similarily reduced to a very polar triol, however, because of the inexpensive commercial availability of (R)-pantolactone, this was not deemed to be a problem. In the case of the p-bromophenylacetic acid derivative, reduction with $LiAlH_4$ lead to quantitative debromination of the aromatic ring as evidenced by the increased complexity of the aromatic region of ^1H NMR specturm. The desired alcohol could however be attained in 64% yield by reduction with borane dimethylsulfide complex in THF (**Table 4**).

Scheme 3: Reduction of the α-Dibenzylamino (R)-Pantolactone Esters

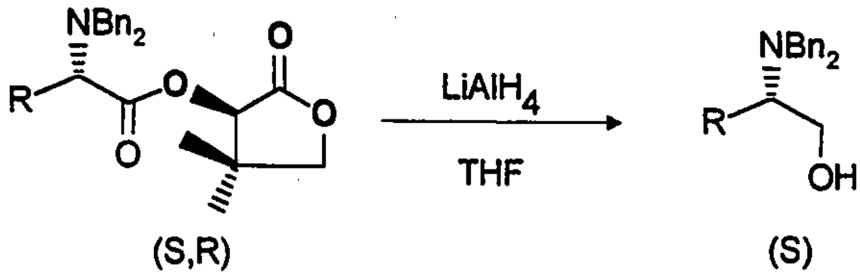


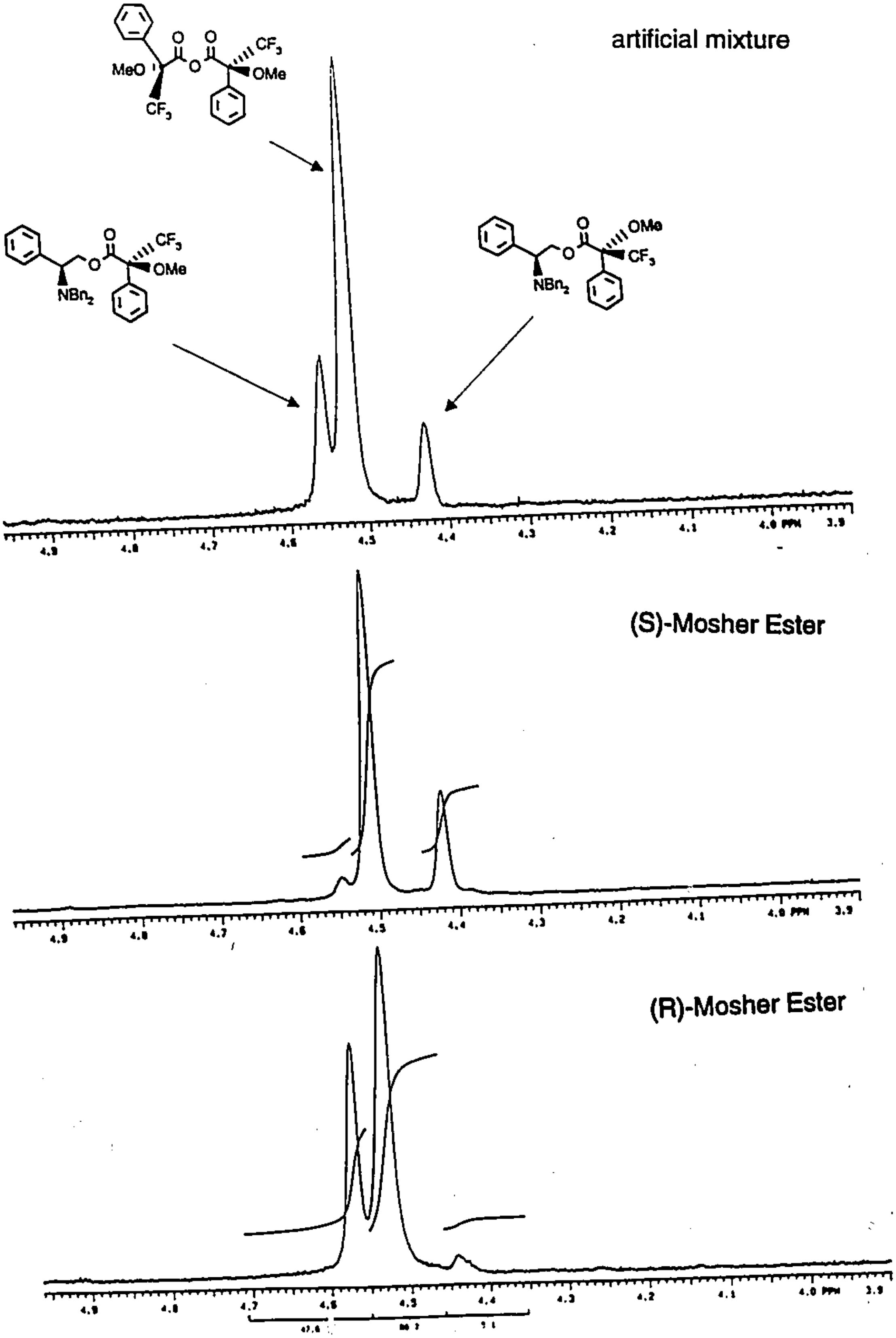
Table 4: Reduction of the Pantolactone Esters

R	Yield	$[a]_D$
Et	76	+42.6
Ph	87	+17.3-
$PhCH_2CH_2$	66	-28.2
cyclohexyl-CH_2CH_2	78	-15.6
p-Br-Ph *	64	+16.2

* - Reducing agent = BMS·THF

The reduction of the esters occured with complete retention of optical integrity. This was predicted owing to the configurational stability of the α-dibenzylamino aldehydes as previously discussed. This aspect of the reaction, however, was proven by preparing both the (S) and (R) Mosher esters of several of the alcoholic products.[36] A chloroform solution containing pyridine and the dibenzylamino alcohol was added, at 0°C, to a solution of the Mosher acid chloride and stirred for 16 hours. Extractive workup, including a $CuSO_4$ wash to remove pyridine, followed by analysis of the crude ^{19}F NMR spectrum revealed diastereomer ratios which were exactly the same as those exhibitted by the α-dibenzylamino (R)-pantolactone esters. The 19F NMR analysis is demonstrated in **Figure 26**.

Figure 26: ^{19}F Analysis of the (S) and (R) Mosher Esters of the β-Amino Alcohols



Attempts to reduce the (R)-pantolactone esters directly to the corresponding aldehydes by using DIBAL-H as the reducing agent, unfortunately, met with no success. No reaction was observed when DIBAL-H was used as the reducing agent and the starting α-dibenzylamino (R)-pantolactone esters were reisolated in quantitative yield.

The oxidation of the dibenzylamino alcohols can be carried out without any racemization via several oxidative procedures. Reports of using Collins reagent,[37] a variety of activated DMSO based oxidations,[38] as well as PDC[39] have all demonstrated the relative ease of oxidizing these β-dibenzylamino alcohols. Because of the massive literature precedent it was deemed unnecessary to carry out the oxidation; these compounds are better stored as the alcohols.

This four step route to Reetz aldehydes has been demonstrated to be efficient and general. Good levels of chiral induction are obtained in all cases and a variety of proteinogenic and nonproteinogenic amino acid residues have been prepared.

This general protocol is superior to many other methodologies for obtaining nonproteinogenic Reetz aldehydes since dibenzylamine is used as the nucleophile, the need for dibenzylation of the amino acid residue is eliminated.

3.0 Improved Chiral Auxiliary to the DKR Process

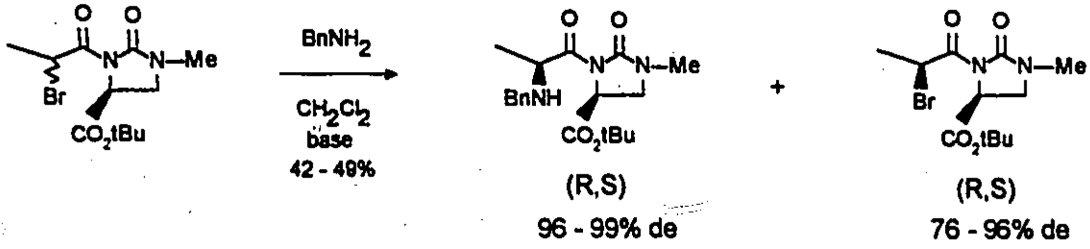
3.1 Introduction

The forementioned DKR process using (R)-pantolactone as the chiral auxiliary has been demonstrated to be quite generally effective. Reasonable levels of diastereoselectivity are obtained with a wide variety of substrates. However, in order to be competitive with the many synthetic methodologies available for creating non-racemic amino acids, the levels of chiral induction had to be increased to >95 % de. Initially, studies involving the effects of solvent, base and nucleophile provided no significant diastereoselectivity increase in the DKR process. Many different chiral auxiliaries had been studied, once again with little or no success.

A report of a remarkably efficient kinetic resolution, utilizing t-butyl-2-oxoimidiazolidine-4-carboxylate as a novel chiral auxiliary irreversibly altered the focus of our investigation into increasing the selectivity of the DKR process.

Kubota, Kubo and Nunami reported that the reaction of tert-butyl (4S)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylate with an equivalent of benzylamine in CH_2Cl_2 proceeded stereospecifically to afford tert-butyl (4S)-1-methyl-3-((2R)-2-benzylaminopropionyl)-2-oxoimidazolidine-4-carboxylate in good yield (**Figure 27**).[40] In this reaction, only one diastereomer of the starting material reacted to provide essentially optically pure displacement product, and the optically enriched, unreative α-bromo derivative was reisolated from the reaction mixture.

Figure 27: Kinetic Resolution of α-Bromo Propionic Acid Derivatives

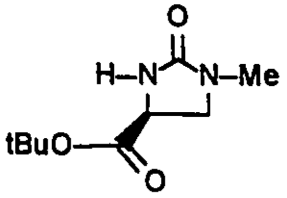


The (R,S) displacement product was isolated with 94 % de and 42 % yield. The unreactive (R,S) α-bromo diastereomer was recovered with 96 % de and 48 % yield. These results are remarkable in that the levels of chiral induction compare to the very best enzymatic kinetic resolutions reported in the literature.[41]

This report demonstrated that the tert-butyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate auxiliary posessed the desired qualities necessary for an improved DKR auxiliary. The prerequisite difference in the reactivities of the two auxiliary modified α-bromo diastereomers seemed to be superior to any previously observed. The total non-reactivity of the less reactive diastereomer with benzylamine encouraged us to explore this imidazolidinone as a potentially effective auxiliary to the DKR process.

3.2 Synthesis and History of the Improved Auxiliary

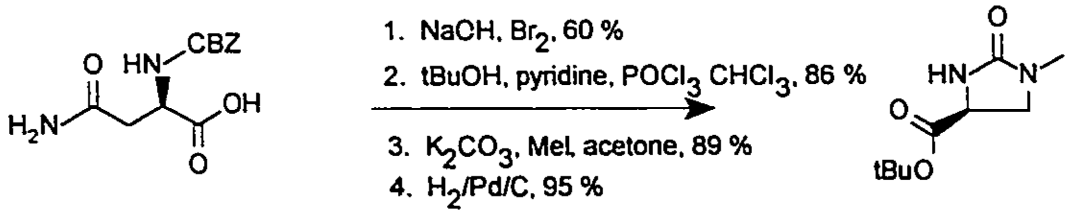
Figure 28: Potential New Auxiliary



tert-butyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate

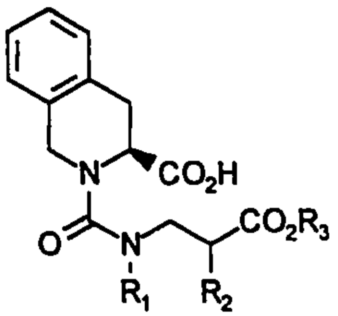
The imidazolidinone was originally synthesized by Kaneko *et al* in 1968.[42] The published synthetic route involves a Hoffman rearrangement of N-CBz-(L)-asparagine[43], which provides the ureido heterocyclic core. The carboxylic acid is converted to its tert-butyl ester by treatment with tBuOH, pyridine and phosphorus oxychloride. The compound is then N-methylated by treatment with methyl iodide in the presence of potassium carbonate. Removal of the CBz protecting group by catalytic hydrogenation using 10% palladium on carbon, furnishes tert-butyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate in 44 % overall yield.

Scheme 4: Synthesis of the Potential New Auxiliary



tert-Butyl-(4S)-1-methyl-2-oxoimidazolidine-4-carboxylate has been previously utilized in a study of potential angiotensin converting enzyme (ACE) inhibitors.[44] During QSAR studies it was observed that N-((carboxyethyl)carbamoyl)-tetrahydroisoquinoline derivatives (**Figure 29**) demonstrated potent ACE inhibition. The ureido carbonyl group was discovered to play an important role as a hydrogen bond acceptor upon interaction with the enzyme.

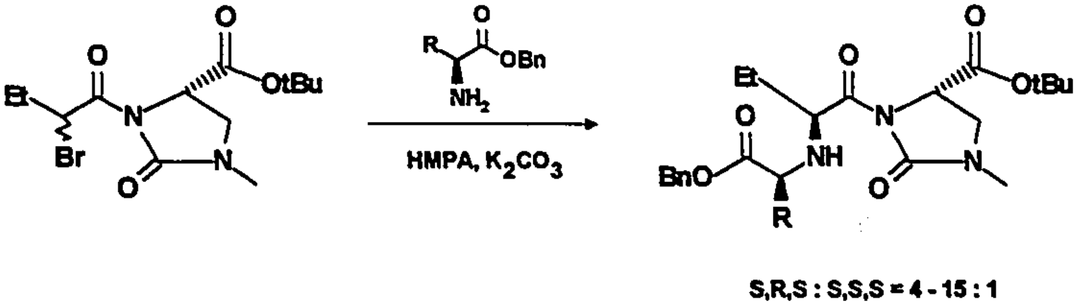
Figure 29: Potent ACE Inhibition by N-((carboxyethyl)carbamoyl) tetrahydro-isoquinoline Derivatives



From the above information, it was postulated that a cyclic imino acid moiety, encorporating a ureido group in the ring would be effective as the C-terminal of ACE inhibitors. The tert-butyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate was anticipated to provide the cyclic imino acid C-terminal.

The diester compounds in **Figure 30** were prepared by condensation of the benzyl esters of several (S)-α-amino acids with racemic α-bromo imidazolidinones in HMPA in the presence of K_2CO_3. The resulting displacement products were obtained as approximately a 4-15 : 1 ratio of diastereomers in favor of the undesired (S,R,S) diastereomer. Since this methodology induced the (R) absolute stereochemistry at the previously halogenated center, and that this was the wrong absolute stereochemisty in the major product, the approach was abandoned.

Figure 30: Preparation of Potential ACE Inhibitors



It is interesting to note that the ~ 4-15 : 1 ratio of displacement products, obtained from racemic α-halo imidazolidinones, was not rationalized. It can be reasoned that this selectivity is a result of DKR utilizing base catalyzed epimerization, in HMPA. It may be possible that this is a mismatched situation and that better selectivity could be obtained by using the corresponding D-amino esters as nucleophiles.

3.3 Observations:

The proposed auxiliary was prepared on relatively large scale (90 g of starting material produced ~20 g of chiral auxiliary) by utilizing the four step sequence described by Kaneko.[42] The spectroscopic and analytical data for the final product and each intermediate corresponded well to the previously reported data. The potassium salt of the imidazolidinone auxiliary was prepared by treating a THF solution of the auxiliary at -50°C with a 0.5M THF solution of potassium tert-butoxide. After stirring the solution for 30 minutes, the metallated auxiliary was coupled efficiently with a variety of α-halo acid chlorides by adding slowly a 0.2M solution of the acid chloride in THF. When the reaction was judged complete by TLC, it was quenched by pouring it carefully onto a 1:1 1% AcOH : Et_2O solution. Isolation of the organic layer, followed by silica gel chromatography, provided the coupled products as essentially racemic mixtures with good to excellent chemical yields.

Scheme 5: Preparation of α-Halo Imidazolidinones

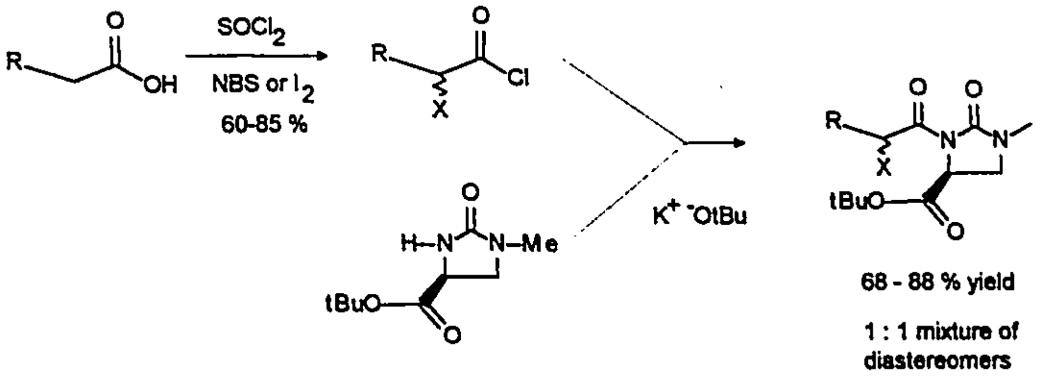
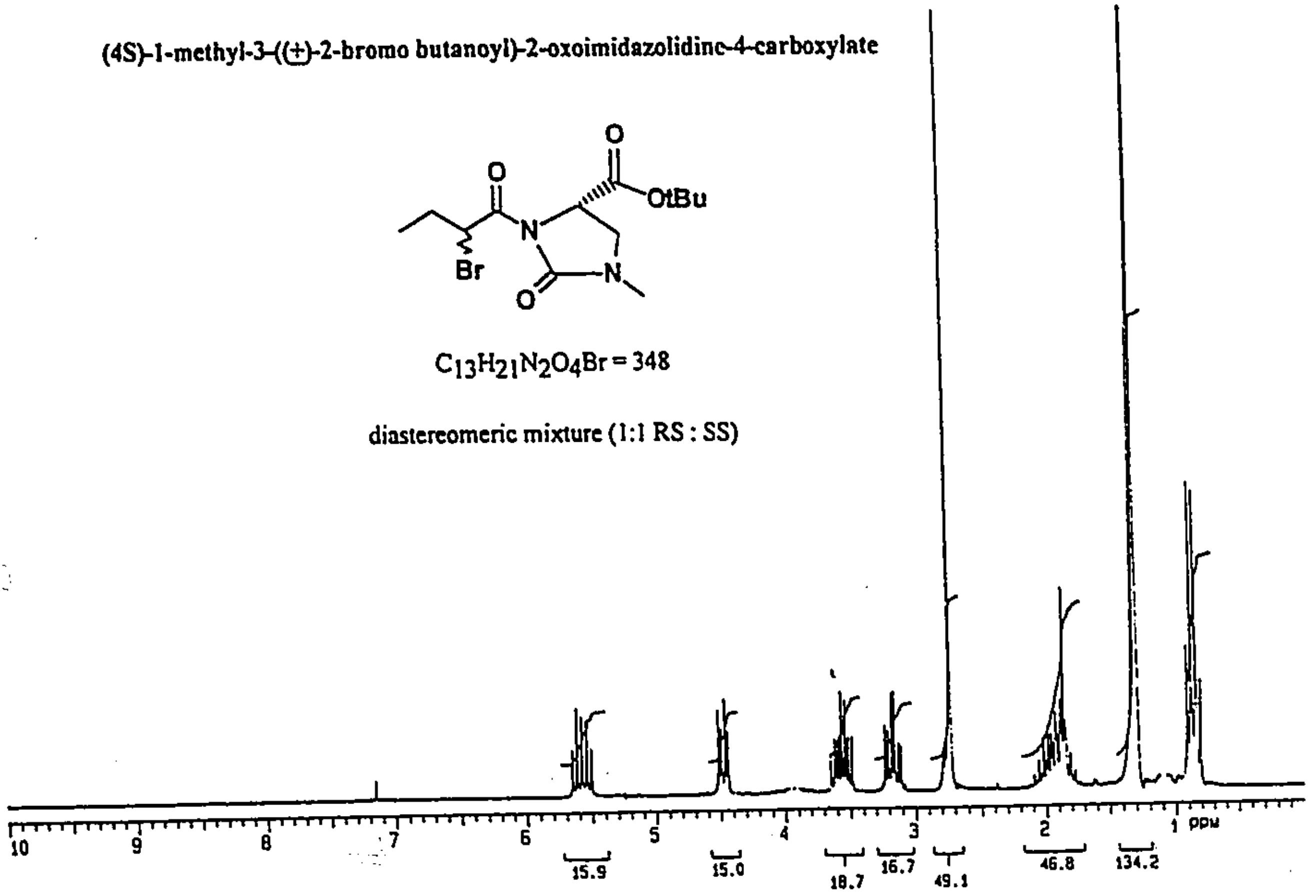


Table 5: Preparation of α-Halo Imidazolidinones

R	X	Yield
Et	Br	88
$Br(CH_2)_4$	Br	73
$Br(CH2)_3$	I	76
$MeO_2C(CH_2)_4$	I	82
$MeO_2C(CH_2)_5$	I	93
$MeO_2C(CH_2)_6$	I	87
Ph	Br	71
$Ph(CH_2)_2$	I	64

The racemic nature of the α-halo imidazoldinones was clearly evident by analysis of the ^{1}H NMR spectrum. A mixture of diastereomers gave rise to spectra which had two distinct triplets at 5.7 - 5.9 ppm, corresponding to the proton at the α-position. Each diastereomer also exhibitted distinct resonances for each of three doublet of doublets at 4.6, 3.6 and 3.2 ppm which arise from the coupling interactions of the imidazolidinone ring protons.

Figure 31: NMR Spectrum of Racemic α-Halo Imidazolidinones

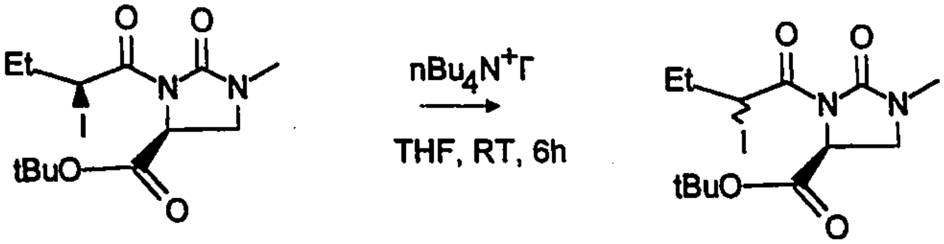


There was a small concern, since potassium tert-butoxide is a relatively strong base, that some degree of racemization at the potentially labile chiral center (α to an ester) of the auxiliary may occur under these coupling reaction conditions. This concern was alleviated by treating the chiral auxiliary with 1.5 equivalents of $K^{+-}OtBu$ in THF at 0°C for 2 hours. It was felt that if no racemization was observed under these harsher conditions, it could be rationalized that no loss of optical purity should occur under the gentler coupling reaction conditions. Indeed, quenching the above reaction with D_2O provided no deuterium incorporation at the 4-position of the imidazoldinone ring as evidenced by an unchanged ^1H NMR spectrum. Had the deuterium been incorporated into the imidazolidinone ring the methine and methylene ring proton resonances, would certainly have had a much different spectroscopic appearance.

It should be noted that the individual diastereomers of the α-halo imidazolidinones not only posess very different reactivity profiles but also have very different polarities as evidenced by the extreme ease with which these isomers are separated by silica gel chromatography. In all cases investigated, the Rf difference between each diastereomer was approximately 0.2 using 33% EtOAc in hexanes as the developing solvent. The only exception to this observation occurred when R=Ph. The individual diastereomers were chromatographically inseparable in this case, however, one diastereomer preferentially crystallizes from a diethyl ether solution. It was subsequently determined, that the chromatographically more polar diastereomer consistently had the (R,S) absolute configuration. The potential of this easy separation of these α-halo imidazolidinones will be discussed in more detail in **Section 9.0**.

In order for the DKR process to be effective, it was necessary to demonstrate that the individual diastereomeric α-halo imidazolidinones were epimerizable under the DKR reaction conditions. Thus, the individual diastereomers of the α-halo imidazolidinone obtained by coupling 2-bromo-butyryl bromide with the potassium salt of the auxiliary, were chromatographically separated. The optical purity of each diastereomer was verified by NMR investigation. In the diastereomeric mixture, each signal in the ^{1}H NMR spectrum appeared doubled, whereas, in the spectrum of the chromatographically separated diastereomers, this doubling of signals was eliminated. The resonance corresponding to the methine on the brominated carbon was demonstrative of this characteristic. The isomerically pure more polar diasteromer gave a triplet at 5.84 ppm whereas the non-polar diastereomer gave a similar triplet at 5.76 ppm. Each isomer was then treated, individually, with 0.2 equivalents of $nBu_4N^+I^-$ in THF at room temperature. NMR investigation, in $CDCl_3$ after six hours revealed the evolution of two distinct triplets at 5.76 and 5.84 ppm in approximately a 1:1 ratio demonstrating that, indeed, epimerization had taken place.

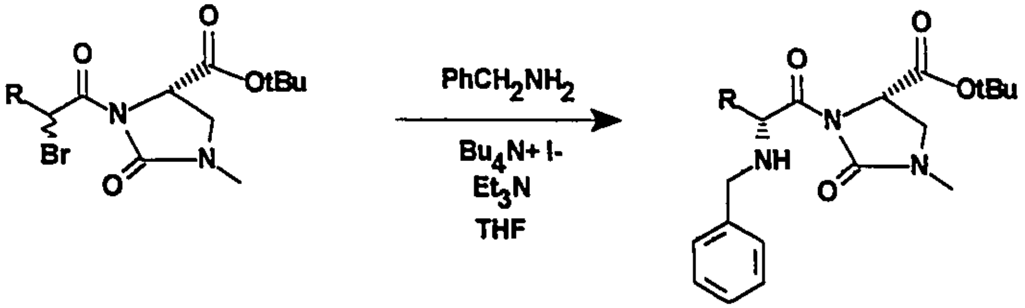
Scheme 6: Epimerization Experiment



The diastereomeric mixtures obtained in the epimerization studies were subsequently treated with benzylamine under the optimized DKR reaction conditions. After 24 hours, the reaction was judged complete by TLC. The two spots at Rf = 0.55 and 0.75 (2:1 hexanes:ethyl acetate) were replaced by a new spot at Rf = 0.48. The reaction mixture was then dilulted with H_2O, the organic compounds were extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo. 200 MHz ^{1}H NMR investigation of this crude reaction mixture revealed the simultaneous disappearance of the two triplets at 5.7 ppm and appearance of a new doublet of doublets at 4.45 ppm.

The crude spectrum posessed a much simpler appearance than that of the racemic starting materials indicating the presence of only one diastereomer. Further anaylsis of the ring proton resonances at 4.6, 3.6 and 3.2 ppm as well as the N-methyl resonance at 2.8 ppm of the observed 500 MHz ^{1}H NMR specrum, in both $CDCl_3$ and d_6-acetone, failed to detect any trace of a second diastereomer. Since the detection limit of a 500 MHz spectrometer is approximately one percent, a lower limit of 99:1 could be placed on the diastereomer ratio obtained in the DKR products.

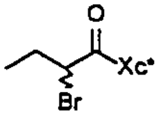
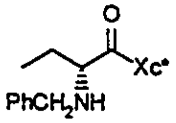
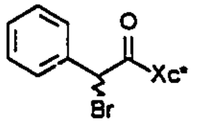
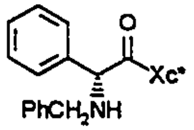
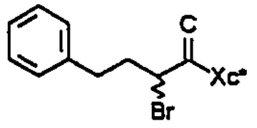
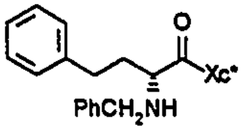
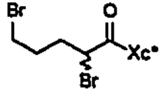
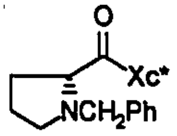
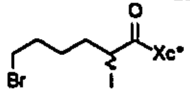
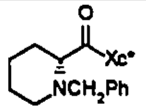
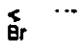
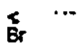
Scheme 7: DKR of α-Bromo Imidazolidinone



The crude reaction mixture was then purified by silica gel chromatography (1:1 hexanes:ethyl acetate) to yield tert-butyl 1-methyl-3-(2-benzylamino-butyryl)-2-oxoimidazolidine-4-carboxylate as the diastereomerically pure displacement product in 92% chemical yield. Broad IR absorptions at 3243 cm^{-1} indicated the presence of a hydrogen bonded amine, and all other spectroscopic and analytical data was consistent with the proposed structure of the displacement product.

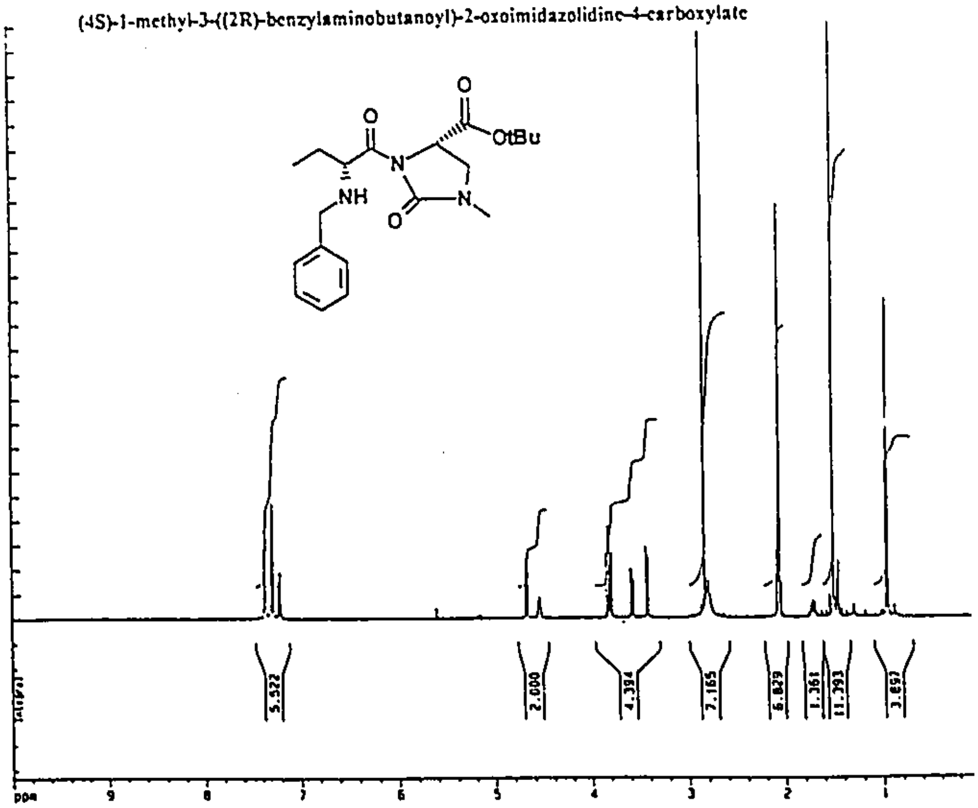
Similar treatment of several other α-halo imidazolidinones provided diastereomerically pure displacement products in excellent chemical yield. The reaction tolerated side chains which were both alkyl and aryl, and once again the cyclic proline and piperidine analogues could be prepared from the 2,5 and 2,6 dihalogenated species respectively. In no case was a second diastereomer evident by 500 MHz ^{1}H NMR investigation of the crude reaction mixture (**Table 6**).

Table 6: DKR of Racemic α-Bromo Imidazolidinones

ENTRY	STARTING (a) MATERIAL	PRODUCT	(b) YIELD (%)	(c) de
1			92 %	>98 %
2			83 %	>98 %
3			88 %	>98 %
4			87 %	>98 %
5			66 %	>98 %
6			0 %	-

a.) Xc* = tert-butyl-(4S)-1-methyl-2-oxoimidazolidine-4-carboxylate b.) yield isolated by silica gel chromatography c.) as determined by 500 MHz ^{1}H NMR

Figure 32: Crude 500 MHz ^{1}H NMR Spectrum of α-Benzylamino Imidazolidinone



It should be noticed that this is an S_N2 process and is therefore quite susceptible to steric effects. For example, the 2-cyclopentyl acetic acid derivative (**Entry 6, Table 6**), when submitted to the optimized DKR conditions, demonstrated no detectable substitution products even after one month. The reaction was heated in refluxing THF for three days and provided some elimination product but no detectable displacement product. This is not surprising because it is well established that S_N2 reactions occur less readily in molecules where the α or β carbons bear alkyl substituents. For example, **Table 7** shows the relative reactivites of various alkyl systems to S_N2 displacement.[45]

Table 7: Average Relative S_N2 Rates of Alkyl Systems

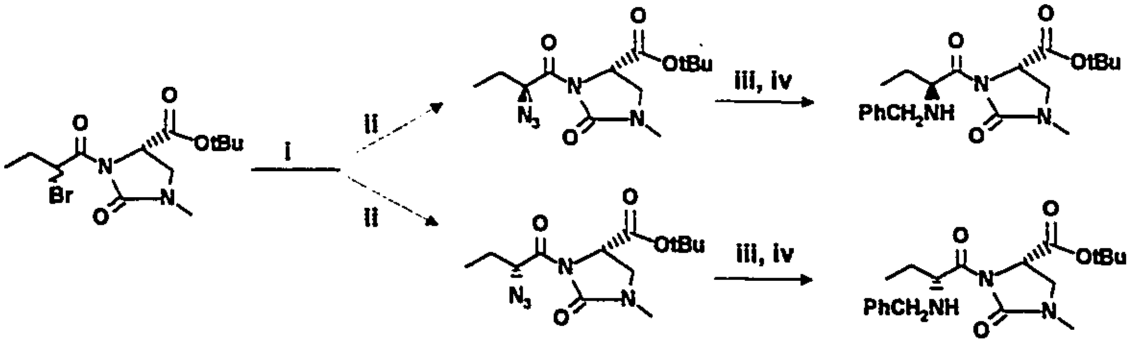
R in R-X	Relative Rate
CH_3	1
CH_3CH_2	3.3×10^{-2}
$CH_3CH_2CH_2$	1.3×10^{-2}
$(CH_3)_2CH$	8.3×10^{-4}
$(CH_3)_3C$	5.5×10^{-5}
$(CH_3)_2CCH_2$	3.3×10^{-7}

The explanation of this decreased reactivity is based on steric effects, in which destabilizing non-bonding interactions occur, in the pentacoordinate transition state, between the substituents and the entering and leaving groups. Interestingly, this substituent effect is more pronounced when the substituents are α to the leaving group than when they are actually directly bonded to the electrophillic halogenated carbon. For example t-butyl bromide reacts 100 times faster than 3-methyl- propyl-bromide. The explanation is that, in the transition state, substituents on the electrophillic halogenated carbon are forced into a planar arrangement which minimizes the destabilizing interactions with the leaving group and nucleophile. When the substituents are on the α-carbon, they are out of the planar arrangement and interact strongly with either the leaving group or nucleophile.

3.4 Verification of NMR Determination of Selectivity

In order to verify that NMR investigation of the crude reaction mixture was a viable means for determining the diastereoselectivity in these DKR reactions, it was deemed necessary to obtain both diastereomers of one of the α-benzylamino compounds. A variety of attempts at directly epimerizing the displacement products were unsuccessful. While nicely demonstrating the configurational stability of these α-amino acid precursors, the displacement product which would be obtained from the non-reactive diastereomer was still required. It was decided that the best way to accomplish this would be to take advantage of the easy separation of the diastereomeric α-bromo compounds. Thus, each diastereomer of the starting material in Entry 1 of **Table 6** (R = Et) was isolated by silica gel chromatography. The NMR spectrum of each diastereomer, as previously discussed, demonstrated only a single triplet at 5.74 ppm in one case and 5.83 ppm in the other (as well as simplification of the entire spectrum). The resolved diastereomers were subsequently treated individually with sodium azide under phase transfer conditions. The corresponding α-azido compounds demonstrated a new doublet of doublets at 4.3 ppm and showed the characteristic sharp azide IR absorption at 2260 cm^{-1}. These α-amino precursors were obtained with very minimal loss of stereochemical purity, however, similar to Evans' observations, a small amount of racemization (2-5%) did occur with NaN_3 as the nucleophile. This racemization is evident by the small, but resolvable doubling of each resonance in the NMR spectrum of each isomer. Evans has reported that this racemization can be eliminated if the azide source is changed to tetramethylguanidinium azide.[46] For our purposes, however, optically pure material was not required. Reduction of the α-azido compounds to the α-amino imidazolidinones was accomplished via catalytic hydrogenation in methanol over a 10% Pd/C. These α-amino compounds were not isolated but directly monobenzylated by treatment of the crude reaction mixture with 1.1 equivalents of benzyl bromide along with triethylamine in THF. The two spectroscopically different α-benzylamino derivatives were isolated by silica gel chromatography without any further detectable racemization as is depicted in **Scheme 8**. The yields in these reactions are unoptimized, as the reaction sequence was carried out only once.

Scheme 8: Preparation of Both Diastereomers of DKR Displacement Product

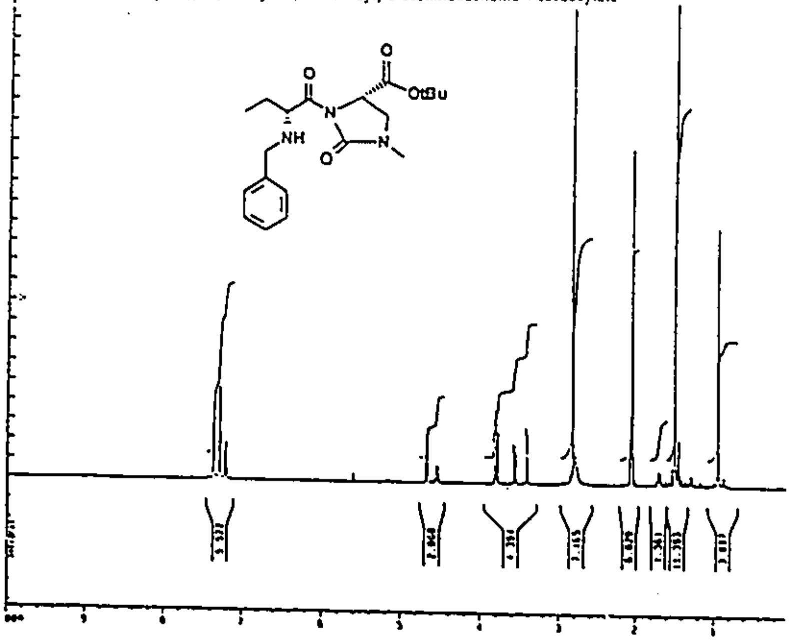


i. chromatographic resolution (3:1 Hex : EtOAc); **ii.** NaN$_3$, CH$_2$Cl$_2$/H$_2$O(3:1), BnEt$_3$N$^+$Cl$^-$ (95%); **iii.** H$_2$/Pd/C; **iv.** BnBr, Et$_3$N, THF (58% for **iii** and **iv**)

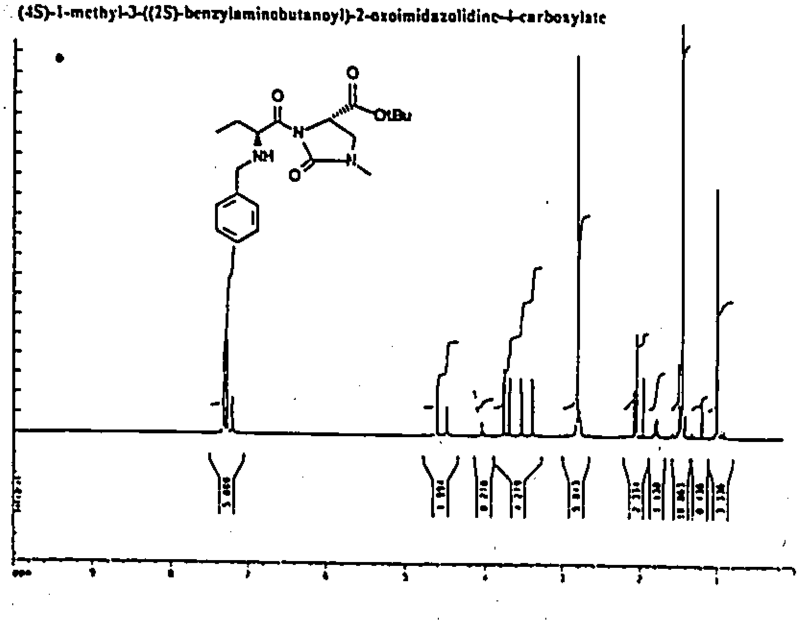
Analysis of the pure materials as well as artificial mixtures of the two diastereomeric α-benzylamino compounds demonstrated that the NMR methodology of diastereomer ratio determination was a reasonable one. The individual diastereomers produced characteristic resolvable signals ~ 0.1 ppm apart. For example, the doublet of doublets corresponding to the proton at the 4-position of the imidazolidinone ring showed distinct resonances at 4.62 ppm for one diastereomer and 4.53 ppm for the second. All of the resonances doubled, the N-methyl gave rise to two singlets at 2.87 and 2.85 ppm, and the t-butyl ester gave two very distinct singlets at 1.49 and 1.44 ppm. The AB spin system observed for the benzylic protons was also quite diagnostic of the optical purity of the DKR reactions, in that both the chemical shift and coupling constant varied dramatically for each diastereomer. The major DKR product gives an AB at 3.68 ppm (J=12.8 Hz) whereas the minor, or not observed, product gives the same AB at 3.61 ppm

(J=13.1 Hz). Closer reexamination of the crude spectra obtained from the DKR process revealed no discernable resonances which would correspond to the non-DKR diastereomer.

Figure 33: ^{1}H NMR Analysis of DKR and Non-DKR Displacement Products

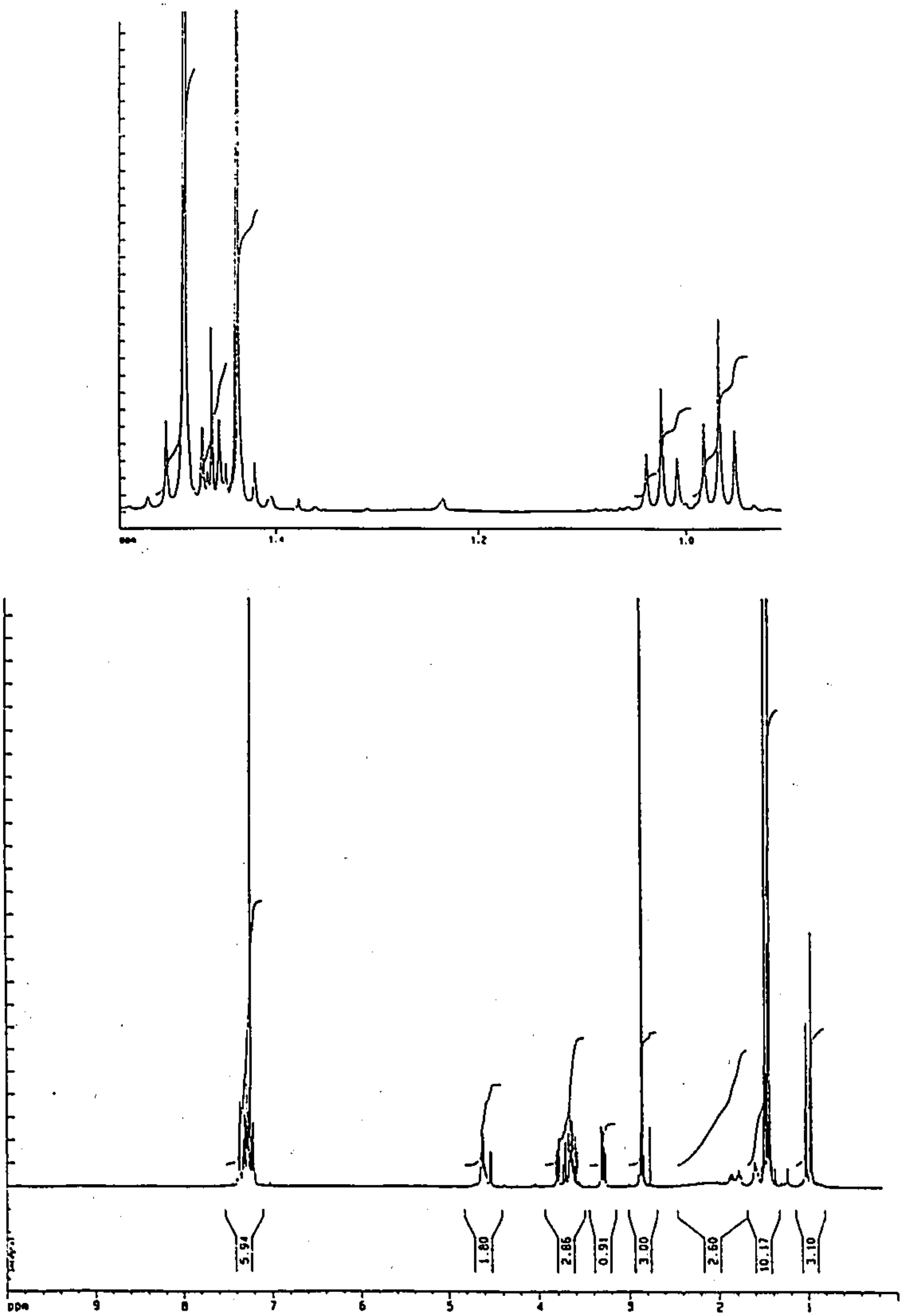

(4S)-1-methyl-3-((2R)-benzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate

DKR Product


(4S)-1-methyl-3-((2S)-benzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate

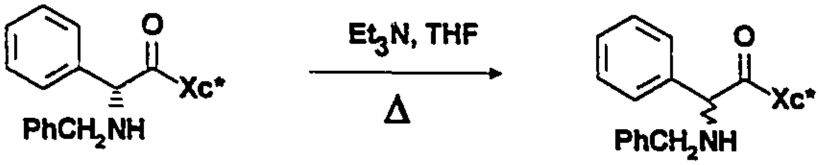
Non-DKR Product

Figure 34: Artificial Mixture of Displacement Products and Determination of Diastereomer Ratio



It was later demonstrated that the displacement product in **Entry 2** (**Table 6**) (R=Ph) could be racemized by heating the compound in the presence of Et_3N. Spectral analysis of the diagnostic areas of this mixture of diastereomers, compared to that obtained from the DKR process further verified our methodology of determining diastereomeric excess. The methine α proton gives rise to a singlet at 5.89 ppm in the DKR product, whereas the same proton is represented at 6.16 ppm in the epimer.

Scheme 9: Racemization of α-Benzylamino Phenyl Derivative



Once again, each resonance doubled. This is demonstrated by comparison of the 500 MHz 1H NMR spectrum of the optically pure material shown in **Figure 35** with that of the racemized material shown in **Figure 36**.

Figure 35: NMR Analysis of DKR Product of α-Benzylamino Phenyl Derivative

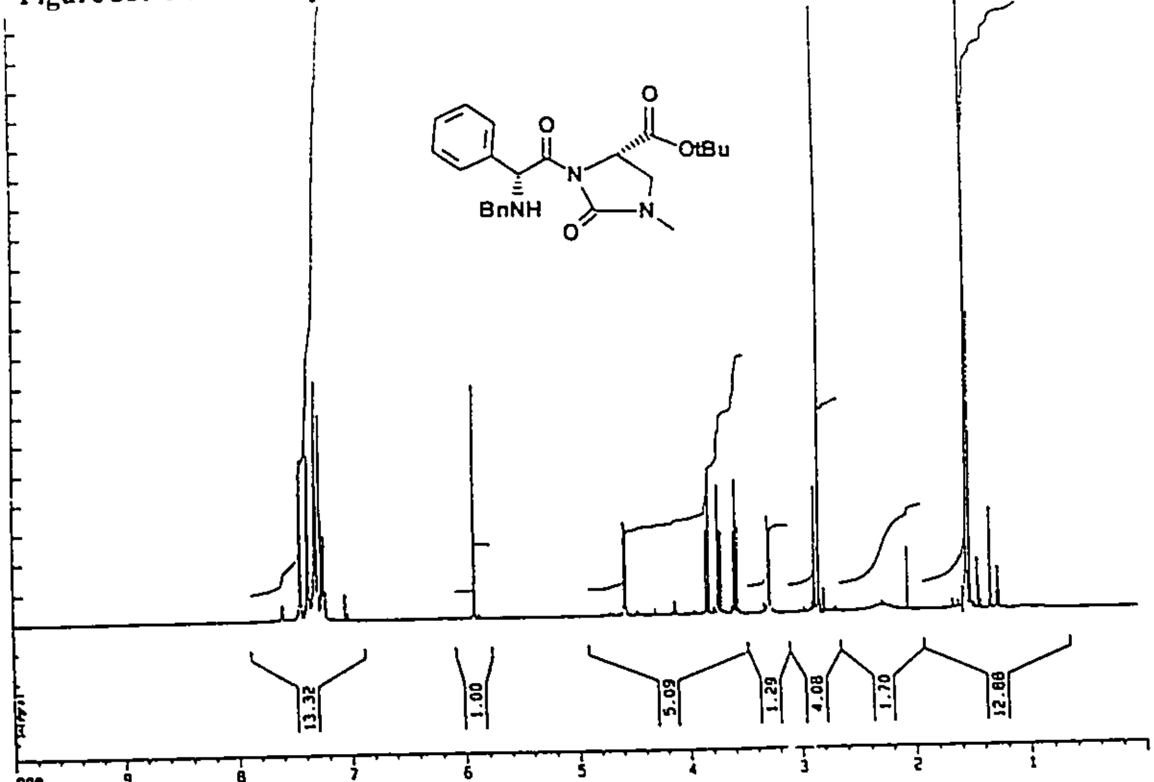
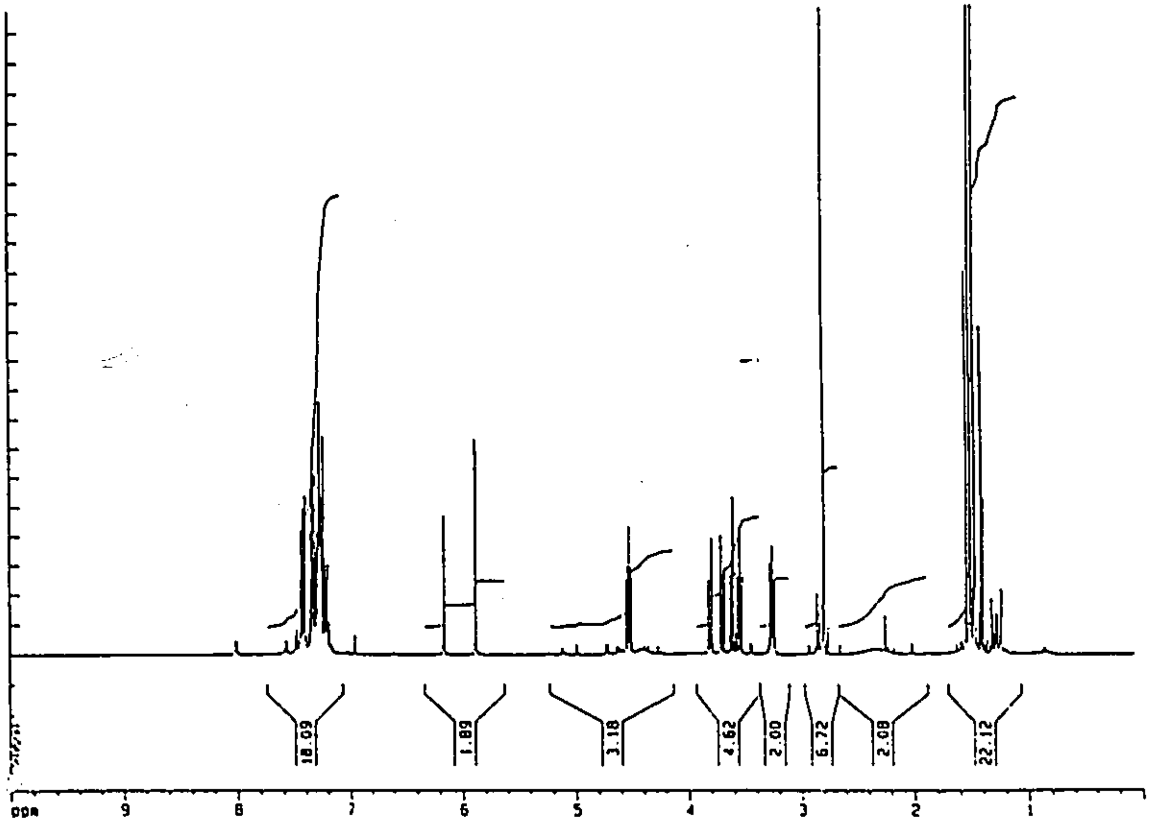


Figure 36: NMR of Racemized α-Benzylamino Phenyl Derivative

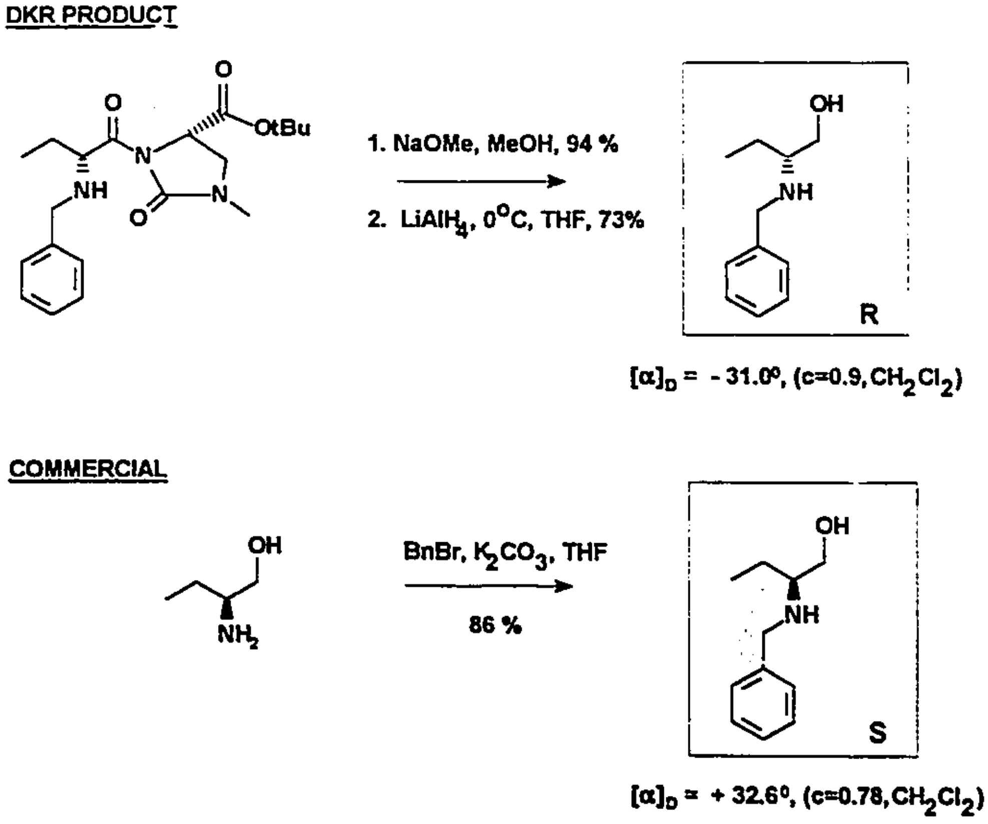


3.5 Determination of Absolute Stereochemistry

The major diastereomer obtained in this process was predicted to posess the (R,S) absolute configuration. This prediction was based on the results quoted by Nunami et al in two previous communications. The kinetic resolution of the 2-bromopropionyl imidazolidinone, which inspired study of this auxiliary, induced the (R,S) configuration in the displacement product. As well, the coupling of the same compound with (S)-α-amino esters provided the undesired (S,R,S) configuration in the potential ACE inhibitors previously discussed.[44]

Further proof of the absolute configuration was accomplished by preparation of non-racemic 2-benzylamino-1-butanol via two different methods (**Scheme 10**). Commercially available 2-aminobutanol[47] was monobenzylated in 82% yield by treatment with benzyl bromide in the presence of K_2CO_3. After recrystallization from hexanes, a white powder (mp, 75 -76 °C, $[\alpha]_D = +32.6$ (c=0.78, CH_2Cl_2)) was isolated. Alternatively, the chiral auxiliary was removed from the DKR displacement product by treatment with NaOMe in MeOH. The α-benzylamino ester, obtained in 92% yield, was subsequently reduced with $LiAlH_4$ to the corresponding alcohol. Similar to above, recrystallization from hexanes produced a white solid (mp, 75 -76 °C, $[a]_D = -31.0$ (c=0.9, CH_2Cl_2)). Comparison of the optical rotation values for these structurally identical compounds, demonstrated that they were antipodes of one another and that the DKR product posessed the R configuration. The slight loss in stereochemical purity of the DKR derived product is likely a result of configurational instability of the α-benzyamino aldehyde intermediate in the $LiAlH_4$ reduction.

Scheme 10: Determination of Absolute Stereochemistry of DKR Products

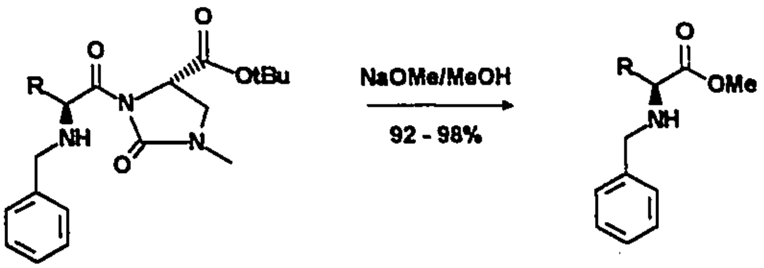


3.6 Cleavage of the Auxiliary

Cleavage of the chiral auxiliary with NaOMe in MeOH proved to be a general method for preparing the α-benzylamino methyl esters (**Scheme 11**). Simply stirring the DKR displacement products in a 0.2M solution of NaOMe in MeOH for 1-4 hours led to quantitative conversion to the methyl ester in every case. The chiral auxiliary could be recovered after mildly acidic work-up, without any loss of optical activity, provided only one equivalent of NaOMe was used. The recovered chiral auxiliary posessed an identical melting point and optical rotation as the originally produced material. Although not proven, it is suspected that some racemization may occur if excess NaOMe is used in the cleavage reaction.

Upon prolonged exposure to these cleavage reaction conditions (2 - 16 hours), the released chiral auxiliary underwent transesterification resulting in the loss of the bulky tert-butyl group as indicated by the replacement of the t-butyl singlet at 1.4 ppm with a methoxy singlet at 3.6 ppm in the NMR specturm.. Significantly lower recovery rates of the chiral auxiliary were observed under these circumstances. This situation can be avoided by utilizing $Mg(OEt)_2$ in 99% EtOH as the alkoxide source. This ethyl ester forming reaction is significantly slower than that with NaOMe requiring stirring for two days, however, the chiral auxiliary is recovered quantitatively upon weakly acidic workup.

Scheme 11: Cleavage of the Chiral Auxiliary



3.7 Effect of Nucleophile on DKR Diastereoselectivity

As was the case with (R)-pantolactone, the steric and/or electronic properties of the nucleophile play vital roles in the observed diastereoselectivity. A variety of nucleophiles have been utilized under the optimized DKR conditions and, in general, bulky molecules with low nucleophilicity provide the highest levels of selectivity in the DKR process.

Small nucleophiles such as azide and halogens, demonstrated little, if any selectivity. For example, when NaN_3 was utilized as the nucleophile under phase transfer conditions, a 1.2 :1 ratio of diastereomers was obtained, and it has been previously demonstrated that bromide and iodide provide essentially racemic mixtures.

The DKR process using the imidazolidinone auxiliary seems to be very sensititve to steric effects in the nucleophile. Unlike the (R)-pantolactone system, really bulky nucleophiles such as dibenzylamine, tritylamine, and aminodiphenylmethane failed to provide any displacement products, even after extended DKR reaction times. In several cases, these bulky amine nucleophiles provided minimal amounts (<10%) of the elimination product however, in no case were displacement products observed. This lack of reactivity with bulky amines was not deemed to be a major problem since benzylamine itself provided essentially optically pure displacement products, thereby eliminating the need for the better selectivity generally observed with bulkier amines.

3.7.1 Oxygenated Nucleophiles

K. Koh and T. Durst have previously demonstrated that most oxygenated nucleophiles, when used in the (R)-pantolactone aided DKR process, provide poor levels of diastereoselectivity. When sodium p-methoxy phenoxide was used as the nucleophile however, diastereoselectivies similar to those observed with benzylamine were obtained (~ 7 : 1 favoring the S,R diastereomer)[18]. This nucleophile is attractive because the resulting α-phenoxy compounds can be converted to the α-hydroxy precursors by treatment with ceric ammonium nitrate (CAN).[48]

When the sodium salt of p-methoxy phenol was used as the nucleophile in the DKR process with the tert-butyl imidazolidinone auxiliary, it was anticipated that high levels of diastereoselectivity would be observed in the α-hydroxy precursor displacement products. This was not the case. 1.1 equivalents of a stock solution of sodium para-methoxyphenoxide was added to a THF solution of (4S)-tert-butyl-(2-bromo-butyryl)-1-methyl-2-oxo-imidazolidine-4-carboxylate and the reaction was allowed to stir for one week at 5 °C. After one week, very little displacement product was observed. The reaction was therefore warmed to room temperature for 48 hours, during which time the desired displacement reaction occurred. Extractive work-up followed by ^{1}H NMR investigation of the crude reaction mixture demonstrated a new product as an 8 : 1 ratio of diastereomers. The diastereomer ratio determination was easily interpretable from the ^{1}H NMR spectrum. Two doublet of doublets at 5.80 and 5.71 ppm, as well as two doublet of doublets at 4.65 and 4.58 ppm both are observed in an 8 : 1 ratio. Two singlets at 1.44 and 1.34 which arise for the tert-butyl protons also were present in an 8 : 1 ratio. Purification by silica gel chromatography provided 67 % of a compound which was demonstrated to be the desired displacement product. Since the level of selectivity was not higher than those observed with the corresponding R-pantolactone esters, no further studies have yet been done using other oxygenated nucleophiles.

Scheme 12: Sodium para-Methoxy Phenolate as the Nucleophile in the DKR Process

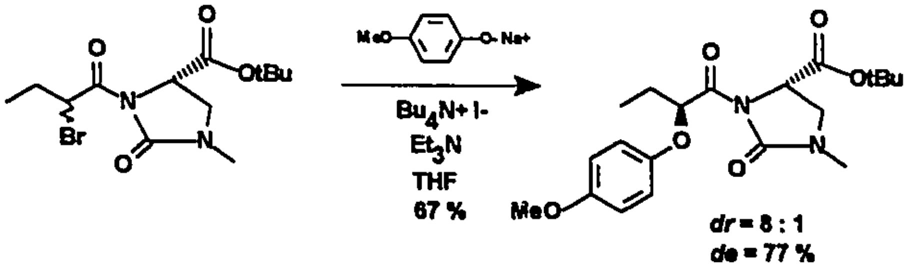
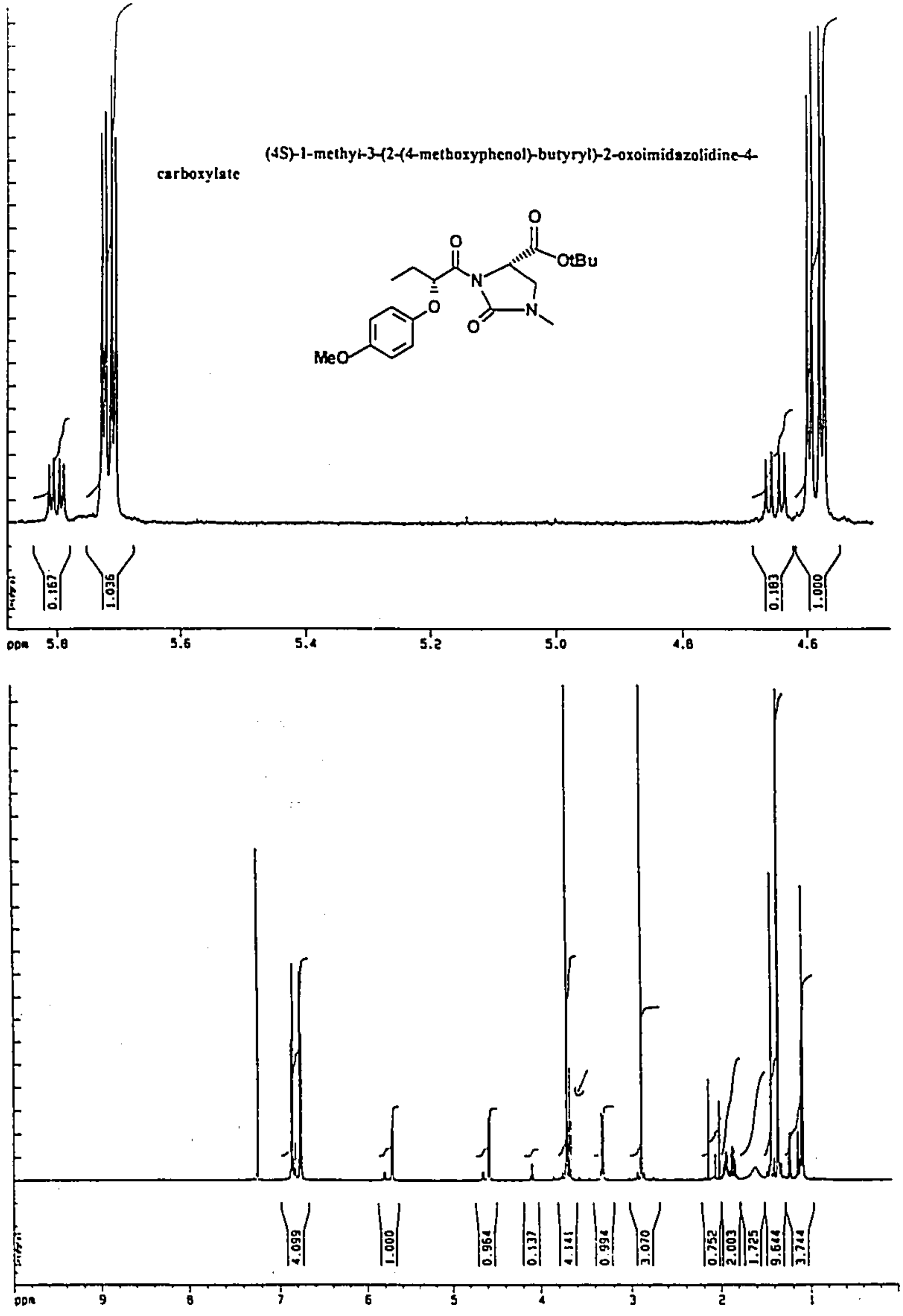


Figure 37: NMR Spectrum of p-Methoxy Phenolate Subsitution Product



(4S)-1-methyl-3-(2-(4-methoxyphenol)-butyryl)-2-oxoimidazolidine-4-carboxylate

4.0 Applications of DKR

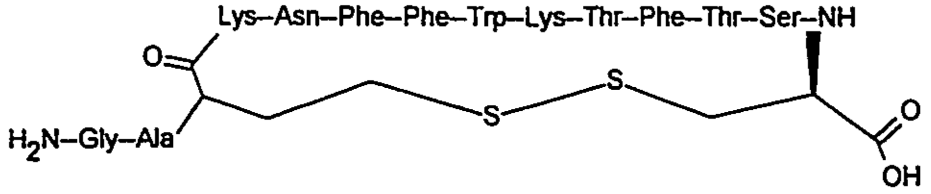
4.1 Synthesis of both L and D-α-amino adipic, pimelic and suberic acid

Dibasic amino acids like glutamic and aspartic acid play vital pharmacological roles in the central nervous system.[49] Longer chain dibasic amino acids like adipic, pimelic and suberic acid (6, 7 and 8 carbons) have also recently been shown to possess interesting pharmacological and chemical properties.[50] In particular, much interest has surrounded α-amino suberic acid, an eight carbon dibasic α-amino acid. It was anticipated, that these long chain dibasic amino acids could be produced in a diastereoselective fashion via the previously described methodology.

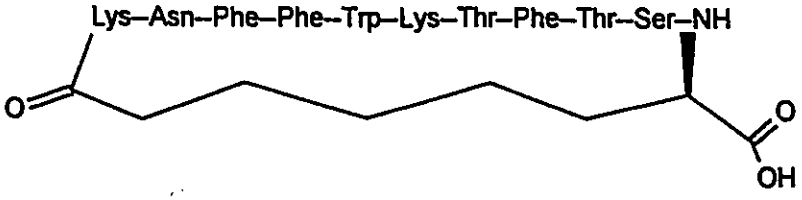
The title compounds, especially L-α amino suberic acid have frequently been utilized as a metabolically stable isosteres for Cys-Cys disulfide linkages in a variety of naturally occurring cyclic hormonal peptides, such as oxytocin, vasopressin,somatostatin, and atrial natriuretic peptides.[51] These long chain α-amino dicarboxylic acids have also found considerable use as glutamate mimicks in QSAR studies involving biologically active compounds containing glutamate residues.

L-α amino suberic acid's use as a metabolically stable isostere is demonstrated by somatostatin analogs. Somatostatin is a tetradecapeptide that was first isolated from sheep hypothalamus and received it name because of its inhibitory effect on growth hormone secretion. It has been found in many other areas particularily the gastrointestinal tract and the pancreas. It has a broad spectrum of biological activity including a potent inhibitory effect on the release of insulin, glucagon, and many other polypeptide hormones resulting in a net lowering of blood glucose. It has also been shown to be an inhibitor of gastrin induced gastric secretion.[51] The structure is shown in **Figure 38.** Structure-activity relationship studies have shown that replacing the sufhydryl bridge with methylene groups leads to a highly active cyclical analog of somatostatin. In the gastric secretion studies it was noted that the L-α-amino suberic acid isosteric compound maintained the same inhibitory effect for about 30 minutes after infusion had stopped, whereas the inhibitory effect of somatostatin was lost rapidly after the infusion had been discontinued. The high biological activity and enhanced metabolic and chemical stability is a result of the absence of the metabolically reducible disulfide linkages.

Figure 38: L-α-amino adipic Acid as a Metabolically Stable Isostere



Somatostatin



L-α-suberic acid analog

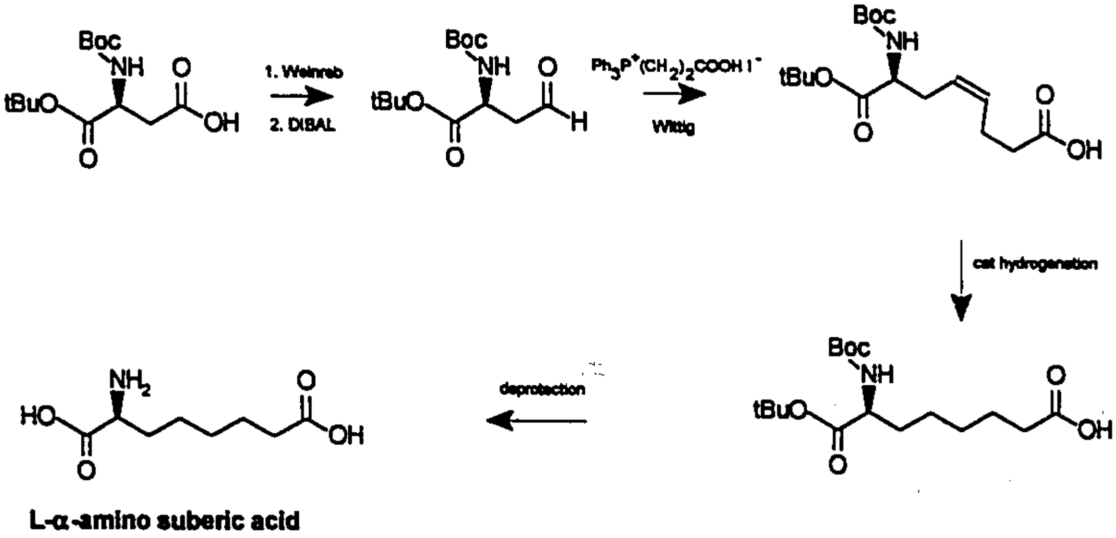
4.2 Stereoselective Synthetic Approaches to L-α-Amino Suberic Acid

To date their has been only three reports on the stereospecific synthesis of α-amino suberic acid. The first method involved lengthy (18 steps) iterative extension of the side chain of L-glutamic acid via the Arndt-Eistert procedure[52] The second one utilized the Kolbe[53] electrolysis of a mixture of derivatized D-glutamic and glutaric acids, upon which the desired unsymmetrical adduct was separated from the two byproduct symmetrical dimers obtained as a statistical mixture. The third enantioselective synthesis came from Bio-Mega[51].

Researchers at Biomega became interested in L-α-aminosuberic acid when SAR studies of synthetic analogues of the atrial natriuretic peptide (ANF (99-126) peptides exhibitted potent natriuretic, diuretic and vasorelaxant activity, inhibition of aldosterone secretion from the adrenal gland and lowering of plasma renin levels. All of these activites result in a decrease in blood pressure. This, it was hoped, could be taken advantage of in the develpement of an antihypertensive.

The Biomega approach to synthesize enantiomerically pure L-α-amino suberic acid involves starting with enantiomerically pure L-aspartic acid, thus encorporating the desired chirality into the starting material. After reduction to the aldehyde via DIBAL reduction of the Weinreb amide, carbon chain extension is achieved via a Wittig reaction with a 4-bromobutyric acid derived phosphonium salt The Wittig reaction is carried out in the presence of LiHMDS to prevent base catalyzed epimerization of the chiral center and provides the Z olefin as the major product. Subsequent catalytic hydrogenation and deprotection led to the desired L-α-amino suberic acid in low overall yield.

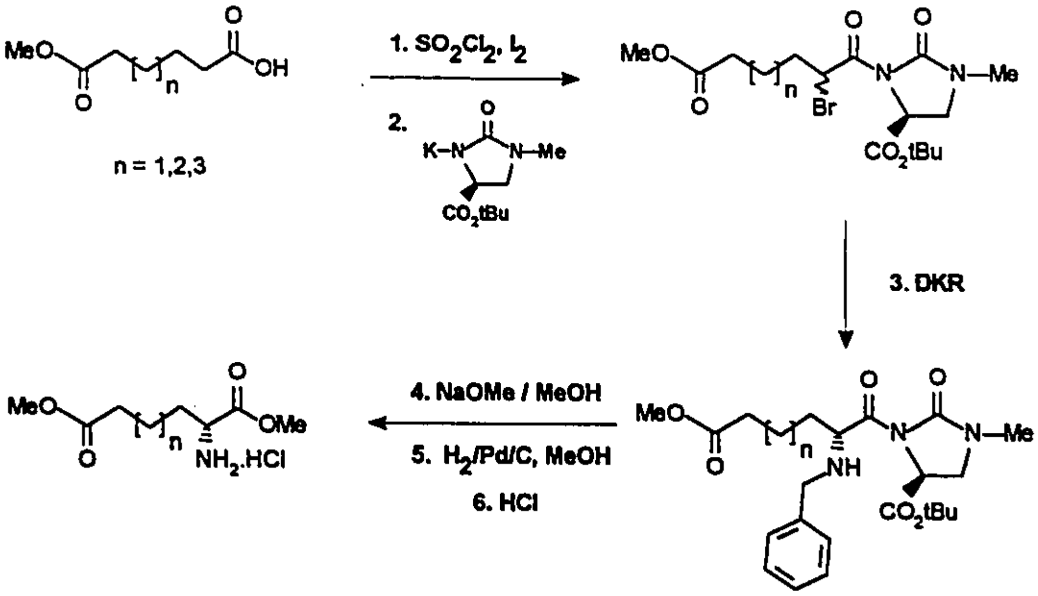
Figure 39: Biomega's Synthetic Route to L-α-Amino Suberic Acid



4.1.2 Proposed Synthetic Route and Results

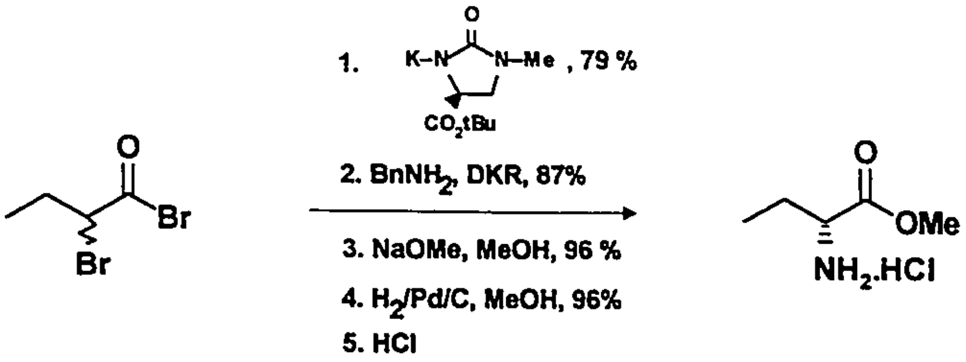
The proposed synthetic route, based on the DKR process is shown in **Scheme 13.** Conversion of the carboxylic acids to their α-halo derivatives, coupling of the chiral auxiliary, DKR using benzylamine as the nucleophile, removal of the chiral auxiliary and subsequent deprotection of the amine should provide access to the desired α-amino esters.

Scheme 13: Proposed General Route to α-Amino Esters



This methodology was demonstrated to be effective for the preparation of (R)-methyl 2-aminobutanoate in five steps from butanoic acid. **Scheme 14** demonstrates that butanoyl chloride is efficientlly coupled with the potassium salt of the auxiliary. DKR, removal of the chiral auxiliary and N-debenzylation are all high yielding (82 % for three steps) and the (R)-methyl 2-aminobutanoate was obtained as a white crystalline compound (mp, 79-81 °C) is obtained in essentially optically pure form in approximately 40 % overall yield. The optical rotation was measured ($[\alpha]_D = -8.0$ ($c = 3.2$, H_2O), lit. ($[\alpha]_D = +7.9$ ($c = 4.0$, H_2O)).[54] and demonstrated that the final product was essentially enantiomerically pure.

Scheme 14: Preparation of (R)-Methyl-2-Amino Butanoate



Similar results were obtained in the preparation of the long chain α-amino dicarboxylic acids. In no case was a second diastereomer evident after the DKR reaction. The results are summarized in **Table 8.** The spectroscopic properties of all the intermediates and final products were consistent with the proposed structures are given in the Experimental Section.

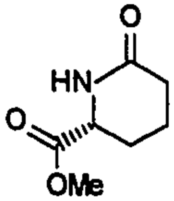
Table 8: Preparation of the Long Chain α-Amino Esters

n	overall yield (6 steps)	de
1 ADIPIC	44 *	> 98 %
2 PIMELIC	38	> 98 %
3 SUBERIC	40	> 98 %

*- the dimethyl α-amino adipic acid analogue cyclizes on work up to provide the cyclic lactam shown in **Figure 40.**

The catalytic removal of the N-benzyl group proceeded in extremely clean fashion. Isolation of the α-amino diesters required simply filtering through a thin pad of celite, the resuting methanolic solution was then saturated with dry HCl and stirred for eight hours. Removal of the methanol under reduced pressure provided the corresponding α-amino ester hydrochlorides, which could be further purified by recrystallization from EtOAc. In the case of the adipic acid analog however, sufficiently pure compound was not obtained from the debenzylation reaction. The crude product contained a mixture of the desired product and the cyclized lactam (**Figure 40**). Attempts to isolate only the desired compound led to quantitative conversion to the cylclized adduct, demonstrating that formation of this six membered ring is a low energy process. While not exactly the desired product, it is a synthetic equivalent since hydrolysis would provide α-amino adipic acid. Alternatively, the hydrogenolysis reaction could have been carried out under acidic conditions so that the amino functionality becomes protonated as it is liberated thus it would no longer be nucleophillic.

Figure 40: Cyclized Lactam From Dimethyl-(D)-α-amino Adipate



Earlier experiments, using (R)-pantolactone as the auxiliary demonstrated that the (S)-α-amino diesters could be obtained by a similar route. The selectivity in the DKR reactions were significantly lower (7-9 : 1) however, the displacement products were obtained in good yield. It has been demonstrated that the (R)-pantolactone auxiliary can be removed under the NaOMe in MeOH conditions developed for the imidazolidinone cleavage. The resulting α-benzylamino diesters can then be reduced as before with 10%

Pd/C and the corresponding α-amino diesters thus obtained.

Scheme 15: DKR of α-Halo (R)-Pantolactone Esters of Adipic, Pimelic and Suberic Acid

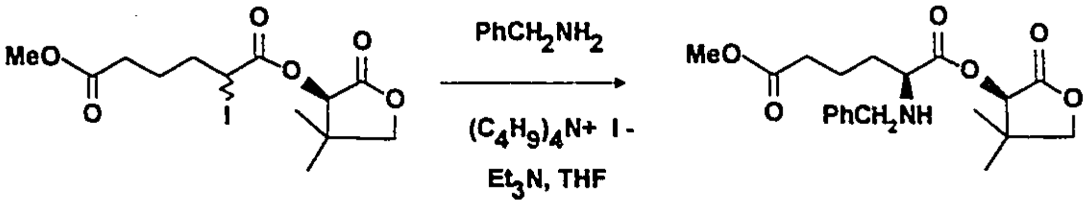


Table 9: (R)-Pantolactone as the Auxiliary in the DKR Production of Long Chain α-Amino Dicarboxylic Acids

n	yield	Diastereomer Ratio	de
1	86	91:9	82
2	81	87:13	74
3	87	87:13	74

The DKR process has been demonstrated to provide access to either enantiomer of the desired α-amino esters. The absolute stereochemisry can be altered simply by altering the chiral auxiliary used in the DKR process. (R)-pantolactone provides the (S) α-amino esters and the tert-butyl imidazolidinone auxiliary induces the (R) configuration in the DKR products.

5.0 Attempted Explanation of Observed Diastereoselectivity

The origin of the observed diastereoselectivity in the (R)-pantolactone was rationalized in **Section 2.4** by taking into account several structural features of the α-halo (R)-pantolactone esters. Briefly, these structural features were the following:

1. The ester functionality exists in its cisoid conformation.
2. The ester and pantolactone carbonyls lie perpendicular to each other as evidenced by molecular modelling and X-ray analysis.
3. The α-halogen is perpendicular to the ester carbonyl oxygen.
4. Lastly, the R group (side chain residue) should prefer to eclipse the ester carbonyl oxygen in the transition state, rather than eclipse the chiral auxiliary.

These observations/predictions allowed the postulation that two and only two transition states exist for each compound, one for each diastereomer and that one is lower in energy than the other.

Items 3 and 4 (above) should remain valid for the imidazolidinone discussion. X-ray crystallography shows that the situation for the pantolactone esters and the imidazolidinones is fundamentally different. In the pantolactone esters the carbonyls lie perpendicular to one another. In contrast, an X-ray study of the slower reacting (R,S) diastereomer, tert butyl 1-methyl-3-(2(R)-bromobutyrl)-2-oxoimidazolidine-4(S)-carboxylate demonstrated that the two carbonyl groups lie in the same plane and anti to one another (**Figure 42**). For clarity, the situation is further depicted in **Figure 41** and it can be seen that C(2) through C(10) lie in the same plane with oxygens (4) and (10) positioned anti to one another.

Figure 41: Structural Characteristics of tert butyl 1-methyl-3-(2(R)-bromobutyrl)-2-oxoimidazolidine-4(S)-carboxylate

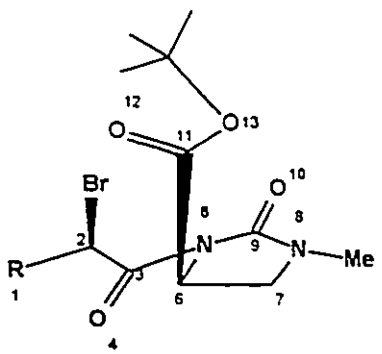
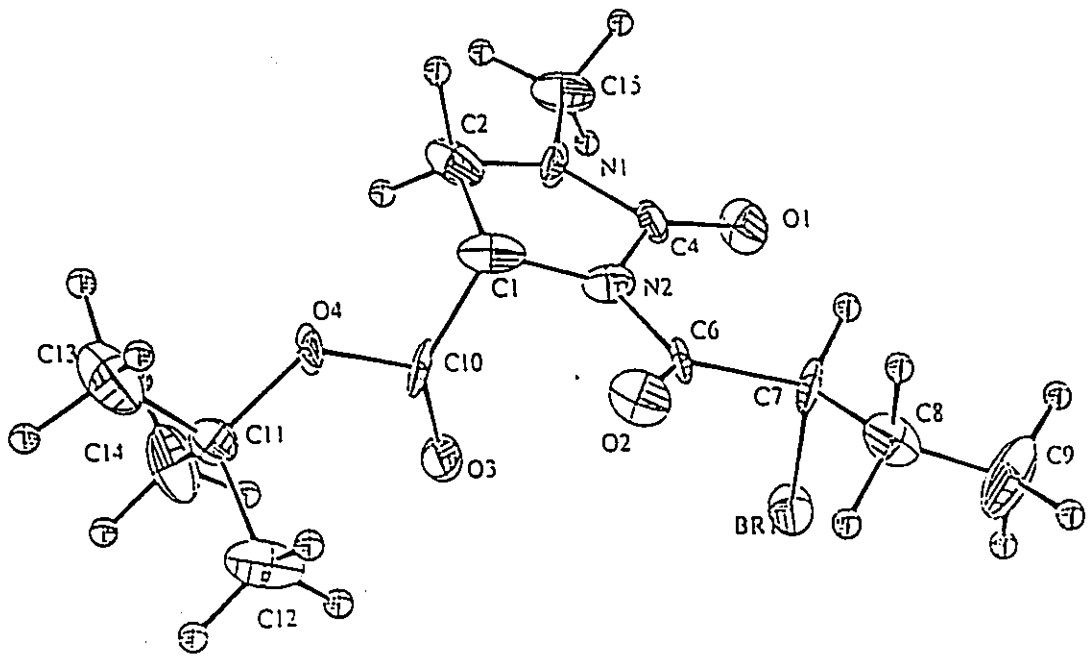
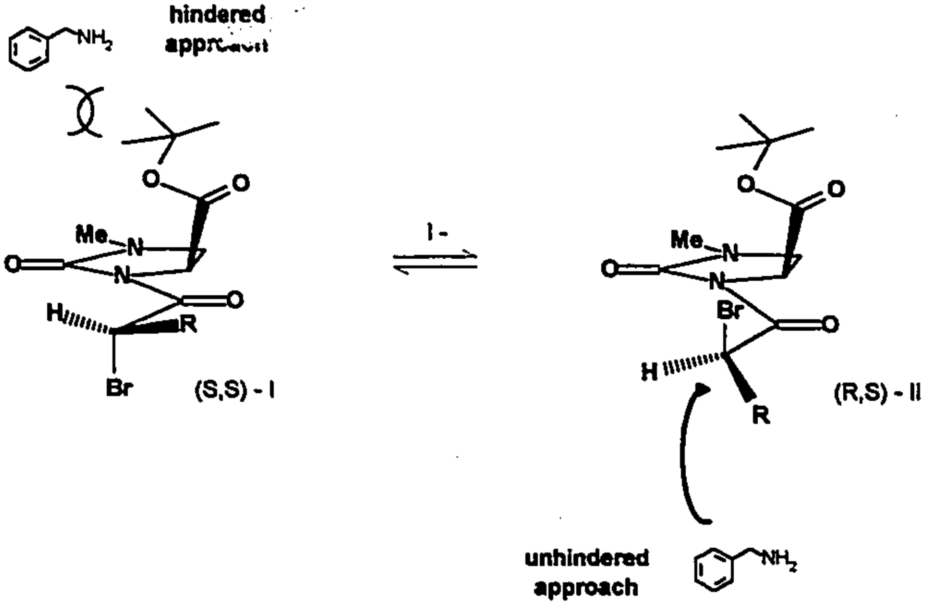


Figure 42: X-Ray Crystal Structure of tert butyl 1-methyl-3-(2(R)-bromobutyrl)-2-oxoimidazolidine-4(S)-carboxylate



As previously discussed, it is well known that the reactivity of α-halocarbonyl compounds towards nucleophiles is highest when the halogen leaving group is perpendicular to the carbonyl group. Of the two possible transition states for each diastereomer those in which the larger R group is eclipsed with the carbonyl oxygen O(4) rather than the imide nitrogen should be preferred. The approach of a nucleophile leading to such a transition state in the (R,S) diastereomer (**Figure 43. II**) is less hindered compared to that for the (S,S) diastereomer (**Figure 43: I**). Thus the former should react at a significantly more rapid rate than the latter with relatively bulky nucleophiles such as benzylamine, however the steric interactions are not great enough to impede small nucleophiles such as halogens (which allows the required isomerization between **II** and **I** to proceed) or azide.

Figure 43: Two Possible Transition States for Displacement Reactions



These two transition states describe the postulated interactions which could account for the high levels of diastereoselectivity observed in the DKR process. This argument, which is analogous to that proposed for (R)-pantolactone is however, fatally flawed in that, this particular model predicts the wrong absolute stereochemistry in the major product. Since this argument is based on the ground state conformation of the α-halo imides,as observed in the X-Ray structure, we must assume that the ground state conformation is not the reactive conformation. The Curtin-Hammett Postulate requires only that the lowest enery transition state be followed and this need not be the ground state conformation.

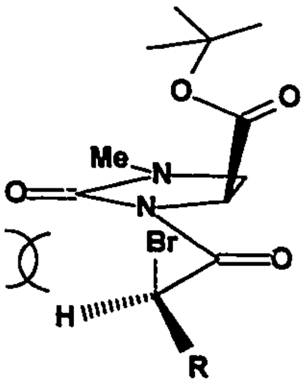
Several of the assumptions which led to the two proposed transition states previously discussed should be valid for any conformation. The perpendicular orientation of the leaving group to the neighbouring carbonyl, and the preference of the side chain residue (R group) to eclipse the carbonyl oxygen in the transition state both lead to a lowering of the transition state energy and must be included in any argument. The most questionable assumption therefore becomes the anti orientation of the two carbonyl oxygens. One observes through inspection of molecular models that if these carbonyl groups attain either an orthogonal or a syn orientation to one another, the bulky tert-butyl group blocks large nucleophiles from attacking the (R,S) diastereomer and this model would then predict the correct absolute stereochemistry in the DKR products.

The orthogonal orientation of the two carbonyls is likely highly disfavored relative to the syn orientation. This is predicted since the syn conformation preserves the coplanarity of the system which permits pi-resonance stabilizaiton between the imide nitrogen and the the carbonyl pi system. This pi resonance contributes a significant amount (approximately 15 kcal/mol) of stabilization to the structure. In the orthogonal orientation no orbital overlap is possible therefore this pi-resonance stabilization is lost and is therefore predicted to be much higher in energy.

A possible explanation of the preference for the syn over anti carbonyl relationship in the transition state can be obtained by model studies. The five coordinate transtion state in which the carbonyls are anti to one another has a very serious steric interaction between the proton at the reactive site and the ureido carbonyl (see **Figure**

44). As the transition state is reached the proton and the ureido carbonyl oxygen become coplanar and the steric repulsion is maximized. This results in an increase in the activation energy of the reaction to such an extent that it is energetically more favorable to rotate about the carbonyl-nitrogen bond to attain the syn rotamer and thereby eliminate this bad steric interaction.

Figure 44: Bad Steric Interaction in the Anti Transition State



In the syn conformation this bad steric interaction is effectively removed at the expense of creating a dipole-dipole destabilizing interaction depicted in **Figure 45**. The magnitude of this interaction can be predicted on the basis of Coulombs law and should therefore be proportional to

$$E = \varepsilon_1 \varepsilon_2 / Dr$$

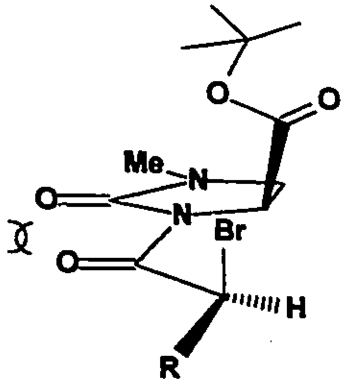
where ε_1 and ε_2 are the magnitudes of the charges, r is the distance between them, and D is the dielectric constant of the surrounding medium. Calculated for two unit charges three angstroms apart (estimate based on a molecular model) the calculation becomes:

$$\mathbf{E = (4.8 \times 10^{-10}\ esu)^2 / D\,(3.00 \times 10^{-8}\ cm) \quad = \quad 7.68 \times 10^{-12} / D \qquad ergs/molecule}$$

$$\mathbf{therefore \qquad E = 110\,506 / D \qquad cal / mole}$$

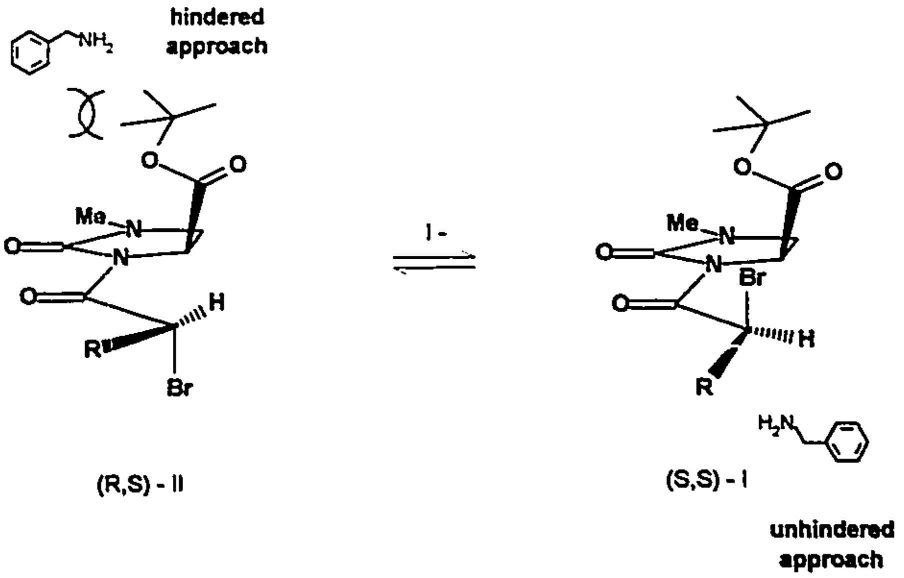
In the solid state, a dielectric constant of one maximizes this interaction thus procluding this structure as the ground state conformation of the solid. In solution however, a higher dielectric constant (ie. for THF D = 7.58) combined with the fact that this should be only a minor resonance structure (less formal charge on the oxygens ie. 10 % of formal unit charge), leads to the prediction that this destabilizing interaction might account for only 1-2 kcal/mole. This methodology for determining intramolecular dipolar interactions is referred to as the Bjerrum method and is far from perfect, but provides an adequate estimation[55].

Figure 45: Destabilizing Interaction in the Syn Rotamer



The two predicted transtion states in the syn conformation then become **I** and **II**. **II** is decreased in reactiviity because the brominated, electrophillic center is sterically shielded by the bulky t-butyl group. **I** on the other hand, suffers no such steric shielding and should therefore be the more reactive of the two.

Figure 46: Postulated Transtion States Leading to Correct Absolute Stereochemistry



Rotation about the C(O)-N bond is necessary in order to obtain the predicted geometry of the transition state. This rotation about an amide bond is typically energetically costly (~ 23 kcal/mole)[56] because of the pi resonance contribution to the C(O)-N bond. In this situation, because the ureido system can delocalize the positive charge over two nitrogens, the resonance structure which prevents rotation has only a minor contribution to the system. The barrier to rotation is decreased substantially and rotation is therefore quite rapid at room temperature. A variable temperature NMR experiment, failed to demonstrate any resolution of the individual rotamers. This could indicate that the barrier to rotation is very small and is much faster than the NMR time scale.

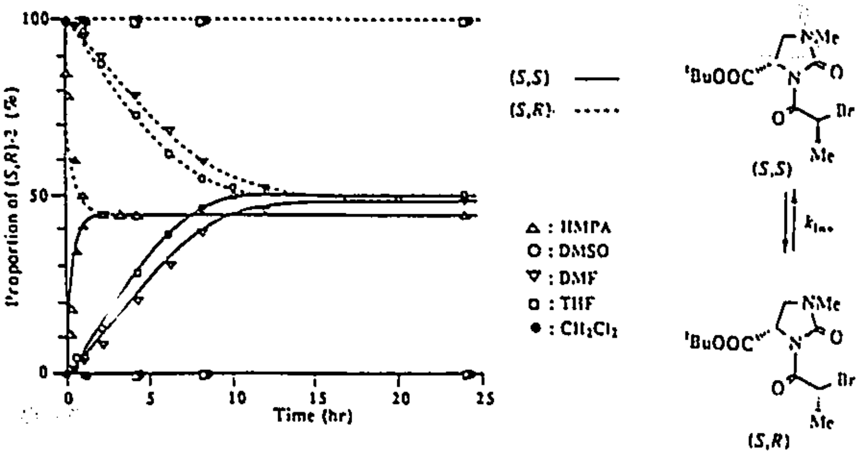
While the given argument appears to adequately describe the observed diastereoselectivity it is in no way meant to be infallible.

6.0 Nunami's Equivalent to this DKR Process

The work describing the effective DKR utilizing the imidazolidinone auxiliary was submitted for publication when a similar approach by Nunami was reported in Tetrahedron Letters. Nunami also realized the possibility of applying DKR to the efficient kinetic resolution previously reported for the tert-butyl imidazolidinone modified α-bromo propionic acid derivative, the same study which prompted us to utilize this auxiliary.

Nunami's approach involved base catalyzed epimerization to supply the dynamic aspect of DKR. He analysed several solvents for evidence of base catalysed epimerization, and observed that while no racemization was evident in THF or CH_2Cl_2, more polar solvents like DMSO, DMF and HMPA permitted the desired in situ epimerization to occur. HMPA, in particular allowed especially rapid epimerization. The results of these epimerization studies are reproduced in **Figure 47.**

Figure 47: Epimerization Studies of α-Bromo-Propionic Imide



The Japanese group then proceeded to analyse the diastereoselectivity of the displacement reactions of these compounds. The reaction with benzylamine as the nucleophile was examined under several conditions (**Table 10**). All reactions afforded the (R,S) displacement product predominantly, but the stereoselectivity was greatly affected by solvent. The best results were obtained with HMPA as the solvent and the corresponding displacement products were obtained as a 16:1 ratio of diastereomers (88% de).

Table 10: Solvent Effect on DKR

Solvent	Yield	Diastereomer Ratio
DMF	97	78 : 22
HMPA	96	94 : 6
DMSO	94	82 : 18
CH_2Cl_2	48	97 : 3

The DKR obtained by base catalyzed epimerization is clearly inferior to the iodide catalyzed epimerization route. There are several possible explanations for this decreased selectivity. An obvious explanation is that the rate of epimerization is slower when base catalyzed. This is especially obvious in the DMSO and DMF reactions, where epimerization is appreciably slower. The result is that the displacement reaction may proceed under non-Curtin Hammett conditions so that buildup of the slow reacting diastereomer occurs. A second explanation is that the small side-chain (R=Me) utlilized in the Japanese study permits a more tolerant transition state in which the R group is not required to eclipse the carbonyl oxygen.

7.0 Reetz Aldehydes II

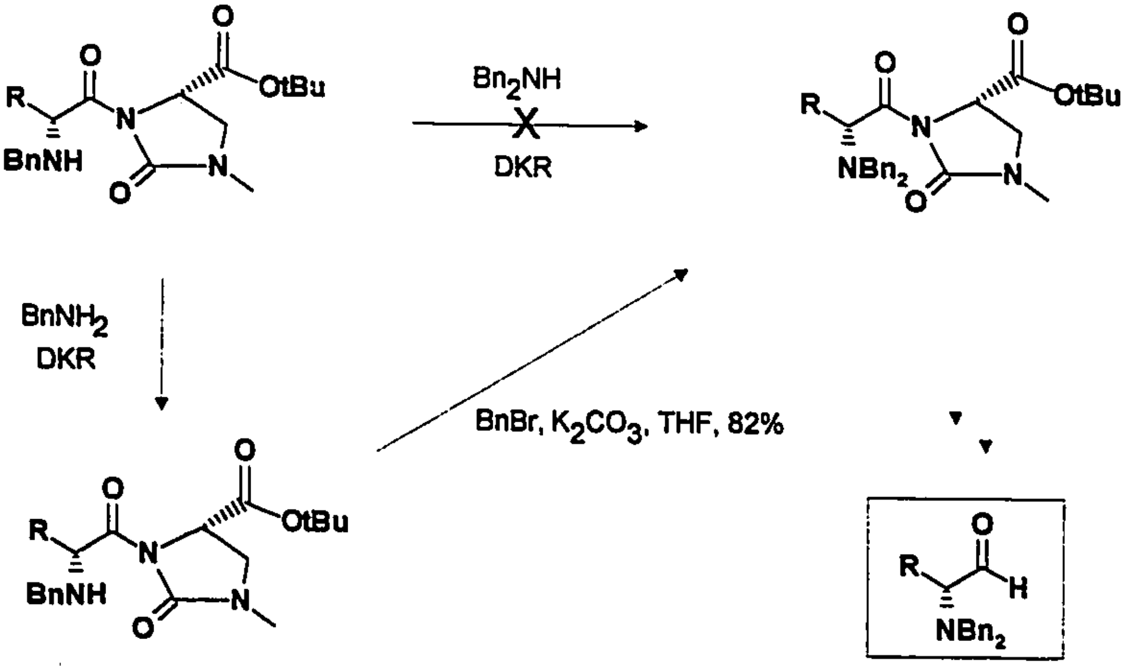
In **Section 2.0** the significance of Reetz aldehydes (α-dibenzylamino aldehydes) was discussed. It was further demonstrated that by using (R)-pantolactone as the chiral auxiliary and dibenzylamine as the nucleophile, the DKR process provides an efficient route for the preparation of (S)-Reetz aldehydes.

It was therefore predicted that by using dibenzylamine as the nucleophile in the DKR process with the tert-butyl imidazolidinone auxiliary the corresponding (R)-Reetz aldehydes could be produced with a high degree of enantiomeric excess. When the experiment was carried out, however, it was discovered that dibenzylamine is a poor nucleophile with the imidazolidinone auxiliary in that the displacement reaction was prohibitively slow. After one week under the optimized DKR process with dibenzylamine as the nucleophile only 10 % conversion to the displacement product was observed. The remaining material was unreacted starting material. No significant acceleration in the rate of reaction was observed even upon heating the DKR reaction in refluxing THF.

This relative unreactivity of dibenzylamine with the imidazolidinone modified α-halo acid derivatives is likely a result of its increased bulk (relative to benzylamine) causing destabilizing steric interactions in the transition state. Since, however, very high levels of diastereoselectivity are obtained with benzylamine, the excess bulk provided by using dibenzylamine as the nucleophile is not necessary for better selectivity. The problem was therefore circumvented by using benzylamine as the nucleophile and simply monobenzylating the crude α-benzylamino displacement products to obtain the (R)-Reetz aldehyde precursors.

The crude DKR displacement products were redissolved in THF and treated with 1.1 equivalents of benzyl bromide. Powdered K_2CO_3 (5.0 equivalents) was added and the reaction was stirred for two days, during which time the benzylation reaction proceeded smoothly. Extractive work-up followed by silca gel chromatography provided the desired α-dibenzylamino imidzolidinone in 82 % yield as only one detectable diastereomer. It was further demonstrated that removal of the chiral imidazolidinone auxiliary, using the NaOMe in MeOH procedure previously discussed, proceeded as expected to provide the corresponding α-dibenzylamino methyl esters. Several methodologies for converting these compounds to their Reetz Aldehyde counterparts are available but were not carried out since the compounds are better stored as their esters. The process is depicted in **Scheme 16.**

Scheme 16: Preparation of (R)-Reetz Aldehydes by DKR



8.0 Structurallly Similar Auxiliaries

The DKR process has been demonstrated to be highly stereoselective when the tert-butyl-imidazolidinone auxiliary is utilized. This represents an efficient methodology for the preparation of essentially optically pure α-amino compounds. The one obvious drawback of this procedure however, is the four step sequence required to attain the chiral auxiliary. In an attempt to minimize the effort required to realize the DKR process, several structurally related compounds were either purchased or facilely synthesized and analysed as potential chiral auxiliaries to this process.

Structurally similar (4S,5R)-(+)-1,5-dimethyl-4-phenyl-2-oxo-imidazolidine, depicted in **Scheme 17**, was purchased from Aldrich and coupled with racemic 2-bromo butyryl bromide using the previously described procedure ($K^{+-}OtBu$ in THF) to provide the corresponding α-halo imidazolidinone in 76% yield. When the resulting DKR precursors were submitted to the optimized DKR conditions using benzylamine as the nucleophile, the desired displacement products were obtained in 87 % yield as a 10:1 ratio of diastereomers. The diastereomer ratio was, once again, ascertained by anaylsis of the crude reaction products by ^{1}H NMR. Two doublets at 5.27 and 5.20 ppm arising from the resonance of the methine at C-4 of the imidazolidinone ring were observed in a 10:1 ratio. Because the level of selectivity was inferior to that exhibitted by the tert-butyl imidazolidinone, further studies with this commercially available chiral auxiliary were not undertaken. The structural similarities between this auxiliary and the tert-butyl substituted imidazolidinone are obvious. Since the absolute stereochemistiy of both auxiliaries is the same, very similar transition states in which identical faces are blocked can therefore be predicted, and the absolute stereochemistry in the DKR products should remain the same. It can therefore be rationalized that the major diastereomer obtained posesses the (R,S) absolute configuration, and that the phenyl substituent is less effective than the tert-butyl ester at providing facial biases during nucleophillic attack.

Scheme 17: DKR with (4S, 5R)-(+)-1,5-dimethyl-4-phenyl-2-oxoimidazolidine as the Auxiliary

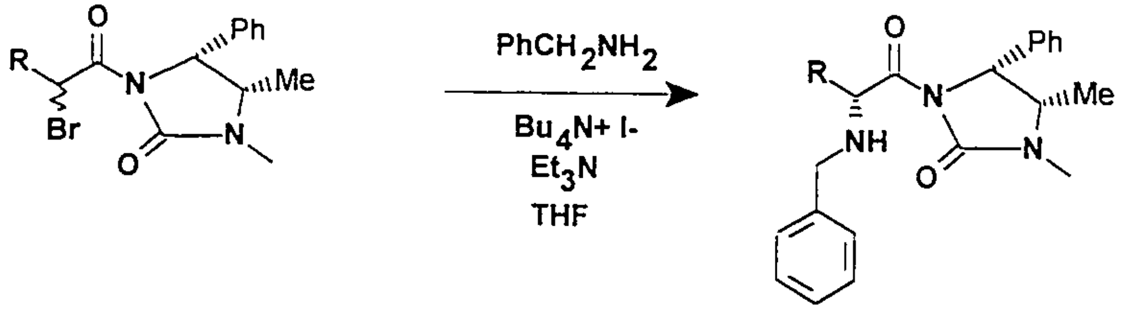
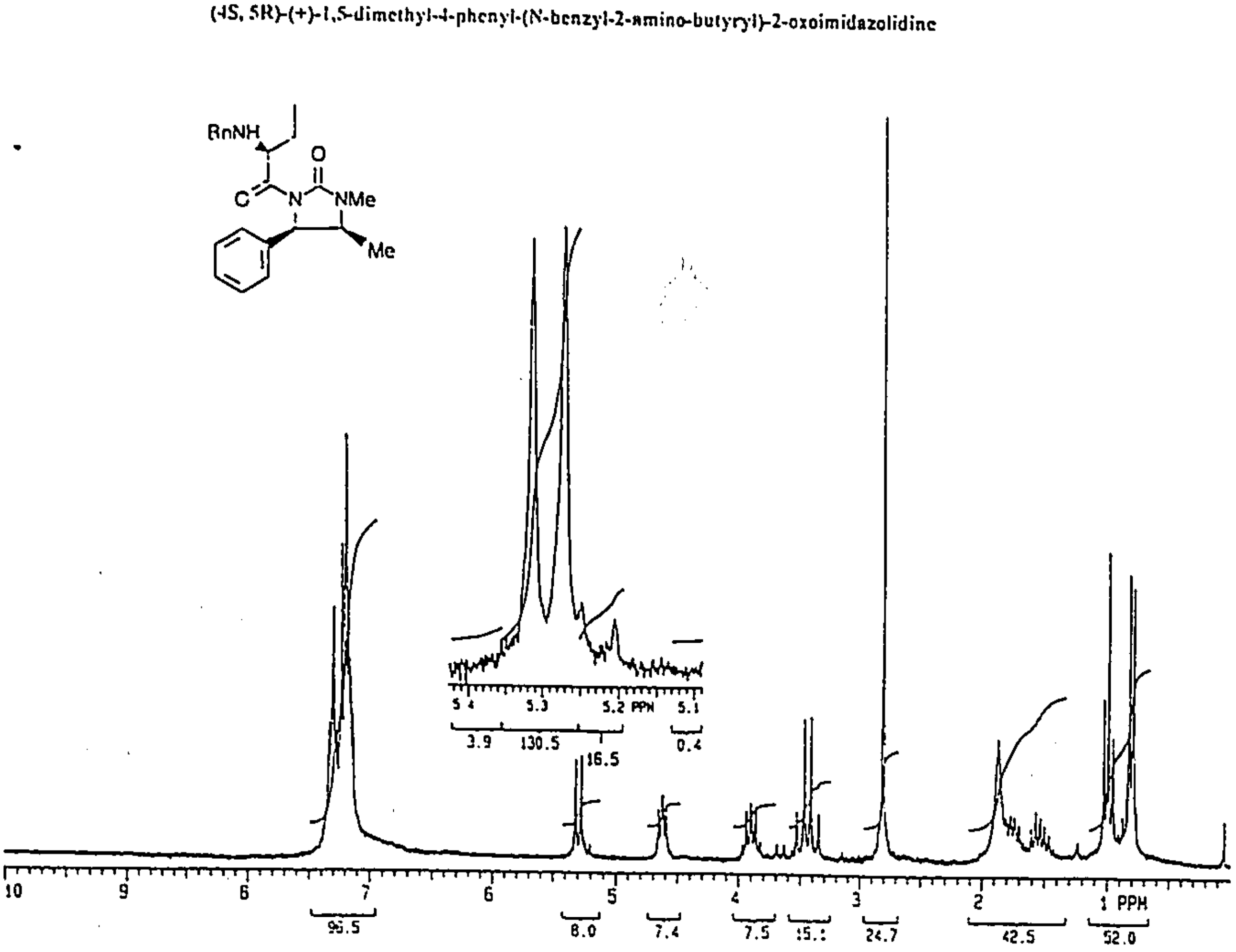
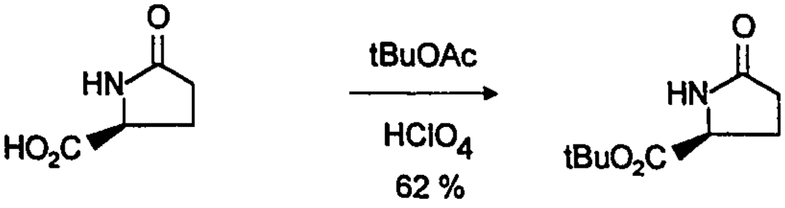


Figure 48: ^{1}H NMR Determination of Diastereomer Ratio in DKR with (4S, 5R)-(+)-1,5-dimethyl-4-phenyl-2-oxoimidazolidine as the Auxiliary



An obvious structurally similar auxiliary is tert-butyl pyroglutamate. This compound is easily prepared in one step from commercially available pyroglutamic acid.[57] Pyroglutamic acid is simply stirred in a large excess of tert-butyl acetate and acidified with several drops of perchloric acid, the resulting slurry is stirred for 72 hours at room temperature in a tightly sealed flask. Basic extraction removes any unreacted pyroglutamic acid as well as the acetic acid byproduct and the desired product is obtained in pure form simply by extraction of the aqueous layer with Et_2O and evaporation of the solvent at reduced pressure. The reaction proceeds by generating the highly reactive electrophile isobutylene which is subsequently trapped by pyroglutamic acid to produce tert-butyl pyroglutamate as depicted in **Scheme 18.**

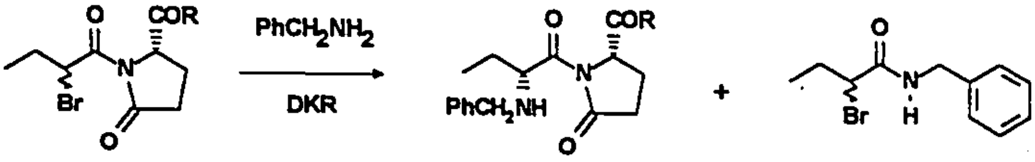
Scheme 18: Preparation of tert-Butyl Pyroglutamate



tert-Butyl pyroglutamate was then efficiently coupled with (±)-2-bromo-butyryl bromide by the standard methodology ($K^{+-}OtBu$ in THF) to provide, after purification by silica gel chromatography, 79 % yield of a 1:1 mixture of diastereomers. The ratio of diastereomers was easily distinguished from the proton NMR. Integration of the two triplets at 5.55 and 5.50 ppm, which correspond to the methine at the brominated postion of each diastereomer, provides the diastereomer ratio. As well, the large singlet expected for the protons of the tert-butyl ester was split into two peaks at 1.44 and 1.43 ppm, further demonstrating the racemic nature of the brominated chiral center. Interestingly, the individual diastereomers, similar to the tert-butyl imidazolidinone compounds, were easily separable by silica gel chromatography (2:1 hexanes : EtOAc). This aspect of these compounds will be discussed in more detail in **Section 9.0**.

The 1:1 mixture of diastereomers of the α-bromo pyroglutamate derivative was then submitted to the optimized DKR reaction conditions using benzylamine as the nucleophile. After 24 h, TLC analysis demonstrated that the starting material had been consumed. The reaction was submitted to extractive workup and ^{1}H NMR investigation of the crude reaction material revealed the presence of several products. Closer examination revealed two new doublet of doublets at 4.64 and 4.60 ppm (24 : 1 ratio), thus indicating that the desired displacement products were obtained with a high degree of diastereoselectivity (94 % de). A third doublet of doublets at 4.04 ppm revealed the presence of a major byproduct which corresponded to unacylated tert-butyl pyroglutamate. This byproduct arises due to an acyl transfer reaction in which the benzylamine nucleophile attacks the carbonyl, rather than the halogenated position, resulting in elimination of the chiral auxiliary and the formation of a benzyl amide. The displacement : acyl transfer products were obtained in a 60 : 40 ratio as determined by combined integration of the two doublet of doublets at 4.64 and 4.60 ppm versus the doublet of doublets at 4.04 ppm. Indeed, when the crude products were isolated by silica gel chromatography the forementioned products were isolated in a 60 : 40 ratio, and characterized.

Scheme 19: DKR of tert-Butyl Pyroglutamate Derivatives



displacement **acyl transfer**

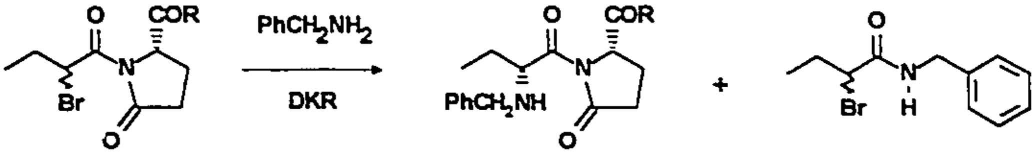
In an effort to further understand this process, the individual diasteromers of the α-bromo pyroglutamate derivatives were chromatographically separated and submitted individually to the DKR reaction conditions. Interestingly, the faster reacting (S,S)-diastereomer provided the traditional 60 : 40 ratio of displacement : acyl transfer products whereas the slow reacting (R,S)-diastereomer provided only acyl transfer product.

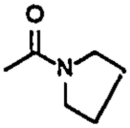
These results could be rationalized if the rate of acyl transfer of the slow reacting diastereomer is faster than the rate of its epimerization. A possible solution to this problem therefore, would be to increase the rate of epimerization of the slow reacting diastereomer by either increasing the temperature or by making the electrophillic brominated position more sterically accessible.

A variety of methods aimed at eliminating this acyl transfer problem observed in the DKR of the pyroglutamate derivatives have been examined. Each, unfortunately, met with no success. Altering the solvent in which the DKR reaction was carried out produced no significant improvement in the product distribution. CH_2Cl_2, DMF, and HMPA all provided identically the same displacement : acyl transfer ratio as observed for THF. Increasing the temperature of the DKR reaction so that it was carried out in refluxing THF, not only decreased the selectivity observed in the desired displacement reaction (4:1 ratio by NMR analysis), but also resulted in the formation of two significant byproducts accounting for 65 % of the reaction products. The familiar acyl transfer product was isolated along with a small amount (~10 %) of the base catalyzed elimination product.

In an unsuccessful attempt to decrease the steric shielding of the electrophillic brominated position, the nature of the ester functionality in the pyroglutamate auxiliary was altered. iso-Propyl pyroglutamate was prepared, coupled to (±)-2-bromo-butyryl bromide and submitted to the DKR reaction. Once again, reasonable levels of selectivity were observed (95 :5 ratio of diastereomers by ^1H NMR) however, the ratio of displacement to acyl transfer product worsened to 40 : 60. The corresponding pyrrollidine amide was also prepared from ethyl pyroglutamate via the Weinreb trimethylaluminum procedure[58]. When this compound was coupled to (±)-2-bromobutyryl bromide and submitted to the DKR process, poor selectivity (4:1 ratio of diastereomers) and a 50 : 50 ratio of displacement products : acyl transfer product was observed. Since the product distribution could be ascertained by NMR analysis of the crude reaction mixture, the products obtained in these reactions were not isolated.

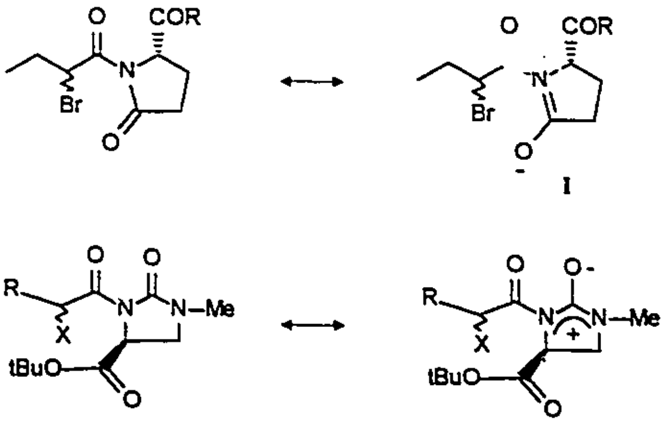
Scheme 20: Alteration of Ester Functionality in the Pyroglutamate Auxiliary



COR	displacement (dr)	acyl transfer
CO_2tBU	60 (97 : 3)	40
CO_2iPr	40 (95 : 5)	60
	50 (80 :20)	50

The increased leaving group ability of the pyroglutamate auxiliary, which leads to this acyl transfer problem can be explained by examining the different resonance structures of the N-acylated pyroglutamate relative to its imidazolidinone counterpart. **Figure 49** demonstrates the different resonance structures possible for the pyroglutamate derivatives. Resonance structure **I**, in which the positive charge is located on the nitrogen, causes the auxiliary to be very effective at accepting a negative charge, thus making it an excellent leaving group. In the imidazolidinone, this positive charge is delocalized over two nitrogens and in fact probably resides for the most part on the N-methylated nitrogen since this electron donating substituent should stablilize the positive charge on the nitrogen more so than the electron withdrawing acyl substituent on the other nitrogen. As a result, the pyroglutamate auxiliary is an excellent leaving group and the problem of acyl transfer exists. In the imidazolidinone auxiliaries, it is not as good a leaving group and the acyl transfer reaction in not observed.

Figure 49: Explanation of Acyl Transfer Problem in Pyroglutamate Derivatives



9.0 Potential Use of tert-Butyl Pyroglutamate as a Resolving Agent

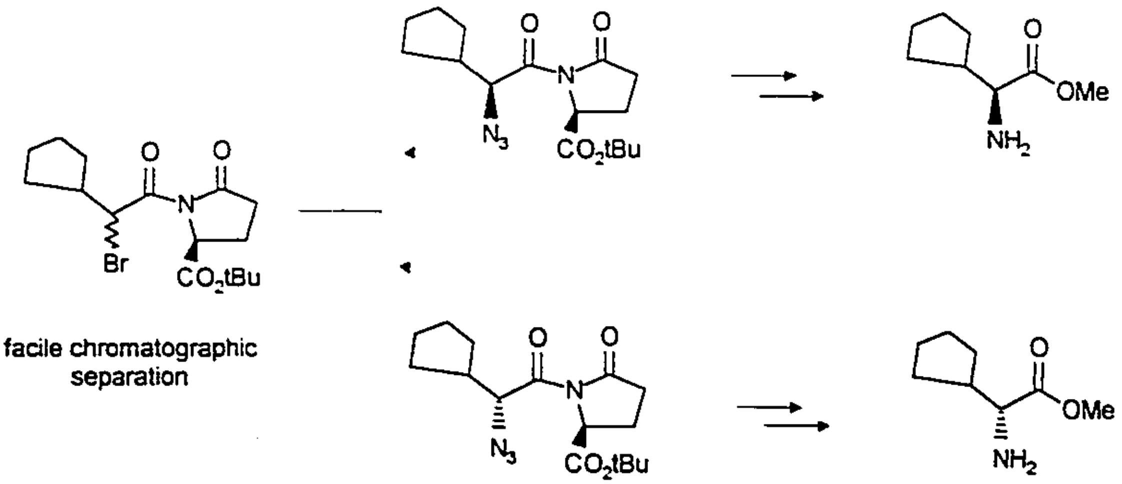
The work done with the pyroglutamate derived auxiliaries did not provide the desired results, however, some interesting results were observed which may provide a practical synthesis of optically active α-amino acids:

The individual diastereomers of the α-bromo tert-butyl pyroglutamate compounds, similar to the tert-butyl imidazolidinone compounds, were very easily separable by silica gel chromatography (2:1 hexanes : EtOAc). This aspect of the ease of chromatographic separation of auxiliary modified α-halo acid derivatives has been previously described in the literature by Song et al[59]. They reported the facile resolution of α-hydroxy and α-halo N-acyloxazolidinones derived from Evans auxiliaries.

The levels of polarity difference between the two diastereomers with both the imidazolidinone and tert-butyl pyroglutamate auxiliaries appear to be superior to those reported by Song for the oxazolidinone. Since tert-butyl pyroglutamate is cheaply and easily prepared on a large scale, it may find use as a valuable derivatizing agent for the chromatographic separation of synthetically versatile α-halocarboxylic acids.

In order to demonstrate the possible synthetic utility of this process, (±)-2-bromo-cyclopentyl acetic acid chloride was prepared in 69 % yield by the procedure of Harpp and coupled to tert-butyl pyroglutamate in 84 % yield using the standard coupling procedure ($K^{+-}OtBu$ in THF). The resulting diastereomeric mixture of α-bromo N-acyl-pyroglutamate derviatives was resolved by silica gel chromatography. The less polar diastereomer ($R_f = 0.50$, 2:1 hexanes : EtOAc) was obtained in an optically pure form in 40 % overall yield and the more polar diastereomer ($R_f = 0.26$, 2 : 1 hexanes : EtOAc) was isolated in 38 % overall yield. The optical purity was demonstrated by the ^{1}H NMR spectrum of each individual diastereomer compared to that of the mixture.

Scheme 21: Chromatographic Separation and Azidination of (5S)-tert-butyl-(2-Bromo-2-Cyclopentyl acetyl)-Pyroglutamate



facile chromatographic separation

Once chromatographically separated, each diastereomer was treated individually with a large excess of sodium azide under phase transfer condtions. The resulting α-azido compounds were obtained with no detectable racemization in essentially quantitative yield (97%). The presence of the azido functionality was easily detected by the presence of a sharp IR signal at 2106 cm^{-1}. The conversion of the α-azido compounds to the corresponding α-amino acids is well documented in the literature[6] and was therefore not carried out.

EXPERIMENTAL:

General Remarks:

All starting materials and reagents were obtained from commercial suppliers and used without further purification. All solvents used were freshly distilled. The dry THF used was distilled from sodium benzophenone ketyl. Triethylamine, benzylamine and dibenzylamine were distilled from calcium hydride and stored over KOH. CH_2Cl_2 was distilled from P_2O_5. The reactions were carried out in flame dried flasks under a dry nitrogen atmosphere and were monitored by thin-layer chromatography (TLC) using various combinations of ethyl acetate-hexanes as the eluent. Visualization of spots was accomplished by either UV light, exposure to iodine vapour or anisaldehyde stain. Short column chromatography was performed using 230-400 Mesh SiO_2 obtained from Terachem Laboratories in the solvent systems specified according to the procedure described by D. F. Taber [60]. The term "concentrated" refers to removal of solvent under reduced pressure with a Buchi Rotovap. Infrared spectra were recorded on a FTIR Bomem MB 100 spectrometer either neat on NaCl pellets or from a reagent grade dichloromethane solution and are reported as λ_{max} in cm $^{-1}$. All ^1H and ^{13}C NMR spectra were obtained, using $CDCl_3$ or d_6-acetone as the solvent, from either a Gemini 200 MHz, a Varian XL-300 MHz or a Bruker 500 MHz spectrometer. The chemical shifts (δ ppm) and coupling constants (in Hertz) are reported in the standard fashion as parts per million downfield from an internal standard, tetramethylsilane (^1H) or the central line (77.0 ppm) of $CDCl_3$ (for ^{13}C). Multiplicities are reported using the following abbreviations; s, singlet; bs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; dt, doublet of triplets; q, quartet; m, multiplet. Low and high resolution mass spectra were recorded on a VG7070 mass spectrometer with a DANI 7070 gas chromatograph. MS peak intensities are given as a percent of the base peak and are shown in parentheses.

General Procedure for the Preparation of α-Halo (R)-Pantolactone Esters

The α-halo (R)-Pantolactone esters used in this study were prepared using one of two synthetic routes

1) *Procedure A: Ketene Trapping Procedure*

A 0.1M solution of the appropriate α-halo acid chloride (obtained commercially or prepared via a literature procedure [34]) in dry THF was added dropwise to a solution of triethylamine and (R)-pantolactone (2.0 equivalents each) in THF at 0°C over a 1h period. The reaction mixture was then quenched with H_2O, and extracted thrice with EtOAc (3 x 20 ml). The combined organic extracts were dried using $MgSO_4$, filtered and evaporated under reduced pressure. Crude products were then purified by column chromatography using the appropriate solvent system and fully characterized.

2) Procedure B: DCC Coupling Method

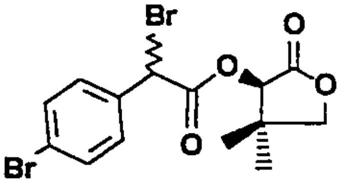
R-pantolactone (1.0 eq), α-halo acid (1.1 eq), DCC (1.1 eq), and DMAP (0.1 eq) were dissolved in dry CH_2Cl_2 and stirred at room temperature under a nitrogen atmosphere until TLC verified that the alcohol had been consumed (16 - 32 h). The precipitate was removed by filtration and the organic phase was washed with 3 x 20 ml of H_2O and 1 x 20 mL of 10% HCl. The organic layer was isolated and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products obtained were purified via column chromatography using the specified eluting solvent systems.

Product Data:

Product Data:

(R)-Pantolacto-2-bromo-2-phenylethanoate, (R)-Pantolacto-2-bromo-butanoate, and (R)-Pantolacto-2-bromo-4-phenyl-butanoate have all been previously reported in the Ph.D. thesis of R. Ben (1994) and all analytical data corresponded to that reported by Dr. Ben.

(R)-Pantolacto-2-bromo-2-(4-bromophenyl)-ethanoate



$C_{14}H_{14}O_4Br_2 = 406$

diastereomeric mixture (1:1 RR : SR)

purification method: silica gel chromatography (5 :1 Hex : EtOAc)

yield: 76 % of a slightly yellow oil

^{1}H NMR (200 MHz, $CDCl_3$): 7.53 - 7.24 (m, 4, arom), 5.37 and 5.32 (2s, 1H), 5.27 and 5.23 (2s, 1H), 3.92 (2s, 2H) 1.20 and 1.13 (2xs, 6H)

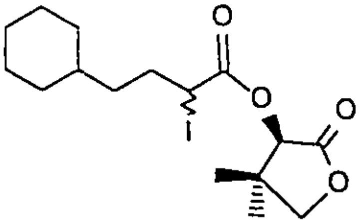
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 171.2, 167.4, 166.8, 134.4, 133.7, 132.3, 132.1, 132.0, 130.7, 130.1, 129.8, 129.6, 123.9, 76.7, 75.5, 76.2, 76.1, 58.2, 57.3, 45.4, 43.8, 23.1, 23.0, 19.8, 19.7

IR: 3072, 1782, 1740

MS: CI (m+1) (m/z %) = 409 (11.0), 407 (22.0), 405 (11.0), 329 (100), 326 (100)

HRMS:	Calculated for $C_{14}H_{14}O_4Br_2$	=	325.0022
	Found:		325.0048

(R)-Pantolacto-2-iodo-(4-cyclohexyl)-butanoate



$C_{16}H_{25}O_4I = 408$

diastereomeric mixture

purification method: silica gel chromatography (5 :1 Hex : EtOAc)

yield: 82 % of a colourless oil

^{1}H NMR (200 MHz, $CDCl_3$): 5.28 and 5.24 (2s, 1H), 4.32 and 4.21 (2t, J = 7.65 Hz, 1H), 3.93 (s, 2H), 1.97 - 1.82 (m, 2H), 1.55 (m, 5H), 1.28 - 1.03 (m, 6H), 1.14 and 1.13 (2s, 3H), 1.08 and 1.06 (2s, 3H), 0.75 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.8, 171.5, 170.9, 170.1, 76.2, 76.1, 75.5, 75.4, 40.8, 40.4, 37.0, 36.9, 36.7, 33.7, 33.0, 32.9, 26.4, 26.1, 22.9, 20.1, 19.8, 19.7

IR: 2932, 2852, 1797, 1745

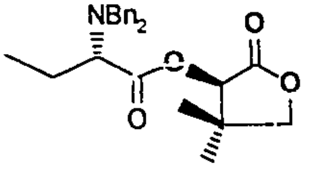
MS: CI (m+1) (m/z %) = 409 (100), 260 (100), 185 (39.0), 133 (100)

α-Dibenzylamino-(R)-Pantolactone Esters - Dynamic Kinetic Resolution General Procedure.

In a dried, nitrogen filled round bottom flask fitted with a magnetic stirrer, α-bromo-(R)-pantolactone ester (1.0 eq), $Bu_4N^+I^-$ (0.2 eq), Et_3N (2.0 eq), and Bn_2NH (1.05 eq) were dissolved in sufficient THF to prepare a 0.2 M solution of starting α-halo ester. The reaction was stirred at room temperature until the α-halo ester was no longer present by TLC (24 - 96h). The reaction was then quenched with distilled H_2O (5 ml). Et_2O (25 ml) was added and the organic phase separated. The aqueous phase was further extracted with ether (2 x 25 ml) and the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated to provide crude product. At this point, a proton NMR was taken of the crude mixture in order to determine the diasteremer ratio. The crude product was subsequently purified by silica gel chromatography using hexane : ethylacetate (5:1) as an eluent.

Product Data:

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-butanoate



$C_{24}H_{29}NO_4 = 395$

diastereomeric mixture (14:1 SR : RR)

purification method: silica gel chromatography (5 :1 Hex : EtOAc)

yield: 66 % of a slightly yellow oil

^{1}H NMR (200 MHz, $CDCl_3$): 7.30 - 7.20 (m, 10H, arom), 5.47 and 5.45 (2s, 1H, 14:1), 4.08 - 4.06 (m, 2H), 3.78 (AB, J_{AB} =14.0 Hz, 4H), 3.36 - 3.33 (m, 1H), 1.83 - 1.76 (m, 2H), 1.20 and 1.13 (2xs, 6H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 171.6, 139.6, 128.9, 128.7, 128.2, 127.0, 127.0, 76.2 74.8, 62.2, 54.2, 40.0, 23.0, 22.9, 20.2, 10.9

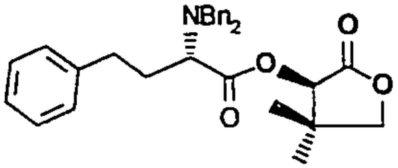
IR: 2810, 1782, 1740

MS: CI (m+1) (m/z %) = 395 (0.3), 131 (100)

Anal.: Calculated for $C_{29}H_{29}NO_4$: C, 72.88; H, 7.39

Found: C, 72.92; H, 7.32

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-4-phenyl-butanoate



$C_{30}H_{33}NO_4 = 471$

diastereomeric mixture (1:1 RS : RR)

purification method: silica gel chromatography (5 :1 Hex : EtOAc)

yield: 56 % of a slightly yellow oil

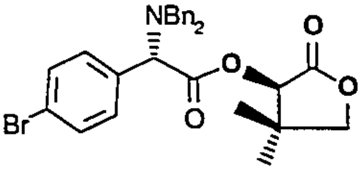
^{1}H NMR (200 MHz, $CDCl_3$): 7.39-7.07 (m, 15 H), 5.48 and 5.46 (2s, 1H, 10:1), 4.03 (s, 2H), 3.97 and 3.67 (2d, J = 13.8 Hz, 4H), 3.50 (t, J=7.7 Hz, 1H), 2.81-2.77 (m, 4H), 1.21 (s, 3H), 1.12 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.3, 171.4, 139.4, 129.0, 128.3, 127.1, 126.0, 76.24, 75.0, 60.2, 54.4, 40.1, 32.4, 31.7, 23.0, 20.4

IR: 1795 (s), 1766 (s)

MS: CI (m+1) (m/z %) = 472 (m+1)

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-2-(4-bromophenyl)-acetate



$C_{28}H_{28}BrNO_4 = 521$

diastereomeric mixture (99:1 SS : RS)

purification method: silica gel chromatography (5 :1 Hex : EtOAc)

yield: 76 % of an off-white solid

m.p. = 145 - 146 °C

^{1}H NMR (200 MHz, $CDCl_3$): 7.48 -7.46 (m, 2H), 7.35 -7.20 (m, 12 H), 5.54 (s, 1H), 4.66 (s, 1H), 4.05 (s, 2H), 3.81 (AB, J =13.9 Hz, 4H), 1.18 and 0.99 (2s, 6H)

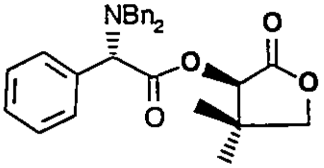
^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.9, 170.4, 138.9, 135.3, 121.6, 130.4, 128.9, 128.4, 127.2, 122.2, 76.2, 75.2, 64.9, 54.0, 40.1, 23.0, 20.1

IR: 2923, 1782 (s), 17

MS: EI (m, m/z %) = 522 (m, 20), 115 (m, 100)

Anal.:	Calculated for $C_{28}H_{28}BrNO_4$:	C, 64.36; H, 5.41; N, 2.68
	Found:	C, 64.35; H, 5.59;, N, 2.43

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-2-phenyl-acetate



$C_{28}H_{29}NO_4$

diastereomeric mixture (12:1 SS : RS)

purification method: silica gel chromatography (3 :1 Hex : EtOAc)

yield: 70% of a pale yellow solid

m.p. = 83 - 85 ^{o}C

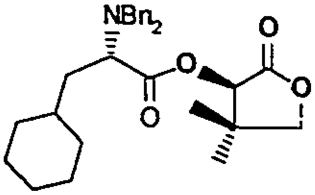
^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20 -7.40 (m, 15H), 5.60 (s, 1H), 4.70 (s, 1H), 4.05 (s, 2H), 3.78 (AB, J_{AB}=9.6 Hz, 4H), 1.27 (s, 3H), 0.95 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 170.5, 138.9, 128.7, 128.4, 128.3, 128.1, 128.0, 127.7, 75.9, 74.7, 65.2, 53.7, 39.8, 22.7, 19.6

IR: (CH_2Cl_2) 2931, 1794, 1748, 1127, 1077
MS: CI (m+1) (m/z %) = 444 (m+1, 50), 288 (100), 91 (100)

Anal.:	Calculated for $C_{28}H_{29}NO_4$:	C, 75.82; H, 6.59
	Found:	C, 75.42; H, 6.58

(R)-Pantolacto-(N,N-dibenzyl)-2-amino-(4-cyclohexyl)-butanoate



$C_{24}H_{29}NO_4$

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (3 :1 Hex : EtOAc)
yield: 70% of a pale yellow oil which was contaminated with ~ 5 % of an α,β unsaturated ester resulting from elimination

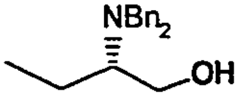
This product could not be obtained in analytically pure form, it coeluted with the elimination by product obtained in the reaction. The material was therefore not characterized and was used as such in the next reaction.

α-dibenzylamino alcohols - General Procedure

In a dried, nitrogen filled round bottom flask, fitted with a magnetic stirrer, α-dibenzylamino-(R)-pantolactone ester (1.0 eq), was dissolved in THF to make a 0.1 M solution. Powdered $LiAlH_4$ (4 eq) was added portionwise over a 30 minute period. The resulting slurry was stirred at RT for 16 hours, then quenched carefully with 25 mL of a 90% sodium potassium tartrate solution and vigorously stirred for 16 hours. EtOAc (50 mL) was added and the organic phase separated. The aqueous phase was further extracted with EtOAc (3 x 15 mL) The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography using hexane : EtOAc (3:1) as the eluent.

Product Data:

(N,N-Dibenzyl)-2-amino-butanol



$C_{18}H_{23}NO = 269$

purification method: silica gel chromatography (3:1 hexanes : EtOAc)

yield: 76 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): 7.31 -7.21 (m, 10H), 3.82 (d, J=13.2 Hz), 3.52 (dd, J=10.6, 4.9 Hz, 2H), 3.40 (m, 3H), 2.74 - 2.66 (m, 1H), 1.83-1.75 (m, 1H), 1.24 (m, 1H), 0.90 (t, J=7.5Hz, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.4, 129.1, 128.5, 127.2, 60.7, 60.5, 53.2, 17.9, 11.8

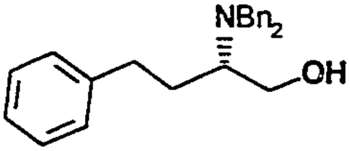
IR: 3434, 2933, 1495, 1052

MS: CI (m+1) (m/z %) = 270 (m+1, 100),91 (96)

Anal.:	Calculated for $C_{18}H_{23}NO$:	C, 80.23; H, 8.62; N, 5.20
	Found:	C, 79.84; H, 8.86; N, 4.89

$[a]_D^{23}$ = +42.6 (CH_2Cl_2, c = 1.16)

(N,N-Dibenzyl)-2-amino-4-phenyl-butanol



$C_{24}H_{27}NO = 345$

purification method: silica gel chromatography (3:1 hexanes :EtOAc)
yield: 76% of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): d= 7.30 -7.13 (m, 15H), 3.77 (d, J= 13.2 Hz, 4H), 3.57 (dd, J= 10.5, 4.9 Hz, 2H), 3.46 (dd, J=10.5, 10.3 Hz, 1H), 3.34 (d, J=13.2 Hz), 3.05 (bs, 1H), 2.82 -2.78 (m, 1H), 2.68 - 2.62 and 2.50 - 2.43 (m, 2H), 2.07 - 1.98 and 1.60 - 1.52 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7, 139.1, 129.0, 128.5, 128.4, 128.3, 127.1, 126.0, 60.6, 58.1, 53.1, 33.2, 27.1

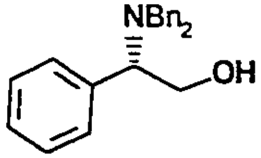
IR: 3611, 3440, 2933, 1603

MS: CI (m+1) (m/z %) = 346 (m+1, 100), 91 (100)

Anal.:	Calculated for $C_{24}H_{27}NO$:	C, 83.42; H, 7.89; N, 4.06
	Found:	C, 83.08; H, 7.74; N, 4.24

$[a]_D^{23}$ = -28.2 (CH_2Cl_2, c = 1.08)

(N,N-Dibenzyl)-2-amino-2-phenyl-ethanol



$C_{22}H_{23}NO$ = 317

purification method: silica gel chromatography (3:1 hexanes :EtOAc)

yield: 87% of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.22(m, 15H), 4.12 (t, J=10.6, 1H), 3.94 - 3.90 (m, 3H), 3.60 (dd, J=10.6, 5.3 Hz, 1H), 3.13 (d, J=13.4 Hz, 2H), 2.98 (bs, 1H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 139.1, 135.0, 129.3, 129.0, 128.6, 128.4, 128.1, 63.1, 60.5, 53.6

IR: 3459, 3029, 2834, 1493, 1028

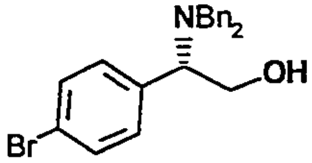
MS: CI (m+1) (m/z %) = 318 (m + 1, 100%), 91 (100)

Anal.: Calculated for $C_{22}H_{23}NO$: C, 83.24; H, 7.32; N, 4.41

Found: C, 83.19; H, 7.14; N, 4.72

$[a]_D^{23}$ = + 17.3 (CH_2Cl_2, c = 1.8)

(N,N-Dibenzyl)-2-amino-2-(4-bromophenyl)-ethanol



$C_{22}H_{22}NOBr = 396$

purification method: silica gel chromatography (3:1 hexanes :EtOAc)

yield: 64 % of a white solid

m.p. = 104 - 105 °C

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.55 - 7.51$ (m, 2H), 7.38 - 7.23 (m, 10 H), 7.13 (m, 2H), 4.08 (t, J=10.6 Hz, 1H), 3.91 - 3.88 (m, 3H), 3.60 (dd, J= 10.6, 5.3 Hz), 3.13 (d, J=13.5 Hz, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 138.8$, 134.2, 131.5, 130.8, 128.9, 128.6, 127.4, 122.0, 62.5, 60.4, 53.5

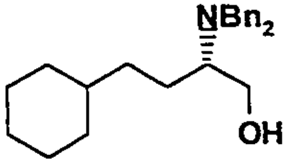
IR: 3468, 2901, 1598

MS: CI (m+1) (m/z %) = 398 (m+1, 94), 91 (100)

Anal.:	Calculated for $C_{22}H_{22}NOBr$:	C, 66.67; H, 5.61; N, 3.53
	Found:	C, 66.71; H, 5.64; N, 3.46

$[a]_D^{23} =$ + 168.2° (CH_2Cl_2, c = 1.00)

(N,N-Dibenzyl)-2-amino-4-cyclohexylbutanol



$C_{23}H_{31}NO = 337$

purification method: silica gel chromatography (3:1 hexanes :EtOAc)

yield: 78 % of a slightly yellow oil

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 - 7.211 (m, 10H), 3.80 (d, J=14.2 Hz, 2H), 3.47 (dd, J=10.2, 4.5 Hz, 1H), 3.39 (d, J= 13.2 Hz, 2H), 3.16 (m, 1H), 2.72 (t, J=4.5 Hz, 2H), 1.69 - 1.64 (m, 5H), 1.57 (bs, 1H), 1.17 (m, 6H), 0.97 (m, 2H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 129.1, 128.5, 127.2, 60.81, 59.2, 53.2, 37.7, 34.7, 33.5, 33.1, 26.6, 26.4, 26.3, 21.9

IR: 3468, 2901, 1598

MS: EI (m, m/z %) = 320 (m- OH, 94), 91 (100)

HRMS:	(m-OH)	Calculated for Found :	$C_{23}H_{30}N$ = 320.2372 320.2367
Anal.:	Calculated for $C_{23}H_{31}NO$:		C, 81.85; H, 9.26
	Found:		C, 81.64; H, 9.38

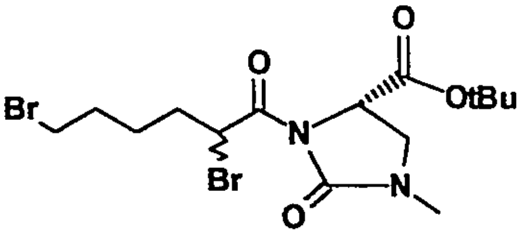
$[a]_D^{23}$ = - 15.6° (CH_2Cl_2, c = 1.06)

General Procedure for the Preparation of (±)-(4S)-1-methyl-(2-halogenated)-2-oxoimidazolidine-4-carboxylates

To a dry, nitrogen filled roundbottom flask was added a 0.1 M THF solution containing tert-butyl-(4S)-1-methyl-2-oxoimidazolidine-4-carboxylate (1.0 eq) which was subsequently cooled to -45°C. A 0.24 M solution of $K^{+-}OtBu$ in dry THF (1.10 eq) was added dropwise over 2 min and the resulting solution is stirred at -45°C for 30 min. The α-halo acid chloride (1.2 eq) was added dropwise via syringe over 2 min and stirring was continued at -30 °C for 1 h and then the reaction mixture was poured into a mixture of Et_2O (50 mL), AcOH (2.0 mL) and brine (50 mL). The organic phase was separated and washed successively with brine, 2% NaOH, and brine. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel with 2:1 hexanes:EtOAc to afford a 1:1 mixture of diastereomers.

Product Data:

(4S)-1-Methyl-3-(2,6-dibromohexanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{15}H_{24}N_2O_4Br_2 = 456$

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 73 % of a slightly yellow oil

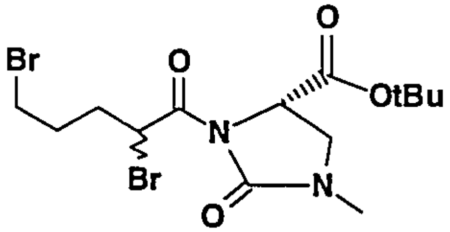
^{1}H NMR (200 MHz, $CDCl_3$): δ=5.70(dt, J = 7.2 Hz, 1H), 4.52 (2 x dd, J=3.8Hz, 10.1 Hz, 1H), 3.60 (2 x dd, J = 10.1, 9.7 Hz, 1H), 3.25 (m, 3H), 2.81 (m, 2H), 1.85 (m, 2H), 1.41 (m, 2H), 1.36 (2 x s, 9H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.1, 168.9, 168.2, 167.9, 153.2, 153.1, 83.4, 83.2, 53.2, 53.1, 46.5, 46.4, 44.3, 43.4, 33.6, 33.2, 31.9, 30.7, 29.7, 27.9, 25.9, 25.8, 25.7

IR: (CH_2Cl_2): 2921, 1741, 1689

MS: CI (m+1) (m/z %) = 455 (m+1, 100), 400 (100), 145 (96)

(4S)-1-Methyl-3-(2,5-dibromopentanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{14}H_{22}N_2O_4Br_2$

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 87 % of a slightly yellow oil

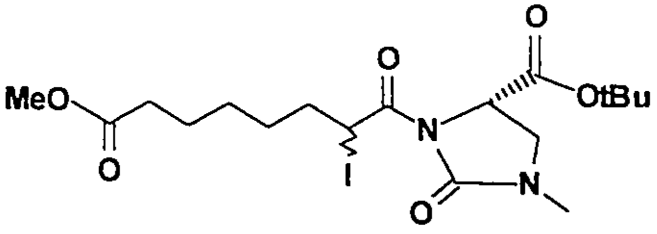
^{1}H NMR (200 MHz, $CDCl_3$): δ=5.79(2 x t, J = 7.2 Hz, 1H), 4.49 (2 x dd, J1=3.8Hz, J2 = 10.1 Hz, 1H), 3.59 (2 x dd, J2=10.1 Hz, J3=9.7 Hz, 1H), 3.256 (m, 2H), 3.25 (2 x dd, J2 = 10.1 Hz, J3 = 9.7 Hz, 1H), 2.76 (s, 3), 2.02 (m, 2H), 1.85 (m, 2H), 1.34 (2 x s, 9H)

^{13}C NMR (200 MHz, $CDCl_3$): δ = 169.9, 168.0, 167.7, 152.8, 83.0, 82.8, 53.0, 52.8, 46.0, 45.9, 34.1, 33.6, 31.9, 31.8, 31.7, 30.4, 27.6, 27.5, 19.1

IR: 1740, 1681

HRMS: $C_{14}H_{22}N_2O_4BrI$ calc = 489.9761
found = 489.9740

(4S)-1-Methyl-3-(8-methyl-2-iodo-suberate)-2-oxoimidazolidine-4-carboxylate



$C_{18}H_{29}N_2O_6I = 496$

diastereomeric mixture (1:1 RS:SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 87 % of a slightly orange oil

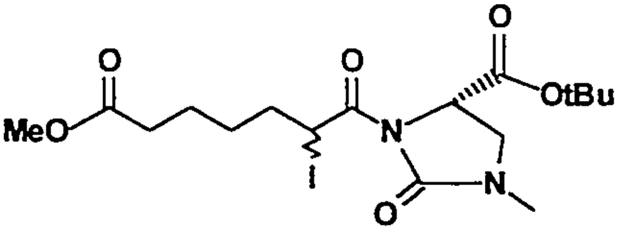
^{1}H NMR (200 MHz, $CDCl_3$): δ=5.76(2xt, 1H), 4.60 (2xdd, 1H), 3.57 (2xs, 3H), 3.23(2xdd, 1H), 2.78 (2xs, 3H), 2.20 (2xt, 2H), 1.90 (m, 2H), 1.52(m, 3H), 1.38(2xs, 9H), 1.25(m, 3H)

^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.1, 170.9, 168.4, 153.2, 82.9, 53.3, 53.1, 51.5, 51.4, 51.3, 46.3, 46.2, 35.5, 35.2, 34.0, 33.9, 30.6, 28.9, 28.7, 28.2, 27.9, 27.8, 24.7, 24.6, 24.5, 21.2, 20.5

IR: 3426, 1738, 1689

MS: CI (m+1) (m/z %) = 497 (m+1, 18), 441 (100), 315 (100), 145 (100)

(4S)-1-Methyl-3-(7-methyl-2-iodo-pimelate)-2-oxoimidazolidine-4-carboxylate



$C_{17}H_{27}N_2O_6I = 482$

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 82 % of a slightly yellow oil which solidifies on standing to a pale yellow solid

m.p. = 80 - 81 °C

^{1}H NMR (200 MHz, $CDCl_3$): δ=5.84(2xt, 1H), 4.61 (2xdd, 1H), 3.66 (2xt, 1), 3.62 (2xs, 3H), 3.34(2xdd, 1H), 2.87 (2xs, 3H), 2.28 (2xt, 2H), 2.00 (m, 2H), 1.65 (m, 2H), 1.50(m, 2H), 1.47 (2xs, 9H),

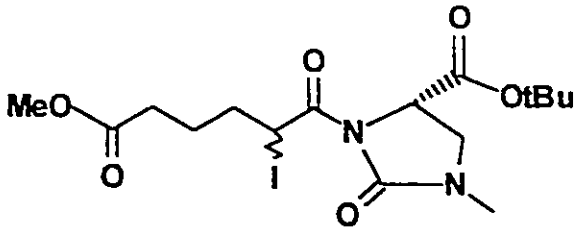
^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7, 170.5, 168.0, 153.1, 83.2, 53.3, 53.1, 51.5, 46.3, 46.2, 46.1, 35.3, 35.0, 33.7, 33.6, 30.7, 28.7, 28.6, 28.5, 27.9, 27.8, 24.0, 20.9, 20.2

IR: 1738, 1689

MS: CI (m+1) (m/z %) = 483 (m+1, 9.2), 427 (100)

Anal.:	Calculated for $C_{17}H_{27}N_2O_6I$:	C, 42.33; H, 5.64; N, 5.81
	Found:	C, 42.79; H, 5.62; N, 5.73

(4S)-1-Methyl-3-(6-methyl-2-iodo-adipate)-2-oxoimidazolidine-4-carboxylate



$C_{16}H_{25}N_2O_6I = 468$

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 93 % of a colorless oil

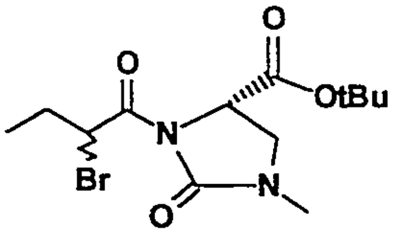
^{1}H NMR (200 MHz, $CDCl_3$): δ=5.86(2xt, J=7.5 Hz, 1H), 4.55 (2xdd, 1H), 3.69 (m,1H), 3.61 (2xs, 3H), 3.30(2xdd, 1H), 2.86 (2xs, 3H), 2.31 (m, 2H), 2.00 (m, 2H), 1.65 (m, 2H), 1.43 (2xs, 9H),

^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4, 173.3, 170.7, 168.3, 168.1, 153.1, 83.3, 83.0, 53.3, 53.1, 53.0, 51.5, 46.5, 46.3, 46.2, 35.1, 34.9, 34.7, 33.1, 32.9, 30.6, 27.9, 27.8, 24.6, 24.5, 24.4, 20.4, 19.7, 19.2

IR: 1738, 1682

MS: CI (m+1) (m/z %) = 469 (m+1, 33.5), 413 (100), 380 (22.8)

(4S)-1-Methyl-3-((±)-2-bromo butanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{13}H_{21}N_2O_4Br$ = 348

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 88 % of a colourless oil which crystallizes over time to a white solid

m.p. = 62 - 63 °C

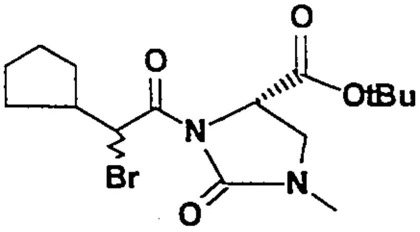
^{1}H NMR (200 MHz, $CDCl_3$): δ=5.78 (2xt, J=6.5 Hz, 1H), 4.66 (2xdd, 1H), 3.70 (2xt, J=9.5 Hz, 1H), 3.29(2xdd, 1H), 2.90 (2xs, 3H), 1.85 - 2.30 (m, 2H), 1.47 (2xs, 9H), 0.92-1.17 (m, 3H)

^{13}C NMR (300 MHz, $CDCl_3$): δ = 169.8, 169.5, 168.9, 168.5, 153.7, 83.7, 83.6, 53.8, 53.7, 46.9, 46.3, 31.2, 28.7, 28.4, 28.1, 14.8, 12.5, 12.4

IR: (CH_2Cl_2) 1738, 1682

MS: CI (m+1) (m/z %) = 349 (m+1, 38.6), 293 (89.5), 215 (100)

(4S)-1-Methyl-3-((±)-2-iodo-2-cyclopentyl-acetyl)-2-oxoimidazolidine-4-carboxylate



$C_{16}H_{25}N_2O_4Br = 388$

diastereomeric mixture (1:1 RS:SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)
yield: 47 % of a slightly orange oil

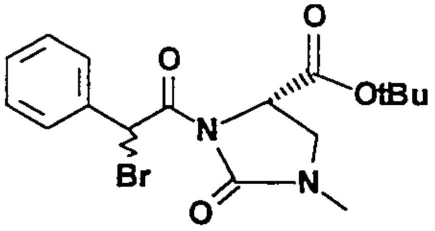
^{1}H NMR (500 MHz, $CDCl_3$): δ=5.76 and 5.68 (2xd, J = 9.8 Hz, 1H), 4.65 (m, 1H), 3.69 (m,1H), 3.30(m, 1H), 2.87 (2xs, 3H), 2.62 (m, 1H), 1.93 (m, 1H), 1.77 (m, 1H), 1.65 - 1.45 (m, 4H), 1.45 (2xs, 9H), 1.24 and 1.07 (2xm, 2H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1, 168.3, 168.0, 83.3, 83.0, 53.3, 53.2, 49.5, 49.1, 46.3, 46.2, 43.4, 43.3, 42.9, 31.6, 31.4, 30.8, 30.6, 27.8, 26.1, 25.1, 24.9

IR: 2915, 1741, 1687

MS: CI (m+1) (m/z %) = 389 (m+1, 45.7), 391 (m+3, 42.5), 333 (86.9), 253 (73.0)

(4S)-1-Methyl-3-((±)-2-bromo-2-phenyl-acetyl)-2-oxoimidazolidine-4-carboxylate



$C_{17}H_{21}N_2O_4Br = 396$

diastereomeric mixture (1:1 RS:SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 77 % of a white solid

m.p.: 166 - 168 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.62 - 7.59 (m, 2H), 7.35 - 7.26 (m, 3H), 7.08 (s, 1H), 4.68 and 4.58 (2xdd, J = 10.3, 4.3 Hz, 1H), 3.68 and 3.60 (2xdd, J= 10.3, 9.8 Hz, 1H), 3.32 and 3.27 (2xdd, J= 9.8, 4.3 Hz, 1H), 2.86 (2xs, 3H), 1.50 and 1.31 (2xs, 9H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0, 167.9, 153.1, 136.1, 136.0, 129.5, 129.4, 129.0, 128.9, 128.7, 128.6, 128.5, 83.3, 83.0, 53.4, 46.4, 46.3, 45.7, 44.7, 30.9, 30.7, 27.9, 26.6

IR: 1741, 1694

MS: CI (m+1) (m/z %) = 396 (m+1, 4), 398 (m+3, 5), 342 (100), 340 (100),

HRMS: on M - C_4H_8 (isobutylene)
calculated for $C_{13}H_{13}N_2O_4Br$ = 340.0033
found 340.0058

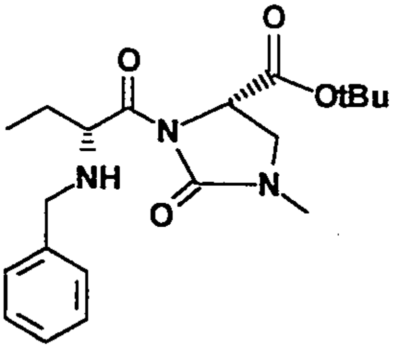
Anal.: Calculated for $C_{17}H_{21}N_2O_4Br$: C, 51.40; H, 5.33; N, 7.05
Found: C, 51.68; H, 5.35; N, 6.98

General Procedure For Dynamic Kinetic Resolution

In a dried, nitrogen filled round bottom flask fitted with a magnetic stirrer, α-halo imidazolidinone (1.0 eq), $Bu_4N^+I^-$ (0.2 eq), Et_3N (2.0 eq), and $BnNH_2$ (1.05 eq) were dissolved in sufficient THF to prepare a 0.2 M solution of starting α-halo imidazolidinone. The reaction was stirred at room temperature until the α-halo imidazolidinone was no longer present by TLC (24 - 96h). The reaction was then quenched with distilled H_2O (5 mL). Et_2O (25 ml) was added and the organic phase separated. The aqueous phase was further extracted with ether (2 x 25 mL) and the organic extracts were combined, dried over $MgSO_4$, filtered and concentrated to provide crude product. At this point, a proton NMR was taken of the crude mixture in order to determine the diastereomer ratio. The crude product was subsequently purified by silica gel chromatography using hexane : ethylacetate (2:1) as an eluent.

Product Data:

(4S)-1-methyl-3-((2R)-benzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{20}H_{29}N_3O_4 = 375$

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 92 % of a clear oil which crystallizes to a white solid on standing

m.p. 88 - 90 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.29(m, 5H), 4.53 (dd, J= 10.3, 4.0 Hz, 1H), 4.57 (dd, J= 7.2, 5.4 Hz, 1H), 3.67 (AB, J=12.4 Hz, 2H), 3.64 (t, J=9.9 Hz, 1H), 3.28 (dd, J= 9.7, 4.0 Hz, 1H), 2.85 (s, 3H), 1.40-1.70 (m, 2H), 1.48 (s, 9H), 0.96 (t, J= 7.5 Hz, 3H)

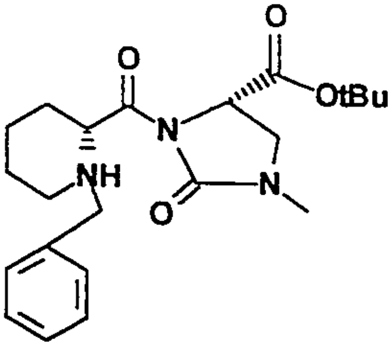
^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 168.8, 153.7, 140.1, 128.5, 128.3, 126.9, 82.9, 60.7, 53.2, 52.0, 46.7, 30.6, 27.9, 26.7, 10.3

IR: (CH_2Cl_2) 3425, 1738, 1677

MS: CI (m+1) (m/z %) = 376 (m+1, 100), 320 (85.1), 208 (84.0)

$[\alpha]_D^{23}$ (R,S) diastereomer = -19.5° (c = 2.6, MeOH)

(4S)-1-methyl-3-((R)-N-benzyl piperidine)-2-oxoimidazolidine-4-carboxylate



$C_{22}H_{31}N_3O_4 = 401$

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 66% of a viscous, yellow oil

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.30(m, 5H), 4.63 (dd, J = 4.2 Hz, 9.9 Hz, 1H), 4.58 (bs, 1H), 3.88 (bm, 1H), 3.64 (t, J=9.9 Hz, 1H), 3.36 (bs, 1H), 3.29 (dd, J = 9.9 Hz, 4.2 Hz, 1H), 3.03 (bs, 1H), 2.86 (s, 3H), 2.15 (bm, 1H), 1.94 (bm, 1H), 1.75 (bm, 1H), 1.52 (bm, 3H), 1.40 (bm, 2H), 1.36 (s, 9H)

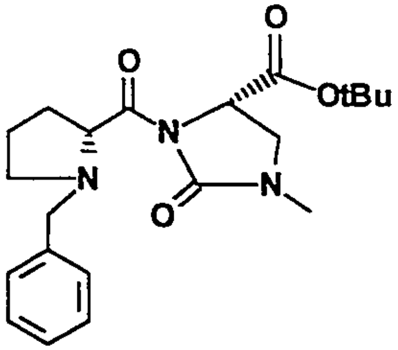
^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 153.4, 129.4, 127.7, 126.6, 82.6, 62.6, 62.5, 53.0, 50.4, 46.2, 30.3, 29.2, 27.5, 24.8, 22.3

IR: 3428, 1738, 1685

HRMS: $C_{22}H_{31}N_3O_4$ calc = 401.2293
found = 401. 2272

$[\alpha]_D^{23}$ = - 2.4° (c = 0.33, CH_2Cl_2)

(4S)-1-methyl-3-((R)-N-benzyl proline)-2-oxoimidazolidine-4-carboxylate



$C_{21}H_{29}N_3O_4 = 387$

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 83 % of a viscous yellow material

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.15(m, 5H), 4.55 (dd, J = 4.3 Hz, 10.2 Hz, 1H), 4.44 (dd, J = 6.0 Hz, 7.0 Hz, 1H), 3.61 (AB, J_{AB} = 9.6 Hz, 2H), 3.55 (dd, J = 10.2, 9.7 Hz, 1H), 3.20 (dd, J = 9.7 Hz, 4.3 Hz, 1H), 2.90 (m, 1H), 2.76 (s, 3H), 2.25 (m, 2H), 1.75 (m, 3H), 1.36 (s, 9H)

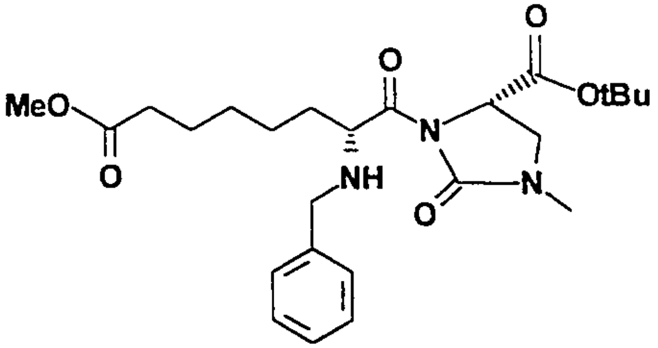
^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.7, 168.6, 153.5, 138.3, 129.0, 127.8, 126.6, 82.5, 64.2, 57.3, 52.9, 51.9, 46.4, 30.3, 29.1, 27.5,22.5

IR: 3426, 1738, 1689

HRMS: $C_{21}H_{29}N_3O_4$ calc = 387.2180
found = 387.2190

$[\alpha]_D^{23}$ = + 13.8° (c = 0.69, CH_2Cl_2)

(4S)-1-methyl-3-((2R)-8-methyl-2-benzylamino-suberate)-2-oxoimidazolidine-4-carboxylate



$C_{25}H_{37}N_3O_6$.= 475

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 74 % of a slightly yellow oil

^{1}H NMR (200 MHz, $CDCl_3$): δ=7.30(m, 5H), 4.61 (dd, J = 10.2, 4.1 Hz, 1H), 4.60 (m, 1H), 3.66(AB, J_{AB} = 12.5 Hz, 2H), 3.65 (dd, J = 10.2, 9.6 Hz, 1H) 3.62 (s, 3H), 3.30(dd, J = 4.1, 9.6 Hz, 1H), 2.86 (s, 3H), 2.30 (t, J=7.3 Hz, 2H), 1.60 (m, 4H), 1.48 (s, 9H), 1.40 (m, 4H)

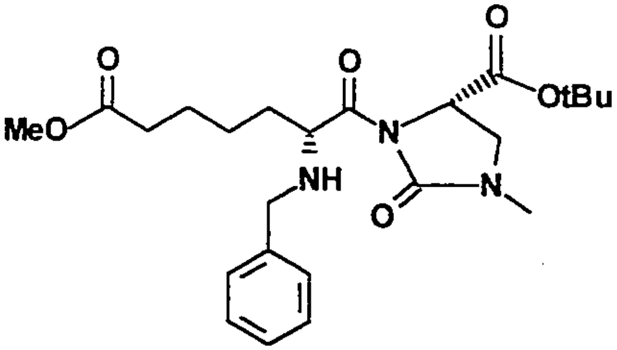
^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 174.3, 168.8, 153.7, 140.3, 131.2, 128.4, 128.2, 126.8, 82.9, 59.5, 53.2, 52.0, 51.4, 46.7, 34.0, 33.5, 30.6, 28.9, 27.9, 27.8, 25.5, 24.8

IR: 3425, 1737, 1678

MS: CI (m+1) (m/z %) = 476 (m+1, 26), 248 (100), 91 (100)

$[\alpha]_D^{23}$ = - 50.5° (c = 0.66, CH_2Cl_2)

(4S)-1-methyl-3-((2R)-7-methyl-2-benzylamino-pimelate)-2-oxoimidazolidine-4-carboxylate



$C_{24}H_{35}N_3O_6 = 461$

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 95 % of a slightly yellow oil

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.25(m, 5H), 4.65 (dd, J = 10.3, 3.7 Hz, 1H), 4.56 (dd, J=8.5, 4.4 Hz, 1H), 3.81 (dd, J = 10.3, 9.7 Hz, 1H), 3.65 (AB, JAB = 12.8 Hz, 2H), 3.62 (s, 3H), 3.40(dd, J = 3.7, 9.7 Hz, 1H), 2.82 (s, 3H), 2.26 (t, J=7.4 Hz, 2H), 2.04 (m, 2H), 1.50 (m, 4H), 1.48 (s, 9H)

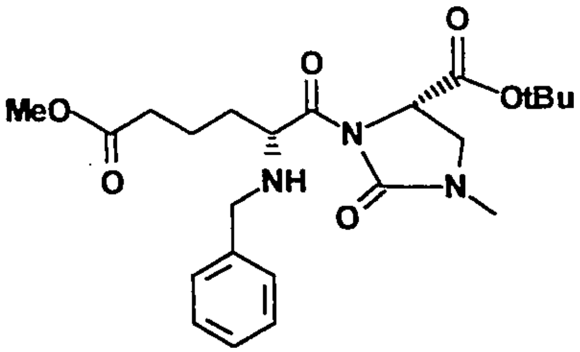
^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.7, 174.1, 168.8, 153.7, 140.5, 128.3, 128.2, 126.7, 82.8, 59.3, 53.2, 51.9, 51.4, 46.7, 33.9, 33.3, 30.6, 27.9, 27.8, 25.4, 24.7

IR: 3425, 1737, 1678

MS: CI (m+1) (m/z %) = 462 (m+1, 100), 406 (21.2), 234 (47.1), 91 (100)

$[\alpha]_D^{23}$ = - 31.5° (c = 0.34, CH_2Cl_2)

(4S)-1-methyl-3-((2R)-7-methyl-2-benzylamino-adipate)-2-oxoimidazolidine-4-carboxylate



$C_{23}H_{33}N_3O_6 = 447$

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 80 % of a slightly yellow oil

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.19 (m, 5H), 4.50 (dd, J = 10.3, 3.7 Hz, 1H), 4.49 (dd, J=8.5, 4.4 Hz, 1H), 3.52 (dd, J = 10.3, 9.7 Hz, 1H), 3.50 (AB, JAB = 12.8 Hz, 2H), 3.52 (s, 3H), 3.20(dd, J = 3.7, 9.7 Hz, 1H), 2.74 (s, 3H), 2.26 (t, J=7.4 Hz, 2H), 1.70 (m, 4H), 1.40 (s, 9H)

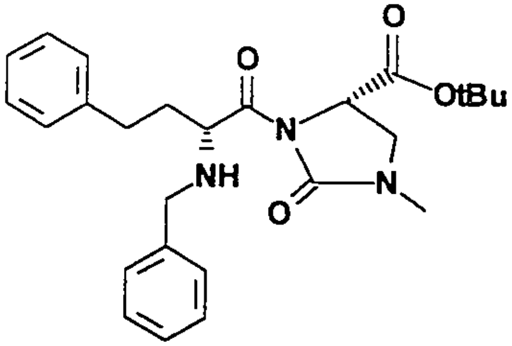
^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 173.5, 168.4, 153.3, 140.1, 128.0, 127.8, 126.4, 82.4, 58.6, 52.8, 51.5, 51.0, 46.2, 33.2, 32.5, 30.1, 27.5, 21.0

IR: 3425, 1737, 1678

MS: CI (m+1) (m/z %) = 448 (m+1, 100), 392 (42.2), 220 (98.4)

$[\alpha]_D^{23}$ = - 21.2° (c = 1.20, CH_2Cl_2)

(4S)-1-methyl-3-((2R)-2-benzylamino-4-phenyl-butanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{26}H_{33}N_3O_4 = 451$

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 86 % of an orange solid

m.p. 76 -78 °C

^{1}**H NMR** (500 MHz, $CDCl_3$): δ= 7.23 (m, 10H), 4.70 (dd, J = 7.5, 5.0 Hz, 1H), 4.51 (dd, J = 10.0, 4.0 Hz, 1H), 3.70 (AB, J_{AB} = 13.0 Hz, 2H), 3.60 (t, J = 10.0 Hz, 1H), 3.27 (dd, J = 10.0 Hz, 4.0 Hz, 1H), 2.86 (s, 3H), 2.68 (m, 1H), 2.03 (m, 1H), 1.80 (m, 1H), 1.49 (s, 9H)

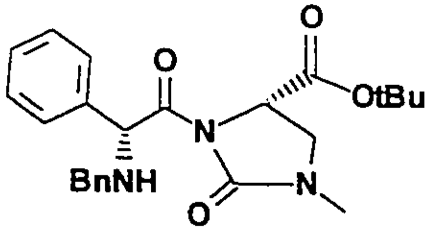
^{13}**C NMR** (75 MHz, $CDCl_3$): δ = 176.4, 168.7, 153.6, 142.1, 140.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 126.7, 125.6, 82.8, 59.5, 53.1, 51.8, 46.6, 35.3, 32.4, 30.5, 27.8

IR: 3425, 1737, 1638

Anal.:	Calculated for $C_{17}H_{21}N_2O_4Br$:	C, 69.16; H, 7.37; N, 9.31
	Found:	C, 69.34; H, 7.25; N, 8.91

$[\alpha]_D^{23}$ = - 23.0° (c = 0.90, CH_2Cl_2)

(4S)-1-methyl-3-((2R)-2-benzylamino-2-phenyl-acetyl)-2-oxoimidazolidine-4-carboxylate



$C_{24}H_{29}N_3O_4 = 423$

purification method: silica gel chromatography (2 :1 hexanes : EtOAc)

yield: 82 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.42 - 7.12 (m, 10H), 5.89 (s, 1H), 4.56 (dd, J = 10.2, 3.8 Hz, 1H), 3.79 (AB, J_{AB} = 12.4 Hz, 2H), 3.56 (dd, J = 10.2, 9.8 Hz, 1H), 3.27 (dd, J = 9.8, 3.8 Hz, 1H), 2.81 (s, 3H), 1.51 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 168.8, 153.3, 139.7, 138.4, 128.9, 128.6, 128.2, 127.8, 127.0, 83.0, 62.5, 53.3, 52.0, 46.5, 30.6, 27.9

IR: 1742, 1680

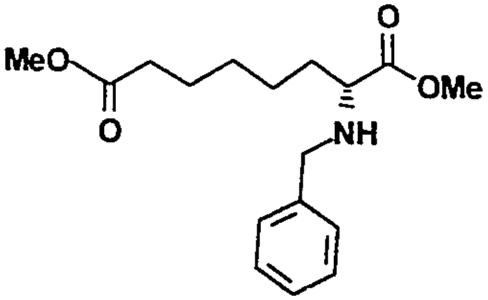
MS: CI (m+1) (m/z %) = 424 (m+1, 100), 368 (21.0), 196 (41.8)

$[\alpha]_D^{23}$ = -12.6 (CH_2Cl_2, c = 0.34)

General Procedure for Removing the Imidazolidinone Chiral Auxiliary

The DKR products (1.0 eq) were dissolved in sufficient MeOH to prepare a 0.2 M solution. A 2.4 M NaOMe solution (1.05 eq) was subsequentlly added via syringe and the resulting solution was stirred until the TLC demonstrated no remaining starting material (2 - 6 h). The reaction was quenched with 1% HCl, and the methanol was removed under reduced pressure. The aqueous layer was extracted with 3 x 20 mL of Et_2O and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting crude material was purified by silica gel chromatography using 3 : 1 hexanes : EtOAc as the eluent.

Dimethyl-(2R)-benzylamino-suberate



$C_{17}H_{25}NO_4 = 307$

purification method: silica gel chromatography (3 :1 hexanes : EtOAc)

yield: 96 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.27(m, 5H), 3.70 (AB, JAB = 12.9 Hz, 2H), 3.69 (S, 3H), 3.62 (s, 3H), 3.23 (t, J=6.5 Hz, 1H), 2.26 (t, J=7.3 Hz, 2H), 1.60 (m, 4H), 1.30 (m, 4H)

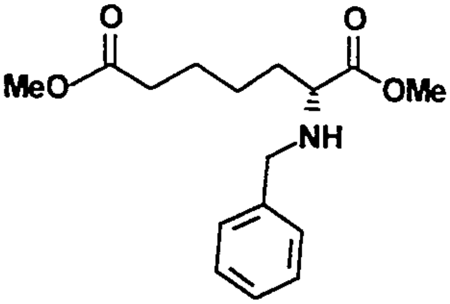
^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 174.1, 139.7, 128.3, 128.2, 127.0, 60.5, 52.1, 51.6, 51.4, 33.9, 33.3, 28.8, 25.3, 24.7

IR: 3425, 1737, 1678

MS: CI (m+1) (m/z %) = 308 (m+1, 100), 248 (61.7)

$[\alpha]_D^{23}$ = + 22.8 (CH_2Cl_2, c = 0.85)

dimethyl-(2R)-benzylamino-pimelate



$C_{16}H_{23}NO_4 = 293$

purification method: silica gel chromatography (3 :1 hexanes : EtOAc)

yield: 97 % of a colourless oil

^{1}**H NMR** (500 MHz, $CDCl_3$): δ=7.24(m, 5H), 3.68 (s, 3H), 3.67 (AB, JAB = 12.9 Hz, 2H), 3.62 (s, 3H), 3.22 (t, J=6.6 Hz, 1H), 2.26 (t, J=7.0 Hz, 2H), 1.60 (m, 4H), 1.41 (m, 2H)

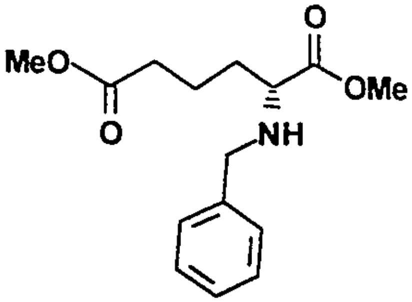
^{13}**C NMR** (75 MHz, $CDCl_3$): δ = 176.5, 174.5, 140.4, 128.9, 128.8, 127.7, 61.0, 52.7, 52.3, 52.1, 34.4, 33.7, 25.9, 25.2

IR: 3425, 1736, 1360

MS: CI (m+1) (m/z %) = 294 (m+1, 100), 234 (80)

$[\alpha]_D^{23}$ = + 24.0 (CH_2Cl_2, c = 1.97)

dimethyl-(2R)-benzylamino-adipate



$C_{15}H_{21}NO_4 = 279$

purification method: silica gel chromatography (3 :1 hexanes : EtOAc)

yield: 96 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.25 (m, 5H), 3.69 (AB, JAB = 13.0 Hz, 2H), 3.70 (s, 3H), 3.64 (s, 3H), 3.24 (t, J=6.6 Hz, 1H), 2.28 (t, J=7.0 Hz, 2H), 1.65 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 173.7, 139.6, 128.3, 128.2, 127.1, 60.3, 52.1, 51.7, 51.5, 33.6, 32.7, 21.3

IR: 3425, 1737, 1678

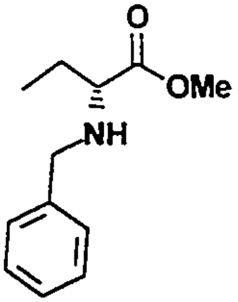
MS: CI (m+1) (m/z %) = 280 (m+1, 100), 220 (75.6)

HRMS: on m/z = 220 (-CO_2Me)

$C_{13}H_{18}NO_2$	calc:	220.1329
	found	220.1321

$[\alpha]_D^{23}$ = + 26.0 (CH_2Cl_2, c = 1.23)

methyl-(2R)-benzylaminobutanoate



$C_{12}H_{17}NO_2 = 207$

purification method: silica gel chromatography (3 :1 hexanes : EtOAc)

yield: 94 % of a colourless oil

^{1}H NMR (200 MHz, $CDCl_3$): δ=7.32–7.27 (m, 5H), 3.70 (AB, J=13.0 Hz, 2H), 3.71 (s, 3H), 3.21 (t, J=6.6 Hz, 1H), 1.89 (pentet, J=6.6 Hz, 2H), 0.92 (t, J=7.5 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 139.8, 128.3, 128.2, 127.0, 61.9, 52.1, 51.6, 25.6, 10.1

IR: (CH_2Cl_2) 3326, 1732

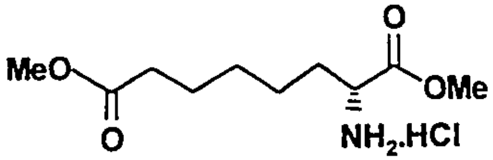
MS: CI (m+1) (m/z %) = 208 (m+1, 32.0), 148 (100), 91 (100)

$[\alpha]_D^{23}$ = + 11.6 ° (c = 3.18, MeOH)

General Procedure for Debenzylation by Catalytic Hydrogenation

A flame dried, two necked flask with a stop cock was charged with the N-benzylated α-amino-methyl ester (1.0 eq) and enough methanol to prepare a 0.1 M solution of the starting material. 10 % Palladium on carbon (10 % of the weight of the starting material) was added and the hydrogen balloon attached. The flask was sequentially evacuated and filled with hydrogen three times. When a sufficiently pure hydrogen atmosphere was provided the mixture was stirred until TLC demonstrated no remaining N-benzylated material (4 - 18 h). After each TLC sample was obtained the reaction was sequentially evacuated and filled with hydrogen three times. When the reaction was judged complete, the reaction mixture was filtered through a thin pad of celite and the celite was subsequently rinsed with methanol (3 x 25 mL). The methanolic filtrate was then saturated with dry HCl (generated by dropping H_2SO_4 on NaCl), stoppered tightly and placed at -5 °C for 12 - 16 h. The solvent was subsequently removed under reduced pressure to provide an oily material which solidfied on standing. The crude product was then purified by recrystallization (see individual compound data for purification method).

dimethyl-D-α-aminosuberate hydrochloride



$C_{10}H_{19}NO_4 = 217$

purification method: recrystallization from hexanes

yield: 92 % of a white solid

m.p. 103 - 104°C

^{1}H NMR (500 MHz, $CDCl_3$): δ=4.22 (t, J=6.4 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 2.47 (t, J=7.4 Hz, 2H), 2.00 (m, 2H), 1.69 (m, 2H), 1.47 (m, 4H)

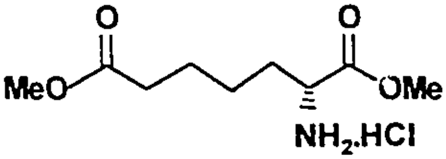
^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 172.4, 54.9, 54.3, 53.5, 34.9, 30.9, 29.1, 25.3, 25.2

IR: 1748, 2348, 2138

MS: CI (m+1) (m/z %) = 218 (m+1, 100), 158 (68.4), 126 (10.3)

$[\alpha]_D^{23}$ = -17.8° (c = 1.20, MeOH)

dimethyl-D-α-aminopimelate hydrochloride



$C_9H_{17}NO_4 = 203$

purification method: recrystallize from 5 : 1 : 1 hexanes : EtOAc : Et_2O

yield: 96 % of an off-white solid

m.p. 79 - 80 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ=4.23 (t, J=6.4 Hz, 1H), 3.92 (s, 3H), 3.77 (s, 3H), 2.50 (t, J=7.4 Hz, 2H), 2.07 (m, 2H), 1.73 (m, 2H), 1.47 (m, 2H)

^{13}C NMR (75 MHz, D_2O): δ = 178.6, 172.2, 111.3, 54.9, 54.1, 53.6, 34.6, 30.8, 25.1

IR: 1748, 2348, 2138

MS: CI (m+1) (m/z %) = 204 (m+1, 100), 172 (27.9), 144 (99.0)

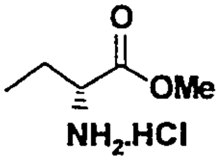
HRMS: on m/z = 144 ($-CO_2Me$)

$C_7H_{14}NO_2$ calc: 144.1034

found 144.1045

$[\alpha]_D^{23}$ = - 16.0 ° (CH_2Cl_2, c= 1.15)

methyl-D-α-aminobutanoate hydrochloride



$C_5H_{11}NO_2 \cdot HCl = 207$

purification method: recrystallization from hexanes

yield: 88 % of an off-white solid

m.p.: 56 - 58 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ=4.18(t, J=6.2 Hz, 1H), 3.91 (s, 3H), 2.05 (m, 2H), 1.07 (t, J = 7.6 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 54.4, 53.1, 23.7, 9.6

IR: (CH_2Cl_2) 3326, 1732

MS: CI (m+1) (m/z %) = 208 (m+1, 32.0), 148 (100), 91 (100)

$[\alpha]_D^{23}$ = - 8.0 o (H_2O, c = 4.0)

Proof of Diastereoselectivity: Preparation of the Non - DKR Diastereomer of (4S)-1-methyl-3-(2-benzylamino-butyryl)-2-oxoimidazolidine-4-carboxylate

The individual diastereomers of (4S)-1-methyl-3-(2-bromo-butanoyl)-2-oxoimidazolidine-4-carboxylate were separated by silica gel chromatography and each was independently submitted to the following reaction conditions:

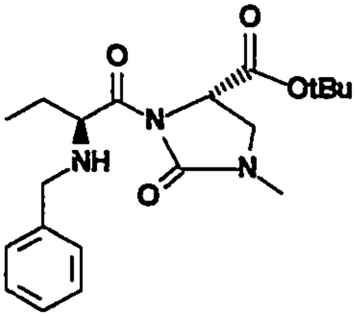
The diastereomerically pure α-bromo imidazolidinone (1.0 eq) was dissolved in sufficient CH_2Cl_2 to prepare a 0.1 M solution. To this solution was added an equal volume of H_2O, NaN_3 (3.0 eq), and $PhEt_3N^+Cl^-$ (0.1 eq). The resulting two phase mixture was stirred vigorously until TLC analysis (2 : 1 hexanes : EtOAc) demonstrated the disappearance of starting material (36 - 48 h). The reaction was then poured into a separatory funnel and the organic phase isolated. The aqueous phase was further extracted with Et_2O (2 x 15 mL), the organics were then combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material thus obtained was a colourless oil and was subsequently analysed by IR and demonstrated a sharp absorbance at 2108 cm-1 thus indicating the presence of the azido functionality. This product was used as such in the following reaction.

Reduction and Monobenzylation of (4S)-1-methyl-3-(2-azido-butyryl)-2-oxoimidazolidine-4-carboxylates

A flame dried, two necked flask with a stop cock was charged with the α-azido imidazolidinone (0.10 g, 0.322 mmole, 1.0 equivalents) and dissolved in MeOH (3.0 mL). 10 % Palladium on carbon (0.02 g) was added and the hydrogen balloon attached. The flask was sequentially evacuated and filled with hydrogen three times. When a sufficiently pure hydrogen atmosphere was provided, the mixture was stirred until TLC analysis demonstrated no remaining starting material. The reaction was judged complete after 3 h and the reaction mixture was filtered through a thin pad of celite and the celite was subsequently rinsed with methanol (3 x 5.0 mL). The methanolic filtrate was then concentrated in vacuo to provide 0.086 g of a clear oil which was not characterized and used as such for the benzylation reaction. The oil was redissolved in dry THF (3.0 mL), Et_3N (0.09 mL, 0.65 mmole, 2.0 equivalents) and benzylbromide (0.04 mL, 0.322 mmole, 1.0 equivalent) were both added by syringe and the resulting solution was stirred for 18 h. The THF was removed under reduced pressure and the resulting sludge was taken up into Et_2O (15 mL), washed with H_2O (5.0 mL) and brine (5.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuo. The crude product was purified by silica gel chromatography using 3 : 1 hexanes : EtOAc as the eluent to provide 0.105 g (87 % for two steps) of a compound which had the following characteristics.

Product Data

(4S)-1-methyl-3-((2S)-benzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{20}H_{29}N_3O_4 = 375$

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 92 % of a clear oil which crystallizes to a white solid on standing

m.p. 120 -122 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.26(m, 5H), 4.62 (dd, J= 10.4, 4.0 Hz, 1H), 4.49 (dd, J= 7.8, 4.5 Hz, 1H), 3.76 (dd, J = 10.4, 9.7 Hz, 1H), 3.61 (AB, J=13.1 Hz, 2H), 3.38 (dd, J= 9.7, 4.0 Hz, 1H), 2.87 (s, 3H), 1.40-1.70 (m, 2H), 1.44 (s, 9H), 1.00 (t, J= 7.4 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 168.7, 153.9, 140.3, 128.4, 128.2, 126.9, 82.9, 60.5, 53.1, 52.3, 46.7, 30.6, 27.7, 26.5, 10.3

IR: (CH_2Cl_2) 3425, 1738, 1677

MS: CI (m+1) (m/z %) = 376 (m+1, 100), 320 (85.1), 208 (84.0)

$[\alpha]_D^{23}$ (S,S) diastereomer = -61.0° (c = 0.29, MeOH)

Determination of Absolute Stereochemistry:

Preparation of 2-benzylamino butanol

A: From DKR Product

The chiral auxiliary was removed according to the previously described procedure (NaOMe in MeOH).

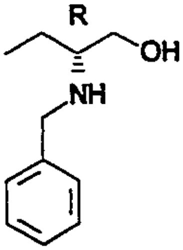
In a flame dried, nitrogen filled round bottom flask fitted with a magnetic stirrer methyl 2-benzylamino butanoate (0.21 g, 1.0 mmole, 1.0 equiv), was dissolved in THF (5 mL) and cooled to 0°C. Powdered LiAlH4 (0.04 g, 4.5 equivalents) was added portionwise over a 10 minute period. The resulting slurry was stirred at 0oC for 1 hour and then allowed to warm to room temperature for 3 hours. The reaction was then quenched carefully with saturated sodium potassium tartrate solution (10 mL) and vigorously stirred for 14 hours. EtOAc (25 mL) was added and the organic phase separated. The aqueous phase was further extracted with EtOAc (3 x 10 mL). The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was then purified by recrystallization from hexanes to yield 0.13 g (78 %) a white crystalline solid as fine white shards.

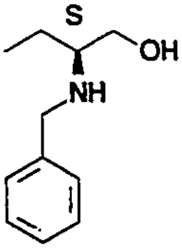
B: From Commercial 2-amino butanol

Commercial 2-amino butanol (0.07 g, 0.785 mmole, 1.0 equivalent) was dissolved in THF. K_2CO_3 (0.54 g, 3.93 mmole, 5.0 equivalents) and benzylbromide (0.10 mL, 0.82 mmole, 1.05 equivalent) was added by syringe and the resulting solution was stirred for 72 h. The resulting slurry was filtered, the THF was removed under reduced pressure and the resulting sludge was taken up into Et_2O (15 mL), washed with H_2O (5.0 mL) and brine (5.0 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuo. The crude product was purified by silica gel chromatography using 3 : 1 hexanes : EtOAc as the eluent and then recrystallized from hexanes to provide 0.12 g (86 %) of a crystalline compound.

Product Data

2-benzylamino butanol





$C_{11}H_{17}NO = 179$

purification method: recrystallization from hexanes

yield: 73 and 86 % of white solid shards

m.p. 75 - 76 °C for both

^{1}**H NMR** (200 MHz, $CDCl_3$): $\delta = 7.31$ (m, 5H), 3.78 (AB, JAB = 13.0 Hz, 2H), 3.64 (dd, J = 10.7, 4.0 Hz, 1H), 3.32 (dd, J = 10.6, 6.2 Hz, 1H), 2.59 (m, 1H), 1.50 (m, 2H), 0.90 (t, J = 7.5 Hz, 3H)

IR: 3425, 3326, 1360

MS: CI (m+1) (m/z %) = 180 (100), 162 (17.2), 148 (51.8)

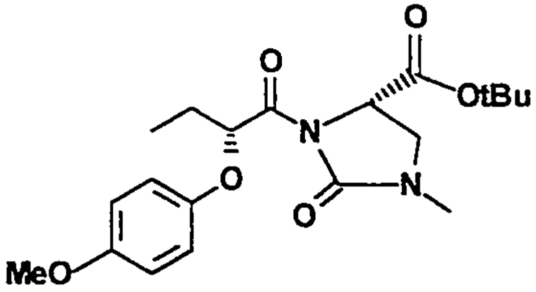
$[\alpha]_D^{23}$ from DKR product = -31.0° (c = 0.90, CH_2Cl_2)

$[\alpha]_D^{23}$ from commercial (S)-2-amino butanol = +32.6° (c = 0.78, CH_2Cl_2)

Anal.:	Calculated for $C_{11}H_{17}NO$:	C, 73.70; H, 9.56; N, 7.81
	Found:	C, 73.68; H, 9.50; N, 7.60

Oxygen Nucleophiles:

Preparation of (4S)-1-methyl-3-(2-(4-methoxyphenol)-butyryl)-2-oxoimidazolidine-4-carboxylate



$C_{20}H_{28}N_2O_6 = 392$

diastereomeric mixture (1:1 RS:SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 77 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.81$ (AB, $J_{AB} = 12.8$ Hz, 4H), 5.72 (dd, J = 8.2, 3.4 Hz, 1H), 4.58 (dd, J = 10.0, 3.7 Hz, 1H), 3.71 (s, 3H), 3.68 (t, J = 10.0 Hz, 1H), 3.32 (dd, J = 10.0, 3.65 Hz, 1H), 2.89 (s, 3H), 1.85 (m, 2H), 1.35 (s, 9H), 1.09 (t, J = 7.3 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.1$, 168.6, 154.1, 153.8, 152.4, 116.8, 114.6, 83.0, 78.0, 55.7, 53.0, 47.0, 30.6, 27.7, 26.7, 10.1

IR: 1739, 1697, 1506

MS: EI (m) (m/z %) = 392 (5.4), 269(11.8), 213 (98.3), 145 (86.2)

HRMS:	calculated for $C_{20}H_{28}N_2O_6$	=	392.1967
	found		392.1987

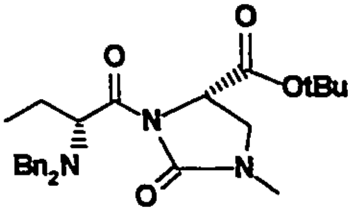
Reetz Aldehyde II

Procedure for Monobenzylation of DKR Products.

A clean, dry nitrogen filled round bottom flask fitted with a magnetic stirring bar was charged with (4S)-1-methyl-3-((2R)-benzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate (0.93 g, 2.5 mmole) which was subsequently dissolved in dry THF (10.0 mL). BnBr (0.47 g, 2.75 mmole), K_2CO_3 (0.76 g, 7.5 mmole) and $Bu_4N^+I^-I$ (0.1 g, 0.1 mmmole) were added and the resulting slurry was stirred for 48 hours. The reaction was filtered and the THF removed. The resulting crude product was extracted with Et_2O (3 x 25 mL) and the combined organics were dried with $MgSO_4$, filtered and concentrated. The crude product obtained was purified by silica gel chromatography (3 : 1 hexanes : EtOAc) to provide a colorless oil (1.0 g, 86 %).

Product Data:

(4S)-1-methyl-3-((2R)-N,N-dibenzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{27}H_{35}N_3O_4 = 465$

diastereomeric mixture (1:1 RS:SS)

purification method: silica gel chromatography (3:1 hexanes : EtOAc)

yield: 86 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41 - 7.17 (m, 10 H), 4.72 (t, J = 7.6 Hz, 1H), 4.62 (dd, J = 10.3, 4.7 Hz, 1H), 3.87 (AB, J_{AB} = 14.5 Hz, 4H), 3.60 (t, J = 9.6 Hz, 1H), 3.29 (dd, J= 9.6, 4.7 Hz, 1H), 2.79 (s, 3H), 1.71 (m, 2H), 1.55 (s, 9H), 0.98 (t, J= 7.3 Hz, 3H)

IR: 3093, 1739, 1697, 1506

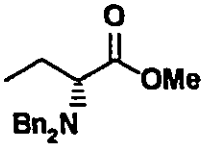
MS: CI (m) (m/z %) = 466(54.8), 410 (10.8), 238 (100), 91 (100)

$[\alpha]_D^{23}$ = - 6.8 (c = 1.1)

The chiral auxiliary was then removed using the standard NaOMe/MeOH procedure:

Product Data:

(4S)-1-methyl-3-((2R)-N,N-dibenzylaminobutanoyl)-2-oxoimidazolidine-4-carboxylate



$C_{19}H_{23}NO_2 = 297$

purification method: silica gel chromatography (3:1 hexanes : EtOAc)

yield: 94 % of a colourless oil

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 (m, 10H), 3.75 (s, 3H), 3.72 (AB, JAB = 13.9 Hz, 4H), 3.24 (t, J = 7.8 Hz, 1H), 1.76 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 140.3, 129.4, 129.3, 128.8, 127.5, 63.1, 55.1, 51.6, 23.4, 11.6

IR: 3680, 1727

MS: EI (m) (m/z %) = 297 (3.1), 238 (100), 205 (100)

$[\alpha]_D^{23}$ = + 51.5° (c = 1.1, CH_2Cl_2)

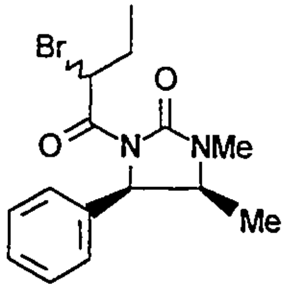
Other Auxiliaries:

General Procedure for the Preparation of (4S, 5R)-(+)-1,5-dimethyl-4-phenyl-(2-bromobutanoyl)-2-oxoimidazolidine

To a dry, nitrogen filled roundbottom flask was added (4S, 5R)-(+)-1,5-dimethyl-4-phenyl-2-oxoimidazolidine (0.25 g, 1.31 mmole, 1.0 eq), and THF (12 mL) and was subsequently cooled to -45°C. A 0.22 M solution of $K^{+-}OtBu$ in dry THF (6.55 mL, 1.44 mmole, 1.10 eq) was added dropwise over 2 min and the resulting solution was stirred at -45°C for 30 min. (±)-2-bromo-butyryl bromide (0.36 g, 1.58 mmole, 1.2 eq) was added dropwise via syringe over 2 min and stirring was continued at -30 °C for 1 h and then the reaction mixture was poured into a mixture of Et_2O (50 mL), AcOH (2.0 mL) and brine (50 mL). The organic phase was separated and washed successively with brine, 2% NaOH, and brine. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel with 3:1 hexanes:EtOAc to afford 0.32 g (72 %) of a clear oil.

Product Data:

(4S, 5R)-(+)-1,5-dimethyl-4-phenyl-(2-bromobutanoyl)-2-oxoimidazolidine



$C_{15}H_{19}N_2O_2Br = 338$

^{1}H NMR (500 MHz, $CDCl_3$): δ=7.15 (m, 5H), 5.72 (2xt, J = 7.0 Hz, 1H), 5.18 (2xd, J = 8.6 Hz, 1H), 3.80 (2xdq, J = 8.6, 6.0 Hz, 1H), 2.70 (2xs, 3H), 1.88 (2xm, 2H), 0.80 (2xt, J = 7.3 Hz, 3H), 0.65 (d, J = 6.0 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 155.5, 136.2, 135.4, 128.6, 128.5, 128.4, 128.2, 128.1, 126.9, 126.8, 59.8, 59.2, 53.7, 46.9, 46.8, 28.3, 28.1, 28.0, 27.9, 27.1, 15.1, 15.0, 14.9, 14.8, 14.7, 12.0, 11.8

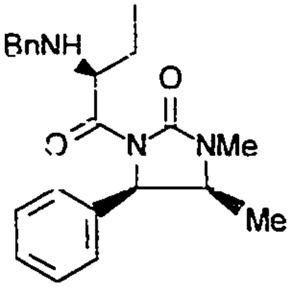
IR: 1736

MS: EI (m) (m/z %) = 338 (25.4), 259 (100)

HRMS:	calculated for $C_{15}H_{19}N_2O_2Br$ =	338.0620
	found	338.0645

(4S, 5R)-(+)-1,5-dimethyl-4-phenyl-(N-benzyl-2-amino-butyryl)-2-oxoimidazolidine

This compound was prepared using the standard dynamic kinetic resolution protocol



$C_{22}H_{27}N_3O_2 = 365$

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 89 % of a white solid (8 : 1 ratio of diastereomers)

m.p. 75 - 77 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.18 (m, 10H), 5.20 (d, J = 8.5 Hz, 1H), 4.54 (dd, J = 7.5, 5.1 Hz, 1H), 3.80 (dq, J = 8.5, 6.5 Hz, 1H), 3.35 (AB, J_{AB} = 12.8 Hz, 2H), 2.71 (s, 3H), 1.80 - 1.30 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H), 0.71 (d, J = 6.5 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.9, 155.5, 140.2, 136.7, 128.5, 128.4, 128.1, 128.0, 126.9, 126.7, 60.9, 59.5, 53.9, 51.6, 28.1, 26.7, 14.8

IR: 3425, 1736, 1360

MS: EI (m) (m/z %) = 365 (100), 336 (14.3), 274 (99.2), 191 (100)

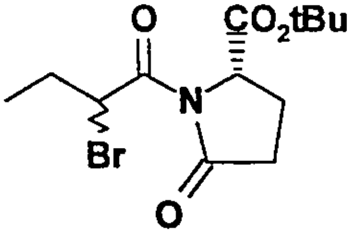
Anal.:	Calculated for $C_{21}H_{27}N_3O2$:	C, 71.36; H, 7.70
	Found:	C, 71.64; H, 7.69

Preparation of tert-Butyl-1-(2-bromo-butyryl)-Pyroglutamate

To a dry, nitrogen filled roundbottom flask was added (2S)-tert-butyl pyroglutamate (0.20 g, 1.08 mmole, 1.0 eq), and THF (10 mL) and was subsequently cooled to -45°C. A 0.41 M solution of $K^{+-}OtBu$ in dry THF (2.66 mL, 1.20 mmole, 1.10 eq) was added dropwise over 2 min and the resulting solution was stirred at -45°C for 30 min. (±)-2-bromo-butyryl bromide (0.37 g, 1.62 mmole, 1.5 eq) was added dropwise via syringe over 2 min and stirring was continued at -30 °C for 1 h and then the reaction mixture was poured into a mixture of Et_2O (50 mL), AcOH (2.0 mL) and brine (50 mL). The organic phase was separated and washed successively with brine, 2% NaOH, and brine. The organic extracts were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel with 2:1 hexanes:EtOAc to afford 0.25 g (70 %) of a clear oil.

Product Data:

tert-Butyl-1-(2-bromo-butyryl)-Pyroglutamate



$C_{13}H_{20}NO_4Br$ = 333

diastereomeric mixture (1:1 RS : SS)

purification method: silica gel chromatography (2:1 hexanes : EtOAc)

yield: 87 % of a clear oil

^{1}**H NMR** (500 MHz, $CDCl_3$): δ= 5.48 (2t, J = 6.1 Hz, 1H), 4.52 (2 x dd, J = 9.7, 3.9 Hz, 1H), 2.80 - 2.56 (m, 2H), 2.40 - 1.95 (m, 4H), 1.44 and 1.42 (2s, 9H), 0.90 (2t, J = 7.8 Hz, 3H)

^{13}**C NMR** (75 MHz, $CDCl_3$): δ = 174.0, 169.4, 169.2, 82.7, 59.0, 47.0, 32.0, 27.8, 27.3, 27.2, 11.9

IR: 1736, 1360

REFERENCES:

1. (a) Davies J.S. Ed.; Barret G.C. Amino Acids and Peptides (VI-27), (1968 - 1995), The Royal Society of Chemistry. (b) Greenstein, J.P.; Winitz, M., Chemistry of the Amino Acids. 1,2 and 3 (1-84), Robert E. Drieger, Malabar, Florida. (c) Izumi, Y., Chibata, I.; Itoh, T. Production and Utilization of Amino Acids, *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 176. (d) O'Donnell, M.J. Ed., α-Amino Acid Synthesis, *Tetrahedron* **1988**, 44, 5253. (e) Williams, R.M., Synthesis of Optically Active α–Amino Acids, **1989**, Pergamon Press, New York, p 1-304

2. Williams R.; Im M., *J. Am. Chem. Soc.* **1991**, 113, 9276

3. For summaries of the bis-lactim ether method, see: (a) Schollkopf, U., *Tetrahedron,* **1983**, 39, 2085. (b) Schollkopf, U. *Pure and Appl. Chem.* **1983**, *55,* 1799. (c) Schollkopf, U., *Topics Curr. Chem.,* **1983**, 109, 65.

4. Shapiro B.M.; Hopkin P.B. *J. Org. Chem.,* **1987**, *52,* 4421

5. Hartwig W.; Bom L. *J. Org. Chem.,* **1987**, *52,* 4352

6. Evans D.A.; Weber A.E. *J. Am Chem.Soc.,* **1986**, *108,* 6757

7. Corey E.J.; Link, J. *J. Am. Chem. Soc.,* **1992**, 114, 1906

8. (a) Moradopour A.; Tsoucaris G. *J. Am. Chem. Soc.,* **1971**, *93,* 2353. (b) Bemstein W.J.; Buchardt O. *J. Am. Chem. Soc.,* **1972**, *94,* 49. (c) Berti G.; Marsili A. *Tetrahedron,* **1966**, *22,* 2977. (d) Hayashi T.; Kumada M. *J. Org. Chem.,* **1983**, *48,* 2195. (e) Sturmer R. *Angew. Chem. Int. Ed. Engl.,* **1990**, *29,* 59. (f) Tokunaga M.; Noryori. R. *Tetrahedron Asymmetry,* **1990**, 1, 1. (g) Koh K.; Ben R.N.; Durst T. *Tetrahedron Lett.,* **1993**, 31, 4473. (h) Lee I.; Sih C.J. *Tetrahedron Lett.,* **1992**, 33, 1953. (i) Inagaki M.; Oda J. *J. Am. Chem. Soc.,* **1991**, *113,* 9360.

9. Moradopour A.; Tsoucaris G. *J. Am. Chem. Soc.,* **1971**, *93,* 2353

10 (a) Noyori, R.; Ohkuma T.; Kitamura M.; Takaya H.; Sayo N.; Kumobavashi H.; Akutagawa S. *J. Am. Chem. Soc.,* **1987**, 109, 5856. (b) Reviews: Noyon R., *Chem. Soc. Rev.,* **1989**, *18,* 187. (c) Noyori R. *Science,* **1990**, 248, 1194. (d) Takaya H.; Ohta T.; Noyori R. Catalytic Asymmetric

Synthesis, VCH, New York (1993), Chap. 1.

11. Frater G.; Muller U.; and Gunther W. *Tetrahedron*, **1984**, 40, 1269.
12. Kawai Y.; Takanobe K.; Tsujimoto M.; Ohno A. *Tetrahedron Lett.*, **1994**, 35, 147
13. Noyori R.; Ohkuma T.; Kitamura M.; Takaya H.; Sayo N.; Kumobayashi H.; Akutagawa S. *J. Am. Chem. Soc.*, **1987**, *109*, 5856.
14. Kitamura M.; Tokunaga M.; Noyori R. *Bulll. Chem. Soc. Jpn.*, **1995**, 68, 36.
15. (a) Collingwood S.P.; Davies S.G. *Tetrahedron Lett.*, **1990**, *31*, 4067. (b) Middlemiss A.; Davies S.G. *J. Chem. Soc. Commun.*, **1990**, 797.
16. Koh K.; Ben R.N.; Durst T. *Tetrahedron Lett.*, **1993**, *34*, 4473.
17. Koh K.; Ben R.N.; Durst T. *Tetrahedron Lett.*, **1994**, *35*, 375.
18. Koh K.; Durst T. J. *Org. Chem.*, **1994**, 59, 4683.
19. Koh K.; Ben R.N. unpublished results.
20. J. March, Advanced Organic Chemistry, Reactions, Mechanisms and Structure, 2nd Edition, McGraw-Hill, 1977
21. Loncharich R.T.; Schwartz T.R.; Houk K.N. *J. Am. Chem. Soc.*, **1987**, *109*, 14.
22. Streitweiser A.; Solvolytic Displacement Reactions; McGraw-Hill Book Company Inc., New York, **1962**, p.-26.
23. Allinger K.B.; Kuchsiag C.; Rahman M.; Pathiaseril A. *J. Am. Chem. Soc.*, **1991**, *13*, 4505.
24. Merck Index, 8th Ed., Merck, Rahway, NJ., USA, **1968**, p.233.
25. (a) Saino T.; Nishizawa R. *J. Med. Chem.*, **1977**, 20, 510. (b) Moon B.J.; Boparai A.S. J. *Org. Chem.*, **1980**, 45, 2288. (c) Rich D.H. J. *Med. Chem.*, **1985**, *28*, 264. (d) Fleet G.W.; Smith P.W. *Tetrahedron Lett.*, **1985**, *26*, 1469.
26. Jurczak J.; Golebiowski A. *Chem Rev.*, **1989**, 89, 149.
27. See ref. 26.
28. Lubell W.D.; Rapoport H. J. *Am. Chem. Soc.*, **1987**, *109*, 236.
29. Reetz M.T.; Drewes M.W.; Schmitz A. *Angew. Chem. Int. Ed Engl.*, **1987**, *26*, 1141. (b)

Reetz M.T.; Drewes M.W.; Harms K. *Tetrahedron Lett.*, **1988**, *29*, 3295. (c) Reetz *M.T. Pure App. Chem.*, **1988**, *60*, 1607. (d) For an excellent review see: Reetz M.T. *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1531.

30. See ref. 29.

31. Garner P.; Park J.M. *J. Org. Chem.*, **1987**, *52*, 2361. (b) Garner P.; Ramakanth S. *J.Org. Chem.*, **1986**, *51*, 2609. (c) Garner P.; Park J.M. *J. Org. Chem.*, **1988**, *53*, 4395.

32. Reetz M.T.; Drewes W.; Lennick K.; Schmitz X. *Tetrahedron Asymm.*, **1990**, 1, 375.

33. Reetz M.T.; Jaeger R.; Drewlies R.; Hubel M.; *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 103.

34. Harpp D.W.; Black C.J.; Gleason J.G.; Smith R.A. *J. Org. Chem.*, **1975**, *40*, 3420.

35. Hassner A.; Alixanian V. *Tetrahedron Lett.*, **1978**, 46, 4475.

36. Dale J.; Dull D.L.; Mosher H.S. *J. Org Chem.*, **1969**, *34*, 2543.

37. Rittle, K.E.; Homnik, C.F.; Ponticello G.S. *J. Org. Chem.*, **1982**, 47, 3016.

38. Luly J.R.; Dellaria J.F.; Plattner J.J.; Soderquist J.L. *J. Org. Chem.*, **1987**, 52, 1487.

39. Stanfield C.F.; Parker J.E.; Kanellis P. *J. Org. Chem.*, **1981**, *46*, 4797.

40. Kubota H.; Kubo A.; Nunami K. *Tetrahedron Lett.*, **1994**, 35, 3107.

41. (a) Chen C.S.; Sih C.J. *Angew. Chem. Int. Ed. Engl.*, **1989**, 28, 695. (b) Guy A.; Doussot R.; Darrequ R. *Tetrahedron Asymmetry*, **1992**, 3, 247.

42. Shiba T.; Koda A.; Kusumoto S.; Kaneko T. *Bull. Chem. Soc. Jpn.*, **1968**, 41, 2748.

43. Obtained commercially from Sigma Chemical Company

44. Hayashi K.; Nunami K.; Kato J.; Yoneda N.; Kubo M.; Ochiai T.; Ishida R. *J. Med.Chem.*, **1989**, 32, 289.

45. Table taken from: Lowry T.H., Richardson K.S., Mechanism and Theory in Organic Chemistry, 3rd Ed., Harper Collins Inc., New York, 1987, pg.377.

46. Evans D.A.; Weber A.E. *J. Am. Chem. Soc.*, **1986**, *108*, 6757.

47. Obtained commercially from Aldrich Fine Chemicals Division.

48. Kronenthal D.R.; Han C.Y.; Taylor M.K. J. *Org. Chem.*, **1982**, 47, 2765.

49. Sato Y.; Sodeoka M.; Shibasaki M. *J. Med. Chem.*, **1977**, 20, 510.

50. Rosowski A.; Forsch R. J. *Med. Chem.*, **1983**, *26*, 1719.

51. Wernic D.; DiMaio J. J. *Org Chem.*, **1989**, 54, 4224.

52. Farkasova H.; Rudinger J. J. *Collect. Chem. Commun.*, **1965**, 30, 3117.

53. Nutt R.F.; Stracha R.G.; Veber D.F. J. *Org. Chem.*, **1980**, 45, 3078.

54. Duhamel L.; Ravard A. *Tetrahedron*, **1988**,44, 5495.

55. Bjerrun N. Z. *Phys. Chem.*, **1923**, *106*, 219.

56. value taken from <u>Organic Chemistry</u> by Voldhardt, K. Peter C., Copyright 1987 by W.H. Freeman and Company pg.,792 (experimental value for formamide)

57. Kolasa T.; Miller M. J. *Org. Chem.*, **1990,** *55*, 1711

58. Weinreb D. *Tetrahedron Lett.*, **1977**,48, 4171

59. Song C.E.; Lee G. J. *Chromatography*, **1993**, *654*, *303*

```
   Space Group and Cell Dimensions    Orthorhombic  P 212121
a   8.8789(12)    b   7.9341(14)   c  22.6264(31)
        Volume  1593.94(2)A**3

Empirical formula : Br O4 N2 C13 H20

Cell dimensions were obtained from  24 reflections with 2Theta angle
in the range  40.00 -  50.00 degrees.

Crystal dimensions :  0.20  X  0.20  X  0.20  mm

FW =    348.21     Z =    4     F(000) =     715.12

Dcalc  1.451Mg.m-3, mu   2.61mm-1, lambda 0.70930A, 2Theta(max)  49.9

The intensity data were collected on a Rigaku   diffractometer,
using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max    0  10;  Kmin,max    0   9;  Lmin,max   0  26
No. of reflections measured                       3212
No. of unique reflections                         2811
No. of reflections with Inet > 2.5sigma(Inet)   2361
Merging R-value on intensities  0.074
No correction was made for absorption


The last least squares cycle was calculated with
 40 atoms, 182 parameters and 1384 out of 1648 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000200

The residuals are as follows :--
For significant reflections,  RF 0.068, Rw 0.098 GoF  3.88
For all reflections,          RF 0.095, Rw 0.099.
where RF = Sum(Fo-Fc)/Sum(Fo),
      Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
     GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was  0.125.

In the last D-map, the deepest hole was  -1.550e/A**3,
and the highest peak   0.660e/A**3.

Secondary ext. coeff.    1.891273      sigma    0.128941

      The following references are relevant to the NRCVAX System.

1. Full System Reference :
   Gabe, E.J., Le Page, Y., Charland, J.-P., Lee, F.L. and White, P.S.
   (1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :
   International Tables for X-ray Crystallography, Vol. IV, (1974)
```

Kynoch Press, Birmingham, England.

The following references may also be relevant.

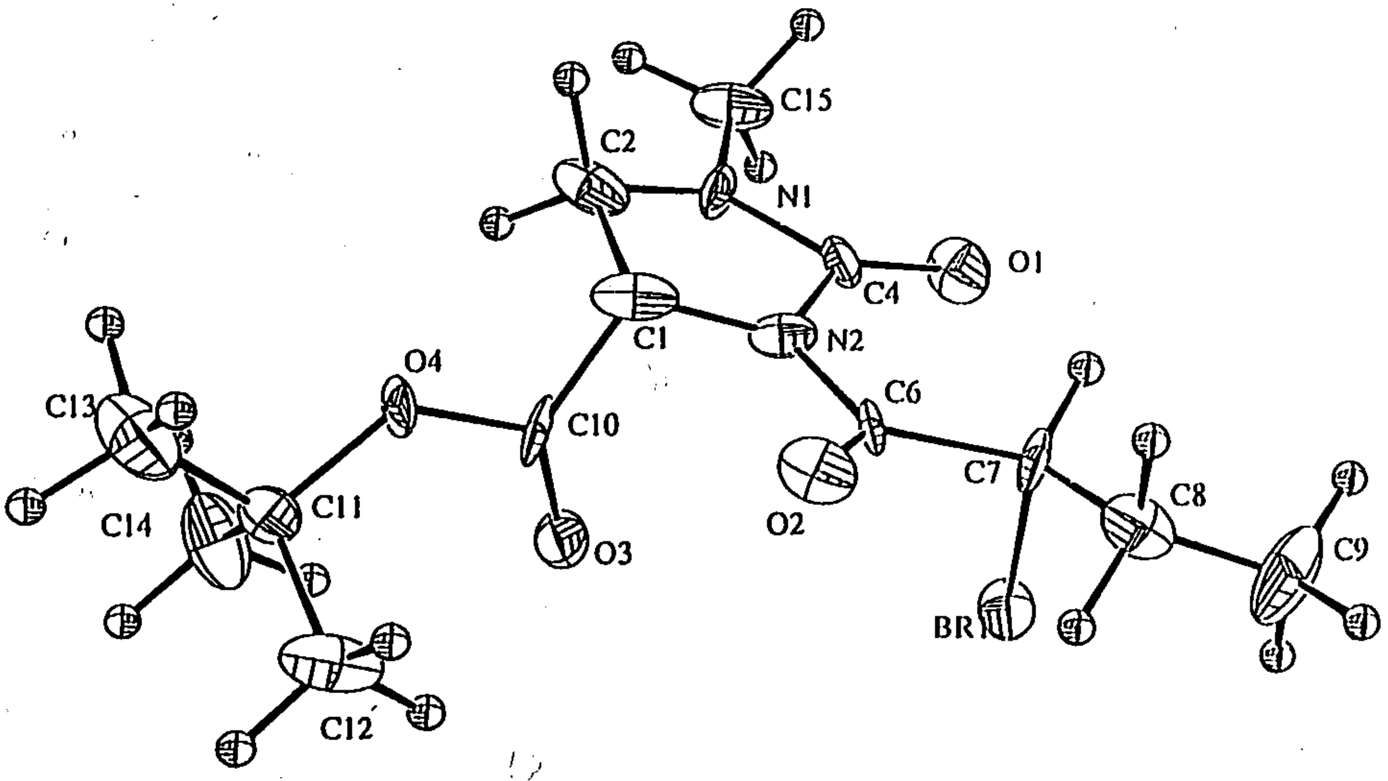
3. ORTEP Plotting :
Johnson, C.K., (1976) ORTEP - A Fortran Thermal Ellipsoid Plot Program, Technical Report ORNL-5138, Oak Ridge

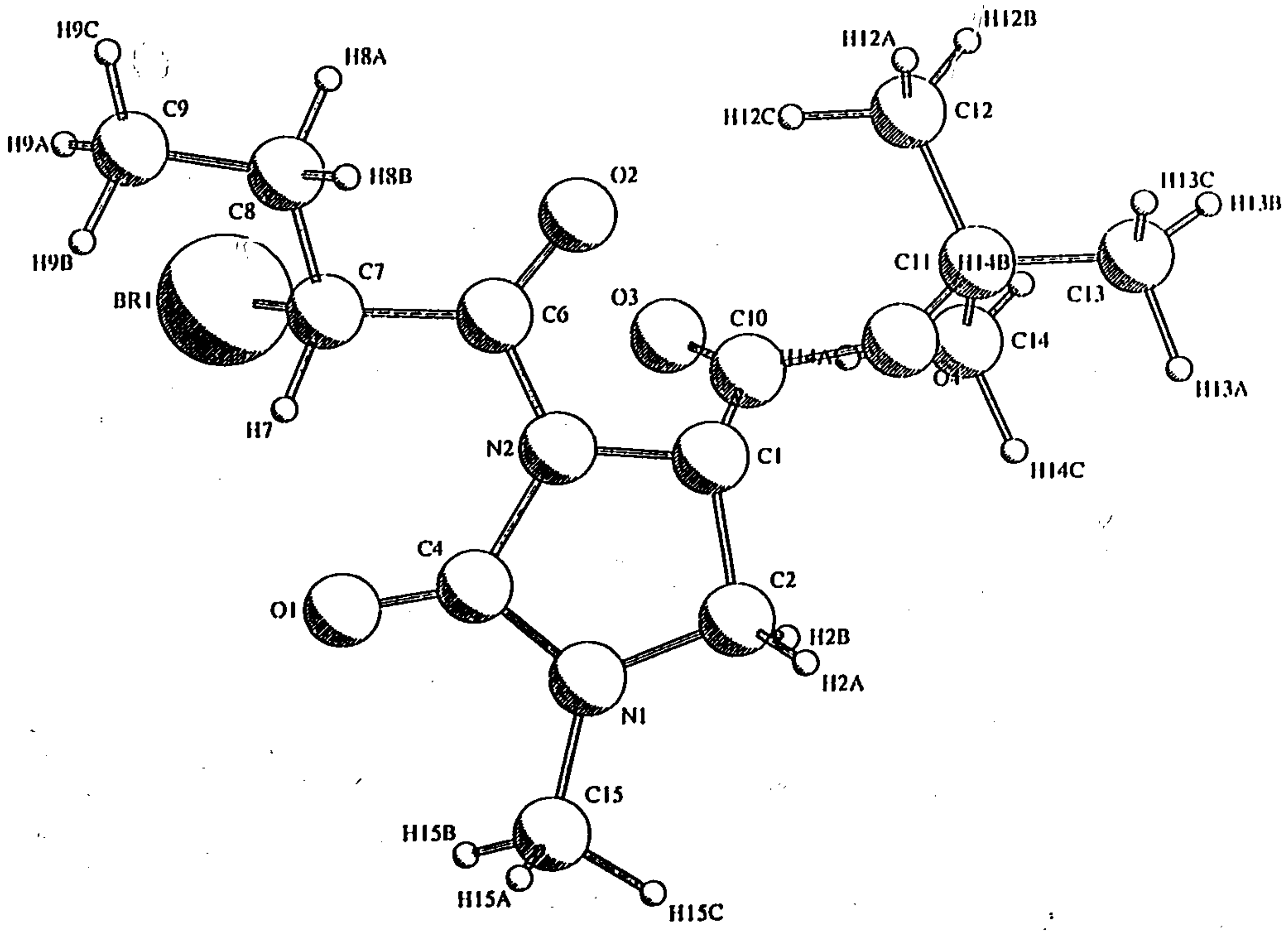
4. Pluto Plotting :
S. Motherwell, University Chemical Laboratory, Cambridge, 1978

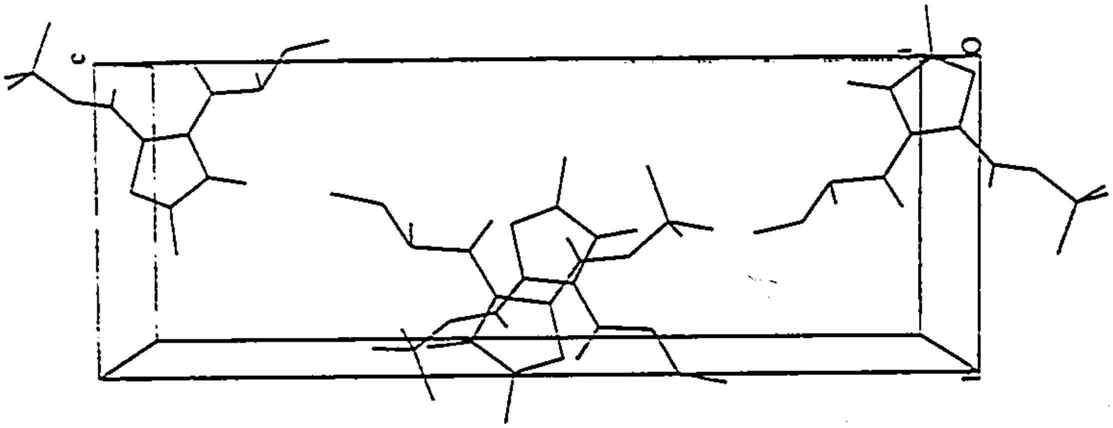
5. Missing Symmetry Treatment by MISSYM :
Le Page, Y., (1988) J. Appl. Cryst., 21, 983-984.

6. Grouping of Equivalent Reflections in DATRD2 :
Le Page, Y. and Gabe, E.J., (1979) J. Appl. Cryst., 12, 464-466.

7. Extinction Treatment :
Larson, A.C., (1970) p.293, Crystallographic Computing, Munksgaard, Copenhagen.


C15
C2
N1
O1
C4
C1
N2
O4
C6
C13
C10
C7
C8
C14
C11
O3
O2
C9
BR1
C12


H9C
H8A
H12B
H12A
C9
C12
H12C
H9A
H8B
O2
H13C
H13B
C8
H9B
C7
C11
H14B
C13
BR1
O3
C10
C6
H14A
C14
O4
H13A
H7
N2
C1
H14C
C4
C2
O1
H2B
H2A
N1
C15
H15B
H15A
H15C


c
O

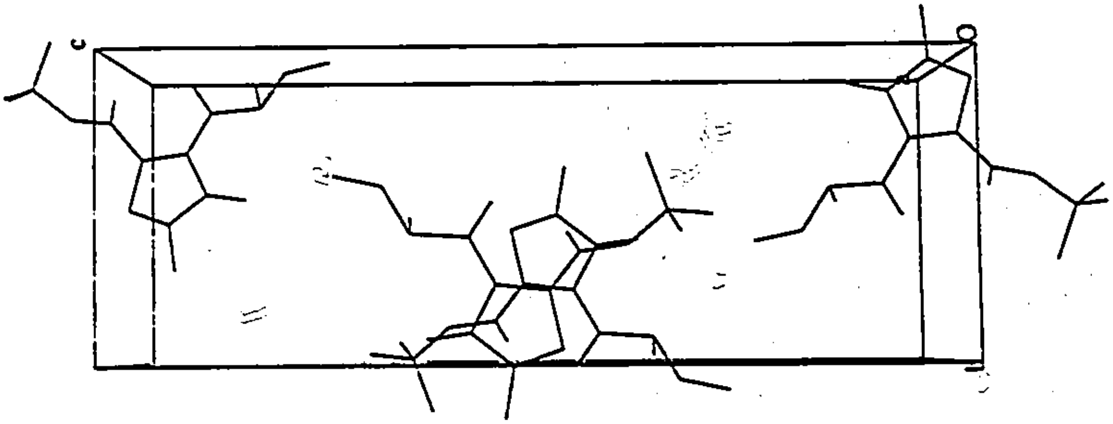

c
O

Table of Atomic Parameters x,y,z and Biso.
E.S.Ds. refer to the last digit printed.

	x	y	z	Biso
BR1	0.28115(16)	0.47689(20)	0.14685(6)	2.41(5)
O1	0.3948 (12)	0.0801 (14)	0.1258 (4)	2.8 (5)
O2	0.5986 (10)	0.5047 (13)	0.0480 (4)	2.7 (5)
O3	0.3179 (11)	0.4262 (13)	-0.0364 (4)	2.5 (4)
O4	0.5003 (11)	0.3783 (14)	-0.1054 (3)	2.1 (4)
N1	0.4107 (12)	-0.0043 (15)	0.0258 (4)	1.8 (5)
N2	0.4887 (13)	0.2534 (14)	0.0448 (5)	2.0 (5)
C1	0.5235 (16)	0.2337 (20)	-0.0150 (7)	2.5 (7)
C2	0.4769 (16)	0.0496 (20)	-0.0293 (6)	2.7 (7)
C4	0.4276 (16)	0.1012 (19)	0.0743 (5)	1.8 (6)
C6	0.5308 (15)	0.4013 (18)	0.0751 (5)	1.3 (5)
C7	0.4978 (16)	0.4131 (19)	0.1415 (5)	2.1 (6)
C8	0.5936 (17)	0.5549 (19)	0.1704 (7)	2.7 (7)
C9	0.5634 (20)	0.591 (3)	0.2312 (7)	4.5 (9)
C10	0.4328 (16)	0.3579 (21)	-0.0499 (5)	2.0 (6)
C11	0.4414 (15)	0.4847 (18)	-0.1514 (6)	2.1 (6)
C12	0.4380 (21)	0.6646 (23)	-0.1276 (8)	4.0 (9)
C13	0.5568 (19)	0.4664 (24)	-0.1995 (7)	4.2 (9)
C14	0.2898 (20)	0.4262 (24)	-0.1702 (7)	4.0 (8)
C15	0.3560 (19)	-0.1750 (20)	0.0365 (7)	2.9 (7)
H2A	0.574	-0.024	-0.041	2.8
H2B	0.396	0.046	-0.065	2.8
H7	0.512	0.294	0.164	3.0
H8A	0.573	0.671	0.145	3.1
H8B	0.712	0.523	0.165	3.1
H9C	0.632	0.689	0.250	4.4
H9A	0.445	0.624	0.239	4.4
H9B	0.584	0.475	0.259	4.4
H12C	0.356	0.677	-0.091	4.2
H12A	0.548	0.700	-0.109	4.2
H12B	0.409	0.755	-0.161	4.2
H13C	0.666	0.505	-0.186	4.5
H13A	0.564	0.331	-0.213	4.5
H13B	0.522	0.536	-0.239	4.5
H14C	0.292	0.296	-0.188	4.8
H14A	0.210	0.425	-0.133	4.8
H14B	0.242	0.505	-0.205	4.8
H15C	0.351	-0.244	-0.006	3.1
H15A	0.431	-0.245	0.065	3.1
H15B	0.244	-0.174	0.055	3.1

Biso is the Mean of the Principal Axes of the Thermal Ellipsoid

Table of u(i,j) or U values *100.
E.S.Ds. refer to the last digit printed

	u11(U)	u22	u33	u12	u13	u23
BR1	2.16(6)	4.13(8)	2.86(6)	0.19(8)	0.12(7)	0.04(8)
O1	3.5 (6)	4.2 (7)	3.0 (5)	-0.3 (6)	1.1 (5)	1.2 (5)
O2	2.8 (6)	3.1 (6)	4.5 (6)	-0.6 (6)	0.4 (5)	0.9 (5)
O3	2.8 (6)	4.3 (6)	2.3 (5)	1.2 (6)	0.2 (5)	0.0 (5)
O4	2.7 (5)	4.4 (7)	0.8 (4)	1.0 (6)	0.6 (4)	0.7 (4)
N1	2.7 (6)	3.0 (7)	1.2 (5)	0.0 (7)	-0.4 (5)	-1.0 (6)
N2	2.1 (7)	1.7 (6)	3.7 (7)	0.1 (7)	0.6 (6)	0.1 (6)
C1	1.4 (7)	1.9 (8)	6.0 (11)	-0.2 (7)	0.5 (8)	0.3 (9)
C2	1.9 (8)	3.7 (10)	4.7 (9)	0.5 (9)	0.6 (7)	2.0 (8)
C4	2.8 (8)	2.6 (8)	1.4 (7)	0.2 (8)	-0.6 (6)	0.6 (6)
C6	1.3 (7)	3.1 (8)	0.6 (6)	0.0 (7)	-0.3 (5)	0.3 (6)
C7	2.3 (7)	4.8 (9)	1.0 (6)	0.3 (8)	0.1 (7)	-1.3 (7)
C8	2.9 (8)	2.8 (9)	4.6 (9)	-0.5 (8)	-1.0 (8)	0.6 (8)
C9	3.5 (10)	8.2 (15)	5.2 (11)	-1.3 (11)	-0.5 (9)	-4.4 (11)
C10	2.1 (8)	4.5 (10)	0.9 (7)	-0.6 (9)	0.0 (6)	-1.4 (7)
C11	2.3 (7)	2.7 (8)	2.8 (7)	0.1 (8)	-0.2 (6)	0.3 (8)
C12	4.4 (11)	3.0 (10)	7.8 (13)	0.8 (10)	-1.0 (10)	0.5 (10)
C13	4.2 (10)	6.8 (14)	5.1 (10)	0.7 (13)	0.3 (9)	2.8 (11)
C14	4.4 (10)	7.2 (13)	3.5 (8)	-1.6 (12)	-2.1 (9)	1.2 (9)
C15	2.8 (9)	2.0 (8)	6.1 (11)	0.1 (9)	0.8 (9)	1.0 (8)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table of Atomic Bond Distances in Angstroms

Br1-C7	1.991(14)
O1-C4	1.213(15)
O2-C6	1.188(16)
O3-C10	1.194(17)
O4-C10	1.402(15)
O4-C11	1.439(16)
N1-C2	1.443(17)
N1-C4	1.389(17)
N1-C15	1.459(20)
N2-C1	1.397(18)
N2-C4	1.483(18)
N2-C6	1.408(18)
C1-C2	1.552(23)
C1-C10	1.498(22)
C2-H2A	1.073(15)
C2-H2B	1.078(15)
C6-C7	1.534(16)
C7-C8	1.554(21)
C7-H7	1.083(15)
C8-C9	1.431(22)
C8-H8A	1.099(15)
C8-H8B	1.086(16)
C9-H9C	1.076(17)
C9-H9A	1.099(18)
C9-H9B	1.123(21)
C11-C12	1.525(23)
C11-C13	1.502(21)
C11-C14	1.486(22)
C12-H12C	1.108(19)
C12-H12A	1.106(18)
C12-H12B	1.071(17)
C13-H13C	1.061(17)
C13-H13A	1.122(20)
C13-H13B	1.086(16)
C14-H14C	1.107(19)
C14-H14A	1.102(18)
C14-H14B	1.086(16)
C15-H15C	1.115(16)
C15-H15A	1.079(16)
C15-H15B	1.076(17)

Table of Atomic Bond Angles in Degrees

C10-O4-C11	124.1(11)
C2-N1-C4	117.4(12)
C2-N1-C15	123.7(11)
C4-N1-C15	117.6(11)
C1-N2-C4	115.2(11)
C1-N2-C6	120.3(11)
C4-N2-C6	123.9(10)
N2-C1-C2	104.4(12)
N2-C1-C10	108.5(12)
C2-C1-C10	111.5(12)
N1-C2-C1	102.0(12)
N1-C2-H2A	111.9(12)
N1-C2-H2B	111.2(12)
C1-C2-H2A	110.5(12)
C1-C2-H2B	110.8(12)
H2A-C2-H2B	110.1(14)
O1-C4-N1	130.6(14)
O1-C4-N2	129.3(13)
N1-C4-N2	100.0(10)
O2-C6-N2	117.4(11)
O2-C6-C7	124.0(13)
N2-C6-C7	118.4(11)
Br1-C7-C6	104.4(8)
Br1-C7-C8	108.9(10)
Br1-C7-H7	107.9(10)
C6-C7-C8	110.6(12)
C6-C7-H7	113.3(12)
C8-C7-H7	111.5(11)
C7-C8-C9	116.5(13)
C7-C8-H8A	107.4(12)
C7-C8-H8B	108.4(13)
C9-C8-H8A	107.3(15)
C9-C8-H8B	109.1(13)
H8A-C8-H8B	107.7(13)
C8-C9-H9C	114.2(16)
C8-C9-H9A	112.1(14)
C8-C9-H9B	110.1(15)
H9C-C9-H9A	108.3(16)
H9C-C9-H9B	106.6(14)
H9A-C9-H9B	105.0(15)
O3-C10-O4	122.8(13)
O3-C10-C1	128.6(12)
O4-C10-C1	108.6(12)
O4-C11-C12	107.5(11)
O4-C11-C13	102.7(11)
O4-C11-C14	110.7(12)
C12-C11-C13	111.1(13)
C12-C11-C14	112.0(13)
C13-C11-C14	112.3(13)
C11-C12-H12C	110.9(14)
C11-C12-H12A	111.1(14)
C11-C12-H12B	112.7(15)
H12C-C12-H12A	105.6(15)
H12C-C12-H12B	108.1(16)
H12A-C12-H12B	108.2(16)
C11-C13-H13C	112.5(14)
C11-C13-H13A	109.5(14)
C11-C13-H13B	110.4(14)
H13C-C13-H13A	107.8(15)
H13C-C13-H13B	110.5(15)
H13A-C13-H13B	106.0(14)
C11-C14-H14C	112.2(15)
C11-C14-H14A	111.7(13)
C11-C14-H14B	112.1(14)
H14C-C14-H14A	106.0(15)
H14C-C14-H14B	107.1(13)
H14A-C14-H14B	107.4(16)
N1-C15-H15C	109.1(12)
N1-C15-H15A	111.8(13)
N1-C15-H15B	111.6(13)
H15C-C15-H15A	107.0(13)
H15C-C15-H15B	107.2(14)
H15A-C15-H15B	109.9(13)

Torsion angles

C11	O4	C10	O3	1.2(7)
C10	O4	C11	C12	60.8(11)
C10	O4	C11	C14	-61.9(11)
C4	N1	C2	H2A	108.5(15)
C15	N1	C2	C1	-176.4(16)
C15	N1	C2	H2B	65.5(11)
C2	N1	C4	N2	10.5(7)
C15	N1	C4	N2	178.0(16)
C2	N1	C15	H15A	106.0(15)
C4	N1	C15	H15C	-178.9(19)
C4	N1	C15	H15B	62.8(11)
C4	N2	C1	C10	121.0(15)
C6	N2	C1	C10	-67.8(11)
C1	N2	C4	N1	-7.3(8)
C6	N2	C4	N1	-178.2(16)
C1	N2	C6	C7	-176.7(16)
C4	N2	C6	C7	-6.2(7)
N2	C1	C2	H2A	-115.2(18)
C10	C1	C2	N1	-113.0(15)
C10	C1	C2	H2B	5.5(6)
N2	C1	C10	O4	160.8(18)
C2	C1	C10	O4	-84.8(13)
O2	C6	C7	C8	-12.5(8)
N2	C6	C7	BR1	-80.6(10)
N2	C6	C7	H7	36.4(7)
BR1	C7	C8	H8A	-60.4(9)
C6	C7	C8	C9	174.1(18)
C6	C7	C8	H8B	-62.3(11)
H7	C7	C8	H8A	-179.3(22)
C7	C8	C9	H9C	179.7(22)
C7	C8	C9	H9B	59.8(12)
H8A	C8	C9	H9A	63.8(13)
H8B	C8	C9	H9C	56.5(12)
H8B	C8	C9	H9B	-63.3(13)
O4	C11	C12	H12A	50.8(10)
C13	C11	C12	H12C	-177.9(21)
C13	C11	C12	H12B	60.8(13)
C14	C11	C12	H12A	172.6(21)
O4	C11	C13	H13C	-59.5(11)
O4	C11	C13	H13B	176.6(21)
C12	C11	C13	H13A	175.0(21)
C14	C11	C13	H13C	-178.4(21)
C14	C11	C13	H13B	57.7(12)
O4	C11	C14	H14A	58.8(11)
C12	C11	C14	H14C	179.9(21)
C12	C11	C14	H14B	59.4(12)
C13	C11	C14	H14A	172.9(21)
C11	O4	C10	C1	178.1(15)
C10	O4	C11	C13	178.0(16)
C4	N1	C2	C1	-9.6(8)
C4	N1	C2	H2B	-127.8(17)
C15	N1	C2	H2A	-58.2(11)
C2	N1	C4	O1	-173.1(17)
C15	N1	C4	O1	-5.5(8)
C2	N1	C15	H15C	-12.2(7)
C2	N1	C15	H15B	-130.5(17)
C4	N1	C15	H15A	-60.7(11)
C4	N2	C1	C2	2.0(8)
C6	N2	C1	C2	173.3(16)
C1	N2	C4	O1	176.2(18)
C6	N2	C4	O1	5.3(7)
C1	N2	C6	O2	-1.4([illegible])
C4	N2	C6	O2	169.1(16)
N2	C1	C2	N1	4.0(6)
N2	C1	C2	H2B	122.5(18)
C10	C1	C2	H2A	127.9(18)
N2	C1	C10	O3	-22.5(8)
C2	C1	C10	O3	91.9(15)
O2	C6	C7	BR1	104.5(13)
O2	C6	C7	H7	-138.5(18)
N2	C6	C7	C8	162.4(16)
BR1	C7	C8	C9	60.0(10)
BR1	C7	C8	H8B	-176.5(12)
C6	C7	C8	H8A	53.8(10)
H7	C7	C8	C9	-58.9(12)
H7	C7	C8	H8B	64.6(12)
C7	C8	C9	H9A	-56.7(12)
H8A	C8	C9	H9C	-59.9(12)
H8A	C8	C9	H9B	-179.7(24)
H8B	C8	C9	H9A	-179.8(25)
O4	C11	C12	H12C	-66.3(12)
O4	C11	C12	H12B	172.4(21)
C13	C11	C12	H12A	-60.8(13)
C14	C11	C12	H12C	55.5(12)
C14	C11	C12	H12B	-65.8(13)
O4	C11	C13	H13A	60.3(11)
C12	C11	C13	H13C	55.2(12)
C12	C11	C13	H13B	-68.7(13)
C14	C11	C13	H13A	-58.6(12)
O4	C11	C14	H14C	-60.1(11)
O4	C11	C14	H14B	179.4(21)
C12	C11	C14	H14A	-61.3(12)
C13	C11	C14	H14C	54.0(11)
C13	C11	C14	H14B	-66.5(13)

```
        BIVOET -- Best Measurable Bijvoet Differences

 This routine selects reflections for which the Bijvoet difference is
 MOST significant, i.e. (Fc+ - Fc-)/Sigma(Fo) is largest.
 If Fo- is available (Fc+ - Fc-) is compared to (Fo+ - Fo-).
 Before running the routine Structure Factors must be calculated with :--
  (1) A refined structure
  (2) The dispersion flag "Yes" for all atoms
  (3) An ETA parameter of 1.0.
 If this has not been done, abort the run by requesting 0 reflections.

         h    k    l   Fc+          Fc-   Del/Sig   Fo+           Fo-   Sense
   1     1    2    2  83.105 <    88.812 -34.526  78.010 <      79.389   +
   2     1    1    6 101.174 <   106.086 -30.688  96.813    >   93.081     -
   3     2    1    1  71.521 <    75.486 -25.369  73.049 <      75.237   +
   4     1    3    6  69.162 <    75.501 -24.859  65.805    >   63.362     -
   5     2    2    4  81.864   >  76.814  24.809  82.251    >   71.313   +
   6     1    2    8  55.991   >  49.249  24.007  50.820    >   38.916   +
   7     3    2    4  50.628   >  43.564  23.494  51.861    >   41.768   +
   8     2    1    3  80.924 <    84.391 -21.478  81.943    >   81.364     -
   9     4    1    1  97.717   >  92.933  20.805  92.372    >   86.759   +
  10     3    1    1  39.398   >  34.047  19.031  40.350    >   34.651   +
  11     3    3    1  60.525   >  55.317  17.017  60.524    >   54.533   +
  12     3    1    6  59.522 <    63.798 -15.888  59.116    >   57.641     -
  13     3    2    6  52.123   >  47.238  15.128  52.292    >   42.275   +
  14     2    3    5  49.758 <    54.804 -14.950  47.850 <      48.033   +
  15     4    2    4  62.932 <    67.593 -14.912  64.215 <      64.520   +
  16     3    2    5  56.044   >  51.742  14.257  54.612    >   45.278   +
  17     3    1    4  53.927   >  50.372  14.004  55.863    >   48.049   +
  18     1    1   10  92.294   >  89.335  13.023  84.716    >   75.156   +
  19     1    2    3  32.411   >  28.837  12.892  32.086    >   26.126   +
  20     2    2    7  71.480   >  68.505  12.266  73.816    >   62.233   +
  21     3    1    8  27.478 <    33.902 -12.231  27.960 <      30.296   +
  22     2    3    2  60.633 <    63.943 -11.886  57.830 <      58.184   +
  23     1    1    7  36.417   >  32.995  11.815  35.851    >   28.961   +
  24     1    2    5  39.222 <    42.363 -11.560  39.503    >   38.020     -
  25     1    1    2  43.997 <    45.745 -11.456  44.472 <      44.765   +
  26     2    1    2 100.476   >  98.834  11.187 100.252    >   94.691   +
  27     1    1    1  65.061   >  63.712  10.975  64.365    >   61.363   +
  28     3    2    2  71.729 <    74.320 -10.712  70.110    >   69.838     -
  29     1    3    5  57.000 <    59.870 -10.681  55.209    >   50.830     -
  30     1    4    3  59.119   >  55.766  10.653  54.428    >   45.441   +
  31     1    1   14  63.332 <    66.894 -10.410  66.831 <      74.634   +
  32     1    1    3 112.567 <   113.823 -10.141 105.223    >  103.769     -
  33     3    2    1  62.368   >  59.785  10.080  61.028    >   57.066   +
  34     1    3    9  35.705 <    40.477  -9.844  32.849 <      33.859   +
  35     2    1    7  45.323   >  42.805   8.959  46.707    >   39.558   +
  36     6    1    1  49.606 <    53.870  -8.916  46.752 <      50.717   +
  37     1    2    7  33.859   >  30.790   8.728  34.120    >   27.606   +
  38     1    3   16  53.356 <    57.772  -8.377  52.969    >   50.881     -
  39     1    3    1  35.692 <    38.457  -8.082  34.612 <      35.798   +
  40     4    2   10  40.262   >  35.991   8.065  41.509    >   31.450   +
  41     2    2    2  10.882   >   6.505   7.735  11.509    >    3.848   +
```

42	3	3	2	18.826	<	23.147	-7.675	18.109	<	21.587	+
43	2	3	6	48.180	>	45.543	7.502	47.414	>	39.079	+
44	2	1	8	41.389	>	38.853	7.343	38.394	>	30.163	+
45	2	3	3	13.332	>	8.778	7.329	14.326	>	9.913	+
46	2	4	1	32.518	<	36.389	-7.275	30.735	<	33.903	+
47	3	2	8	69.310	>	67.238	7.141	73.552	>	62.809	+
48	3	1	20	19.169	>	12.002	7.141	21.583	>	15.944	+
49	5	2	3	18.540	<	23.585	-7.132	18.143	<	23.547	+
50	4	1	3	54.311	>	52.160	7.106	55.073	>	49.917	+
51	2	4	2	37.500	>	34.088	7.095	35.425	>	29.828	+
52	1	5	4	59.734	<	62.464	-7.043	55.742	>	52.294	-
53	1	3	18	37.245	<	42.246	-6.857	41.170	<	41.391	+
54	3	4	4	26.182	>	21.678	6.700	27.775	>	21.315	+
55	2	4	10	34.204	>	30.155	6.672	35.149	>	23.182	+
56	5	2	4	50.610	<	53.518	-6.603	48.393	>	47.380	-
57	3	1	3	11.195	>	8.168	6.578	11.222	>	6.392	+
58	7	3	3	63.712	>	60.371	6.411	62.137	>	54.413	+
59	4	4	3	44.627	>	41.421	6.389	44.821	>	38.589	+
60	4	2	13	32.722	>	27.982	6.371	33.637	>	23.707	+
61	5	5	1	12.028	<	18.368	-6.357	15.071	<	21.356	+
62	5	2	1	28.392	<	32.482	-6.353	28.092	<	32.080	+
63	4	2	17	34.072	>	28.349	6.322	34.176	>	25.017	+
64	2	2	14	49.903	>	47.073	6.262	51.707	>	42.239	+
65	8	2	7	43.921	<	49.064	-6.254	41.913	>	41.139	-
66	1	3	7	28.128	>	25.164	6.213	28.664	>	22.698	+
67	2	2	9	9.173	>	5.658	6.166	12.619	>	6.877	+
68	1	1	4	109.067	<	109.879	-6.034	102.950	>	97.210	-
69	2	3	9	25.138	<	29.114	-5.991	26.094	>	25.849	-
70	2	3	7	41.121	>	38.600	5.953	39.281	>	32.627	+
71	4	4	6	58.852	<	61.433	-5.927	60.187	>	54.084	-
72	3	3	10	58.952	<	61.323	-5.913	58.973	>	50.399	-
73	5	1	6	46.423	>	43.758	5.882	46.163	>	38.089	+
74	6	2	11	42.576	>	38.636	5.870	44.739	>	34.799	+
75	3	1	2	11.350	>	7.457	5.829	14.916	>	10.583	+
76	3	1	10	68.746	<	70.507	-5.794	70.681	>	62.905	-
77	1	6	1	37.530	>	33.873	5.747	37.693	>	33.010	+
78	1	3	10	66.341	>	64.440	5.740	59.597	>	52.830	+
79	3	3	16	18.711	>	14.144	5.731	17.025	>	11.551	+
80	1	2	12	61.786	<	63.731	-5.689	59.075	>	57.325	-
81	2	5	7	30.986	>	26.774	5.656	30.673	>	22.062	+
82	2	4	4	89.733	>	88.156	5.612	88.880	>	78.943	+
83	4	2	2	47.271	>	45.259	5.609	48.103	>	44.844	+
84	2	3	15	17.730	<	22.166	-5.600	16.993	<	31.584	+
85	1	4	11	30.077	>	26.042	5.595	28.803	>	22.061	+
86	5	2	1	50.851	>	48.060	5.561	47.393	>	43.495	+
87	3	2	15	33.900	>	29.731	5.538	33.576	>	24.809	+
88	2	4	7	37.764	>	35.014	5.538	39.642	>	32.190	+
89	4	1	6	49.445	>	47.535	5.535	53.318	>	45.855	+
90	2	1	6	105.628	<	106.620	-5.529	100.489	>	92.644	-
91	5	3	2	27.430	>	23.131	5.528	25.936	>	19.933	+
92	3	3	8	18.796	<	22.474	-5.510	18.854	<	20.570	+
93	1	2	16	67.721	>	65.378	5.502	64.603	>	55.990	+
94	1	3	8	39.893	<	42.079	-5.436	38.269	>	35.855	-
95	2	1	5	74.711	<	75.712	-5.380	76.454	>	71.534	-

```
  96      6     2    7  67.107   >    64.713   5.314  65.758   >    56.613   +
  97      4     1    5  58.126 <      59.770  -5.272  58.472   >    54.922     -
  98      3     2   10  29.271   >    26.128   5.264  31.223   >    23.827   +
  99      6     5    5  21.987   >    15.594   5.221  25.083   >    14.451   +
 100      4     6    2  32.762   >    28.330   5.129  32.160   >    23.904   +

Out of 100 TOTAL measurements, (Fo+ - Fo-) has the SAME sign as (Fc+ - Fc-)
in  78 cases and the OPPOSITE sign in  22 cases.


                    Cumulative Binomial Distribution

The Absolute Structure of the Model is CONFIRMED
Based on 100 Measurements,  78 of which Support the Model
The Probability that the Above Statement is WRONG is 0.7954E-08
```

```
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
 l  kFo   Fc   Sig     l  kFo   Fc   Sig     l  kFo   Fc   Sig     l  kFo   Fc   Sig
    0,  0, 1           8  255  288   32      4   80   99   63      5  207  199   57
 2  473  906    6      9  351  324   27      5  339  347   33      6  269  276   65
 4  846 1111    8     10  982 1051   16      6  868  880   19      7   60   14  176*
 6  957 1121   10     11  263  214   27      7   87   98   64      8  122  129   71
 8  360  339   20     12  102   73   54      8  168  165   50      9  393  376   50
10 1483 1668   13     13  157  203   50      9  204  224   51     10  305  313   63
12  513  522   24     14  486  548   33     10  640  691   26     11   38   58  505*
14  327  373   39     15  257  423   74     11  275  280   51     12   95  115  131
16  496  500   33     16  249  410   80     12  118   74   61     13  132  143   78
18  463  485   41     17    5  270 3591*    13  246  240   64     14  179  145   60
20  392  363   53     18  407  506   53     14  346  312   51     15  250  232   75
22   38  105  422*    19    5  230 2845*    15  408  384   47     16  184  172   65
24  342  335   78     20  222  285   65     16  373  309   54     17    6    8 4484*
26  130  168  141     21    5   10 4550*    17  176  105   88     18  148  119   87
    0,  1, 1          22    5   14 4434*    18  311  314   71     19  216  207   74
 1  974 1052    7     23    5   79 4768*    19  241  299   74     20  279  272   86
 2  425  474    9     24  335  353   83     20  325  348   68         0,  7, 1
 3  126   89   26     25    6  122 5148*    21    5  110 3018*     1   64  102  188*
 4  508  598   11     26  132   88  145     22    6   36 4796*     2  135  126   71
 5  119   95   32         0,  3, 1          23  260  217   78      3  388  386   54
 6  565  656   13      1  953  969   14     24  197  214  111      4    5   76 3990*
 7  356   71   19      2 1152 1179   13         0,  5, 1           5   85   72  146
 8  763  837   14      3  617  633   16      1  611  627   26      6  137  132   73
 9  271  202   38      4  130  148   42      2  528  556   29      7  359  343   60
10    3   95 2747*     5  475  527   20      3  288  287   47      8  118  106   88
11    3  139 4082*     6  454  508   22      4   59   26  138*     9   63   42  336*
12 1082 1196   17      7  335  410   29      5   91   75   72     10   44    8  400*
13    4   54 4893*     8  601  671   20      6  297  330   48     11  220  199   73
14  289  294   47      9  111  135   45      7  579  551   29     12  172  207   67
15    4   49 4084*    10  181  192   43      8  328  358   46     13  238  223   72
16  487  557   34     11  281  297   43      9  131  132   57     14   97   72  160
17    4  118 4362*    12  620  650   25     10   81   62   95     15   75   74  334*
18  311  321   59     13  275  139   42     11  471  482   39     16   54   58  309*
19    5   63 4324*    14    4  104 3355*    12  293  322   60     17  257  241   78
20  270  296   77     15  193  226   58     13   66  127  169*    18  151  113  120
21    5   82 4783*    16  126  130   69     14   95   76  123         0,  8, 1
22  468  446   53     17  344  360   57     15  174  151   61      0  193  209   85
23    5   33 4906*    18  249  385   75     16  140   74   94      1  243  232   68
24   84  107  196*    19    5   73 4563*    17  410  401   57      2  104   95  139
25    6   13 4958*    20  198  218   64     18  260  226   77      3  134  142   86
26  288  279   85     21    5   50 4595*    19  120   72  131      4   30   61  768*
    0,  2, 1          22  295  317   86     20    6   53 4632*     5  235  233   72
 0 1893 2231   14     23    6  122 4977*    21  165  142   83      6   38   25  502*
 1  399  387   15     24   98  111  181     22  178  172   82      7    5   19 4376*
 2  473  460   13     25    6   56 5054*        0,  6, 1           8    6    8 3609*
 3   89   79   29         0,  4, 1           0  199  189   80      9  304  270   84
 4  909 1018   11      0  764  787   26      1  307  285   54     10  121  119  105
 5  363  352   19      1  105   79   46      2   98  101   81     11    6   76 4538*
 6  806  920   13      2   70   46   71      3  311  292   55     12    6    5 3745*
 7   86   83   41      3   37   43  154*     4  218  237   76     13  138  128   99
```

```
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
  l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
     0,  8, 1         11  238  252   59     5  552  570   27     2  309  312   58
 14  123  117  114    12  383  308   43     6  658  692   26     3  256  278   71
     0,  9, 1         13  281  235   62     7  287  281   48     4  557  597   39
  1  160  161   84    14  668  633   34     8  383  399   40     5  369  411   54
  2   26   69 1032*   15    4  149 4842*    9  328  357   48     6  234  248   83
  3  143  146   94    16  418  443   55    10  596  663   33     7   59  114  328*
  4    6   41 3807*   17   62  137  380*   11  177  191   71     8  311  310   70
  5    6   40 4662*   18  372  352   71    12  168  249   79     9  314  330   72
  6   64   22  351*   19  220  253   90    13  314  332   67    10  280  283   83
  7  151  201   93    20  482  491   66    14  577  597   45    11  237  239  101
  8   64   71  442*   21  357  327   93    15  123  269  103    12  194  164   92
     1,  0, 1         22  168  177  100    16  530  534   53    13  239  225  111
  1  427  420    7    23    5   76 6565*   17    5  184 5921*   14  498  495   62
  2  787  820    7    24  385  334  101    18  412  372   73    15  118  290  138
  3  322  300   12    25    6   55 6978*   19    5  111 6125*   16    5  133 6310*
  4  394  423   12    26   94   86  220*   20  338  321   97    17    5   51 6124*
  5  248  234   20         1,  2, 1       21   61  158  562*   18  267  217  127
  6  905 1019   11     0  205  197   37    22    5   88 6517*   19    5  190 6876*
  7  101  126   31     1  536  526   19    23   83  135  453*   20    6  172 6844*
  8  489  537   17     2  780  831   17    24  290  275  100    21    6  121 6919*
  9  357  350   24     3  321  324   28    25    6   84 7252*   22    6   85 7045*
 10  426  428   23     4  620  641   20         1,  4, 1            1,  6, 1
 11  601  612   20     5  395  392   27     0   58   23  117*    0   99   65  115
 12  548  701   23     6  916  949   19     1  252  287   57     1  377  375   64
 13  350  338   34     7  341  339   35     2  550  594   31     2  317  338   75
 14  171  129   45     8  508  560   28     3  544  591   31     3  358  372   66
 15  402  170   37     9  449  473   33     4  325  370   46     4  166  170   79
 16  779  799   25    10  219  279   64     5  162  163   63     5  141  126   80
 17  364  232   53    11  247  290   63     6  343  371   47     6  134  118   87
 18  260  273   68    12  591  618   34     7  424  448   42     7  423  409   62
 19    5   27 4136*   13    4   59 4520*    8  477  503   41     8  344  356   76
 20  182  228   67    14   90  162  105     9  295  332   63     9  206  219   89
 21   99  249  146    15  197  218   76    10  168  194   80    10  143  122   92
 22  395  417   64    16  646  677   43    11  288  301   72    11  303  304   94
 23    5   51 5087*   17  195  258   95    12  362  386   65    12  176  154   82
 24   36   50  600*   18  260  255  102    13  243  260  101    13  315  292   99
 25    6   63 5163*   19  108  112  129    14  153  237   84    14  242  225   93
 26  356  326   86    20  375  353   82    15  181  259   87    15  113   90  143
     1,  1, 1         21  130  172  126    16  276  353  108    16  152  158  112
  0  837  882   11    22  401  380   90    17  218  334  107    17  256  248  101
  1  644  651   12    23   72   75  508*   18    5  244 6625*   18   49  179  567*
  2  445  440   15    24   45   89  830*   19    5  117 6484*   19    6   28 6914*
  3 1052 1126   12    25    6   62 7061*   20  205  200   85    20  154  113  132
  4 1030 1091   13    26  311  281  140    21   96  187  192         1,  7, 1
  5  417  433   21         1,  3, 1       22  239  248  115     0  177  165   79
  6  968 1012   16     0  672  699   23    23   47  140  883*    1  320  315   90
  7  359  364   29     1  346  357   34    24    6   66 7161*    2  164  183   83
  8  442  484   27     2  277  290   41         1,  5, 1        3  120   90  112
  9  298  300   41     3  233  238   48     0  342  346   55     4  322  316   89
 10  847  923   23     4  688  737   23     1  324  353   56     5  397  393   75
```

```
  Columns are  10Fo   10Fc   100Sig, * for Insignificant
 l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    1,  7, 1        11  537  551   23     5  162  177   68     1  307  325   53
 6  200  221   82   12  168  157   47     6  641  666   25     2  354  375   48
 7    5   77 5610*  13    4   26 3026*    7  738  715   24     3  235  218   70
 8  151  171   97   14  518  549   29     8  361  363   41     4  889  897   28
 9  248  223  122   15   45   43  311*    9  126   92   57     5  480  494   41
10  163  156   95   16  278  280   57    10  675  679   30     6   40   96  435*
11  208  209   90   17  328  357   52    11  226  233   76     7  396  378   50
12    5   70 6150*  18  306  303   60    12   55   44  158*    8  327  333   61
13  230  163  106   19  175  132   69    13  256  269   76     9  191  205   73
14  227  223  112   20  322  319   65    14  517  499   45    10  351  342   61
15  187  204   99   21  217   56  102    15   91   79  117    11  196  184   78
16   79   33  481*  22  134  132   88    16  190  242   87    12  190  165   82
17   28   52 1412*  23  173   75  103    17  342  348   76    13  352  330   69
    1,  8, 1        24  215  200   72    18  196  215   98    14  503  523   55
 0   99   82  166   25  119   35  151    19  159  138   90    15  164  193   82
 1  217  213   89   26   40   32  474*   20  386  372   84    16  136  119  102
 2  124  118  131       2.  1, 1         21  157  169  106    17  291  266  105
 3  249  268   95    0  243  255   29    22  191  188   92    18  217  195  104
 4  124  100  132    1  730  715   16    23  229  227   95    19  130  138  126
 5  181  173   91    2 1003 1005   15    24  240  205  117    20  221  223   92
 6    5   92 4329*   3  819  809   16    25  123  118  169    21  159  143  115
 7  255  252   96    4  597  609   19        2,  3, 1         22  200  176   99
 8  118  121  146    5  765  747   19     0  829  828   23    23  202  216  103
 9  133  142  132    6 1005 1056   18     1  302  312   43        2,  5, 1
10    6   31 6311*   7  467  453   28     2  578  606   28     0  378  416   54
11  201  201   92    8  384  414   35     3  143  133   62     1  233  235   85
12    6   48 6522*   9  265  201   51     4  595  627   29     2  479  486   46
13  177  196  112   10  301  297   50     5  479  498   34     3  381  419   56
14   62   97  641*  11  156  156   70     6  474  482   35     4  407  414   53
    1,  9, 1        12  618  592   33     7  393  411   42     5  288  313   74
 0   69   38  548*  13  203  204   89     8  633  644   32     6  324  336   69
 1  133  171  146   14   42   83  446*    9  261  251   66     7  307  310   74
 2  113   82  167   15  332  322   66    10  337  303   55     8  469  460   53
 3   16   84 2391*  16  521  507   48    11  351  344   57     9  147  161   78
 4    6   59 6563*  17  128  108   93    12  578  610   41    10  265  265   90
 5  188  193  104   18  416  408   67    13  245  261   87    11  204  214   85
 6   51   76  757*  19  284  251  100    14  227  260   99    12  436  426   63
 7   89   79  220*  20  106   78  138    15  170  177   79    13  276  266   98
    2,  0, 1        21  170  198   94    16  549  561   52    14  148  168   94
 0  872  899   13   22  522  502   72    17  130  134  105    15   56   77  526*
 1 1074 1152    9   23  205  207   91    18  255  249  115    16  322  337  101
 2  805  814   10   24   78   22  483*   19  153  163  100    17  183  186   91
 3  137  109   35   25  118   88  171    20  187  171   88    18  159  150  109
 4  761  777   11   26  253  256  122    21  210  177   96    19    6   76 6534*
 5  327  301   20       2,  2, 1         22  324  294  117    20  196  173   98
 6  923  951   12    0  777  810   19    23   86  128  453*   21  139  178  145
 7  726  781   15    1  380  372   28    24   39   59 1032*   22   80  139  532*
 8  265  270   31    2  115  109   57    25    6   39 7396*       2,  6, 1
 9  150  164   46    3  226  268   45        2,  4, 1          0  392  403   65
10  589  657   20    4  823  819   20     0  522  539   36     1  230  259  105
```

```
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
 l   kFo    Fc   Sig     l   kFo    Fc   Sig     l   kFo    Fc   Sig     l   kFo    Fc   Sig
      2,   6, 1         10     6    50  6382*   11   331   332    56      7   330   352    55
 2   228   208   106    11   142   143   133     12   210   156    90      8   189   188    67
 3   113    96   104    12     6    80  6612*   13   202   196    70      9   306   312    64
 4   224   213   110    13   181   163   111     14   403   421    57     10   590   590    40
 5   419   443    64          2,   9, 1         15    58    36   389*    11   362   393    62
 6   155   127    80     0    17    65  2200*   16   249   244    99     12   229   201    98
 7   201   191    90     1    47    52   807*   17   314   304    85     13   171   157    78
 8   205   185    90     2   100    66   186     18   353   381    81     14   258   213    96
 9   214   233    88     3   212   220   103     19   166   139    86     15   238   207   110
10   234   236    83     4    80    66   235*   20   216   192   100     16   170   187    80
11   275   284   104     5   113   122   169     21   146   153   111     17   239   217    85
12   159   147    91     6     6    67  6495*   22   168   162   103     18   270   282   112
13   299   268   107          3,   0, 1         23    70    91   263*    19   215   242   105
14   301   301   110     1   554   542    15     24   194   208   102     20   279   267   123
15   223   252    88     2   892   911    13     25    46    63   903*    21   201   212    89
16   122    85   142     3   345   321    22           3,   2, 1          22   174   178   109
17   185   172    99     4   414   396    20      0    68    65    80     23   200   172   101
18   135   158   143     5   645   673    16      1   610   624    26     24   180   188   118
19   210   212    97     6   627   599    17      2   701   717    24           3,   4, 1
20    92   100   230*    7   162   167    54      3   417   427    34      0   116   148    72
      2,   7, 1          8   698   746    18      4   519   506    30      1   493   519    41
 0    53    61   520*    9   496   544    24      5   546   560    30      2   531   541    39
 1   353   370    83    10     4    19  2865*    6   523   521    32      3   190   194    94
 2   351   355    85    11   157   140    52      7   260   272    59      4   278   262    67
 3   254   251   114    12   956   981    20      8   736   693    29      5   342   333    59
 4   138   128   102    13    71    82   105      9   355   369    50      6   463   476    47
 5   258   231   114    14   158   113    52     10   312   293    60      7   271   302    76
 6   170   170    86    15   349   274    47     11   289   262    68      8   418   439    54
 7   280   284   108    16   207   202    57     12   740   725    35      9   343   321    66
 8   294   288   104    17     5    39  3724*   13   337   314    67     10   228   241   101
 9   125   108   121    18   406   425    49     14   247   191    93     11   346   363    72
10   148   145   106    19   200   203    63     15   336   339    75     12   509   503    55
11   211   191    90    20   209   183    64     16   309   308    85     13   149   180    87
12   182   156    94    21   272   295    84     17   177   182    88     14    71    89   188*
13   202   212    88    22   431   454    59     18   398   371    74     15   430   421    70
14   185   141    99    23   205   193    81     19   333   331    93     16   273   287   110
15   154   138   124    24   147   102    99     20   164   170    97     17   315   309   100
16   132   118   149    25   188   142    77     21   105   133   161     18   248   258    93
17   173   177   119          3,   1, 1         22   382   360    99     19   115   158   148
      2,   8, 1          0  1792  1981    17     23   131   146   147     20   124   156   145
 0    61    63   538*    1   404   394    28     24    71    51   570*    21   107    88   177
 1   224   238   105     2   149   114    67     25    75   111   569*    22   193   176   105
 2   254   269    94     3   112   112    46           3,   3, 1          23   116    72   182
 3   159   168   104     4   559   539    25      0  1059  1091    24           3,   5, 1
 4   164   121   100     5   358   333    36      1   605   605    31      0   235   270    89
 5   230   232   104     6   591   595    27      2   181   188    56      1   243   273    88
 6   132    98   126     7   491   476    32      3   330   324    47      2   103   108   100
 7    45   127   733*    8   280   275    53      4   348   366    47      3   311   323    72
 8   161   144   107     9   471   462    37      5   206   190    77      4   216   220   103
 9   206   226   100    10   707   687    30      6   486   491    39      5   411   425    60
```

```
  Columns are  10Fo   10Fc   100Sig. * for Insignificant
 l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    3.  5, 1         11  173  148  101         4.  1, 1        23   75   44  259*
 6  341  335   71    12  240  222  106     0    3   59 3685*   24  272  235  110
 7  232  232  103    13  156  157  117     1  924  977   23         4.  3, 1
 8  190  200   91    14    6   78 4607*    2  692  696   26     0  113  131   71
 9  307  284   85    15  257  261  109     3  551  543   30     1  403  398   45
10  342  316   80    16  178  169  113     4  190  192   74     2  421  420   44
11  175  194   78        3.  8, 1          5  585  581   31     3  456  459   43
12  160  156   88     0  167  174  102     6  533  494   35     4  313  299   59
13  259  271  114     1   76   69  224*    7   93  127   86     5  473  486   44
14  161  158   94     2  117  110  147     8  655  643   33     6  527  516   42
15  341  345   96     3  203  205  101     9  637  622   35     7  288  246   70
16  331  293  101     4  176  176  100    10  389  369   53     8  292  284   72
17  146  147  116     5  147  119  121    11  560  527   42     9  539  527   46
18  144  134  123     6   67   79  535*   12  472  504   50    10  227  245  100
19  216  209  101     7  249  245  107    13  409  389   60    11  258  255   92
20  264  263  108     8  141   95  132    14  132  129   90    12  244  213  102
21  152  142  137     9   73   66  521*   15  433  439   63    13  254  239  104
    3.  6, 1         10  167  154  115    16  607  593   51    14  171  148   80
 0  355  356   74    11  127  130  156    17  140  161  101    15  338  348   88
 1  314  300   82    12  135  157  145    18  137  127  109    16  362  335   87
 2  424  436   66        3.  9, 1         19  224  207  100    17  263  198  121
 3  364  368   75     0   98   77  198*   20  262  283   92    18  233  212  102
 4  128  140  101     1  177  177  113    21  175  147  100    19  318  274  112
 5   39   37  337*    2  189  164  106    22  161  152  114    20  187  159   96
 6  273  273  101        4.  0, 1         23  228  205   99    21  125  139  147
 7  302  298   94     0  871  859   22    24   95   69  214*   22  233  208   97
 8  305  300   96     1  391  398   25        4.  2, 1         23  195  180  106
 9  255  264   83     2  184  173   48     0  271  278   54         4.  4, 1
10  131  153  114     3  578  579   20     1  435  440   37     0  278  300   72
11  306  296  105     4  688  692   19     2  481  473   36     1  409  426   52
12  323  305  103     5  308  323   34     3  614  612   31     2  229  237   88
13  197  204   97     6  411  420   28     4  642  629   31     3  448  446   50
14  126   87  132     7  315  331   36     5  247  229   66     4  263  269   81
15  129  118  133     8  354  359   34     6  406  401   45     5  297  281   74
16  186  168   96     9  246  244   49     7  252  259   71     6  602  589   44
17  187  170  100    10  348  385   39     8  321  313   60     7  270  296   86
18  180  181  109    11  231  255   59     9  431  435   49     8  172  151   77
19  228  220  106    12  140  127   50    10  415  403   53     9  381  359   68
    3.  7, 1         13  319  324   50    11  461  452   51    10  394  365   68
 0    5   54 5626*   14  494  484   36    12  302  295   77    11  282  255   95
 1  209  206  100    15   68   25  159*   13  336  327   74    12  317  325   89
 2  181  184   83    16  251  278   73    14  489  479   57    13  255  248  113
 3  250  229   86    17  331  322   60    15  208  220   91    14  328  285   94
 4   74   75  407*   18  241  249   69    16  321  287   90    15  330  301   98
 5  202  216   89    19    5   55 4159*   17  342  341   91    16  280  296  118
 6  144  121  108    20  363  378   65    18  376  288   86    17  155  164  110
 7   75   92  420*   21  264  275   74    19  108  114  151    18  130  151  136
 8  183  186   90    22   53   53  475*   20  210  245   96    19  186  157   98
 9  302  298  114    23  113   90  144    21  332  336  111    20  147  152  128
10  127  100  134    24  346  340   83    22   66  107  562*   21  204  245   98
```

```
    Columns are  10Fo   10Fc   100Sig, * for Insignificant
 l  kFo    Fc  Sig     l  kFo    Fc  Sig     l  kFo    Fc  Sig     l  kFo    Fc  Sig
     4,  4, 1          5    5    58 6171*    4  618   608   35      4  573   559   43
22  118   150  174     6  116    92  143     5  292   286   64      5  151   144   70
     4,  5, 1          7  269   241  130     6  462   464   45      6  283   261   80
 0  271   272   85     8  122   132  143     7  701   722   36      7  589   567   46
 1  334   365   72     9  243   250  106     8  357   362   60      8  257   204   92
 2  183   186   90    10  165   152  111     9  188   205   80      9  160   115   75
 3  247   238   97    11  201   171   93    10  486   479   51     10  277   274   94
 4  221   184  109    12  108    97  177    11  411   407   61     11  353   342   79
 5  310   326   84    13   19   137 2101*   12  298   289   84     12  391   382   74
 6  235   218   78    14  222   208  107    13  337   350   79     13  350   331   86
 7  337   325   80         4,  8, 1        14  340   307   82     14  435   415   74
 8  250   238  109     0  133   151  131    15  180   173   79     15  216   176  103
 9  492   492   62     1  117    89  151    16  133   126  111     16  297   297  115
10  188   198   88     2  125   111  144    17  468   472   73     17  355   338  101
11  245   222  122     3   83    59  437*   18  141   141  118     18   96   103  186
12    5    30 4217*    4  140   150  133    19    5   111 6493*    19  142   137  131
13  226   196  100     5  157   192  121    20  318   323  118     20  178   142  110
14  278   225  121     6   87   109  439*   21  212   194  104     21   80   160  510*
15  211   184   95     7   70    76  275*   22  149   113  134     22  202   188  105
16  185   161   97     8  184   181  108    23  197   196  106          5,  4, 1
17  187   193   99     9  146   133  138         5,  2, 1          0  564   571   46
18  194   199   99         5,  0, 1         0  707   711   33      1  381   379   63
19  257   236  110     1  265   256   43     1  281   284   64      2  327   321   72
20  181   166  112     2  229   247   49     2  350   355   55      3  345   339   70
     4,  6, 1          3   50    28  218*    3  181   185   71      4  321   321   77
 0   52    52  247*    4  209   174   55     4  484   506   44      5  520   516   53
 1  241   242  112     5  838   859   21     5  869   849   32      6  250   235  100
 2  322   328   86     6  186   187   54     6  217   221   92      7  311   321   85
 3  242   232  115     7   89    73   71     7  311   300   69      8  244   236  109
 4  368   369   81     8  236   248   58     8  268   285   82      9  242   224  112
 5  249   260  119     9  329   358   45     9  312   284   75     10  334   330   87
 6  311   297   97    10   74    84   97    10  189   181   88     11  308   261   97
 7  130   107  114    11  604   621   30    11  358   389   72     12  196   176   89
 8  229   222   95    12  175   177   58    12  261   245   99     13  241   220   93
 9  275   261  117    13  589   605   34    13  286   319   95     14  167   173   98
10  121   112  132    14    5    63 3009*   14  103    91  135     15  185   185   92
11  146   133  113    15  448   500   46    15  579   523   58     16  149   134  118
12  231   195  107    16  325   363   63    16  268   230  118     17   54    58  340*
13  106   101  166    17  121   129   86    17  232   201  101     18  131   104  146
14  204   208   90    18  153   165   72    18  178   179   96     19  264   221  108
15  216   196  102    19  456   478   55    19  339   315  109     20    6    78 7152*
16  128   142  152    20   73   113  216*   20  156   128  120          5,  5, 1
17  110   101  181    21  167   174   76    21  273   260  103      0  376   399   73
18    6   114 6938*   22  208   196   69    22   96   134  213*     1  151   130   84
     4,  7, 1         23  332   315   87    23  220   264  102      2  330   318   81
 0  183   186   84         5,  1, 1              5,  3, 1          3  240   223  111
 1  153   159  101     0  291   282   57     0  180   164   75      4  273   245  100
 2  127   126  123     1  659   673   32     1  281   279   71      5  124   107  109
 3  269   274   86     2  208   184   79     2  259   274   78      6  267   246  105
 4  240   258   98     3  690   706   32     3  381   394   57      7  320   297   92
```

Columns are 10Fo 10Fc 100Sig, * for Insignificant

l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig	l	kFo	Fc	Sig
	5,	5, 1		5	129	131	156	0	582	598	43	5	126	140	107
8	176	163	84	6	160	159	128	1	474	509	50	6	225	211	89
9	134	144	112		6,	0, 1		2	94	104	111	7	375	336	80
10	256	228	123	0	377	389	54	3	453	451	53	8	222	221	95
11	188	172	86	1	512	496	31	4	280	278	81	9	203	226	87
12	295	273	117	2	251	265	55	5	4	108	5135*	10	222	220	101
13	269	223	131	3	566	612	29	6	356	370	69	11	333	357	102
14	209	209	87	4	267	285	54	7	658	671	45	12	144	136	116
15	91	64	202*	5	4	53	3338*	8	55	64	448*	13	291	280	122
16	134	145	144	6	194	190	55	9	319	305	85	14	65	35	547*
17	247	188	116	7	644	683	29	10	358	351	80	15	108	91	171
18	221	183	110	8	83	30	122	11	447	426	67	16	229	204	99
	5,	6, 1		9	501	518	37	12	113	110	128	17	271	264	107
0	196	191	86	10	337	341	53	13	396	396	81	18	177	162	119
1	249	252	119	11	521	544	39	14	120	110	129		6,	5, 1	
2	159	148	93	12	50	24	361*	15	70	93	462*	0	271	258	108
3	213	201	100	13	320	327	62	16	153	150	111	1	268	277	109
4	261	260	121	14	272	313	76	17	431	381	88	2	163	164	88
5	328	345	99	15	42	41	486*	18	105	91	178	3	332	338	91
6	277	247	117	16	25	37	724*	19	62	109	627*	4	215	229	100
7	199	203	95	17	355	396	68	20	178	112	115	5	251	220	122
8	5	35	236*	18	69	65	225*	21	237	248	106	6	220	224	101
9	171	164	99	19	162	159	77		6,	3, 1		7	198	199	81
10	326	296	111	20	6	30	4602*	0	278	286	85	8	165	160	99
11	68	87	522*	21	327	336	87	1	452	467	56	9	262	250	130
12	99	92	186	22	30	9	955*	2	194	201	85	10	310	308	115
13	240	203	113		6,	1, 1		3	282	279	87	11	201	200	89
14	195	188	103	0	137	147	71	4	89	61	133	12	261	249	100
15	186	170	110	1	468	496	48	5	387	393	68	13	197	182	95
16	113	89	187	2	172	167	82	6	298	283	87	14	169	150	115
	5,	7, 1		3	230	240	89	7	60	121	430*	15	228	228	103
0	180	186	92	4	100	111	103	8	212	216	91	16	181	192	116
1	112	123	148	5	602	598	43	9	397	397	75		6,	6, 1	
2	244	255	100	6	65	105	337*	10	261	266	112	0	255	283	91
3	109	125	157	7	92	87	122	11	247	216	123	1	181	190	89
4	164	170	106	8	211	170	79	12	321	310	99	2	274	277	123
5	153	155	116	9	575	568	50	13	275	283	120	3	264	258	127
6	184	183	98	10	214	208	86	14	131	104	126	4	83	68	199*
7	146	163	126	11	126	114	104	15	383	342	95	5	108	126	157
8	161	159	116	12	135	122	102	16	178	159	102	6	198	191	89
9	148	122	129	13	315	313	94	17	53	67	703*	7	230	232	110
10	150	162	131	14	100	79	150	18	92	95	213*	8	180	162	101
11	80	40	495*	15	393	355	84	19	231	236	104	9	21	73	1747*
12	132	120	157	16	183	200	91	20	99	133	214*	10	191	166	100
	5,	8, 1		17	5	48	6440*		6,	4, 1		11	185	194	106
0	75	84	248*	18	212	193	100	0	239	254	109	12	242	210	118
1	136	132	139	19	399	383	100	1	320	311	82	13	242	249	100
2	99	100	193	20	131	109	152	2	254	245	103	14	35	3	1066*
3	142	126	137	21	130	117	160	3	390	418	73		6,	7, 1	
4	134	122	147		6,	2, 1		4	230	224	83	0	274	268	132

```
   Columns are  10Fo   10Fc    100Sig. * for Insignificant
 l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    6,  7, 1         18   86   88  470*    6  281  269  115     6   45   14  459*
 1  122  161  148    19    6  111 7246*    7  170  157   95     7  465  501   50
 2    6   57 6370*       7,  2, 1          8  143  118  116     8  124  130   86
 3  104   96  177     0   50   34  282*    9  431  431   85     9   63   64  343*
 4  168  167  112     1  433  450   63    10  168  188  105    10  101   66  136
 5   36   52 1046*    2  159  159   79    11  122  157  148    11  206  219   66
 6  176  180  112     3  297  311   90    12    6   54 6663*   12    5   43 4381*
 7  132  125  150     4    5   54 5410*   13  197  191   97    13  400  455   65
 8  113  110  179     5  328  309   85    14  151  132  131    14   91   49  182
 9    6  107 6990*    6  242  225  113    15  260  235  113    15  248  265   76
    7,  0, 1          7  136  152  102    16  162  148  132    16   63    6  425*
 1  424  438   43     8  216  218   96        7,  5, 1         17  269  324   86
 2  241  249   69     9  525  529   63     0   58   50  386*       8,  1, 1
 3  197  199   54    10  251  244  125     1  281  301  118     0  212  220   93
 4   52   52  200*   11  262  216  124     2  161  171  101     1  304  311   96
 5  458  480   42    12    5    9 6225*    3  322  336  106     2  154  137   92
 6  148  145   59    13  261  242   94     4  102  128  163     3  126  140  113
 7  101  109  113    14   78  132  449*    5  166  174  102     4   83   71  173*
 8  128  132   72    15  244  263  108     6  185  169   94     5  528  526   64
 9  391  401   52    16  148  143  128     7  288  286  127     6  131  140  116
10  164  155   60    17    6   45 6922*    8  203  189   90     7  123  121  126
11  204  201   64    18   57   23  715*    9  155  148  120     8  185  201   87
12   72  100  284*   19  319  294  137    10    6   53 6713*    9  376  356   92
13   56   72  381*       7,  3, 1         11  198  195  100    10    5   44 6380*
14   54   35  411*    0    5   12 5404*   12  203  197   99    11  315  327  113
15  438  462   58     1  291  283   93    13  191  203  109    12  106  100  169
16  126  142   96     2  205  209   94    14   75   70  282*   13  275  282   98
17   73  111  170*    3  621  637   52        7,  6, 1         14   24  108 1633*
18   50   25  516*    4   46   96  607*    0  294  314  123    15  397  380  105
19  175  182   78     5  112  124  126     1  136  128  130    16   85  111  488*
20  118  121  121     6  188  177   90     2   48   77  738*   17  122   87  174
    7,  1, 1          7  423  426   76     3  110  120  164        8,  2, 1
 0  127  110   92     8  119  114  128     4  250  266  106     0  138  138  105
 1  381  404   67     9  241  235   94     5  209  195  104     1  254  275  117
 2  170  170   71    10   66   24  344*    6  163  152  118     2  133  120  110
 3  609  619   48    11  232  206  103     7  107   75  181     3  455  480   73
 4   79   57  155    12  127  107  136     8  131  159  152     4  107  112  141
 5   49  124  514*   13  348  353  108     9  178  180  116     5  209  207   86
 6  159  170   82    14   95   74  195*   10  145  130  143     6  108   94  146
 7  545  538   56    15  105  126  182        7,  7, 1          7  419  439   82
 8    5   20 5682*   16  134  109  148     0   42   12  911*    8   71   82  232*
 9  325  328   92    17  334  302  128     1   71  107  558*    9  151  158  113
10  102   78  144    18  151  121  143     2  203  208   99    10    5   68 4574*
11  467  462   71        7,  4, 1             8,  0, 1         11  333  313  112
12  139  144  114     0  230  259   89     0   54   56  508*   12  151  131  123
13  335  316  102     1  257  267  116     1  353  348   58    13  292  295  133
14  211  209   94     2   65   60  448*    2   34   92  575*   14    6   64 6982*
15   66   81  378*    3  143  160  104     3  502  545   44    15  149  150  138
16  128  110  144     4  235  234   93     4   69   93  185*   16    6  107 7247*
17  350  295  113     5  345  312   92     5  145  140   69        8,  3, 1
```

```
  Columns are  10Fo    10Fc    100Sig. * for Insignificant
 l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig      l  kFo   Fc  Sig
    8,  3, 1          1  424  466   58     6  129  153  148     -4  972 1099   14
 0  311  309  103     2   44   36  516*    7  295  290  136     -5  379  435   22
 1  258  257  122     3  263  281   74     8  184  171  109     -6  931 1061   16
 2  106  114  146     4    5   22 3071*    9  163  164  126     -7  290  330   33
 3  160  136   98     5  443  473   57    10  197  159  106     -8  405  483   28
 4  276  310  121     6  140  151   85    11  278  283  112     -9  289  320   41
 5  531  528   68     7  190  214   64        9,  4, 1         -10  752  893   24
 6    5   60 6302*    8   78   67  204*    0  183  146  103    -11  299  246   48
 7  126  137  135     9  493  525   56     1  305  322  128    -12  415  308   40
 8    5   37 6459*   10    6   49 4560*    2    6   61 6638*   -13  727  236   31
 9  338  319  110    11  213  228   72     3  147  159  132    -14  746  669   32
10  204  201   92    12    6   83 4683*    4  162  145  121    -15  707  161   41
11  283  264  136    13  371  381   78     5  253  235  113    -16  415  470   56
12   77   65  503*   14    6   84 4814*    6   68  107  592*   -17   13  114 2336*
13  246  239  118        9,  1, 1          7   10   69 3995*   -18  296  375   99
14  155  184  135     0    5   98 6069*    8  135  111  156    -19    5  271 8481*
15  306  269  141     1  241  253   99       10,  0, 1         -20    5  510 8059*
    8,  4, 1          2  149   89  110     0  265  276  103    -21    5  324 8570*
 0    5   38 6043*    3  420  409   85     1  126  107  105    -22    5  196 7633*
 1  136  152  122     4    5   65 6302*    2   54   39  487*   -23    5   74 7756*
 2  231  222  103     5  122  126  142     3  397  407   72    -24  358  323  109
 3  289  285  121     6    5   44 6422*    4  176  179   77    -25    6   51 7908*
 4  182  170   95     7  388  391   98     5   73    8  231*   -26    6   82 7185*
 5    5   45 6426*    8   67  119  549*    6  137  146  101        -1, -2, 1
 6   53   96  671*    9  204  203   94     7  332  352   88     -1  503  518   21
 7  419  415   92    10   62  115  359*    8    6   88 4822*    -2  794  888   18
 8  218  223  101    11  243  228  117       10,  1, 1          -3  261  288   32
 9    6   70 6773*   12    6  127 7093*    0  100   35  188     -4  571  650   20
10   47   87  830*   13  305  295  141     1  291  327  135     -5  380  424   28
11  177  156  115        9,  2, 1          2  189  188  102     -6  824  958   20
12  208  213  101     0  141  147  119     3  167  181  117     -7  276  308   40
13  214  198  101     1  348  389  103     4  174  153  113     -8  389  492   33
    8,  5, 1          2  161  137  106     5  233  246  101     -9  416  486   34
 0  223  256   94     3  185  183   94     6  115   73  175    -10  240  283   58
 1  241  241  107     4  200  205   88     7  123  139  169    -11  432  278   40
 2  141  138  129     5  424  443   91     8  223  216  111    -12  573  637   35
 3   98  130  189     6    6   33 6510*       10,  2, 1         -13  352   61   54
 4  244  267  111     7  100  119  185     0  188  212  104    -14    4  137 4901*
 5  330  342  120     8  165  182  115     1  179  183  110    -15    4  247 7418*
 6  223  192  101     9  402  396  102     2  123  104  160    -16  560  654   52
 7   85   11  466*   10  115  136  175     3  310  316  132    -17    5  232 7545*
 8  150  140  135    11  169  171  121     4  157  123  129    -18  126  244  113
 9  253  227  117    12   40   52 1059*    5    6   26 6956*   -19    5  130 6817*
10  138  123  153        9,  3, 1          6  127  110  165    -20  218  312  105
    8,  6, 1          0    6   33 6307*       10,  3, 1         -21    5  161 7809*
 0    6   82 6642*    1  208  225  100     0  104   58  193    -22  346  384  106
 1   47   35  838*    2  186  176   97       -1, -1, 1          -23    5   62 7724*
 2  213  219   95     3  290  287  128    -1  614  637   13    -24    6   88 6791*
 3  160  169  127     4  141  169  131    -2  448  457   15    -25    6   50 7482*
    9,  0, 1          5    6   57 6676*   -3 1038 1138   13    -26  279  277  112
```

```
Friedel Pair
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
  l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    -1, -3, 1        -24    6   66 7159*   -5  344  379   85   -15  310  328   66
 -1  358  385   34      -1, -5, 1          -6  227  248   88   -16  462  514   52
 -2  230  278   48    -1  327  370   58    -7   43   68  637*  -17  319   92   75
 -3  217  256   51    -2  267  304   66    -8  167  195   86   -18  413  397   64
 -4  622  746   24    -3  247  297   71    -9  191  215   89   -19  379  235   74
 -5  508  599   28    -4  523  625   40   -10  158  179   96   -20  288   81  103
 -6  634  755   26    -5  333  395   57   -11  197  199   93   -21  408  211   85
 -7  227  252   58    -6  245  269   78   -12    5   62 6023*  -22  513  510   73
 -8  359  421   42    -7  105  111   90   -13  162  148  106   -23  424  197   95
 -9  339  405   47    -8  306  328   70   -14  275  219  130   -24    6   18 6853*
-10  528  644   36    -9  320  356   70   -15  190  188   97   -25    6   93 7247*
-11  176  197   68   -10  265  294   88   -16    6   11 6636*  -26  234  255  107
-12  154  246   69   -11  219  229   77   -17   77   41  514*     -2, -2, 1
-13  236  339   96   -12  194  156   90      -1, -8, 1           -1  370  379   28
-14  540  603   48   -13  213  221   87    -1  218  203  106    -2   38   65  231*
-15    4  253 6769*  -14  510  522   60    -2   72  121  447*   -3  218  277   45
-16  509  578   57   -15  251  252  117    -3  235  256  100    -4  713  768   21
-17    5  172 7120*  -16  134   96 1[illegible] -4   70   84  457*   -5  112  150   46
-18  414  422   74   -17    5   37 6042*   -5  162  161  101    -6  557  657   26
-19    5  124 6738*  -18  223  198  108    -6   55   86  345*   -7  622  685   26
-20  260  325  127   -19  210  205   99    -7  259  279   94    -8  301  371   46
-21    5  153 6549*  -20  170  177  110    -8  130  122  129    -9   69   57   97
-22    5  108 6605*  -21    6  121 6857*   -9   61  138  568*  -10  589  692   31
-23    6  125 7184*  -22    6   76 7066*  -10    6   28 6175*  -11  173  215   64
-24  261  267  112      -1, -6, 1         -11  187  194   97   -12   38   56  423*
-25    6  105 7424*   -1  330  339   72   -12    6   55 6498*  -13  192  274   95
    -1, -4, 1         -2  299  310   78   -13  174  186  112   -14  422  471   50
 -1  225  272   64    -3  350  394   67      -1, -9, 1          -15  108   47   95
 -2  499  584   33    -4  156  161   71    -1  138  168  137   -16  312  234   74
 -3  454  558   35    -5  107  111  103    -2   53   71  715*  -17  358  372   71
 -4  302  391   49    -6   15   84 1545*   -3    6   81 6376*  -18  240  186  109
 -5  150  163   67    -7  409  440   62    -4   91   57  206*  -19  323  110   92
 -6  277  360   57    -8  316  347   80    -5  160  179  121   -20  405  370   79
 -7  399  468   44    -9  183  216   79    -6    6   64 6552*  -21  359  205   97
 -8  455  513   42   -10  142  120   91    -7   73   86  532*  -22  232  184  110
 -9  261  330   70   -11  219  263   90      -2, -1, 1          -23  216  226  104
-10  178  210   75   -12  163  166   88    -1  752  755   16   -24  237  213   98
-11  221  260   92   -13  317  332   99    -2  947  988   15   -25  118  111  178
-12  362  384   63   -14  259  227  121    -3  814  844   16      -2, -3, 1
-13  278  271   84   -15  123  105  132    -4  570  618   20    -1  297  321   43
-14  246  250   99   -16  185  149   92    -5  715  757   19    -2  582  639   28
-15  213  237   86   -17  272  265  135    -6  926 1066   19    -3   99   88   61
-16  294  343  100   -18  214  195  101    -7  396  428   30    -4  547  626   30
-17  383  383   83   -19    6   19 6768*   -8  302  389   40    -5  480  548   33
-18  278  269  114   -20  137  121  150    -9  233  213   54    -6  391  455   40
-19    5  116 6431*     -1, -7, 1         -10  244  278   57    -7  326  386   47
-20  115  184  154    -1  291  290   96   -11  130  158   64    -8  547  647   34
-21    5  202 7012*   -2  141  163   97   -12  530  601   36    -9  258  291   63
-22  236  248  118    -3   60   94  320*  -13  185  213   92   -10  237  281   73
-23  121  122  165    -4  271  305  105   -14   27   71  649*  -11  292  329   63
```

```
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
  l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    -2, -3, 1        -12  393  433   68      -2, -8, 1          -3  396  437   34
-12  506  619   43   -13  222  252   84    -1  212  251   89    -4  418  436   34
-13  203  231   99   -14  104  142  130    -2  228  259  102    -5  453  517   33
-14  200  242   76   -15   51  107  567*   -3  160  176  102    -6  423  472   36
-15  316  222   75   -16  283  338  112    -4  137  138  119    -7  240  280   60
-16  488  568   55   -17  157  152  102    -5  220  237  107    -8  628  672   31
-17  210  105   89   -18  163  153  104    -6   61   89  541*   -9  275  351   59
-18  250  238  114   -19  104  102  171    -7    6  135 6036*  -10  238  261   71
-19  207  170   85   -20  202  194   94    -8  153  150  112   -11  252  276   72
-20  216  199   87   -21  128  159  155    -9  231  229  109   -12  625  736   37
-21  173  167  106   -22  133  137  156   -10    6   59 6413*  -13  263  308   77
-22  307  300  121       -2, -6, 1        -11  159  159  117   -14  177  163   84
-23  107   97  179    -1  220  261   75   -12    6   71 6584*  -15  248  297   92
-24    6   45 6895*   -2  202  226   82   -13  193  181  104   -16  243  278   98
    -2, -4, 1         -3  103  123  112      -2, -9, 1         -17  160  201   78
 -1  339  364   48    -4  206  225   81    -1  102   67  187   -18  346  379   81
 -2  298  341   54    -5  374  457   69    -2   76   72  488*  -19  278  299  104
 -3  241  245   67    -6   84  102  142    -3  205  227   92   -20  200  197   87
 -4  789  882   30    -7  168  188   73    -4   72   64  513*  -21  303  166  110
 -5  416  508   44    -8  190  181   94    -5   72  123  368*  -22  335  366  107
 -6   36   79  449*   -9  164  220   79    -6   87   68  438*  -23  252  146  103
 -7  322  350   56   -10  192  217   81      -3, -1, 1         -24  123   62  157
 -8  288  353   65   -11  237  295   84    -1  347  340   31   -25  157  132  132
 -9  134  170   68   -12  116  134  124    -2  106   75   52       -3, -3, 1
-10  232  302   86   -13  298  271  104    -3   64   82   77    -1  545  553   32
-11  174  201   84   -14  300  307  107    -4  480  504   27    -2  216  231   66
-12  148  147   72   -15  236  272  100    -5  347  351   36    -3  288  320   52
-13  302  343   77   -16  121   92  142    -6  576  638   27    -4  333  368   47
-14  420  511   63   -17  151  166  120    -7  449  491   33    -5  156  156   67
-15  197  216   92   -18  147  165  129    -8  303  339   46    -6  438  500   40
-16  154  111   88   -19  206  208   97    -9  427  479   38    -7  306  370   56
-17  257  264  116   -20  107  107  193   -10  629  705   31    -8  206  225   82
-18  211  182  103       -2, -7, 1        -11  307  344   55    -9  257  316   70
-19   71  120  462*   -1  316  367   91   -12  193  163   90   -10  504  613   43
-20  190  212   92    -2  336  354   85   -13  161  188   66   -11  293  383   69
-21    6  168 6771*   -3  251  267  112   -14  302  393   68   -12  204  232   72
-22   92  163  216*   -4  117  137  118   -15   18   65 1156*  -13  117  137   91
-23   36  230 1204*   -5  215  225   94   -16  216  244  106   -14  247  250   94
    -2, -5, 1         -6  140  156  102   -17  275  322   90   -15  240  236  101
 -1  269  261   71    -7  220  265   95   -18  292  394   91   -16  116  141  108
 -2  450  494   48    -8  242  281   88   -19  127  129  106   -17  235  224  114
 -3  354  428   58    -9   72  124  423*  -20  159  120   90   -18  257  261  111
 -4  341  415   61   -10  155  157  100   -21  152  174  102   -19  263  245   82
 -5  245  304   82   -11  197  195   95   -22  160  139  104   -20  263  253  124
 -6  258  322   81   -12  146  128  114   -23  176   63  101   -21  219  230   90
 -7  221  268   95   -13  203  225   87   -24  197  217   96   -22  172  170  106
 -8  394  462   59   -14  141  129  127   -25  202   71  100   -23  201  160   96
 -9  163  200   78   -15  143  130  131      -3, -2, 1         -24  196  191  104
-10  211  257   77   -16  108  116  181    -1  571  598   26       -3, -4, 1
-11  188  240   90   -17  138  158  147    -2  698  743   24    -1  458  500   42
```

```
Friedel Pair
   Columns are  10Fo    10Fc    100Sig, * for Insignificant
  l  kFo    Fc  Sig     l  kFo    Fc  Sig     l  kFo    Fc  Sig     l  kFo    Fc  Sig
    -3, -4, 1          -5   49    35  359*   -3  499   522   32    -3  439   479   43
 -2  516   554   39    -6  248   285  105    -4  194   209   69    -4  275   284   64
 -3  186   210   92    -7  295   338   92    -5  549   598   31    -5  419   470   46
 -4  213   217   82    -8  278   302   98    -6  459   475   37    -6  463   521   44
 -5  299   323   63    -9  231   245   85    -7   95   107   77    -7  257   264   73
 -6  424   484   48   -10  151   163   92    -8  587   650   34    -8  228   257   85
 -7  258   331   75   -11  274   306  109    -9  566   630   36    -9  465   526   48
 -8  334   419   61   -12  263   310  118   -10  359   387   53   -10  225   265   92
 -9  281   319   75   -13  155   171  100   -11  479   532   44   -11  239   284   90
-10  173   214   86   -14  152   126  105   -12  386   494   55   -12  216   242  104
-11  301   376   76   -15  103   103  161   -13  333   376   66   -13  257   274   92
-12  413   503   61   -16  141   150  123   -14  103   129  105   -14  120   117  102
-13  111   164  107   -17  161   189  113   -15  367   465   68   -15  290   364   92
-14   51    49  482*  -18  143   177  133   -16  494   597   56   -16  272   317  103
-15  360   423   78   -19  183   224  110   -17  127   157  101   -17  245   208  117
-16  244   268  115       -3, -7, 1         -18  150   155   91   -18  215   226   81
-17  251   284   83    -1  229   230   89   -19  217   230   94   -19  270   278  118
-18  227   246   97    -2  193   207   86   -20  227   293   97   -20  168   149   98
-19  140   150  115    -3  243   230  120   -21   59   142  551*  -21  162   146  107
-20  129   162  133    -4   64    36  444*  -22  148   129  115   -22  225   207   95
-21  145    77  126    -5  170   192   86   -23  209   212  100   -23  154   198  126
-22  164   177  118    -6    5   104 5691*  -24  145    61  133       -4, -4, 1
-23  129    73  157    -7  123   106  122       -4, -2, 1          -1  417   439   51
    -3, -5, 1          -8  164   176   94    -1  439   456   37    -2  215   234   90
 -1  211   246   69    -9  251   294   91    -2  448   453   37    -3  386   414   55
 -2  117   135   86   -10    5    76 5978*   -3  560   603   32    -4  228   251   87
 -3  309   333   70   -11  141   142  118    -4  645   676   31    -5  245   265   83
 -4  142   168   73   -12  197   227   88    -5  238   235   65    -6  541   614   45
 -5  350   398   66   -13  160   171  110    -6  383   420   45    -7  251   306   86
 -6  296   332   76   -14    6    89 6358*   -7  241   293   69    -8  191   190   80
 -7  165   204   78   -15  214   244   89    -8  302   335   59    -9  320   349   74
 -8  160   184   71   -16  115   165  170    -9  359   434   53   -10  315   348   76
 -9  244   258   99       -3, -8, 1         -10  315   360   62   -11  217   246   79
-10  301   327   84    -1  102    91  162   -11  389 4[illegible]1 55 -12  261   332   97
-11  151   197   84    -2  109   117  151   -12  232   281   90   -13  187   229   80
-12  165   186   79    -3  198   206   98   -13  237   280   94   -14  277   299  100
-13  228   279   86    -4  166   184  101   -14  425   493   59   -15  239   280   85
-14   58   118  487*   -5  125   130  135   -15  182   239   77   -16  231   318   92
-15  286   340  107    -6    6    92 6166*  -16  272   302   96   -17  104   134  147
-16  275   304  116    -7  203   233   88   -17  250   283  108   -18  142   178  113
-17   60   131  378*   -8   49    96  426*  -18  295   302   99   -19  168   170  100
-18  160   157  107    -9    6    39 6324*  -19   59   126  503*  -20  153   135  115
-19  224   211   93   -10  108   153  172   -20  175   231   90   -21  170   223  110
-20  258   253  105   -11  142   130  135   -21  263   312  129   -22   82   161  474*
-21  151   134  131       -3, -9, 1         -22   91   100  190*      -4, -5, 1
    -3, -6, 1          -1  192   180  101   -23  183    32  102    -1  294   346   80
 -1  304   325   84    -2  191   178  101   -24  218   230   91    -2  230   210   98
 -2  426   462   64       -4, -1, 1             -4, -3, 1          -3  208   221   78
 -3  302   334   85    -1  868   929   24    -1  398   402   45    -4  170   156   77
 -4  138   162   89    -2  654   688   27    -2  407   433   45    -5  324   360   76
```

```
Friedel Pair
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
  l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    -4, -5, l             -4, -8, l       -16  203  233   80   -20   91   91  204*
 -6  220  208  108    -1  105  110  165   -17  161  179   90        -5, -5, l
 -7  321  351   79    -2  128  119  135   -18  145  178  105    -1  214  184   84
 -8  204  212   86    -3  102   78  169   -19  314  347  105    -2  320  332   82
 -9  419  498   66    -4  130  148  134   -20  153  150  109    -3  217  224   84
-10  180  214   84    -5  168  181  105   -21  206  253  100    -4  255  240  101
-11  182  195   86    -6    6  112 6224*  -22  126  134  146    -5  141  149   90
-12   73   81  376*   -7   66   75  545*       -5, -3, l          -6  231  261   81
-13  186  219   78    -8  135  181  138    -1  280  298   71    -7  284  309   96
-14  194  201   90    -9  124  107  151    -2  199  231   97    -8  153  166   88
-15  170  190   92        -5, -1, l        -3  368  423   58    -9  108  140  126
-16  145  133  112    -1  658  678   32    -4  511  542   45   -10  188  212   88
-17  198  217   99    -2  166  168   68    -5  152  163   75   -11  158  174   92
-18  192  190   92    -3  651  705   32    -6  266  270   80   -12  225  261   96
-19  214  230   87    -4  571  612   36    -7  498  554   49   -13  206  222   88
-20  147  148  131    -5  254  273   68    -8  211  207  102   -14  194  218   95
    -4, -6, l         -6  381  438   50    -9  122  118   89   -15    6   65 6012*
 -1  261  269  102    -7  631  734   36   -10  221  245  104   -16  107  126  160
 -2  239  283  112    -8  305  357   64   -11  291  342   86   -17  193  190   93
 -3  207  216   91    -9  135  164   70   -12  281  360   91   -18  183  185  102
 -4  335  370   84   -10  399  461   55   -13  294  325   90        -5, -6, l
 -5  251  242  110   -11  321  380   69   -14  338  407   83    -1  259  258  113
 -6  279  315  102   -12  235  290   96   -15  160  168   87    -2  128  120  113
 -7   89  107  154   -13  285  354   84   -16  253  307  119    -3  200  214   84
 -8  225  237   90   -14  286  323   87   -17  294  341  107    -4  236  241   88
 -9  235  259   88   -15  144  182   88   -18   63  112  503*   -5  261  337  117
-10  126  145  117   -16   63  123  418*  -19  101  117  164    -6  246  248  122
-11  103  110  147   -17  397  469   75   -20  140  139  124    -7  134  187  112
-12  178  180   89   -18   97  102  152   -21  146  151  125    -8   60   73  505*
-13    5  117 5947*  -19   45   96  678*  -22  171  176  112    -9  133  174  116
-14  180  201   94   -20  268  331  125       -5, -4, l         -10  253  278   91
-15  159  169  110   -21  166  174  103    -1  377  398   64   -11  111   99  146
-16  156  165  115   -22   48  114  743*   -2  318  328   72   -12   67   90  352*
-17   92  119  203*  -23  172  198  110    -3  326  351   72   -13  193  227   90
-18   88   98  442*       -5, -2, l        -4  319  346   74   -14  145  174  123
    -4, -7, l         -1  321  325   57    -5  475  514   54   -15  144  163  127
 -1  159  176   95    -2  340  351   55    -6  204  202   80   -16   91  108  207*
 -2  108   99  139    -3  235  236   75    -7  223  295  108        -5, -7, l
 -3  248  256   88    -4  474  535   44    -8  194  230   88    -1  142  141  116
 -4  214  244  103    -5  804  857   32    -9  191  223   92    -2  210  258   92
 -5   76   74  404*   -6  194  227   97   -10  295  341   89    -3  122  116  134
 -6   35   96  623*   -7  229  270   85   -11  247  249  107    -4  176  172   93
 -7  265  267  123    -8  246  306   82   -12  163  174   83    -5  136  173  122
 -8  141  135  115    -9  272  280   78   -13  208  225   96    -6  154  193  108
 -9  200  245   97   -10  180  189   82   -14  141  188  103    -7  138  160  122
-10  119  130  143   -11  294  385   78   -15  158  197   95    -8  144  151  119
-11  148  157  117   -12  210  241   78   -16   54  138  582*   -9   54   95  638*
-12  118  110  151   -13  247  319   99   -17    5   87 5900*  -10   82  152  439*
-13   71  128  517*  -14   70  118  356*  -18   99  116  171   -11   20   75 1796*
-14  182  199  105   -15  480  538   61   -19  185  223   97   -12  128  130  147
```

```
    Columns are  10Fo   10Fc   100Sig, * for Insignificant
  l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    -5, -8, 1        -21  213  269  103    -9  176  204   86   -18   92  101  190*
 -1  118  137  158       -6, -3, 1        -10  253  288  126   -19   83  115  436*
 -2  113   99  163    -1  445  475   57   -11  205  226   90       -7, -2, 1
 -3  121  130  153    -2  192  211   84   -12  202  248   94    -1  436  456   62
 -4    6  134 6399*   -3  269  261   86   -13  137  195  122    -2  158  164   78
 -5   46  120  811*   -4   64   54  351*  -14  167  177  103    -3  295  310   86
 -6  138  149  136    -5  345  385   72   -15  154  201  116    -4   70   83  175*
    -6, -1, 1         -6  250  262   96   -16  145  197  127    -5  299  302   87
 -1  507  539   45    -7   99  136  120       -6, -6, 1          -6  180  210   82
 -2  193  183   72    -8  177  217   81    -1  166  170   96    -7  132  166   97
 -3  202  237   99    -9  355  411   75    -2  306  315  108    -8  197  197   94
 -4   37   89  526*  -10  225  243   82    -3  249  264   92    -9  452  540   66
 -5  544  596   44   -11  189  206   82    -4   79   51  398*  -10  209  264   96
 -6   79   89  128   -12  258  305  109    -5   62  100  509*  -11  252  244  114
 -7   55   99  381*  -13  243  285  118    -6  168  169   96   -12   40   31  725*
 -8  148  137   73   -14  115  138  127    -7  211  232   91   -13  254  268  120
 -9  509  577   51   -15  253  301   87    -8  162  164  102   -14   83  107  185*
-10  184  193   90   -16  130  136  121    -9   26   57 1265*  -15  195  249   96
-11  104  117  114   -17   88   51  184*  -10    6  155 6105*  -16  137  151  121
-12  138  150   90   -18   97   96  177   -11  179  206   98   -17   65   58  264*
-13  268  324  100   -19  205  248  102   -12  214  238   98   -18    6   24 6148*
-14  113   61  117   -20  107  137  174   -13  182  241  103   -19  235  295  114
-15  300  326   97       -6, -4, 1            -6, -7, 1             -7, -3, 1
-16  127  169  115    -1  272  275   95    -1  154  147  115    -1  287  311   96
-17   49   47  619*   -2  254  242  101    -2   90   77  197*   -2  152  192   88
-18  161  183  100    -3  389  422   70    -3  122   93  144    -3  544  604   57
-19  318  378  108    -4  250  240  102    -4  174  178  102    -4  130  129  102
-20  111   97  158    -5  114  109  111    -5   57   65  617*   -5   99  108  134
-21   86  125  432*   -6  179  196   85    -6  206  193   88    -6  163  178   84
    -6, -2, 1         -7  346  360   80    -7   69  136  526*   -7  411  459   72
 -1  435  481   53    -8  234  230  116    -8  103  124  179    -8  118  139  118
 -2  133  135   77    -9  182  231   88    -9    6   99 6313*   -9  164  216   88
 -3  439  458   53   -10  214  245   94       -7, -1, 1         -10   51   44  281*
 -4  226  242   94   -11  260  336  115    -1  391  412   64   -11  173  193   87
 -5  112  129   94   -12  151  131   98    -2  162  156   72   -12   92  111  165
 -6  327  381   71   -13  244  295   90    -3  568  606   49   -13  296  362  111
 -7  566  647   47   -14   66   45  333*   -4   86   72  136   -14   82   87  196*
 -8    5   73 4891*  -15   70   82  469*   -5  117  135  102   -15  109  126  152
 -9  277  319   88   -16  179  184   96    -6  154  192   79   -16   92  122  187*
-10  338  373   75   -17  235  291  107    -7  492  536   57   -17  259  290  100
-11  348  386   76   -18  129  168  142    -8   50   41  354*  -18   97  121  193
-12  100  118  129       -6, -5, 1         -9  292  335   91       -7, -4, 1
-13  343  424   83    -1  303  316   96   -10   97  101  136    -1  272  260  107
-14   49  122  571*   -2  158  165   89   -11  400  469   74    -2    5   37 5618*
-15   50   58  328*   -3  312  350   95   -12  114  130  123    -3  133  152  107
-16  117  150  129    -4  223  248   91   -13  270  314  111    -4  202  211   83
-17  341  409   97    -5  145  156   99   -14  182  206   83    -5  313  328   97
-18   71   91  231*   -6  206  226   99   -15   61   72  354*   -6  274  280  110
-19   43  112  786*   -7  176  212   84   -16  130  117  124    -7  177  172   84
-20  136  118  132    -8  136  161  109   -17  272  290  127    -8  106  119  141
```

```
   Columns are  10Fo   10Fc   100Sig, * for Insignificant
  l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig     l  kFo   Fc  Sig
    -7, -4, 1         -8  157  192   93    -3  272  283  124    -5  377  433   95
 -9  384  436   86    -9  282  315  110    -4  164  146  100    -6   50   59  382*
-10  159  193   99   -10    5   37 5684*   -5    5   52 6018*   -7   45  110  752*
-11  126  182  127   -11  254  322  126    -6  120  117  138    -8  148  181  117
-12   71   69  228*  -12   64   99  499*   -7  382  420   93    -9  343  380  107
-13  184  205   91   -13  235  280  101    -8  166  198  103   -10   89  112  200*
-14   67  107  513*  -14  108  110  156    -9   60   37  399*  -11  149  169  122
-15  185  239   98   -15  342  383  107   -10    6   73 6143*  -12   75   71  243*
-16   57  147  648*  -16  100  118  179   -11  143  162  125        -9, -3, 1
    -7, -5, 1        -17   77   84  478*  -12  171  222  107    -1  233  209  107
 -1  287  304  114        -8, -2, 1       -13  182  195  103    -2  158  190  112
 -2  125  130  127    -1  282  296  105        -8, -5, 1        -3  276  310  130
 -3  308  330  107    -2  118  109  120    -1  230  227  110    -4  123  171  142
 -4  133  143  119    -3  446  477   70    -2  152  142  116    -5   64   70  543*
 -5  153  166  104    -4  124  127  116    -3  125  105  141    -6  106  150  167
 -6  138  157  117    -5  150  193   97    -4  212  255   99    -7  273  285  134
 -7  252  292   93    -6  119  105  123    -5  287  348  130    -8  164  161  111
 -8  169  200   98    -7  411  491   79    -6  183  204  100    -9  160  160  115
 -9    6  142 6029*   -8   19  104 1107*   -7    6   19 6232*  -10  133  141  139
-10   63   63  540*   -9  122  138  126    -8  127  149  145   -11  226  278   98
-11  159  199  110   -10   65   74  483*   -9  218  244  100        -9, -4, 1
-12  164  212  108   -11  289  338  115   -10  140  146  135    -1  302  348  127
-13  178  206  103   -12  120  131  137        -8, -6, 1        -2  108   69  171
-14   81   57  229*  -13  223  276   89    -1    6   61 6585*   -3  159  172  118
    -7, -6, 1        -14    6   68 6082*   -2  198  216   99    -4  171  161  109
 -1  141  128  123   -15  144  160  124    -3  131  164  149    -5  226  209   96
 -2   70   69  246*  -16   84  116  438*       -9, -1, 1         -6    6  105 6481*
 -3   52  129  670*       -8, -3, 1        -1  242  245   96    -7   64   65  414*
 -4  219  254   94    -1  286  280  110    -2   78   76  207*   -8  133  120  143
 -5  203  205  101    -2  118  120  128    -3  388  413   89       -10, -1, 1
 -6  135  157  131    -3  189  172   81    -4   39   60  475*   -1  327  351  120
 -7   74   81  478*   -4  277  305  113    -5  118  125  138    -2  211  201  103
 -8  134  153  135    -5  455  512   74    -6    5   65 6036*   -3  172  182  110
 -9  175  185  106    -6   22   52 1370*   -7  356  409   99    -4  170  149  111
-10  139  142  134    -7  121  125  129    -8  124  129  135    -5  234  254  115
    -7, -7, 1         -8    5   31 5842*   -9  154  189  112    -6   43   84  874*
 -1  124  107  156    -9  261  268  126   -10   40  106  612*   -7   83  139  461*
 -2  191  201  102   -10  179  207   93   -11  184  210   98    -8  186  212  105
    -8, -1, 1        -11  220  266  110   -12  107  123  169       -10, -2, 1
 -1  262  293  109   -12    6   66 6060*  -13  249  300  107    -1  196  194   99
 -2  136  143  101   -13  210  247   99        -9, -2, 1        -2    6   85 6631*
 -3  162  165   85   -14  137  173  132    -1  358  403   99    -3  279  292  100
 -4   74   78  374*  -15  226  272   96    -2  109  144  154    -4   41  100  939*
 -5  476  511   65        -8, -4, 1        -3  172  186   98    -5   64   11  593*
 -6  106  128  134    -1  182  183   90    -4  150  184  112    -6  116  130  167
 -7   39  107  738*   -2  226  246  103
```