UNIVERSITY OF CALGARY

The Synthesis and Application of 6-Aminospiro[4.4]nonan-1-ol as a Chiral Auxiliary for Diastereoselective Diels-Alder Reactions

by

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Abstract

A review shows that spiro systems had not been thoroughly examined as chiral auxiliaries for Diels-Alder reactions. 6-(2,2-Dimethylpropamido)spiro[4.4]nonan-1-ol was investigated as an extension of work with *cis*,*cis*-spiro[4.4]nonane-1,6-diol for this purpose.

A 10 step stereoselective synthesis of (+)-*cis*,*trans*-6-(2,2-dimethylpropamido)spiro[4.4]nonan-1-ol in 29% yield from (±)-ethyl 2-oxocyclopentanecarboxylate is presented. A correction to the previously published baker's yeast reduction of (±)-2-ethoxycarbonyl-2-(2-propenyl)cyclopentanone is reported, where the absolute stereochemistry of the reduction product, 2-ethoxycarbonyl-2-(2-propenyl)cyclopentanol, was assigned to be 1*S*,2*S* by X-ray crystallography. The absolute stereochemistry of (+)-*cis*,*trans*-6-(2,2-dimethylpropamido)spiro[4.4]nonan-1-ol was assigned by an X-ray crystal structure of its *p*-bromobenzoate derivative to be 1*R*,5*S*,6*S*.

Application of (+)-*cis*,*trans*-6-(2,2-dimethylpropamido)spiro[4.4]nonan-1-ol as a chiral auxiliary for diastereoselective Diels-Alder reactions is investigated. Moderate to excellent results were obtained using dienophile ester derivatives with a variety of dienes. Diastereomeric excesses greater than 97% (97% ee after cleavage) were obtained in some cases.

Acknowledgements

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Finally, I would like to thank my family for their support. My parents (Charles and Alice) and sister (Colleen) without whom I could never have come this far.

To the members of my family

(past, present, and future)

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List of Abbreviations

°C	degrees Celsius	Et	ethyl
Å	angstroms	equiv.	equivalent(s)
abs.	absolute	GC	gas chromtaography
Ac	acetate	GC-MS	gas chromatography-mass spectrometry
Ar	aryl group		
BINOL	2,2'-binapthyl-1,1'-diol	h	hour
Bn	benzyl	H_f	heat of formation
Bu	butyl	HMDS	hexamethyldisilazide
cal	calories	i	iso
calc'd	calculated	K	Kelvin
cat.	catalytic	LDA	lithium diisopropyl amide
CD/ORD	circular dichroism/ optical rotary dispersion		
config.	configuration	M	metal, or moles/litre
de	diastereomeric excess	Me	methyl
DIBAL-H	diisobutyl aluminum hydride	min.	minute
		mol	mole
DMF	dimethyl formamide	Ms	methane sulfonyl
e	2.718	*n*	normal
E	energy	NMR	nuclear magnetic resonance
ee	enantiomeric excess		

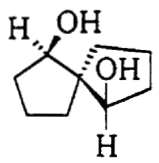
[O]	oxidation	wrt	with respect to
p	*para*		
Ph	phenyl		
Pr	propyl		
pyr.	pyridine		
R	alkyl group, or		
	gas constant (equation 1)		
R^*	chiral auxiliary		
rt	room temperature		
S_N2	substitution, nucleophilic, bimolecular		
t	tertiary		
T	temperature in Kelvin		
TBDMS	*t*-butyldimethylsilyl		
TEA	triethylamine		
Tf	triflouromethane sulfonyl		
THF	tetrahydrofuran		
TLC	thin layer chromatography		
TMEDA	*N,N,N',N'*-tetramethylethylene		
	diamine		
TMG	1,1,3,3-tetramethyl guanidine		
Ts	*p*-toluenesulfonyl		
VT	variable temperature		

Chapter 1

1. Induction of Chirality in Diels-Alder Reactions via Substrate Bound Dienophiles

The synthesis of novel, chiral auxiliaries continues to be a field of extensive research in organic chemistry. Previous results from our laboratory on the use of 1,3-diol spiro systems **1** (Figure 1.1) as chiral scaffolds for various asymmetric transformations,[1] revealed that good to excellent levels of diastereomeric excess (de) can be achieved with these compounds in Diels-Alder reactions. We were therefore interested in expanding these results by developing a similar system with possible solid support capability. This chapter describes the importance of performing enantioenriched reactions as well as the methods available for this process. Subsequently, this chapter provides a review of the literature on the various types of substrate bound chiral auxiliaries up to the end of 1999. This literature review will:

1) summarise the results for other types of substrate bound dienophiles
2) show the limited use of spiro systems; and
3) display the novelty of using 1,3-amino alcohols.

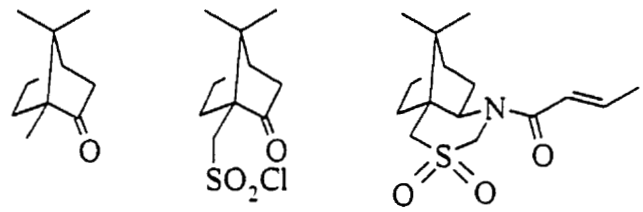


1

Figure 1.1. 1,3-Diol Spiro System **1** used by Keay for Asymmetric Transformations[1]

1.1. Introduction

For over one hundred years, one of the most important areas of organic chemistry has been the isolation of natural products. In this time period, a countless number of compounds have been isolated, most of which are optically pure (enantiopure). If the natural product is readily abundant and inexpensive, it is placed into what has been termed as the "chiral pool".[2] This group of compounds is important to modern organic synthesis as an excellent source of chirality, either directly or indirectly,[3] for a synthetic sequence. Figure 1.1 shows (+)-(*R*)-camphor (**2**), a member of the "chiral pool" (direct), and two commonly used chiral derivatives, (+)-(*R*)-camphor sulfonyl chloride (**3**) and Oppolzer's sultam **4**[4] which are derived from (+)-(*R*)-camphor **2** (indirect).



2 **3** **4**

Direct Indirect Indirect

Figure 1.2. An Example of a Chiral Pool Compound and Derivatives

1.1.1 Importance of Enantioselective Synthesis

Prior to 1961, pharmaceuticals were administered as racemates without concern for differing biological activity of the individual enantiomers. This was found to be a tragic mistake with the introduction of (±)-thalidomide in Europe that year.[5a] Treatment of pregnant women with (±)-thalidomide resulted in a high incidence of limb deformities, where it was found that one enantiomer, namely (-)-(*S*)-thalidomide, was a potent teratogen. Later,

it was shown that the desired sedation and antinausea effects were a direct result of the (+)-(*R*)-enantiomer, which upon testing, did not cause birth defects even in high dosages.[5b] This case is not the only example of biological systems behaving differently towards two enantiomers. A few examples of this behavior can be seen in Figure 1.3.

As a direct result of these cases, federal drug administrations around the world have changed their policies to require testing of individual enantiomers and their individual biological effects in all new drug applications. These changes have had a dramatic effect on the synthetic process in industry where the amount of single enantiomer drugs sold commercially has continued to increase as seen in Table 1.1.[6] This increase in the need for enantiopure compounds has caught the attention of academics in the field of organic chemistry. There are a vast number of researchers around the world currently seeking new and better methodology for enantiopure synthesis.

Table 1.1. Chiral Drug Sales for 1997-98[6]

Drug Type	**1997 Sales (Millions of $)**	**1998 Sales (Millions of $)**	**Annual Change (%)**
Antibiotics	21,031	23,250	11
Cardiovascular	19,551	21,145	8
Hormones	9,903	11,585	17
Central NS	7,573	7,805	3
Cancer	6,913	7,605	10
Antiviral	4,893	6,220	27
Hematology	5,923	6,185	4
Respiratory	3,159	4,255	35
GI	1,314	1,420	8
Other	6,535	6,910	6
Total	**86,795**	**96,380**	**11**

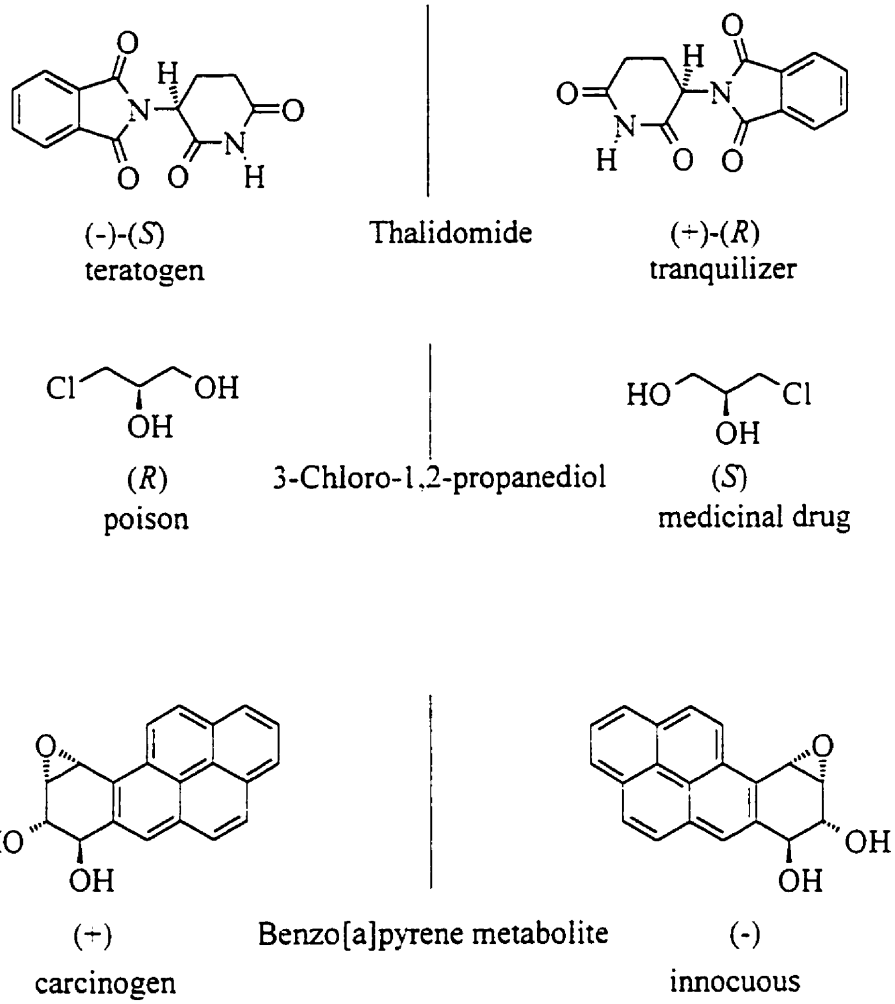


Figure 1.3. Some Examples of Enantiomers with Varying Biological Effects

1.1.2 Methods for the Production of Enantiopure Compounds

This section provides an outline of the five known procedures for the production of enantiopure products. One or more of these methods may be required in conjunction to obtain an enantioenriched product. These five methods are:[7]

1) **Resolution:** This procedure involves placing a racemic or scalemic mixture in a chiral environment to either produce diastereomers or cause diastereotopic interactions, which are important for kinetic or thermodynamic resolution of enantiomers. The formation

of either diastereomers or diastereotopic interactions resulting in enantiomer separation based on different physical properties is termed racemate resolution.

2) **Chiral Template:** This method involves the formation of a new optically pure product via the stereogenic centre(s) of previously prepared chiral compounds.[8] Molecules for this purpose are predominately from the "chiral pool". The stereochemistry at any centre in the template can be inverted, maintained, or destroyed in the process of synthesizing the enantiopure product.

3) **Chiral Influence:** This process involves the diastereotopic interaction of circularly polarised light or other non-reagent or non-catalytic entities with the compound to cause a reaction to proceed enantioselectively. Some examples of this method would involve the use of a chiral solvent or circularly polarised photochemical excitation.[5c]

4) **Metal, Reagent or Catalyst Bound Chiral Auxiliaries:** This procedure involves the use of one or more chiral ligands bound to a catalyst, reagent, or metal which is involved in the transition state of a reaction. This thereby creates diastereotopic interactions, leading to enantioenriched product(s). This method commonly employs binding Lewis acids or bases to a chiral auxiliary, such as in the case of trimethyl aluminum with (+)- or (-)-2,2'-binapthol derivatives.[9]

5) **Substrate Bound Chiral Auxiliaries:** This method involves the attachment of a chiral auxiliary to a prochiral substrate via a covalent bond. The auxiliary influences the outcome of the reaction to produce diastereomers, which upon removal of the auxiliary, results in enantioenriched product.

Review of the literature reveals many examples which illustrate the usefulness of the above five methods for the preparation of enantiopure or enantioenriched products.[2b,5d,10]

however, the use of Chiral Influence (Method 3) is very uncommon. For the purpose of this thesis, substrate bound chiral auxiliaries, as used in Diels-Alder reactions, will be reviewed.

1.2 Enantioselective Diels-Alder Reactions

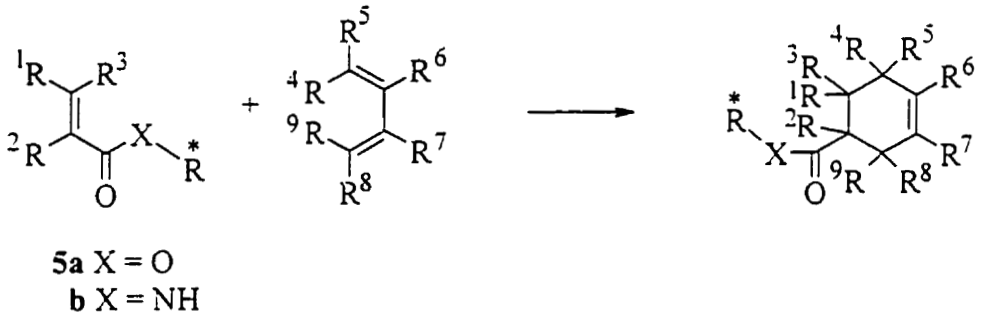
1.2.1 Introduction

Since its discovery, the Diels-Alder reaction[11] has become one of the most useful reactions in organic synthesis. In the most part, this is due to its ability of creating up to four new asymmetric centres in a single reaction. This fact thereby creates the need for developing methodology for asymmetric Diels-Alder reactions, which would be of great importance to the organic chemist. Early attempts by Davis *et al.*[12,13] at achieving this goal yielded little success. However, since then, there have been numerous examples of Diels-Alder reactions which proceed with good to high levels of asymmetric induction. These results have been the subject of many general reviews[4,14,15,16,17,18] and several with special emphasis on catalytic asymmetric Diels-Alder reactions.[19,20,21,22,23]

Generally, Diels-Alder reactions can be performed asymmetrically by using one of four methods: 1) attaching a chiral auxiliary to the dienophile; 2) attaching a chiral auxiliary to the diene; 3) using a chiral catalyst; or 4) a chiral tether between the diene and dienophile. In recent years, the use of a chiral auxiliary attached to the dienophile remains the most common method and shall be the emphasis of this section.

1.2.2. Chiral Auxiliary Bound Dieneophiles

Several of the readily available "chiral pool" compounds have been utilized as chiral auxiliaries (R*) for attachment to dienophiles in an effort to achieve good levels of asymmetric induction in Diels-Alder reactions. The most common point of attachment is via an ester or amide linkage on **5** as seen in Scheme 1.1.



5a X = O
b X = NH

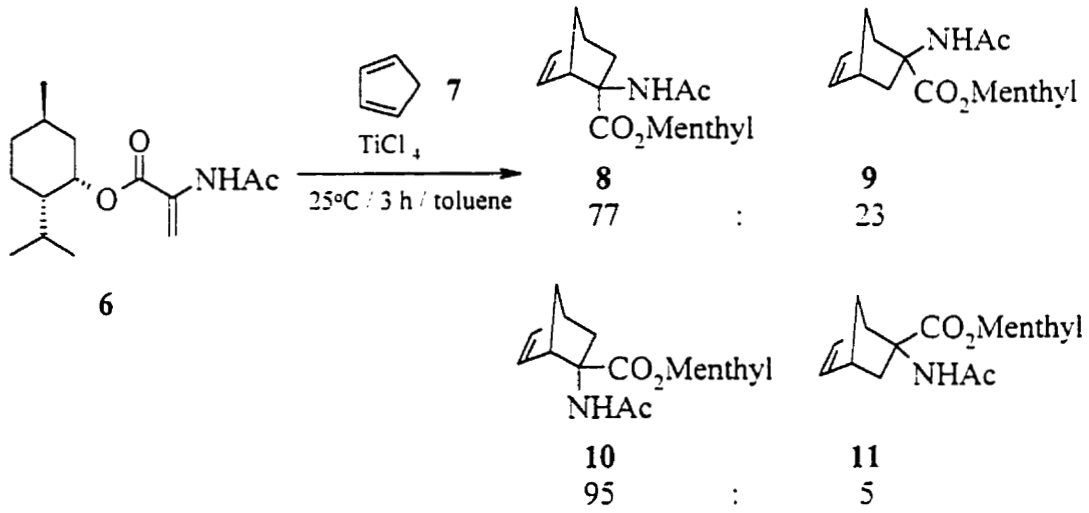
Scheme 1.1.

The following sections will present a literature review on known chiral auxiliaries, which when bound to various dienophiles, have been used to perform asymmetric Diels-Alder reactions.[24]

1.2.2.1. Terpenes

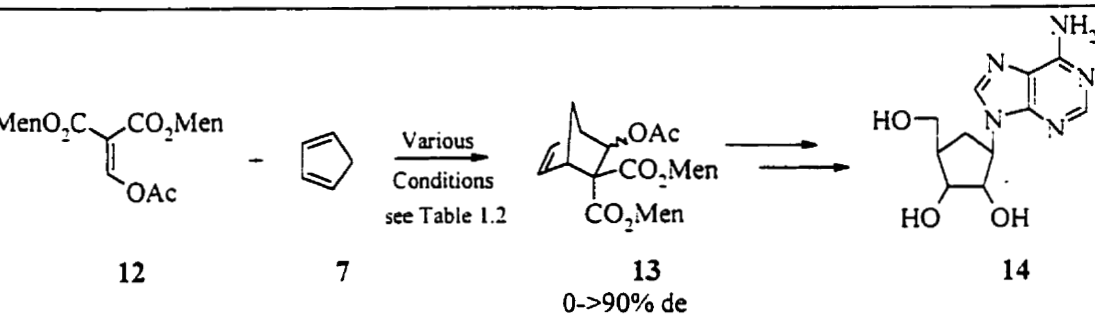
The ready availability of terpene derived chiral materials give a wide variety of possible auxiliaries, of which menthol has been used most extensively. Direct esterification of menthol to an acrylate moiety for use in Diels-Alder reactions provided only modest asymmetric induction (74% *endo* de, $BF_3{\cdot}Et_2O$, -20°C, CH_2Cl_2),[4] which was improved by performing the reaction on alumina.[25] However, Mayoral and co-workers found that by functionalizing the acrylate into the *N*-acetyl menthyl ester (**6**) improved asymmetric induction upon reaction with cyclopentadiene (**7**).[26] High yields of a 69:31 mixture of *endo*-

and *exo*- adducts (**8-11**) were produced employing $TiCl_4$ as a catalyst as seen in Scheme 1.2. Diastereomeric excess (de) values of 95:5 were found for *exo*- adducts **10** and **11**, while the *endo*-adducts **8** and **9** were produced in a de ratio of 77:23.



Scheme 1.2.

The reaction of a di-menthyl ester **12** with cyclopentadiene (**7**) has also been used for the asymmetric synthesis of nucleoside derivatives (**14**)[27] as seen in Scheme 1.3. The Diels-Alder product is produced with de values ranging from 0-90% and the *endo:exo* ratios varied depending on conditions used (Table 1.2).

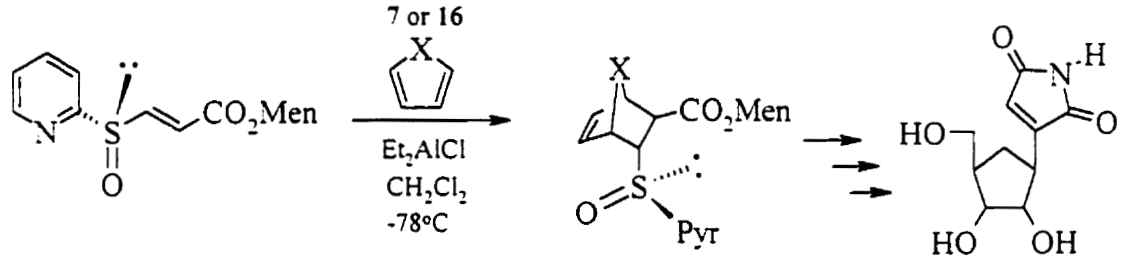


Scheme 1.3.

Table 1.2. Reaction Conditions Attempted for the Reaction of **12** with Cyclopentadiene (**7**)

Lewis Acid (Equiv.)	Temp. (°C)	Time (h)	Yield (%)	*endo*:*exo*	*endo* de
$TiCl_4$ (0.1)	-78	5	83	3:1	>90
$TiCl_4$ (0.1)	-15	0.5	79	2:1	79
$TiCl_4$ (0.1)	rt	0.5	34	1:1	67
Et_2AlCl (1)	-78	3.5	49	5:1	33
Et_2AlCl (1)	-15	3	23	2:1	0
Et_2AlCl (0.1)	-15	3	0	-	-

In a similar fashion, the reactive vinyl sulfoxide **15** can be used in Diels-Alder reactions with cyclopentadiene (**7**) or furan (**16**, X=O) to yield adducts **17** (96% de) and **18** (92% de) (Scheme 1.4). This method has been used extensively for the synthesis of pseudo-sugars such as showdomycin (**19**).[28]



15

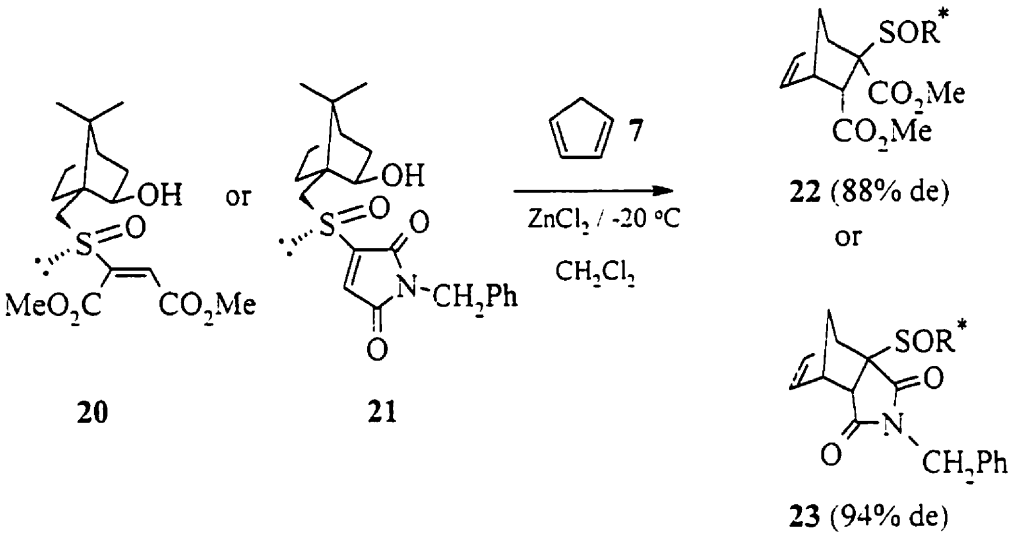
17 X = CH_2 (96% de)
18 X = O (92% de)

19

Scheme 1.4.

1.2.2.2. Isoborneol Derivatives

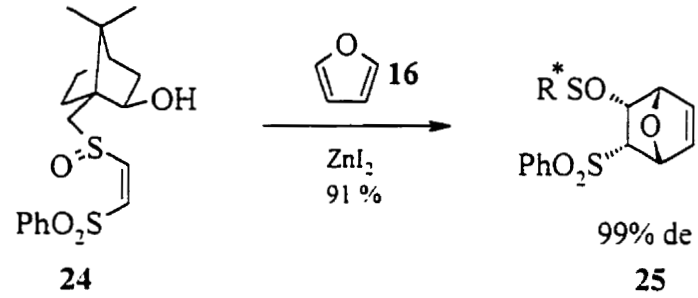
Exceptionally high de values (>99%) using isoborneol-10-sulfinyl auxiliaries (Scheme 1.5) have been reported when used with doubly activated dienophiles, such as **20** and **21**, in the reaction with cyclopentadiene (7) to yield adducts **22** and **23** respectively.[29]



20 **21**

Scheme 1.5.

Recently, Arjona *et al.* have reported the use of a isoborneol sulfone (**24**) for performing asymmetric Diels-Alder reactions with furan (**16**) (Scheme 1.6).[30] Excellent results were obtained (**25**, 99% de); however, several steps are required to remove the auxiliary.

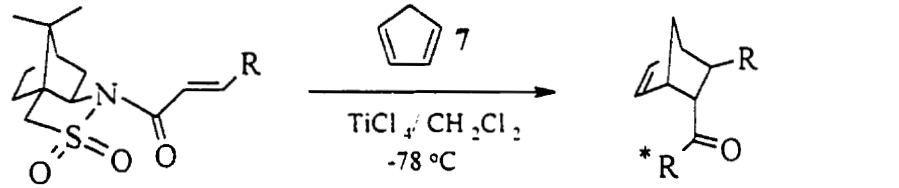


24 **25**

Scheme 1.6.

1.2.2.3. Sultam Derivatives

Sultam derivatives, such as **4** (Scheme 1.7), were first introduced by Oppolzer[4] and have proven to be one of the most useful chiral auxiliaries and are the subject of review.[31] An X-ray structure of a $TiCl_4$ complex with **4** has been reported by Oppolzer and co-workers[32] which supports previously postulated mechanisms for *Re* facial selectivity.



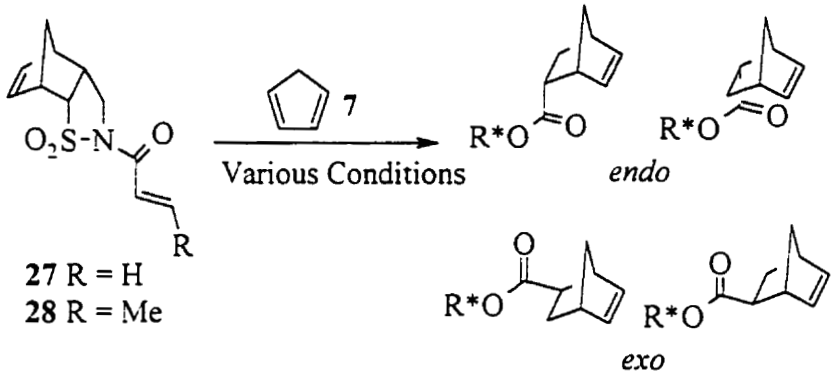
4a R = H
b R = Me

26a R = H, 94% de
b R = Me, 93% de

Scheme 1.7.

The only other research to date involving sultams as chiral scaffolds for Diels-Alder reactions is reported by Mak *et al.*[33] Sultams **27** and **28** have been reacted with cyclopentadiene (**7**) using various Lewis acids. The results can be seen in Table 1.3, where *endo*:*exo* values of 98:2 can be found, having an *endo* % de of 88.

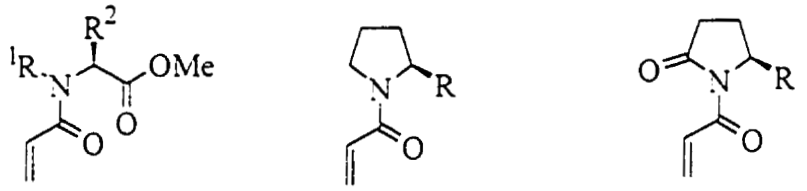
Table 1.3. Results for the Diels-Alder Reactions of Sultams **27** and **28** with Cyclopentadiene (7)



27 R = H
28 R = Me

Dienophile	Lewis Acid	Temp (°C)	*endo*:*exo*	*endo* %de
27	$SnCl_4$	-78	98:2	88
27	$TiCl_4$	-78	96:4	72
28	$ZnBr_2$	20	91:9	24
28	$TiCl_4$	-78	97:3	88

1.2.2.4. Amino Acids



29a: R^1 = H, R^2 = Bn
b: R^1 = H, R^2 = Me
c: R^1 = Me, R^2 = Me

30a: R = CO_2Me
b: R = CH_2OBn

31a: R = OCH_2OMe
b: R = CH_2OBn

Figure 1.4. Various Amino Acids Used as Chiral Scaffolds

The chirality provided by amino acids has also been exploited for use in asymmetric Diels-Alder reactions. *N*-Acryloyl amides **29a-c** have been used to give variable de values (*endo* 30-60% de, *exo* 14-94% de) using a range of Lewis acid-catalysed ($TiCl_4$ or $AlMe_3$) conditions.[34] Conversion of ester **30a** to the corresponding benzyl ether **30b** (Figure 1.4) provided up to 94% *endo* de ($TiCl_4$, -10°C, CH_2Cl_2) upon reaction with cyclopentadiene (7)

with various Lewis acids ($TiCl_4$, $SnCl_4$, $ZnCl_2$, BF_3, $EtAlCl_2$).[35] It was found that the Lewis acid catalyst used in the cycloaddition affected the sense of asymmetric induction. Models have been proposed to explain this effect where single chelation by zinc, boron, and aluminum provide opposite facial selectivity than that provided by doubly coordinated titanium and tin (Figure 1.5).

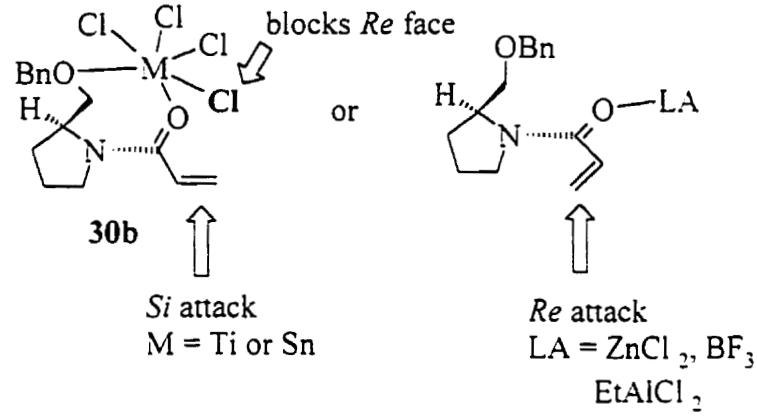
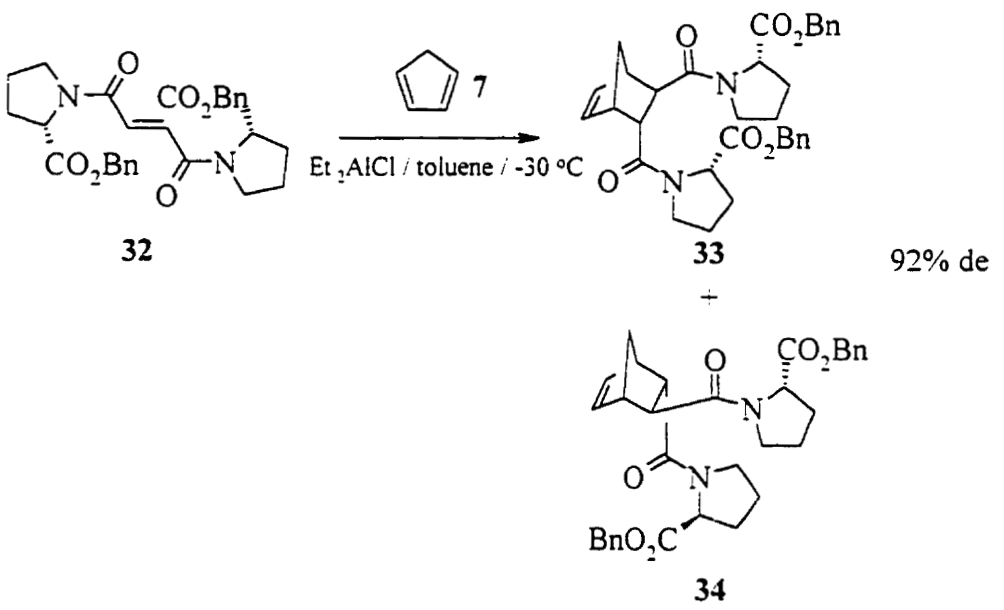


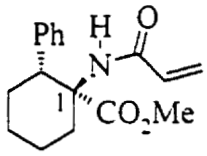
Figure 1.5. Lewis Acid Effect on Facial Selectivity

Pyrrolidinone derivatives such as **31a** and **31b** also afforded high de values in Diels-Alder reactions (Figure 1.4). Activation of **31a** with strong alkylating agents, or by Lewis acids, afforded *endo* de values of >95% upon reaction with cyclopentadiene (**7**, 1.12 equiv. Et_2AlCl, toluene, -78°C, 1.2 h).[36] In the case of pyrrolidinone derivatives, it can be assumed that the diene approaches from the opposite face of the R group.

Waldmann and Draeger have incorporated two amino acid auxiliaries onto fumaric acid to form compound **32** (Scheme 1.8). Compound **32** is a highly diastereoselective dienophile under both thermal and Lewis acid-catalysed conditions, providing **33** and **34** with a 92% de when reacted with cyclopentadiene (**7**).[37]



Scheme 1.8.



35
36 = C^1 epimer

Figure 1.6. α-Amino Acids Prepared by Avenoza *et al.*[38]

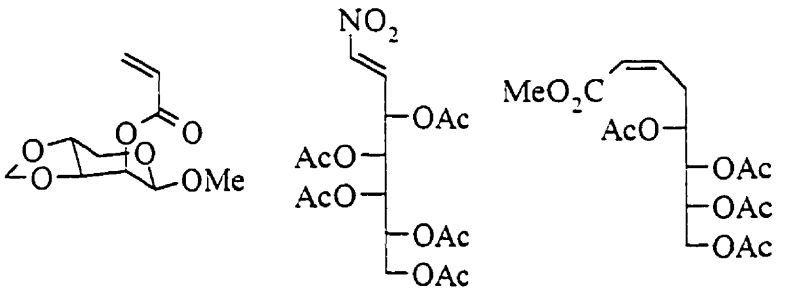
Finally, α-amino acids **35** and **36** (Figure 1.6) have recently been reported by Avenoza *et al.* to provide excellent *endo*:*exo* ratios; however, only 80% de was observed on reaction with cyclopentadiene (**7**) and various Lewis acid catalysts (Table 1.4).[38]

Table 1.4. Diels-Alder Reaction Conditions and Results Using **35** and **36** with Cyclopentadiene (7)

Dienophile	Lewis Acid	Conditions (°C, h)	*endo*:*exo*	*endo* %de
35	$TiCl_4$	0,30	91:9	66
35	$EtAlCl_2$	-30,48	94:6	66
35	$EtAlCl_2$	-54,52	98:2	70
35	$EtAlCl_2$	-78,72	99:1	80
36	$EtAlCl_2$	-30,22	94:6	40

1.2.2.5. Carbohydrates

As seen with the amino acids, readily available natural sources are commonly used to influence Diels-Alder reactions. Similarly, carbohydrates fit into this category and their use as chiral auxiliaries has been the source of a major review.[39] Nouguier and co-workers report that arabinose acrylate **37**, under Lewis acid-catalysed conditions (2 equiv. $TiCl_4$, toluene, -78°C, 10 h), gives products having 94% *endo* de with cyclopentadiene (7).[40] Several dienes have also been used with open-chain carbohydrate analogues **38** and **39**,[41] and in the case of cyclopentadiene (7), levels of >95% *endo* de have been achieved (Figure 1.7).[42]

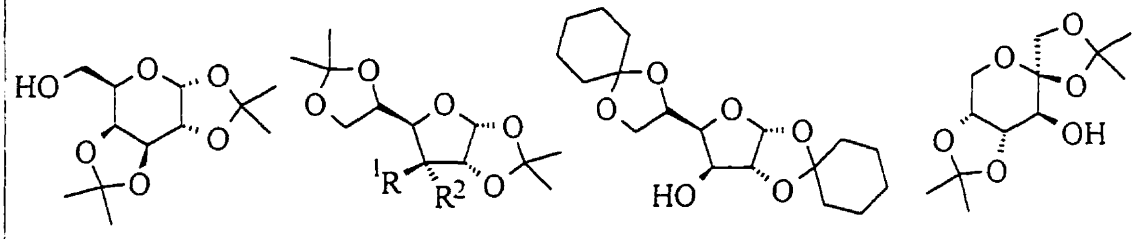


37 **38** **39**

Figure 1.7. Some Carbohydrate Derived Chiral Scaffolds

The most recent research in this area has encountered some difficulties. Ferriera and co-workers have investigated compounds **40-43** derived from D-galactose, D-fructose, and

D-glucose (Figure 1.8).[43] Although excellent *endo*:*exo* ratios have been reported, the π-facial selectivities were from low to moderate. The best results achieved using the acrylate esters of each of these four auxiliaries can be seen in Table 1.5.



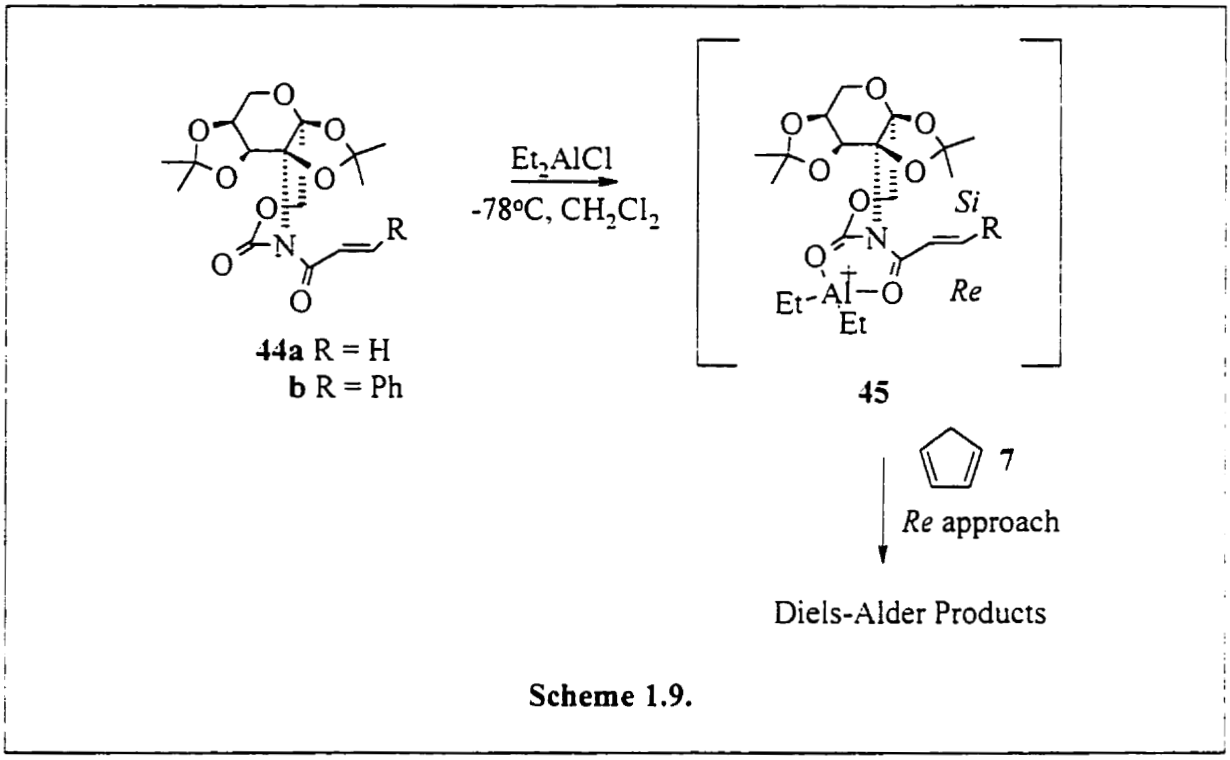
40 **41a** R^1 = H, R^2 = OH; **b** R^1 = OH, R^2 = H **42** **43**

Figure 1.8. Carbohydrate Auxiliaries by Ferriera and Co-Workers[43]

Table 1.5. Best Diels-Alder Results for Acrylate Ester Derivative of **40-43** with Cyclopentadiene (7) in CH_2Cl_2 at –78°C using Et_2AlCl

Dienophile	Yield (%)	*endo*:*exo*	%de *endo*
40	11	>98:2	40
41a	27	>98:2	60
41b	53	80:20	20
42	56	>98:2	40
43	61	80:20	0

Moderate results were also achieved by Banks *et al.* using their fructose-based homochiral 1,3-oxazin-2-one **44**, where the proposed transition state of this reaction with cyclopentadiene (7) can be seen in Scheme 1.9.[44] For both dienophiles, the reaction occurred at the relatively unhindered *Re*-face via the bidentate complex **45** to produce predominately one *endo* product. The results for these Diels-Alder reactions can be seen in Table 1.6.

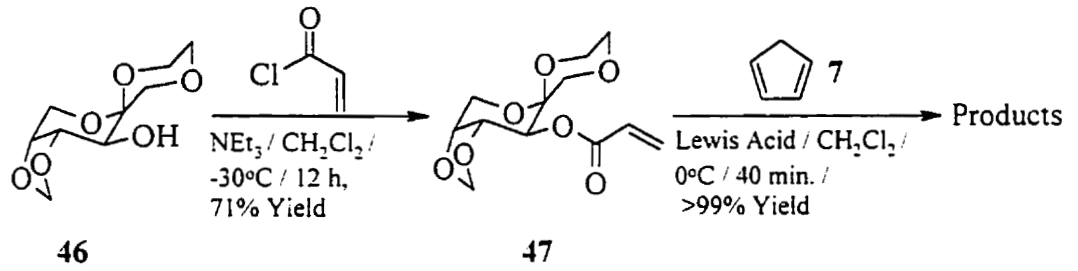


Scheme 1.9.

Table 1.6. Lewis Acid Catalysed Diels-Alder Cycloaddition Reactions of **44a** and **44b** with Cyclopentadiene (7)

Dienophile	% Yield	*endo*:*exo*	*endo* %de
44a	95	100:0	87
44b	95	4:1	63

Nouguier has also continued his earlier work in this field[40] and has recently reported excellent results using the novel carbohydrate derivative **46**[45] seen in Scheme 1.10. Reaction of the acrylate derivative with excess cyclopentadiene (7) yielded the results presented in Table 1.7, where it can be seen that using tin tetrachloride produces an *endo*:*exo* ratio of 98:2 with an *endo* diastereoselectivity of 98%.



46 **47**

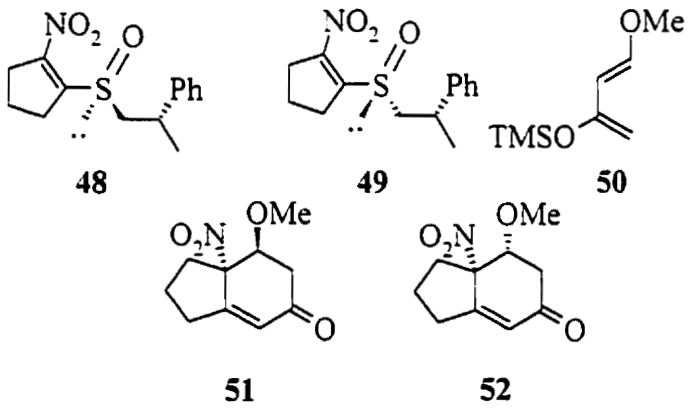
Scheme 1.10.

Table 1.7. Results of Diels-Alder Reaction of **47** with Excess Cyclopentadiene (7)

Lewis Acid	Time (h)	Temp	% Yield	*endo*:*exo*	*endo* %de
$SnCl_4$	0.6	0	>99	98:2	98
$EtAlCl_2$	0.6	0	>99	95:5	50
$EtAlCl_2$	6	-78	96	99:1	80

1.2.2.6. Sulfoxides

In addition to the chiral sulfoxides bound to isoborneol as seen in Scheme 1.5, several researchers have also reported the use of chiral sulfoxides attached to electron-deficient alkenes as a means of controlling stereoselectivity. Nitroalkenes **48** and **49** have been reported to provide ee values of >95% when reacted with Danishefsky's diene **50** to afford adducts of type **51** and **52** (Figure 1.9).[46,47]

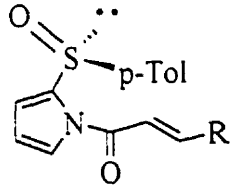


48 **49** **50**

51 **52**

Figure 1.9. Some Chiral Sulfoxide Diels-Alder Auxiliaries and Resultant Products

Since the first publications of this work, there have been several groups continuing to investigate the use of chiral sulfoxides for this purpose: in particular, Arai and co-workers.[48] and Carreno *et al.*[49] The most recent paper involving chiral sulfoxides for this purpose is presented by Arai and co-workers.[50] They have developed chiral sulfoxides **53-55**, as seen in Figure 1.10. The chirality of the sulfoxide determines from which face the diene must approach, i.e. opposite the large *p*-tolyl group; however, the exact mechanism is yet to be determined due to possible C-S bond rotation. The results of the various Diels-Alder reactions attempted can be seen in Table 1.8, where the reaction using samarium triflate as the Lewis acid provides excellent *endo*:*exo* ratio of 95:5 with an *endo* de of 96% (Entry 9).



53 R = Ph
54 R = Me
55 R = Et

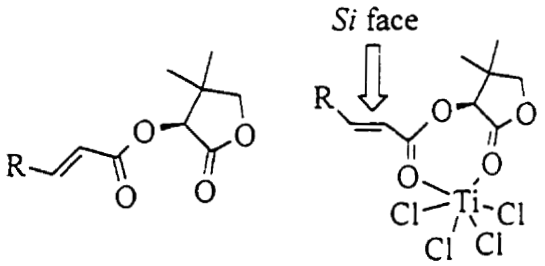
Figure 1.10. The Latest Chiral Sulfoxide for Asymmetric Diels-Alder Reactions

Table 1.8. Diels-Alder Results using **53-55** with Cyclopentadiene (**7**) at 25°C in CH_2Cl_2

Dienophile	Lewis Acid	Time (h)	*endo*:*exo*	*endo* %de
53	$ZnCl_2$	29	77:23	38
53	$AlCl_3$	13	95:5	98
53	$AlCl_3$	6	59:41	11
53	$Yb(OTf)_3$	45	69:31	89
53	$Yb(OTf)_3$	16	80:20	80
54	$Yb(OTf)_3$	9	92:8	93
54	$AlCl_3$	13	91:9	92
55	$Yb(OTf)_3$	23	95:5	84
55	$Sm(OTf)_3$	23	95:5	96
55	$Nd(OTf)_3$	22	96:4	90

1.2.2.7. α-Hydroxy Esters

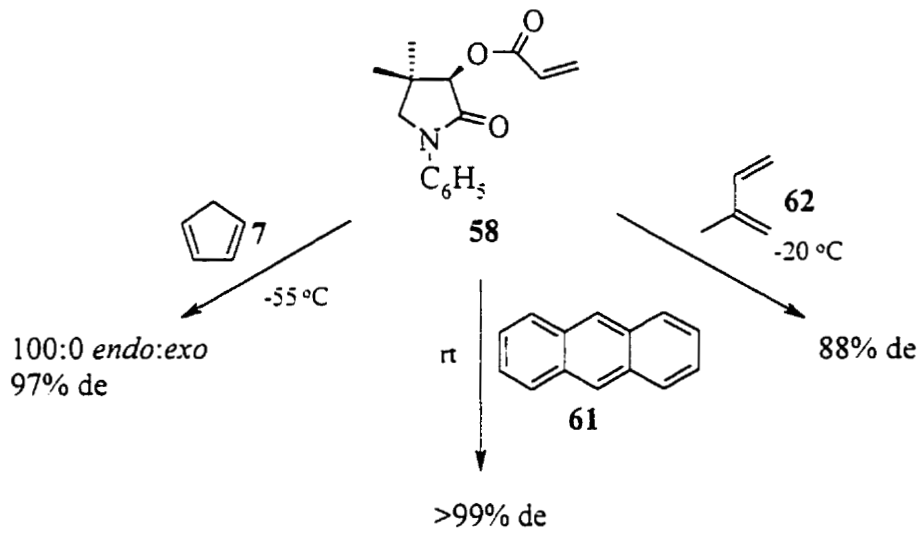
It is understood that a highly efficient, recoverable, dienophile auxiliary is desirable for asymmetric Diels-Alder reactions. The α-hydroxy ester derivatives fall into this class and have been used extensively due to their ease of recovery and efficiency. Auxiliaries, such as pantolactone derivative **56**, have been reported to provide >94% de in most cases[51,52] and is believed to proceed via double coordination to a Lewis acid, such as titanium, as seen in Figure 1.11 (**57**). The diene can only approach from the *Si*-face of the dienophile due to Lewis acid shielding of the *Re* face.



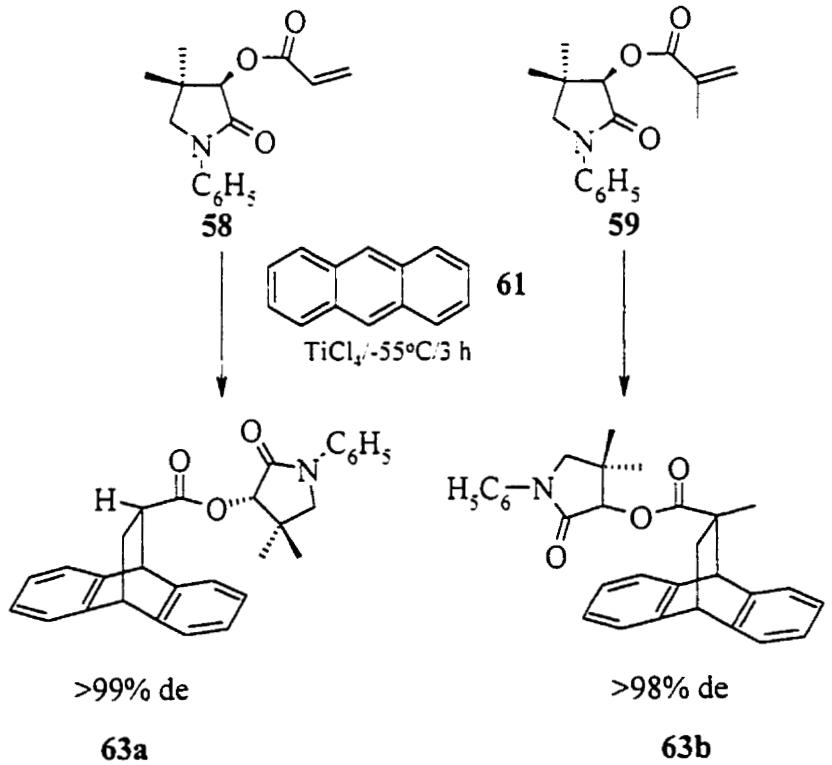
56 **57**

Figure 1.11. Pantolactone Derivative **56** and Its Titanium Bound Proposed Transition State **57**

More recently, a similar approach using pyrrolidinone derivatives **58-60** has been undertaken by Camps and co-workers.[53] Reaction of **58** with cyclopentadiene (**7**), anthracene (**61**), and isoprene (**62**), under $TiCl_4$ catalysed conditions at various temperatures, provided 97% (100:0 *endo*:*exo*), >99%, and 88% de respectively via the *Re* face (Scheme 1.11).



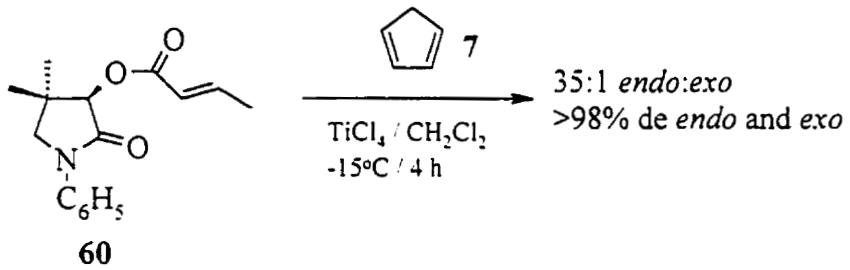
Scheme 1.11.



Scheme 1.12.

Reaction of the methacrylate derivative **59** yielded different results. No reaction was seen using isoprene (**62**) and an *endo*:*exo* of 1:1 was seen with cyclopentadiene (**7**). A reaction did occur with anthracene (**61**); however, opposite facial selectivity (compare **63a** with **63b**) was observed as compared to the acrylate example (Scheme 1.12).

Pyrrolidinone **60** failed to react with isoprene (**62**) and anthracene (**61**); however, it reacted smoothly with cyclopentadiene (**7**) to provide a 35:1 *endo*:*exo* selectivity with >98% de for the *endo* isomer (Scheme 1.13).

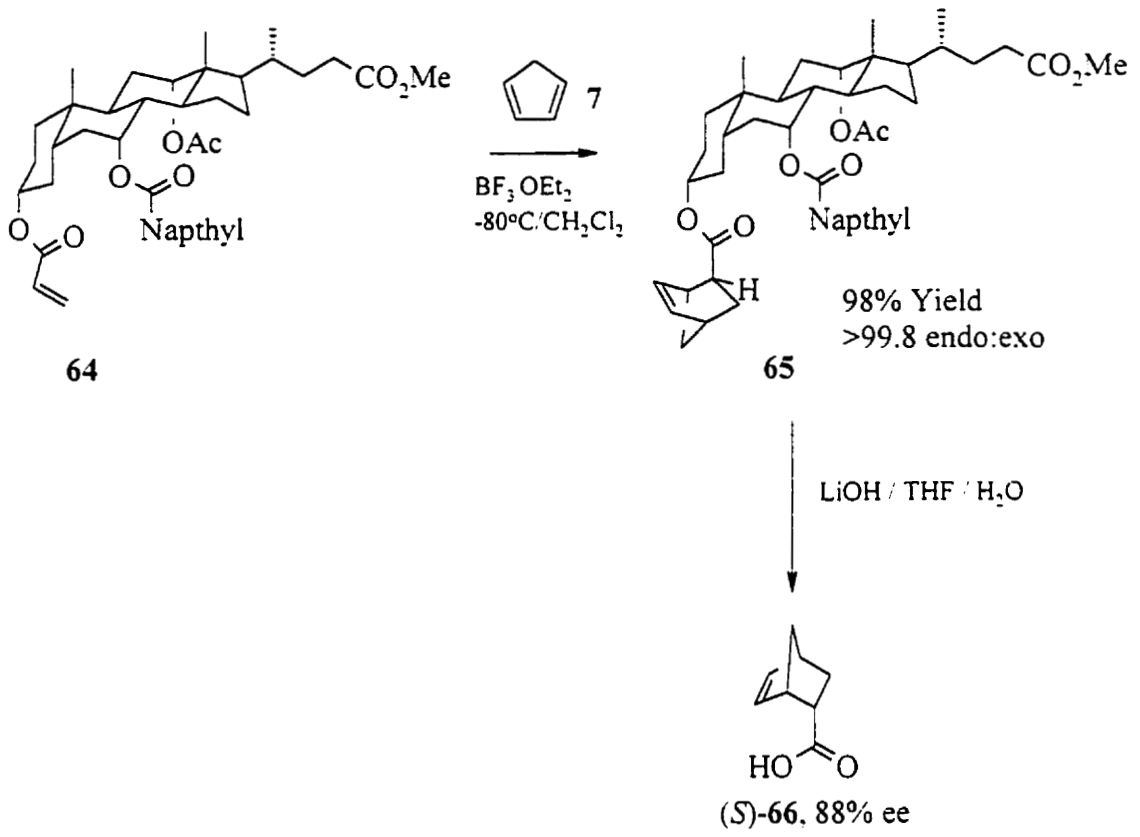


60

Scheme 1.13.

1.2.2.8. Steroids

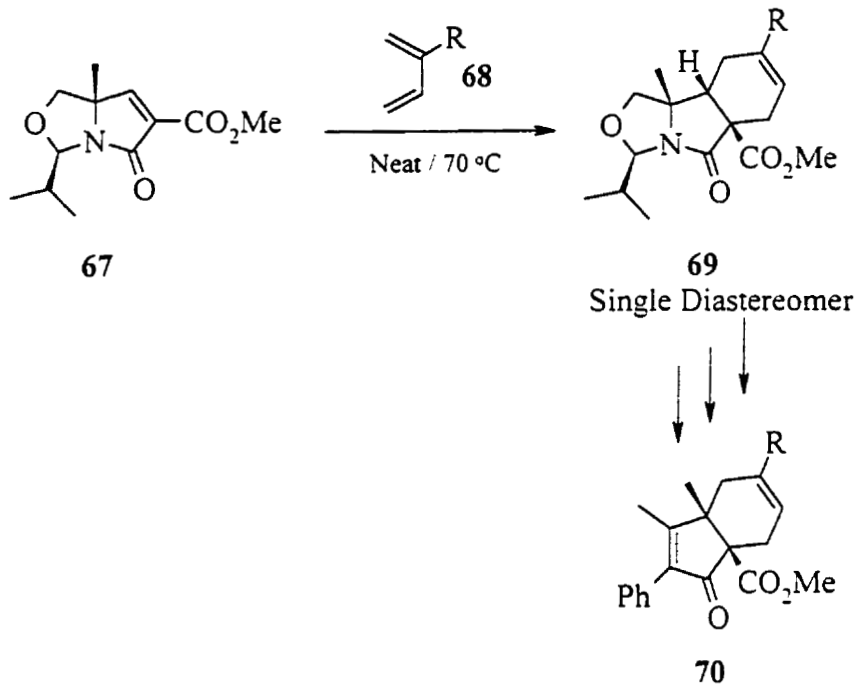
The only example of a steroid based chiral auxiliary for performing asymmetric Diels-Alder reactions involves the use of a cholic acid acrylic ester. This work was performed by Maitra and Mathivanan[54] and can be seen in Scheme 1.14. The reaction of **64** with cyclopentadiene (**7**) using boron trifluoride etherate ($BF_3 \cdot OEt_2$) provided **65** with >99.8 *endo* selectivity. Removal of the cycloadduct with $LiOH/THF/H_2O$ afforded (*S*)-**66** with an 88% ee.



Scheme 1.14.

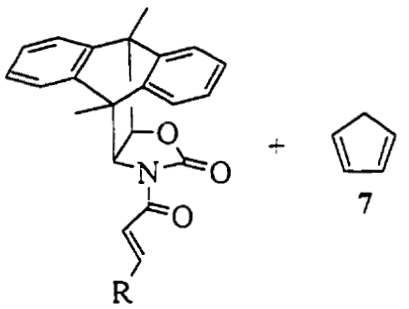
1.2.2.9. Oxazolidinones

The type of chiral auxiliary that has received the most investigation as a scaffold for asymmetric Diels-Alder reactions is the oxazolidinones. Work by Evans, in which the ability of oxazolidinones to serve as chiral auxiliaries in a wide range of reactions,[55] was expanded by Meyers who pioneered the use of oxazolidine derivatives such as **67**. For example, reaction of **67** with diene structures **68** provide **69** as single diastereomers (Scheme 1.15).[56] These types of adducts can be readily transformed into carbocycles **70**.



Scheme 1.15.

More recently, the use of oxazolidinone derivatives for similar Diels-Alder reactions have been investigated extensively by Kunieda and co-workers, where a 9,10-dimethylanthracene oxazolidinone derivatives **71**, upon reaction with cyclopentadiene (**7**), provides products with high diastereoselectivity.[57] The results of this work can be seen in Scheme 1.16.



71a R = H
b R = Me

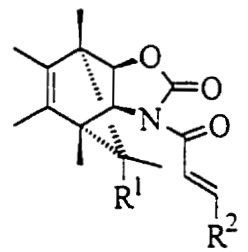
+ 7

Et_2AlCl / CH_2Cl_2 / -78°C → Products

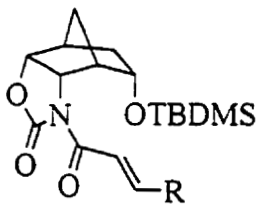
Dienophile	Yield	*endo*:*exo*	*endo* de
71a	94	99:1	94%
71b	97	99:1	99%

Scheme 1.16.

Kunieda continued work in this field, where research using oxazolidinones for Diels-Alder reactions with cyclopentadiene (**7**) was expanded to include sterically constrained tricyclic systems, such as **72**[58] and **73**.[59] Cyclopentadiene (**7**) was reacted with compounds **72a-d** (Et_2AlCl catalyst, CH_2Cl_2, -78°C, 30 min.), **73a** ($BF_3{\cdot}Et_2O$ catalyst, CH_2Cl_2, -78°C, 30 min.), and **73b** (Et_2AlCl catalyst, CH_2Cl_2, -78°C, 30 min.) to yield the results seen in Figure 1.12.



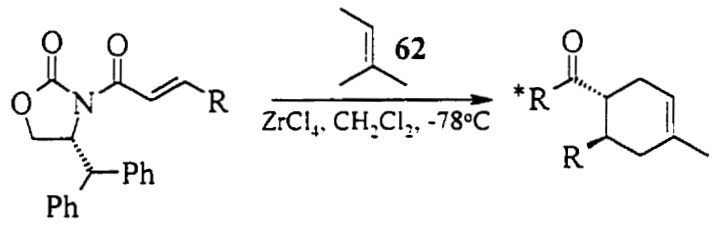
	endo:*exo*	*endo* de
72a R^1 = H, R^2 = H	99:1	98%
b R^1 = H, R^2 = Me	99:1	99%
c R^1 = Me, R^2 = H	99:1	97%
d R^1 = Me, R^2 = Me	99:1	99%



	endo:*exo*	*endo* de
73a R = H	65:1	98%
b R = Me	99:1	>99%

Figure 1.12. Asymmetric Diels-Alder Results by Kuneida and Co-workers[58,59]

Oxazolidinone derivatives prepared from D-diphenylalaninol as well as from amino indanol skeletons have also been reported. Sibi and co-workers, using the D-diphenylalanol derivatives **74**, have achieved > 99% de upon reaction with isoprene (**62**) using a zirconium tetrachloride Lewis acid.[60] A summary of the results can be seen in Scheme 1.17.

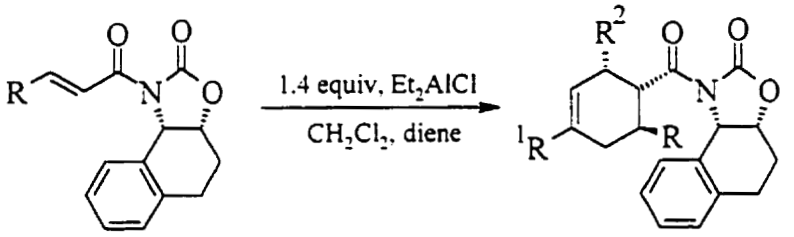


74a R = Me
b R = Ph

75a 86% yield, >99% de
b 84% yield, >99% de

Scheme 1.17.

Two separate groups have investigated the use of amino indanol oxazolidinone derivatives **76** for use in asymmetric Diels-Alder reactions. Work by Davies *et al.* is summarized in Scheme 1.18 and Table 1.9.[61] The best result obtained is a 50:1 *endo*:*exo* ratio with a 98.4% de upon reaction of their derivative with piperylene.



76a R = H
b R = Me

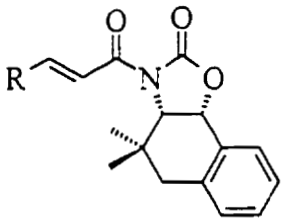
77a R = H, R^1 = Me, R^2 = H
b R = H, R^1 = Me, R^2 = Me
c R = Me, R^1 = Me, R^2 = H
d R = Me, R^1 = Me, R^2 = Me

Scheme 1.18.

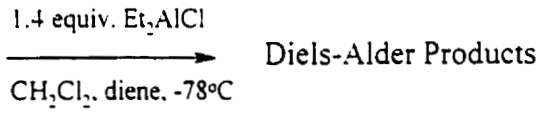
Table 1.9. Results of Diels-Alder Reactions with Auxiliaries **76a** and **76b**

Dienophile	Diene	Product	Temp (°C)	% de	*endo:exo*
R = H	isoprene	**77a**	-70	87.5	-
	piperylene	**77b**	-70	98.4	50:1
R = Me	isoprene	**77c**	-35	93.4	-
	isoprene	**77c**	-15	92.9	-
	piperylene	**77d**	-35	98.4	30:1
	piperlyene	**77d**	-15	93.7	25:1

More recently, the use of this type of auxiliary was investigated by Saigo and co-workers.[62] Their work involved the oxazolidinone derivative of *cis*-2-amino-3,3-dimethyl-1-indanol **78** (Scheme 1.19). This compound was tested with a wide variety of dienes with excellent results that are summarized in Table 1.10.



78a R = H
b R = Me



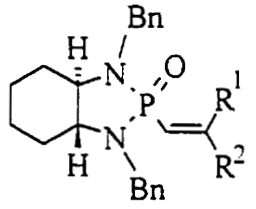
Scheme 1.19.

Table 1.10. Results of Diels-Alder Reactions by Saigo Using **78**

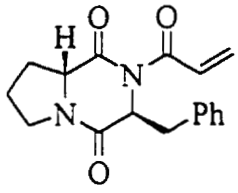
Diene	R	*endo*:*exo*	Diastereomeric Ratio
cyclopentadiene	H	97:3	98:2
	Me	99:1	>99:1
cyclohexadiene	H	99:1	99:1
	Me	98:2	96:4
isoprene	H	-	>99:1
	Me		>99:1
2,3-dimethylbutadiene	H	-	98:2
	Me		-

1.2.2.10. Miscellaneous Derivatives

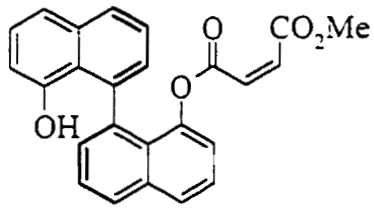
There are some chiral auxiliaries which do not fit into any of the above mentioned categories. Compounds such as **79-84** (Figure 1.13) have also been used in asymmetric Diels-Alder reactions. However, compounds **79**[63] and **80**[64] will not be discussed in this thesis due to their inability to be cleaved from the resulting cycloadducts.



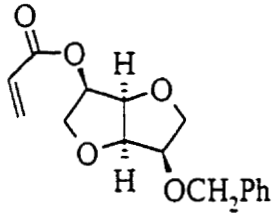
79a R^1 = H, R^2 = CO_2Me
b R^1 = CO_2Me, R^2 = H



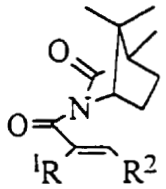
80



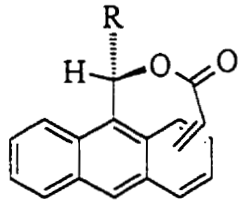
81



82



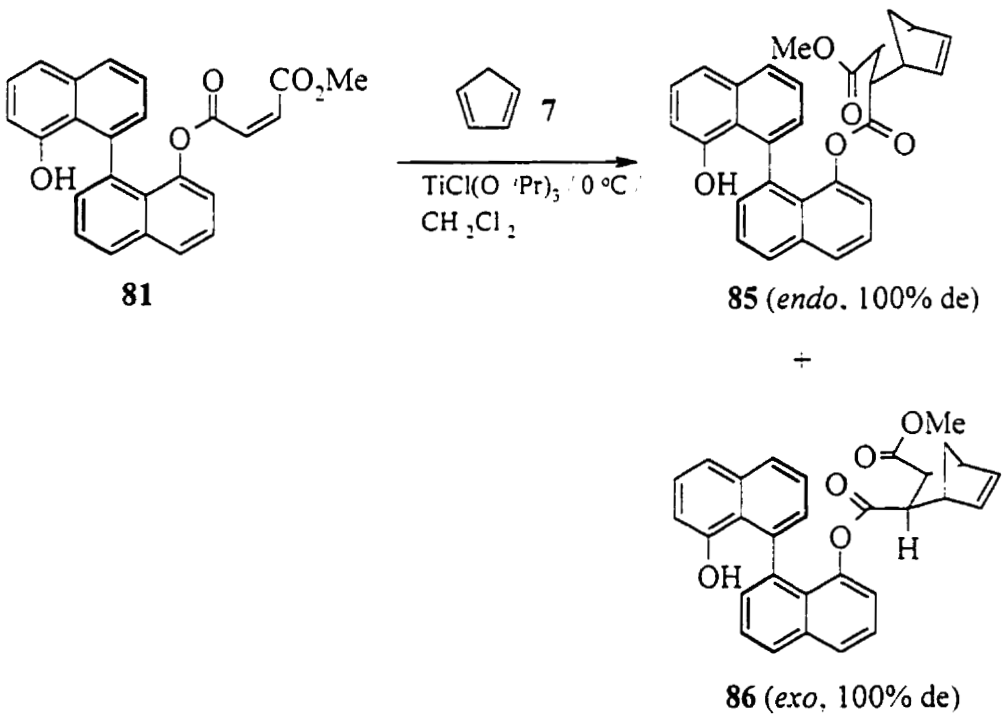
83a R^1 = Me, R^2 = H
b R^1 = H, R^2 = Me



84a R = CF_3
b R = *t*-Bu
c R = Me

Figure 1.13. Miscellaneous Chiral Auxiliaries

The use of axially chiral C_2 symmetrical 1,1'-binaphthalene-2,2'-diol (BINOL) and related compounds have been extensively investigated in the field of asymmetric reactions.[65] In contrast, the corresponding 8,8'-diols[66] had received little attention until Fuji and co-workers investigated their use as asymmetric scaffolds for Diels-Alder reactions.[67] Reaction of **81** with cyclopentadiene (**7**, 2 equiv.) using various Lewis acid catalysts was investigated. The best result obtained used $TiCl(O^iPr)_3$ at 0°C in CH_2Cl_2 to produce an *endo*:*exo* ratio of 86:14 with 100% de for both the *endo* (**85**) and *exo* (**86**) adducts (Scheme 1.20).



81

85 (*endo*, 100% de)

+

86 (*exo*, 100% de)

Scheme 1.20.

Loupy and Monteux have investigated chiral auxiliary **82**, derived from readily available isosorbide.[68] The most promising result using this chiral dienophile was a 92% de for the *endo* isomer upon reaction with cyclopentadiene (**7**, 2 equiv. $EtAlCl_2$, CH_2Cl_2, -70°C,

1h), with an *endo*:*exo* value of >99:1. Other reactions using various Lewis acids, solvents, and temperatures yielded only moderate diastereoselectivity. It is postulated that the (*R*)-*endo* selectivity with their auxiliary can be due to a π-stacking interaction between the acrylate double bond and the phenyl moiety of the benzyl protecting group.

Imide derivatives have been developed by Boeckman and co-workers[69] in an effort to alter the rotational preference about the C_1-C_2 bond, thereby removing detrimental nonbonding interactions in α-substituted dienophiles. Derivatives **83a** and **83b** were tested with a variety of dienes with their most successful result being reaction of **83b** with isoprene (**62**, 1.5 equiv. $MeAlCl_2$, CH_2Cl_2, -78°C) to yield a product with 92% de in 83% yield.

Novel auxiliaries **84a-c** for use in asymmetric Diels-Alder reactions have been developed by Carriere and Virgili.[70] Aryl carbinols have previously been used as NMR resolving agents;[71] however, further chemistry with these compounds had yet to be researched. Attempts to use **84** for asymmetric Diels-Alder reactions with cyclopentadiene (**7**) provided excellent *endo*:*exo* selectivity, however, the highest %de achieved was a modest 70%. These results are summarized in Table 1.11.

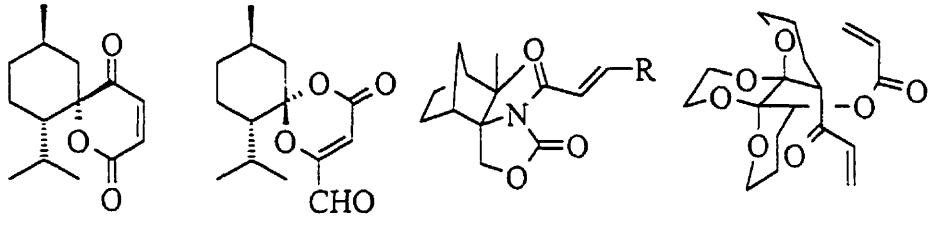
Table 1.11. Diels-Alder Results Using Dienophiles **84a-c**

Dienophile	Lewis Acid	Temp. (°C)	Solvent	*endo*:*exo*	*endo* %de
84a	$EtAlCl_2$	-70	CH_2Cl_2	100:0	40
84a	$EtAlCl_2$	-30	CH_2Cl_2	100:0	30
84a	$EtAlCl_2$	-30	$PhCH_3$	100:0	30
84a	$EtAlCl_2$	-70	CH_2Cl_2/C_6H_{14}	100:0	26
84a	$EtAlCl_2$	-70	CH_2Cl_2	100:0	70
84a	BF_2Et_2O	0	$PhCH_3$	87:13	24
84a	$TiCl_4$	-70	CH_2Cl_2	92:8	10
84a	$TiCl_4$	-70	$PhCH_3$	100:0	10
84a	$TiCl_4$	-70	CH_2Cl_2/C_6H_{14}	-	-
84b	$EtAlCl_2$	-30	CH_2Cl_2	100:0	12
84b	$EtAlCl_2$	-30	CH_2Cl_2/C_6H_{14}	100:0	14
84b	BF_2Et_2O	-30	CH_2Cl_2	90:10	26
84c	$EtAlCl_2$	-70	CH_2Cl_2/C_6H_{14}	100:0	14

1.3. Spiro Systems as Chiral Auxiliaries

1.3.1. Introduction

To our knowledge, spiro systems have not been thoroughly investigated as a possible chiral scaffolds for performing asymmetric Diels-Alder reactions. Compounds such as **87**,[72] **88**,[73] **89**,[74] and **90**[75] (Figure 1.14) have been used for this purpose, however, **87** cannot be used in this context as the cycloadducts cannot be removed without destroying the chiral auxiliary.



87 **88** **89a** R = H **90**
b R = Me
c R = Ph

Figure 1.14. Various Spiro Chiral Auxiliaries For Diels-Alder Reactions

Sato and co-workers[73] have reported that spiro system **88** reacts with a 50 molar excess of cyclopentadiene (benzene, room temperature, 3 days, 66% yield), without the presence of Lewis acid, to yield a 14:1 *endo*:*exo* ratio. Unfortunately, de values are not given in this publication.

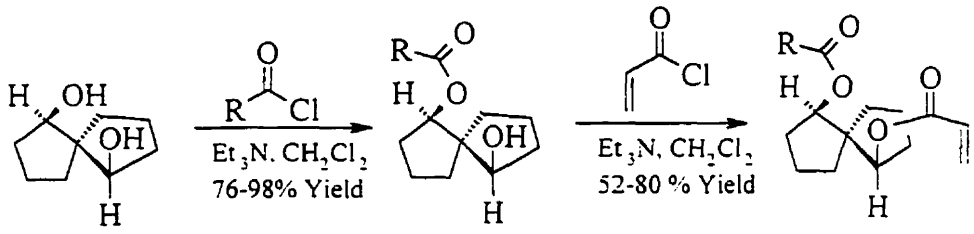
Spiro oxazolidinone **89**, however, has been used as a Diels-Alder scaffold quite successfully.[74] The results for the Et_2AlCl catalysed reactions of **89a-c** with cyclopentadiene (**7**) at –78°C in CH_2Cl_2 are given in Table 1.12. Unfortunately, *endo*:*exo* ratios were not given; however, very high % *endo* de values were reported.

Table 1.12. Results for the Reaction of **89** with Cyclopentadiene (**7**)

Dienophile	% Yield of Products	*endo* % de
89a	98	>95
89b	99	99
89c	97	98

Spirodiketal **90** has also been used for this purpose in 1994 by Ley.[75] These authors reported excellent *endo*:*exo* ratios (>99:1) upon reaction with cyclopentadiene (**7**); however, they did not report de values for the cycloadducts. It is important to note that Diels-Alder reactions occurred on both of the attached acrylate moieties.

The most extensive research towards the use of spiro systems as chiral auxiliaries for Diels-Alder reactions has been performed in our laboratory.[1] This research describes the results obtained when a variety of groups are attached to spiro diol **1** containing an acrylate dienophile and subjected to Diels-Alder reactions with cyclopentadiene in the presence of a variety of Lewis acids (Table 1.13). The best result was obtained with the mono-pivalate mono-acrylate bis-ester (Entry 19) where de values of >97% were achieved. The required starting bis-esters **92** were prepared as per Scheme 1.21.



1 **91** **92**

Scheme 1.21.

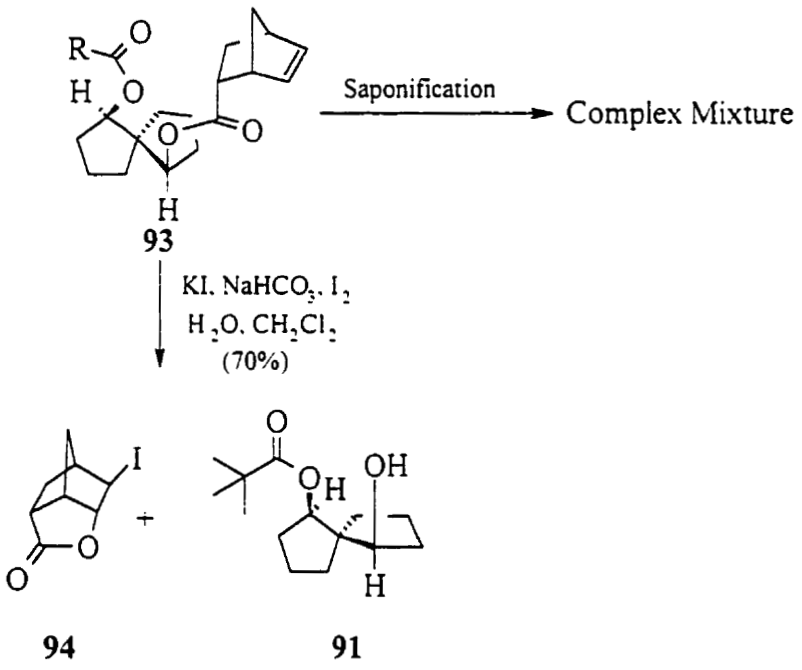
Table 1.13. Results for the Diels-Alder Reaction of **92** with Cyclopentadiene (7)

Entry	R	Equiv. of Lewis Acid	Lewis Acid	% Yield of *endo*	*endo* %de
1	2-Np	-	-	84	7
2	2-Np	2	$BF_3 \cdot Et_2O$	98	73
3	2-Np	1.1	$TiCl_4$	97	54
4	2-Np	3	$TiCl_4$	96	40
5	2-Np	1.1	$SnCl_4$	95	80
6	2-Np	3	$SnCl_4$	-	-20
7	2-Np	3	$SiCl_4$	-	54
8	2-Np	2	$SbCl_5$	94	53
9	2-Np	2.1	$MeAlCl_2$	97	59
10	2-Np	3	BCl_3	96	75
11	(*R*)-1-Np[a]	2	BCl_3	98	75
12	Ph_2CH	2	BCl_3	97	47
13	Ph	2	BCl_3	99	85
14	Ph	2	BCl_3	99	88
15	*p*-NO_2Ph	2	BCl_3	98	84
16	*p*-MeOPh	2	BCl_3	98	88
17	(*R*)-Ph[a]	2	BCl_3	99	88
18	(*S*)-H_2C=CH[a,b]	2	BCl_3	99	75
19	(*S*)-Me_3C	2	BCl_3	99	>97

a) The letter in brackets refers to the absolute stereochemistry of the diol used. b) Both acrylates undergo Diels-Alder reaction.

1.3.2. Conclusion

Although auxiliaries like **92** have proven very useful, difficulty was encountered on cleaving the desired cycloadduct to yield the free acid. Iodolactonization was required to remove the cycloadduct as saponification procedures resulted in complex mixtures with cleavage of either one or both of the ester functionalities. The drawback to using iodolactonization is that further chemistry is required to convert **94** to the free bicyclo acid (Scheme 1.22). The addressing of this problem is the goal of this thesis.



Scheme 1.22.

1.4. Summary

The results illustrated in this review on substrate bound chiral auxiliaries, for the purpose of performing asymmetric Diels-Alder reactions, show that several types of chiral scaffolds have been employed quite successfully. Moreover, only a few spiro systems exist

for this purpose, with the emphasis being on what was previously presented from our laboratory.[1] An extension of this work, in hopes of developing a more universal system, shall be the topic of discussion of this thesis.

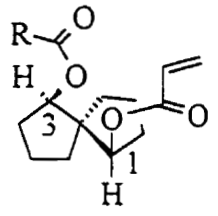
1.5. Project Goals

1.5.1. Introduction

In early 1992, research in the Keay lab began to focus on the use of chiral auxiliaries in asymmetric synthesis. Literature at that time revealed that spiro diol systems had not been used for this purpose, and since hydroxyl groups could be converted to amino and phosphino groups,[76] a wide range of auxiliaries with various applications could be produced. With the relative success of *cis,cis*-spiro diol **1** as a substrate bound chiral auxiliary, expansion of this work could help answer several questions. These questions include:

1) Can the cycloadducts formed from the Diels-Alder reaction be selectively cleaved to form the free acids without the use of iodolactonization?

2) Can we alter the type of substituents in the 1,3 positions and yield the same diastereoselectivity (Figure 1.15)?



92

Figure 1.15. The 1,3 Relationship in Spiro Systems

3) Is the *cis,cis* orientation of the 1,3 substituents necessary for good asymmetric induction?

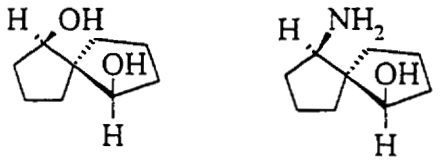
It is the goal of this project to answer these questions and expand the understanding of how spiro systems can serve as chiral auxiliaries in Diels-Alder reactions.

1.5.2. Determination of the Appropriate Spiro System

Several criteria were deemed important in the design of a suitable spiro system. These include: 1) the size of the spiro rings; 2) what substituents should be at the 1,3 sites; and 3) the relative orientation of the substituents to one another, i.e., *cis,cis*; *cis,trans*; or *trans,trans* relationship.

The first criterion to be considered is that of the ring size for the system. This is an important consideration due to possible problems that can be associated with conformational changes, for example, chair↔chair interconversion with six-membered rings. Consideration of the problems related to conformational ring rotation led us to consider a spiro[4.4]nonane system, as five membered rings are easily prepared. This choice would also provide a more rigid spiro system, which is preferential for good asymmetric induction.[77]

The second criteria would stem from an adaptation of the previous work,[1] whereby conversion of the pivalyl ester to a functionality which could withstand cycloadduct cleavage selectively. Here it was decided to change the pivalyl ester of **91** (Scheme 1.22) to a pivalamide. With all other things being equal, this would hopefully allow for selective saponification of the cycloadducts to the free acid and regenerate our chiral auxiliary, as it is known that amides are generally stable to basic conditions, i.e., saponification. This means that the logical target for the chiral auxiliary should be the 1,3-amino alcohol spirononane system **95** (Figure 1.16).



1 **95**

Figure 1.16. 1,3-Amino Alcohol System **95**

The last criterion left to determine was the best stereochemical orientation of the 1,3-amino alcohol substituents. Figure 1.17 displays the three diastereomeric possibilities for the placement of the amino and alcohol groups, namely the *cis,cis*-, *cis,trans*- and *trans,trans*-isomers, **95**, **96**, and **97** respectively. Of these three, only the *cis,cis* isomer would be capable of bidentate complexation, an important requirement for many chiral auxiliaries, but not required for our purposes. Nevertheless, with other possible applications in mind like the coordination of Lewis acids to the amino and alcohol groups, the *cis,cis*-1,3-amino alcohol spiro[4.4]nonane system **95** was selected as a target for synthesis in order to study its effectiveness in asymmetric Diels-Alder reactions, and to compare the results with the *cis,cis* diol system.

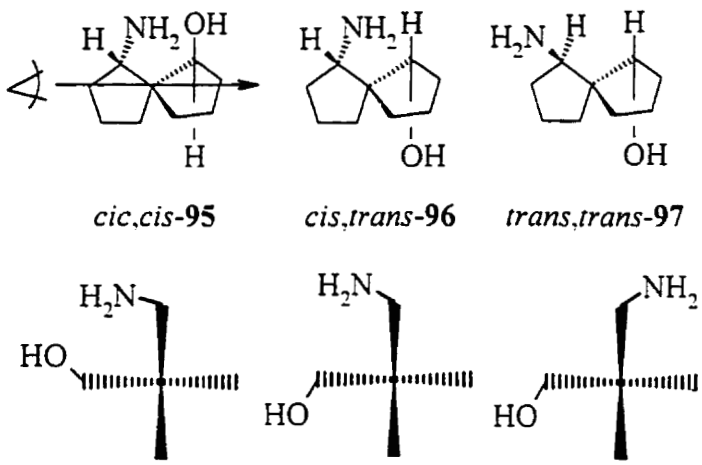


Figure 1.17. Three 1,3-Amino Alcohol 3-Dimensional Arrangements for 6-Aminospiro[4.4]nonan-1-ols along with Edge on Views of Their Spatial Arrangements

1.5.3. 1,3-Aminoalcohols

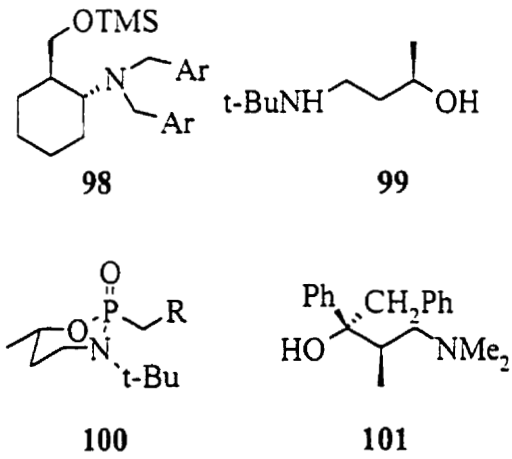
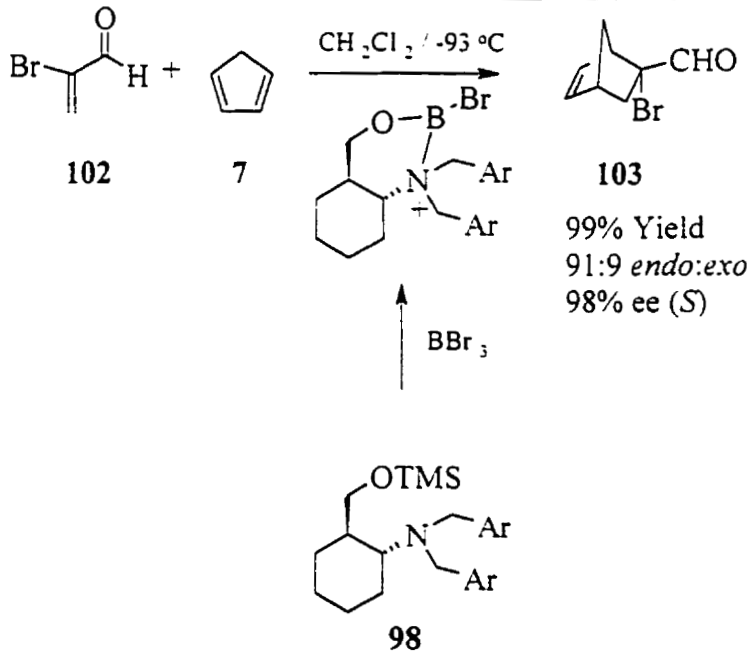


Figure 1.18. Various 1,3-Aminoalcohols in the Current Literature used for Asymmetric Transformations

As the amino and alcohol functionalities are in a 1,3-relationship, a search of the literature was undertaken to determine what, if any, chemistry has been done with these systems. This search revealed that 1,2-amino alcohol systems have been used extensively for

asymmetric transformations and is the topic of a major review;[78] however, very little work has been done with 1,3-amino alcohol systems. In fact, no applications of substrate bound chiral auxiliaries for Diels-Alder reactions were found. However, **98-101** (Figure 1.18) have been reported for use in other asymmetric transformations. Compound **98** has been used as a chiral super-Lewis acidic catalyst for enantioselective Diels-Alder reactions of 2-bromoacrolein (**102**) with cyclopentadiene (**7**) upon complexation to boron tribromide, yielding ee values of up to 98% (Scheme 1.23).[79]



Scheme 1.23.

Compound **99** was employed for the synthesis of 1,3,2-oxazaphosphorane **100**, which was used for the synthesis of chiral alkylphosphonic acids.[80,81]

Finally, aminoalcohol **101** was used to generate *in situ* chiral reducing agents to react with prochiral ketones. Aryl alkyl ketones are reduced to secondary alcohols with very good enantiomeric excesses (>90% ee).[82,83,84]

1.6. Conclusion

The target spiro system for synthesis and investigation as a chiral auxiliary, due to its more favorable recoverability, relative rigidity of the 5-membered ring system, as well as the novel nature of using a 1,3-amino alcohol spiro system, is *cis*,*cis*-6-aminospiro[4.4]nonan-1-ol (**95**, Figure 1.17). The next two chapters will discuss 1) the synthesis of **95**; and 2) the results obtained for its use as a scaffold for Diels-Alder reactions, respectively.

Chapter 2

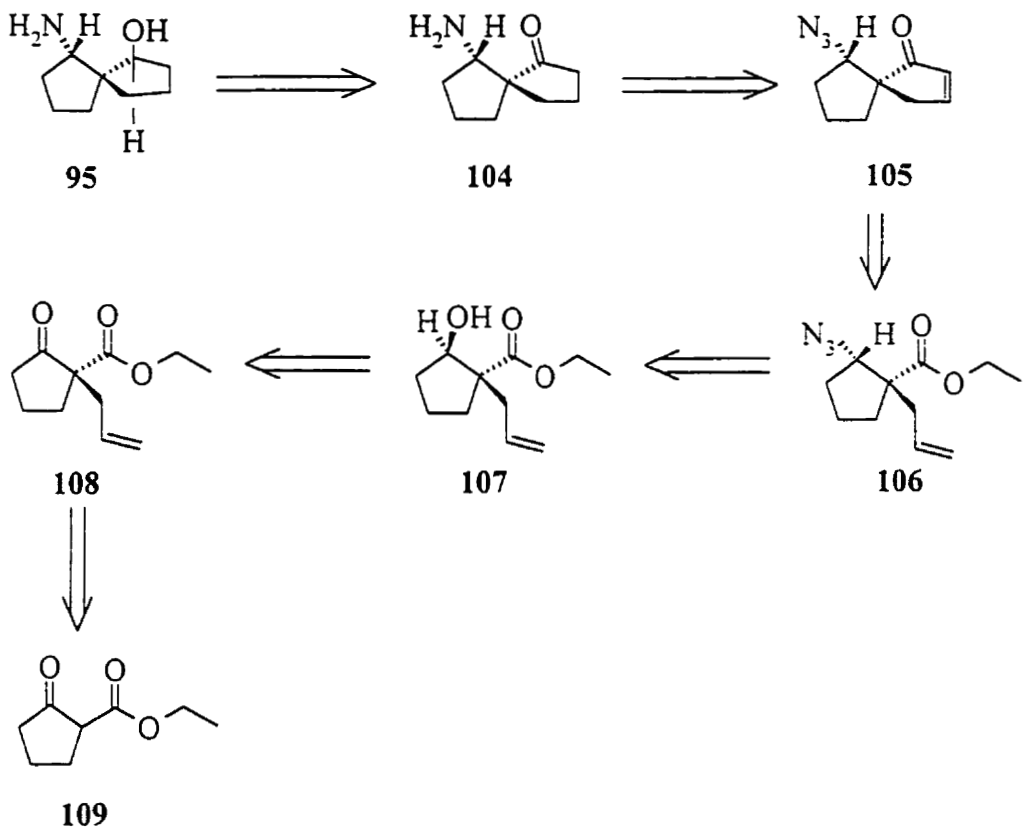
2. Synthesis of *cis,cis*-6-Aminospiro[4.4]nonan-1-ol (95)

2.1. Introduction

In order for a chiral auxiliary to be considered versatile, it must be 1) obtainable in large quantities, 2) have both optically pure enantiomers readily available, and 3) be inexpensive to buy or produce. This chapter describes the retrosynthetic approach to this compound, as well the synthetic steps required for its synthesis in detail.

2.2. Retrosynthesis

A retrosynthetic analysis of **95** can be seen in Scheme 2.1. It was envisioned that amino alcohol **95** could be readily prepared by a diastereoselective reduction of the ketone functionality of **104**. In turn, compound **104** could be prepared via simple hydrogenation of azido-α,β-unsaturated ketone **105**. Ring disconnection of **105** would produce azidoester **106**, which could be generated via functional group conversion from the known compound **107**.[85] Alcohol **107** results from diastereoselective reduction of enantiopure **108**. This could be produced via alkylation of the readily available β-ketoester **109**, where **108** could be resolved by known enzymatic methods.[86,87]

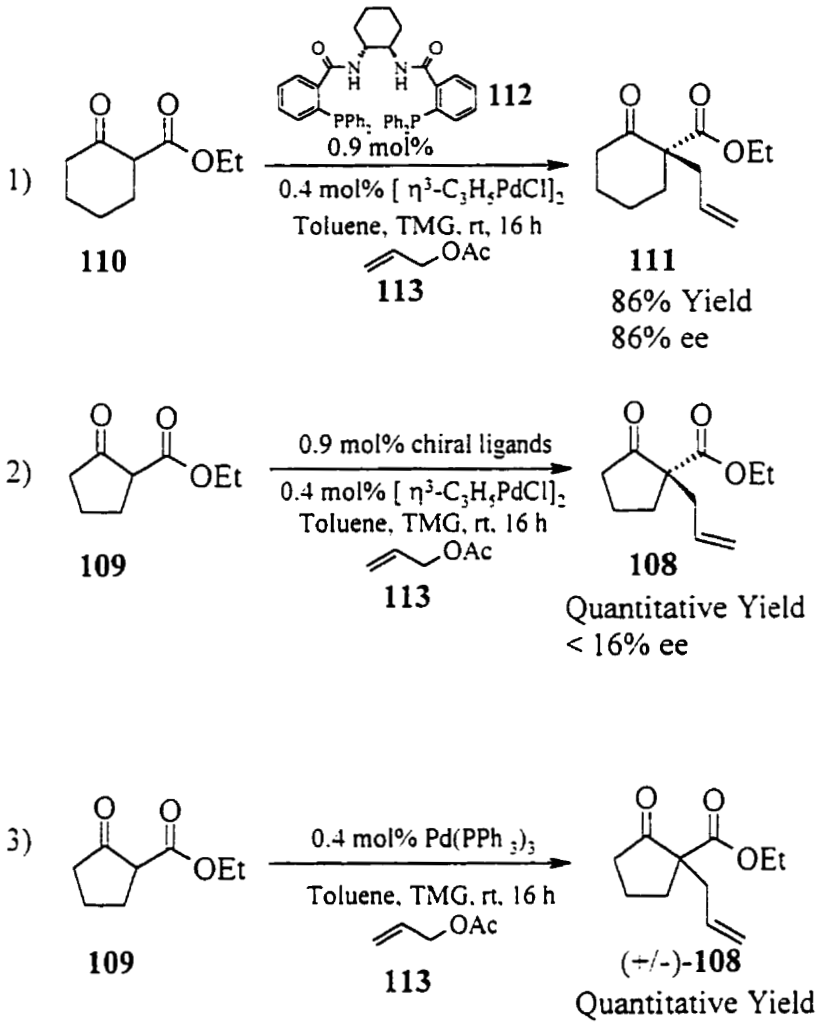


Scheme 2.1.

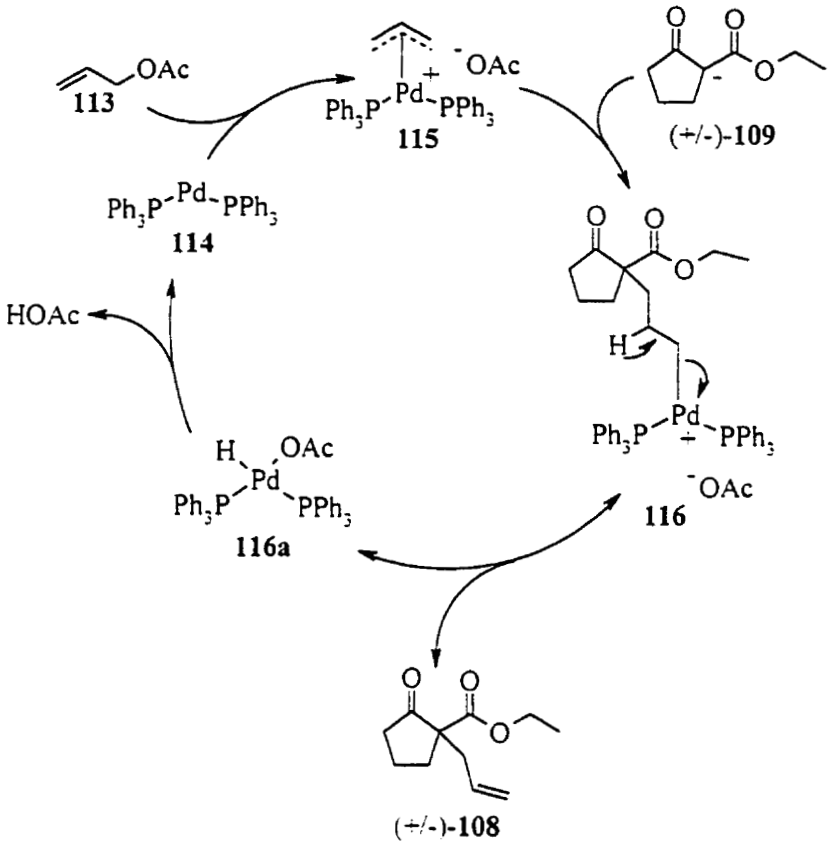
2.3. Attempted Synthesis

The allylation of 2-ethoxycarbonyl-1-cyclopentanone (**109**) has been performed several times using various bases and allyl bromide in moderate to high yields.[85,88,89,90] However, work on asymmetric allylations of 2-ethoxycarbonyl-1-cyclohexanone (**110**) by Trost,[91] (reaction 1, Scheme 2.2) achieved excellent yields of **111** (60-90%) using palladium catalyzed methods in good to excellent enantiomeric excesses (ee's, 70-86%). Although **108** was desired in enantiopure form, attempted allylations of **109** via this method in our laboratory provided ee's that were no greater than 16%[92] (reaction 2, Scheme 2.2) using a

variety of asymmetric ligands (**112** and others). Therefore, a modified procedure taking advantage of the high yield was used. Tetrakis(triphenyphosphine) palladium (0) ($Pd(PPh_3)_4$, 0.4 mol%), in place of 0.4 mol% $[\eta^3\text{-}C_3H_5PdCl]_2$ and 0.9 mol% chiral ligand **112**, with allyl acetate (**113**) produced quantitative yields of the desired product (±)-**108** (reaction 3, Scheme 2.2). The appearance of a new signal for an allyl group (δ 5.80 ppm, 1H, m; δ 5.15 ppm, 2H, m) and the loss of the methine proton in the ^{1}H-NMR spectrum, as well the continued presence of the ethyl ester, confirmed (±)-**108** had been obtained. The mechanism of this reaction can be seen in Scheme 2.3 and is described as follows: 1) active palladium catalyst **114** forms *in situ* from $Pd(PPh_3)_4$ and inserts into the allyl acetate (**113**) bond forming complex **115**; 2) the anion of **109** attacks the palladium complex forming **116**; 3) the desired product **108** is eliminated leaving **116a**; 4) reductive elimination of a molecule of acetic acid regenerates the active catalyst to continue the cycle.


1)
OEt
110
112
PPh2 Ph2P
0.9 mol%
0.4 mol% [η3-C3H5PdCl]2
Toluene, TMG, rt, 16 h
OAc
113
OEt
111
86% Yield
86% ee
2)
OEt
109
0.9 mol% chiral ligands
0.4 mol% [η3-C3H5PdCl]2
Toluene, TMG, rt, 16 h
OAc
113
OEt
108
Quantitative Yield
< 16% ee
3)
OEt
109
0.4 mol% Pd(PPh 3)3
Toluene, TMG, rt, 16 h
OAc
113
OEt
(+/-)-108
Quantitative Yield

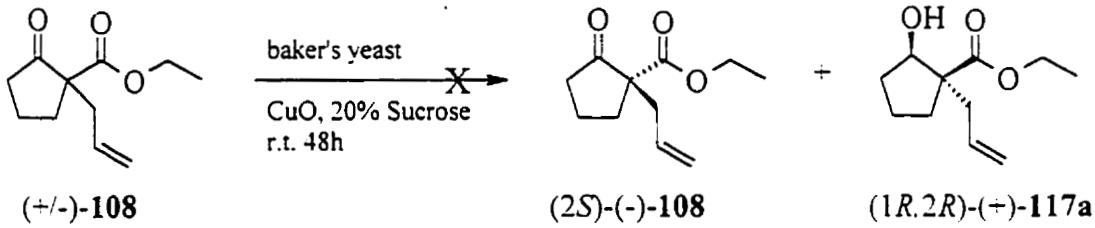
Scheme 2.2.



Scheme 2.3.

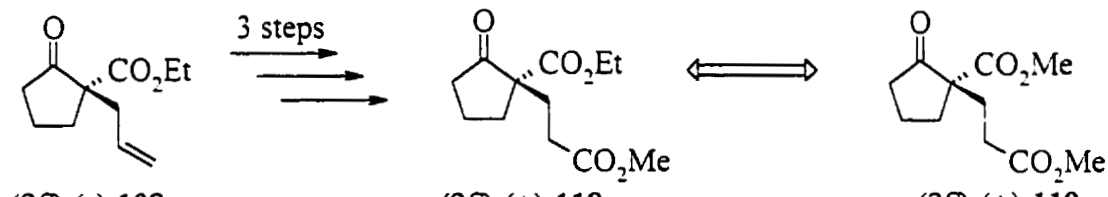
With (±)-**108** in hand, a method for resolving its enantiomers was then investigated. A procedure reported by Fraga and Barreiro,[86,87] in which (±)-**108** can be selectively reduced by *Saccharomyces cerivisiae* (baker's yeast) in the presence of CuO was reported to yield unreacted (2*S*)-(-)-**108** and (1*R*,2*R*)-(+)-**117a** (Scheme 2.4). The configuration of the secondary alcohol (+)-**117a** was assigned by default after the absolute stereochemistry of (-)-**108** was determined by: 1) measuring the CD/ORD spectrum of (-)-**108**; and 2) by comparing the sign of the optical rotation of (2*S*)-(+)-**118**, which was prepared from (-)-**108** in three steps, with the known diester (2*S*)-(+)-**119**[93] as seen in Scheme 2.5. Based on this correlation, Fraga *et al.* claimed the reduction of (±)-**108** with baker's yeast was an exception to Prelog's rules for β-keto esters,[94] i.e., pro-*R* delivery of H instead of pro-*S*.

Due to the fact that enantiopure **108** is a key starting material for the synthesis of **95**, it was necessary to unambiguously assign the absolute stereochemistry of the reduction product. When the same enzymatic reducing conditions described by Fraga *et al.* were used,[86,87] the unreacted enantiomer (-)-**108** as well as (+)-**117b** were isolated (Scheme 2.6). The alcohol (+)-**117b** was subsequently esterified with (1*S*)-(+)-10-camphorsulfonyl chloride (**3**) to provide (+)-**120a** as a white solid. The X-ray crystal structure of (+)-**120a** clearly showed that the absolute configuration of (+)-**117** was in fact the product predicted by Prelog's rules, namely (1*S*,2*S*)-(+)-**117b** (Scheme 2.6).[95] Performing a Bijvoet analysis[96] on the crystal structure confirmed the absolute stereochemistry as shown in Figure 2.1. Using baker's yeast, yields of 78% and 80% for (2*R*)-(-)-**108** and (1*S*,2*S*)-(+)-**117b** were achieved.



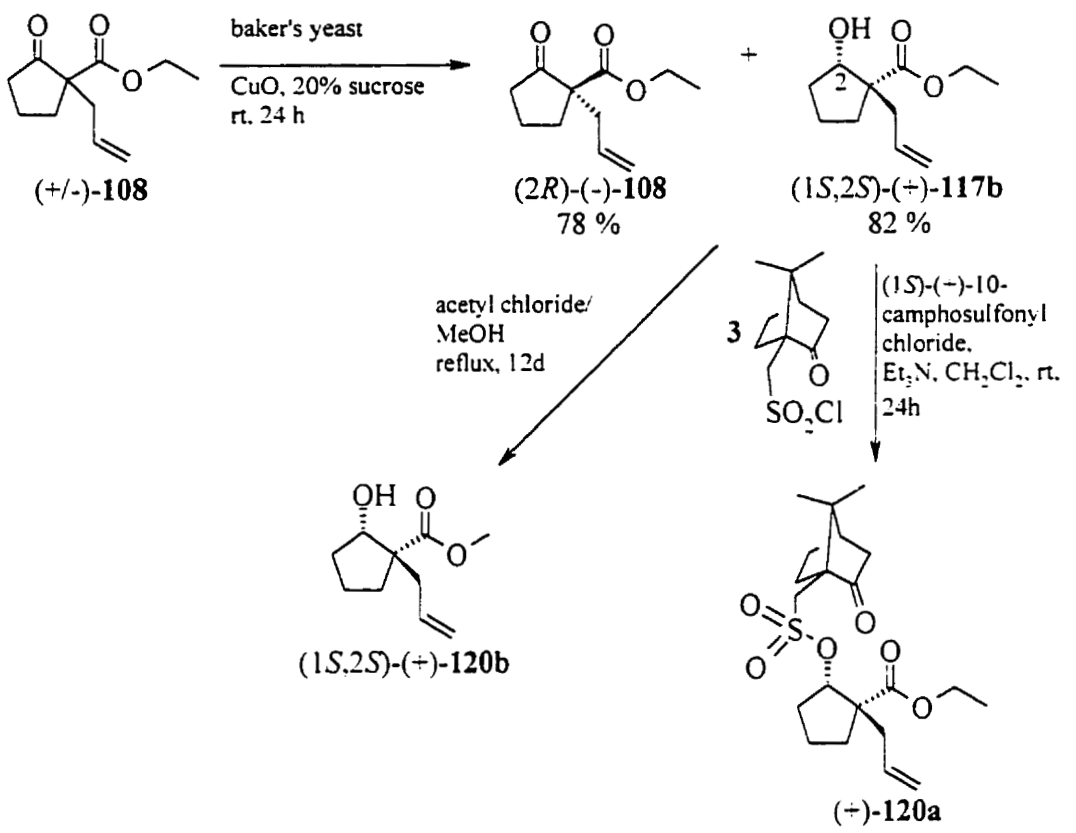
(+/-)-**108** (2*S*)-(-)-**108** (1*R*,2*R*)-(+)-**117a**

Scheme 2.4.



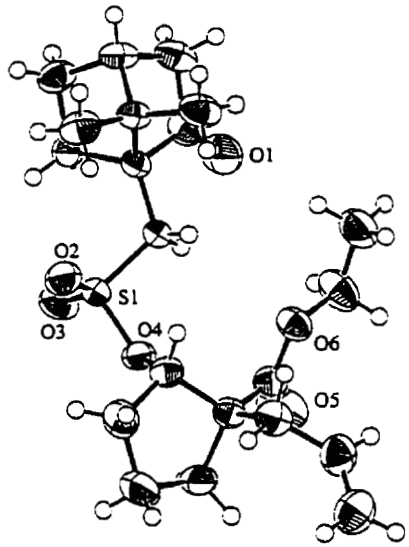
(2*S*)-(-)-**108** (2*S*)-(+)-**118** (2*S*)-(+)-**119**

Scheme 2.5.



Scheme 2.6.

As secondary proof of the absolute configuration of (+)-**117b**, it was decided to convert (1*S*,2*S*)-(+)-**117b** into (1*S*,2*S*)-(+)-**120b**, whose absolute configuration has been reported.[97] Transesterification of (1*S*,2*S*)-(+)-**117b** with HCl in refluxing MeOH in the presence of acetyl chloride for 12 d yielded methyl ester (1*S*,2*S*)-(+)-**120b** (Scheme 2.6). Compound (1*S*,2*S*)-(+)-**120b** had an optical rotation of $[\alpha]_D^{21.1}$ +25.6 (1.875, $CHCl_3$) that closely matched the optical rotation reported by Seebach[97] $[\alpha]_D^{20.5}$ +26.3 (1.87, $CHCl_3$), thereby further confirming the absolute configuration of (1*S*,2*S*)-(+)-**117b**.



(+)-**120a**

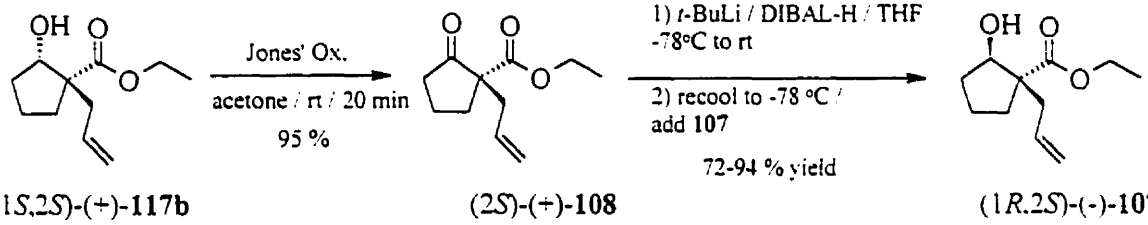
Figure 2.1. The X-ray Crystal Structure of (+)-**120a**

Unfortunately, baker's yeast reduction of the ketone functionality of (±)-**108** provided the incorrect relative stereochemistry at C2 in (+)-**117b** required for the synthesis of **95** (Scheme 2.6). Therefore, another diastereoselective reduction was required to reduce the ketone of (-)-**108** to give the alcohol with opposite configuration at C2.

With (1*R*,2*R*)-(+)-**117b** already in hand from baker's yeast reduction, access to (+)-**108** was readily achieved via Jones' oxidation in excellent yield (95% yield, acetone, rt) (Scheme 2.7). Attempted reductions of (+)-**108** using diisobutylaluminum hydride (DIBAL-H) in various solvents (THF, CH_2Cl_2, hexanes) at various temperatures (-100, -78, 0, rt °C) gave complex mixtures of products with no selectivity; both the ester and ketone were reduced.

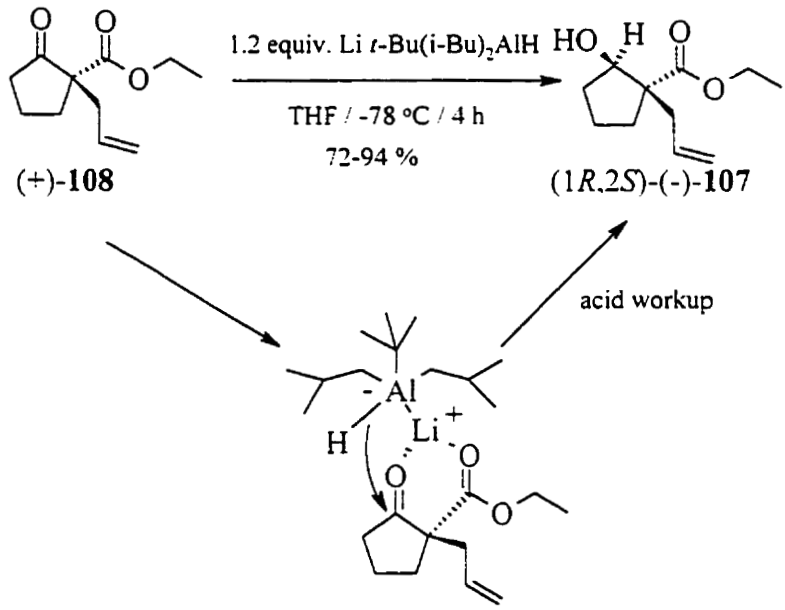
Work in this laboratory on the reduction of spiro[4.4]nona-1,3-diones,[7] provided the method which was next attempted. Reaction of DIBAL-H first with *tert*-butyllithium

(*t*-BuLi, 1 equiv.) to create an aluminate (Li *t*-Bu(i-Bu)$_2$AlH) increases the steric hindrance at the aluminum center. A postulated mechanism by which the directed reduction of the ketone occurs can be seen in Scheme 2.8, where chelation of the lithium to both carbonyl groups directs reduction of the more reactive ketone to occur *syn* to the ester. Using this method, yields from 72-94% of the correct diastereomer, (1*R*,2*S*)-(-)-**107**, were achieved. This was evident in the ^{1}H NMR spectrum as the C**H**-OH proton appears at δ 4.34 ppm in (-)-**107** versus δ 4.07 ppm when compared to the yeast produced diastereomer (+)-**117b**. The ^{1}H-NMR spectra of a) Li *t*-Bu(i-Bu)$_2$AlH produced alcohol (-)-**107**; b) yeast produced alcohol (+)-**117b**; and c) the starting β-keto ester (+)-**108** are seen in Figure 2.2.



(1*S*,2*S*)-(+)-**117b** (2*S*)-(+)-**108** (1*R*,2*S*)-(-)-**107**

Scheme 2.7.



Scheme 2.8.

With (-)-**107** in hand, conversion of the hydroxyl group to the required nitrogen containing functionality was necessary. It can be seen that S_N2 displacement of the hydroxyl group with a nitrogen based nucleophile would provide the desired stereochemistry for **95**. This was accomplished by first converting the hydroxyl group of (-)-**107** to the corresponding mesylate using a catalytic nucleophilic substitution reaction. Various conditions were attempted and it was found that those using two equivalents of methanesulfonyl chloride (MsCl) in pyridine proceeded in high yields (>90%). The shift of the signal for the C**H**-O- proton from δ 4.34 ppm to δ 5.30 ppm and the presence of a new methyl singlet at δ 3.08 ppm in the ^{1}H-NMR spectrum confirmed the presence of a mesylate in **121** (Scheme 2.9).

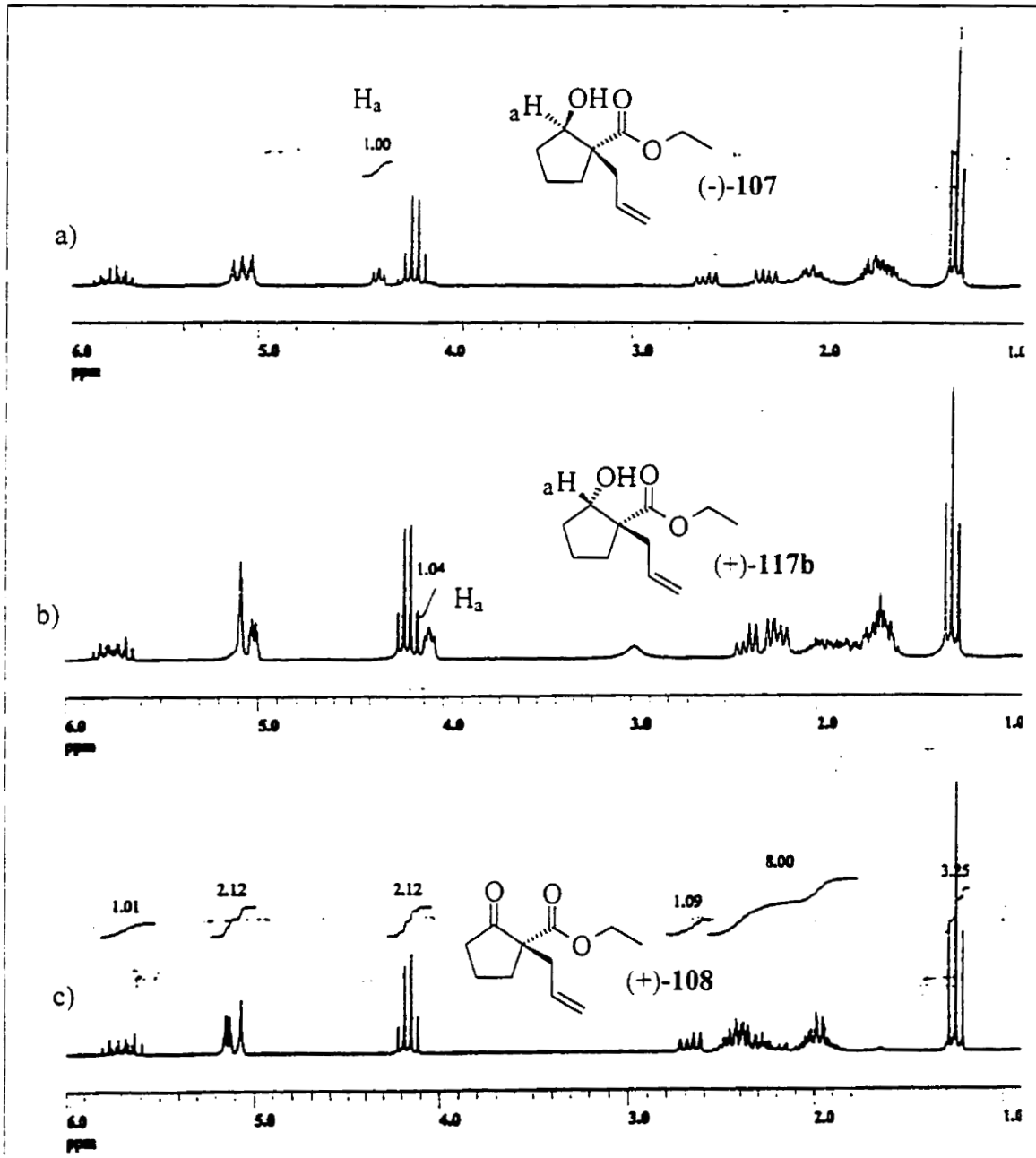
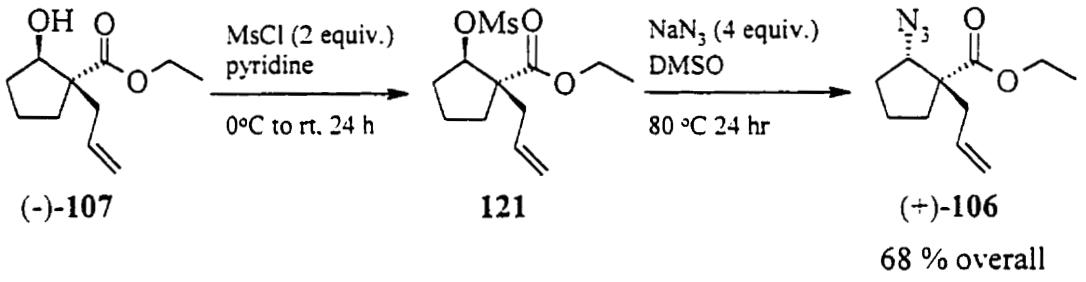


Figure 2.2. ^{1}H-NMR Spectra of a) (1*R*,2*S*)-(-)-**107**; b) Alcohol (1*S*,2*S*)-(+)-**117b**; and c) Allyl Ester (2*S*)-(+)-**108**.

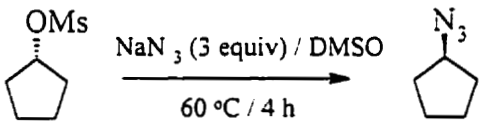
With the mesylate **121** in hand, S_N2 displacement by azide was then attempted. A modified procedure by Zwierzak,[98] which converted the mesylate of cyclopentanol **122** to the corresponding azide **123** (Scheme 2.10), was then attempted. Compound **121** was heated to 80°C with 4 equivalents of sodium azide in dimethyl sulfoxide overnight providing isolated yields of (+)-**106** in a modest 68% over two steps from (-)-**107** (Scheme 2.9). The change in shift of the C**H**-O- proton in the ^{1}H-NMR spectrum from δ 5.30 ppm in **121** to δ 3.89 ppm (C**H**-N_3) as well as the presence of a N=N stretch at 2200 cm^{-1} in the IR spectra confirmed that product (+)-**106** had been formed. Efforts to improve this reaction with various solvents, azide equivalents, and temperatures were not successful as can be seen in Table 2.1.



(-)-**107** **121** (+)-**106**

68 % overall

Scheme 2.9.



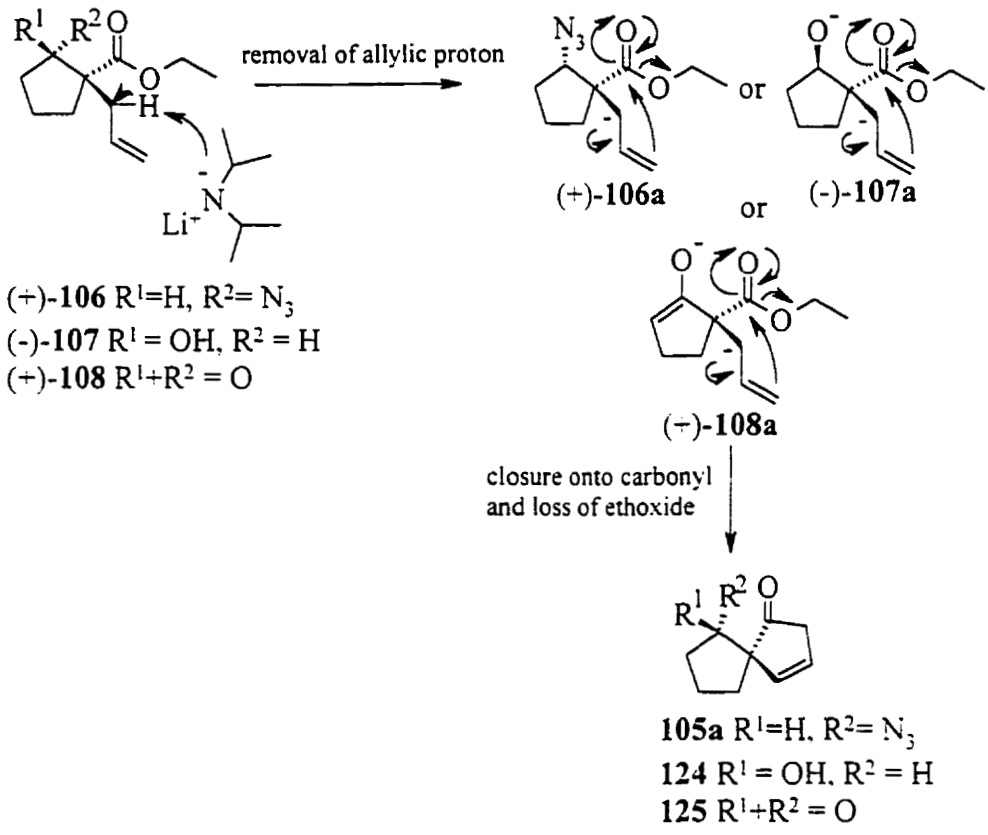
122 **123**

Scheme 2.10.

Table 2.1. Various Conditions Attempted for the Conversion of (+)-**106** from Mesylate **121**

Solvent	Temp. (°C)	Azide Equiv.	Overall Yield (%)
DMSO	80	2	52
DMSO	80	3	59
DMSO	80	4	68
DMSO	100	4	64
2% H_2O/DMF	100	4	No Rxn.

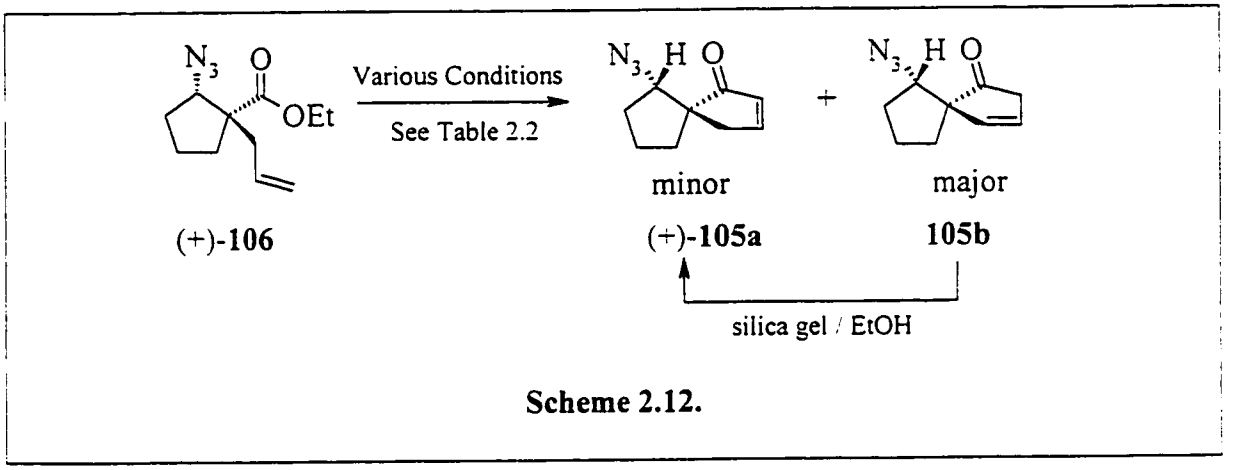
The next required transformation was the conversion of (+)-**106** to the required spiro system **105** (Scheme 2.11). It was hoped that formation of the allylic anion of (+)-**106**, (-)-**107**, or (+)-**108** would result in cyclization onto the ester to form the desired spiro system **105**, **124**, or **125**, respectively (Scheme 2.11). Initial attempts to form the spiro system from either (-)-**107** or (+)-**108** were unsuccessful even though the exact reaction was reported to be facile and quantitative by Thebtaranonth and co-workers.[99] Both (-)-**107** and (+)-**108** presumably have to cyclize through dianions (-)-**107a** and (+)-**108a**. However, the reaction of (+)-**106** would only require a mono-anion **106a**. Thus the cyclization was attempted on ester azide (+)-**106**.



Scheme 2.11.

Treatment of (+)-**106** with various equivalents of LDA in THF at various temperatures were performed, both with and without TMEDA. These results can be seen in Table 2.2, where it was found that four equivalents of LDA in the absence of TMEDA at 0°C yielded the most significant amount of the desired products **105a** and **105b**. The formation of **105b** was unexpected based on the report by Thebtaranoth *et al.*[99] The crude residue was then stirred in ethanol for 24 hours over silica gel in order to migrate the double bond into conjugation, which upon column chromatography yielded up to 76% of the desired system (+)-**105a** (Scheme 2.12). Product (+)-**105a** was confirmed by examination of the ^{1}H-NMR spectrum, where the signals for the ethoxy group of the ester at δ 4.16 ppm (2H, q) and δ

1.24 ppm (3H, t), as well as the allyl group at δ 5.80 ppm (1H, m) and δ 5.15 ppm (2H, m) had disappeared. New signals for the α,β-unsaturated ketone appeared at δ 7.65 ppm (1H, dt), δ 6.15 ppm (1H, dt), along with the allylic CH_2 at δ 2.71 (2H, qt).



Scheme 2.12.

Table 2.2. Attempted Conditions for the Cyclization of (+)-**106**

Solvent (THF:TMEDA)	Temp (°C)	Base (equiv.)	Time (h)[a]	Yield of 105a + 105b (%)
4:1	-78, rt	LDA (2)	6, 18	0
4:1	-78, 0	LDA (2)	1, 8	22
4:1	-78, 0	LDA (2)	0.5, 12	24
4:1	0	LDA (2)	8	55
4:1	0	LDA (4)	8	66
4:1	0	LDA (4)	8	75
100:0	0	LDA (4)	8	76
100:0	-78, rt	LiHMDS (2)	8, 18	nr
100:0	rt	LiHMDS (4)	18	nr

a) times separated by a comma refer to hours at respective temperatures

With (+)-**105a** in hand, work turned to the reduction of the double bond and azido functionality to produce the desired spiro amino ketone **104** (Scheme 2.13). It was hoped that simple hydrogenation over a suitable metal catalyst would serve the dual purpose of reducing both the double bond and azido functionality to the desired saturated spiro amino ketone. It is known that azide functions are hydrogenated with retention of configuration at a

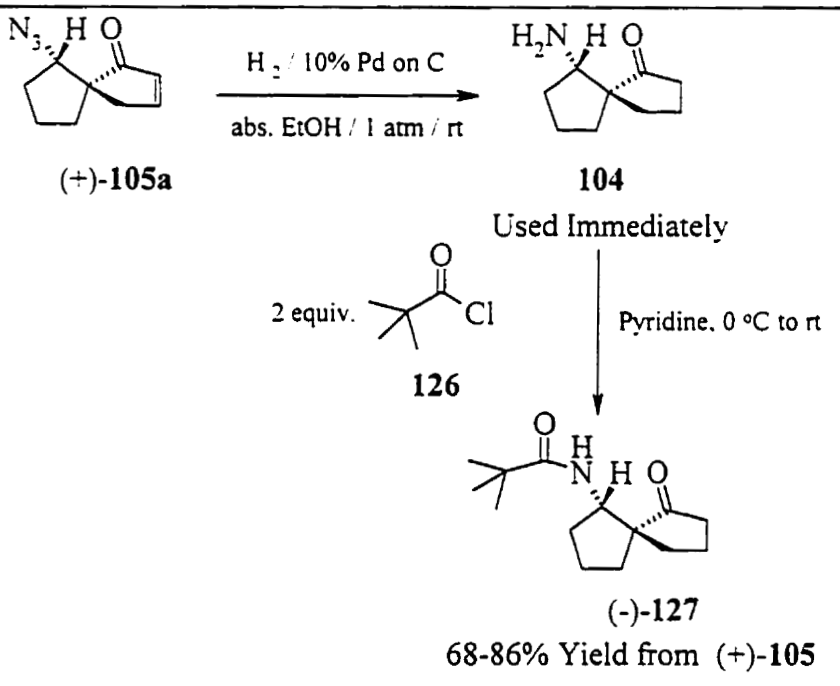
stereogenic center[100] and several metal catalysts, such as palladium, platinum, and Raney nickel have all been employed under mild conditions for this purpose.[101,102]

Many suitable conditions exist for the hydrogenation of carbonyl compounds to the corresponding alcohols; however in our case, it was desired to only have reduction of the olefinic function whilst leaving the carbonyl group untouched. For this purpose, palladium can be used for olefinic hydrogenation with minimal carbonyl reduction (Scheme 2.13).[103,104,105,106]

With this in mind, (+)-**105a** was taken up in absolute ethanol under an atmosphere of hydrogen and reduced in the presence of catalytic 10% palladium on activated carbon at one atmosphere overnight (Scheme 2.13). The reaction was then checked by a ^{1}H-NMR analysis of an aliquot to ensure the loss of the olefin. Filtration of the reaction mixture and removal of solvent resulted in the desired amino ketone **104** in high yield (93%) with only minor impurities as evident in the ^{1}H NMR spectrum. The crude residue was placed on the top of a silica gel column and rinsed with a mixture of 2:1 hexanes: ethyl acetate to remove the minor impurities evident by thin layer chromatography (TLC). Rinsing of the column with methanol provided the desired crude product **104** in 93% yield. Unfortunately, it was found that this compound readily polymerized with time, probably through intermolecular imine formation, so it was used immediately in the next reaction.

2.4. Synthesis of Pivalamidospiro[4.4]nonan-1-one, (-)-(127)

As **104** was unstable, the amino group was protected immediately as a pivalamide. The pivalamide was chosen since the pivaloate in **92** (Chapter 1, p.36, R = $C(CH_3)_3$) gave the best results in the Diels-Alder reaction with the spiro diol system. Treatment of **104** with 2,2-dimethylpropanoyl chloride (**126**, pivaloyl chloride, 2 equiv.) in pyridine (0°C to room temperature) overnight gave (-)-**127**, after purification by column chromatography, in isolated yields of 69-86% (2 steps from (+)-**105**) (Scheme 2.13). The presence of a large singlet for the *t*-butyl group at δ 1.14 ppm (9H, s), C**H**-N- signal at δ 4.24 (1H, m), and amido proton at δ 6.05 (1H,br s) in the ^{1}H-NMR spectrum confirmed the pivalamide was present. In addition the absence of the IR band at 2200 cm^{-1}, presence of an N-H stretch at 3378 cm^{-1}, amide C=O at 1657 cm^{-1}, and ketone C=O at 1728 cm^{-1} provided further evidence that product (-)-**127** had been prepared.

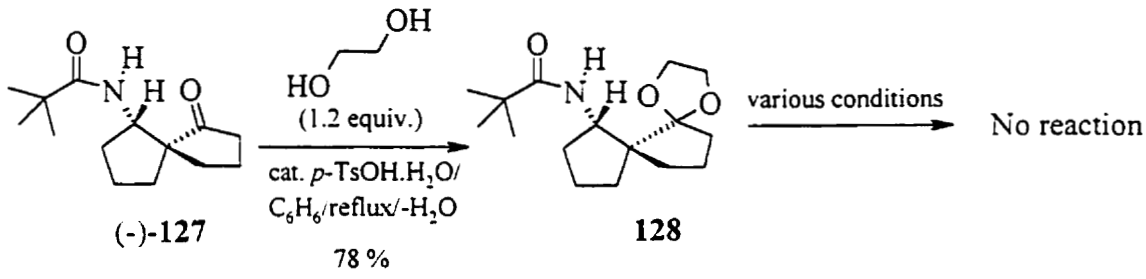


Scheme 2.13.

2.4.1. Attempts to Mimic Solid Supported Chiral Auxiliaries

Recently, a great deal of synthetic organic chemistry has been performed on solid supports. In hopes of entering this field, it was decided to evaluate a model system of (-)-**127** for possible solid supported chemistry as a side project. Due to the trivalency of nitrogen atoms, placing a third substituent onto the nitrogen atom was undertaken in hopes of mimicking a linker which could ultimately be attached to a polymer resin. Removal of the amido proton with base and treatment with a suitable polymer resin mimic electrophile would hopefully provide us access to a chiral auxiliary that then could be used as an alternative in this field. Treatment of (-)-**127** with sodium hydride (NaH, 2 equiv.), at either 0°C or reflux in THF, followed by addition of benzyl bromide (2 equiv., basic alumina filtered) yielded complex mixtures which were believed to be primarily due to substitution of the enolate of the ketone. This was assumed based on the presence of the amido proton in the ^{1}H-NMR spectrum.

It was therefore decided to first protect the carbonyl group as the ketal and repeat the experiment. Compound (-)-**127** was treated with 1.2 equiv. of 1,2-propanediol, using standard conditions.[107] to produce the ketal **128** in 78% yield (Scheme 2.14). Unfortunately, the nitrogen atom could not be alkylated under any of the attempted conditions as seen in Table 2.3. The electrophile was changed to methyl iodide (Entry 7, Table 2.3), in hopes of ruling out steric problems in relation to the benzyl bromide, but this reaction was also unsuccessful. We postulate that the steric bulk of the ketal must interfere either with the anion formation or attack of the anion upon the electrophile.



(-)-127 **128**

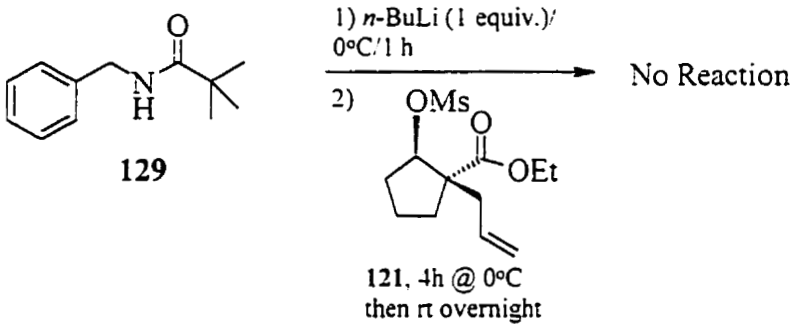
Scheme 2.14.

Table 2.3. Attempted Conditions for the Alkylation of (-)-**127**

Entry	Solvent	Base (equiv.)	Temp. (°C)	Time (h)	Electrophile	Result
1	THF	LiHMDS (2)	0, rt	1,18	BnBr	nr
2	THF	NaH (60%,2)	reflux	18	BnBr	nr
3	DMF	KH (neat,2)	rt, 100	2,18	BnBr	nr
4	THF	NaH (neat,2)	reflux	18	BnBr	nr
5	DMF	NaH (neat,2)	rt, 50	18,18	BnBr	nr
6	DMF	NaH (neat,2)	50,50	18,18	BnBr	nr
7	THF	NaH (neat,10)	reflux	18	MeI	nr

In an effort to overcome the assumed steric problems mentioned above, it was hoped that mesylate **121** could be treated with the anion of *N*-benzyl pivalamide. Therefore, *N*-benzyl pivalamide **129** was treated with 1 equiv. of *n*-butyl lithium (*n*-BuLi) in THF at -78°C and then allowed to warm to 0°C for 0.5 hours. At this point, mesylate **118** (1 equiv.) as a precooled solution in THF was added and the reaction kept at 0°C. After 4 h, no reaction had occurred; therefore the mixture was warmed to room temperature and stirred overnight (Scheme 2.15). Upon workup, ^{1}H-NMR, GC-MS, and TLC revealed no reaction. It was

then concluded that a different method would be required to prepare a trisubstituted nitrogen system for solid support applications and research initiatives then returned to the preparation of an efficient chiral auxiliary for Diels-Alder reactions.



129

Scheme 2.15.

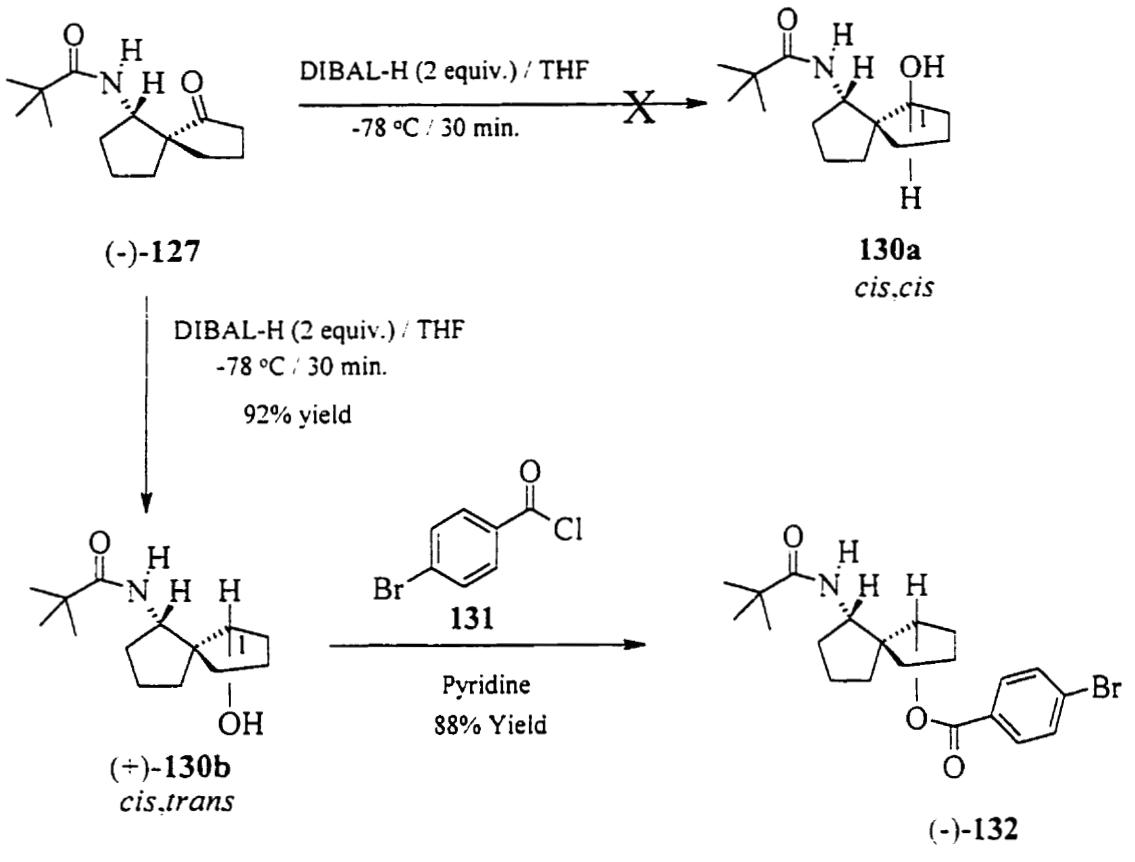
2.5. Attempted Synthesis of *cis,cis*-6-Pivalamidospiro[4.4]nonan-1-ol (130a): Synthesis of *cis,trans*-6-Pivalamidospiro[4.4]nonan-1-ol (+)-130b and Proof of Absolute Stereochemistry

With (-)-**127** in hand, it was hoped that reduction of the ketone would occur from the less hindered side of the spiro system, opposite the large steric bulk provided by the pivalamide, to give the *cis,cis*-amidospiro alcohol **130a** (Scheme 2.16). Initially, DIBAL-H (2 equiv., 1 M solution in THF) was added to a solution of (-)-**127** in THF at –78 °C and stirred for thirty minutes. TLC analysis at this point revealed no starting material remained and the presence of only one product. Column chromatography allowed for the isolation of the reduction product in which the ^{1}H-NMR spectrum revealed only one diastereomer based on the triplet, i.e., overlapping doublet of doublets, for the C**H**-OH. The yield of the reduction was 92%.

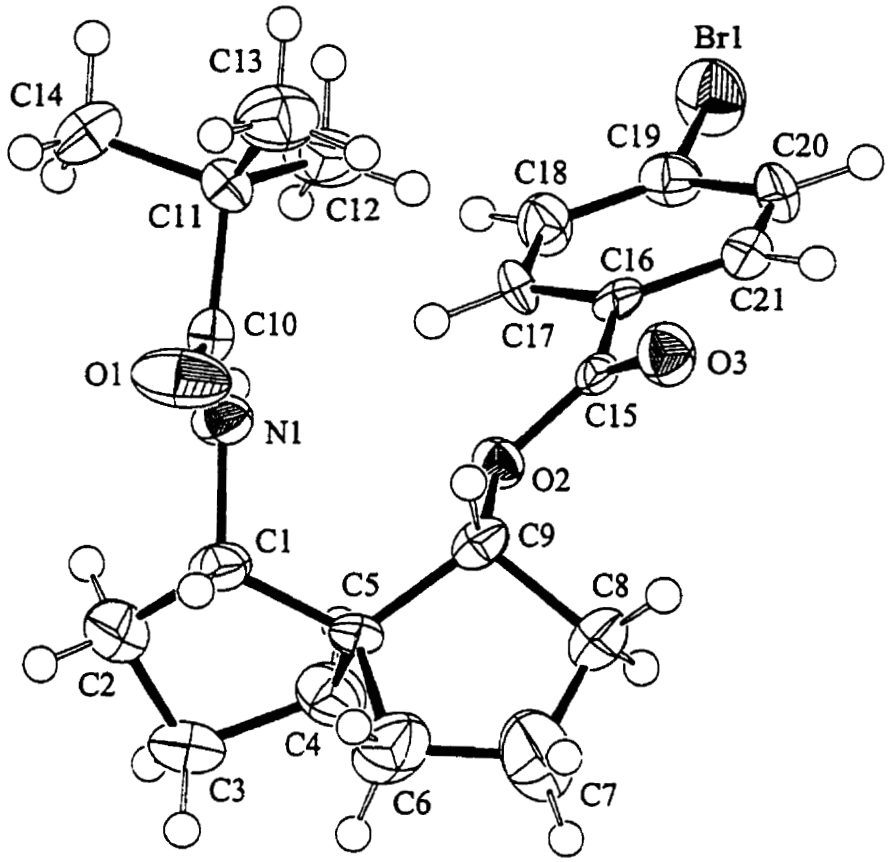
Efforts were then turned to the synthesis of a derivative of **130a** for X-ray analysis in order to confirm the relative stereochemistry at C1. *p*-Bromobenzoyl chloride **131**

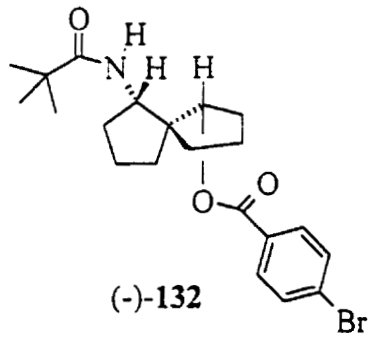
(1.3 equiv.) was placed in pyridine at room temperature for 10 minutes at which point 1 equiv. of compound **130a** was added and the reaction allowed to stir overnight. Acidic workup and column chromatography yielded 88% of the desired product (-)-**132** as a white solid (Scheme 2.16). Recrystallization of the solid from hexanes yielded clear needle-like crystals that were suitable for X-ray analysis.

Unfortunately, X-ray analysis revealed that the incorrect diastereomer had been formed in the reduction of (-)-**127** as seen in Figure 2.3. The X-ray crystal structure indicated that reduction of (-)-**127** with DIBAL-H must have occurred from the top face to produce the *cis,trans*-amido alcohol (+)-**130b** (Scheme 2.16). There may be two possible explanations for this observation. 1) A molecular model of compound (-)-**127** revealed that if the pivalamido proton hydrogen bonds to the ketone, the spiro ring system changes its conformation slightly resulting in the bottom face of the carbonyl becoming partially blocked by a methylene group on the adjacent ring. This results in the top face becoming a pseudo six membered ring as seen in Figure 2.4; 2) The lone pair on the amido nitrogen could coordinate to the reducing agent (DIBAL-H) thereby directing the hydride to the carbonyl group from the top face (Figure 2.4). Whatever the rationale, compound (+)-**130b** was formed exclusively and in good yield. Bijvoet analysis[96] of the crystal structure of (-)-**132** was also performed and provided more evidence for the absolute stereochemistry of spirosystem (+)-**130b**. Therefore, it was decided to use (+)-**130b** as a auxiliary for asymmetric Diels-Alder reactions.


DIBAL-H (2 equiv.) / THF
-78 °C / 30 min.
(-)-127
130a
cis,cis
DIBAL-H (2 equiv.) / THF
-78 °C / 30 min.
92% yield
(±)-130b
cis,trans
131
Pyridine
88% Yield
(-)-132

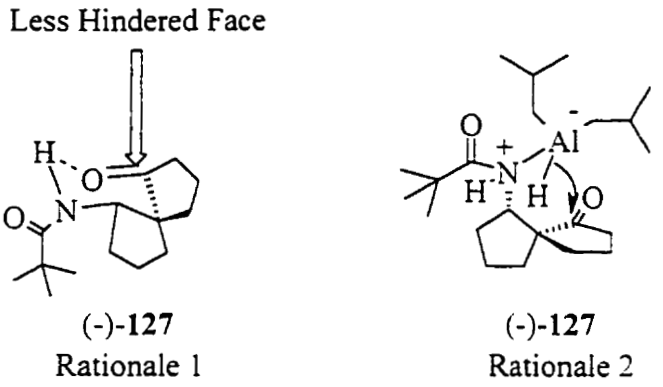
Scheme 2.16.





(-)-**132**

Figure 2.3. X-ray Crystal Structure of (-)-**132**: *p*-Bromobenzoate Derivative of (+)-**130b**



(-)-**127**
Rationale 1

(-)-**127**
Rationale 2

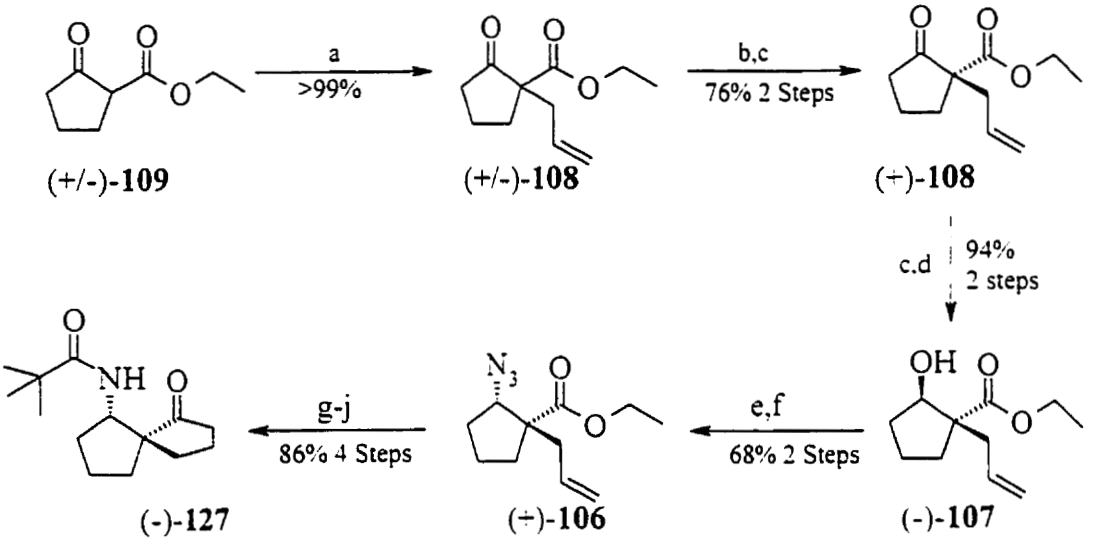
Figure 2.4. Rationale for the Diastereoselective Reduction of (-)-**127**

To date, preparation of the *cis,cis*-amido alcohol (+)-**130a** continues to be a challenge via this route to other workers in the Keay group. Attempts to first remove the amido proton with sodium hydride followed by reduction have proven unsuccessful as has the use of non-coordinating reducing agents, such as sodium borohydride and lithium *t*-butyl aluminum hydride.

2.6. Conclusion

In summary, compound (+)-**130b** can be prepared in 10 steps with a 29% overall yield from (±)-**109** as summarized in Scheme 2.17. Important results which stemmed from this work include: 1) the absolute stereochemistry of the baker's yeast reduction of (±)-**108** was reassigned and the correction published;[95] 2) ring closure using (-)-**107** or (+)-**108**, as published by Thebtaranoth,[99] proved unsuccessful, however, it was found that cyclization of (+)-**106** proceeds smoothly at 0°C in the absence of TMEDA; 3) reduction of (-)-**127** with DIBAL-H produces exclusively (+)-**130b** in excellent yield.

With (+)-**130b** in hand, investigation was then turned to its possible use as a chiral auxiliary for asymmetric Diels-Alder reactions. Esterification of the resultant hydroxyl functionality with various dieneophiles and investigation of their uses as chiral scaffolds in Diels-Alder reactions will be discussed in the following chapter.



a) allyl acetate (**113**), $Pd(PPh_3)_4$, toluene, rt, 18h
b) baker's yeast, CuO, 20% aq. sucrose, 8h
c) Jones' [O], acetone, rt, 15 min.
d) Li $^tBu(i\text{-}Bu)_2Al$-H, THF, -78°C, 4h
e) MsCl, pyridine, 0°C to rt, 18h
f) NaN_3, DMSO, 80°C, 18h
g) LDA, THF, 0°C, 6h
h) silica gel, EtOH, 18 h
i) H_2 (1 atm), EtOH, 18 h
j) pivaloyl chloride (**126**), pyridine, 0°C to rt, 18 h
k) $(i\text{-}Bu)_2Al$-H, THF, -78°C, 30 min

Scheme 2.17.

Chapter 3

3. The Use of *cis,trans*-Pivalamido Alcohol (+)-130b as a Chiral Auxiliary for Diastereoselective Diels-Alder Reactions

3.1. Introduction

With *cis,trans*-pivalamido alcohol (+)-**130b** in hand, it can be seen that esterification with an olefin containing moiety would yield a chiral substrate bound dienophile suitable for diastereoselective Diels-Alder reactions. Removal of the adduct from the chiral auxiliary would then hopefully lead to products with high enantiomeric excesses. The following chapter will discuss the synthesis of three different dienophiles from (1*R*,5*S*,6*S*)-(+)-6-(2,2-dimethylpropamido)spiro[4.4]nonan-1-ol ((+)-**130b**) and the results of their Diels-Alder reaction with several dienes.

3.2. Synthesis of Dienophiles for Diels-Alder Reactions

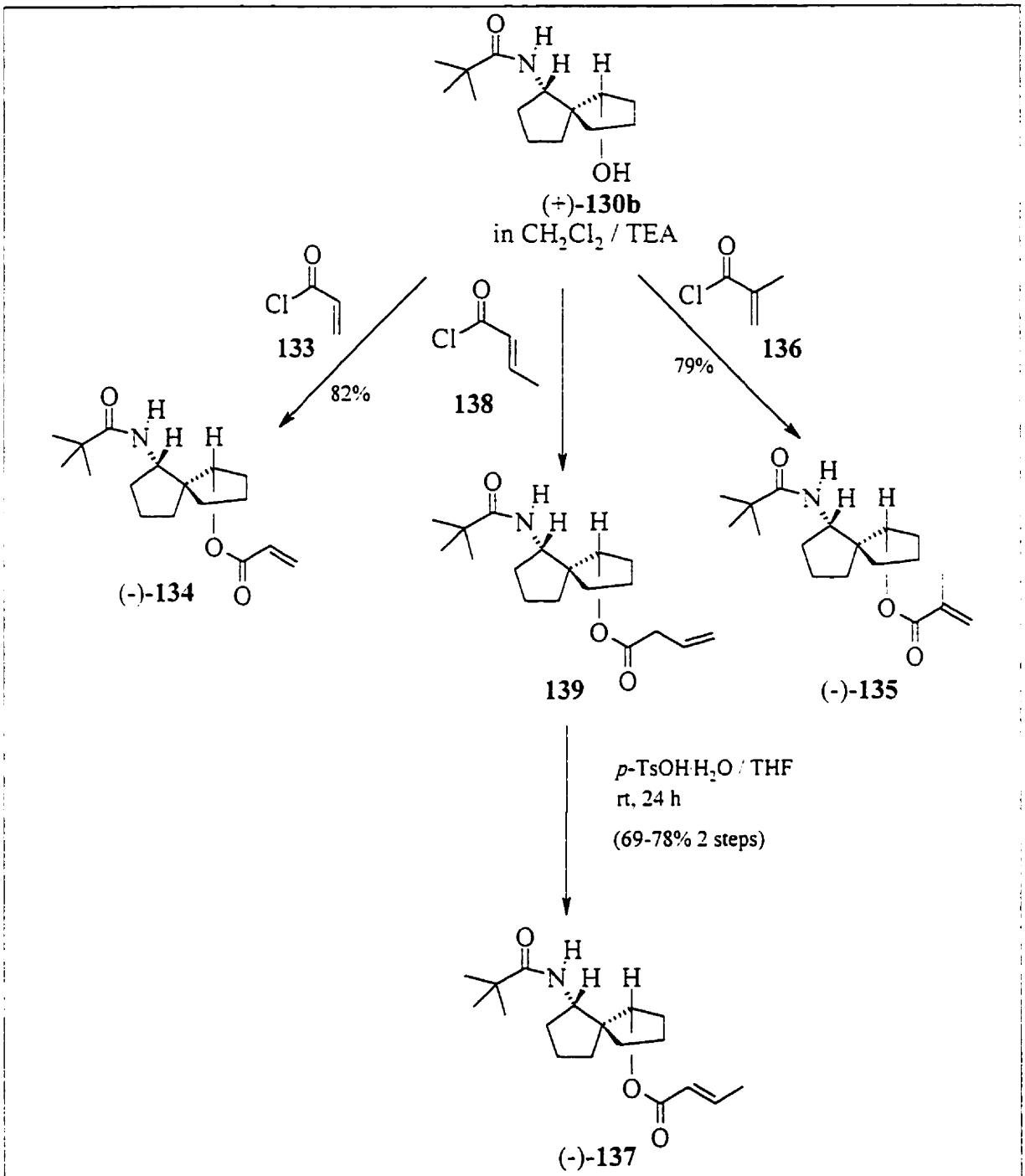
The most common dieneophiles used in the literature for testing new chiral auxiliaries are the acrylate, methacrylate, and crotonate moieties. It was therefore decided to use these functionalities for the testing of (+)-**130b** as a chiral auxiliary. Simple catalytic nucleophilic substitution conditions were used for this purpose. Compound (+)-**130b** (1 equiv.) was dissolved in pyridine at 0°C where 1 equiv. of acryloyl chloride (**133**) was added. Immediately, a thick orange paste resulted and the reaction was allowed to stir for 6 h. TLC analysis at this point revealed no reaction as stirring had ceased due to the viscosity of the reaction mixture. Therefore, CH_2Cl_2 was added in hopes of dissolving the thick mixture, however after allowing the mixture to warm to room temperature overnight, TLC revealed mostly starting material. Acidic workup and column chromatography allowed for only a 17% isolated yield of the desired product (-)-**134** (Scheme 3.1).

Therefore, similar conditions using triethylamine (TEA) in place of pyridine were attempted. Compound (+)-**130b** (1 equiv.) was dissolved in CH_2Cl_2 at 0°C and 2 equiv. of TEA were added followed by 2 equiv. of **133**. The reaction mixture remained clear and after allowing the reaction to warm to room temperature overnight, TLC analysis revealed no starting material. Acidic workup and column chromatography allowed for 82% isolated yield of (-)-**134**. The shift of the C**H**-O proton from δ 4.02 ppm (1H, dd) to δ 5.10 ppm (1H, m) and the presence of a vinyl group attached to a carbonyl moiety (δ 6.43 ppm (1H, dd); δ 6.13 (1H, dd); δ 5.87 (1H, dd)) confirmed the presence of (-)-**134**. These reaction conditions were then repeated for the synthesis of the methacryl derivative ((-)-**135**, 79% yield) using methacryloyl chloride (**136**) and the crotonoyl derivative ((-)-**137**, 69-78% yield)) using crotyl chloride (**138**) as seen in Scheme 3.1.

Methacryl derivative (-)-**135** was confirmed by the ^{1}H-NMR shift of the C**H**-O proton from δ 4.02 ppm (1H, dd) to δ 5.07 ppm (1H, dd) and the presence of the α-methyl vinyl group at δ 6.11 (1H, s), δ 5.58 (1H, s), and δ 1.95 (3H, s).

Scheme 3.1 reveals that an extra step was required for the synthesis of (-)-**137**. ^{1}H-NMR analysis showed that the isolated product of the esterification was the unconjugated product **139**. Migration of the double bond into conjugation was performed by placing **139** in THF and adding 0.5 equiv. of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) and allowing the mixture to stir overnight at room temperature to give 69-78% overall yield of (-)-**137** from (+)-**130b**. The structure of compound (-)-**137** was verified by the ^{1}H-NMR shift of the C**H**-O proton from δ 4.02 ppm (1H, dd) to δ 5.07 ppm (1H, dd) and the presence of the vinyl protons and the β-methyl group at δ 6.99 ppm (1H, dq), δ 5.85 (1H, dq), and δ 1.89 (3h, dd) respectively.

With (-)-**134**, (-)-**135**, and (-)-**137** in hand, the determination of the appropriate Lewis acid to employ as a catalyst, as well as the number of equivalents to use, was investigated.



Scheme 3.1.

3.3. Low Temperature NMR Binding Studies

Looking back at the previous results obtained in our laboratory for Lewis acid catalysed Diels-Alder reactions with spirodiols like **92** (Ch. 1, Table 1.13, p. 34), it was decided that boron trichloride (BCl_3) should be tried first as it had earlier provided the best results. Since compound **92** was a diester spiro system and (-)-**134** an amido ester, it was decided to investigate the binding selectivity of BCl_3 to help determine the appropriate number of equivalents of BCl_3 that should be used in the Diels-Alder reaction. This was accomplished by variable temperature ^{1}H-NMR experiments.

Methyl acrylate (**140**) was chosen as a model system for proton shift behavior upon binding with BCl_3 (Figure 3.1). It is known that esters prefer to sit in a *cisoid* geometry with respect to the C=O and C=C bonds in the absence of Lewis acid at room temperature and in a *transoid* geometry in the presence of a Lewis acid.[108] Compound **140** was dissolved in CD_2Cl_2, placed in a dry NMR tube, and sealed with a rubber septum. The temperature of the spectrometer probe was set to –78°C, the temperature at which all Diels-Alder reactions were to be performed, and the ^{1}H-NMR spectra recorded. Figure 3.1 reveals that upon addition of one equivalent of BCl_3, all olefinic protons shift considerably (compare spectrums (a) and (b)). Next, investigation of (-)-**134** was performed under similar conditions to investigate its behavior under Lewis acidic conditions.

Compound (-)-**134** was used in place of **140** as described in the preceding paragraph. ^{1}H-NMR spectra were then taken with 1 and 2 equiv. of BCl_3 added and the results can be seen in Figure 3.2. These spectra reveal the first equivalent of BCl_3 binds to the amide, which was indicated by the significant shift of the amido proton (H_d) from δ 6.62 ppm (1H, d) to δ 10.5 ppm (1H, d) and the insignificant shift of the olefinic protons (H_{a-c}, compare

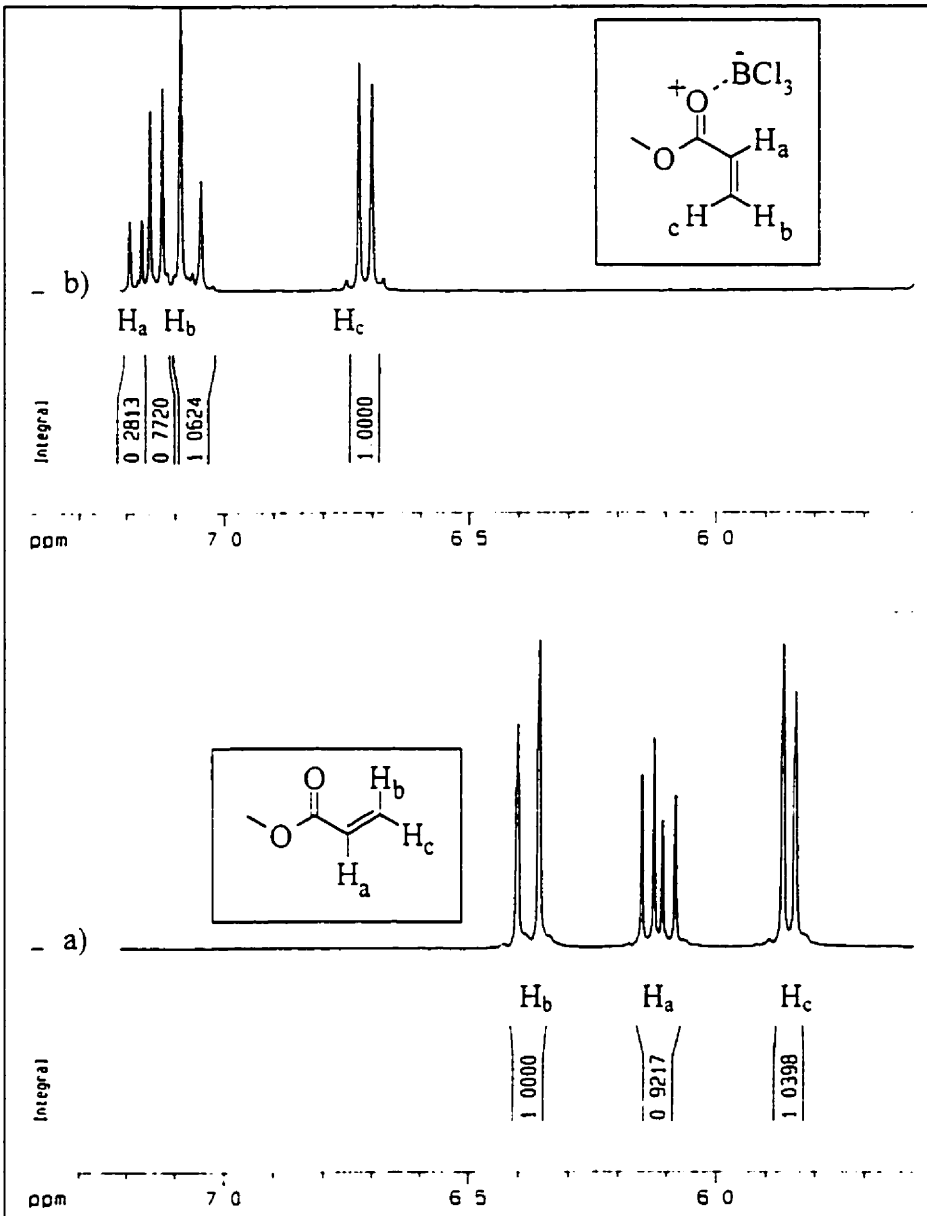


Figure 3.1. NMR Results of **140** with a) no BCl_3; b) 1 equiv. BCl_3 at -78°C in CD_2Cl_2

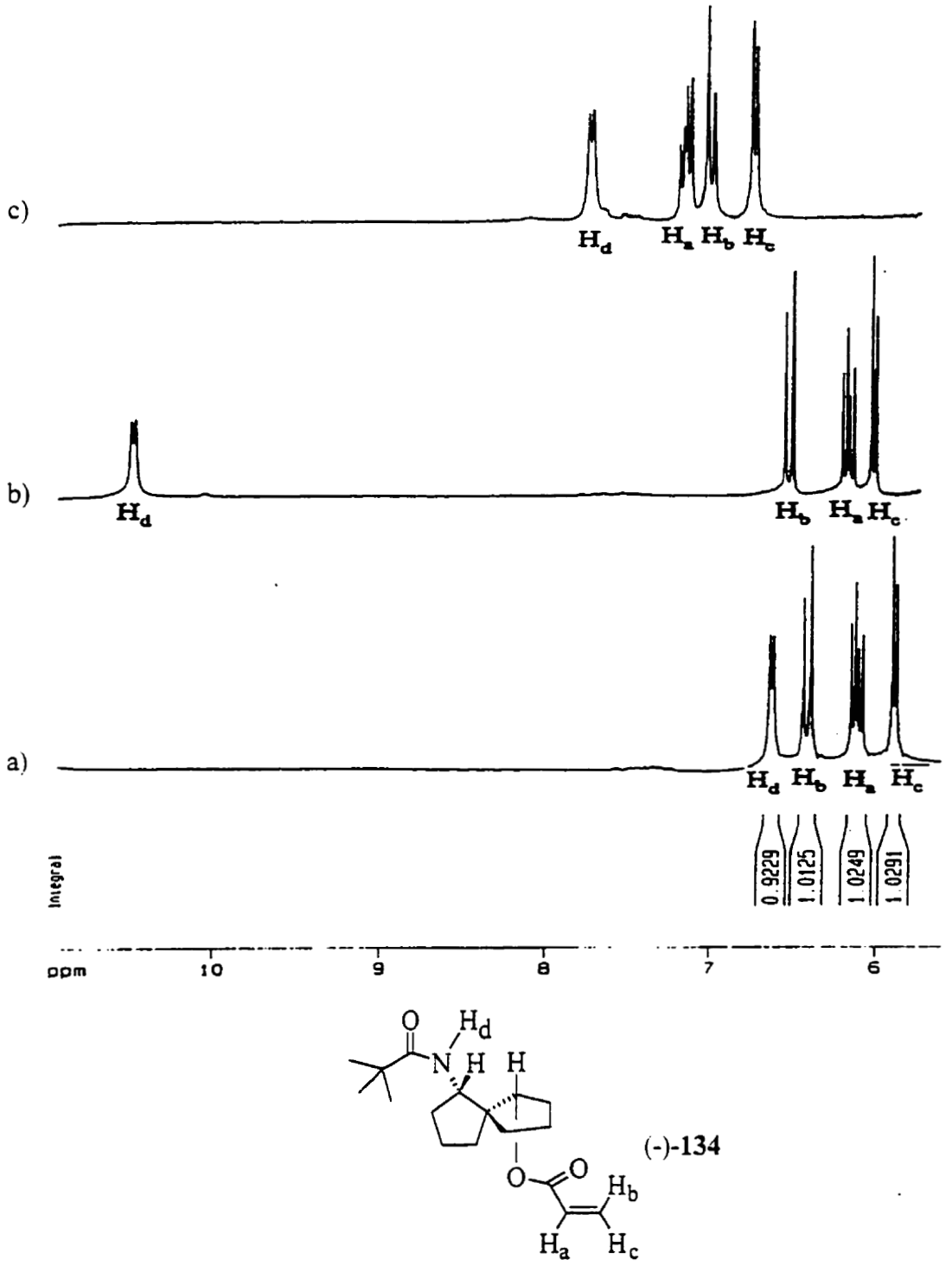


Figure 3.2. NMR Results of (-)-**134** with a) no BCl_3; b) 1 equiv. BCl_3; and c) 2 equiv. BCl_3 at –78°C in CD_2Cl_2

spectrum a and b). However, upon addition of the second equivalent of BCl_3 (spectrum c), all three olefinic protons shift downfield with H_a shifting most significantly, as with the model system **140** (Figure 3.1), from δ 6.12 ppm (1H, dd) to δ 7.17 ppm (1H, dd). H_b from δ 5.89 ppm (1H, dd) to δ 6.75 ppm (1H, dd), and H_c from δ 6.50 ppm (1H, dd) to δ 7.02 ppm (1H, dd). An interesting observation is that H_d shifts upfield from δ 10.5 ppm (1H, d) to 7.75 ppm (1H, d). A possible explanation is given in the following sequence:

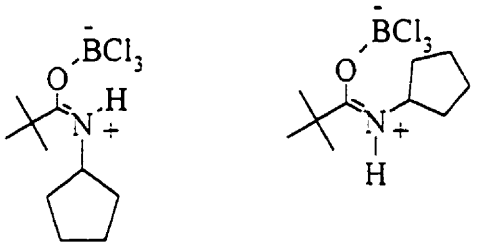
1) Amides are known to have double bond character due to the overlap of the nitrogen lone pair with the π electrons in the carbonyl group.[5e] Thus, amides can sit in a *cisoid* or *transoid* geometry (with respect to the carbonyl O and *N*-alkyl groups) having a barrier to rotation on the order of 20 kcal/mol.[109] This can be seen for *N*-methylacetamide (**141**) in Scheme 3.2, where the equilibrium lies towards the *cisoid* geometry (97:3 *cisoid*:*transoid*, experimental values) at room temperature. Semi-empirical calculations[110] (PM3) for BCl_3 bound cyclopentyl pivalamide (**142**) shows that the *transoid* geometry is preferred, possibly due to an unfavorable steric interaction between the cyclopentyl group and the BCl_3 in the *cisoid* geometry, or a favorable agostic interaction between hydrogen and boron (Scheme 3.3). At this point, it must be noted that any calculations performed here, or in the following pages, are done in the gas phase and the level of theory does not take into account π-π interactions.

With this knowledge in hand, and the fact that amides are known to be more basic than esters,[111] we believe the first equivalent of BCl_3 coordinates to the amide carbonyl group, which results in the significant deshielding of the amido proton (H_d) due to hydrogen bonding with the ether oxygen of the ester. The semi-empirical PM3 minimal energy conformer of (-)-**134** can be seen in Figure 3.3, where the amido hydrogen-ether oxygen

bond length is only 1.887 Å and the amide can be seen adopting the *transoid* geometry, as suggested by the calculations seen in Scheme 3.3. Figure 3.3 also reveals the ester in the preferred *cisoid* geometry.[108]

141		**141**
97	:	3
cisoid		*transoid*

Scheme 3.2.



142	**142**
H_f (kcal/mol) = -202.789	-197.352
transoid	*cisoid*

Scheme 3.3.

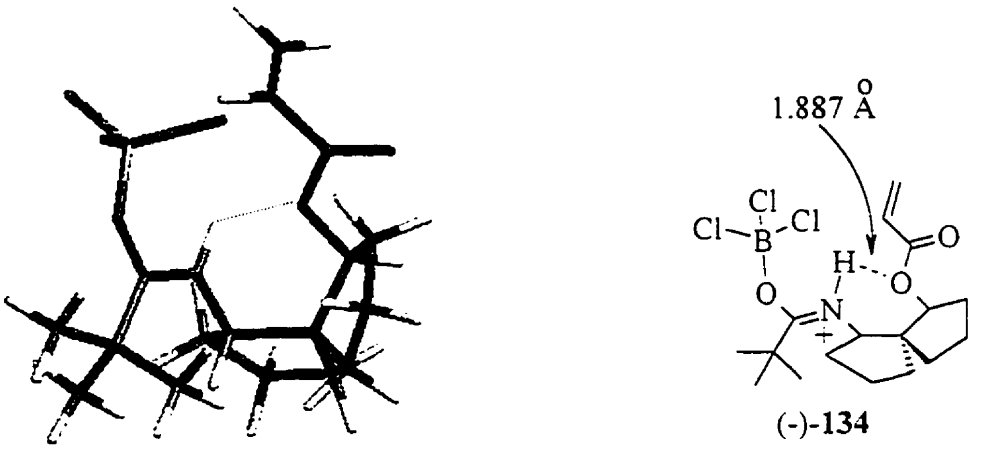
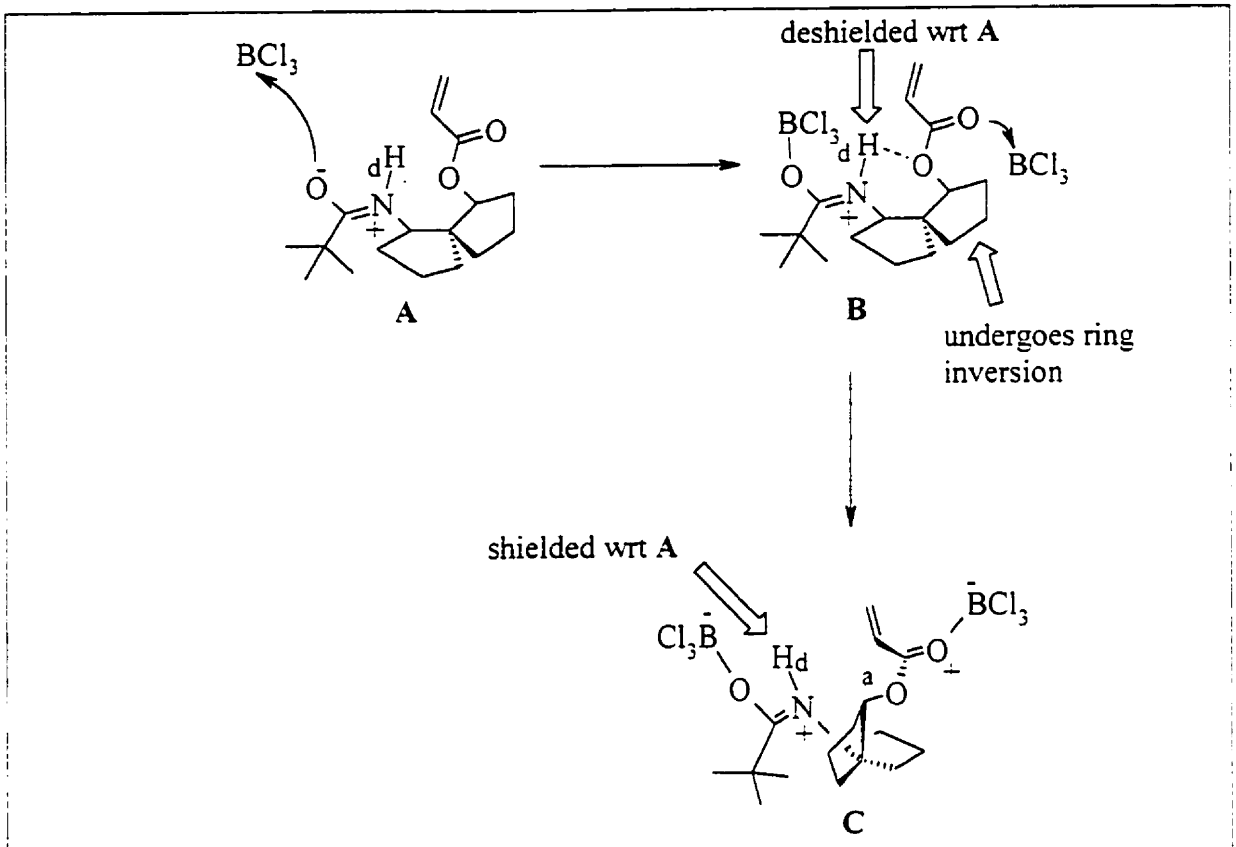
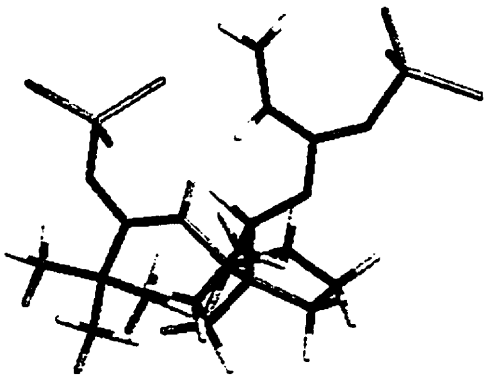


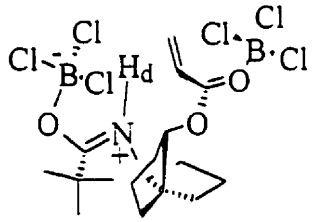
Figure 3.3. The Low Energy Conformer of Mono-BCl_3 Substituted (-)-**134**

2) Semi-empirical calculations[110] (PM3) for di-BCl_3 substituted (-)-**134** reveal that when the BCl_3 coordinates to the ester, a ring envelope flip occurs (**B** to **C**, Scheme 3.4) to minimize steric constraints, resulting in the hydrogen bond between H_d and the ether oxygen of the ester to be destroyed, which in turn, results in an upfield shift of H_d. The breaking of this hydrogen bond could also be due to the lowered basicity of the ether oxygen of the ester due to boron complexation. However, the signal for H_d remains further downfield than its original position due to the complexation of the amide to the first equivalent of BCl_3. The minimized di-BCl_3 structure can be seen in Figure 3.4 and the overall process of these experiments in Scheme 3.4.



Scheme 3.4.





(-)-**134**

Figure 3.4. The Low Energy Conformer of Di-BCl_3 Substituted (-)-**134**

From these results, it was concluded that two equivalents of BCl_3 would be required to activate the dienophile for Diels-Alder reactions.

3.4. Diels-Alder Reactions of (-)-134, (-)-135, and (-)-137 with Various Dienophiles

Using a modified procedure to that used in our laboratory for Diels-Alder reactions,[1a] dienophiles (-)-**134**, (-)-**135**, and (-)-**137** were reacted with various dienes in order to evaluate the asymmetric induction created by our novel spiro system **95**. Compound (-)-**134**, (-)-**135**, or (-)-**137** were dissolved in CH_2Cl_2 and placed in a dry round bottomed flask containing crushed, flame-dried, molecular sieves. The solution was then cooled to –78°C under a N_2 atmosphere where 2 equiv. of BCl_3 (1 M in CH_2Cl_2) were added via syringe. After stirring for 15 minutes, 5 equiv. of pre-cooled diene were added dropwise down the side of the flask. The reaction was maintained at –78°C for 8 h, at which point TLC analysis revealed no staring material. The reaction was then filtered through a silica gel plug packed in CH_2Cl_2 and the plug rinsed with Et_2O. The organic solvents were then removed *in vacuo* and the residue submitted to column chromatography to provide the cycloadducts. Analysis of the cycloadduct mixture via 400 MHz ^{1}H-NMR was then performed to determine the product ratios.

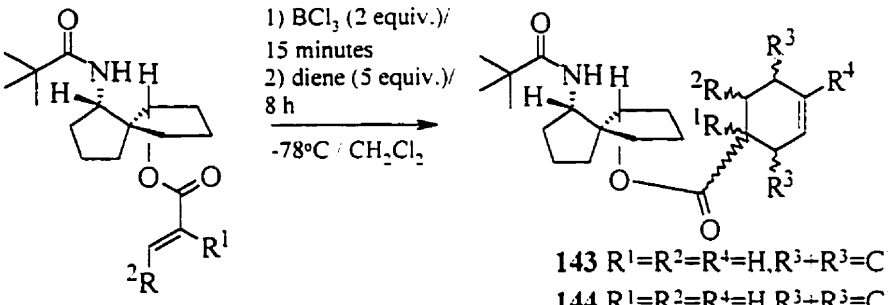
A summary of the results obtained can be seen in Table 3.1, where moderate to excellent diastereomeric ratios (2:1 – 100:0) can be seen with low to excellent de values (21% - >98%). Reaction of (-)-**134** with cyclopentadiene (**7**) or cyclohexadiene provided 100:0 *endo*:*exo* ratios with de values >97%. This selectivity drops dramatically upon reaction with furan (**16**) to only a 2:1 *endo*:*exo* ratio; however, moderate de values were obtained (79% *endo* de, 78% *exo* de). It was found that the products of the reaction between

(-)-**134** and isoprene (**62**) did not provide a ^{1}H-NMR handle for determination of de values. Therefore, the stereoselectivity of this reaction was not determined by this method.

3.4.1. Diastereomeric Analysis of Cycloadducts

An example of the use of ^{1}H-NMR spectroscopy for the purpose of measuring the diastereoselectivity can be seen in Figure 3.5, where reaction of (-)-**134** with cyclopentadiene (**7**) was performed under Lewis acid catalysed conditions at –78°C to give one *endo* product (>97% de) and a >99:1 *endo*:*exo* ratio (spectrum a). This same reaction was performed with no catalyst from 0°C to room temperature as it is known that both *endo* and both *exo* products are formed under these reaction conditions.[40] Spectrum (b) (Figure 3.5) shows the peaks for both *endo* and both *exo* products. Integration of the peaks in spectrum (a) indicated the *endo* isomer was preferentially formed in >97% de.

Table 3.1. Results of Diels-Alder Reactions Using (-)-**134**, (-)-**135**, and (-)-**137** as Dienophiles with Various Dienes



(-)-**134** $R^1 = R^2 = H$
(-)-**135** $R^1 = Me$, $R^2 = H$
(-)-**137** $R^1 = H$, $R^2 = Me$

143 $R^1=R^2=R^4=H, R^3+R^3=CH_2$
144 $R^1=R^2=R^4=H, R^3+R^3=CH_2\text{-}CH_2$
145 $R^1=R^2=R^4=H, R^3+R^3=O$
146 $R^1=R^2=R^3=H, R^4=Me$
147 $R^1=Me, R^2=R^4=H, R^3+R^3=CH_2$
148 $R^1=R^4=H, R^2=Me, R^3+R^3=CH_2$
one or more diastereomers

SM	Diene	Product & Yield	*Endo*:*Exo* Ratio	de *Endo*	de *Exo*
(-)-**134**		**143** 70%	>99:1	>97%	-
(-)-**134**		**144** 82%	>99:1	>97%	-
(-)-**134**		**145** 74%	2:1	79%	78%
(-)-**134**		**146** 79%	na	na	na
(-)-**135**		**147** 72%	>99:1	21%	-
(-)-**137**		**148** 81%	8:1	86%	64%

na = not applicable

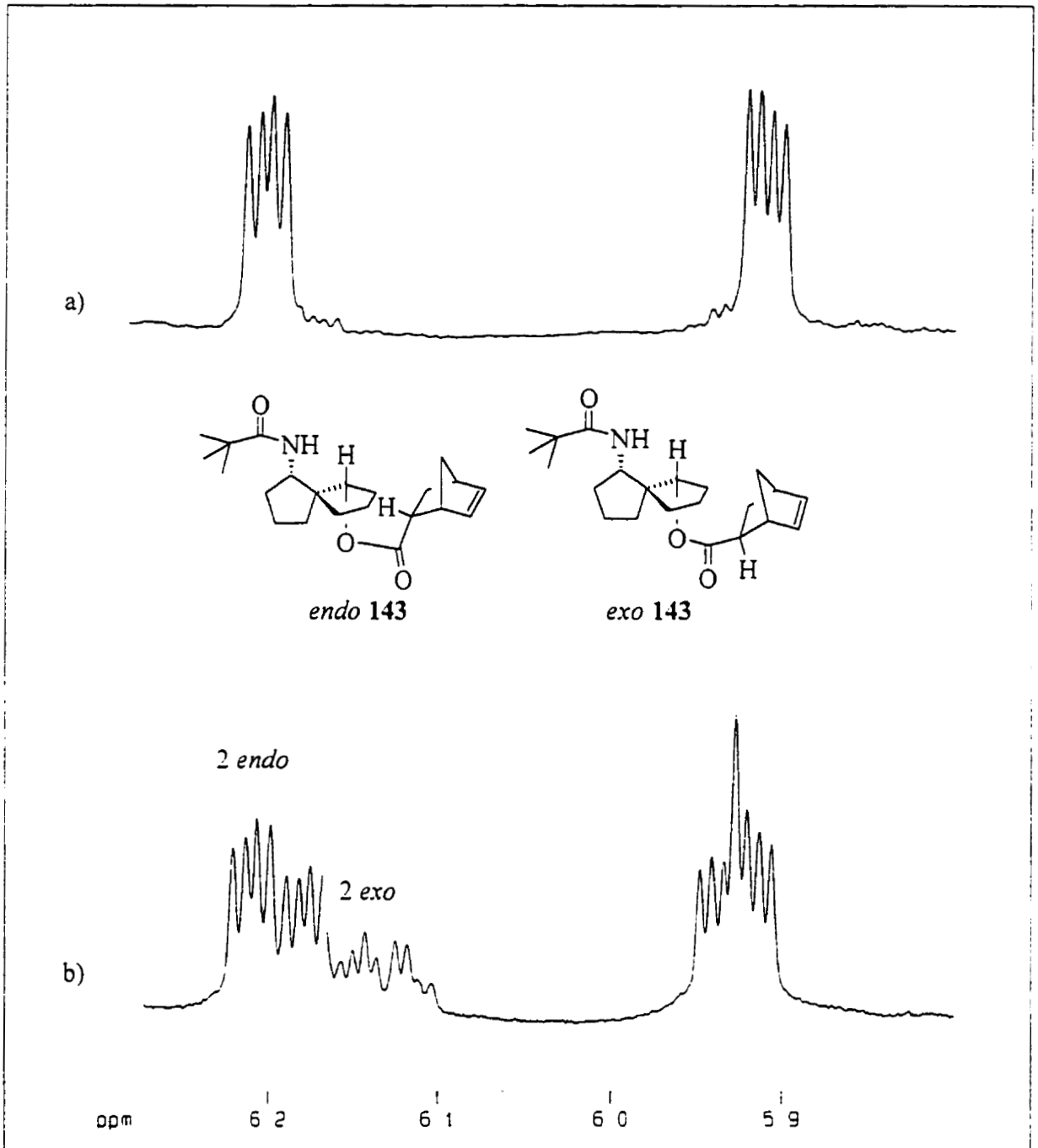
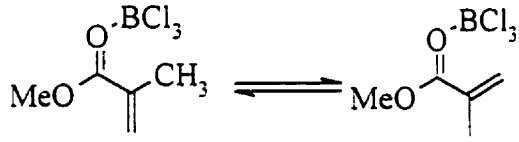


Figure 3.5. 400 MHz ^{1}H-NMR Spectra of Cycloadducts from Reaction of (-)-**134** with **7**: a) Catalysed by BCl_3 at –78°C; and b) no BCl_3 from 0°C to Room Temperature

A less successful example is shown in Figure 3.6. Reaction of (-)-**134** with furan (**16**) provided only a 2:1 *endo*:*exo* ratio with 79% *endo* de and 78% *exo* de. Signals for these diastereomers are readily identifiable for determination of these values where peaks A and B represent the olefin signals due to the two *endo* diastereomers. Peaks C and D represent the signals for the protons α to the carbonyl functions in the two *exo* diastereomers.

Reaction of methacryl derivative (-)-**135** with **7** reveals a detrimental effect on diastereoselectivity. An excellent *endo*:*exo* ratio (100:0) was achieved, however, only a 21% *endo* de was observed. Attempts to improve this result by further cooling the reaction to -93°C were unsuccessful and produced no product due to the freezing of the solvent. We postulate that the α-methyl group is similar in steric bulk to the methylene group. This forces the existence of two different conformers which results in the poor *endo* de. These two conformers have been found to have similar energies at the semi-empirical (PM3) level[110] using methyl methacrylate (**149**) as a model (Scheme 3.5). Arguably, this result can be verified by the results obtained for (-)-**137**.



149	**149**
H_f (kcal/mol) = -190.185	-191.740

Scheme 3.5.

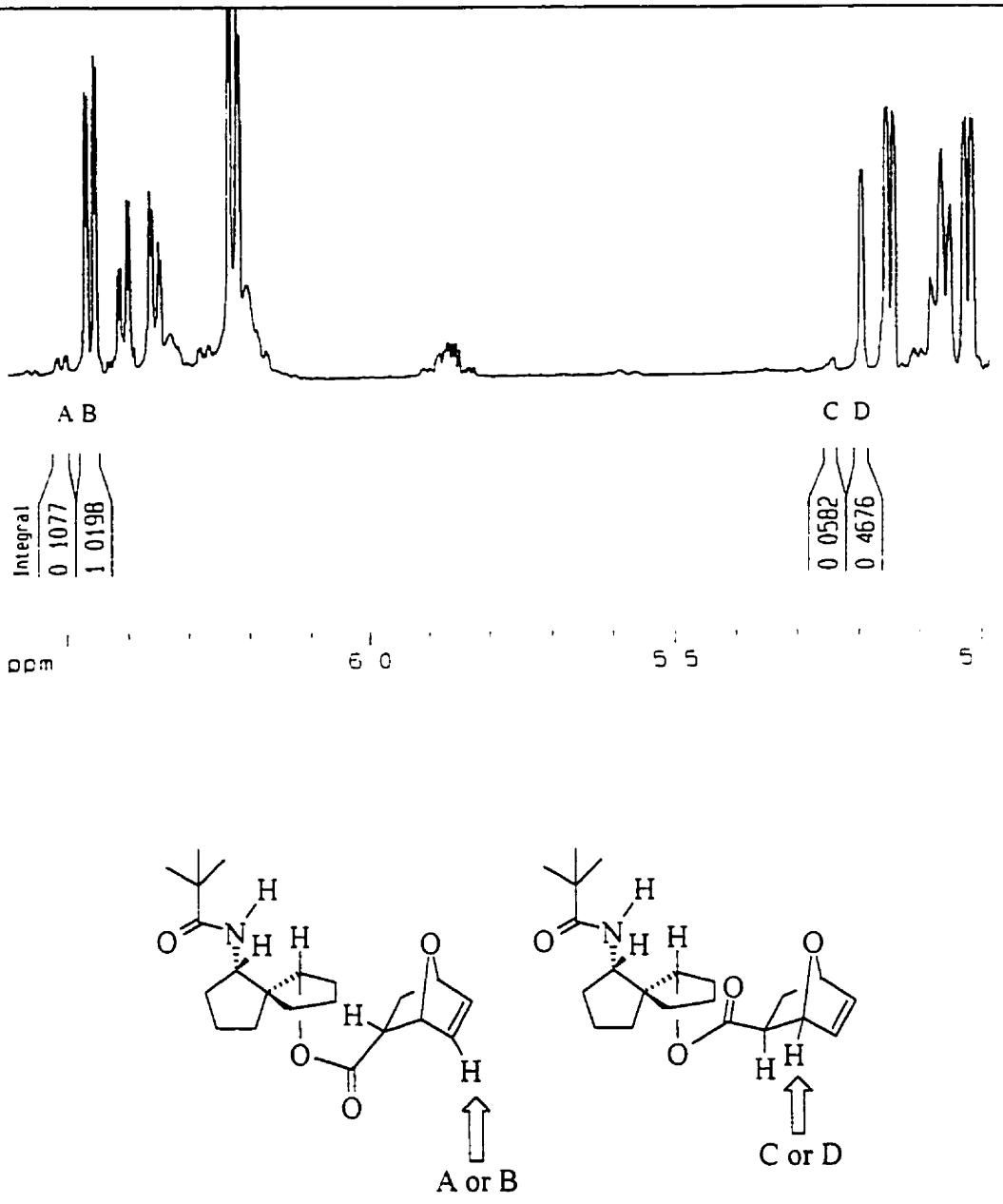


Figure 3.6. Reaction of (-)-**134** with Furan (**16**) in a Diels-Alder Reaction to

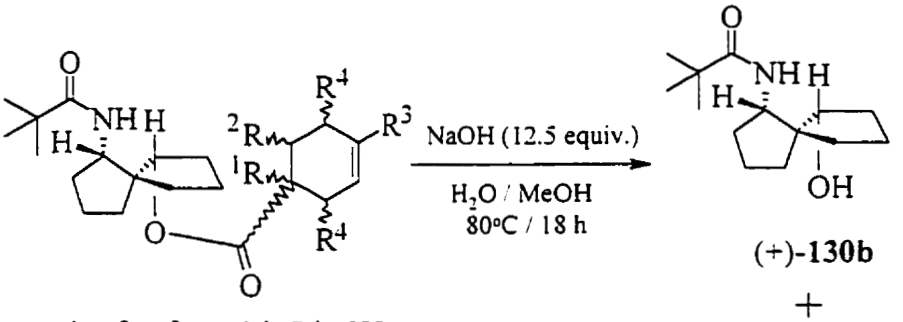
Reaction of crotyl derivative (-)-**137** with **7** reveals a moderate *endo*:*exo* ratio (8:1) with a good *endo* de value of 86% as compared to that using (-)-**135** (21% *endo* de). This confirms that α-methyl groups detrimentally affect the *endo* diastereoselectivity of these reactions. It also appears that β-methyl groups result in poorer *endo*:*exo* selectivity.

3.4.2. Saponification of Cycloadducts 143-148

As mentioned previously, one of the reasons for having an amido ester, instead of a diester similar to **92**, was to be able to selectively cleave the ester cycloadduct such that the chiral auxiliary could be recovered and reused. Several methods were attempted for the saponification of cycloadducts **143-148**. Initial attempts using lithium hydroxide in a mixture of THF and water (H_2O)[112] resulted in incomplete saponification as did a mixture of sodium hydroxide (NaOH, 2 M in H_2O) in THF and water.[113] Complete saponification to the free acid and (+)-**130b** was readily achieved upon reaction with 12.5 equiv. of NaOH (2.5 M in H_2O) and methanol (MeOH) and heating to 80°C for 18 hours.[114] Acidic workup at 0°C, extraction with ethyl acetate, and column chromatography provided the free acids **150-155** in good yield and recovery of the chiral auxiliary (+)-**130b**. Optical rotations of the free acids were then performed and compared to known values for determination of the absolute stereochemistry and enantiomeric excess.

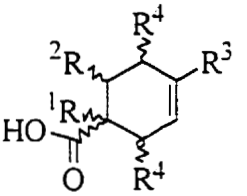
The yields for the saponification and absolute configuration of the free acids **150-155** can be seen in Table 3.2. These results show that the diastereomeric values determined by ^{1}H-NMR matched optical purity values within 1%, thereby confirming these results. The absolute stereochemistry of the major endo adducts was found to be *R* in all cases. The following section will attempt to rationalize this observation.

Table 3.2. Results for the Saponification of Cycloadducts **143-148**: Yields of (+)-**130b** as well as the Yields and Absolute Configurations of **150-155**



143a $R^1=R^2=R^3=H$, $R^4+R^4=CH_2$
144a $R^1=R^2=R^3=H$, $R^4+R^4=CH_2-CH_2$
145a $R^1=R^2=R^3=H$, $R^4+R^4=O$
b $R^1=R^2=R^3=H$, $R^4+R^4=O$
146 $R^1=R^2=R^4=H$, $R^3=Me$
147a $R^1=Me$, $R^2=R^3=H$, $R^4+R^4=CH_2$
148a $R^1=R^3=H$, $R^2=Me$, $R^4+R^4=CH_2$
b $R^1=R^3=H$, $R^2=Me$, $R^4+R^4=CH_2$

a corresponds to *endo* isomers
b corresponds to *exo* isomers



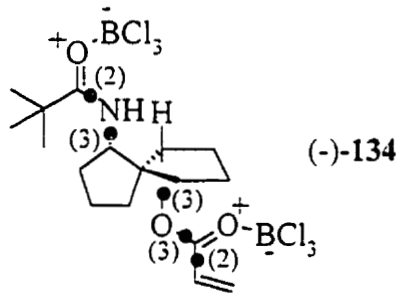
(+)-**150a** $R^1=R^2=R^3=H$, $R^4+R^4=CH_2$
(+)-**151a** $R^1=R^2=R^3=H$, $R^4+R^4=CH_2-CH_2$
152a $R^1=R^2=R^3=H$, $R^4+R^4=O$
b $R^1=R^2=R^3=H$, $R^4+R^4=O$
(+)-**153** $R^1=R^2=R^4=H$, $R^3=Me$
154a $R^1=Me$, $R^2=R^3=H$, $R^4+R^4=CH_2$
(+)-**155a** $R^1=R^3=H$, $R^2=Me$, $R^4+R^4=CH_2$
155b $R^1=R^3=H$, $R^2=Me$, $R^4+R^4=CH_2$

Adduct	Yield Acid (%)[a]	Yield (+)-130b (%)	Product (% ee)[a]	Product $[\alpha]_D$	Lit. Value $[\alpha]_D$, (*R*,*S*)[f]
143	79	81	(+)-**150a** (>98%)	+69.2	+68.6(*R*)[115]
144	87	85	(+)-**151a** (>98%)	+34.2	+34.2(*R*)[116]
145	78	84	**152** (-)[d]	-	-
146	81[b]	82	(+)-**153** (92%)[b]	+98.4	+107(*R*)[117]
147[c]	-	-	-	-	-
148	82	86	(+)-**155a**[e] (86%)	+134	+116(*R*)[118]

a) *endo* adducts only; b) no *endo*/*exo* possible, enantiomers only; c) due to low selectivity, saponification was not performed; d) *endo* and *exo* acids could not be separated; e) no *exo* adduct isolated; f) reference to known material

3.5. Rationale for *R* Stereochemistry

As seen in Table 3.2, the absolute stereochemistry of the free acids was found to be *R* in all of the cases where it could be determined. This section will present the rationale for this observation based on PM3 semi-empirical calculations.[110] A conformational search was done using Spartan on the di-BCl_3 coordinated (-)-**134** with rotation around the bonds marked as seen in Figure 3.7. A total of one hundred and sixty-two initial conformations were minimized to provide a set of twenty-seven minimized structures. Only the lowest eight structures were analyzed further as they made up >97% of the Boltzman distribution. The results for the low eight conformations are shown in Table 3.3



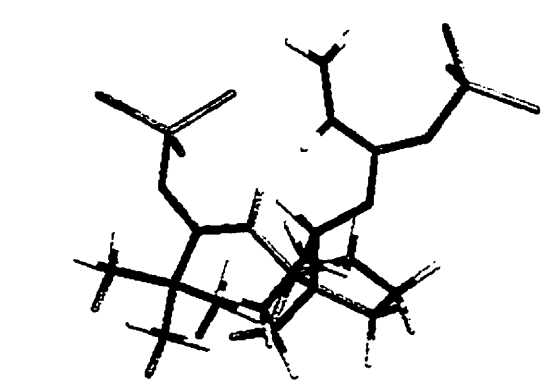
(-)-**134**

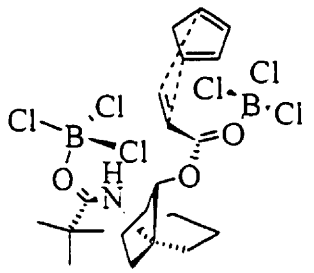
Figure 3.7. Structure Used for Spartan PRO Semi-Empirical Calculations.[110] Rotated Bonds are Marked with a ● and the Number of Rotations in Parentheses

Table 3.3. The Boltzman Distribution for the Eight Lowest Energy Conformers of (-)-**134**

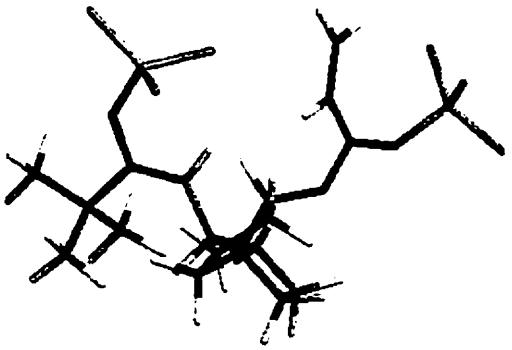
Entry	-E (cal / mol)	-E / RT	$e^{-E/RT}$ (x 10^{201})	$\frac{e^{-E/RT}}{\Sigma e^{-E/RT}}$ (%)	Abs. Config.
1	382477.508	468.7914	392.2	49.08	*R*
2	381969.240	468.1684	210.4	26.32	*R*
3	381085.292	467.0850	71.19	8.909	*S*
4	380766.729	466.6945	48.18	6.029	*R*
5	380141.582	465.9283	22.39	2.802	*R*
6	380006.804	465.7631	18.98	2.375	*R*
7	379368.164	464.9803	8.678	1.086	*R*
8	379131.653	464.6905	6.494	0.813	*R*
		sum =	778.5	97.4	

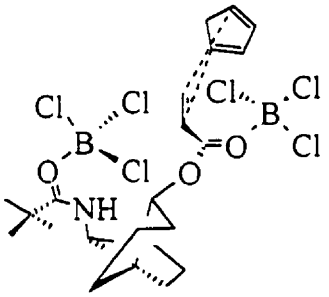
Figures 3.8 depicts the Spartan[110] generated images of (-)-**134** (Entries 1-8, Table 3.3) on the left next to their proposed *endo* transition states with cyclopentadiene (**7**).



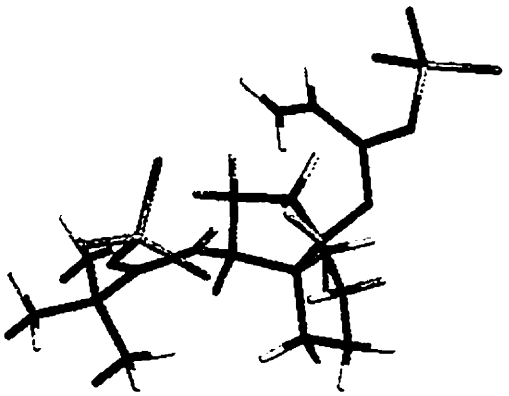


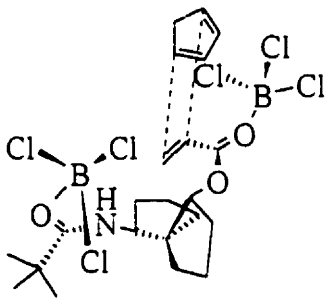
Entry 1: Yields *R*
49.08% Distribution





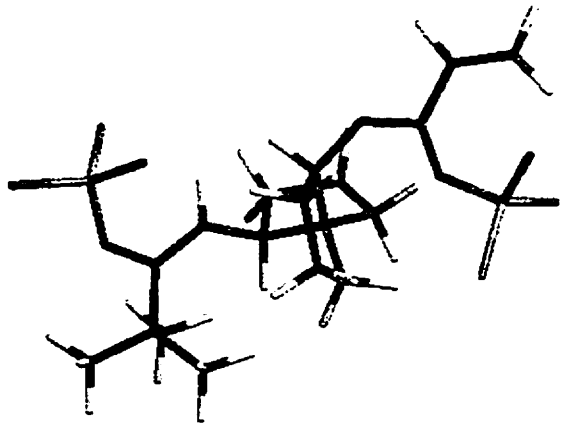
Entry 2: Yields *R*
23.32% Distribution

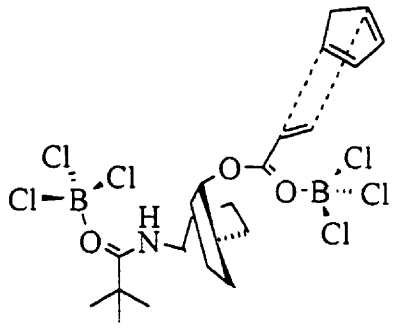




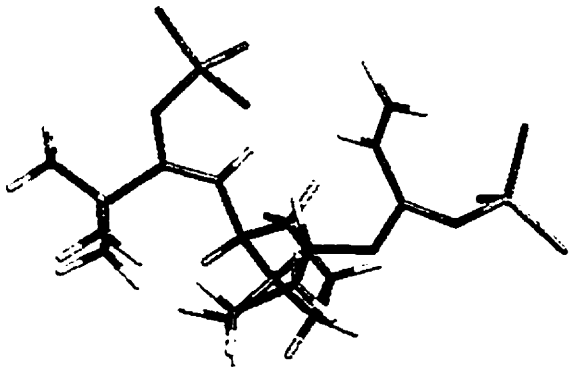
Entry 3: Yields S
8.909% Distribution

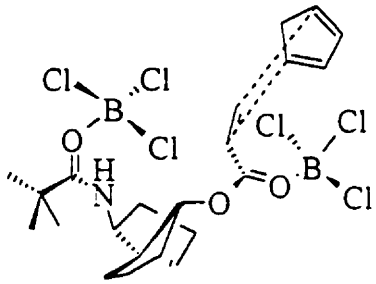
Figure 3.8.1.: Compound (-)-134 Conformers 1-3 (left) and Proposed *endo* Transition State with 7 (right)



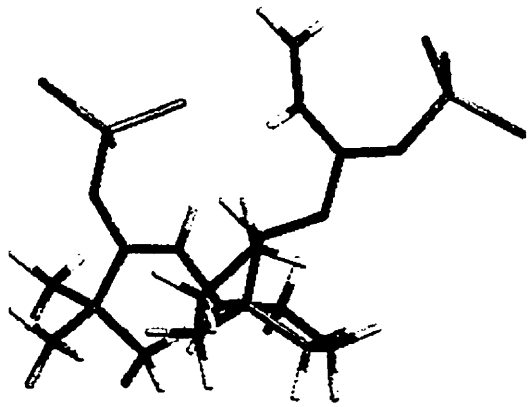


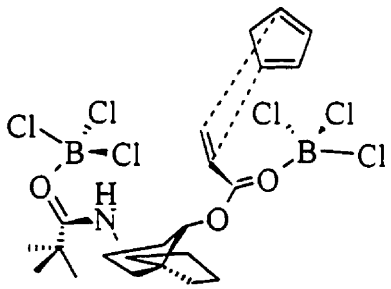
Entry 4: Yields *R*
6.029% Distribution





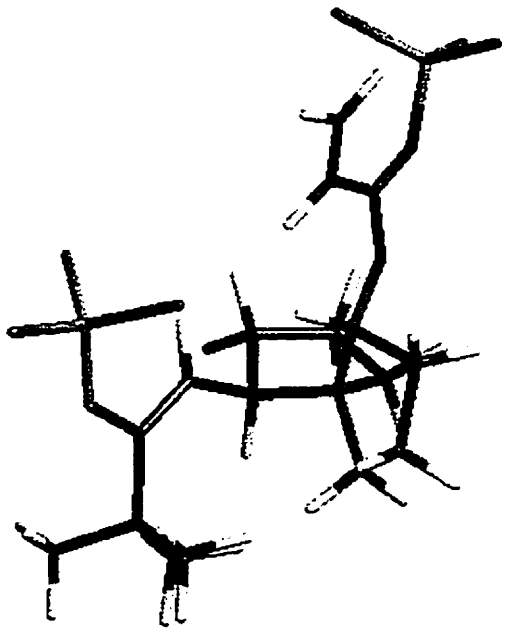
Entry 5: Yields *R*
2.802% Distribution

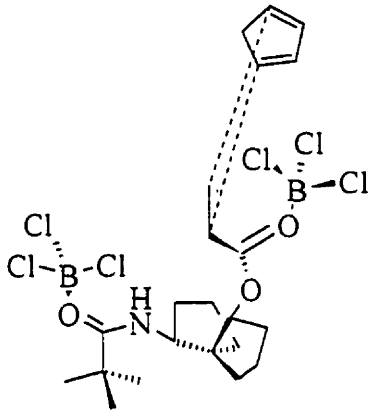




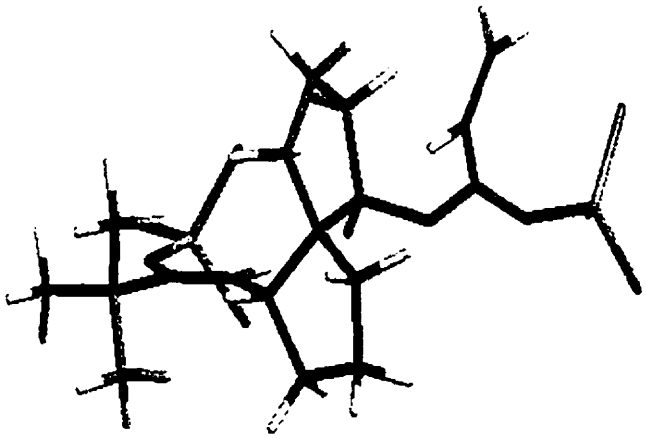
Entry 6: Yields *R*
2.375% Distribution

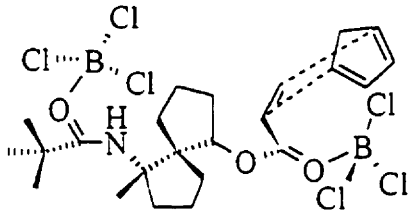
Figure 3.8.2.: Compound (-)-**134** Conformers 4-6 (left) and Proposed *endo* Transition States with 7 (right)





Entry 7: Yields *R*
1.086% Distribution





Entry 8: Yields *R*
0.813% Distribution

Figure 3.8.3.: Compound (-)-**134** Conformers 7 and 8 (left) and Proposed *endo* Transition States with 7 (right)

The Boltzman distribution was calculated using formula 1:

$$\frac{e^{-E/RT}}{\Sigma e^{-E/RT}} \qquad (1)$$

where e = 2.718, E = conformer energy (cal/mol), R = gas constant (4.184 cal/mol K), and T = temperature of the reaction (195 K). The results for these calculations were then divided by the sum of the individual calculations and multiplied by one hundred to yield the % abundance of each conformer in the reaction mixture (Column 6, Table 3.3).

The results from Table 3.3 support our observed *R* absolute stereochemistry for the free acids **150-155**. Seven of the eight lowest energy conformations would provide the *R* stereochemistry of the free acid portion of the cycloadduct. Conformations which would provide the *R* stereochemistry were found to compromise ~91.1 % of the conformer distribution.

Although these calculations support our observed stereochemistry, it must be restated that these calculations are done in the gas phase and the level of theory does not take into account π-π interactions. It is also important to note that the lowest energy conformation may not be the active species in the reaction process, a common incorrect assumption often taken by synthetic chemists, however, the majority of the conformers (>90%) heavily favors the production of the *R* stereochemistry in the free acids **150-155**.

3.6. Conclusion

In review, compound (+)-**130b** can be converted to dienophiles (-)-**134**, (-)-**135**, and (-)-**137** in high yields of 82, 79, and 78% respectively. We have shown that dienophile (-)-**134** can be used in diastereoselective Diels-Alder reactions to provide cycloadducts in good yields (70-82%) with >97% de (Table 3.1, entries 1 and 2), which upon saponification,

allowed for the isolation of free acids with >98% ee (*R*) in an 81-85% yield (Table 3.2, entries 1 and 2).

The Diels-Alder reaction of (-)-**134** with furan (**16**, Table 3.1, entry 3) provided a mixture in good yield (74%) with a moderate 2:1 *endo*:*exo* selectivity having a 79% *endo* de and a 78% *exo* de. Unfortunately, separation of either the cycloadducts **145a** and **145b** or the free acids **152a** and **152b** could not be accomplished preventing verification of the de values via optical rotation measurements.

Using isoprene (**62**) as the diene, the Diels-Alder reaction of (-)-**134** (Table 3.1, entry 4) provided a mixture of diastereomers in good yield (79%) of which the selectivity could not be determined by 400 MHz ^{1}H-NMR (Table 3.1, entry 4). Fortunately, saponification to the free acid allowed for determination of the absolute stereochemistry, where (+)-**153** was found to have a 92% ee (*R*, 92% yield, Table 3.2, entry 4).

Switching to the use of dienophile (-)-**135**, the Diels-Alder reaction was performed with **7**, where a detrimental effect of an α-methyl group on diastereoselectivity was observed. This was attributed to the relative ease of interconversion between the *cisoid* and *transoid* geometries (Refer to Scheme 3.6 for a model compound). A high yield of cycloadduct **147a** was produced (72%) and excellent *endo* selectivity was observed (100:0, Table 3.1, entry 5). However, only a 21% de was obtained.

Use of (-)-**137** in the Diels-Alder reaction with **7** also produced a high yield of a mixture of cycloadducts **148a** and **148b** (81%) and revealed only a moderate 8:1 *endo*:*exo* selectivity with 85% *endo* de and a 64% *exo* de (Table 3.1, entry 6). This verified the detrimental effect of an α-methyl group on *endo* diastereoselectivity, as well as indicate a detrimental β-methyl group effect on *endo*:*exo* selectivity. Saponification of the cycloadduct

mixture **148a** and **148b** yielded only the isolation of the *endo* acid (+)-**155a** (86% yield), with no detection of the *exo* acid **155b**. Compound (+)-**155a** was found to have an 86% ee (*R*, Table 3.2, entry 6). In all cases, re-isolation of the chiral auxiliary (+)-**130b** was readily achieved in high yields (81-86%).

It was also found that di-BCl_3 coordinated semi-empirical calculations[110] (PM3) of (-)-**134** mimicked the observed absolute stereochemistry of the free acids for seven of the eight lowest energy conformations, which were found to make up 91.1% of the Boltzman distribution. This result agreed with the observed absolute stereochemistry found in free acids **150-155**.

In summary, we have demonstrated that (+)-**130b** can serve as an efficient chiral auxiliary in diastereoselective Diels-Alder reactions. Compound (+)-**130b** has been shown to be readily recoverable for reuse and has demonstrated none of the problems associated with previous work in our laboratory using **92**. Although we were initially trying to prepare the *cis,cis* isomer, the *cis,trans* isomer (+)-**130b** has provided results that were better than initially expected.

3.7. Future Work

There are many directions left for applications of this project. Some potential future work would involve the attachment of a polymer resin through the nitrogen atom in hopes of observing similar results for diastereoselective Diels-Alder reactions as well as extending the number of dienophiles and dienes used to further investigate the scope of the reaction.

An obvious extension of this work is to discover a route for the synthesis of a *cis,cis*-amino alcohol **95**. The 1,3-relationship of amine and alcohol in this compound would enable investigation as a chiral auxiliary in epoxidations, epoxide opening, conjugate additions, as

well as tying up Lewis acidic metals to serve as a chiral Lewis acid. This last application could also be applied to solid supports, a field where little research has been reported.

Other extensions for this project in the future could involve development of the next generation of chiral spiro auxiliaries by alteration of the carbon framework, for example, *cis,cis*-7-aminospiro[5.5]undecan-1-ol. All of these project continuations are interesting, but time constraints prevented further study for this thesis.

Chapter 4

4. Experimental Methods

4.1. General

All compounds are named according to IUPAC rules. Melting points were determined on solids purified by column chromatography using an Electrothermal® melting point apparatus and are uncorrected. Boiling points are uncorrected and refer to air-bath temperatures using a Kugelrohr short path distillation apparatus with the pressure in parentheses. Optical rotations were measured with a Rudolph Research Autopol® III polarimeter at 589 nm using a 1 dm path length cell and listed with concentration (g / 100 mL) and solvent in parentheses.

Infrared spectra were recorded using a Mattson Galaxy Series 4030 FT-IR spectrometer. Solid samples were fused to potassium bromide (KBr) discs from methylene chloride (CH_2Cl_2) solutions, while liquid samples were placed neat between KBr plates. Main absorptions are listed in wavenumbers (cm^{-1}) followed by the assignment in parentheses.

Nuclear magnetic resonance spectra were obtained on either a Bruker ACE-200 (^1H 200 MHz, ^{13}C 50 MHz) or a Bruker AM-400 (^1H 400 MHz, ^{13}C 100 MHz) spectrometer using deuteriochloroform as solvent. ^{13}C-NMR were referenced to the ^{13}C resonance of deuteriochloroform (δ 77.0) or deuterioacetone (δ 205.7). ^1H-NMR spectra were referenced to the ^1H resonance of residual chloroform (δ 7.27). ^1H-NMR spectra are listed with the following format: chemical shift in ppm (multiplicity, number of protons, coupling constant (Hz), assignment). In the cases where compounds are characterized as mixtures of *endo* and *exo* adducts, *endo* or *exo* will follow the assignment with a designation of minor or major

adduct in parentheses. The following abbreviations are used to describe multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). ^{13}C-NMR are listed in the following format: (solvent), chemical shift (in ppm), (methyl (CH_3), methylene (CH_2), methine (CH), or quaternary carbon (C_q), as determined by DEPT experiments). In cases where the assignment of signals is identical, the signals and assignment are grouped together. The numbering of atoms in the compounds to allow for the assignment of spectra may differ from the numbering used to name the compound according to IUPAC rules.

Low resolution mass spectra were either obtained using: 1) a Hewlett Packard 5890 Series II gas chromatograph interfaced with a Hewlett Packard 5971A mass selective detector; or 2) acquired by Mrs. Q. Wu (University of Calgary) using a VG-7070 spectrometer; or 3) acquired by Mrs. D. Fox (University of Calgary) with fast atom bombardment (FAB) ionization technique on a Kratos MS-80 spectrometer. The data is listed using the following format: mass (m/z), (relative intensity, assignment). High resolution mass spectra were obtained by Mrs. D. Fox on a Kratos MS-80 spectrometer. Elemental analyses were also performed by Mrs. D. Fox using a Control Equipment Corporation 440 Elemental Analyzer. X-ray crystal structures were determined by Dr. M. Parvez (University of Calgary).

Analytical gas liquid chromatography was performed on a Shimadzu GC-9A gas chromatograph equipped with a flame ionization detector using a 25 m x 0.53 mm (i.d.) x 3 μm (film thickness) 007 Series Methyl Silicone (Quadrex Corporation) fused silica column with helium as the carrier gas. Method information in parentheses is in the following format: (initial temperature (°C)/initial time (min.)/temperature raise (°C/min.)/final temperature (°C)/final time (min.))

Aluminum-backed silica gel plates (E. Merck, 0.2 mm silica gel 60, F_{254}) were used for thin layer chromatography (TLC). Solvent systems refer to mixtures, by volume, of hexanes to ethyl acetate (EtOAc) unless otherwise stated. The plates were visualised with an ultraviolet lamp (254 nm) and/or by heating with a hot air gun after immersion in a developing solution (0.56 g *p*-anisaldehyde, 180 mL 95:5 EtOH:H_2O, 4 mL concentrated H_2SO_4, 0.2 mL glacial acetic acid). Flash column chromatography was accomplished with silica gel 60 (E. Merck, 0.04-0.063 mm, 230-400 mesh) using the method of Still *et al.*[119]

All glassware employed in anhydrous reactions was dried overnight in an oven set at 120°C. Reaction vessels were then dried under a stream of nitrogen, while syringes were cooled in a dessicator containing Drierite.® Moisture sensitive reactions were performed under a nitrogen atmosphere.

The following cooling baths[120] were used to maintain sub-ambient temperatures: dry ice-acetone (-78°C) and liquid N_2-CH_2Cl_2 (-95°C).

Solvents and reagents were purified by standard methods[121] where necessary. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl, while methylene chloride (CH_2Cl_2), dimethyl sulfoxide (DMSO), pyridine (pyr.), triethylamine (TEA), and toluene were distilled from calcium hydride before use. Other solvents were used as purchased from the BDH Chemical Company and were ACS grade.

All semi-empirical calculations were performed at the PM3 level using PC SPARTAN PRO (Version 1.0).[110]

4.2. General Experimental Procedures

4.2.1. General Procedure 1 for Esterification of (+)-130b

Compound **130b** was dissolved in CH_2Cl_2 (2 mL per mmol of (+)-**130b**) in a one-necked round bottomed flask and cooled to 0 °C in an ice/water bath. To the solution was added TEA (2 equiv.), followed by the appropriate acid chloride (2 equiv.). The reaction was warmed to room temperature overnight after which TLC (2:1) analysis was performed to ensure completion. The reaction was then quenched by the addition of more CH_2Cl_2 (10 mL per mmol of (+)-**130b**) and the mixture was transferred to a seperatory funnel where 10% HCl (20 mL per mmol of (+)-**130b**) was added. The organic phase was separated and rinsed with saturated $NaHCO_3$ (20 mL per mmol of (+)-**130b**). The organic layer was dried over Na_2SO_4, filtered, and the CH_2Cl_2 was removed *in vacuo*. The crude ester was purified by column chromatography.

4.2.2. General Procedure 2 for Diels-Alder Reactions

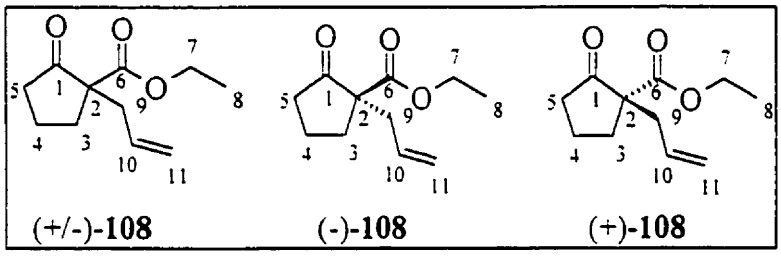
To a mixture of dieneophile (1 equiv.) and 4Å molecular sieves (100 mg per 0.4 mmol of dienophile, flame dried while under vacuum (~0.1 Torr)) was added CH_2Cl_2 (7 mL per 0.4 mmol dienophile) and the mixture cooled to –78 °C, at which point BCl_3 was added (2 equiv., 1.0 M in CH_2Cl_2). After the mixture was stirred for 30 minutes, precooled diene (0°C, 5 equiv.) was added dropwise down the inside of the flask. The reaction was allowed to stir for 8 hours and then filtered through a silica gel plug (~ 5 g/mol dienophile) packed in CH_2Cl_2. This silica gel was then rinsed with Et_2O and the combined volatile fractions were removed *in vacuo*, resulting in crude product. Purification was achieved by column chromatography (4:1).

4.2.3. General Procedure 3 for Saponification of Cycloadducts

The cycloadduct (1 equiv.) was dissolved in a minimal amount of MeOH (3 mL / 50 mg) and 5 M aqueous NaOH was added (10 mL / 50 mg). The mixture was heated to 80°C overnight (18 h) at which point the MeOH was removed *in vacuo*. The remaining mixture was cooled to 0 °C where 5 M aqueous HCl was added dropwise until pH 2. The acidic mixture was then extracted with EtOAc (3 x (50 mL / 100 mg)). Volatile material was then removed *in vacuo* and the crude residue submitted to flash chromatography (4:1) to provide the free carboxylic acids. The isolated carboxylic acids were then compared to the literature for determination of enantiomeric excess via optical rotation measurements.

4.3. Experimental Procedures Pertaining to Chapter 2

(2*RS*)-, (2*R*)-, and (2*S*)-2-Ethoxycarbonyl-2-(2-propenyl)cyclopentanone, (±)-, (+)-, and (-)-108



A. Compound (±)-**108**

A modification of the procedure developed by Trost and co-workers was followed.[91] In a 1000 mL round bottom flask under N_2 was placed $Pd(PPh_3)_4$ (381.3 mg, 0.33 mmol) in 500 mL of dry toluene. The solution was allowed to stir at room temperature for ten min., at which point 1,1,3,3- tetramethylguanidine (16.8 g, 146 mmol) and allyl acetate (15.4 g, 154 mmol) was added. After five min., ethyl 2-oxocyclopentanecarboxylate (**109**, 20.0 g, 128 mmol) was added and the reaction allowed to stir vigorously overnight. After 18 h, 200 mL of saturated NH_4Cl was added and the reaction transferred to a 1L separatory funnel where the organic layer was removed and the aqueous layer extracted with

Et_2O (3 x 150 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent evaporated, resulting in a yellow oil. Flash chromatography (4:1) provided the desired product as a colourless oil (12.4 g, 63.1 mmol) in 99% yield. Compound (±)-**108** has been previously characterised by Hwu and co-workers.[122] bp 118-122 °C (10 mmHg), lit.[85] bp 133 °C (16 mmHg); IR 3079 (vinyl C-H), 1750 (ester C=O), 1727 (ketone C=O), 1641 (vinyl C-H); ^{1}H-NMR δ 5.80-5.56 (m, 1H, H10), 5.16-5.05 (m, 2H, H11), 4.16 (q, 2H, $J_{7,8}$ = 7.2 Hz, H7), 2.67 (ddd, 1H, J_{gem} = 13 Hz; $J_{9a\text{ or }b,10}$ = 5.98 Hz; $J_{9a\text{ or }b,11}$ = 1.19 Hz, H9a or b), 2.54 – 1.84 (m, 7H, H3-H5, H9a or b), 1.25 (t, 3H, $J_{8,7}$ = 7.2 Hz, H8); ^{13}C-NMR ($CDCl_3$) 214.5 (C_q), 170.0 (C_q), 133.5 (CH), 118.8 (CH_2), 61.3 (C_q), 60.0, 37.2, 36.8, 32.0, and 19.9 (CH_2), 14.3 (CH_3); mass spectrum[122] 168 (13, $[M\text{-}C_2H_4]^+$), 139 (12, $[M\text{-}C_4H_9]^+$), 95 (100, $[M\text{-}C_5H_9O_2]^+$); exact mass calc'd for $C_9H_{12}O_3$: 168.99257 ($M^+\text{-}C_2H_4$). Found 168.99168.

B. Compound (-)-**108**

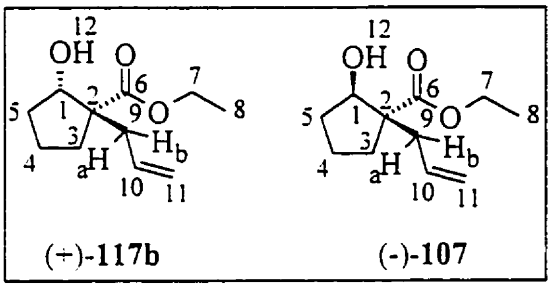
The procedure followed had been reported by Fraga and co-workers.[86,87] In a 2L Erlenmeyer flask with mechanical stirring at 25 °C was placed sucrose (200 g, 0.584 mol) and distilled water (800 mL) to provide a 20% w/w solution. Once the sugar was dissolved, baker's yeast (31.8 g, *Saccharomyces cerevisiae*) and copper(II)oxide (3.8 g, 52 mmol) were added and the solution allowed to stir for 15 minutes. At this point, (±)-**108** (5.01 g, 25.5 mmol) was added and the reaction monitored by GC (100/2/2/150/5) analysis of aliquots until a 1:1 ratio of starting material to alcohol (1*S*,2*S*)-(+)-**117b** was present. The reaction was then filtered through a Celite® pad and the yeast cake rinsed with water (100 mL). The filtrate was transferred to a 3L separatory funnel. The cake was rinsed further with EtOAc (200 mL) and the filtrate transferred to the funnel. The layers were separated and the

aqueous phase extracted with EtOAc (3 x 200 mL). The combined organic phase was dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to provide a pale yellow oil. Flash chromatography (5:1) provided enantiopure (-)-**108** (1.95 g, 9.9 mmol) in 78% yield of the possible 50% overall yield, and the reduced product (1*S*,2*S*)-(+)-**117b**. The boiling point and spectral data matched that provided for (±)-**108**. $[\alpha]_D^{20.1}$ -37.8 (1.201, $CHCl_3$).

C. Compound (+)-**108**

In a 150 mL Erlenmeyer flask was placed (1*S*,2*S*)-(+)-**117b** (5.02 g, 25.3 mmol) in 25 mL of acetone. Jones' reagent (9.8 mL, 2.64 M CrO_3 in 4.14 M H_2SO_4) was added dropwise with swirling and the reaction vessel was cooled periodically in an ice bath so as to maintain room temperature. Aliquots (0.1 mL) were diluted with H_2O (3 mL) in a 2 dram vial and extracted with Et_2O (1 mL) to provide a sample for TLC (2:1) analysis. Once the starting material had disappeared, the reaction was then washed into a separatory funnel (250 mL) with water (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed once with distilled water (100 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to provide a colourless oil which was purified by flash chromatography (4:1). The resulting oil, (+)-**108** (4.70 g, 24.0 mmol, 95% yield), had identical spectroscopic properties and boiling points as (±)-**108**. $[\alpha]_D^{19.3}$ +38.0 (1.213, $CHCl_3$)

(1*S*,2*S*)- and (1*R*,2*S*)-2-Ethoxycarbonyl-2-(2-propenyl)cyclopentanol, (-)-107 and (+)-117b



(+)-**117b** (-)-**107**

A. Compound (+)-**117b**

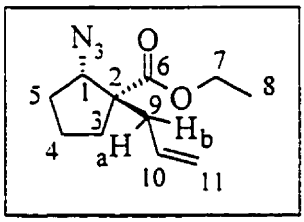
The procedure used is the same as the one followed for the synthesis of (-)-**108**. Compound (+)-**117b** (2.02 g, 10.2 mmol) was isolated in 80% yield of the possible 50% overall yield. Compound (+)-**117b** has been partially characterized by Ovadia and co-workers.[85] bp 124-130 °C (13 mmHg); IR 3488 (O-H), 3077 (vinyl C-H), 1725 (C=O), 1640 (vinyl C-H); ^{1}H-NMR δ 5.87-5.67 (m, 1H, H10), 5.18-5.02 (m, 2H, H11), 4.19 (q, 2H, $J_{7,8}$ = 7.0 Hz, H7), 4.07 (dd, 1H, $J_{1,5a} = J_{1,5b}$ = 5.1 Hz, H1), 2.99 (br s, 1H, H12), 2.38 (dd, 1H, $J_{9b,10}$ = 7.0 Hz; J_{gem} = 13.9 Hz, H9b), 2.21 (dd, 1H, $J_{9a,10}$ = 7.4 Hz; J_{gem} = 13.9 Hz, H9a), 2.10-1.55 (m, 6H, H3-H5), 1.28 (t, 3H, $J_{8,7}$ = 7.0 Hz); ^{13}C-NMR ($CDCl_3$) δ 176.8 (C_q), 134.3 (CH), 117.9 (CH_2), 78.2 (CH), 61.5 (C_q), 56.4, 35.8, 32.0, 29.3, and 18.9 (CH_2), 14.0 (CH_3); $[\alpha]_D^{20\,6}$ +27.9 (1.202, $CHCl_3$).

B. Compound (-)-**107**

In a 250 mL round bottom flask under N_2 was placed 35.1 mL of a 1M solution of DIBAL-H (35.1 mmol) in THF. This was cooled to -78 °C where 20.6 mL of 1.7M *tert*-butyllithium in pentane (35.1 mmol) was added dropwise. Upon completion of addition, the reaction was allowed to stir for 10 min. at which point the bath was removed and reaction allowed to warm to room temperature where it turned from a yellow to a clear solution. At this point, the reaction was recooled to -78 °C where (+)-**108** (5.73 g, 29.2 mmol) was added dropwise down the side of the flask via syringe as a solution in 20 mL of dry THF. The

reaction was monitored by TLC (2:1), where the reaction appeared complete after 3 hours. The bath was removed and 10% HCl was carefully added dropwise until no evidence of hydrogen evolution remained. The reaction was then extracted with Et_2O (3 x 150 mL), dried over anhydrous Na_2SO_4, filtered and the solvent removed *in vacuo*. Flash chromatography (5:1) provided (-)-**107** as a colourless oil (5.32 g, 26.9 mmol) in 92% yield. Compound (-)-**107** has been characterized by Ovadia and co-workers.[85] bp 124-130 °C (13 mmHg); IR 3488 (O-H), 3077 (vinyl C-H), 1725 (C=O), 1640 (vinyl C-H); ^{1}H-NMR δ 5.87-5.67 (m, 1H, H10), 5.18-5.02 (m, 2H, H11), 4.34 (dd, 1H, 1H, $J_{1,5a} = J_{1,5b} = 5.0$ Hz, H1), 4.15 (q, 2H, $J_{7,8} = 7.2$ Hz, H7), 2.99 (br s, 1H, H12), 2.38 (dd, 1H, $J_{9b,10} = 7.0$ Hz; $J_{gem} = 13.9$ Hz, H9b), 2.21 (dd, 1H, $J_{9a,10} = 7.4$ Hz; $J_{gem} = 13.9$ Hz, H9a), 2.10-1.55 (m, 6H, H3-H5), 1.28 (t, 3H, $J_{8,7} = 7.0$ Hz); ^{13}C-NMR ($CDCl_3$) δ 176.8 (C_q), 134.3 (CH), 117.9 (CH_2), 78.2 (CH), 61.5 (C_q), 56.4, 35.8, 32.0, 29.3, and 18.9 (CH_2), 14.0 (CH_3); $[\alpha]_D$ -17.1 (1.211, 20.3, $CHCl_3$).

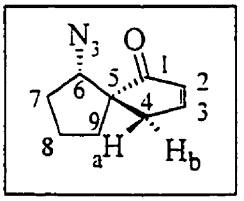
(1*S*,2*S*)-1-Azido-2-ethoxycarbonyl-2-(2-propenyl)cyclopentane, (+)-106



In a 100 mL round bottom flask was placed (-)-**107** (4.51 g, 22.8 mmol) in 50 mL of dry pyridine under a N_2 atmosphere. This was cooled to 0 °C where methanesulfonyl chloride (3.35 g, 29.2 mmol) was added and the reaction allowed to warm to room temperature overnight with stirring. Water was then added (50 mL) and the reaction allowed to stir a further 30 min. when the reaction was then transferred to a 500 mL separatory funnel. The mixture was then extracted with Et_2O (3 x 100 mL) and the combined organic phase rinsed once with saturated $NaHCO_3$ and once with 10% HCl to remove residual methanesulfonic acid and pyridine respectively. The organic phase was then dried over Na_2SO_4, filtered, and the solvent removed *in vacuo* to yield a pale yellow oil. This was transferred to a 100 mL round bottom

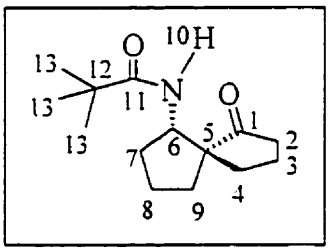
flask equipped with an air condenser, 40 mL of DMSO was added, and the reaction was heated to 80 °C. At this point, sodium azide (5.93 g, 91.2 mmol) was added and the reaction allowed to stir overnight. After 24 h, 50 mL of water was added while the reaction mixture remained hot and then it was allowed to cool to room temperature and transferred to a 250 mL separatory funnel. Here it was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were rinsed with brine (3 x 75 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to yield a brown oil. Flash chromatography (4:1) yielded (+)-**106** (3.41 g, 15.3 mmol) in 69% yield. IR 2972 (vinyl C-H), 2101 (N=N), 1730 (C=O); ^{1}H-NMR δ 5.82-5.57 (m, 1H, H10), 5.17-4.97 (m, 2H, H11), 4.15 (q, 2H, $J_{7,8}$ = 7.1 Hz, H7), 3.95-3.82 (m, 1H, H1), 2.53 (dd, 1H, $J_{9b,10}$ = 7.0 Hz; J_{gem} = 14.0 Hz, H9b), 2.08-1.56 (m, 7H, H3-H5, H9a), 1.25 (t, 3H, $J_{8,7}$ = 7.1 Hz, H8); ^{13}C-NMR ($(CD_3)_2CO$) δ 173.0 (C_q), 134.0 (CH_2), 118.1 (CH), 70.7 (CH), 60.6 (CH_2), 58.8 (C_q), 40.6, 30.2, 30.0, and 20.9 (CH_2), 14.0 (CH_3); mass spectrum: 194 (6,$[M-C_2H_5]^-$), 178 (5, $[M-C_2H_5O]^+$), 166 (22, $[M-C_2H_5N_2]^-$), 148 (17, $[M-C_3H_7O_2]^-$), 122 (92, $[M-C_3H_5N_2O_2]^-$); mass calc'd for $C_9H_{12}N_3O_2$ (M^--29): 194.09295, found: 194.09225; analysis calc'd for $C_{11}H_{17}N_3O_2$: C, 59.17%, H, 7.67%, found: C, 60.85%, H, 7.97%; $[\alpha]_D^{23.6}$ +43.2 (1.251, $CHCl_3$).

(5*S*,6*S*)-6-Azidospiro[4.4]non-2-en-1-one, (+)-105a



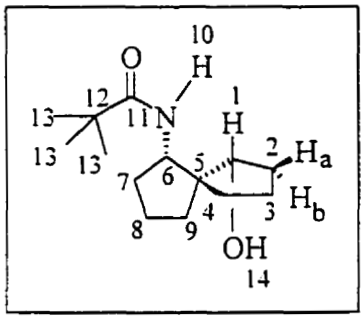
A modified procedure developed by Thebtaranoth and co-workers was followed.[99] In a 250 mL round bottom flask under N_2 was placed 75 mL of anhydrous THF and diisopropylamine (5.50 g, 54.2 mmol). This was cooled to –78 °C where 22.4 mL of a 2.3 M *n*-butyllithium in hexanes (51.5 mmol) was added dropwise. The reaction was allowed to stir for 10 min. and then transferred to an ice bath (0 °C) and allowed to stir for 1 h. At this point (+)-**106** (3.02 g, 13.5 mmol) was added as a 0 °C solution in 25 mL of anhydrous THF. The reaction was then allowed to stir at 0 °C, where after 4 h, TLC (4:1) revealed no starting material. At this point, 50 mL of water was added and the reaction removed from the ice bath. The mixture was diluted with another 50 mL of water, transferred to a 500 mL separatory funnel, and extracted with EtOAc (3 x 150 mL), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. The crude residue was then fused to silica gel (~ 5 g) for 24 h at which point it was taken up in EtOH and allowed to stir for a further 4 h. The EtOH was then removed *in vacuo* and the silica layered on top of a flash column (4:1). Chromatography provided 1.82 g (10.3 mmol, 76% yield) of the desired product (+)-**105a**. IR 2107 (N=N), 1703 (C=O), 1592 (vinyl C-H); ^{1}H-NMR δ 7.65 (dt, 1H, $J_{3,2}$ = 5.8 Hz; $J_{3,4}$ = 2.7 Hz, H3), 6.15 (dt, 1H, $J_{2,3}$ = 5.8 Hz; $J_{2,4}$ = 2.1 Hz, H2), 3.73 (dd, 1H, $J_{6,7a} = J_{6,7b}$ = 7.1 Hz, H6), 2.76 (ddd, 1H, J_{gem} = 19.1 Hz; $J_{4b,3}$ = 2.5 Hz; $J_{4b,2}$ = 2.4 Hz, H4b), 2.67 (ddd, 1H, J_{gem} = 19.1 Hz; $J_{4a,3}$ = 2.5 Hz; $J_{4a,2}$ = 2.4 Hz, H4a), 2.13-1.65 (m, 6H, H7-H9); ^{13}C-NMR ($(CD_3)_2CO$) δ 210.0 (C_q), 162.7 (CH), 133.1 (CH), 69.8 (CH_2), 56.9 (C_q), 43.1, 33.9, 29.8, and 21.2 (CH_2); mass spectrum: 177 (2, M^+), 149 (5, $[M-N_2]^+$), 134 (6, $[M-HN_3]^+$); mass calc'd for $C_9H_{11}N_3O$: 177.09021, found: 177.09013; $[\alpha]_D^{18.4}$ +47.8 (1.146, $CHCl_3$).

(5*S*,6*S*)-6-(2,2-Dimethylpropamido)spiro[4.4]nonan-1-one, (-)-127:



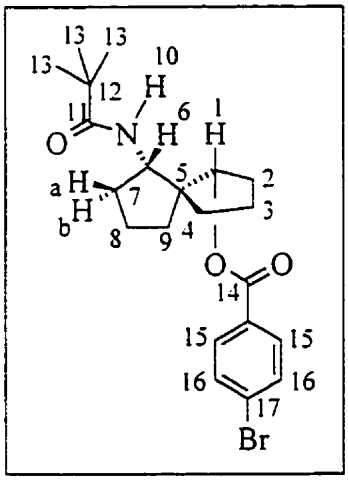
In a 25 mL round bottom flask charged with 10 mL of H_2 purged absolute ethanol under an H_2 atmosphere (1 atm) was placed (+)-**105a** (644 mg, 4.74 mmol) and a catalytic amount of 10% Pd on activated carbon. This was allowed to stir under H_2 overnight after which the palladium was removed using a Celite® filter and rinsed with absolute ethanol. The ethanol was removed *in vacuo* and the crude residue immediately dissolved in 10 mL of dry pyridine, and the flask was capped, and flushed with nitrogen. The vessel was then cooled to 0 °C where pivaloyl chloride (**126**, 853.2 mg, 7.11mmol) was added and the reaction allowed to stir overnight. At this point, the reaction was diluted with 40 mL of water, extracted with CH_2Cl_2 (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated to provide a yellow oil which was submitted to flash chromatography (2:1). Compound (-)-**127** (813 mg, 4.17 mmol) was provided as a colourless oil in 88% isolated yield. bp 112-120 °C (0.06 mmHg); IR 3378 (N-H), 1728 (ketone C=O), 1657 (amide C=O); ^{1}H-NMR δ 6.05 (br s, 1H, H10), 4.24 (m, 1H, H6), 2.38-1.38 (m, 12H, H2-H4 and H7-H9), 1.14 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$) δ 223.4 (C_q), 178.5 (C_q), 59.2 (C_q), 57.3 (CH), 39.2 (CH_2), 38.9 (C_q), 37.8, 36.5, and 33.8 (CH_2), 27.8 (CH_3), 23.1, and 20.1 (CH_2); mass spectrum: 237 (16, M^+), 141 (100, $[C_8H_{15}NO]^+$); mass calc'd for $C_{14}H_{23}NO_2$: 237.17288, found: 237.17192; analysis for $C_{14}H_{23}NO_2$: C 70.85%, H 9.77%, N 5.90%, found: C 70.56%, H 10.09%, N 5.88%; $[\alpha]_D^{20.3}$ -73.7 (1.206, $CHCl_3$).

(1*R*,5*S*,6*S*)-6-(2,2-Dimethylpropamido)spiro[4.4]nonan-1-ol, (+)-130b:



In a 10 mL round bottom flask under N_2 was placed (-)-**127** (108 mg, 0.46 mmol) in 2 mL of anhydrous THF. This was then cooled to -78 °C and 0.91 mL of a 1M DIBAL-H solution in THF (0.91 mmol) was added dropwise via syringe. After 10 min. the reaction appeared complete by TLC (1:1), the bath removed, and 10% HCl added dropwise until H_2 evolution ceased. The reaction was then diluted with 20 mL of 10% HCl and extracted with EtOAc (3 x 50 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered through a silica gel plug to provide (+)-**130b** (101 mg, 0.42 mmol) in 92% yield after flash chromatography (2:1). mp 70-73 °C, IR 3343 (N-H and O-H), 1639 (C=O); ^{1}H-NMR δ 6.74 (br s, 1H, H10), 4.02 (dd, 1H, $J_{1,2a}$ = 7.7 Hz; $J_{1,2b}$ = 7.6 Hz, H1), 3.93 (m, 1H, H6), 2.11-1.86 (m, 4H, H2 and H7), 1.74-1.32 (m, 8H, H3,H4, H8, and H9), 1.19 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$) δ 178.7 (C_q), 77.6 (C_q), 76.4 (CH), 59.2 (CH), 39.1 (C_q), 36.5, 33.6, 33.5, and 29.0 (CH_2), 28.0 (CH_3), 21.9, and 19.4 (CH_2); mass spectrum: 239 (19, M^+), 221 (1, $[M-18]^+$), 120 (46, $[M-C_5H_{13}NO_2]^+$), 102 (100, $[C_5H_{12}NO]^+$); mass calc'd for $C_{14}H_{25}NO_2$: 239.18853, found: 239.18816; analysis for $C_{14}H_{25}NO_2$: C 70.25%, H 10.53%, N 5.85%, found: C 69.96%, H 10.75%, N 5.79%; $[\alpha]_D^{19.4}$ +19.1 (1.296, $CHCl_3$).

(1*R*,5*S*,6*S*)-1-(*p*-Bromophenylcarbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (-)-132

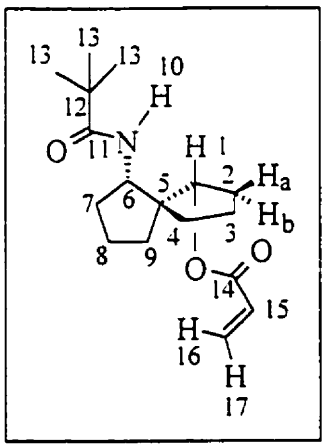


In a dry 25 mL round bottomed flask under an atmosphere of N_2 was placed 5 mL of dry pyridine and *p*-bromobenzoyl chloride (**131**, 101.0 mg, 0.46 mmol). After stirring for 10 min. at room temperature, (+)-**130b** (100 mg, 0.41 mmol) was added and the reaction allowed to stir overnight (~ 18 h). TLC (2:1) revealed no starting material at this point. Therefore, the reaction was transferred to a 250 mL separatory funnel and 100 mL of 10% HCl was added. The mixture was then extracted with EtOAc (3 x 75 mL) and the combined organic layers washed with saturated $NaHCO_3$ (2 x 50 mL), dried over Na_2SO_4, and removed *in vacuo* to provide a solid white residue. Flash chromatography (2:1) provided (-)-**132** as a white solid. The crystals were then dissolved in a minimal amount of boiling hexanes and allowed to sit at room temperature to provide 153 mg (0.36 mmol, 88% yield) of (-)-**132** as clear needlelike crystals. mp 115-117°C; IR 3365 (N-H), 1715 (ester C=O), 1659 (amide C=O); ^{1}H-NMR δ 7.89 (d, 2H, $J_{15,16}$ = 6.7 Hz, H15), 7.60 (d, 2H, $J_{16,15}$ = 6.7 Hz, H16), 6.38 (d, 1H, $J_{10,6}$ = 7.5 Hz, H10), 5.28 (dd, 1H, $J_{1,2a}$ = 7.4 Hz; $J_{1,2b}$ = 6.7 Hz, H1), 4.24 (ddd, 1H, $J_{6,7a}$ = $J_{6,10}$ = 7.5 Hz; $J_{6,7b}$ = 9.0 Hz, H6), 2.15-1.50 (m, 12H, H2-H4 and H7-H9), 1.23 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$) δ 178.9 (C_q), 166.5 (C_q), 132.3 (CH), 131.4 (CH), 129.6 (C_q), 128.8 (C_q), 78.6 (CH), 77.6 (C_q), 55.8 (CH), 39.2 (C_q), 37.1, 32.5, 32.2, and 31.1 (CH_2), 28.0 (CH_3), 21.4 and 20.7 (CH_2); mass spectrum: 421 (1, M^+), 336 (23, $[M-C_5H_9O]^+$), 221 (27, $[M-C_7H_4O_2Br]^+$), 136 (31, $[M-C_{12}H_{13}O_3Br]^+$), 120 (100, $[M-C_{12}H_{15}NO_3Br]^+$); mass calc'd for $C_{21}H_{28}NO_3{}^{79}Br$: 421.12526, found: 421.12557; analysis for $C_{21}H_{28}NO_3Br$: C

59.72%, H 6.68%, N 3.32%, found: C 59.48%, H 6.66%, N 3.30%; $[\alpha]_D^{23.8}$ -71.4 (1.060, $CHCl_3$); X-ray crystal data: monoclinic $P2_1$ (#4); a = 8.979(2) Å, b = 10.228(4) Å, c = 10.910(3) Å, β = 93.02(2)°, V = 1000.6(5) Å^3; Z = 2; R = 0.044; R_w = 0.091; Flack parameter[123] = -0.01(2). Bijvoet analysis was performed.[96] A refinement of the inverted structure was carried out which converged with R = 0.069, R_w = 0.157 and the Flack parameter = 1.01(2) and was therefore rejected as the absolute configuration present in the crystal.

4.4. Experimental Procedures Pertaining to Chapter 3

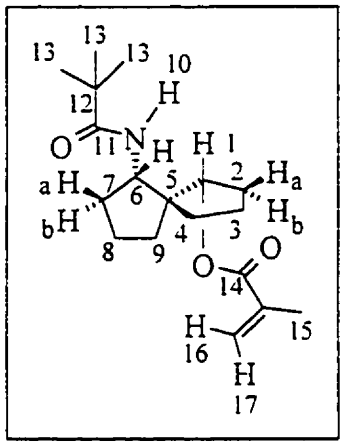
(1*R*,5*S*,6*S*)-1-(1-Oxo-2-propenyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (-)-134:



General procedure 1 was employed using (±)-**130b** (364.6 mg, 1.53 mmol), triethylamine (309.1 mg, 3.06 mmol), and 2-propenoyl chloride (275.4 mg, 3.06 mmol). Flash chromatography (2:1) provided (-)-**134** (367.6 mg, 1.25 mmol) as a colourless oil in 82% yield. bp 98-104 °C (0.06 mmHg): IR 3370 (N-H), 2873 (vinyl C-H), 1713 (ester C=O), 1650 (amide C=O); ^{1}H-NMR δ 6.43 (m, 2H, $J_{16,17}$ = 1.7 Hz; $J_{16,15}$ = 17.1 Hz, H16 and H10), 6.12 (dd, 1H, $J_{15,17}$ = 10.3 Hz; $J_{15,16}$ = 17.3 Hz, H15), 5.87 (dd, 1H, $J_{17,16}$ = 1.7 Hz; $J_{17,15}$ = 10.3 Hz, H17), 5.10 (dd, 1H, $J_{1,2a}$ = 7.5 Hz; $J_{1,2b}$ = 6.8 Hz, H1), 4.20 (m, 1H, H6), 2.15-1.42 (m, 12H, H3-H4 and H7-H9), 1.23 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$) δ 178.4 (C_q), 167.5 (C_q), 136.4 (CH), 125.8 (CH_2), 77.2 (CH), 55.4 (CH), 55.1 (C_q), 38.8 (C_q), 36.7, 32.2, 31.5, and 30.4 (CH_2), 27.6 (CH_3), 21.0 and 20.1 (CH_2); mass spectrum: 293 (4, M^+), 238 (7,

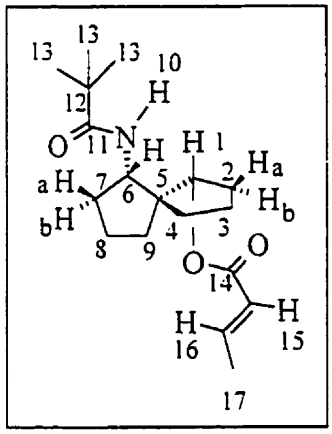
$[M\text{-}C_3H_3O]^+$), 208 (34, $[M\text{-}C_5H_9O]^+$), 120 (100, $[M\text{-}C_8H_{15}NO_3]^+$); mass calc'd for $C_{17}H_{27}NO_3$: 293.19909, found: 293.20144; $[\alpha]_D^{18.6}$ -30.6 (1.008, $CHCl_3$).

(1*R*,5*S*,6*S*)-1-(2-Methyl-1-oxo-2-propenyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (-)-135:



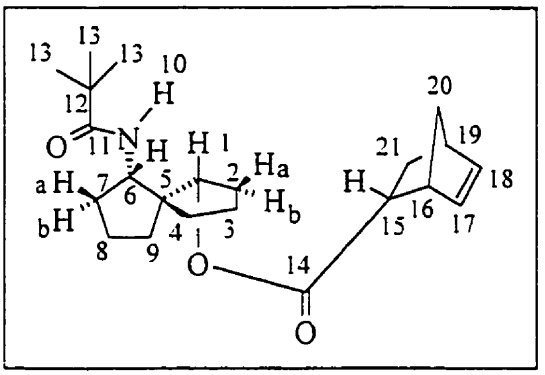
General procedure 1 was employed using (÷)-**130b** (302.3 mg, 1.26 mmol), triethylamine (255.0 mg, 2.52 mmol), and 2-methyl-2-propenoyl chloride (263.4 mg, 2.52 mmol). Flash chromatography (2:1) provided (-)-**135** (306.1 mg, 1.00mmol) as a colourless oil in 79% yield. bp 116-120°C (0.06 mmHg); IR 3370 (N-H), 2873 (vinyl C-H), 1824 (vinyl C-H), 1713 (ester C=O), 1655 (amide C=O); ^{1}H-NMR δ 6.38 (br d, 1H, $J_{10,6}$ = 7.6 Hz, H10), 6.11 (dq, 1H, J_{gem} = 0.9 Hz; $J_{16,15}$ = 1.0 Hz, H16), 5.58 (dq, 1H, J_{gem} = 0.9 Hz; $J_{17,15}$ = 1.5 Hz, H17),), 5.08 (dd, 1H, $J_{1,2a}$ = 7.5 Hz; $J_{1,2b}$ = 6.8 Hz, H1), 4.20 (ddd, 1H, $J_{6,7b}$ = 9.0 Hz; $J_{6,7a}$ = $J_{6,10}$ = 7.6 Hz, H6), 2.08-1.88 (m, 5H, $J_{15,16}$ = 1.0 Hz; $J_{15,17}$ = 1.5 Hz, H2 and H15), 1.81-1.40 (m, 10H, H3, H4, and H7-H9), 1.22 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$) δ 178.5 (C_q), 167.6 (C_q), 136.4 (C_q), 125.7 (CH_2), 77.3 (CH), 55.4 (CH), 55.0 (C_q), 38.8 (C_q), 36.6, 32.1, 31.6, and 30.4 (CH_2), 27.6 (CH_3), 21.0 and 20.1 (CH_2), 18.2 (CH_3); mass spectrum: 307 (5, M^+), 238 (17, $[M\text{-}C_4H_5O]^+$), 222 (39, $[M\text{-}C_5H_9O]^+$), 120 (72, $[M\text{-}C_9H_{17}NO_3]^+$), 57 (100, C_4H_9); mass calc'd for $C_{18}H_{29}NO_3$: 307.21474, found: 307.21341; $[\alpha]_D^{21.0}$ -27.9 (1.094, $CHCl_3$).

(1*R*,5*S*,6*S*)-1-(3-Methyl-1-oxo-2-propenyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (-)-137:



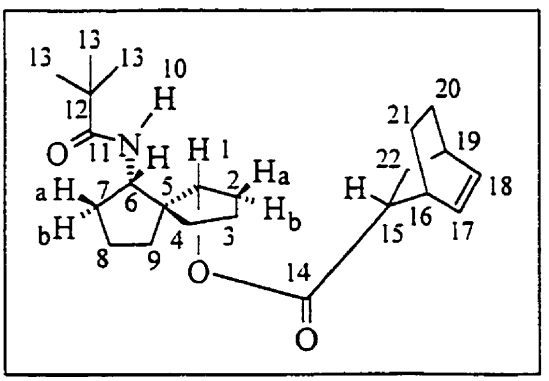
General procedure 1 was employed using (+)-**123b** (302.0 mg, 1.26 mmol), triethylamine (255.0 mg, 2.52 mmol), and *trans*-2-butenoyl chloride (263.4 mg, 2.52 mmol). The crude residue was dissolved in THF and *p*-TsOH·H_2O (199.1 mg, 1.26 mmol) was added. The reaction was allowed to stir at room temperature for 18 h at which point the THF was removed *in vacuo*. Flash chromatography (2:1) provided (-)-**137** (301.7 mg, 1.96 mmol) in 78% yield as a colourless oil. bp 113-118°C (0.06 mmHg); IR 3372 (N-H), 2873 (vinyl C-H), 1724 (ester C=O), 1650 (amide C=O); ^{1}H-NMR δ 6.99 (dq, 1H, $J_{16,15}$ = 15.5 Hz; $J_{16,17}$ = 6.9 Hz, H16), 6.51 (br s, 1H, H10), 5.84 (dq, 1H, $J_{15,16}$ = 15.5 Hz; $J_{15,17}$ = 1.7 Hz, H15), 5.07 (dd, 1H, $J_{1,2a}$ = 7.5 Hz; $J_{1,2b}$ = 6.8 Hz, H1), 4.19 (ddd, 1H, $J_{6,7a}$ = $J_{6,10}$ = 7.9 Hz; $J_{6,7b}$ = 9.2 Hz, H6), 1.90-1.88 (m, 5H, $J_{17,16}$ = 6.9 Hz; $J_{17,15}$ = 1.7 Hz, H2 and H17), 1.70-1.34 (m, 8H, H3, H4, and H7-H9), 1.22 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$) δ 178.6 (C_q), 167.0 (C_q), 145.3 (CH), 122.8 (CH), 76.7 (CH), 55.3 (CH), 54.9 (C_q), 38.8 (C_q), 36.7 (CH), 32.0, 31.6, and 30.5 (CH_2), 27.6 (CH_3), 20.9 and 20.0 (CH_2), 18.0 (CH_3); mass spectrum: 307 (5, M^+), 238 (7, $[M-C_4H_5O]^+$), 222 (44, $[M-C_4H_5O_2]^+$), 120 (100, $[C_9H_{12}]^+$); mass calc'd for $C_{18}H_{29}NO_3$: 307.21474, found: 307.21168; $[\alpha]_D^{21.2}$ -23.5 (1.300, $CHCl_3$).

(1*R*,5*S*,6*S*)-6-(2,2-Dimethylpropamido)-1-((2*R*)-norborn-5-ene-2-*endo*-carbonyloxy)spiro[4.4]nonane, 143a:



General procedure 2 was followed using dienophile (-)-**134** (113.8 mg, 0.39 mmol), 100 mg of molecular sieves, 0.77 mmol BCl_3, and diene (7) (103.0 mg, 1.56 mmol) to produce the single *endo* isomer **143a** (98.0 mg, 0.27 mmol, >98% de) as a clear oil in 70% yield after flash chromatography. IR 3366 (N-H), 2872 (vinyl C-H), 1716 (ester C=O), 1644 (amide C=O); ^{1}H-NMR δ 6.36 (br s, 1H, H10), 6.20 (dd, 1H, $J_{17,18}$ = 5.6 Hz; $J_{17,16}$ = 3.1 Hz, H17), 5.91 (dd, 1H, $J_{18,17}$ = 5.6 Hz; $J_{18,19}$ = 2.8 Hz, H18), 4.95 (m, 1H, H1), 4.14 (m, 1H, H6), 3.20 (m, 1H, H15), 2.94-2.91 (m, 2H, H16 and H19), 1.96-1.25 (m, 14H, H2-H4, H7-H9, and H21), 1.20 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$); δ 178.7 (C_q), 175.3 (C_q), 137.9 (CH), 133.1 (CH), 77.3 (CH), 55.9 (CH), 55.6 (CH), 54.9 (C_q), 45.6 (CH), 44.3 (CH), 43.3 (C_q), 43.0, 42.0, 38.8, 31.8, 31.5, and 30.1 (CH_2), 27.6 (CH_3), 21.0, and 20.3 (CH_2); mass spectrum (FAB): 360 (25, $[M+1]^+$), 222 (90, $[M-C_8H_9O_2]^+$); mass calc'd for $C_{14}H_{24}NO$ ($[M-C_8H_9O_2]^+$): 222.18579, found 222.18489.

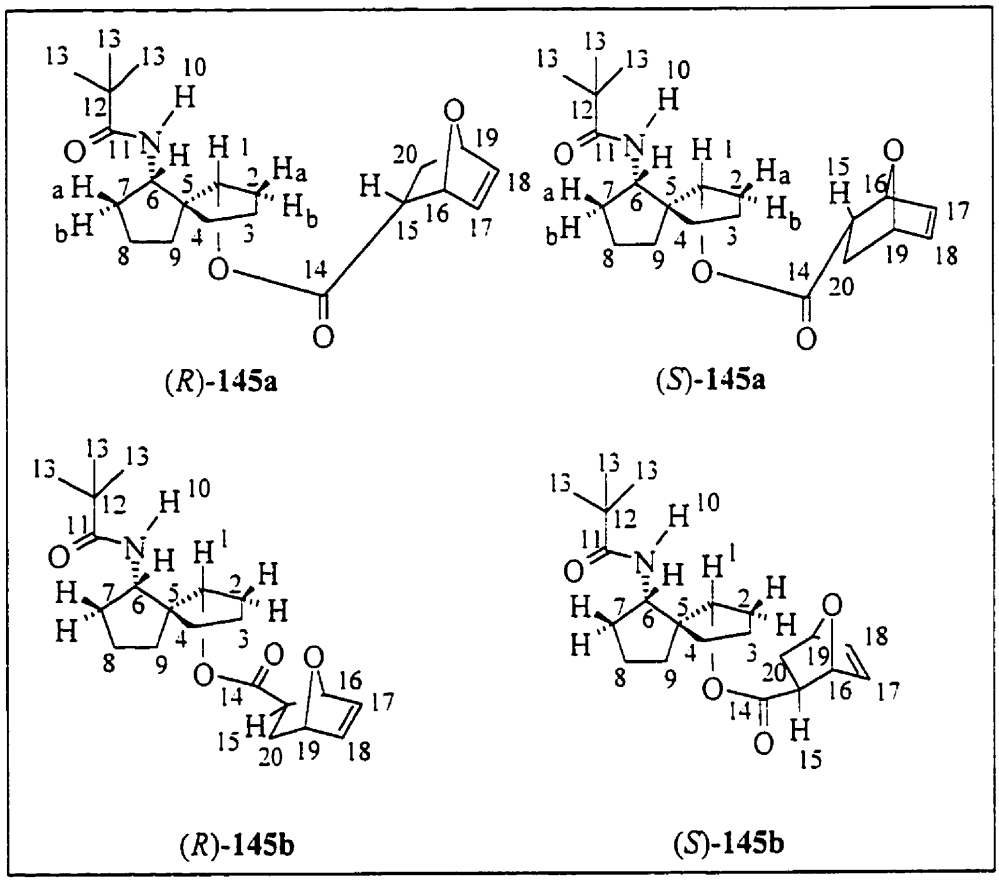
(1*R*,5*S*,6*S*)-1-((2*R*)-Bicyclo[2.2.2]oct-5-ene-2-*endo*-carbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, 144a:



General procedure 2 was followed using dienophile (-)-**135** (91.5 mg, 0.31 mmol), 100 mg of molecular sieves, 0.62 mmol BCl_3, and 1,3-cyclohexadiene (125.1 mg, 1.55 mmol) to

produce the single *endo* isomer **144a** (94.8 mg, 0.25 mmol, >98% de) as a clear oil in 82% yield after flash chromatography. IR 3370 (N-H), 2868 (olefin C-H), 1716 (ester C=O), 1660 (amide C=O); ^{1}H-NMR δ 6.38 (br d, 1H,$J_{10,6}$ = 8.2 Hz, H10), 6.29 (dd, 1H, $J_{17,18}$ = $J_{17,16}$ = 7.1 Hz, H17), 6.08 (dd, 1H, $J_{18,17}$ = $J_{18,19}$ = 7.1 Hz, H18), 4.95 (dd, 1H, $J_{1,2a}$ = 5.9 Hz; $J_{1,2b}$ = 7.6 Hz, H1), 4.14 (ddd, 1H, $J_{6,7b}$ = $J_{6,10}$ = 8.2 Hz; $J_{6,7a}$ = 7.9 Hz, H6), 2.91 (m, 1H, H15), 2.71-2.48 (m, 2H, H16 and H19), 2.05-1.20 (m, 16H, H2-H4, H7-H9, and H20-H22), 1.18 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$); δ 178.5 (C_q), 175.8 (C_q), 135.4 (CH), 131.2 (CH), 77.3 (CH), 55.6 (CH), 55.4 (CH), 55.1 (C_q), 43.2 (CH), 38.8 (CH), 36.0 (C_q), 32.5, 32.4, 30.7, and 29.8 (CH_2), 29.3 (CH_3), 28.2, 27.9, 27.7, 21.0, and 20.7 (CH_2); mass spectrum (FAB): 374 (25, $[M+1]^+$), 222 (100, $[M-C_9H_{11}O_2]^+$); mass calc'd for $C_{18}H_{26}NO_2$ ($[M-C_5H_9O]^+$): 288.19635, found 288.19377.

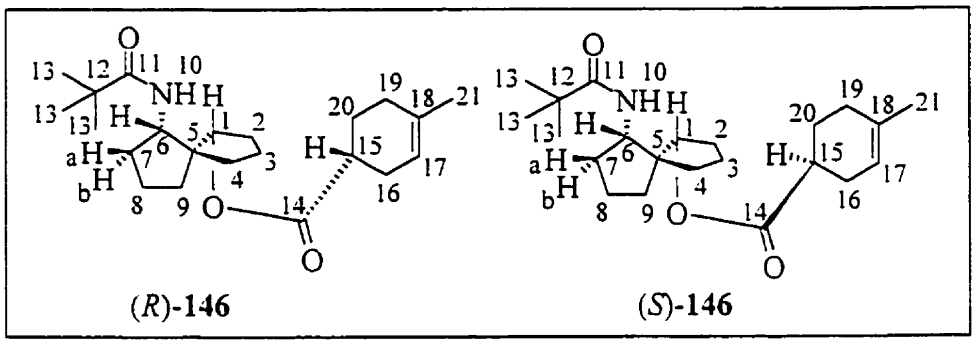
(1*R*,5*S*,6*S*)-6-(2,2-Dimethylpropamido)-1-((2*R*)-, and (2*S*)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-*endo*-carbonyloxy)spiro[4.4]nonane, (*R*)-145a and (*S*)-145a, (1*R*,5*S*,6*S*)-6-(2,2-dimethylpropamido)-1-((2*R*)-, and (2*S*)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-*exo*-carbonyloxy)spiro[4.4]nonane, (*R*)-145b and (*S*)-145b:



General procedure 2 was followed using (-)-**134** (162 mg, 0.55 mmol), 100 mg of molecular sieves, 1.1 mmol BCl_3, and furan (**16**, 187.2 mg, 2.75 mmol) to produce a 147 mg mixture of all four isomers as a clear oil (74% yield) which crystallized upon standing. ^{1}H-NMR revealed a 2:1 mixture of *endo* adducts (*R*)-**145a** and (*S*)-**145a** to *exo* adducts (*R*)-**145b** and (*S*)-**145b**. Several attempts to separate the *endo* and *exo* adducts via flash chromatography in various solvent systems (hexanes:EtOAc, $CHCl_3$:MeOH, benzene:hexanes) failed to produce any separation. Therefore, (*R*)-, (*S*)-**145a**, and (*R*)-, (*S*)-

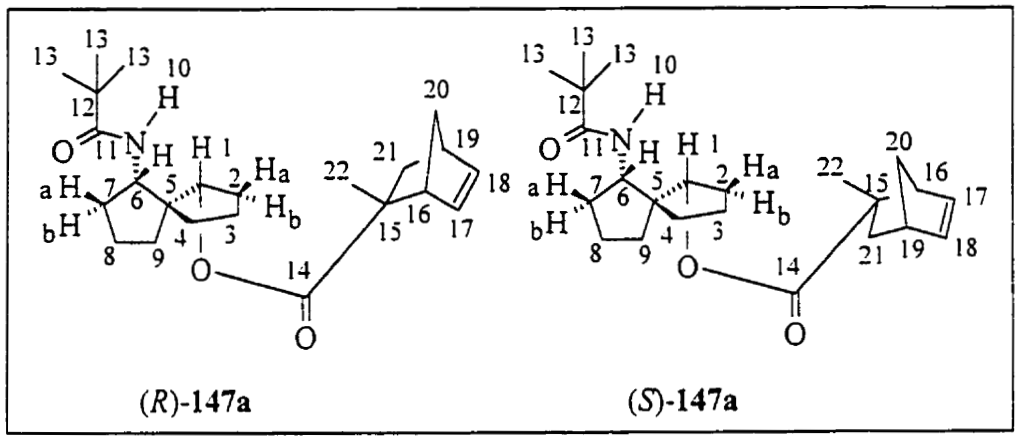
145b were characterized as the mixture of *endo* and *exo* adducts. IR 3370 (N-H), 1723 (ester C=O), 1659 (amide C=O); ^{1}H-NMR δ 6.51 (dd, 0.1H, $J_{17,16}$ = 1.7 Hz; $J_{17,18}$ = 5.8 Hz, H17 (minor *endo*)), 6.46 (dd, 1H, $J_{17,16}$ = 1.7 Hz; $J_{17,18}$ = 5.8 Hz, H17 (major *endo*)), 6.41 (m, 0.5H, $J_{17,16}$ = 1.7 Hz; $J_{17,18}$ = 5.8 Hz, H17 (minor and major *exo* overlapping)), 6.36 (m, 0.5H, $J_{18,17}$ = 5.8 Hz; $J_{18,19}$ = 1.7 Hz, H18 (minor and major *exo* overlapping)), 6.27 (dd, 0.1H, $J_{18,17}$ = 5.8 Hz; $J_{18,19}$ = 1.7 Hz, H18 (minor *endo*)), 6.23 (m, 2H, $J_{18,17}$ = 5.8 Hz; $J_{18,19}$ = 1.7 Hz, H18 (major *endo*), H10), 5.24 (d, 0.05H, $J_{16,17}$ = 1.7 Hz, H16 (minor *exo*)), 5.20 (d, 0.5H, $J_{16,17}$ = 1.7Hz, H16 (major *exo*)), 5.15 (dd, 1H, $J_{16,17}$ = 1.6 Hz; $J_{16,15}$ = 4.8 Hz, H16 (major *endo*)), 5.06 (m, 1H, H1), 5.02 (dd, 1H, $J_{16,17}$ = 1.7 Hz; $J_{16,15}$ = 4.8 Hz, H19 (major *endo*)), 4.96 (dd, 1H, $J_{6,7a}$ = 7.4 Hz; $J_{6,7b}$ = 5.4 Hz, H6), 3.09 (m, 1.1H, H15 (minor and major *endo* overlapping)), 2.42 (m, 0.5H, H15 (major and minor *exo* overlapping)), 2.18-1.39 (m, 14H, H2-4, H7-9, and H20), 1.21 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$, major *endo* peaks only); δ 178.6 (C_q), 172.6 (C_q), 137.2 (CH), 132.5 (CH), 77.3 (CH), 55.6 (CH), 55.4 (CH), 55.1 (C_q), 42.8 (CH), 38.8 (CH), 32.7 (C_q), 31.9, 31.5, 31.1, 29.7, and 29.0 (CH_2), 27.5 (CH_3), 21.0, and 20.5 (CH_2); mass spectrum (FAB): 362 (9, $[M+1]^+$), 294 (28, $[M-C_4H_4O]^+$), 222 (73, $[M-C_7H_7O_3]^+$); mass calc'd for $C_{17}H_{27}NO_3$ ($[M-C_4H_4O]^+$): 293.19909, found 293.19789.

(1*R*,5*S*,6*S*)-1-((2*R*)-, and (2*S*)-4-Methylcyclohex-3-ene-2-carbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (*R*)-146 and (*S*)-146



General procedure 2 was followed using (-)-**134** (109 mg, 0.37 mmol), 100 mg of molecular sieves, 0.75 mmol BCl_3, and isoprene (**62,** 126 mg, 1.85 mmol) to produce 105 mg of (*R*)-, and (*S*)-**146** as a clear oil after flash chromatography. Diastereomeric excesses could not be determined by 400 MHz ^{1}H-NMR. Compounds (*R*)-**146** and (*S*)-**146** were characterized as the mixture of diastereomers. IR 3370 (N-H), 1716 (ester C=O), 1666 (amide C=O); ^{1}H-NMR δ 6.39 (d, 1H, $J_{10,6}$ = 8.4 Hz, H10), 5.35 (m, 1H, H17), 5.01 (dd, 1H, $J_{1,2a} = J_{1,2b}$ = 6.3 Hz, H1), 4.16 (ddd, 1H, $J_{6,7a} = J_{6,7b} = J_{6,10}$ = 8.4 Hz, H6), 2.49 (m, 1H, H15), 2.20 (br s, 2H, H20), 2.03-1.82 (m, 7H, H20 and H21), 1.75-1.41 (m, 16H, H2-H4, H7-H9, H16, and H19), 1.20 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$, major adduct only) δ 178.6 (C_q), 176.4 (C_q), 133.9 (CH), 119.0 (C_q), 77.3 (CH), 55.3 (CH), 54.9 (C_q), 39.6 (CH_3), 38.8 (C_q), 36.7 (CH), 32.0, 31.6, 30.5, 29.2 and 28.0 (CH_2), 27.6 (CH_3), 27.3, 23.4, 20.9 and 20.0 (CH_2); mass spectrum: 361 (6, M^+), 276 (12, $[M-C_5H_9O]^+$), 238 (12, $[M-C_8H_{11}O]^+$), 222 (100, $[M-C_8H_{11}O_2]^+$); mass calc'd for $C_{22}H_{35}NO_3$ (M^+): 361.26169, found 361.25873.

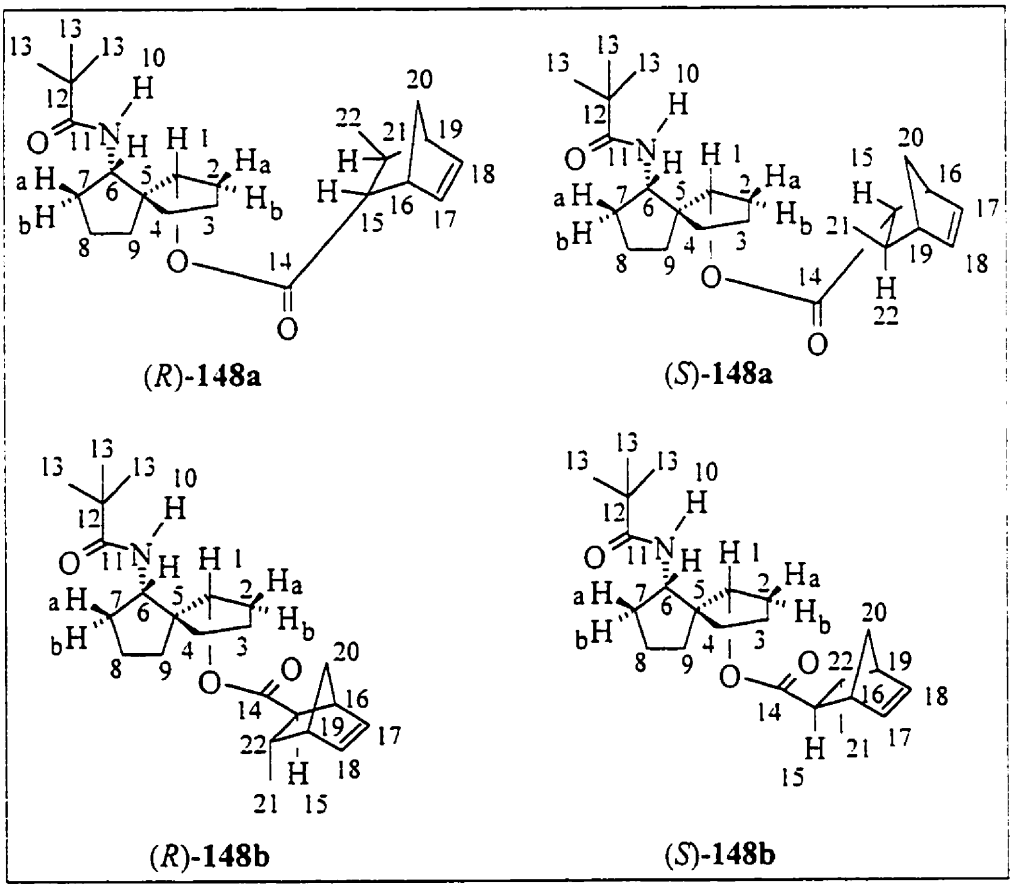
(1*R*,5*S*,6*S*)-1-((*2R*)-2-Methylnorborn-5-ene-2-*endo*-carbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (*R*)-147a, and (1*R*,5*S*,6*S*)-1-((*2S*)-2-methylnorborn-5-ene-2-*endo*-carbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (*S*)-147a



General procedure 2 was followed using dienophile (-)-**135** (89 mg, 0.29 mmol), 100 mg of molecular sieves, 0.58 mmol BCl_3, and cyclopentadiene (**7**, 96 mg, 1.45 mmol) to produce 78 mg of both *endo* diastereomers (*R*)-**147a** and (*S*)-**147a** as a clear oil after flash chromatography (72% yield). A 21% de was determined by 400 MHz ^{1}H-NMR. IR 3374 (N-H), 1713 (ester C=O), 1651 (amide C=O); ^{1}H-NMR δ 6.35 (br dd, 2H, $J_{10,6}$ = 8.8 Hz, H10 (both *endo* isomers)), 6.22 (dd, 1H, $J_{17,18}$ = 3.2 Hz; $J_{17,16}$ = 5.7 Hz, H17 (major *endo*)), 6.12 (dd, 0.7H, $J_{17,18}$ = 3.2 Hz; $J_{17,16}$ = 5.7 Hz, H17 (minor *endo*)), 6.08 (dd, 1H, $J_{18,17}$ = 3.2 Hz; $J_{18,19}$ = 5.7 Hz, H18 (major *endo*)), 6.02 (dd, 1H, $J_{18,17}$ = 3.2 Hz; $J_{18,19}$ = 5.7 Hz, H18 (minor *endo*)), 5.01 (dd, 1H, $J_{1,2a}$ = 7.4 Hz; $J_{1,2b}$ = 5.6 Hz, H1 (major *endo*)), 4.91 (dd, 0.6H, $J_{1,2a}$ = 7.4 Hz; $J_{1,2b}$ = 5.6 Hz, H1 (minor *exo*)), 4.18 (ddd, 1.7H, $J_{6,10}$ = $J_{6,7a}$ = $J_{6,7b}$ = 8.8 Hz, H6 (major and minor isomers)), 3.00 (br s, 1H, H16 (major *endo*)), 2.82 (br s, 1.7H, H19 (major *endo*) and H16 (minor *endo*)), 2.76 (br s, 0.7H, H19 (minor *endo*)), 2.01-1.40 (m, 19H, H2-H4, H7-H9, and H20-H22); ^{13}C-NMR ($CDCl_3$, major *endo* peaks only) δ 179.0 (C_q), 178.5

(C_q), 138.8, 133.5, 77.3, and 55.5 (CH), 55.0 (C_q), 54.6 (CH), 37.0 (CH_3), 38.8 (C_q), 36.7 (CH), 32.0, 31.6, 30.5, and 29.6 (CH_2), 26.6 (CH_3), 27.6, 24.1, 21.0 and 20.3 (CH_2); mass spectrum: 373 (30, $M^{+\cdot}$), 307 (50, $[M-C_6H_6]^+$), 238 (88, $[M-C_9H_{11}O]^-$), 222 (96, $[M-C_9H_{11}O_2]^-$); mass calc'd for $C_{22}H_{35}NO_3$ ($M^{+\cdot}$): 373.26169, found 373.26267.

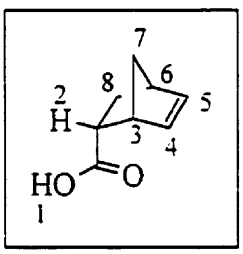
(1*R*,5*S*,6*S*)-1-((2*R*,3*S*)-, and (2*S*,3*R*)-3-Methylnorborn-5-ene-2-*endo*-carbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (*R*)-148a and (*S*)-148a, (1*R*,5*S*,6*S*)-1-((2*R*,3*S*)-, and (2*S*,3*R*)-3-methylnorborn-5-ene-2-*exo*-carbonyloxy)-6-(2,2-dimethylpropamido)spiro[4.4]nonane, (*R*)-148b and (*S*)-148b



General procedure 2 was followed using (-)-**137** (95 mg, 0.31 mmol), 100 mg of molecular sieves, 0.62 mmol BCl_3, and cyclopentadiene (**7**, 102 mg, 1.54 mmol) to produce a 94 mg mixture of both *endo* diastereomers (*R*)-**148a** and (*S*)-**148a** and both *exo* diastereomers

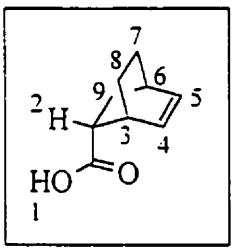
(*R*)-**148b** and (*S*)-**148b** as a clear oil after flash chromatography (81% yield). The oil was characterised as the mixture of diastereomers. IR 3373 (N-H), 1715 (ester C=O), 1651 (amide C=O); ^{1}H-NMR δ: 6.30 (br d, 1H, $J_{10,6}$ = 8.0 Hz, H10 (all isomers)), 6.25 (dd, 1H, $J_{17,18}$ = 5.6Hz; $J_{17,16}$ = 3.2 Hz, H17 major endo), 6.19 (dd, 0.1H, H17 minor endo), 6.08 (m, 0.14H, H17 (both exo), H18 (minor endo)), 6.01 (dd, 0.03H, H18 minor exo), 5.97 (dd, 1H, $J_{18,17}$ = 5.6 Hz; $J_{18,19}$ = 3.2 Hz, H18 major endo), 5.06 (m, 0.1H, H1 minor endo), 4.94 (m, 1H, H1 major endo), 4.16 (m, 1.1H, H6 both endo), 3.08 (br s, 1H, H15), 2.45 (br s, 1H, H16), 2.33 (m, 1H, H19), 2.01-1.38 (m, 18H, H2-H4, H7-H9, and H20-H22), 1.19 (s, 9H, H13); ^{13}C-NMR ($CDCl_3$, major *endo* peaks only) δ 178.5 (C_q), 175.1 (C_q), 138.7 (CH), 133.2 (CH), 77.0 (CH), 55.3 (CH), 54.9 (C_q), 53.0 (CH), 48.8 (CH), 46.2 (CH_2), 45.9 (CH), 38.8 (C_q), 38.2 (CH), 36.7 (CH_2), 32.3 (CH_2), 31.9 (CH_3), 31.3 and 30.8 (CH_2), 27.6 (CH_3), 20.2 and 18.0 (CH_2); mass spectrum (FAB): 374 (8, $[M+1]^+$), 308 (3, $[M-C_5H_6]^+$), 222 (52, $[M-C_9H_{11}O]^+$); mass calc'd for $C_{14}H_{24}NO$ ($[M-C_9H_{11}O]^+$): 222.18579, found 222.18667.

(+)-(2*R*)-Norborn-5-ene-2-*endo*-carboxylic acid, (+)-150a



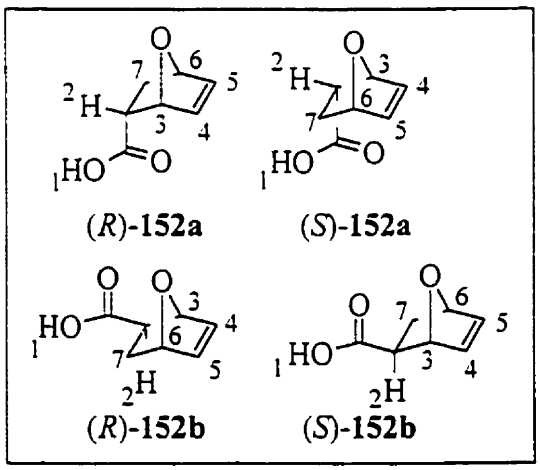
General procedure 3 was followed. Cycloadduct **143a** (45 mg, 0.13 mmol), 5 M NaOH (10 mL, 200 mg, 50 mmol), and MeOH (3 mL) were heated to 80 °C overnight. Workup provided the free acid (+)-**150a** (14 mg, 0.10 mmol, 79% yield) as a white solid. Compound (+)-**150a** has been previously characterized.[44,115] ^{1}H-NMR δ 7.11 (br s, 1H, H1), 6.25 (dd, 1H, $J_{4,3}$ = 3.0 Hz; $J_{4,5}$ = 5.6 Hz, H4), 6.04 (dd, 1H, $J_{5,4}$ = 5.6 Hz; $J_{5,6}$ = 3.0 Hz, H5), 3.77 (m, 1H, H2), 3.32-3.24 (br s, 1H, H6), 2.96-2.85 (br s, 1H, H3), 2.15-1.65 (m, 2H, H7), 1.68 (m, 2H, H8); $[\alpha]_D^{22}$ +69.2 (0.48, $CHCl_3$); lit.[115] $[\alpha]_D^{20}$ +68.6 (0.53, $CHCl_3$)

(+)-(2*R*)-Bicyclo[2.2.2]oct-5-ene-2-*endo*-carboxylic acid, (+)-151a



General procedure 3 was followed. Cycloadduct **144a** (62 mg, 0.17 mmol), 5 M NaOH (10 mL, 200 mg, 50 mmol), and MeOH (3 mL) were heated to 80 °C overnight. Workup provided the free acid (+)-**151a** (22.0 mg, 0.14 mmol, 87% yield) as a white solid. Compound **144a** has been previously characterized.[44,116] ^{1}H-NMR δ 9.05 (br s, 1H, H1), 6.32 (dd, 1H, $J_{4,3} = J_{4,5}$ = 7.7 Hz, H4), 6.17 (dd, 1H, $J_{5,6} = J_{5,4}$ = 7.7 Hz, H5), 3.03-2.92 (m, 1H, H2), 2.75-2.55 (m, 2H, H3 and H6), 1.95-1.15 (m, 6H, H7-H9); $[\alpha]_D^{20}$ +34.2 (0.581, abs. EtOH), lit.[116] $[\alpha]_D^{21}$ +34.8 (0.6, abs. EtOH)

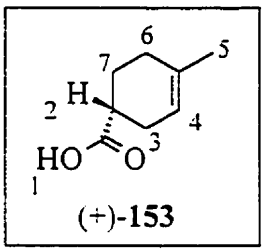
(2*R*)-, and (2*S*)-7-Oxa-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid, (*R*)-152a and (*S*)-152a, (2*R*)-, and (2*S*)-7-oxa-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid, (*R*)-152b and (*S*)-152b



General procedure 3 was followed. Cycloadducts (*R*)-, (*S*)-**145a** and (*R*)-, (*S*)-**145b** (62 mg, 0.17 mmol), 5 M NaOH (10 mL, 200 mg, 50 mmol), and MeOH (3 mL) were heated to 80 °C overnight. Workup provided the free acids (*R*)-, (*S*)-**152a** and (*R*)-, (*S*)-**152b** (22 mg, 0.14 mmol, 87% yield) as a white solid. The *endo* and *exo* acids could not be separated from one another using a variety of chromatography conditions (hexanes:EtOAc, MeOH:$CHCl_3$, benzene:hexanes). A mixture of *endo* and *exo* acids has been characterized by Tran and Crout.[124] ^{1}H-NMR δ 7.75 (br s, 1H, H1), 6.46 (dd, 1H, $J_{4,5}$ = 5.8 Hz; $J_{4,3}$ = 1.8 Hz, H4), 6.30 (dd, 1H, $J_{5,4}$ = 5.8 Hz; $J_{5,6}$ = 1.6 Hz, H5), 5.19 (m, 1H, H6),

5.05 (m, 1H, H3), 3.17 (m, 1H, H2 (*endo* and *exo*)), 2.13 (ddd, 1H, $J_{7,2}$ = 4.8 Hz; $J_{7,6}$ = 9.2 Hz; J_{gem} = 11.3 Hz, H7 (*endo*)), 1.56 (dd, 1H, $J_{7,6}$ = 3.9 Hz; J_{gem} = 11.3 Hz, H7 (*exo*)).

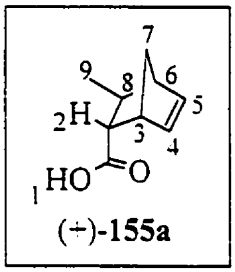
(+)-(2*R*)-4-Methylcyclohex-3-ene-2-carboxylic acid, (+)-(*R*)-153



(+)-**153**

General procedure 3 was followed. Cycloadducts (*R*)- and (*S*)-**146** (96 mg, 0.26 mmol), 5 M NaOH (10 mL, 200 mg, 50 mmol), and MeOH (3 mL) were heated to 80 °C overnight. Workup provided the free acid (+)-(*R*)-**153** (30.0 mg, 0.21 mmol, 81% yield) as a white solid. Compound (+)-**153** has been previously characterized.[44, 117] ^{1}H-NMR δ 5.37 (br s, 1H, H4), 2.60-2.51 (m, 1H, H2), 2.25 (br s, 2H, H6), 2.03 (br s, 4H, H3 and H6), 1.73 (m, 2H, H7), 1.65 (s, 3H, H5); $[\alpha]_D^{20}$ +98.4 (0.41, 95% EtOH); lit.[117] $[\alpha]_D^{20}$ +107 (0.6, 95% EtOH).

(+)-(2*R*,3*S*)-3-Methylnorborn-5-ene-2-*endo*-carboxylic acid, (+)-155a



(+)-**155a**

General procedure 3 was followed. Cycloadducts **143a** (42.0 mg, 0.11 mmol), 5 M NaOH (10 mL, 200 mg, 50 mmol), and MeOH (3 mL) were heated to 80°C overnight. Workup provided only the major *endo* free acids (+)-(*R*)-, and (*S*)-**155a** (14.4 mg, 0.10 mmol, 82% yield) as a white solid with no isolation of *exo* acids (*R*)-, and (*S*)-**155b**. Compound **155a** has been previously characterized.[118] ^{1}H-NMR δ 6.27 (dd, 1H, $J_{4,3}$ = 3.1 Hz; $J_{4,5}$ = 5.6 Hz, H4), 6.03 (dd, 1H, $J_{5,6}$ = 2.8 Hz; $J_{5,4}$ = 5.6 Hz, H5), 3.13 (br s, 1H, H2), 2.48 (br s, 1H, H6), 2.45-2.35 (br s, 1H, H3), 1.85-1.75 (m, 1H, H8), 1.55-1.45 (m, 2H, H7), 1.18 (d, 1H, $J_{9,8}$ = 7.1 Hz, H9); $[\alpha]_D^{22}$ +116 (0.35, $CHCl_3$); lit.[118] $[\alpha]_D^{20}$ +134 (0.7, $CHCl_3$).

References and Notes

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