Pergamon

Tetrahedron 54 (1998) 1317–1348

TETRAHEDRON

Tetrahedron report number 439

DEVELOPMENT AND APPLICATIONS OF AMINO ACID-DERIVED CHIRAL ACYLNITROSO HETERO DIELS-ALDER REACTIONS

Paul F. Vogt and Marvin J. Miller*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, IN 46556.

Received 18 April 1997

Contents

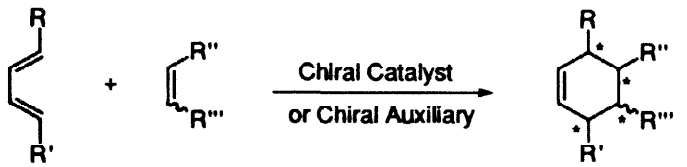
I. Introduction

The Diels-Alder cycloaddition has become one of the most used and dependable reactions in all of organic synthesis.[1] One reason for its popularity is that asymmetric versions of the Diels-Alder reaction give chemists the power to create up to four contiguous chiral centers in one step. This can be accomplished either with chiral catalysts and achiral dienes and dienophiles or, as often used, with chiral auxiliaries on the diene, the dienophile or both (Eq. 1).[2]

E-mail: Marvin.J.Miller.2@nd.edu FAX: 219-631-6652

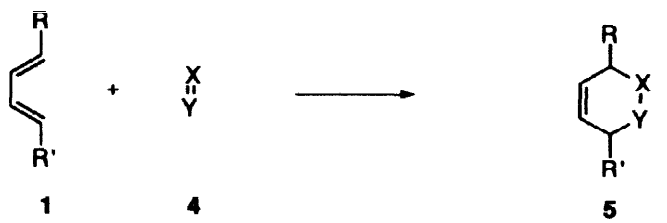
PII: S0040-4020(97)10072-2

The use of chiral auxiliaries in the Diels-Alder reaction has led to the stereoselective synthesis of many interesting products.



1 2 3 (Eq. 1)

Hetero Diels-Alder reactions, by definition, are [4 + 2] cycloadditions of dienes and dienophiles in which one or more carbons of the reactive species has been replaced with a heteroatom.[3] A large variety of hetero dienophiles **4** have been studied (Figure 1). The list in Figure 1, although not inclusive, does indicate the diversity of the hetero dienophiles that have been examined. Asymmetric all carbon, or homo Diels-Alder reactions, provide routes to chiral six membered carbon rings. Asymmetric hetero Diels-Alder reactions provide access to chiral heterocyclic compounds **5** in a similar fashion. These chiral heterocyclic compounds can be the synthetic targets themselves or be highly functionalized intermediates in the synthesis of other molecules.



1 4 5

X=Y	
C=O	C=S
O=O	N=N
C=N	N=S
C≡N	N=O

Fig. 1. Examples of Known Hetero Dienophiles

This review will describe cycloadditions of nitroso dienophiles **6**, especially acylnitroso dienophiles **7** (R = carbon or heteroatom). The focus will be on the use of these dienophiles in hetero Diels-Alder reactions,

6 7

including a brief historical section on the use of chiral auxiliaries with acylnitroso species **7**. Special emphasis will then be given to the use and applications of chiral, amino acid-derived acylnitroso dienophiles for the preparation of enantiomerically pure, functionally rich heterocyclic precursors of biologically relevant products.

II. *C*-Nitroso Dienophiles

A wide range of *C*-nitroso compounds have been used in hetero Diels-Alder reactions including arylnitroso **8**, α-chloronitroso **9**, cyanonitroso **10**, *C*-nitroso sugar derivatives **11**, vinylnitroso **12**, iminonitroso **13** and the aforementioned acylnitroso species **7** (Figure 2). In the next several sections a discussion of the properties of compounds **8-13**, as well as some examples of their use in synthesis, will be given. For a more detailed account of their properties see the previous reviews by Weinreb[3b,c] and Waldmann.[3d,f] An in-depth review of acylnitroso dienophiles **7** will follow.

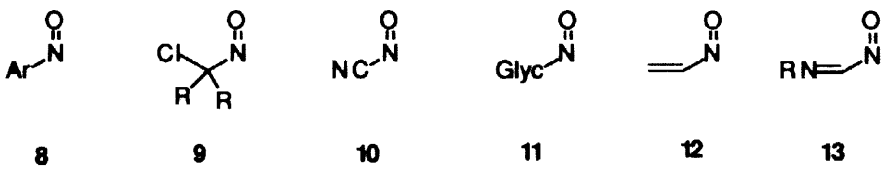
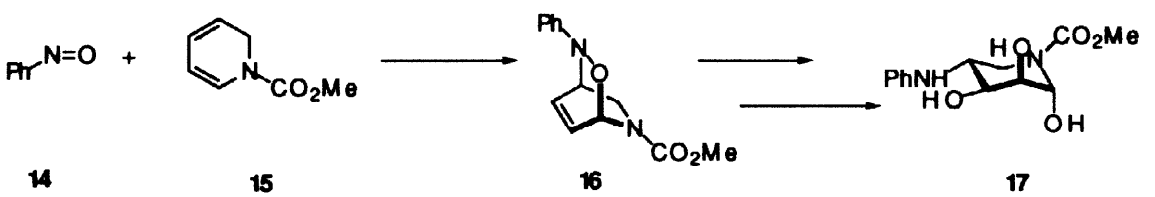


Fig. 2. Examples of Nitroso Species

A. *Arylnitroso Dienophiles*

Arylnitroso dienophiles **8**[4] are very stable compounds and are much less reactive in hetero Diels-Alder reactions when compared to acylnitroso dienophiles **7**. However, arylnitroso derivatives are readily available synthetic intermediates and, when they can be induced to react, they do so regioselectively with most 1,3-dienes. As an example, nitrosobenzene **14** and 1,2-dihydropyridine **15** underwent the hetero Diels-Alder reaction to give cycloadduct **16** exclusively and in good yield (Scheme 1). Cycloadduct **16** was later transformed into *lyxo*piperidinose derivative **17**.[5] When acylnitroso dienophiles **7** were used with diene **15**, the opposite regioisomers were formed.[6]

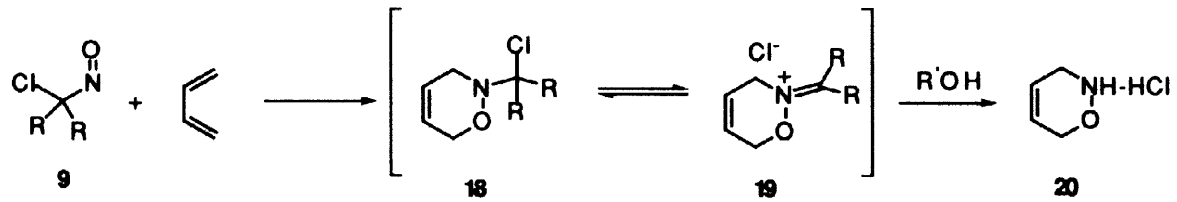


Scheme 1

Recent work has generated arylnitroso species **8** *in situ* by oxidation of the corresponding aromatic amines.[7]

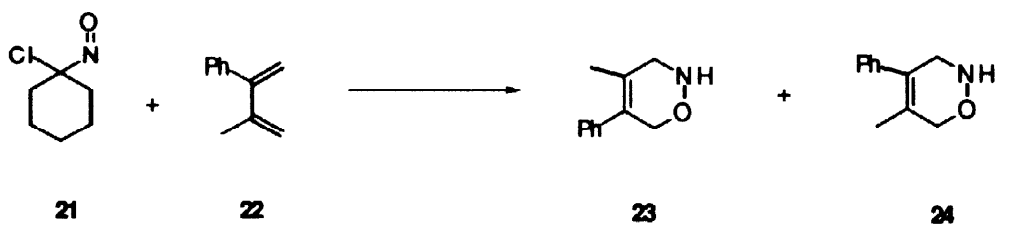
B. *α-Chloronitroso Dienophiles*

Readily available α-chloronitroso dienophiles **9** are relatively sluggish partners in hetero Diels-Alder reactions but have been used on a number of occasions since first reported in 1947.[8] When forms of **9** were treated with 1,3-dienes, the products were unstable adducts **18** and **19**. When the reactions were run in alcoholic solvents, the isolated products were dihydro-1,2-oxazines related to **20** (Scheme 2).



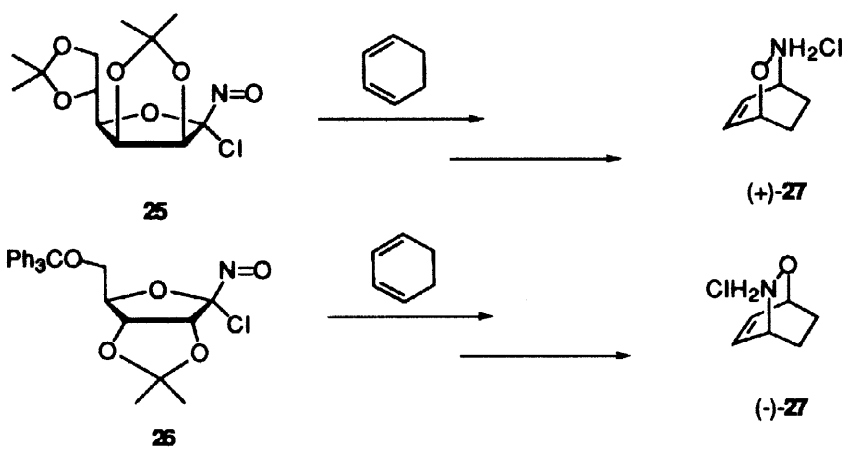
Scheme 2

As an example, cyclohexanone-derived α-chloronitroso dienophile **21** was treated with 2-methyl-3-phenyl-1,3-butadiene (**22**) to yield the expected adducts **23** and **24** in a 7:3 ratio (Scheme 3).[9] Kresze *et. al.* have used **21** in the synthesis of a variety of inosamine derivatives.[10]



Scheme 3

Kresze,[11] as well as many others,[12] have published studies on chiral α-chloronitroso dienophiles. Two of these chiral α-chloronitroso dienophiles are mannose derivative **25** and D-ribose derivative **26**. Both give

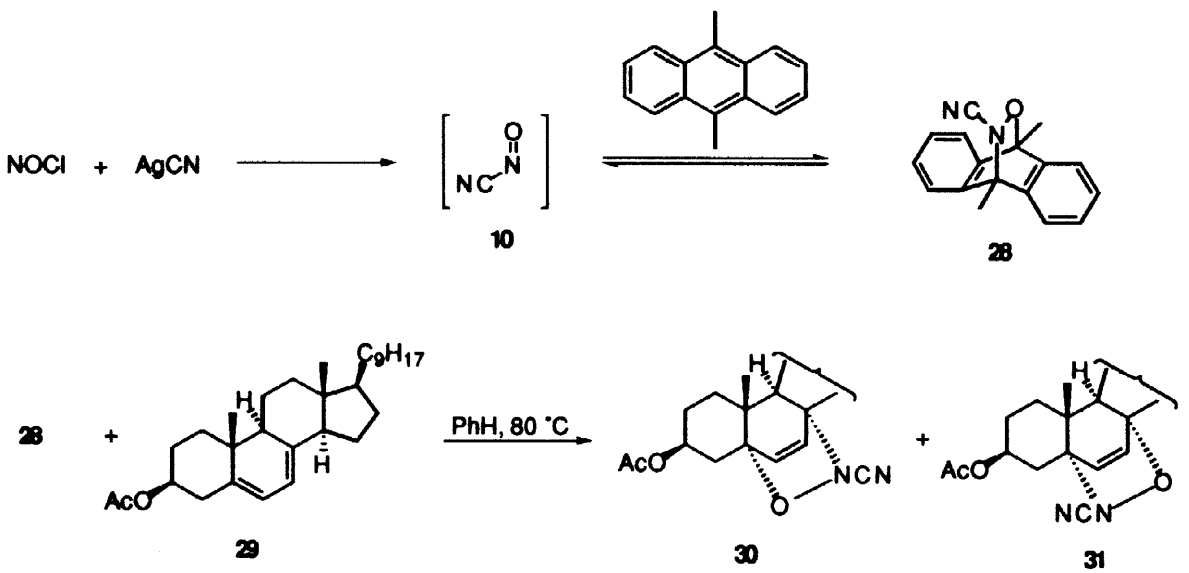


Scheme 4

good yields of the expected cycloadducts in very good enantiomeric excesses (>96%) upon reaction with cyclohexadiene and related dienes. (Scheme 4). Interestingly, the report did not describe reactions with cyclopentadiene. Preliminary studies in our group indicate that the diastereoselectivity of the cycloaddition with cyclopentadiene is significantly lower, as indicated by decreased enantiomeric purity of the eventual cycloadducts.[13]

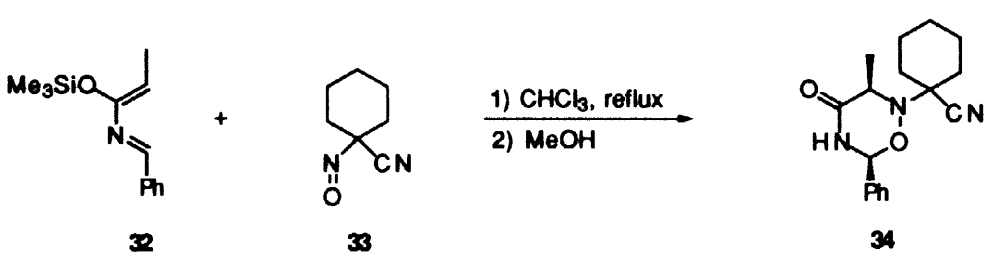
C. *Cyanonitroso Dienophiles*

Nitrosocyanide (**10**) is seldom used as a dienophile but can be prepared by reaction of nitrosyl chloride with silver cyanide. Reactions of **10**, generated this way, led to the desired cycloadducts as well as several unwanted side products. However, the cyanonitroso species was conveniently stored as an adduct (**28**) with 9,10-dimethylanthracene and cleanly unveiled for synthetic use by a retro-Diels-Alder reaction (Scheme 5).[14]



Scheme 5

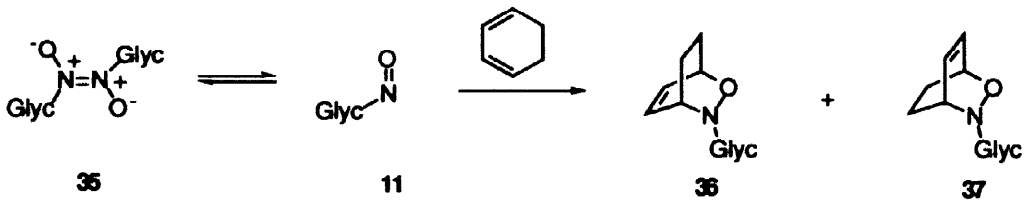
In a recent example, α-cyanonitroso dienophile **33** underwent reaction with hetero dienophile **32**, whereas reaction of the same diene with α-chloronitroso derivatives **9** failed (Scheme 6).[15]



Scheme 6

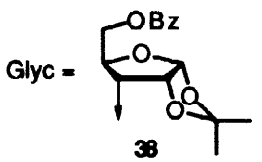
D. *C-Nitroso Sugar Derivatives*

Recently, *C*-nitroso sugar derivatives **11** have been developed and used in hetero Diels-Alder reactions with cyclohexadiene (Scheme 7).



Scheme 7

Compound **38** is one of several sugar nitroso derivatives that was investigated and shown to be effective in cycloaddition reactions.[16]

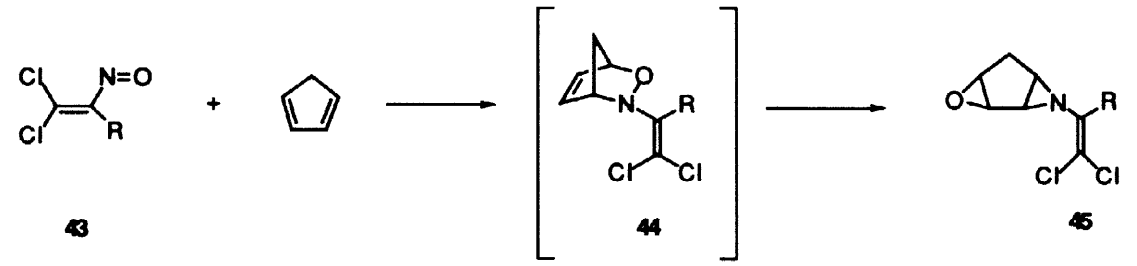


E. *Vinylnitroso Dienophiles*

Vinylnitroso species **12**[17] are unique in that they can participate in the hetero Diels-Alder reaction as either the diene or the dienophile. Their reactivity is dependant on their structure, as well as on the structure of the other component of the reaction system. Vinylnitroso species are unstable and are usually generated *in situ* by treatment of α-haloximes **39** with base (Scheme 8). In Scheme 8, fluorinated vinylnitroso species **40** reacted as a diene.[18]

Scheme 8

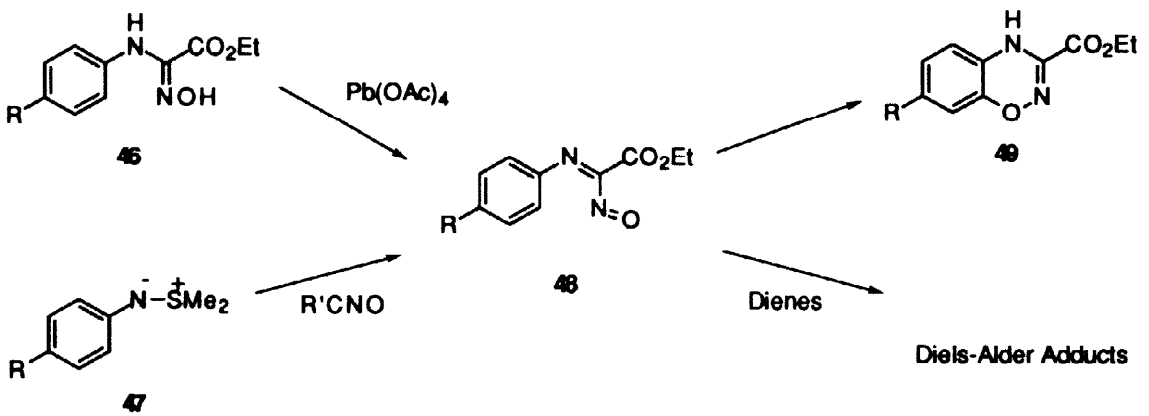
The use of vinylnitroso species as dienophiles can lead to interesting products (**45**) by rearrangement of the initially formed cycloadducts **44** (Scheme 9).[19]



Scheme 9

F. *Iminonitroso Dienophiles*

Iminonitroso species **48** have been prepared by oxidation of *N*-arylamidoximes **46** or by the reaction of *N*-aryl-*SS*-dimethyl-sulphimides **47** with nitrile oxides. The iminonitroso species can then cyclize to give 1,2,4-benzoxadiazines **49**. Intermediate **48** can also be trapped with dienes to give the expected Diels-Alder cycloadducts (Scheme 10).[20]



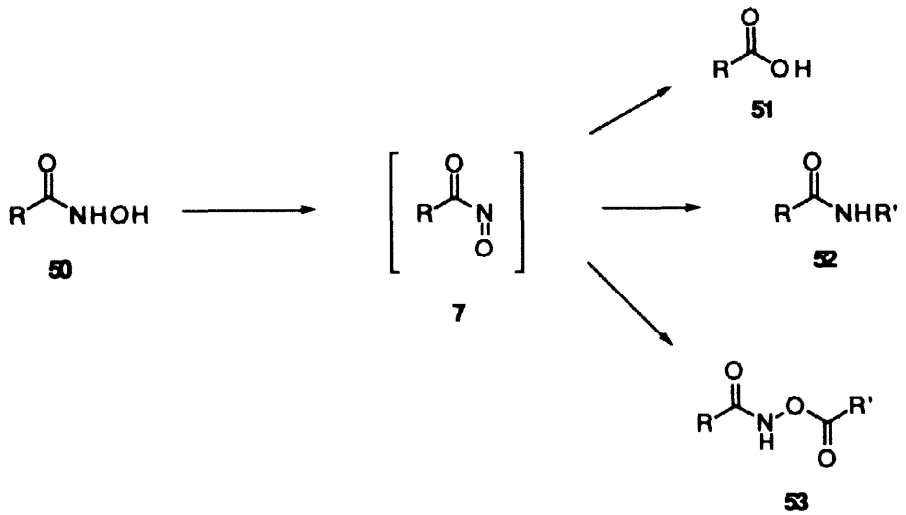
Scheme 10

III. Acylnitroso Dienophiles

Acylnitroso species **7** are unstable and very reactive. They are usually prepared *in situ* as transient intermediates by periodate, Swern, or lead oxide[21] oxidation of the corresponding hydroxamic acid. They also have been generated by oxidation of nitrile oxides[22] and by cycloreversion from the corresponding 9,10-dimethylanthracene adduct (*vide infra*).[23] When generated in the presence of appropriate 1,3-dienes, **7** leads at once to the expected cycloadducts in good yields. The use of **7** in hetero Diels-Alder reactions has been studied more extensively than any other of the nitroso dienophiles, and in the following sections some of this work will be presented.

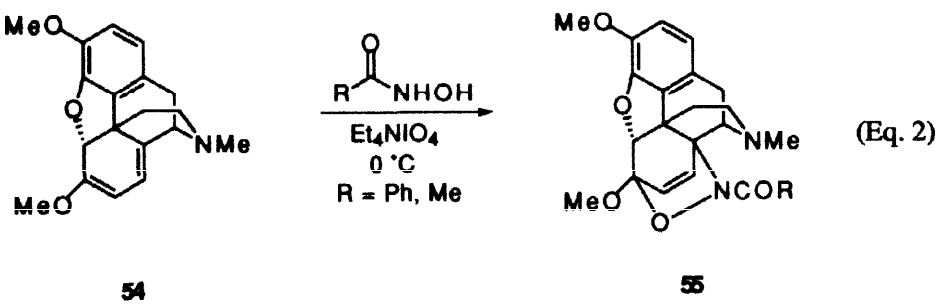
A. *Discovery of the Acylnitroso Species*

Acylnitroso species **7** were first proposed as transient intermediates in the oxidative cleavage of hydroxamic acids **50**. Acylnitroso species **7** could not be isolated and the only evidence for their exsistence were products **51-53** resulting from nucleophilic attack at the acylnitroso carbonyl (Scheme 11). [24]



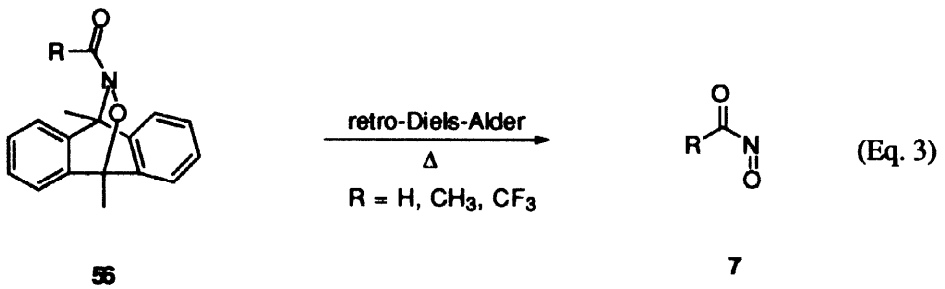
Scheme 11

Acylnitroso species **7** were postulated to be highly dienophilic, if they did exist long enough to participate in cycloaddition reactions. Kirby tested this theory by separately oxidizing benzo- and aceto-hydroxamic acids in the presence of thebaine **54**. The oxidations led to formation of the corresponding acylnitroso species, which were trapped by the conjugated diene, to yield Diels-Alder cycloadducts **55** in high yield (Eq. 2).[25]



(Eq. 2)

Although numerous synthetic uses for achiral acylnitroso dienophiles were developed and utilized in synthesis,[26] the first direct spectroscopic evidence for acylnitroso species **7** did not come until 1991 when Schwarz and co-workers liberated acylnitroso groups by retro-Diels-Alder reactions of cycloadducts **56** (Eq. 3). The acylnitroso moieties so generated were directly detected by neutralization-reionization mass spectrometry.[27]



56 7 (Eq. 3)

B. *Chiral Auxiliaries and Acylnitroso Dienophiles*

The use of chiral auxiliaries in acylnitroso hetero Diels-Alder cycloadditions is a relatively new area of study; however, several useful auxiliaries have appeared in the literature. This section will describe the use of several chiral auxiliaries and the diastereoselectivities that have been achieved in cycloaddition reactions. A summary of these auxiliaries appears in Table 1.

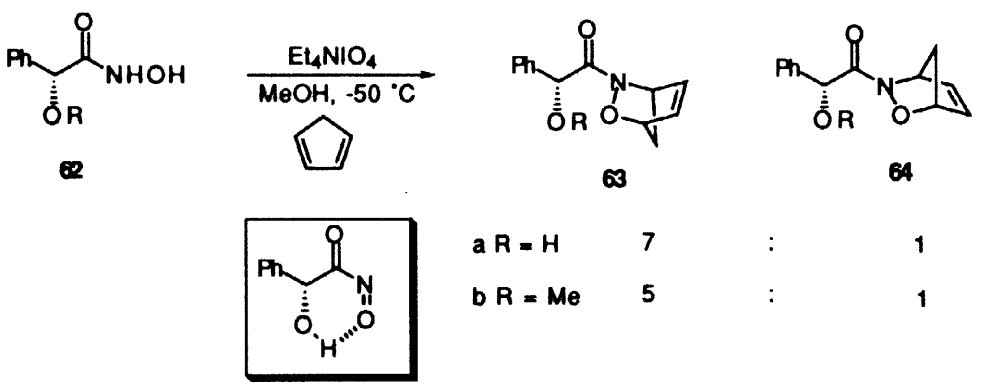
N-Hydroxycarbamate **57**, derived from camphor, was oxidized under Swern conditions to the corresponding chiral nitroso dienophile and treated with various dienes. The overall reactions proceeded in very good chemical yields and in excellent diastereomeric ratios of the expected cycloadducts.[28]

The bornane sultam of N-hydroxyurea **58**[29] also has been used successfully as a chiral auxiliary in the nitroso hetero Diels-Alder reaction. Oxidation of **58** and subsequent cycloaddition with cyclopentadiene and cyclohexadiene produced high chemical yields and diastereoselectivity, but much lower yields were observed with a highly functionalized diene.

C_2-Symmetric disubstituted pyrrolidine-derived *N*-hydroxyurea **59** gave good yields of cycloadducts in excellent diastereomeric excesses.[30] Another C_2-symmetric chiral *N*-hydroxyurea, **60**, also provided very good diastereomeric induction in the hetero Diels-Alder cycloaddition.[31]

N-Hydroxyurea **61**, derived from a homochiral imidazolidin-2-one, also has been used as an a chiral auxiliary in nitroso Diels-Alder reactions, but the diastereoselectivity observed was not as high as reported for the other cases shown in Table 1.[32]

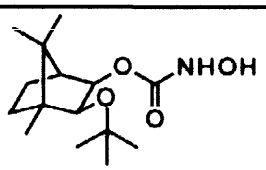
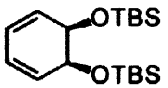
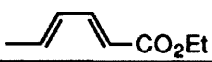
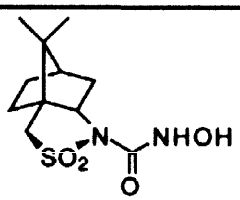
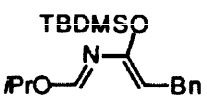
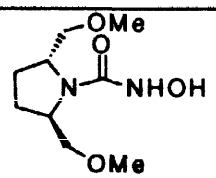
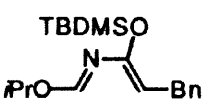
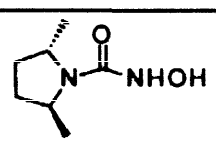
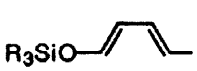
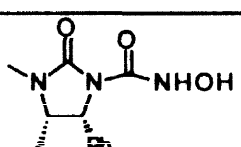
Mandelic acid derivatives have also been used as chiral auxiliaries in the acylnitroso hetero Diels-Alder reactions.[33] Oxidation of mandelohydroxamic acid **62a** in the presence of cyclopentadiene led to cycloadducts



62 63 64

Scheme 12

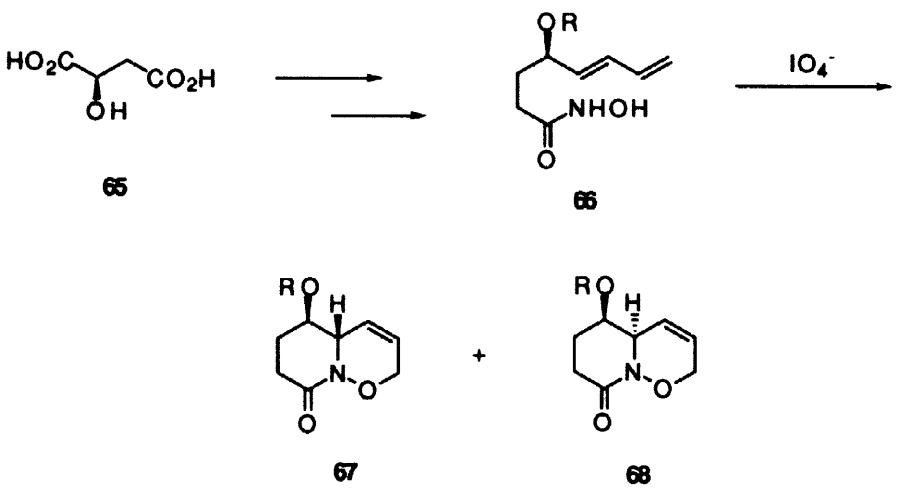
Table 1. Chiral Auxiliaries in the Acylnitroso Hetero Diels-Alder Reaction

Auxiliary	Diene	Diastereomeric Excess (%)	Yield (%)
 **57**		≥95	62
	cyclohexadiene	95	93
	cyclopentadiene	91	89
	1,4-dimethyl-1,3-butadiene	≥96	84
		≥95	65
 **58**		not determined	25
	cyclopentadiene	≥98	91
	cyclohexadiene	≥98	94
 **59**		93	65
	cyclopentadiene	87	91
	cyclohexadiene	>98	88
	cycloheptadiene	>98	70
 **60**		98	99
	cyclohexadiene	98	81
 **61**	cyclohexadiene	86	73
	cyclopentadiene	74	64

63a - 64a. Cycloaddition with methyl ether **62b** led to expected diastereomers **63b - 64b** but in a lower diasteromeric excess (Scheme 12). Procter and co-workers proposed a hydrogen bonded transition state to explain these results in which the hydrogen of the hydroxyl coordinates with the nitroso oxygen. More recently, the same group has demonstrated that the mandelic acid component of the cycloadducts can be removed, thus making it a true chiral auxiliary.[34]

Several other racemic α-hydroxyacylnitroso compounds have been studied,[35] and intramolecular hydrogen bonding has been invoked in the all carbon Diels-Alder reaction of α-hydroxy enone dienophiles.[36]

Asymmetric induction in the acylnitroso hetero Diels-Alder reaction also has been achieved intramolecularly, but will only be mentioned here briefly as an excellent review on this aspect of nitroso cycloaddition chemistry was published recently.[37] In a representative case, starting from D-malic acid (**65**), Kibayashi *et. al.* synthesized hydroxamic acid **66** which, upon oxidation to the corresponding nitroso compound, underwent cycloaddition to give expected products **67** and **68** (Scheme 13).[38] Depending on the reaction conditions, product ratios varied between 1.3 - 4.4 to 1, with **67** being the favored cycloadduct.



Scheme 13

Other work using nonchiral acylnitroso compounds with chiral dienes[39] and with chirality in both species[40] has been examined.

IV. Amino Acid-Derived Chiral Auxiliaries

Our laboratory has recently developed an asymmetric hetero Diels-Alder reaction involving chiral, α-amino acid-derived, acylnitroso dienophiles.[41] Prior to this work, the only known account of amino acid-based hydroxamic acids in acylnitroso hetero Diels-Alder reaction used L-proline-derived **69** and L-prolinol-derived hydroxamic acids **70** and **71**.[42] Moderate to good diastereoselectivities were obtained with these auxiliaries and cyclohexadiene, but, interestingly, no report of their reactivity or selectivity with cyclopentadiene was given (Figure 3).

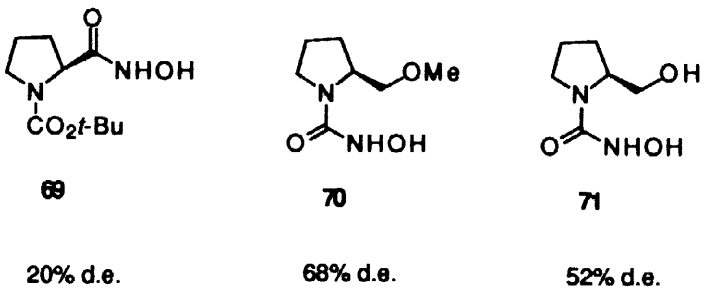
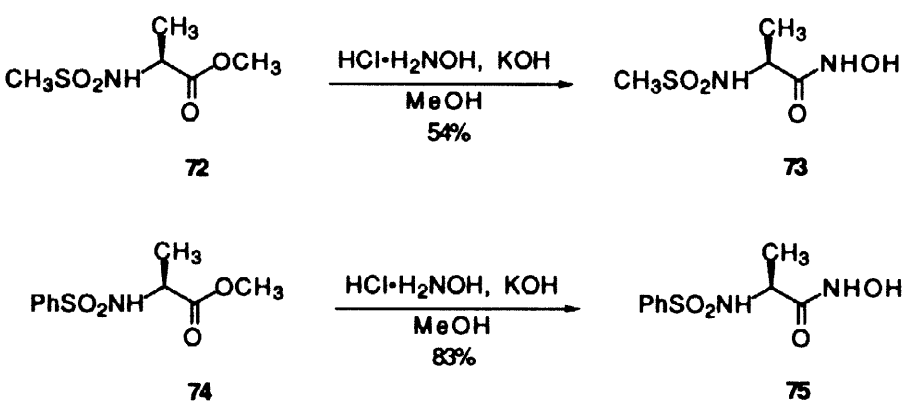


Fig. 3. L-Proline-Derived Chiral Auxiliaries

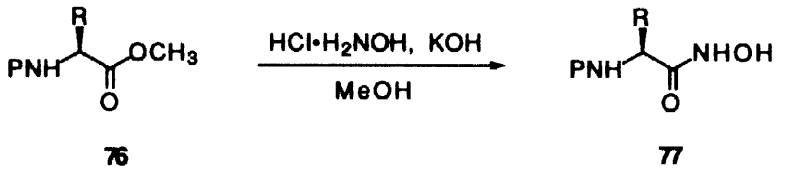
Although this use of an amino acid-derived hydroxamic acid in acylnitroso hetero Diels-Alder reactions was previously reported, a thorough study of this chemistry was lacking. Amino acids were chosen as chiral auxiliaries for a number of reasons. First, they are relatively inexpensive, readily available starting materials and are available in both enantiomeric forms. Also, the synthesis of the hydroxamic acids from amino acids was straightforward, and, finally, amino acids as chiral auxiliary adds versatility since they can either be incorporated into target molecules or removed by use of the Edman degradation. This section will give an overview of studies to determine the diastereoselectivity of α-amino acid-based acylnitroso hetero Diels-Alder reactions.[43]

A. *Chiral Hydroxamic Acid Synthesis*

The hydroxamic acids used in this study were prepared by several different methods. The first was direct hydroxaminolysis of the corresponding methyl esters with hydroxylamine hydrochloride.[44] The hydroxaminolysis approach was used to prepare various α-amino protected amino acid hydroxamates including sulfonamides **73** and **75** (Scheme 14) as well as the more versatile *N*-protected hydroxamic acids **77a-d** (Scheme 15, P = *tert*-butoxycarbonyl or benzyloxycarbonyl).[45]



Scheme 14

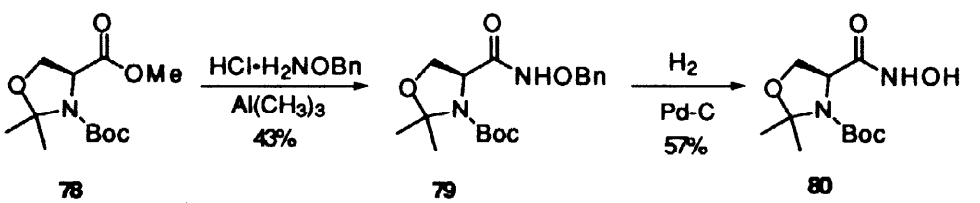


76 **77**

		Yield (%)
a	R = CH_3	98
b	R = Bn	92
c	R = ^{i}Pr	93
d	R = CH_2-*p*-C_6H_5OH	80

Scheme 15

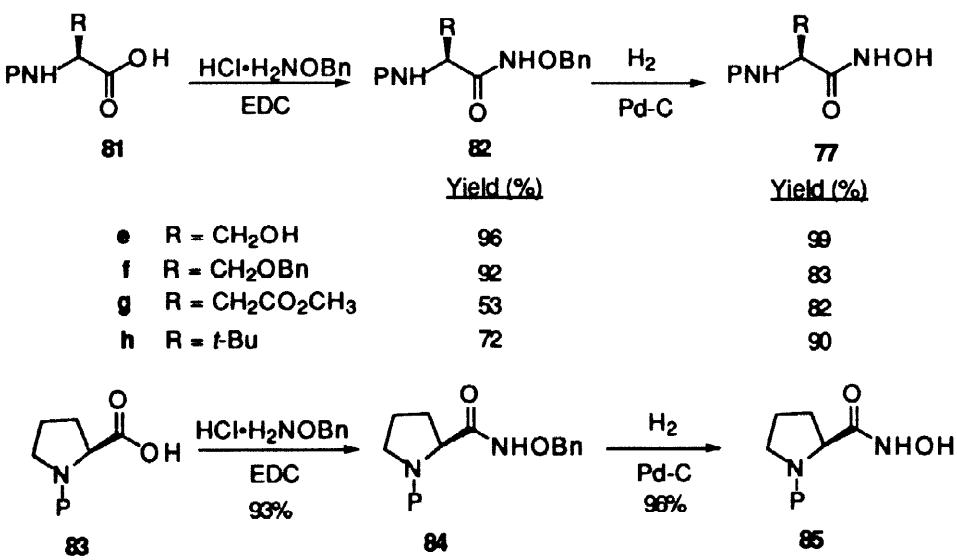
In a slight but very useful modification, hydroxamic acid **80** was prepared by Weinreb's amination[46] of the known fully protected cyclic serine derivative **78**,[47] followed by hydrogenolysis (Scheme 16).



78 **79** **80**

Scheme 16

Another method involved water soluble carbodiimide (EDC)-mediated coupling of *N*-protected-L-amino acids **81** with *O*-benzylhydroxylamine[48] followed by hydrogenolysis to afford hydroxamic acids **77e-h** and **85** in good yields (Scheme 17).[49]



81 **82** **77**

		Yield (%)	Yield (%)
e	R = CH_2OH	96	99
f	R = CH_2OBn	92	83
g	R = $CH_2CO_2CH_3$	53	82
h	R = *t*-Bu	72	90

83 **84** **85**

Scheme 17

B. *Polar Effects with Amino Acid-Derived Chiral Auxiliaries*

Extensive investigations into polar effects on the diastereoselectivity of amino acid derived chiral auxiliaries has included much work on examining possible influences of hydrogen bonding interactions. Based on the mandelic acid chiral auxiliary and other α-hydroxy acylnitroso dienophiles (Scheme 12), we examined serine where, although less likely, either a seven-membered hydrogen bonded transition state could be invoked, similar to the transition state proposed for mandelic acid, or alternative hydrogen bonding combinations might help order the cycloaddition transition state (Figure 4).

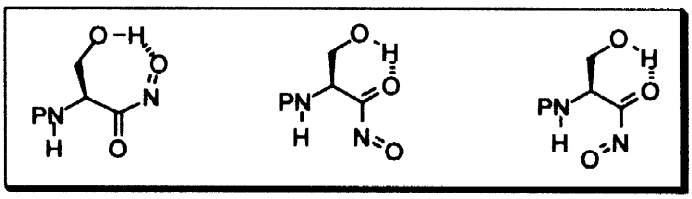
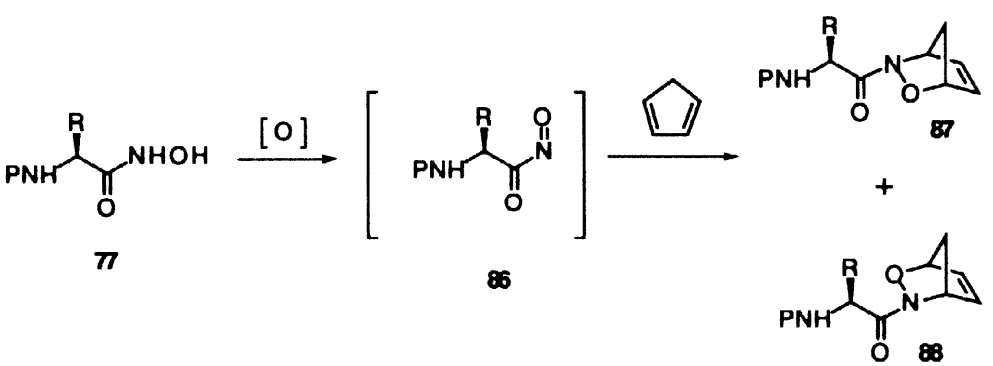


Fig. 4. Proposed Hydrogen Bonded Interactions for Serine-Based Hydroxamates

Thus, hydroxamic acid **77e** was oxidized with sodium periodate, in a MeOH:H_2O solvent mixture, to acylnitroso species **86e**, which was trapped with cyclopentadiene to give a 17% yield of diastereomers **87e** and **88e**[50] in a 2.5 to 1 ratio[51] (Scheme 18: Table 2: Entry 1). Both the low yield and moderate diastereoselectivity were investigated further. As for the diastereoselectivity, it could be argued that the acylnitroso species was hydrogen bonding with the solvent (MeOH:H_2O) and not with the hydroxyl group of serine. Changing to an aprotic solvent, methylene chloride, required a change in oxidant from sodium periodate to tetrabutylammonium periodate due to the insolubility of sodium periodate in methylene chloride. Thus, hydroxamic acid **77e** was oxidized with tetrabutylammonium periodate, in methylene chloride, to acylnitroso species **86e**, in the presence of cyclopentadiene, to give diastereomers **87e** and **88e** with only modest improvement in the yield (35%) and with approximately the same diastereoselectivity (Scheme 18: Table 2: Entry 2). This apparently ruled out solvent disruption of a hydrogen bonded transition state.



Scheme 18

Table 2. Polar Amino Acid Chiral Auxiliaries in the Acylnitroso Hetero Diels-Alder Reaction

Entry	Hydroxamic Acid	R	Oxidant	Solvent	Yield (%)	d. e. (%)
1	**77e**	CH_2OH	$NaIO_4$	MeOH:H_2O	17	43
2	**77e**	CH_2OH	Bu_4NIO_4	CH_2Cl_2	35	43
3	**77e**	CH_2OH	Dess-Martin	CH_2Cl_2	35	43
4	**77f**	CH_2OBn	$NaIO_4$	MeOH:H_2O	80	38
5	**77d**	CH_2-*p*-C_6H_5-OH	$NaIO_4$	MeOH:H_2O	67	45
6	**77g**	$CH_2CO_2CH_3$	$NaIO_4$	MeOH:H_2O	53	0

Competitive oxidation of the serine hydroxyl group, although not usually observed with periodate oxidants, was considered a potential cause of the low yield. Use of a different oxidant, the Dess-Martin reagent, known to readily oxidize primary alcohols to aldehydes,[52] afforded similar results with no aldehyde formation observed (Scheme 18: Table 2: Entry 3).[53] This, as expected, suggested that the hydroxamic acid was more readily oxidized than the alcohol.

Next, the hydroxyl group of serine was protected as a benzyl ether to give **77f**, which eliminated any possible hydrogen bond donor participation of the hydroxy group during cycloaddition of the corresponding nitroso derivative (Figure 4). Oxidation of hydroxamic acid **77f** with sodium periodate and *in situ* reaction with cyclopentadiene led to diastereomers **87f** and **88f** with similar diastereoselectivity to hydroxamic acid **77e** but in dramatically improved chemical yield (Scheme 18: Table 2: Entry 4). The similarity in diastereoselectivity between hydroxamic acids **77e** and **77f** suggested that the hydroxyl group played little role in the diastereoselectivity of this reaction. However, the reason for the increase in yield is still unknown, but might be attributed to minimization of competitive hydrolysis of the intermediate acylnitroso moiety by steric shielding from the relatively large peripheral benzyl group.

Intermolecular or intramolecular attack of the β-hydroxyl group of **77e** on the carbonyl of the intermediate acylnitroso species also needed to be considered as alternative competitive reactions that might decrease the chemical yield of the cycloaddition products. Tyrosine-based hydroxamic acid **77d** was subjected to the hetero Diels-Alder reaction with cyclopentadiene and afforded diastereomers **87d** and **88d** in 67% yield and 45% d.e. (Scheme 18: Table 2: Entry 5). None of the product from attack of the hydroxyl on the acylnitroso species was observed. Since the phenolic hydroxyl did not intermolecularly attack the acylnitroso species, it is reasonable to assume that the less nucleophilic primary β-hydroxy group of the nitroso compound generated from serine hydroxamate **77e** also did not attack intermolecularly. This still did not rule out the prospect of an intramolecular attack of the hydroxyl group of **77e** to form the strained β-lactone. Also, the reasonably similar diastereoselectivities obtained upon oxidative cyclizations with **77e** and **77d** appeared inconsistent with an ordered intramolecularly hydrogen bonded transition state.

One other hydrogen bonded transition state needed to be considered. The hydrogen on the amino acid nitrogen of any form of **86**, derived from amino acid hydroxamates **77**, might coordinate with the oxygen of the acylnitroso species to form a six membered ring (Figure 5). To determine if this alternative hydrogen bonded intermediate was potentially influencing the diastereoselective outcome of the cycloaddition reactions, the amino

acid protecting group was changed to a sulfonamide, which decreased the pK_a of the nitrogen hydrogen from ~25 for the carbamate to ~11 and might be expected to promote hydrogen bonding. The amino acid was also changed to alanine, to remove any potential competitive hydrogen bonding of the β-hydroxyl group.

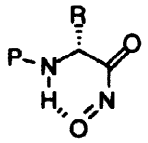
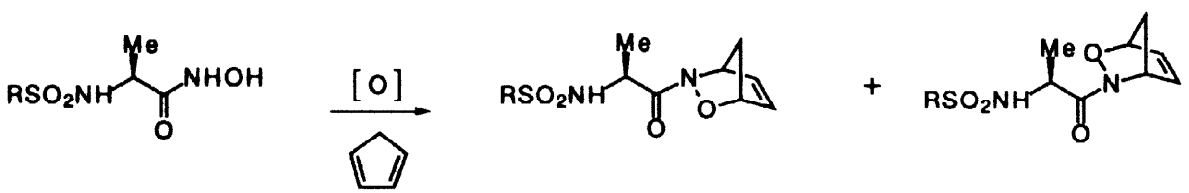


Fig. 5. Another Possible Hydrogen Bonded Transition State

Thus, sulfonamide-containing hydroxamic acids **73** and **75** were oxidized with sodium periodate and trapped with cyclopentadiene under the usual conditions to give the expected cycloadducts in a 1.5 to 1 and 2 to 1 ratio respectively (Scheme 19: Table 3: Entries 1 and 2). Again the effect of solvent on the cycloaddition was examined. Changing to nonhydrogen bonding solvents led to varying yields and to no major increase in diastereoselectivity (Scheme 19: Table 3: Entries 4-6). Thus, little variation in diastereoselectivity was observed upon use of the sulphonamides relative to other α-amino protecting groups.



73 R = CH_3
75 R = Ph

89 R = CH_3
91 R = Ph

90 R = CH_3
92 R = Ph

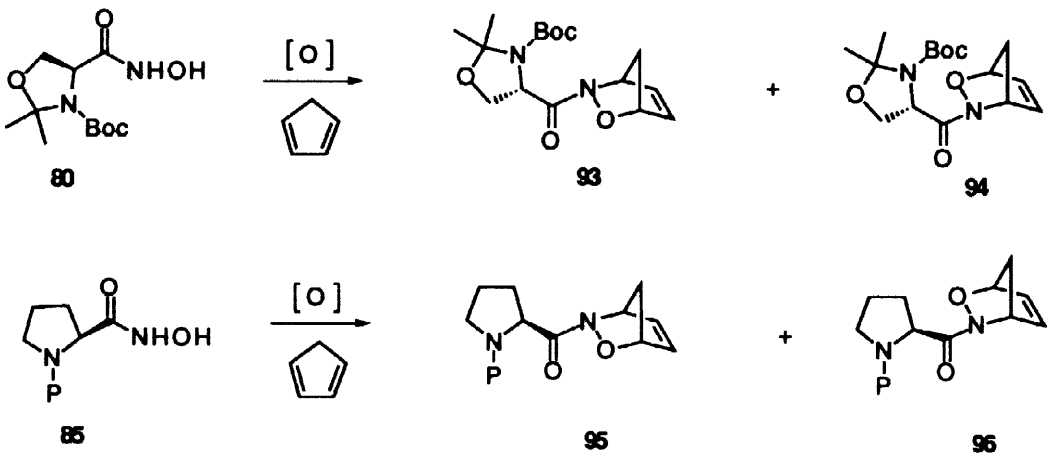
Scheme 19

Table 3. Sulfonamide-Containing Amino Acid Chiral Auxiliaries in Acylnitroso Hetero Diels-Alder Reactions

Entry	Hydroxamic Acid	Oxidant	Solvent	Yield (%)	Diastereomeric Excess (%)
1	**73**	$NaIO_4$	MeOH:H_2O	86	33
2	**75**	$NaIO_4$	MeOH	20	20
3	**75**	Bu_4NIO_4	Toluene	12	20
4	**75**	Bu_4NIO_4	CH_2Cl_2	45	33
5	**75**	Bu_4NIO_4	Acetonitrile	60	33
6	**75**	Bu_4NIO_4	Nitromethane	78	43

To further rule out any possible intramolecularly hydrogen bonded ordering of the acylnitroso species shown in Figures 4 and 5, hydroxamic acids **80** and **85**, with no free hydrogen on either the amino acid side chain nor on the amino acid nitrogen were investigated. These substrates also were chosen to determine if their

structural rigidity would have an influence on diastereoselectivity during the cycloaddition reaction. Oxidation of hydroxamic acids **80** and **85** led to cycloadducts **93, 94, 95** and **96** with moderate diastereoselectivities (Schemes 20: Table 4: Entries 1 and 2). With the hydroxamic acids discussed so far all producing similar diastereomeric ratios of Diels-Alder adducts upon oxidation and cycloaddition, the effect of hydrogen bonding on these cycloadditions appeared to be minimal.



Scheme 20

Table 4. Cyclic Amino Acid Chiral Auxiliaries in the Acylnitroso Hetero Diels-Alder Reaction

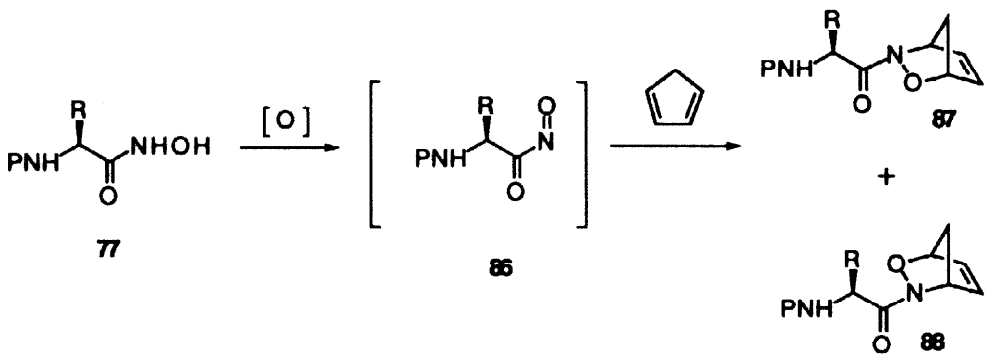
Entry	Hydroxamic Acid	Oxidant	Solvent	Temperature (°C)	Yield (%)	d. e. (%)
1	**80**	$NaIO_4$	$MeOH:H_2O$	rt	75	33
2	**85**	$NaIO_4$	$MeOH:H_2O$	rt	75	43
3	**80**	Et_4NIO_4	MeOH	-50	70	33

Hydroxamic acid **80** was also oxidized with tetraethylammonium periodate at -50° C to determine if lower reaction temperatures influenced the cycloaddition diastereoselectivity. The ratio of diastereomers **93** and **94** was identical to the reaction run at room temperature; however, the required reaction time increased from ten minutes to three hours (Scheme 20: Table 4: Entry 3). This suggested that cooling the reaction mixture only slowed down the oxidation step and had no effect on the diastereoselectivity of the cycloaddition.

With the hydrogens on the hydroxyl group and amide nitrogens apparently having no effect on the diastereoselectivity of the cycloaddition, another peripheral polar group, an ester, was examined. Oxidation of hydroxamic acid **77g**, derived from aspartic acid, produced a 60% yield of diastereomers **87g** and **88g**; however, no diastereoselectivity was observed (Scheme 18: Table 2: Entry 6). This anomaly is the only example of a chiral hydroxamic acid observed so far to have no effect on the diastereomeric outcome of the nitroso Diels-Alder reaction and the reason has yet to be determined.

C. *Steric Effects with Amino Acid-Derived Chiral Auxiliaries*

Since little change in diastereoselectivity of cycloaddition reactions of amino acid-based acylnitroso derivatives was observed when polar side chains were used, steric variations were studied with representative amino acids. These included hydroxamic acids derived from alanine **77a**, phenylalanine **77b**, valine **77c**, and *tert*-leucine **77h**. Under the standard reaction conditions good yields and moderate to very good d.e.'s were observed (Scheme 21: Table 5: Entries 1-4). Considering the diastereoselectivities of hydroxamic acids **77a** and **77c**, an increase in diastereoselectivity was observed as the steric bulk of the R group increased. Increasing the steric bulk further by using a *tert*-butyl group at the α-position led to a 7 to 1 ratio of diastereomers **87h** and **88h** (Scheme 21: Table 5: Entry 4). This indicated that steric bulk at the α-position of the hydroxamic acid, and not polar effects, probably had the major affect on diastereoselectivity.



Scheme 21

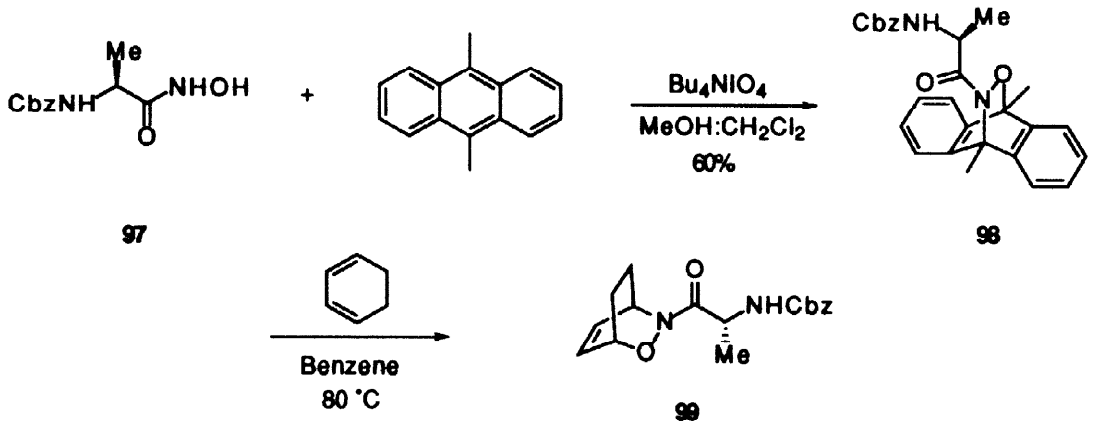
Table 5. Non-Polar Amino Acid Chiral Auxiliaries in the Acylnitroso Hetero Diels-Alder Reaction

Entry	Hydroxamic Acid	R	Oxidant	Solvent	Yield (%)	d. e. (%)
1	**77a**	CH_3	$NaIO_4$	MeOH:H_2O	90	50
2	**77b**	Bn	$NaIO_4$	MeOH:H_2O	79	30
3	**77c**	*i*-Pr	$NaIO_4$	MeOH:H_2O	85	60
4	**77h**	*t*-Bu	$NaIO_4$	MeOH:H_2O	63	72

D. *9,10-Dimethylanthracene Adducts*

Trapping of acylnitroso intermediates as 9,10-dimethylanthracene adducts prior to reaction with desired cycloaddition reaction partners is advantageous as it allows storage of the nitroso equivalent, its release in the absence of an oxidative environment and often minimizes separation problems during the reaction workup. With these advantages in mind, hydroxamic acid **97** was oxidized with tetrabutylammonium periodate in the presence of 9,10-dimethylanthracene to give adduct **98** in 60% yield. Adduct **98** was then heated in the presence of cyclohexadiene in benzene. The acylnitroso species was liberated *via* a retro-Diels-Alder reaction and trapped with cyclohexadiene to give cycloadduct **99** and its diastereomer in quantitative yield and in a 5 to 3 ratio

(Scheme 22). Interestingly, despite the significant change of solvent and other reaction conditions, the diastereomeric ratio of cycloadducts was very similar to that observed earlier (Table 5: Entry 1).



Scheme 22

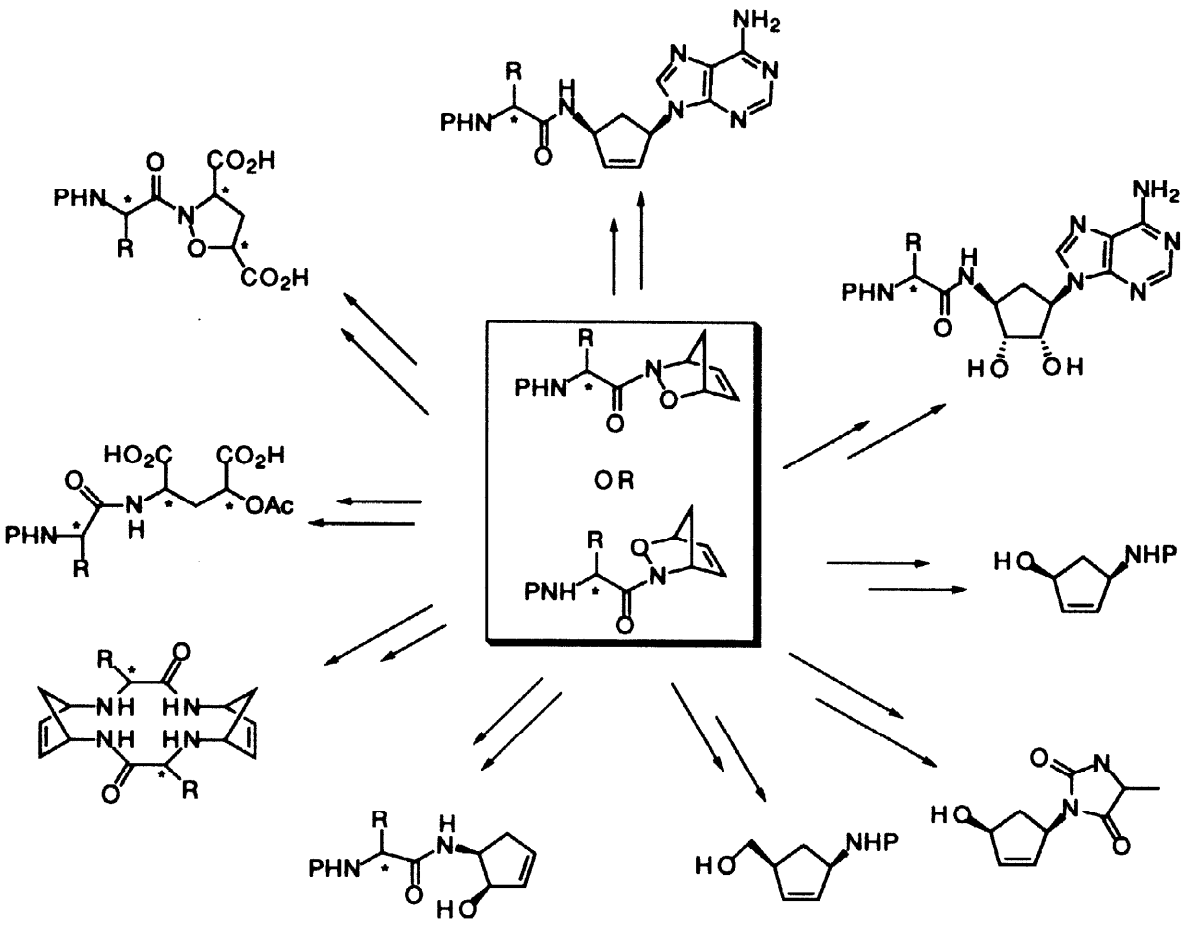
V. Synthetic Uses of the Amino Acid-Derived Cycloadducts

Although only moderate to good diastereoselectivities are obtained using amino acid-derived chiral auxiliaries in the acylnitroso hetero Diels-Alder cycloadditions described above, the functionally rich diastereomeric cycloadducts are readily separated by direct recrystallization or chromatography and each optically pure diastereomer is useful for elaboration to a variety of useful products. A general summary of some of these products is shown in Scheme 23 and more detailed discussions of their syntheses follow.

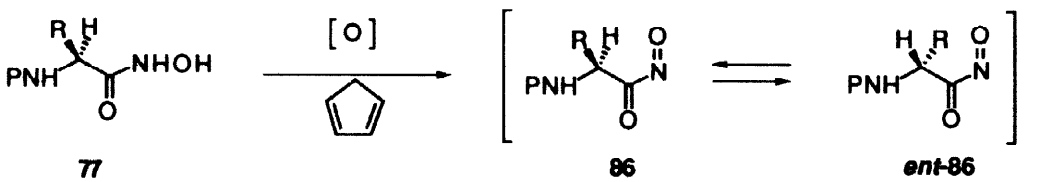
A. *Determining Enantiomeric Purity of Cycloadducts.*

Use of diastereomeric acylnitroso cycloadducts for the asymmetric synthesis of representative biologcially relevant target molecules required unambiguous demonstration of their optical purity. This was especially important since biological activity usually is correlated with a single enantiomer.[54] Concern about the enantiomeric integrity of the cycloadducts was due to the highly electrophilic nature of the acylnitroso intermediate **86** (Scheme 24). Some amino acid chlorides and active esters, which also are very electrophilic, are prone to racemization. If, during or subsequent to its generation, racemization of the chiral auxiliary (**86** to ***ent*-86**) occurred faster than cycloaddition, a mixture of enantiomers would have resulted for each diastereomer formed in the cycloaddition process.

The enantiomeric purity of the cycloadducts was determined by mild derivatization of the Diels-Alder cycloadducts. As shown below, three transformations were carried out in a single step (Scheme 25). The Diels-Alder adducts were separated, and the diastereomerically pure adducts **100a-d** (from L-alanine and L-phenylalanine) were reduced under one atmosphere of hydrogen in 80% to 90% yield to give the corresponding amino alcohols **101a-d**. The olefin was reduced, the Cbz group was removed, and the N-O bond was efficiently reduced, typically, in less than three hours.

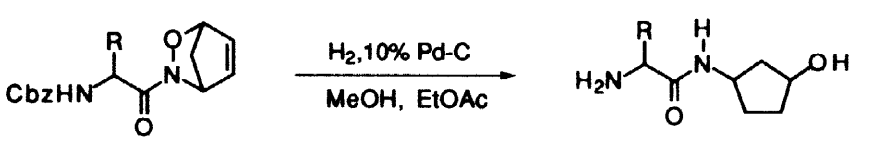


Scheme 23



77 86 ent-86

Scheme 24



100

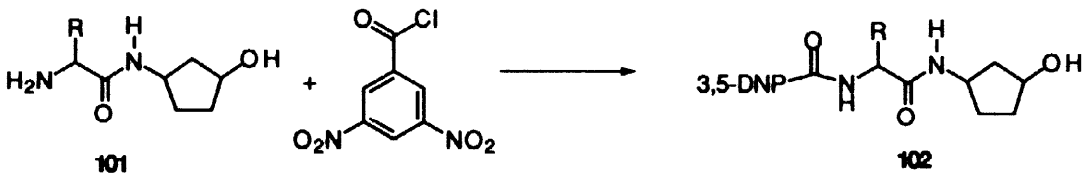
a R=Me, major diastereomer
b R=Me, minor diastereomer
c R=Bn, major diastereomer
d R=Bn, minor diastereomer

101

a R=Me, major diastereomer
b R=Me, minor diastereomer
c R=Bn, major diastereomer
d R=Bn, minor diastereomer

Scheme 25

Further derivatization using standard procedures was carried out on reduced amino alcohols **101a-d.** Acylation with 3,5-dinitrobenzoyl chloride gave dinitrobenzamides **102a-d**, substrates ideally suited for quantitative analysis by chiral HPLC (Scheme 26).[55] When a diastereomerically pure cycloadduct was derivatized, a single peak was observed in the chiral HPLC trace. To verify this result, both D- and L-amino acid auxiliaries were examined. This method of analysis was extremely effective and provided excellent resolution of enantiomers. The HPLC retention times of the D- and L-alanine enantiomers differed by 37 minutes, and the D- and L-phenylalanine enantiomers separated by 50 minutes.



Scheme 26

All products formed were ninhydrin negative, verifying that N- and not O-acylation had occurred during reaction with the dinitrobenzoylchloride. The enantiomeric purity of the hetero Diels-Alder reaction products was determined to be greater than 97%, using L-alanine, D-alanine, and L-phenylalanine as sources of chiral acylnitroso dienophiles. With enantiomeric purity of the cycloadducts ascertained, their use in asymmetric synthesis could then be examined.

B. *Carbocyclic Nucleoside Analogs.*

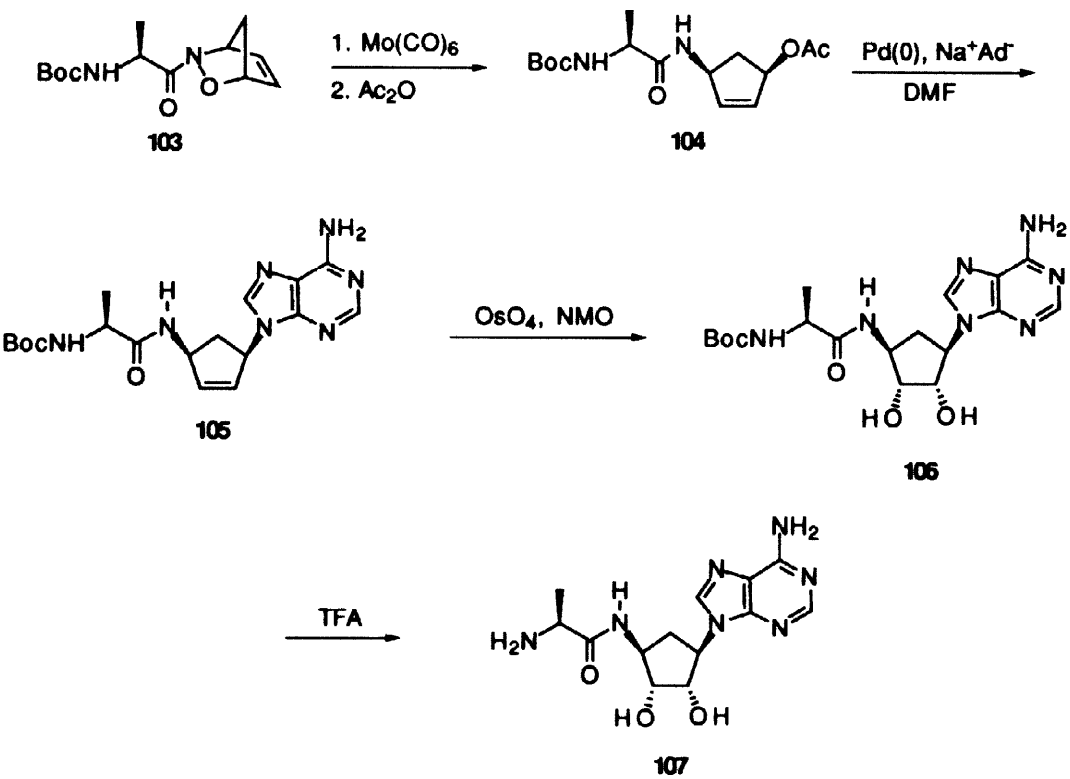
Nucleosides display a wide range of biological activities,[56] and the discovery and synthesis of modified nucleosides has been quite extensive.[57] A very important class of these modified nucleosides is that represented by *carbocyclic nucleosides*.[58] Carbocyclic nucleosides are identical to normal nucleosides except that the furanose oxygen has been replaced by a methylene group. This change provides enhanced metabolic stability as carbocyclic nucleosides are resistant to the action of nucleoside hydrolase enzymes which cleave the glycosidic linkage of normal nucleosides. The structural similarity of these functionalized cyclopentanes to normal nucleosides allows them to mimic the parent nucleosides as substrates for enzymes involved in nucleoside transformations. The development of asymmetric routes to carbocyclic nucleosides, their derivatives, and to novel analogs has been an important and longstanding goal.

Using amino acid-based acylnitroso Diels-Alder reactions with cyclopentadiene, our laboratory has synthesized several 4'-amino-carbocyclic nucleosides where amino acids replace the hydroxymethyl group at the 4'-position of the cyclopentane ring. The method is general and compatible with several amino acids, including alanine, proline, phenylalanine, serine and others. The following discussion describes studies with alanine-derived cycloadducts as representative.[59]

Molybdenum hexacarbonyl[60] efficiently (90-95%) cleaved the hydroxamate N-O bond of cycloadduct **103** to give the corresponding amino cyclopentanol. Acetylation of the resulting alcohol produced allylic acetate

104 in 87% yield (Scheme 27). Next, precisely one equivalent of the sodium salt of adenine was formed by the addition of one equivalent of sodium hydride to adenine in DMF, followed by the addition of a mixture of one equivalent of allylic acetate **104** and Pd(0) tetrakistriphenylphosphine (5-10 mole percent relative to allylic acetate) in DMF to yield nucleoside analogs **105** and its N^7 isomer (4:1) in up to 92% yield.[61] Apparently, no prior reports of 4'-amino noraristeromycin derivatives such as **105** have appeared in the literature.

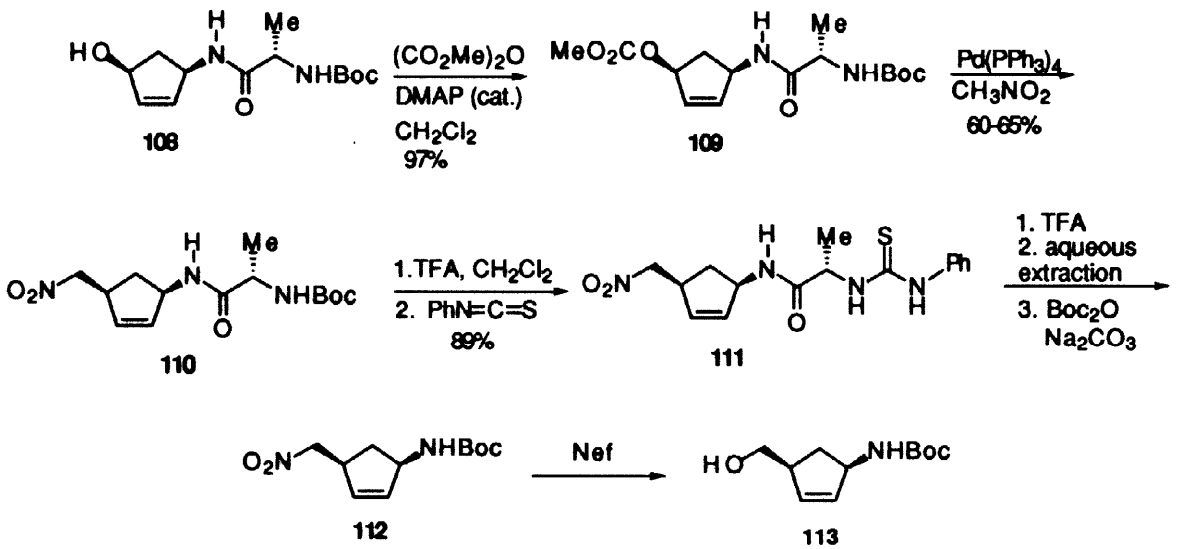
Further derivatization of **105** was accomplished by *cis*-dihydroxylation with catalytic osmium tetroxide to provide a 90% yield of a mixture of diols which were converted to their acetonides for ease of structural assignment. The major diastereomer formed (**106**) had the diol functionality *anti* to the two nitrogen ring substituents. Based on mass recovery from the chromatographic separation of the diastereomeric diols, a 3:2 mixture was obtained in the dihydroxylation. While the formation of diastereomeric diols was expected to be more selective,[62] diol **106** was isolated and deprotected with trifluoroacetic acid. The resulting free base diol **107** was purified by ion exchange chromatography. Preliminary biological studies indicated that while **107** and derivatives have no anti-HIV activity, they do display select antiviral and anticancer activity.[63]



Scheme 27

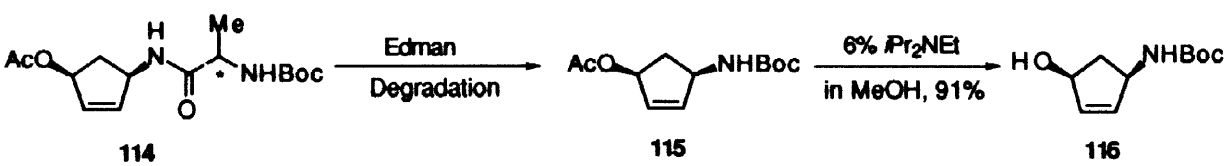
With an interest in developing a synthetic route to known carbocyclic nucleosides analogs, methods were developed for both removal of the amino acid chiral auxiliary and the introduction of an hydroxyl methyl side chain. Thus, alcohol **108**, an isolated and purified single diastereomer of **101**, was first converted to carbonate **109** in 97% yield. Reaction of **109** with nitromethane in a Pd(0)-mediated alkylation furnished **110** (Scheme

28).[64] All attempts to hydrolytically remove the amino acid auxiliary were unsuccessful. However, classical Edman degradation conditions were considered to be a feasible alternative.[65] Thus, the free amine obtained after removal of the Boc group from **110** was treated with phenylisothiocyanate. The resulting crystalline thiourea **111** was treated with TFA to produce the amine salt which was subsequently extracted into an aqueous layer and protected with Boc anhydride to yield **112**. Although all these intermediates were isolated and characterized, this four step transformation, starting from **110** and including the Boc protection of the free amine, has been performed in one pot to give optically active **112** directly.[66] With **112** in hand, a modified Nef reaction[67] provides optically pure forms of **113**. The synthesis of **113** yields a versatile intermediate for the preparation of carbovir, aristeromycin, and related carbocyclic nucleoside analogs.



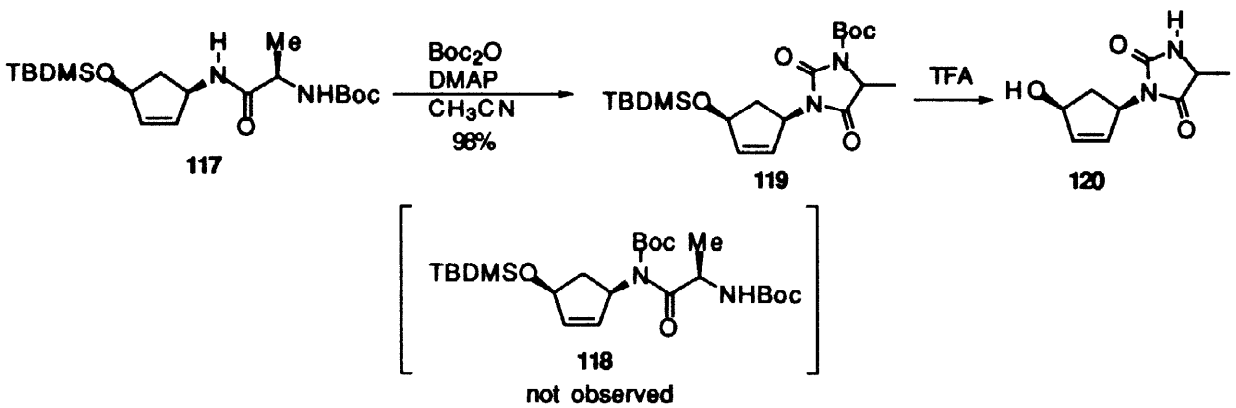
Scheme 28

Carbocyclic nucleosides in which the hydoxymethyl group has been replaced with a hydroxyl group, so-called 5'-nor carbocyclic nucleosides have been synthesized and their strong antiviral properties have been evaluated.[68] With the development of the Edman degradation as a simple, clean process to remove the amino acid chiral auxiliary the synthesis of precursors to 5'-nor carbocyclic nucleosides became apparent. Edman degradation of **114** yielded allylic acetate **115** in 75% yield. Treatment of **115** with 6% Hünig's base in MeOH gave the target alcohol **116** in 91% yield. Alcohol **116** is an important precursor for the asymmetric synthesis of 5'-nor carbocyclic nucleosides. Also, aminocyclopentitols are important synthetic targets as potential glycosidase inhibitors.[69]



Scheme 29

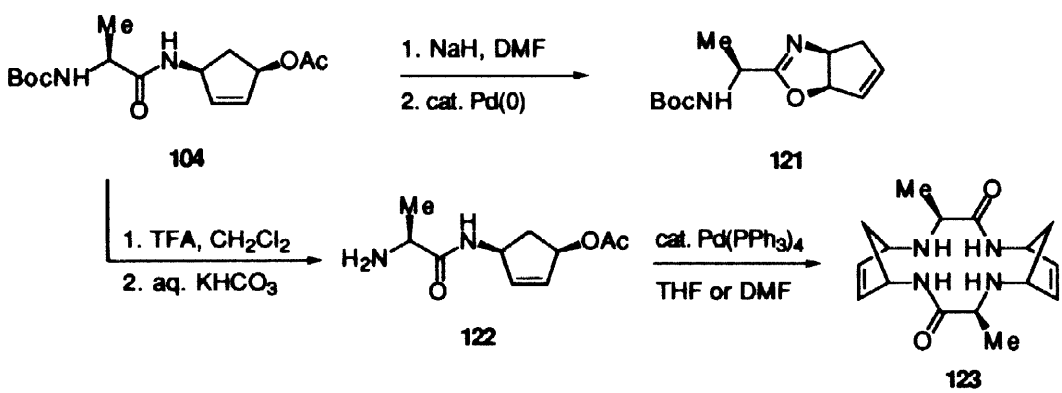
Although the removal of the amino acid chiral auxiliary with the Edman degradation provides a good route to carbocyclic nucleoside analogs, it does have the disadvantage of requiring subsequent elaboration of the heterocyclic base from the resulting free amine. If the nitrogen could be converted to a good leaving group, Pd(0) chemistry might be used to replace the allylic nitrogen with various nucleophiles.[70] In an attempt to make the nitrogen a better leaving group,[71] the preparation of *N*-*t*-Boc allylic amide **118** was examined (Scheme 30).[72] N-*t*-Boc secondary amides and lactams were reported by Grieco *et. al.*, and were subsequently shown to undergo facile amide hydrolysis under mild conditions (LiOH).[73] Although somewhat unexpected,[74] a serendipitous discovery of the rather interesting hydantoin derivative **119** was achieved and none of the originally intended molecule **118** was isolated.



Scheme 30

C. *1,2-cis-Amino Alcohols.*

While studying the Pd(0)-catalyzed substitution reactions of **104**, a side product from internal cyclization of the substrate was obtained. Although several isomeric structures of the new compound were considered, careful analysis of the spectral data allowed for its assignment as oxazoline **121**. The cyclization could be induced deliberately by reaction of **104** with sodium hydride followed by 5 mol% $Pd(PPh_3)_4$ to give **121** in 80% yield (Scheme 31).

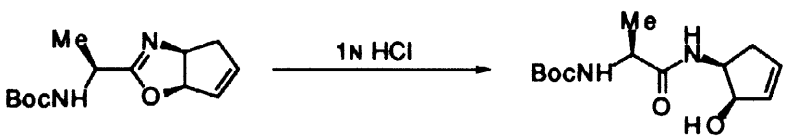


Scheme 31

The reaction can be rationalized as an intramolecular Pd(0)-promoted alkylation of the amide oxygen after anion formation from **104**.

Given the fact that amines have also been used successfully as nucleophiles in the Pd(0)-catalyzed allylic substitution,[75] the reactivity of the free amine **122** in cyclization reactions was examined. Boc-protected compound **104** was again deprotected with TFA and the resulting amine salt was neutralized with saturated $KHCO_3$ solution to produce **122** (72%). Reaction of **122** with $Pd(PPh_3)_4$ gave a low yield (10% in THF, 44% in DMF) of a cyclized product (Scheme 31). Mass spectrometric and NMR data strongly supported the interesting dimeric macrocyclic structure **123**.

The utility of the oxazoline synthesis in the functionalization of cyclopentadiene was demonstrated by acid hydrolysis of oxazoline **121** to furnish the aminocyclopentenol derivative **124** in 67% yield (Scheme 32). The striking similarities between chiral oxazolines **121** and the glycosidase inhibitors trehazolin and allosamidin[76, 33d] and the great synthetic potential of optically active oxazolines[77] underlines the usefulness of this methodology.



121 **124**

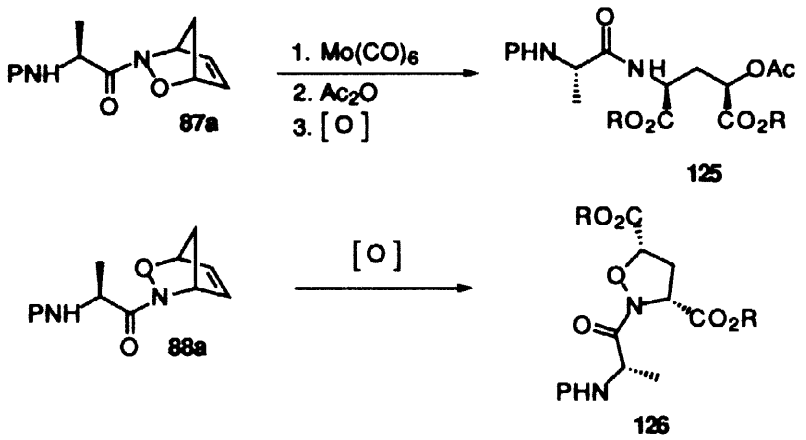
Scheme 32

D. *Novel Amino Acids and Peptides.*

The synthesis of novel amino acids and peptides from the cycloadducts was also achieved.[78] Consequently, oxidative cleavage of the double bond of cycloadducts **87a** and **88a** and reduction of the N-O bond was anticipated to release various forms of the masked amino acid generated by the Diels-Alder reaction. Thus, oxidation of the alkene of **88a** with ruthenium (III) chloride and periodate provided diacid **126** in 94% yield. Dipeptide **126** contains a novel cyclic amino acid structure similar to proline or a conformationally restricted glutamate. N-O bond reduction prior to alkene oxidation would generate a peptide with a γ-hydroxyglutamate residue.

Alternatively, $Mo(CO)_6$-induced reduction of cycloadduct **87a** followed by protection of the liberated hydroxyl group as the acetate and oxidation with Sharpless' catalytic ruthenium tetroxide procedure[20] gave dipeptide **125**.

The newly formed amino acid in peptide **126**, derived from cycloadduct **88a**, has the (*R*) configuration at the α-center, corresponding to a D-amino acid, whereas starting with diastereomeric cycloadduct **87a** provides peptides with the new C-terminal amino acids having the (*S*) configuration corresponding to the "natural" L-amino acids, as in **125**. Thus, either optical form (D or L) of the new amino acids are readily available by this methodology.



Scheme 33

VI. Summary and Outlook

Several enantiomerically pure hydroxamic acids have been synthesized, oxidized to reactive acylnitroso intermediates and the diastereoselectivities of the subsequent hetero Diels-Alder cycloadditions have been determined. In the amino acid-based series, the major influence on diastereoselectivity came from steric bulk at the α-position of the hydroxamic acid while other changes in the reaction conditions (solvent, oxidant, temperature) had little impact. The easily separable, functionally rich, diastereomeric cycloadducts have been, and continue to be converted into a variety of interesting products including carbocyclic nucleoside analogs in which the original amino acid component has been removed or retained.

Future work in this area includes examining intramolecular acylnitroso Diels-Alder reactions with the amino acid-derived chiral auxiliaries and the use of these auxiliaries on solid support. Amino acid-derived acylnitroso derivatives are an important addition to the field of nitroso chemistry and the synthetic utility of the heterocycles produced is apparent.

VII. Acknowledgments

We appreciate the use of the NMR facilities of the Lizzadro Magnetic Resonance Research Center at the University of Notre Dame. We wish to gratefully acknowledge Professor A. Meyers of Colorado State University for his generous gift of the amino acid *tert*-L-leucine. We also gratefully acknowledge the NIH for financial support of our research described in this overview.

VIII. References

1. For reviews of the Diels-Alder reaction, see: (a) Oppolzer, W. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon Press: New York, 1991; pp. 315-399. (b) Roush, W. R. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon Press: New York, 1991; pp. 513-550.

2. Whiting, A. in *Advanced Asymmetric Synthesis*; Stephenson, G. R. Ed.; Chapmann & Hall: New York, 1996; pp. 126-144.
3. For reviews of hetero Diels-Alder reactions, see: (a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869-2939. (b) Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087-3128. (c) Weinreb, S. M. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A. Eds.; Pergamon Press: New York, 1991; pp. 401-512. (d) Waldmann, H. *Synthesis* **1994**, 535-551. (e) Boger, D. L.; Weinreb, S. M. in *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic: New York, 1987. (f) Waldmann, H. in *Organic Synthesis Highlights II*; VCH Publishing: New York, 1995; pp 37-47.
4. For a recent review of the chemistry of nitrosobenzene, see: Zuman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621-1641.
5. (a) Streith, J.; Augelmann, G.; Fritz, H.; Strub, H. *Tetrahedron Lett.* **1982**, *23*, 1909-1912. (b) Augelmann, G.; Streith, J.; Fritz, H. *Helv. Chim. Acta* **1985**, *68*, 95-103. (c) Knaus, E. E.; Avasthi, K.; Giam, C. S. *Can. J. Chem.* **1980**, *58*, 2447-2451.
6. For a discussion on the regiochemistry of nitroso Diels-Alder reactions, see: (a) Kresze, G.; Firl, J. *Fort. Chem. Forsch.* **1969**, *11*, 245-284. (b) Labaziewicz, H.; Riddell, F. G. *J. Chem. Soc., Perkin Trans. I* **1979**, 2926-2929. (c) Gilchrist, T. L. in *Heterocyclic Chemistry*; Longman Scientific & Technical: New York, 1992; pp 59-121. (d) Sauer, J.; Sustmann, R. *Ang. Chem., Int. Ed. Eng.* **1980**, *19*, 779-807. (e) Defoin, A.; Fritz, H.; Schmidlin, C.; Streith, J. *Helv. Chim. Acta* **1987**, *70*, 554-569. (f) Aped, P.; Senderowitz, H. in *The Chemistry of amino, nitroso, and related groups*; Patai, S. Ed.; Wiley: New York, 1996; 1-84.
7. (a) Møller, E. R.; Jørgensen, K. A. *J. Org. Chem.* **1996**, *61*, 5770-5778. (b) McClure, K. M.; Danishefesky, D. *J. Org. Chem.* **1991**, *56*, 850-853.
8. (a) Wichterle, O. *Coll. Czech. Chem. Commun.* **1947**, *12*, 292-304. (b) Wichterle, O.; Novak, J. *Coll. Czech. Chem. Commun.* **1950**, *15*, 309-321.
9. (a) Labaziewicz, H.; Lindfors, K. R. *Heterocycles* **1989**, *29*, 929-938. (b) Sabuni, M.; Kresze, G.; Braun, H. *Tetrahedron Lett.* **1984**, *25*, 5377-5380.
10. Krezse, G.; Dittel, W. *Liebigs Ann. Chem.* **1981**, 610-611.
11. Felber, H.; Krezse, G.; Prewo, R.; Vasella, A. *Helv. Chim. Acta* **1986**, *69*, 1137-1146.
12. For examples, see: (a) Schürrle, K.; Beier, B.; Piepersberg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, *10*, 2407-2412. (b) Defoin, A.; Sarazin, H.; Strechler, C.; Streith, J. *Tetrahedron Lett.* **1994**, *35*, 5653-5656. (c) Defoin, A.; Sarazin, H.; Streith, J. *Synlett* **1995**, 1187-1188.
13. Zhang, D.; Süling, C; Miller, M. J. *manuscript in preparation.*
14. (a) Horsewood, P.; Kirby, G. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1587-1591. (b) Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1. (c) Horsewood, P.; Kirby, G. W.; Sharma, R. P.; Sweeny, J. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1802-1806.
15. Gouvernuer V.; Ghosez, L. *Tetrahedron* **1996**, *52*, 7585-7598.
16. Tronchet, J. M. J.; Jean, E.; Barbalat-Rey, F.; Bernardinelli, G. *J. Chem. Research* **1992**, (S) 228-229, (M) 1871-1890.
17. Gilchrist, T. L.; Gonsalves, A. M. d'A. R.; Pinhoe Melo, T. M. V. D. *Pure Appl. Chem.* **1996**, *68*, 853-858.

18. Zimmer, R.; Reissig, H.-U. *J. Org. Chem.* **1992**, *57*, 339-347.
19. (a) Viehe, H. G.; Merényi, R.; Francotte, E.; Van Meerssche, M.; Germain, G.; Declercq, J. P.; Bodart-Gilmont, J. *J. Amer. Chem. Soc.* **1977**, *99*, 2340-2342. (b) Faragher, R.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. I* **1979**, 249-257.
20. Gilchrist, T. L.; Harris, C. J.; Hawkins, D. G.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. I* **1976**, 2166-2170.
21. Dao, L. H.; Dust, J. M.; Mackay, D.; Watson, K. N. *Can. J. Chem.* **1979**, *57*, 1712-1719.
22. Quadrelli, P.; Invernizzi, A. G., Caramella, P. *Tetrahedron Lett.* **1996**, *37*, 1909-1912.
23. Keck, G. E.; Webb, R. R.; Yates, J. B. *Tetrahedron* **1981**, *37*, 4007-4016.
24. Kirby, G. W. *Chem. Soc. Rev.* **1977**, 1-24.
25. Kirby, G. W.; Sweeny, J. G. *J. Chem. Soc., Chem. Comm.* **1962**, 704-711.
26. For examples, see (a) Baldwin, J. E.; Aldous, D. J.; Chan, C.; Harwood, L. M.; O'Niel, I. A.; Peach, J. M. *Synlett* **1989**, 9-14. (b) Baldwin, J. E.; Bailey, P. D.; Gallacher, G.; Otsuka, M.; Singleton, K. A.; Wallace, P. M.; Prout, K.; Wolf, W. M. *Tetrahedron* **1984**, *40*, 3695-3708. (c) Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, *19*, 4763-4766. (d) Strieth, J.; Defoin, A. *Synthesis* **1994**, 1107-1117. (e) Defoin, A.; Fritz, H.; Geffroy, G.; Streith, J. *Tetrahdron Lett.* **1986**, *27*, 4727-4730. (f) Boger, D. L.; Patel, M.; Takusagawa, F. *J. Org. Chem.* **1985**, *50*, 1911-1916.
27. O'Bannon, P. E.; Sulzle, D.; Schawrz, H. *Helv. Chim. Acta* **1991**, *74*, 2068-2072.
28. (a) Martin, S. F.; Hartmann, M.; Josey, J. A. *Tetrahedron Lett.* **1992**, *33*, 3583-3586. (b) For a recent example of a camphor derived chiral auxiliary, see: Lin, C.-C.; Wang, Y.-C.; Hsu, J.-L.; Chiang, C.-C.; Su, D.-W.; Yan, T.-H. *J. Org. Chem.* **1997**, *62*, 3806-3807.
29. Gouverneur, V.; Dive, G.; Ghosez, L. *Tetrahedron: Asymmetry* **1991**, *2*, 1173-1176.
30. (a) Gouverneur, V.; Ghosez, L. *Tetrahedron: Asymmetry* **1990**, *1*, 363-366. (b) Gouverneur, V.; Ghosez, L. *Tetrahedron Lett.* **1991**, *31*, 5249-5352.
31. (a) Strieth, J.; Defoin, A. *Synlett* **1996**, 189-200. (b) For a discussion of other C_2-symmetric chiral auxiliaries, see: Shustov, G. V.; Rauk, A. *Tetrahedron Lett.* **1995**, *36*, 5449-5452.
32. Cardillo, B.; Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1535-1540.
33. (a) Miller, A.; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1041-1042. (b) Miller, A; Procter, G. *Tetrahedron Lett.* **1990**, *31*, 1043-1047. (c) Miller, A.; McC. Patterson, T.; Procter, G. *Synlett*, **1989**, 32-34. (d) For the use of the mandelohydroxamic acid chiral auxiliary in the synthesis of Mannostatin A, see: King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562-570.
34. (a) Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7535-7538. (b) Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7539-7540. (c) Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7541-7544.
35. (a) Kirby, G. W.; Nazeer, M. *Tetrahedron Lett.* **1988**, *29*, 6173-6174. (b) Kirby, G. W.; Nazeer, M. *J. Chem. Soc., Perkin Trans. I* **1993**, 1397-1402.
36. Choy, W.; Reed, L. A.; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137-1139.
37. Aoyagi, S.; Kibayashi, C. *Synlett* **1995**, 873-879.

38. (a) Naruse, M; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1993**, *59*, 1358-1364. (b) For another example, see: Keck, G. E.; Romer, D. R. *J. Org. Chem.* **1993**, *58*, 6083-6089.
39. Defoin, A.; Pires, J.; Streith, J. *Synlett* **1991**, 417-419.
40. Defoin, A.; Pires, J.; Tissot, I.; Tschamber, T.; Bur, D.; Zehnder, M.; Streith, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1209-1221.
41. Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1994**, *59*, 4602-4611. (b) Vogt, P. F.; Miller M. J.; Mulvihill, M. J.; Ramurthy, S.; Savela, G. C.; Ritter, A. R. *Enantiomer: A Journal of Stereochemistry, in press.*
42. Strieth, J.; Defoin, A; Brouilliard-Poichet, A. *Tetrahedron Lett.* **1989**, *30*, 7061-7064.
43. (a) For the use of amino acid chiral auxiliaries in the all-carbon Diels-Alder reaction, see: Bueno, M. P.; Cativiela, C.; Mayoral, J. A.; Avenoza, A.; Charro, P.; Roy, M. A.; Andrés J. M. *Can. J. Chem.* **1988**, *66*, 2826-2829. (b) For a general review on the use of amino acids as stoichiometric auxiliaries in asymmetric syntheses, see Studer, A. *Synthesis* **1996**, 793-815.
44. (a) Miller, M. J.; Biswas, A.; Krook, M. A. *Tetrahedron* **1983**, *39*, 2571-2575. (b) Fishbein, W. N.; Daly, J.; Streeter, C. L. *Anal. Biochem.* **1969**, *28*, 13-24.
45. The choice of either Boc or Cbz as a protecting group had no effect on the diastereoselectivity of the cycloaddition.
46. (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171-4174. (b) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth. Coll. Vol. IV* **1988**, 492-495. (c) Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Rider, P. J. *J. Org. Chem.* **1994**, *59*, 1231-1233.
47. Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361-2364.
48. (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem Soc.* **1980**, *102*, 7026-7032. (b) Romine, J. L. *Organic Prep. and Proc. International* **1996**, *3*, 251-288.
49. Pirrung, M. C.; Chau, J. H.-L. *J. Org. Chem.* **1995**, *60*, 8084-8085.
50. Absolute stereochemistry of the cycloadducts was determined by an X-ray structure of the major diastereomer with D-alanine as the chiral auxiliary.
51. Using the L-series of amino acids, when diastereoselectivity was observed, the lower numbered diastereomer was the major diastereomer.
52. For a review, see: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165-185.
53. Aldehyde formation was checked by the Purpald® test: Durst, H. D.; Gokel, G. W. *J. Chem. Ed.* **1978**, *55*, 206.
54. Crosby, J. *Tetrahedron* **1991**, *47*, 4789-4846.
55. Pirkle, W, H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991-5000.
56. Isono, K. *J. Antibiot.* **1988**, *41*, 1711-1739.
57. Periguad, C.; Gosselin, G.; Imbach, J.-L. *Nucleosides Nucleotides* **1992**, *11*, 903-945.
58. For reviews of carbocyclic nucleosides, see: (a) Jones, M. F. *Chemistry in Britain* **1988**, November, 1122-1127. (b) Marquez, V. E.; Lim, M. I. *Med. Res. Rev.* **1986**, *6*, 1-39. (c) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571-623. (d) Agrofogilo, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S. R.; Earl, R. A.; Guedj, R. *Tetrahedron* **1994**, *50*, 10611-10670.

59. Ghosh, A.; Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 5808-5813.
60. (a) Cicchi, S.; Gati, A.; Brandi, A.; Gvarna, A.; DeSanto, F. *Tetrahedron Lett.* **1990**, *31*, 3351-3354. (b) For a discussion on the mechanism of metal-carbonyl-induced reduction of isoxazoles, see: Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401-1406.
61. (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422. (b) Garner, P.; Ramakanth, S. *J. Org. Chem.* **1988**, *53*, 1294-1298. (c) Jones, J. W.; Robins, R. K. *J. Am. Chem. Soc.* **1962**, *84*, 1914-1919. (d) Kline, P. C.; Serianni, A. S. *J. Org. Chem.* **1992**, *57*, 1772-1777.
62. Trost, B. M.; Kou, G. H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621-622.
63. Miller, M. J. Second International Symposium on Recent Advances in the Chemistry of Antiinfective Agents, Churchill College, Cambridge, England, July 10, 1996.
64. Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365-367.
65. For a related use of the Edman degradation, see: Girijavallabhan, V.; Ganguly, A. K.; Saksena, A. K.; Cooper, A. B.; Lovey, R.; Loebenberg, D.; Rane, D.; Desai, J.; Pike, R.; Jao, E. in *Recent Advances in the Chemistry of Anti-Infective Agents*, Bently, P. H.; Ponsford, R., Eds., Royal Society of Chemistry Special Publication No. 119, **1993**, pp 192-204.
66. Zhang, D.; Ghosh, A.; Süling, C.; Miller, M. J. *Tetrahedron Lett.* **1996**, *37*, 3799-3802.
67. For a review of the Nef reaction, see: Pinnick, H. W. in *Organic Reactions*; John Wiley: New York, 1990; Vol. 38, pp 655-792.
68. (a) Patil, S. D.; Schneller, S. W.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 3372-3377. (b) Siddiqi, S. M.; Chen, X.; Schneller, S. W.; Ikeda, S.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 551-554..
69. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444-458 and references therein.
70. For a recent example of the use of an allylic nitrogen functionality for the formation of a π-allylpalladium complexes, see: Jung, M. E.; Rhee, H. *J. Org. Chem.* **1994**, *59*, 4719-4720.
71. Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393.
72. Ghosh, A.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 6399-6402.
73. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426.
74. Facile hydantoin formation has been encountered during coupling of bis(Boc) amino acids with amino acid esters, see: (a) Carpino, L. A.; Masour, E.-S. M. E.; El-Faham, A. *J. Org. Chem.* **1993**, *58*, 4162-4164. (b) Gunnarsson, K.; Ragnarsson, U. *Acta. Chem. Scand.* **1990**, *44*, 944-951.
75. Trost, B. M.; Keinan, E. *J. Org. Chem.* **1979**, *44*, 3451-3457.
76. Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813-822.
77. For a recent review, see; Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297-2360.
78. Ritter, A. R.; Miller, M. J. *Tetrahedron Lett.* **1994**, *35*, 9379-9382.

Biographical sketch

Paul Vogt

Marvin Miller

Paul Vogt received his B.S. in chemistry from Seton Hall University in 1992. While there, he conducted undergraduate research under the direction of Dr. Paul Zucker and for his efforts was named the 1991-92 Berlex Scholar. He is currently completing work towards his Ph.D. at the University of Notre Dame under the guidance of Professor Marvin J. Miller. His research interests include the synthesis of carbocyclic nucleoside analogs as well as investigations into the diastereoselectivity of hetero Diels-Alder reactions.

Marvin Miller was born and raised in Dickinson, ND. His interest in organic chemistry was inspired by the enthusiasm of Professor S. P. Pappas, his undergraduate mentor, at North Dakota State. Professor Marc Loudon introduced him to hydroxamic acid chemistry during Ph.D. studies at Cornell. Subsequent to an NIH postdoctoral fellowship with Professor Henry Rapoport at Berkeley, Dr. Miller joined the faculty of Notre Dame in 1977, where he is now the George and Winifred Clark Professor of Chemistry. Current research interests include synthesis and studies of biologically important molecules. He is sustained by the love of his wife, Patty and children, Chris, Katie, Joe and Carl.