DISSERTATION

CHIRAL ARYL OXAZOLINES AS TEMPLATES IN THE ENANTIOSELECTIVE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

Submitted by

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In partial fulfillment of the requirements

for the degree of Doctor of Philosophy

Colorado State University

Spring 2000

COLORADO STATE UNIVERSITY

December 17, 1999

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ANDREW P. DEGNAN ENTITLED CHIRAL ARYL OXAZOLINES AS TEMPLATES IN THE ENANTIOSELECTIVE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS BE ACCEPTED AS FULFILLING IN PART REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work

Advisor

Department Head

ABSTRACT OF DISSERTATION:

CHIRAL ARYL OXAZOLINES AS TEMPLATES IN THE ENANTIOSELECTIVE SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS

Lithium dialkylamides underwent a highly enantioselective conjugate addition to chiral naphthyloxazolines to afford, upon electrophilic trapping, 1,1,2-trisubstituted dihydronaphthyloxazolines. This method was used to install the ethylene ketal of 4-piperidone. Hydrolysis of the ketal and a double retro-Michael addition liberated the primary amine. The synthetic sequence culminated in the preparation of a novel, N-tosyl-hexahydrobenz[e]indole.

Lithium dimethylphenylsilyllithium also underwent the tandem addition reaction to afford the 1,1,2-trisubstituted dihydronaphthyloxazoline as a single diastereomer. The silicon, thus incorporated, was protodesilylated and underwent Tamao oxidation to afford the corresponding alcohol. By chemical modification of the oxazoline, both the γ- and δ-lactones were prepared. Reduction of each lactone followed by oxidation of the ensuing diol gave the keto aldehyde. Double reductive amination of the 1,4-dicarbonyl (from the γ-lactone) allowed the synthesis of two novel hexahydrobenz[e]indoles. Double reductive amination of the 1,5-dicarbonyl (from the δ-lactone) gave access to two novel octahydrobenzo[f]quinolines.

A chiral, non-racemic bicyclic lactam was utilized to create a chiral cyclopentane, containing vicinal quaternary carbon centers which is common to (-)-herbertenediol, (-)-

mastigophorene A, and (-)-mastigophorene B. The benzylic methyl group of *O,O'*-dimethylherbertenediol was oxidized to the benzoic acid and condensed with amino alcohols to afford the corresponding oxazoline. An oxazoline-mediated asymmetric Ullmann coupling was then utilized to create the chiral biaryl axis of mastigophorene A and mastigophorene B. Through the course of this synthesis, it was clearly demonstrated that smaller chiral auxiliaries lead to higher levels of atroposelection - a previously unknown phenomenon of the asymmetric Ullmann coupling.

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ACKNOWLEDGMENTS

I would like to express my deepest thanks to Professor A.I. Meyers for his support, guidance, and friendship. His 'hands-off' approach to his role as my mentor has allowed me the freedom to mature and flourish as an independent scientist. I respect and appreciate his unwavering warmth and optimism. I can recall so many times that a project had beaten me down to an emotional low, only to discuss the problem with professor Meyers and be lifted to a level of excitement at the possibilities my 'problem' suggested

Professor Aristotle G. Kalivretenos influenced my undergraduate years in a similar fashion, and provided the inspiration for the path I have chosen. My work in his laboratory gave me an immeasurable advantage upon my arrival at CSU.

Thanks to the Meyers group, past and present, for my interactions with you all Our discussions were always fun, stimulating, and educational. There's a little bit of all of you in this dissertation.

My deepest thanks go out to my closest friends - Denis, Jake, and AJ in particular. Denis, you stood by me through the UMBC years and the years since have only brought you closer. I love that you can always make me laugh and that you always seem to bring out the best in me. Jake has tolerated my short-comings with unending support. You have incorporated me into your life at every opportunity and I was proud to be able to stand by you at your wedding. AJ has been my primary source of local strength. The year we spent as roommates was my favorite in Colorado. You can sleep on my couch

anytime. I cannot fully express the role all of the aforementioned friends have played in my years away from home. I would not have made it without them.

Finally I wish to thank my family. I will never be able to fully atone for my lack of presence over the last four and a half years. I will not soon miss another Thanksgiving. My parents deserve full credit for the work at hand. Their support for me has never wavered. They let me cry on their shoulders during finals week as an undergraduate and have selflessly supported my studies in Colorado. I am so fortunate to have been born to two such caring and devoted parents. I could not have asked for a better pair of role models. I love you both so much (all the way around and twisted).

A special word of thanks goes out to my father. His knowledge and love of science was made evident with his every word. It was this feeling that inspired me to pursue a career in the sciences, and has resulted in the degree at hand.

Thank you all.

Andy

In loving memory of my grandparents,

Harry L. Henry and Mary J. Henry

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List of Selected Abbreviations, Acronyms, and Formulae

Ac_2O	acetic anhydride
AcOH	acetic acid
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Bu	butyl
Bz	benzoyl
calcd	calculated
conc.	concentrated
CD	circular dichroism
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
Dess-Martin	1,1,1-triacetoxy-1,1,dihydro-1,2-benziodoxol-3(1*H*)-one
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DIEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
ee	enantiomeric excess
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment mass spectrometry
GC	gas chromatography
HMPA	hexamethylphosphoramide
HOAc	acetic acid

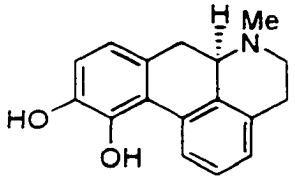
Jones	chromium trioxide, sulfuric acid, water, acetone
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Me	methyl
MEK	methyl ethyl ketone
MOM	methoxymethyl
MoOPH	oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)
Ms	methanesulfonyl
NMO	N-methylmorpholine N-oxide
nOe	nuclear Overhauser enhancement
PCC	pyridinium chlorochromate
Pd/C	palladium on carbon
PDC	pyridinium dichromate
Ph	phenyl
phephos	$Me_2NCH(Bn)CH_2PPh_2$
Pr	propyl
PTC	phase transfer conditions
pyr	pyridine
RBF	round bottomed flask
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
rt	room temperature
S.M.	starting material
Swern	oxalyl chloride, dimethylsulfoxide, triethylamine
Tf	trifluoromethansulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	p-toluenesulfonyl

Chapter One

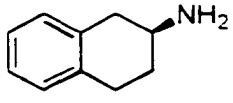
The Enantioselective Synthesis of Novel 2-Aminotetralins

A. *Aminotetralin Background*

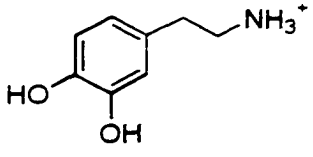
Recent reports of the potent anti-Parkinsonian activity of apomorphine (**1**) have triggered research into the development of drugs which mimic this agent.[1] The postulated mechanism of action of **1** involves a selective binding of it to the D-1 and D-2 (dopamine) receptors.[2] A structurally simplified analog of **1**, 2-aminotetralin (**2**), has been shown to maintain binding affinity to the serotonin and dopamine receptors.[3] The neurotransmitters dopamine (**3**) and serotonin (**4**) have been implicated in central nervous system related disorders such as anxiety, depression, schizophrenia, and Parkinson's disease.[4]



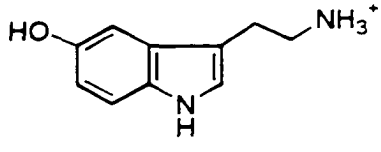
Apomorphine, **1**



2-Aminotetralin, **2**



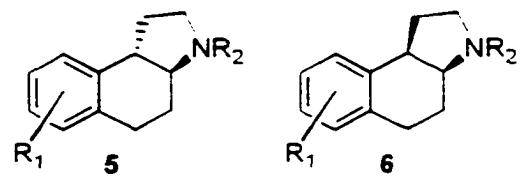
Dopamine, **3**



Serotonin, **4**

Although dopamine and serotonin possess no center of asymmetry, it is apparent from *in vivo* assays that their respective receptors possess a high degree of chirality, discriminating between enantiomeric dopaminergic and serotoninergic agonists.[5] As such there is a need to synthesize these molecules in a highly enantioselective fashion.

Lin *et al.*[4] synthesized a series of more structurally rigid pyrrolidine-fused aminotetralins (**5**, **6**), formally referred to as hexahydrobenz[e]indoles, and tested them for their ability to bind specifically to dopamine and serotonin receptors. It was found that analogs with 9-methoxy substitution showed mixed 5-HT_{1A} and D-2 agonism. In contrast, it was found that analogs with 9-hydroxy substitution showed binding only to 5-HT_{1A} receptors. The ability to change the binding selectivity to favor one or the other through modification of the substituents present poses not only potential medicinal value, but also makes these more rigid pyrrolidine-fused aminotetralins useful in fundamental research into the mechanism by which neurotransmitters function.



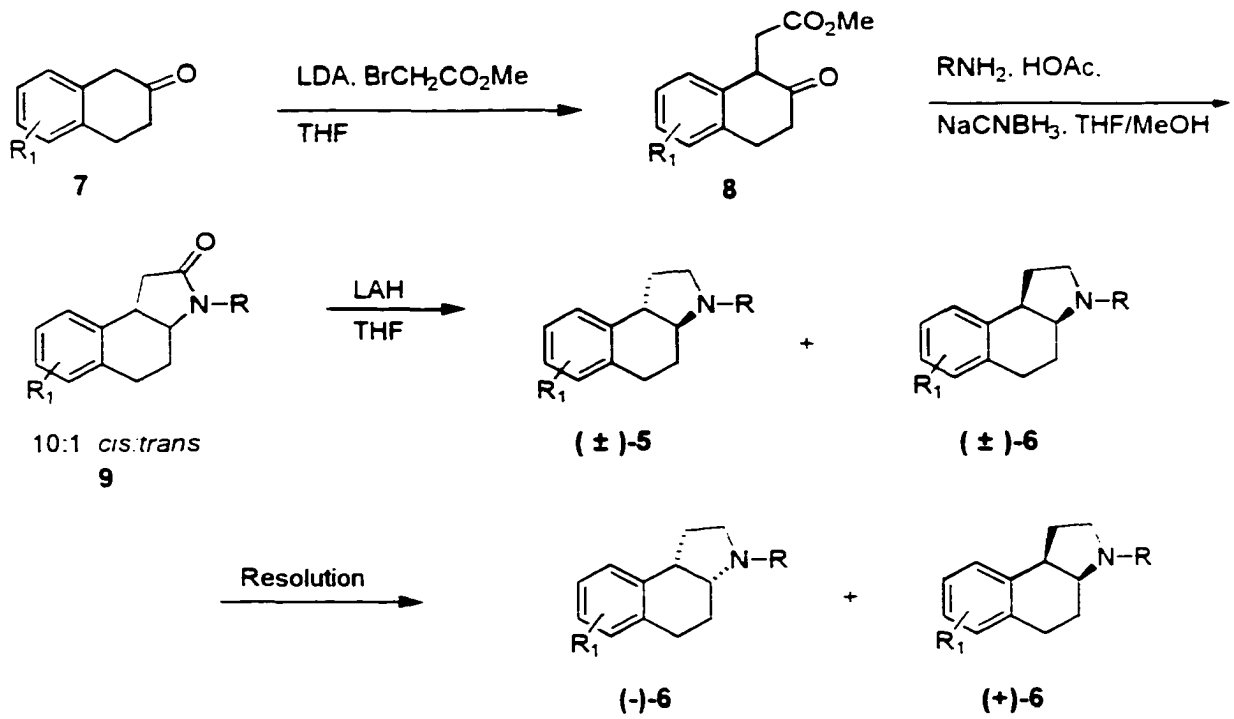
5 **6**

R_1 = H, OMe, OH
R_2 = allyl, *n*-propyl, cyclopropylmethyl

In order to synthesize them, Lin began with the appropriately substituted tetralone **7** (Scheme III). Deprotonation followed by addition of an appropriate α-haloester afforded the γ-keto-ester **8**. Reductive amination with the desired amine yielded the

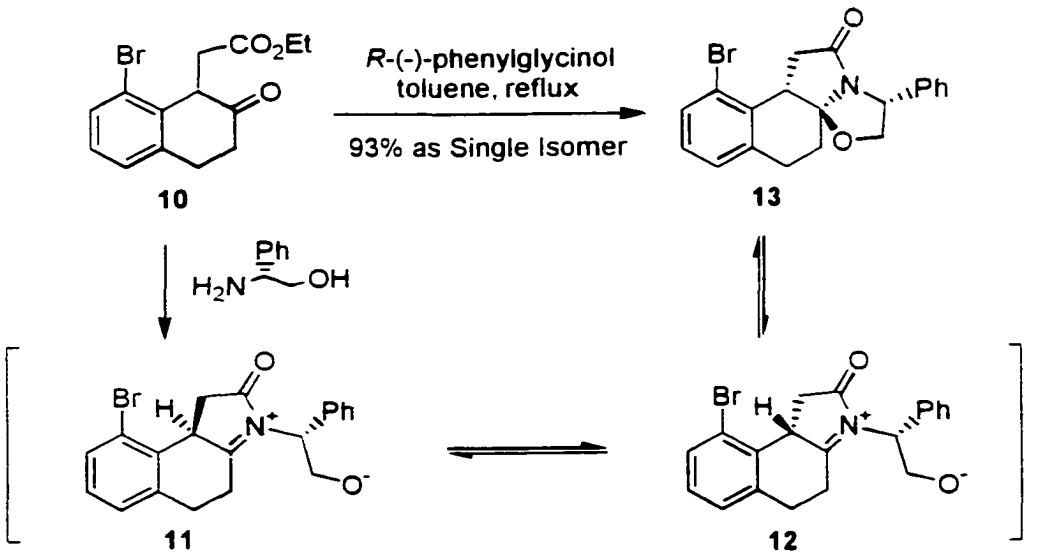
tricyclic lactam **9**. Upon $LiAlH_4$ reduction, a mixture of the *trans* (±)-**5** and *cis* (±)-**6** fused rings were obtained as their racemates which were later resolved.

Scheme 1



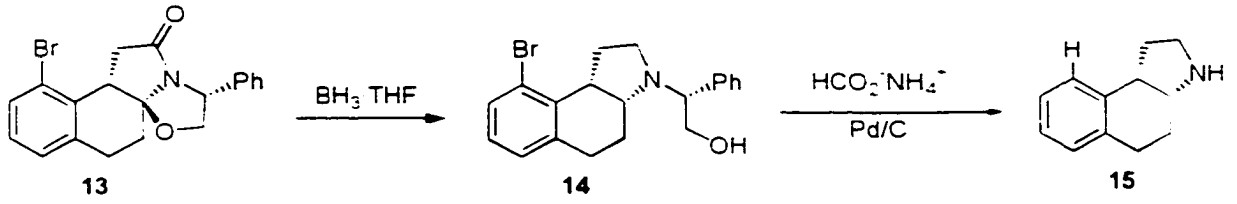
In 1996, Ennis *et al.*[6] published the most eloquent of approaches to effect the synthesis of hexahydrobenz[e]indoles, utilizing Meyers[7] bicyclic lactam methodology. To do so, they began with γ-ketoester **10** as its racemate. Upon heating it to reflux in toluene with (*R*)-phenylglycinol, they were afforded the chiral bicyclic lactam **13** as a single stereoisomer in 93% yield (Scheme 2). The observation of complete stereochemical control over both stereogenic centers is a result of the ability of both stereocenters to equilibrate (11 ⇋ 12 ⇋ 13), leading to the thermodynamically most stable product.

Scheme 2



Lactam **13** was then reduced *via* iminium ion **12** by the action of borane, to yield *cis*-fused benz[e]indole **14**. Hydrogenation using ammonium formate in the presence of catalytic Pd/C gave the hexahydrobenz[e]indole **15**, directly. It is important to note that the aryl bromide was utilized in order to install additional functionality for screening.

Scheme 3

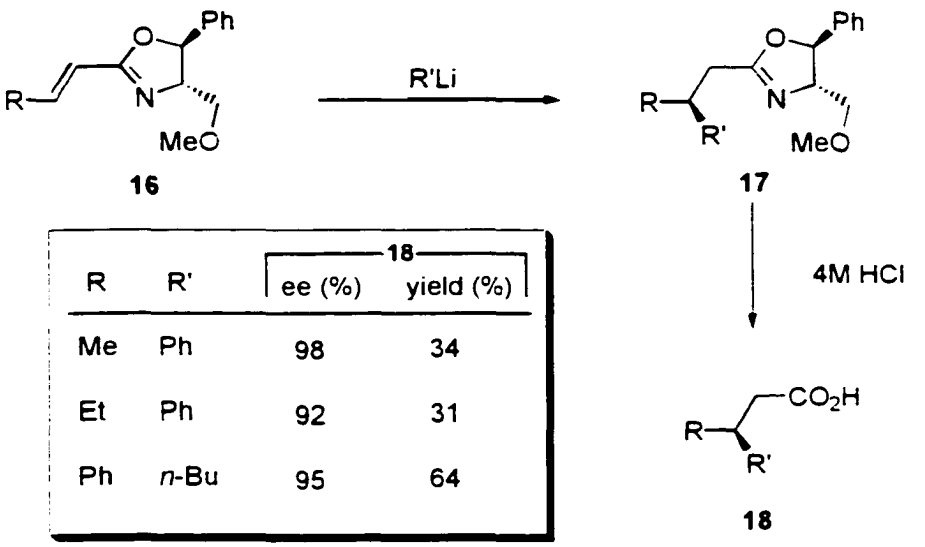


B. Conjugate Additions to Chiral Aryl Oxazolines

Meyers and Whitten[8] first reported a Michael type addition of nucleophiles to chiral oxazolines[9] in 1975. In this pioneering work, it was found that treatment of acyclic

α,β-unsaturated oxazolines (**16**) with alkyllithium reagents gave saturated oxazolines in good yields and high levels of diastereoselectivity (Scheme 4). Hydrolysis of the oxazoline moiety with strong mineral acid afforded several chiral 3-substituted alkanoic acids (**18**) with outstanding levels of enantiomeric excess. It is important to note that reversal of the order of incorporation of substituents R and R', allowed the generation of enantiomeric 3-substituted alkanoic acids.

Scheme 4



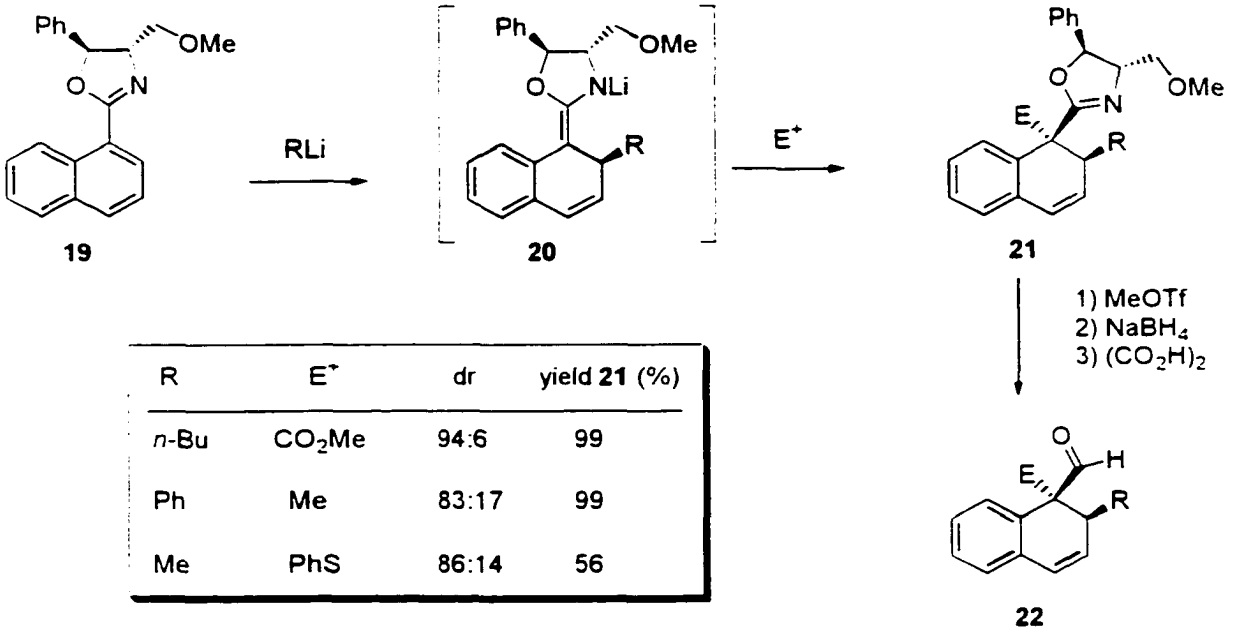
R	R'	18 ee (%)	18 yield (%)
Me	Ph	98	34
Et	Ph	92	31
Ph	*n*-Bu	95	64

Although asymmetric conjugate additions to α,β-unsaturated ketones and sulfoxides had been reported previously, the above method proved itself to be the most general, allowing the synthesis of either enantiomer of the desired alkanoic acid and recovery of the chiral auxiliary.

This set the stage for the eventual discovery of conjugate additions to chiral aryl oxazolines. This process was first reported by Meyers and Barner[10] in 1984 in a paper describing the diastereoselective addition of organolithium reagents to chiral naphthyloxazoline **19**. This chemical transformation proceeded with surprising facility.

considering the requirement of ~10 kcal/mol[11] to interrupt the naphthalene resonance. Further, it was found that the intermediate aza-enolate (**20**), once formed, was susceptible to electrophilic attack to give **21**, generating two adjacent chiral centers in one chemical transformation. This process has been termed the 'tandem addition reaction'. The oxazoline moiety of the resulting 1,1,2-trisubstituted dihydronaphthalenes were eventually converted to the corresponding aldehydes (**22**) *via* a new, and very mild method of reduction and hydrolysis.

Scheme 5

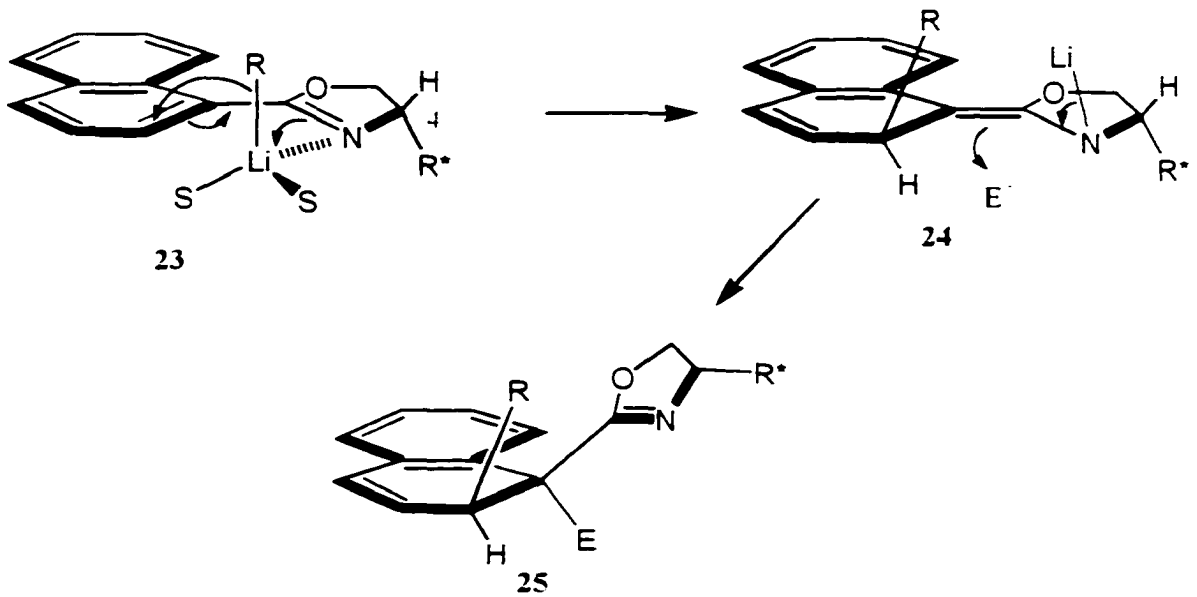


R	E^+	dr	yield **21** (%)
n-Bu	CO_2Me	94:6	99
Ph	Me	83:17	99
Me	PhS	86:14	56

Such nucleophilic additions to aromatic hydrocarbons have historically been difficult due to the inherent electron density of the π system and the loss of aromaticity in the product. By attaching an oxazoline moiety to naphthyl (or higher order aromatic) systems, one capitalizes on its intrinsic electron-withdrawing character to effect the conjugate addition of a nucleophile. The stereochemical outcome was rationalized[12] by

using a combination of coordination and steric arguments (Scheme II). It was envisioned that the nitrogen of oxazoline **23** coordinates to the metal, while the nucleophile is guided to the face of the molecule opposite the substituent in position 4 of the oxazoline[5]. The electrophile is then trapped on the face opposite that of the recently added nucleophile to afford a *trans*-disposition of nucleophile to electrophile.

Scheme 6

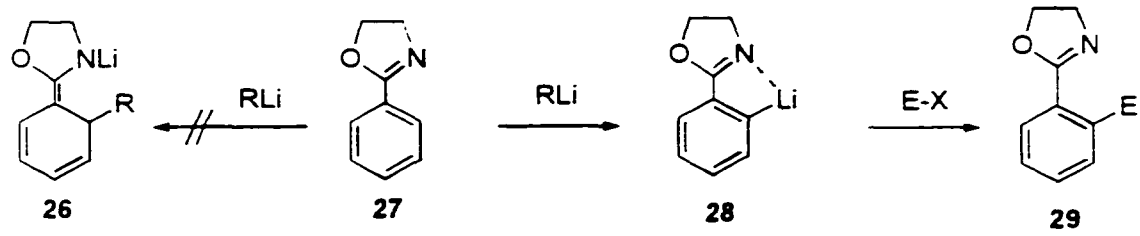


Since its discovery, the tandem addition reaction has shown great utility in the synthesis of natural products such as (+)-phyltetralin[12] and (-)-podophylotoxin.[13] Further, it has been shown that a wide range of nucleophiles undergo addition to the naphthalene core. These include alkyllithium reagents, Grignard reagents, lithium dialkylamides, and trialkylsilyllithiums.

Treatment of phenyloxazolines with alkyllithium reagents does not give rise to the highly unstable aza-enolate (**26**). Instead, the oxazoline renders *ortho*-protons kinetically

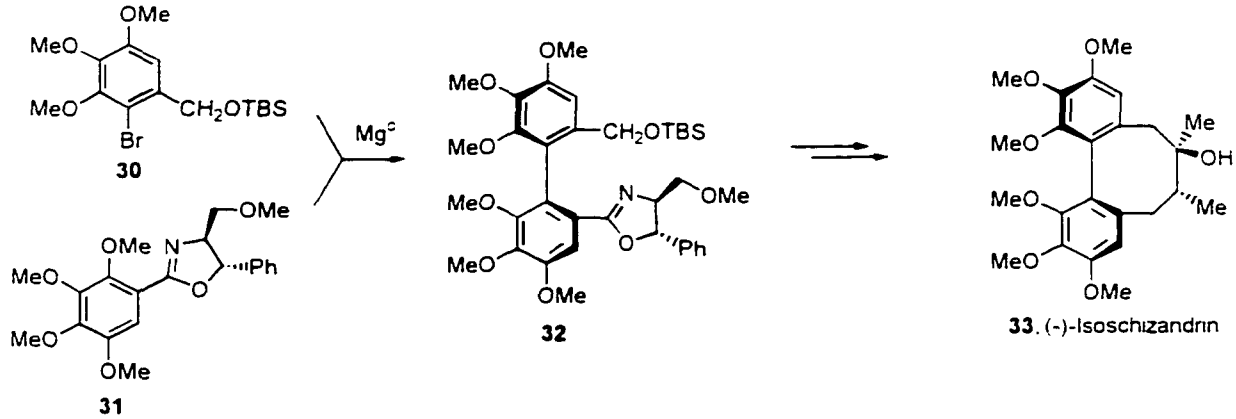
acidic, facilitating *ortho*-metallation of the arene. Thus, treatment of **28** with an electrophile gives rise only to electrophile-quenched arene **29** (Scheme 7)[9]

Scheme 7



If however, an *ortho* fluoro or methoxy group is incorporated into the aryl core, conjugate addition to the oxazoline is again observed, and the resulting aza-enolate is quenched by elimination of fluoride or methoxide. This reaction again renders the point of reaction planar and no longer creates either of the two stereocenters formed in the case of the aforementioned tandem addition reactions. This reaction takes on an aspect of diastereoselectivity only when the nucleophile is a metallated arene. When this is the case a biaryl axis is created which may be a stereocenter by virtue of hindered rotation about that axis. An example of this work appeared in the synthesis of (-)-isoschizandrin[14] (**33**) and is illustrated in Scheme 8. This topic will be addressed further in 2C

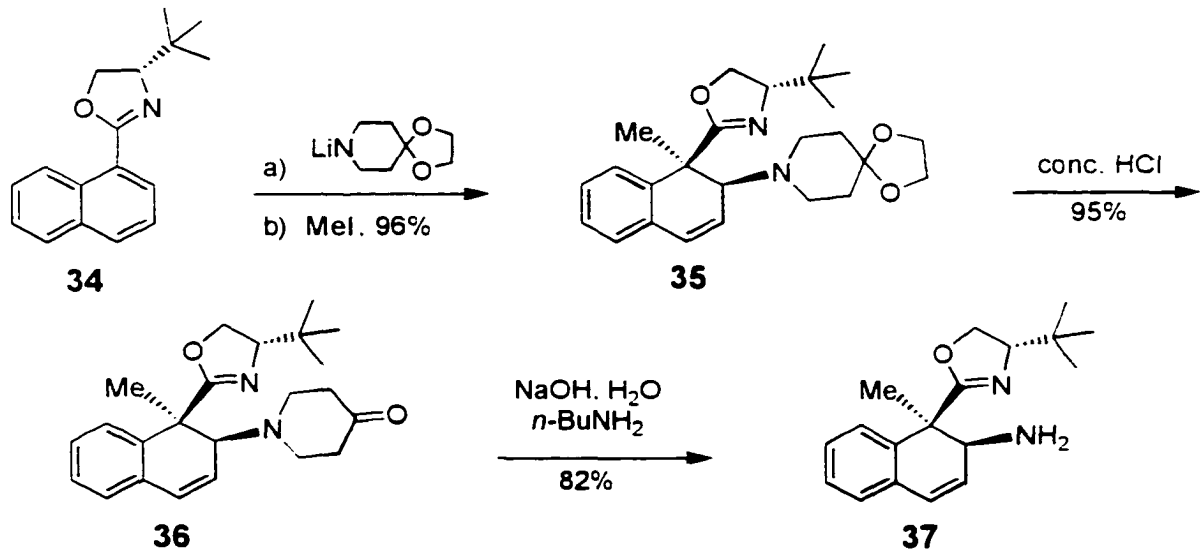
Scheme 8



C. Synthesis of Novel 2-Aminotetralins *via* the ConjugateAddition of Lithium Dialkylamides to Chiral Naphthyloxazolines

In 1995, Meyers and Shimano[15] reported that lithium dialkyl amides (but not $LiNH_2$) add directly to chiral naphthyl oxazoline **34** to afford, upon trapping with an electrophile, the β-amino-α-alkyl-α-oxazolinylnaphthalenes in a highly diastereoselective fashion (Scheme 9). Using this methodology, they were able to install the ethylene ketal of 4-piperidone with >98% de. Removal of the ketal, followed by treatment with aqueous base in the presence of an excess of *n*-butylamine afforded the substituted 2-aminotetralin **37**.

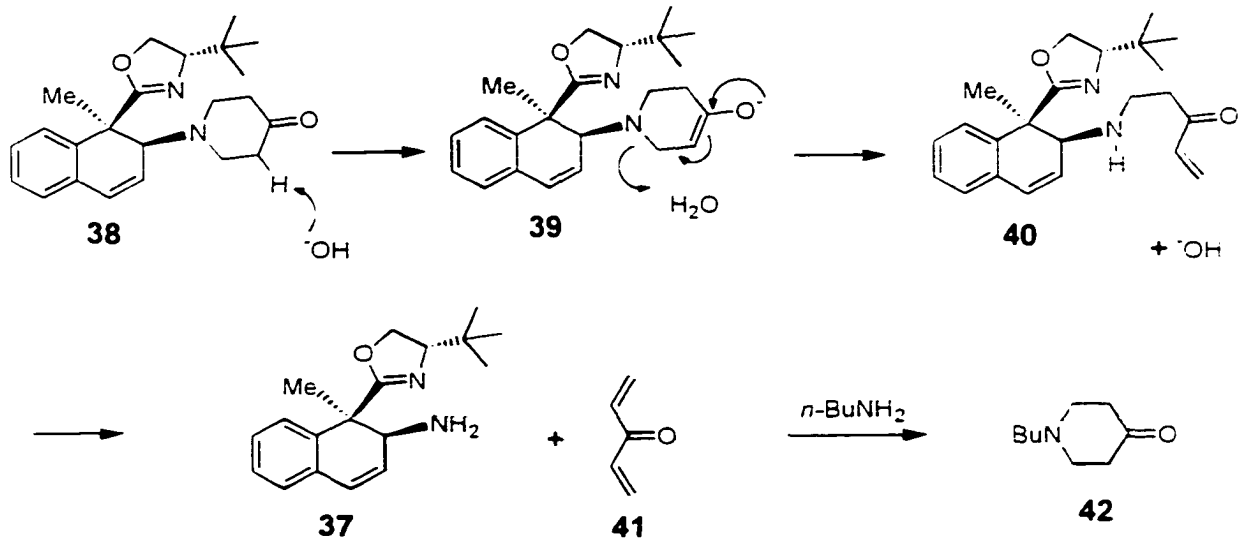
Scheme 9



34 **35** **36** **37**

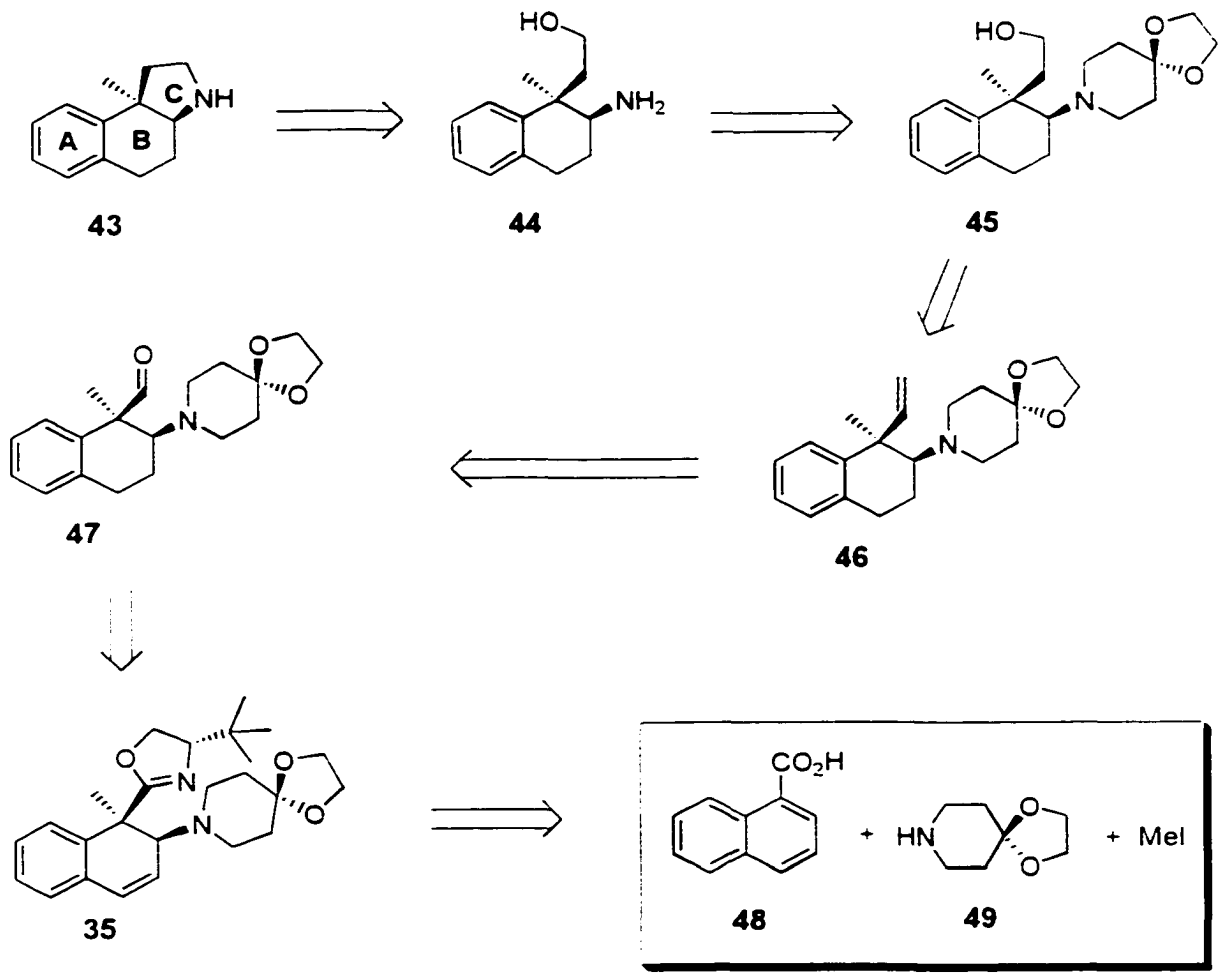
The mechanism (Scheme 10) begins with deprotonation of the ketone to form enolate **39**. β-Elimination of nitrogen affords the vinyl ketone. This process is repeated to liberate the primary amine (**37**), thus circumventing the failure to directly introduce $LiNH_2$.

Scheme 10



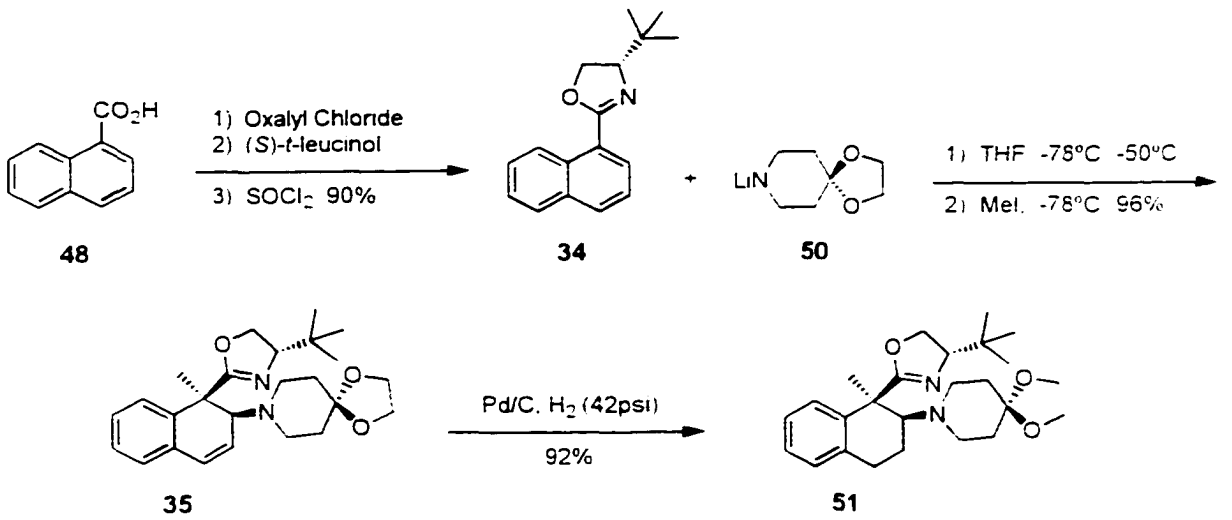
It was the original goal of these studies to extend this methodology to afford a number of structurally rigid aminotetralin analogs, containing a chiral quaternary carbon center in the benzylic position. Our work was first focused on the preparation of **43**, which will be referred to as the *cis*-pyrrolidine-fused aminotetralin. A retrosynthetic analysis for the preparation of **43** is depicted in Scheme 11. It was envisioned that the C ring would be formed from the chiral amino alcohol **44** through an intramolecular Mitsunobu[16] reaction. The primary amine would be obtained *via* a double retro-Michael addition of the piperidone derived from **45**. The alcohol functionality could be installed through hydroboration of the appropriate olefin **46**. The vinyl moiety would be added in a Wittig[17] methylenation with the aldehyde **47** which, in turn, would be synthesized from reductive removal of the oxazoline. The piperidone would then be synthesized *via* a tandem addition reaction of the ethylene ketal of 4-piperidone (**49**) with the oxazoline derived from 1-naphthoic acid.

Scheme 11



To begin, the (*S*)-*tert*-leucinol derived naphthyloxazoline **34** was synthesized by the method outlined by Shimano (Scheme 12).[15] Tandem addition to the naphthalene ring with lithiopiperidone ketal **50**, trapping the anionic intermediate with methyl iodide, gave **35**. The double bond was hydrogenated, using 10 wt% Pd/C and H_2 (42 psi), affording the product (**51**) in 92% yield.

Scheme 12

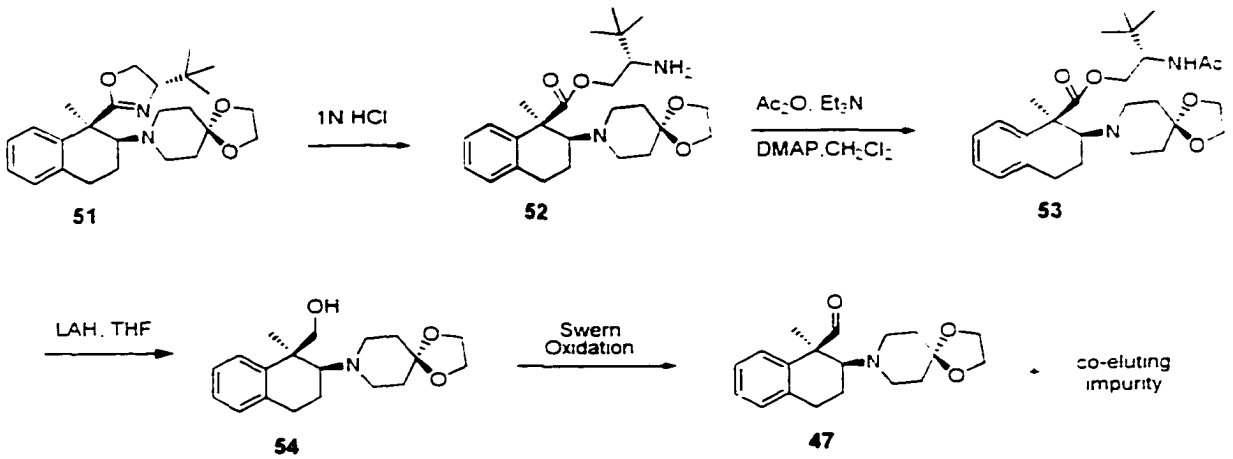


48 34 50 35 51

The next step was an attempt to convert oxazoline **51** into the aldehyde (**47**) *via* the quaternization of the nitrogen with MeOTf, followed by treatment, in turn, with $NaBH_4$ and oxalic acid. However, this reaction sequence yielded a very complex reaction mixture which could not be characterized. Presumably, quaternization with MeOTf is also occurring at the piperidyl nitrogen. Therefore, this method was abandoned in favor of the hydrolysis of oxazoline **51** to amino ester **52** (Scheme 13).

It was originally thought that acid catalyzed ring opening of **51** would proceed without a problem despite the acid-labile ketal because Shimano reported that the same transformation proceeded in quantitative yield when the naphthyl olefin (of **35**) was left intact. However, the change in conformation associated with the hydrogenation apparently renders the ketal vulnerable to cleavage to the ketone. By integration of the ^1H NMR, 23% of the crude mixture appeared to be the ketone, and could not be separated from the desired product by flash chromatography.

Scheme 13

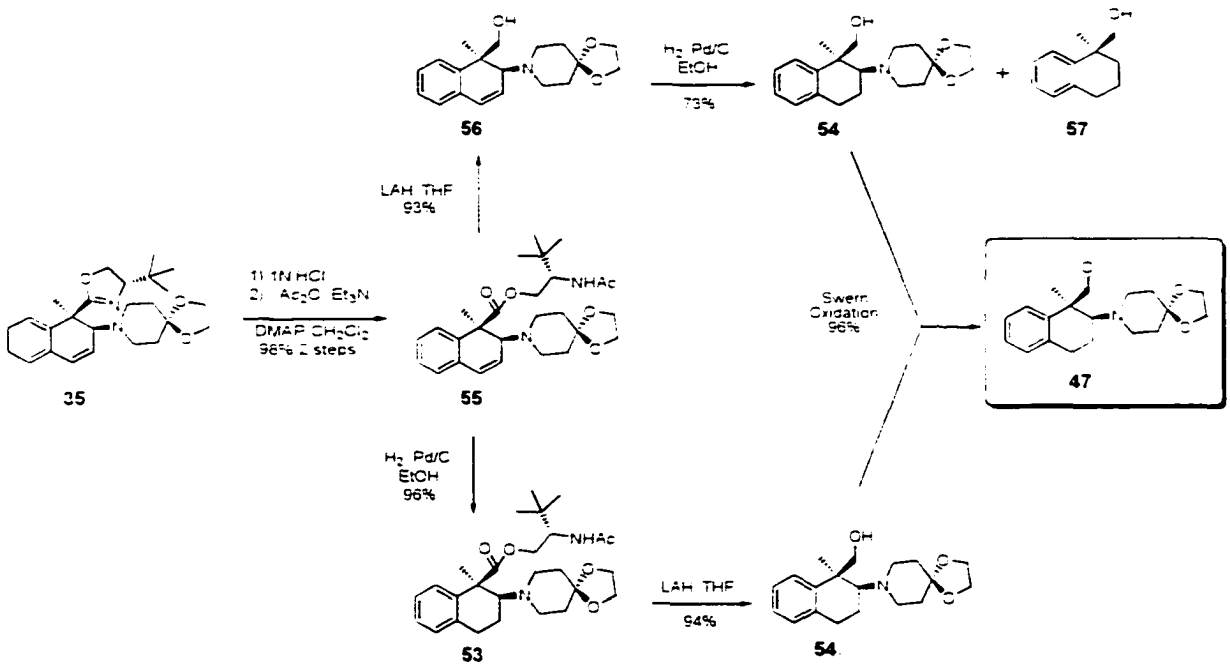


However, the mixture was taken on in the hopes that it could be purified at a later stage. Attempted reduction of aminoester **52** to carbinol **54** without prior protection of the free amino group gave, unsurprisingly, a complex reaction. Acylation of the primary amine of **52** with acetic anhydride proceeded in good yield, but still the mixture from the preceding step could not be purified. Attempts to cleave acylaminoester **53** directly to aldehyde **47** using one equivalent of DIBAL afforded only starting material. Reduction with LAH apparently proceeded well, but again the product (**54**) could not be completely purified. Finally, oxidation under Swern conditions[18] appeared to effect the desired transformation, but aldehyde **47** could not be purified either. At this point, it was decided that a new route had to be found.

As it had been shown previously by Shimano and Meyers that hydrolysis of the oxazoline proceeded without event when the dihydronaphthalene **35** was left intact, it was decided that the latter's olefinic bond would be allowed to remain in place until after hydrolysis of oxazoline **35**, thus avoiding the undesirable deprotection of the ketal (Scheme 14). The primary amine was then converted into acetamide **55** and reduced by

the action of LAH. Attempts to then reduce the olefin, **56**, by treatment with H_2 and Pd/C resulted in unsatisfactory yields (< 75%) of tetrahydronaphthalene **54**. Interestingly, the remainder of the mass balance corresponded to the reductive removal of the piperidone to give **57**. This was easily corrected by performing the hydrogenation prior to the LAH reduction, yielding the tetrahydronaphthalene **53** in 96% yield. The latter, thereafter, then underwent clean reduction by LAH to the desired alcohol (**54**). At this stage, a number of oxidative methods (PCC, PDC, Swern) were explored to effect the transformation of the alcohol into the corresponding aldehyde (**47**). Only the Swern oxidation gave the aldehyde in high yield, furnishing nearly quantitative yields of **47**.

Scheme 14



With aldehyde **47** in hand, it was transformed by a Wittig olefination (Scheme 15) utilizing Ph_3PCH_3Br/*n*-BuLi in THF to give an 81% yield of the desired alkene (**46**). At this juncture it was deemed appropriate to liberate the primary amino group. Removal of the ketal of **46** proceeded cleanly in concentrated HCl. Shimano[15] reported that the double retro-Michael addition proceeded in 82% from the initial tandem addition product **35**. However, following his exact procedure on this substrate resulted in only 14% of the desired product (**59**) - the remainder of the mass balance consisting of decomposition products and a large quantity of starting material. Merely, running the reaction longer (a total of 24 h) and slightly warmer (130°C) afforded the product in 60% yield. This yield was deemed to be too low to be acceptable, so improved reaction conditions were sought. None, however, were found to be superior to that reported above. The results of these attempts are summarized in Table 1. It is important to note that the best case retro-Michael conditions improved to a consistent 80% yield upon scale up.

Scheme 15

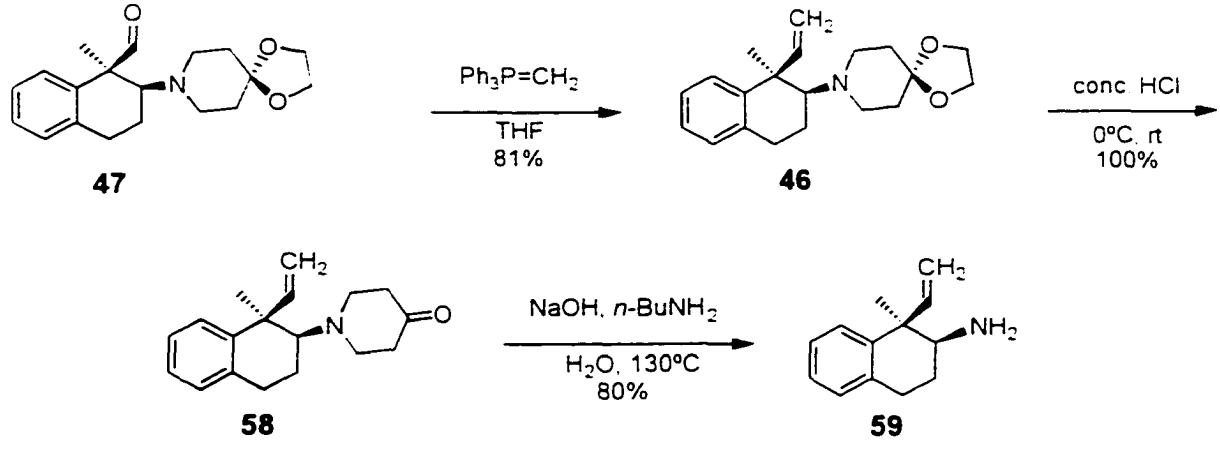
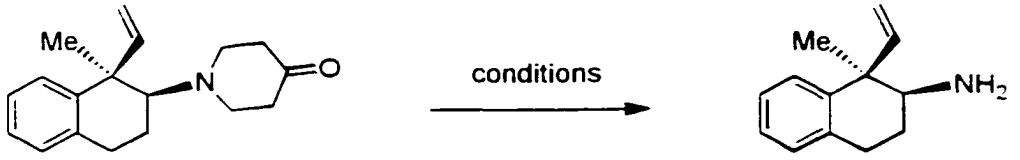


Table 1 - Optimization of Double, Retro-Michael Addition



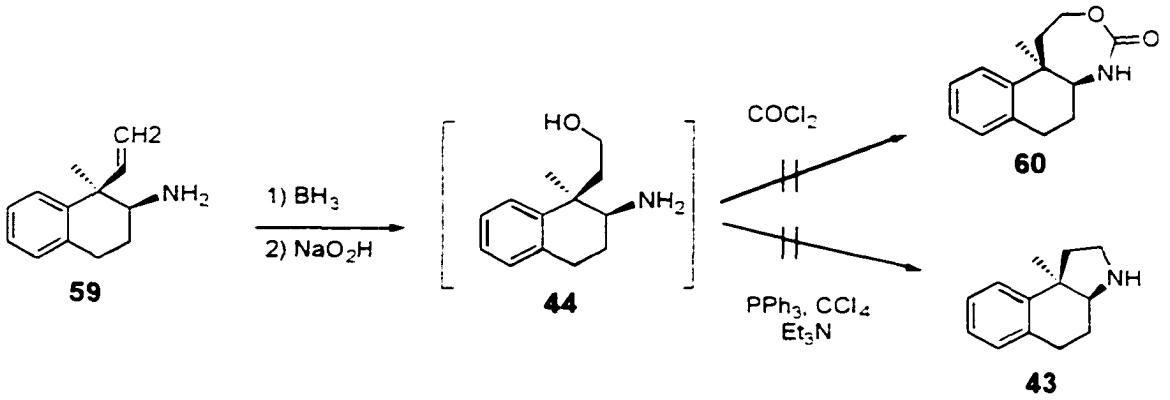
58 **59**

Reagents	Solvent	Time(hrs)/Temp	Result
nBuNH$_2$, NaOH	H$_2$O	24 / 130°C	60%*
nBuNH$_2$, NaOH	THF	5 / 122°C	No Reaction
nBuNH$_2$, NaOH	1:1 THF/H$_2$O	8 / 120°C	Slight Decomposition
nBuNH$_2$, Na°	MeOH	3 / reflux	Slight Decomposition
nHexNH$_2$, NaOH	H$_2$O	12 / reflux	Slight Decomposition
t-butylNH$_2$, NaOH	H$_2$O	10 / 120°C	No Reaction
NaOH	nBuNH$_2$	8 / 120°C	Slight Decomposition
DBU	nBuNH$_2$	3 / reflux	Slight Decomposition
HOAc	nBuNH$_2$	9 / rt	No Reaction
H$_2$SO$_4$	nBuNH$_2$	1 / rt	Some Decomposition
H$_2$NNH$_2$, NaOH	H$_2$O	8 / 120°C	Some Decomposition
Me$_2$NNH$_2$, NaOH	H$_2$O	8 / 120°C	No Reaction
8 eq LDA	THF	10 / -78°C, rt	No Reaction
LiNH$_2$	NH$_3$ (liq)	3 / -78°C, -35°C	No Reaction
KOH, NBu$_4$OH, nBuNH$_2$	CH$_2$Cl$_2$ / H$_2$O	10 / rt	No Reaction

*Upon scale up (35 mg → 1.0 g) the yield improved to a consistent 80%

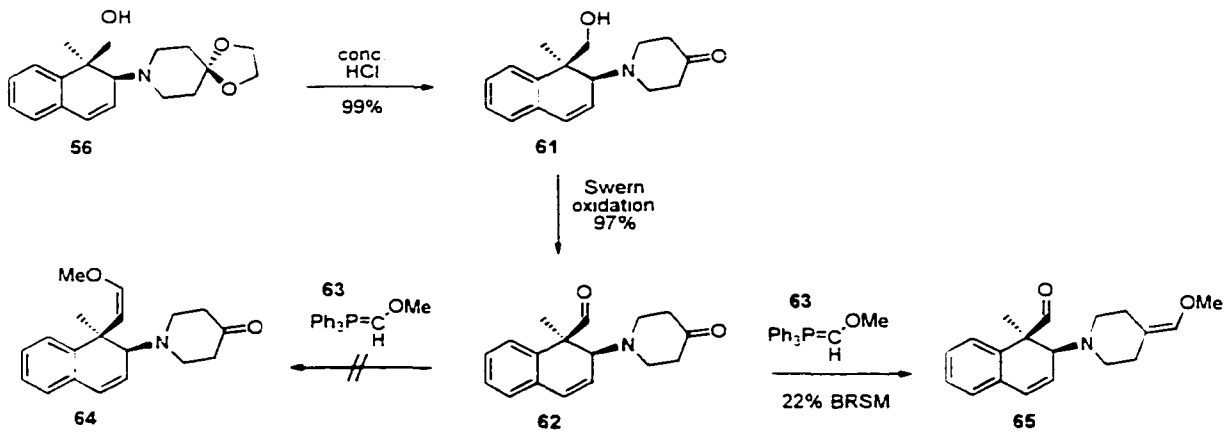
Upon accessing amino-olefin **59**, all of the requisite atoms were now in place for the final pyrrolidine product (**43**). All that remained was to cyclize the amino-olefin. Initial studies examined the incorporation of a leaving group, using the olefin as a platform. It seemed as though the best course of action would be to perform a hydroboration addition to the terminal olefin to afford the amino alcohol **44**, followed by displacement of the hydroxyl group *via* its conversion to a leaving group, or through an intramolecular Mitsunobu reaction. Brown[19] previously reported on the hydroboration of alkenes in the presence of other functional groups. Among those studied was 4-amino-1-butene. In the presence of the pendant primary amine, the reaction was reported to proceed in 71% (GC Yield). Attempts to apply the procedure to **59**, resulted in the disappearance of the vinyl protons from the ^{1}H NMR, however all attempts to purify the expected amino alcohol were unsuccessful. Attempts to derivatize the amino alcohol to cyclic carbamate **60** through the action of phosgene (Scheme 16) gave none of the desired product. In the same vein, attempts to perform the intramolecular Mitsunobu[16] on the crude reaction mixture by treating it with PPh_3, CCl_4, and Et_3N (Scheme 16) also gave none of the desired 2-aminotetralin (**43**).

Scheme 16



A few studies were then performed to ascertain the feasibility of closing the final ring *via* an intramolecular, reductive amination of the primary amine with the appropriate aldehyde. In order to access this compound, addition of a methoxymethine in the Wittig reaction was envisioned to afford the latent aldehyde with the necessary one carbon homologation (Scheme 17). In order to accomplish this goal, carbinol **56** was treated with HCl to remove the ketal. This had to be done at this stage since any conditions which would remove the ketal, would also hydrolyze the methyl enol ether (**64**). Furthermore, the aldehyde, in turn, may not be stable to the conditions of the retro-Michael addition. Hydroxy ketone **61** underwent clean Swern oxidation to afford keto-aldehyde **62.** Despite the marked preference of ylides to add to aldehydes in the presence of ketones,[17] the opposite chemoselectivity was observed; attacking only the piperidone. This can only be rationalized by the sterically demanding environment of the neopentyl aldehyde.

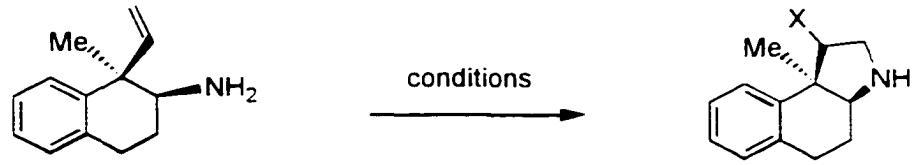
Scheme 17



A look at other cyclization options based upon rendering the olefin of **59** electrophilic were next considered. Initial attempts at performing an amino-mercuration by treatment in turn with $Hg(NO_3)_2$ and $NaBH_4$ to afford **43** directly were unsuccessful.

yielding only starting material (Table 2). This route was not pursued any further as it was anticipated that the conditions required to force **41** to undergo cyclization would favor oxidation of the primary amine by Hg(II).

Table 2 - Attempts to Cyclize Amino-Olefin 59



59 **43**, X=H **66**, X=I

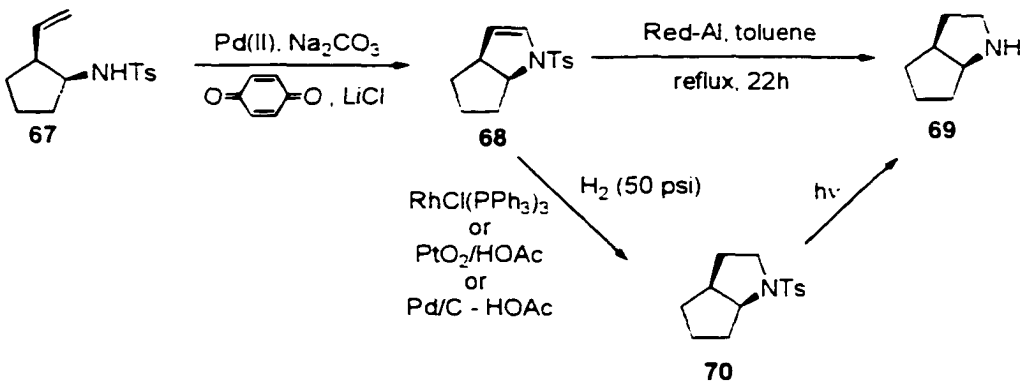
1) $Hg(NO_3)_2$, THF 2) $NaBH_4$, THF	Starting Material
I_2, $NaHCO_3$, CH_3CN	Mostly S.M., some decomp
I_2, $NaHCO_3$, THF	Mostly S.M., some decomp

The next attempt of this type was that of an iodo-amination. No successful literature precedents could be found for this reaction with a simple primary amines. All attempts with simple amines failed, owing to the basicity/nucleophilicity of nitrogen. All successful attempts have entailed converting the nitrogen to an amide or carbamate, and O-alkylation is generally preferred.[20] Regardless of the literature precedents, the iodoamination was nevertheless attempted using standard iodocyclization techniques (I_2, $NaHCO_3$ in CH_3CN or THF).[21] Treatment of **59** with iodine led to instantaneous decolorization, suggesting that the iodine had undergone some sort of reaction. However,

upon workup there was some decomposition, but most of the starting material was recovered unchanged. It is believed that an unproductive N-iodo species was made, and was reduced back to starting material upon treatment of the crude reaction mixture with $Na_2S_2O_3$, during the workup.

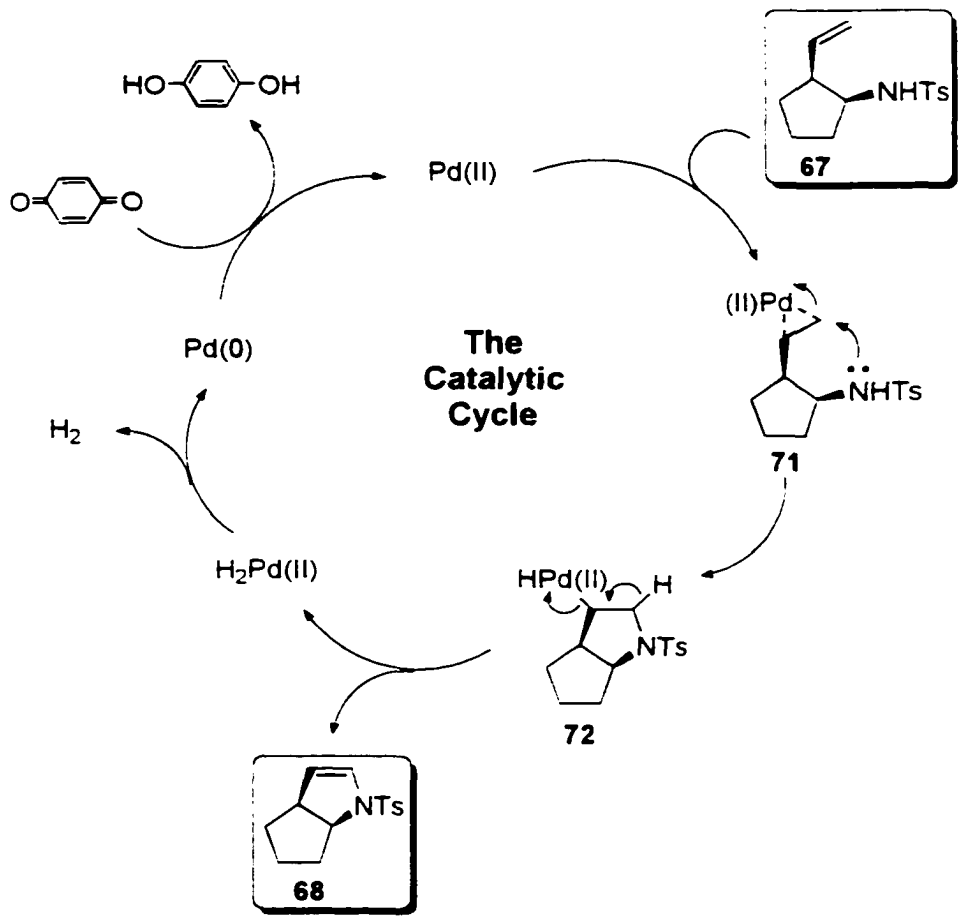
It was then suggested that palladium may induce the cyclization. However, Hegedus[22] found that attempts to cyclize primary amino-olefins were unsuccessful, yielding stable, isolable complexes of palladium, instead. To bypass this coordination, the primary amine was converted to the less basic tosylamide **67**. The latter was subjected to cyclization conditions and afforded good yields of N-tosylheterocycle **68** (Scheme 18) The example shown represents the most analogous system in the Hegedus study Formation of the 5-membered ring from the pendant terminal olefin was their poorest reported example (57%) and likely reflects the desire of the sulfonamide to attack the more substituted carbon, but this would require the formation of a 4-membered ring. The enamide (**68**) was reported by Hegedus[22] to undergo conversion to the saturated amine (**69**) *via* a one-step Red-Al reduction or by a two step hydrogenation/detosylation procedure (**68** → **70** → **69**).

Scheme 18



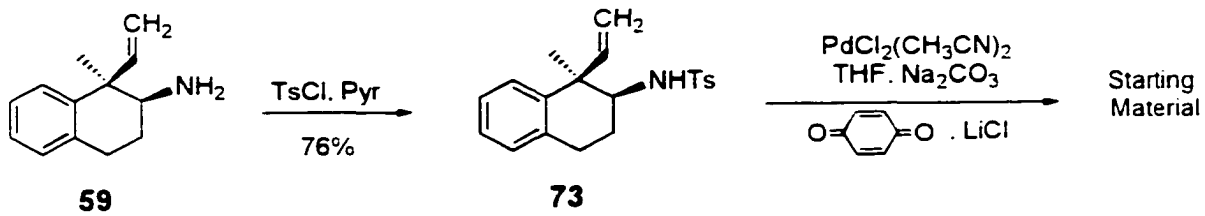
The mechanism (Scheme 19) is believed to proceed *via* coordination of Pd(II) to the olefin, followed by intramolecular attack of nitrogen to give cyclic organopalladium intermediate **72**. β-Hydride elimination of **72** effects product formation (**68**), eliminating Pd(0). Benzoquinone reoxidizes palladium to Pd(II), making the process catalytic in palladium.

Scheme 19



In line with the above studies, tosylation of amino olefin **59** proceeded well, affording sulfonamide **73** in 76 % yield (Scheme 20). Direct attempts to exactly repeat this process in the system at hand (**73**) were completely unsuccessful, affording complete recovery of starting material.

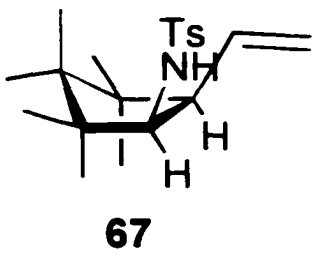
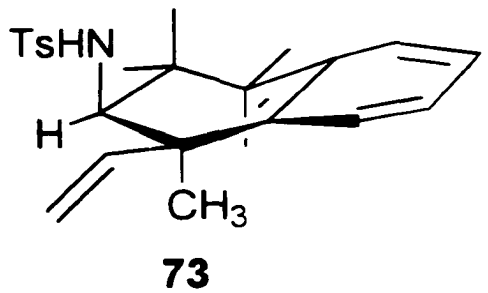
Scheme 20



59 **73**

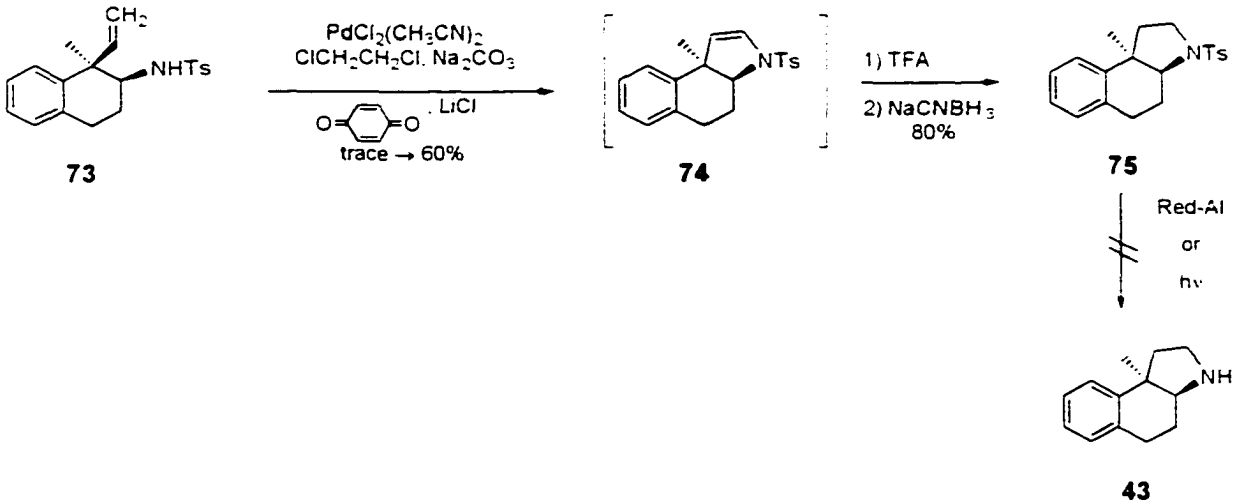
It was believed that perhaps the present olefin (**73**) is not in a position to undergo coordination to Pd(II), or once coordinated, to undergo intramolecular cyclization. The primary difference between **73** and **67** was the inclusion of the quaternary carbon in **73** which rendered the olefin adjacent to a neopentyl center. Palladium coordination is known to be highly sensitive to steric requirements,[23] and may not have been able to coordinate given the hindered nature of olefin **73**. Further, there may be differences in the conformation associated with differences between a *cis*-1,2-disubstituted cyclopentane (**67**) and a benz-fused *cis*-1,2-disubstituted cyclohexane (**73**). These differences are shown in the Figure 1, contrasting the two.

Figure 1

 **67**	 **73**
Olefin is properly aligned to undergo cyclization, placing the palladium in an unencumbered position.	In order to undergo cyclization, palladium must align itself such that it is very close to the axial methyl and the adjacent proton.

Given the above, it was thought that if the steric requirements of Pd(II) were decreased it may be possible to get the more hindered **73** to undergo cyclization. With this in mind a number of different solvents (CH_2Cl_2, $ClCH_2CH_2Cl$, 2,5-dimethyl-THF, DME, toluene, DMF, CH_3CN) and conditions (temperatures and reoxidants) were surveyed. The most effective process found involved the use of 3 portions of 5% catalyst in dichloroethane, yielding the tricycle in up to 60% (Scheme 21). However, this reaction proved to be highly capricious, affording **74** in yields ranging from trace to the above 60%. Further, **74** was found to be very unstable - an observation also noted by Hegedus in similar systems.[22] Consequently, the material had to be taken on directly

Scheme 21



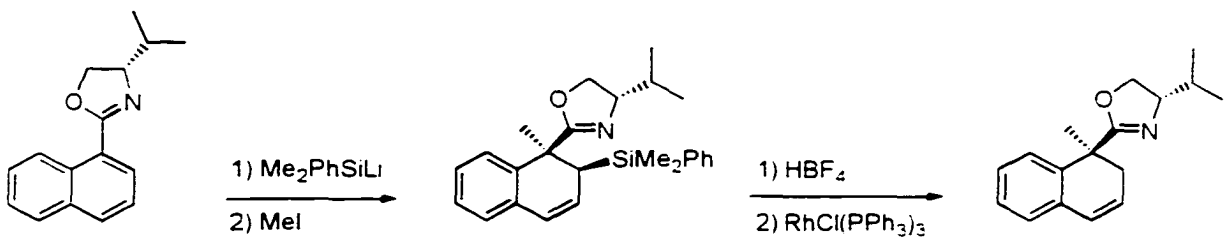
Reduction of the C-C double bond was attempted under several sets of conditions which included hydrogenation using PtO_2 (60 psi H_2), $RhCl(PPH_3)_3$ (1 atm H_2), and treatment of tosylenamide **74** in sequence with TFA and $NaCNBH_3$. Only the last method proved successful, affording **75** in 80% yield.

Both of the cleavage conditions outlined by Hegedus were attempted to remove the sulfonamide protecting group, yet, these failed to liberate the secondary amine The length of the route, coupled to irreproducibility in the palladium-catalyzed cyclization, and inability to cleave the sulfonamide prompted us to investigate yet another path.

D. Synthesis of Novel 2-Aminotetralins *via* the Conjugate Addition of DimethylPhenylSilyllithium to Chiral Naphthyloxazolines

It was shown by Meyers and Hulme[24] that dimethylphenylsilyllithium undergoes the tandem addition reaction on **76** to afford **77** as a single diastereomer. In their work, the silane was a mere proton surrogate, allowing the creation of chiral 1,1-disubstituted dihydronaphthalenes, **78**. This is outlined in Scheme 22. It was found that protodesilylation was accompanied by isomerization of the double bond. Exposure of the olefinic mixture to Wilkinson's catalyst allowed isomerization back to the styrene-conjugated alkene, **78**.

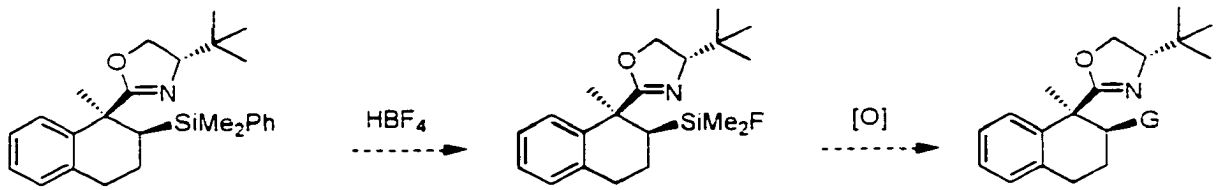
Scheme 22



76 **77** **78**

It was felt that this same methodology would allow installation of a hydroxy group (Scheme 23) *via* protodesilylation of the phenyl group and subsequent Tamao oxidation [25] It was hoped that carbinol **81** (G=OH) could be converted to a leaving group which would then be displaced by nitrogen, affording the 2-amino derivative, **81** ($G=NH_2$) which still remained as the goal of this study.

Scheme 23



79 **80** **81**. G=OH, NH_2

Table 3 - Optimization of Silyllithium Additions to 34

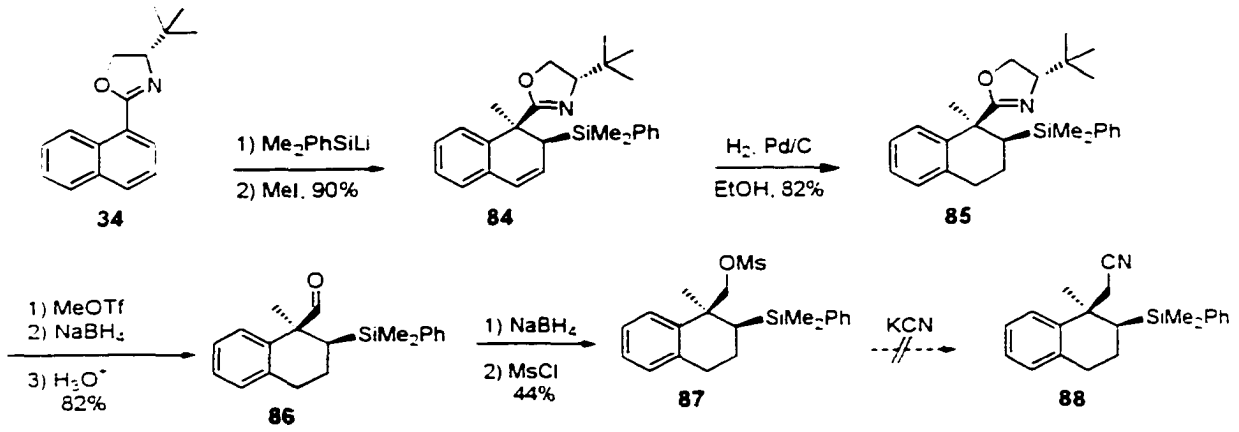
34 **83**

Nucleophile	Solvent, Temp	Result
Ph_3SiLi	THF, -78°C	Complete recovery of S.M.
$MePh_2SiLi$	THF, -78°C	52% as 1 diastereomer / the remainder appears to be 1,6 addition as 1:1 ratio of diastereomers
$MePh_2SiLi$	4:1 Et_2O/THF, -78°C	Complete recovery of S.M
$Me_2PhSiLi$	4:1 Et_2O/THF, -78°C	90% isolated as a single diastereomer

To this end, naphthyloxazoline **34** was treated with a number of trialkylsilyllithiums which are prone to protodesilylation. The results of these attempts are summarized on Table 3. The final example confirms Hulme's work. Inspection of the vinyl region of the ^{1}H NMR of the crude reaction mixture obtained from $Me_2PhSiLi$ addition reaffirms Hulme's assertion that addition is completely stereoselective, exhibiting only one set of signals for the double bond.

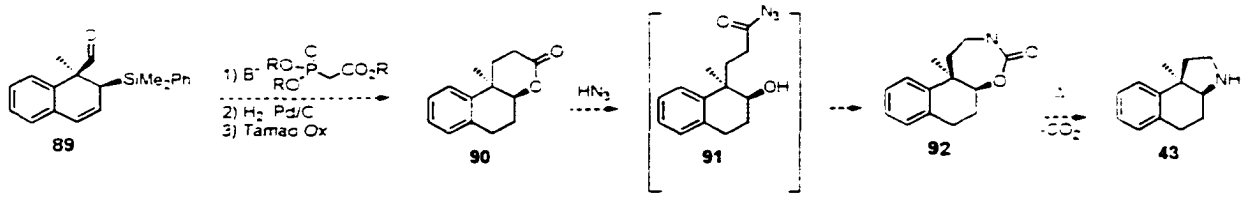
As the addition of $Me_2PhSiLi$ remained the most successful, it was used in subsequent work. Hydrogenation with Pd/C was performed immediately to fortify the stereochemical integrity of the allylsilane to give tetrahydronaphthyloxazoline **85**. Subsequent reductive hydrolysis by previously established procedures afforded aldehyde **86** in 82% yield. The aldehyde was reduced with sodium borohydride and then converted to mesylate **87**. It was envisioned that the necessary C-N tether would be incorporated by displacement of the sulfonate with KCN. Furthermore, it was recognized that this represented displacement of a neopentyl leaving group, but hopes were high that this barrier could be overcome. Attempts to displace the mesylate with KCN in polar aprotic solvents (DMF and DMSO) at elevated temperatures led to some decomposition, but no detectable nitrile (**88**). Finally an attempt was made wherein the reaction was performed in acetonitrile in the presence of 18-crown-6 to liberate the 'naked' cyanide ion.[26] This too, was unsuccessful. This strategy was then abandoned in favor of other potential reactions of the readily available aldehydes **86** or **89**.

Scheme 24



It was felt that aldehyde **89** could be elaborated to δ-lactone **90** *via* a Horner-Wadsworth-Emmons olefination,[27] followed by hydrogenation, and Tamao oxidation as depicted in Scheme 25. Addition of hydrazoic acid across the lactone should then achieve an equilibrium concentration of acyl azide, which should undergo a Curtius rearrangement[28] followed by intramolecular trapping by the hydroxyl group to afford the cyclic urethane (**92**). This would install the necessary nitrogen functionality and allow thermal extrusion of CO_2 which would provide completion of the synthesis with some degree of flexibility.

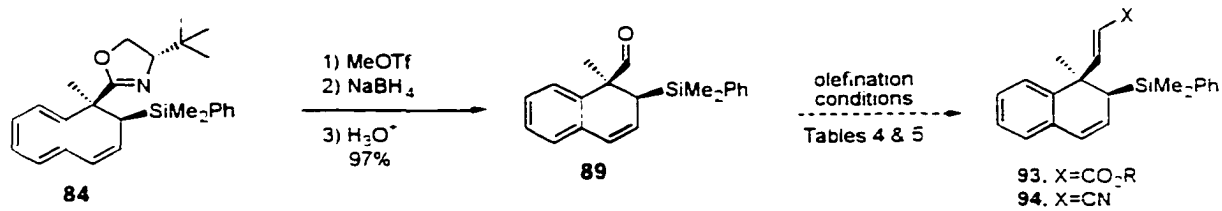
Scheme 25



It was deemed desirable to leave the double bond of the dihydronaphthyl system (**89**) intact so as to require only one hydrogenation to effect reduction of both that unsaturation and that installed in the olefination. The requisite unsaturated aldehyde (**89**)

was prepared in an analogous fashion (Scheme 26), affording quantitative yields of **89**. Olefination of the resulting aldehyde was found to be very problematic, giving rise to variable mixtures of product and desilylated material.

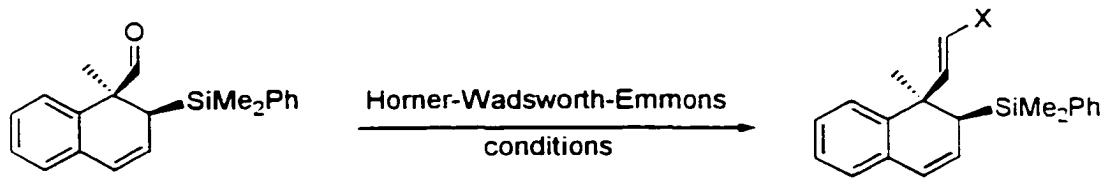
Scheme 26



An exhaustive review of reaction conditions, varying the nature of the organophosphorous reagent, base, and solvent was pursued in order to optimize olefination of the aldehyde. The first series of experiments evaluated the behavior of aldehyde **89** in the Horner-Wadsworth-Emmons olefination. The results of these studies are tabulated in Table 4. Installation of the ester of **93** could not be increased above 17% and incorporation of the nitrile of **94** could not be optimized above 34%.

It was hoped that this obstacle might be overcome by using less reactive organophosphorous reagents, such as stabilized ylides. The results of these experiments are outlined in Table 5. Initially it was found that low-boiling solvents gave no reaction and attempts to increase the reactivity by proceeding to higher temperatures was accompanied by decomposition products. Suspecting that the allyl silane functionality was the point of decomposition, it was assumed that the substrate may be rendered more stable by reduction of the olefin.

Table 4 - Horner-Wadsworth-Emmons Olefination of 89



89

93, X=CO_2R
94, X=CN

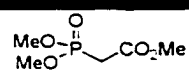
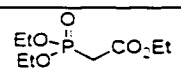
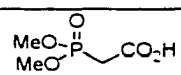
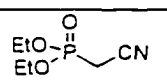
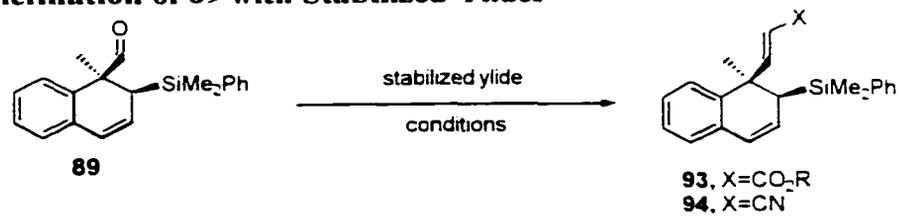
HWE reagent	base	solvent	result
	LiCl, DBU	CH_3CN	17%
same	LiCl, DIEA	CH_3CN	~17%
same	LiBr, Et_3N	THF	S.M.
same	NaH	THF	decomp
same	KH	THF	decomp
	LiCl, DBU	CH_3CN	~17%
	n-BuLi	THF	decomp
	LiCl, DBU	CH_3CN	34%
same	LiCl, DBU	Et_2O	42%
same	LiCl, DBU	toluene	15-20%
same	LiCl, DBU	CH_2Cl_2	15-20%
same	LiCl, DBU	THF	33%
same	LiCl, DBU	Hexanes	<15%
same	NaH	THF	decomp

Table 5 - Olefination of 89 with Stabilized Ylides

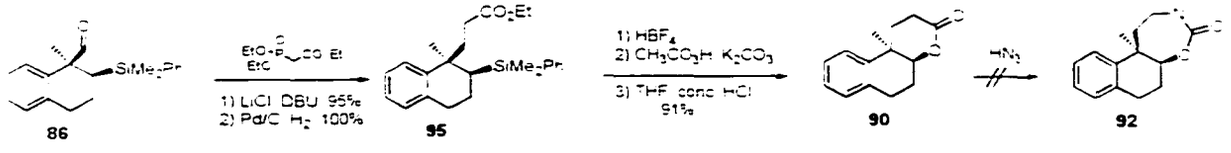


89

93, X=CO_2R
94, X=CN

stabilized ylide	conditions	result
$Ph_3P{=}CHCO_2Me$	CH_2Cl_2, reflux	S.M.
same	$ClCH_2CH_2Cl$, reflux	S.M.
same	chlorobenzene, reflux	decomp
same	DMF, 80C	decomp
same	EtCN, reflux	decomp
$Ph_3P{=}CHCN$	$ClCH_2CH_2Cl$, reflux	S.M.

Scheme 27

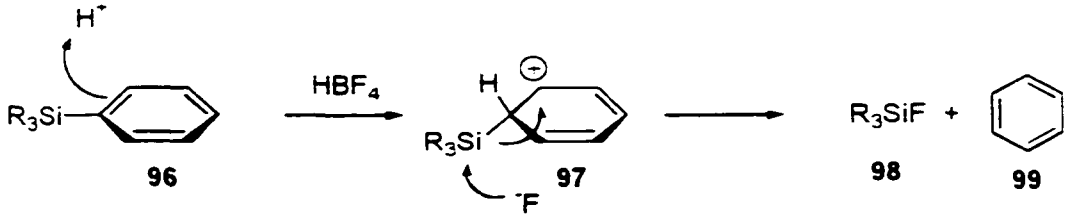


86 **95** **90** **92**

Horner-Wadsworth-Emmons olefination proceeded smoothly on the saturated aldehyde, **86**, affording the unsaturated ester (**93**) exclusively as the Z isomer in 95% chemical yield (Scheme 27). The olefin underwent clean reduction to give a quantitative yield of the saturated, aliphatic ester (**95**) which set the stage for conversion of the silyl group to a carbinol, and ultimately to lactone **90**. The first step of this sequence requires that one of the alkyl groups on silicon to be replaced with fluoride. This transformation

was effected without event by treatment with HBF_4 and is believed to occur *via* protonation of the phenyl ring followed by fluoride attack on silicon to displace benzene (Scheme 28).

Scheme 28



The silyl fluoride (**98**) was taken on directly to the Tamao oxidation, utilizing excess peracetic acid and K_2CO_3 in acetic acid. Although most of the hydroxy ester cyclized to lactone **90** under the reaction conditions, it was found to be beneficial to include a separate acid-catalyzed lactonization step to afford lactone **90** in 91% yield over 3 steps. However, all attempts to utilize this material in the Curtius rearrangement failed. Its failure is presumed to be due to disfavored energetics associated with hydroxy acyl azide **91**, favoring lactone **90** instead (**90** ⇋ **91**, Scheme 25).

The next series of experiments focused on the ring opening of lactone **90** with electrophiles to afford carboxylic acid derivatives with a pendant leaving group (Scheme 29). Should this be successful, the Curtius rearrangement may again install the requisite nitrogen which might cyclize spontaneously to afford the target aminotetralin (**43**). These studies are summarized in Table 6. Unfortunately, all reaction conditions employed either returned starting material unchanged or led to extensive decomposition products.

Scheme 29

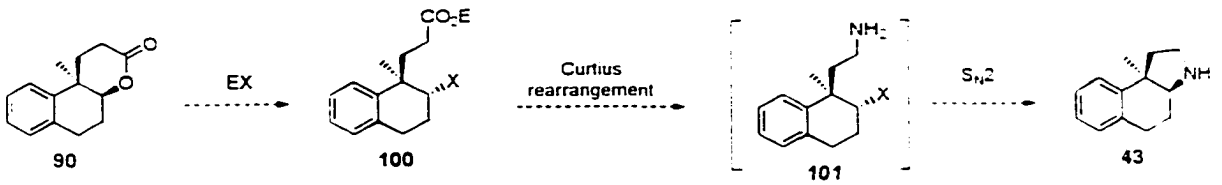
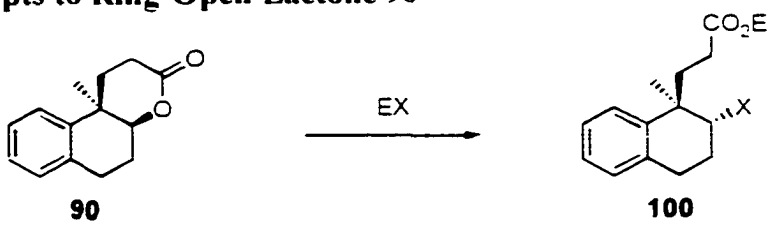


Table 6 - Attempts to Ring-Open Lactone 90

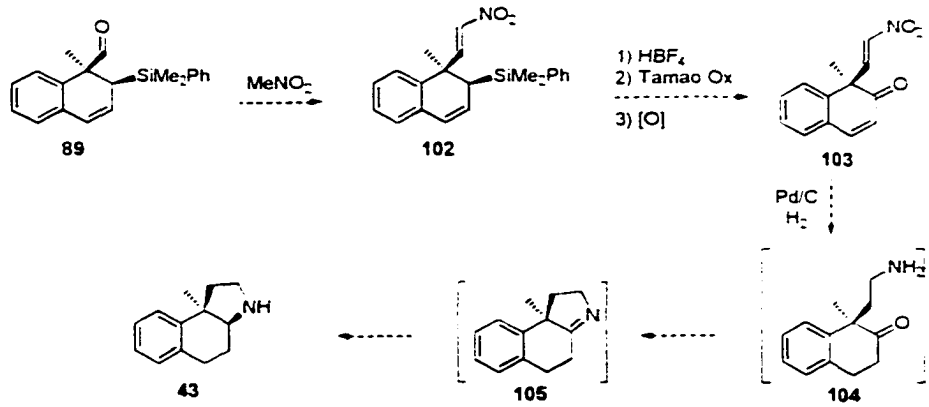


TMSCl/KI	CH_2Cl_2	S.M.
TMSI [I_2/ $(Me_3Si)_2$]	CH_2Cl_2	decomp
$TiCl_4$	CH_2Cl_2	S.M.
$TiBr_4$	CH_2Cl_2	S.M.
BBr_3	CH_2Cl_2	decomp
$SOCl_2$	neat	decomp
HBr	CH_2Cl_2/H_2O	S.M.

Another, totally different route was explored; one in which the requisite nitrogen functionality and one carbon homologation would be installed *via* the Henry reaction[29] (nitromethane + **89**). Beginning with aldehyde **89**, treatment with nitromethane should afford nitro olefin **102** (Scheme 30). With this in place, protodesilylation and Tamao oxidation would be attempted to give the carbinol which would be oxidized to afford the nitro ketone (**103**). It is conceivable that treatment of **103** with Pd/C and a hydrogen source would introduce 6 moles of hydrogen to liberate the target compound. *Thus, the*

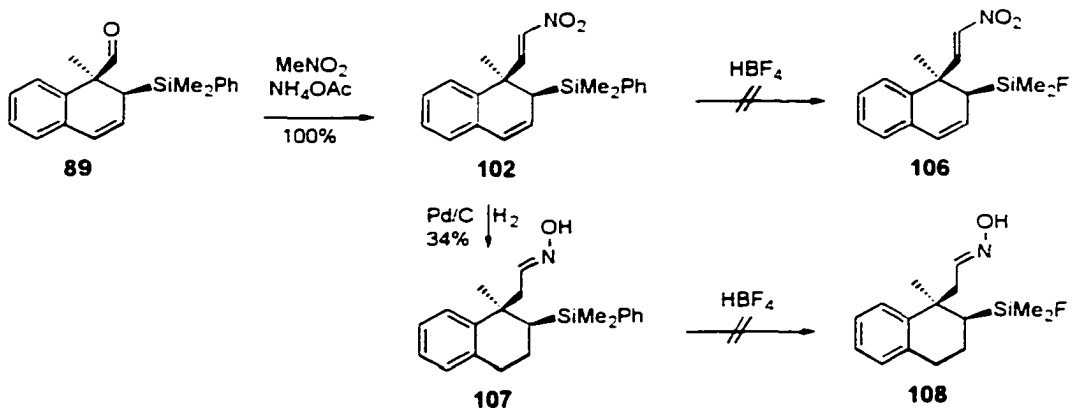
*target (**43**), in enantiomerically pure form, could be accessed in a single hydrogenation step by reduction of nitroketone **103**.*

Scheme 30

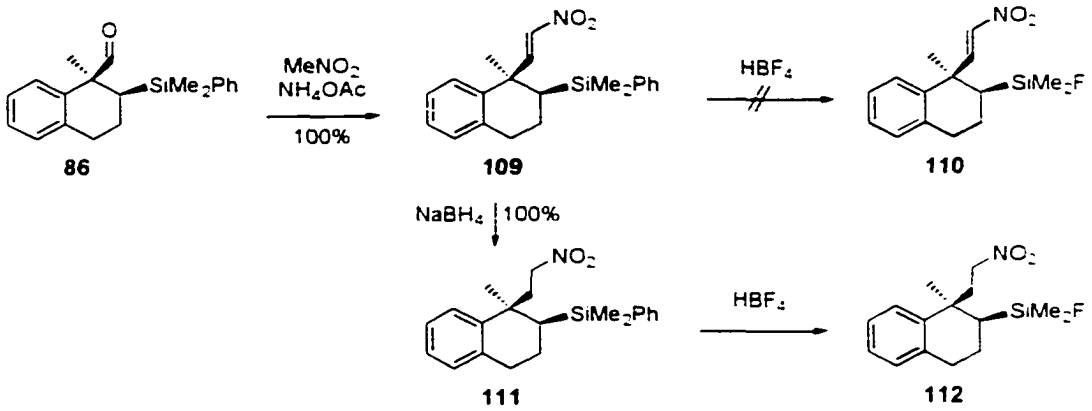


The Henry reaction proceeded smoothly affording a quantitative yield of nitro olefin **102** (Scheme 31). However, all attempts to protodesilylate this material to **106** were unsuccessful giving rise to heavy decomposition. This was not wholly unexpected as allyl silanes are known to undergo conjugate addition reactions with α,β-unsaturated nitro compounds. It was felt that this could be overcome by reduction of one or both of the C-C double bonds. Pd-catalyzed hydrogenation gave oxime[30] **107** which was also found to be unstable to the protodesilylation conditions, furnishing none of **108**

Scheme 31



Scheme 32



Returning to aldehyde **86** wherein the styrene double bond had been reduced (Scheme 32), this also underwent the Henry reaction to give a quantitative yield of nitro olefin **109**. Subjection of this compound to protodesilylating conditions also gave rise to decomposition products. In the interest of completeness, the remaining double bond adjacent to the nitro group was quantitatively reduced by a method reported[31] many years ago from these labs. Subjection of this fully saturated nitrocompound (**111**) to HBF_4 gave clean conversion to the silylfluoride (**112**) which underwent the Tamao oxidation to give the hydroxy nitro compound (**113**). Although well precedented[32] in the literature, all attempts to oxidize alcohol **113** to a nitro ketone (Table 7) surprisingly gave mixtures of the desired product (**114**) and lactone **115**, in favor of the lactone.

Scheme 33

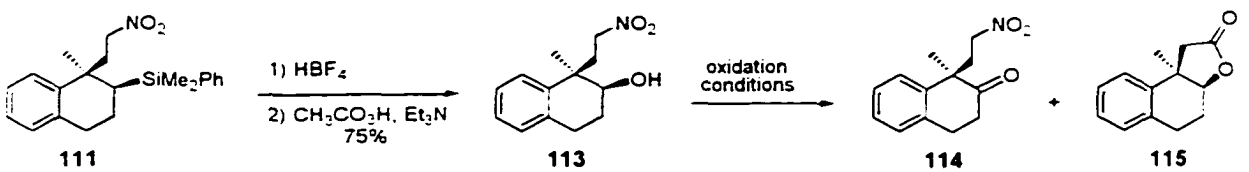


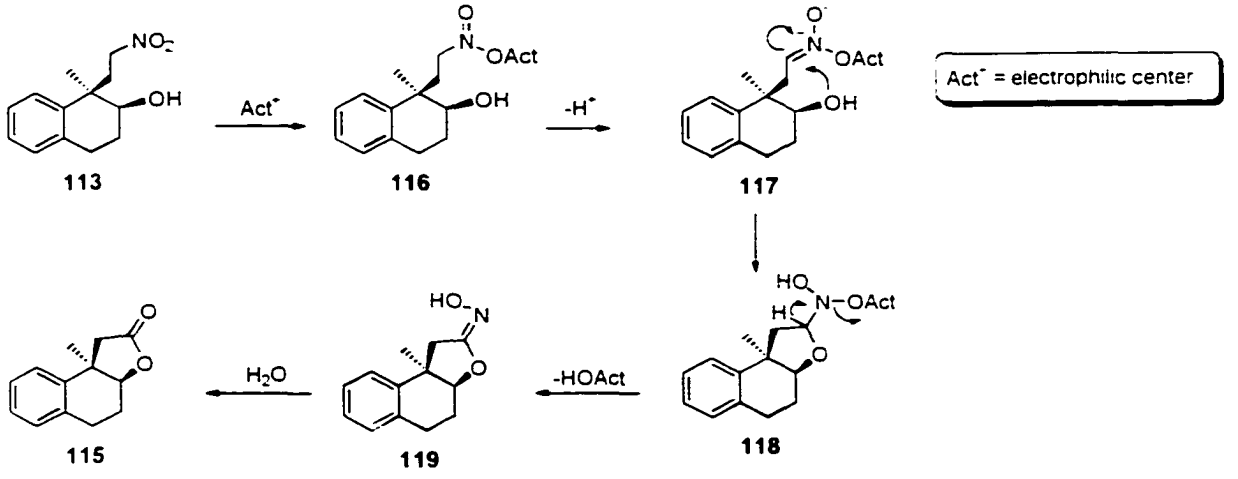
Table 7 - Attempts to Oxidize 113 to 114

Oxidation Conditions	Ratio of 114 : 115
$(COCl)_2$, DMSO (Swern Ox.)	1 : 3.0
PCC, CH_2Cl_2	1 : 1.8
PDC, CH_2Cl_2	1 : 1.8
Dess-Martin periodinane, CH_2Cl_2	1 : 2.8
Jones reagent	1 : 3.5
TPAP, NMO, mole sieves, CH_2Cl_2	1 : 19

Generation of lactone **115** from nitro alcohol **113** was completely unexpected. A search of the literature revealed no precedents for this transformation. In fact, there are several reports[32] of the oxidation hydroxy nitro compounds to nitro ketones. It is believed that this transformation occurs *via* the mechanism shown in Scheme 34. In the proposed mechanism it is postulated that the electrophilic center of the oxidant coordinates to the nitro group rather than the neopentyl alcohol (**116**), activating it toward enolization (**117**). The hydroxyl group then adds intramolecularly to the aci-nitro form of **117** to afford **118**. This intermediate can in turn eliminate the activated oxygen of the nitro group to afford the *N*-hydroxyimidate (**119**). Hydrolysis completes the formation of **115**. It is expected that this transformation is not very general, and arises because of two factors. First, the sterically demanding nature of the neopentyl alcohol inhibits the coordination of the electrophile to the hydroxyl lone pairs. Second, the close proximity of the alcohol to the

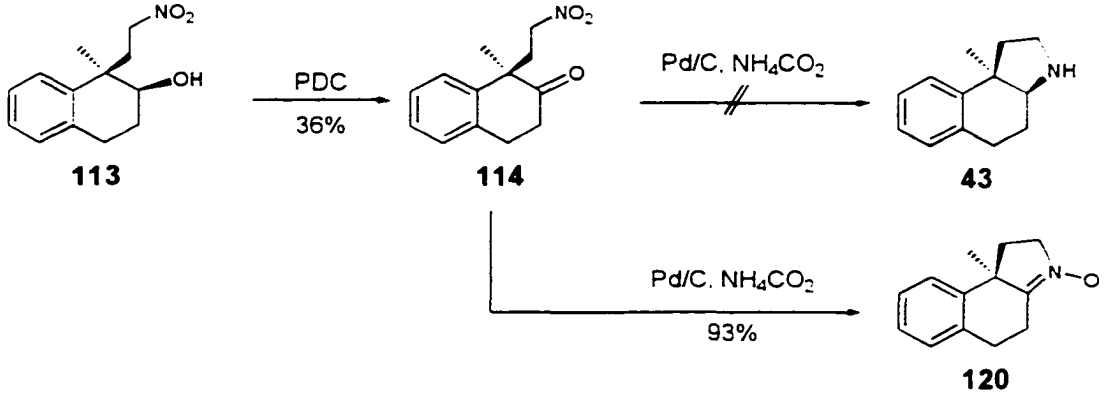
α-carbon of the nitro group provides for very rapid intramolecular cyclization to give intermediate **118**.

Scheme 34



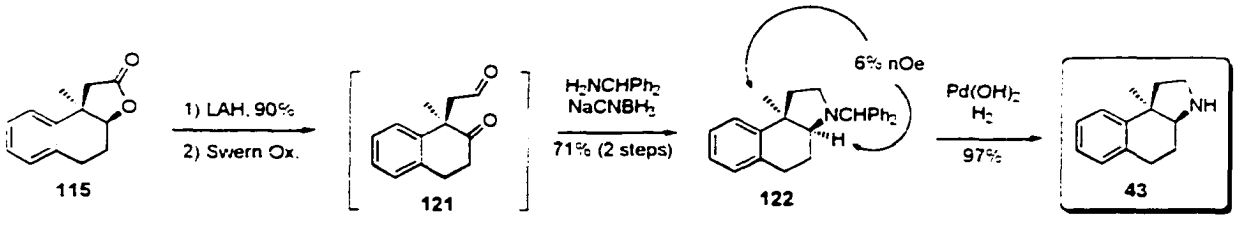
Even though oxidation to **114** could not be improved beyond a 36% yield, the reduction to **43** was attempted. Treatment of nitro ketone **114** with Pd/C under phase transfer hydrogenation conditions gave nitrone **120** as the only product (Scheme 35). A survey of the literature revealed that this is a known process[33] and arises from intramolecular cyclization of the hydroxylamine intermediate before hydrogenation of the nitro group is completed.

Scheme 35



As the yield of nitro ketone **114** could not be improved beyond 36%, and the literature dictates that nitrones generally require a two-step reduction[34] (cleavage of the N-O bond and reduction of the imine) to the corresponding saturated amine, this route was abandoned. As it was found that lactone **115** could be prepared exclusively by treatment with TPAP/NMO in high yield (93%), it was decided to use this intermediate to complete the synthesis of aminotetralin **43** (Table 7). Reduction of **115** with LAH afforded the diol in 90% yield which was then oxidized to keto aldehyde **115** (Scheme 36). The keto aldehyde proved to be highly unstable and was utilized directly without purification. Double reductive amination was effected by treatment of keto aldehyde **121** with benzhydryl amine and sodium cyanoborohydride to give a 71% yield of the desired ring system (**122**) as a 9:1 ratio of diastereomers which were readily separable by column chromatography. The relative stereochemistry of the major diastereomer (**122**) was unambiguously established by nOe studies of the quaternary methyl with the α-hydrogen which confirmed the *cis*-fused ring system. The benzhydryl group of **122** was readily cleaved under hydrogenolysis conditions to afford aminotetralin **43** - *the main target of these studies*.

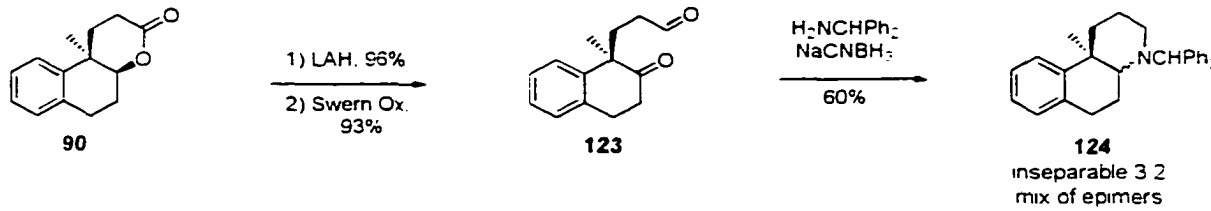
Scheme 36



Since the γ-lactone was nicely converted to the pyrrolidine-fused tetralin (**43**), it was felt that elaboration of the analogous δ-lactone might provide access to the piperidine-

fused tetralin. With this in mind, **90** was reduced with LAH to afford the diol in 96% yield which in turn was oxidized under Swern conditions to give 93% of keto aldehyde **123** (Scheme 37). This keto aldehyde proved itself to be much more stable than that described in the previous series, thus allowing purification by column chromatography and complete characterization. Double reductive amination on **123** with benzhydrylamine and $NaCNBH_3$ proceeded in good chemical yield, but gave **124** as a 1.5 : 1.0 ratio of diastereomers. All attempts to fully separate the epimers failed.

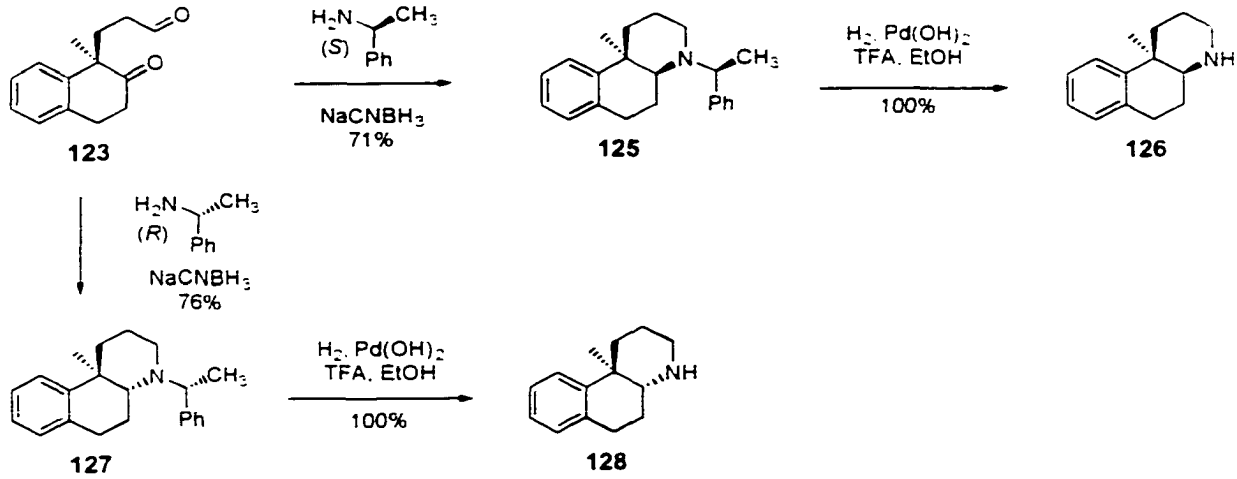
Scheme 37



90 **123** **124**
inseparable 3:2
mix of epimers

Due to the poor diastereoselectivity observed and the inability to separate the isomers, the reductive amination on **123** was again examined. In order to assess whether the use of a chiral amine may direct the reductive amination to favor either the *cis* or *trans*-fused isomer, keto aldehyde **123** was condensed, separately, with each enantiomer of α-methylbenzylamine (Scheme 38). Furthermore, introduction of an additional stereocenter could be expected to further differentiate the *cis* and *trans*-fused product, allowing their chromatographic separation. When (*S*)-α-methylbenzylamine was used, the double reductive amination went with complete diastereoselectivity, affording only the *cis*-fused ring system (**125**) as determined by an nOe analysis. Treatment of this compound with Pearlman's catalyst (palladium hydroxide) in the presence of H_2 gave rise to the *cis*-fused-6,6-aminotetralin **126**.

Scheme 38

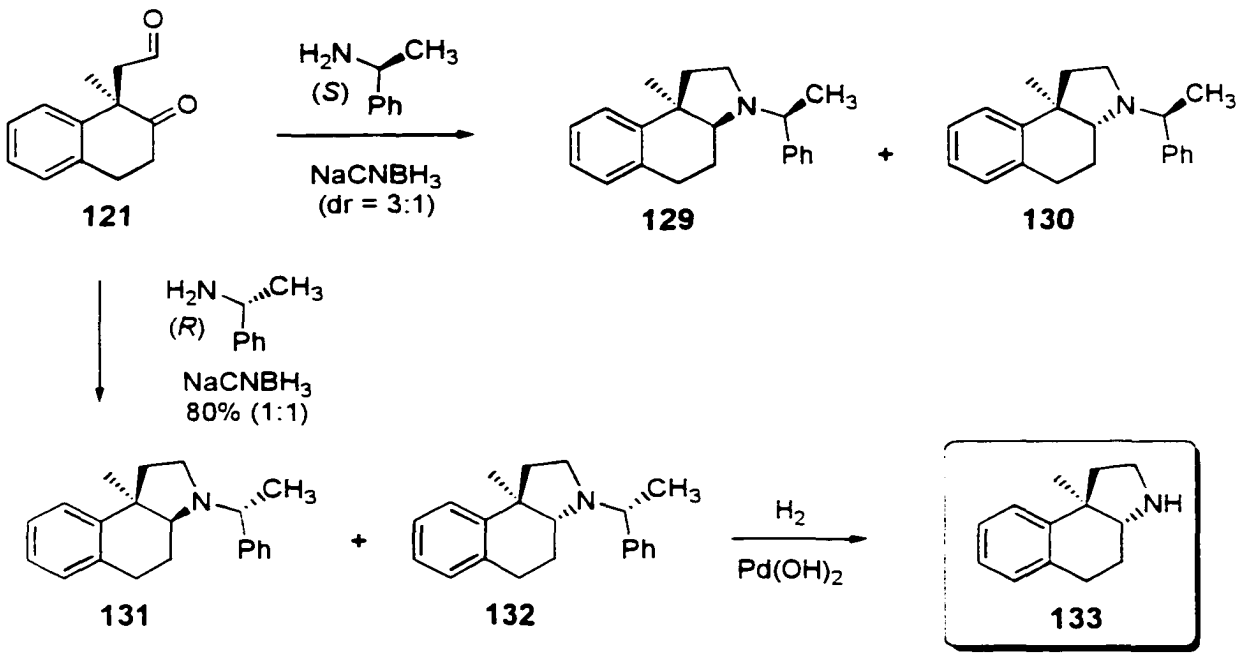


Alternately, if (*R*)-α-methylbenzylamine was condensed with keto aldehyde **123**, only the *trans*-fused ring system was observed. This was at first suggested by distinct differences in the 1H NMR and the lack of an nOe response between the angular methyl and the adjacent methine. It was later confirmed by hydrogenolysis of the benzylamine to give an aminotetralin that differed from *cis*-fused aminotetralin **126**, prepared above.

Given this apparent directing affect associated with the use of chiral α-methylbenzylamines in the double reductive amination, it was felt that the same directing effect may be observed in the pyrrolidine-fused tetralin (**43**) even though the earlier synthetic route gave a separable 9:1 ratio. If this was to hold true, it was expected that use of (*S*)-α-methylbenzylamine would give rise to the *cis*-fused aminotetralin (**43**) as a single diastereomer. Alternately it was hoped that use of (*R*)-α-methylbenzylamine would overcome the internal preference to form the *cis*-fused ring system, affording the *trans*-fused aminotetralin (**132**) preferentially.

Unfortunately, condensation of the 1,4-dicarbonyl compound (**121**) with (*S*)-α-methylbenzylamine gave rise to a mixture of **129** and **130** as a 3 : 1 ratio of diastereomers. As this was well below the diastereoselectivity observed with benzyhydryl amine, attempts to improve the diastereomeric ratio above 9:1 in favor of the *cis*-fused aminotetralin were abandoned. In retrospect, it was wishful thinking to hope that the transition state leading to the 5-membered ring would resemble that leading to the 6-membered products

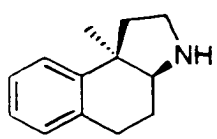
Scheme 39



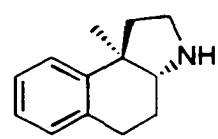
Even with the poor diastereoselectivity observed above, it still seemed worthwhile to condense the 1,4-dicarbonyl compound (**121**) with the other enantiomer of α-methylbenzylamine in the hopes of attaining significant quantities of the *trans*-fused aminotetralin (**133**). Condensation of the 1,4-dicarbonyl compound (**121**) with (*R*)-α-methylbenzylamine gave rise to a 1:1 mixture of stereoisomers. This finding was more consistent with the hypothesis that (*R*)-α-methylbenzylamine would favor the formation of

the *trans*-fused ring system. Given the considerable bias for **121** to form the *cis*-fused ring juncture, a 1 1 mixture of epimers represents a significant effect on selectivity The epimers were separated *via* column chromatography and their structures were assigned on the basis of the presence or absence of an nOe interaction between the angular methyl and the adjacent methine. Reductive removal of the chiral auxiliary of **132** gave the *trans*-fused pyrrolidine (**133**) which, as expected, differed spectroscopically from *cis*-fused pyrrolidine (**43**)

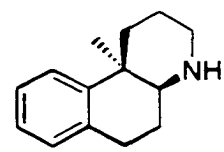
In conclusion, dimethylphenylsilyllithium underwent the tandem addition reaction to naphthyloxazoline **34** with complete diastereoselectivity to afford **84** The silicon served as a surrogate first for oxygen and later for nitrogen. As oxygen anions are not sufficiently nucleophilic to undergo the tandem addition reaction, this represents an important entry into this important class of compounds. This oxygen substitution was readily transformed into four novel, rigid 2-aminotetralins (**43**, **133**, **126**, **128**) enantioselectively. Biological screening of these novel, enantiomerically pure heterocycles should be done in the near future.



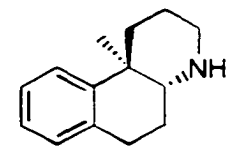
43



133



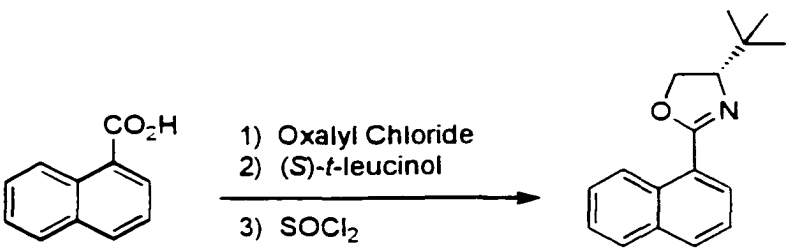
126



128

E. Experimental Section

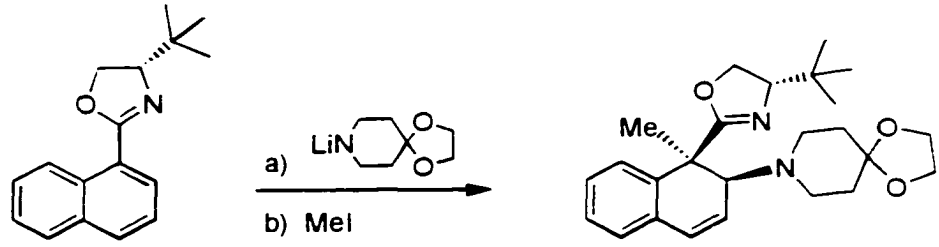
Thin layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230-400 mesh). All reagents were purchased from Aldrich. All non-aqueous reactions were conducted under an argon atmosphere in oven or flame-dried apparatus. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia.



48 **34**

Naphthyloxazoline, 34. To a stirred solution of **48** (10.0 g, 58 mmol) in CH_2Cl_2 (120 mL) was added oxalyl chloride (11.0 g, 87 mmol), followed by 3 drops of DMF. After 2 h, the solution was concentrated, redissolved in CH_2Cl_2 (200 mL), and cooled to 0 °C. To this was added a solution of (S)-*t*-leucinol (7.5 g, 64 mmol) and Et_3N (7.0 g, 70 mmol) in CH_2Cl_2 (15 mL). The ice bath was removed and the mixture was stirred overnight. The solution was poured into 2% $NaHCO_3$, the layers separated, and extracted twice more with CH_2Cl_2. The organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (260 mL), treated with $SOCl_2$ (13.8 g, 116 mmol), and stirred overnight. The solvent was removed, and the residue dissolved in CH_3CN (250 mL), treated with 20% K_2CO_3 (200 mL), and heated to reflux. After 5h, the heterogeneous mixture was concentrated to remove the CH_3CN, and

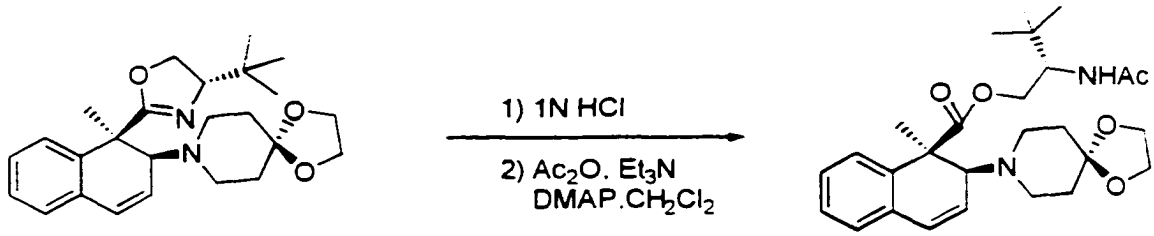
extracted with ether (3X). The extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography gave 13.2 g (90%) as an oil. ^1H NMR (300MHz, $CDCl_3$) δ 1.05 (s, 9H), 4.15-4.42 (m, 3H), 7.44-7.63 (m, 3H), 7.86 (d, J = 7.8, 1H), 7.93 (d, J = 8.2, 1H), 8.07 (dd, J = 7.2, 1.3, 1H), 9.17 (d, J = 8.7, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 26.0, 34.1, 67.7, 77.1, 124.6, 124.8, 126.0, 126.5, 127.2, 128.4, 128.8, 131.3, 131.7, 133.7, 163.1. Spectra are in complete agreement with those previously reported [15]



34 **35**

Tandem addition product. 35. To a stirred, cooled (-5 °C) solution of 4-piperdone ethylene ketal **49** (0.16 mL, 1.3 mmol) in THF (9 mL) was added n-butyllithium (0.54 mL, 1.2 mmol, 2.20 M in hexane solution). After stirring for 45 min at -5 °C, the mixture was cooled to -78 °C, treated with HMPA (0.21 g, 1.2 mmol), and stirred for 5 min. To this was added **34** (0.20 g, 0.79 mmol) in THF (0.5 mL). The resulting solution was maintained at -78 °C for 1 h, allowed to warm to -50 °C over 1 h, recooled to -78 °C, and treated with methyl iodide (84 μL, 1.34 mmol). After stirring for 20 min at -78 °C, the mixture was allowed to warm to -20 °C over 3h. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water (2x) and brine, dried over Na_2SO_4, and concentrated under vacuum. Flash chromatography gave 0.31 g (96%) as an oil. ^1H NMR (300MHz, $CDCl_3$) 0.98 (s, 9H), 1.48 (s, 3H), 1.50 (m,

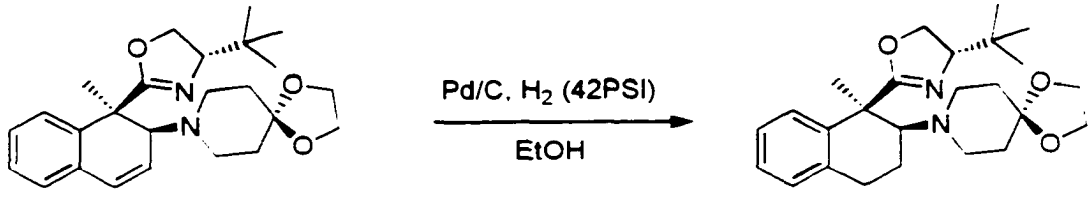
4H), 2.42-2.70 (m, 4H), 3.38 (d, J = 5.3, 1H), 3.84 (s, 4H), 3.88 (t, J = 8.1, 1H), 4.20 (d, J = 8.1, 1H), 5.90 (dd, J = 9.9, 5.4, 1H), 6.64 (d, J = 9.9, 1H), 7.00-7.18 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) 25.9, 29.7, 33.7, 35.7, 46.0, 47.0, 64.0, 68.0, 68.7, 75.2, 107.3, 122.2, 126.4, 127.3, 129.0, 131.0, 138.9, 170.4. Spectra are in complete agreement with those previously reported.[15]



35 **55**

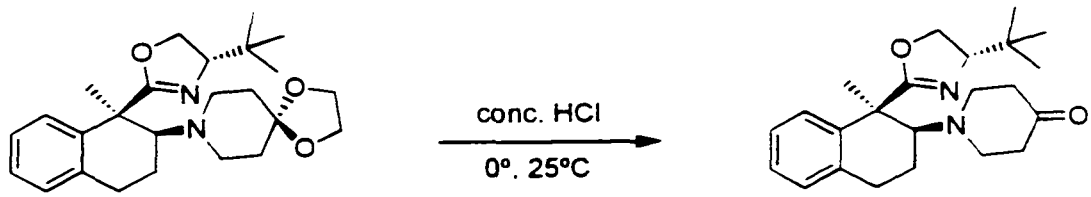
Acetamide, 55. Oxazoline **35** (0.20 g, 0.49 mmol) was dissolved in 3.7 mL 1N HCl. The solution was stirred for 6 h, poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3X), dried over $MgSO_4$, and concentrated to give the crude amino ester which was taken on without purification. The crude amino ester was dissolved in 5 mL CH_2Cl_2 and treated, in turn, with acetic anhydride (50 μL, 0.516 mmol), triethylamine (72 μL, 0.520 mmol), and a spatula tip of DMAP. The solution was allowed to stir at rt for 12 h. The solution was poured into water, and extracted with CH_2Cl_2 (2X). The organic layers were combined, extracted with brine, dried over Na_2SO_4, and concentrated under vacuum to yield 0.227 g (98%) as a white solid. mp 108-110 °C; $[\alpha]_D$ +511.5 (c 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 9H), 1.4 (s, 3H), 1.52 (m, 4H), 2.03 (s, 3H), 2.55 (bs, 4H), 3.46 (d, J = 5.4, 1H), 3.86 (s, 3H), 4.19 (d, J = 8.1, 1H), 4.26 (m, 2H), 5.46 (bd, J = 8.1, 1H), 5.85 (dd, J = 9.9, 5.4, 1H), 6.65 (d, 10.2, 1H), 7.06 (dd, J = 6.0, 1.8, 1H), 7.18 (m, 2H),

7.39 (dd, 6.9, 1.5, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 23.70, 26.90, 28.38, 33.94, 35.67, 46.55, 51.86, 56.22, 63.93, 64.23, 66.45, 107.2, 120.8, 127.6, 127.8, 127.9, 129.9, 131.2, 138.0, 170.0, 174.4; IR (thin film) 1736, 1650 cm^{-1}.



35 **51**

Tetrahydronaphthyl oxazoline, 51. Oxazoline **35** (5.05 g, 12.3 mmol) was dissolved in EtOH (20 mL) in a pressure tube. To this was added Pd/C (0.50 g, 10 wt%) The pressure tube was sealed, flushed with 3 portions of H_2, and finally sealed under 42 psi of H_2. The heterogeneous mixture was vigorously stirred for 12 h. The crude product was run through a short plug of silica gel to remove the Pd/C and concentrated under vacuum to yield an amorphous white semi-solid. Trace impurities were removed *via* flash chromatography (1:1 EtOAc/Hex) to yield 4.66 g (92%) as a white solid. mp 46-48; $[\alpha]_D$ -186.5 (3.8, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.65-1.83 (m, 4H), 1.74 (s, 3H), 2.02 (m, 1H), 2.55-3.05 (m, 7H), 3.75 (dd, J = 10.2,7.2), 3.85-4.02 (m, 2H), 3.94 (s, 4H), 7.09 (m, 3H), 7.27 (m, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.13, 26.40,27.51, 31.04, 34.23, 35.92, 45.52, 49.60, 64.28, 68.39, 70.77, 75.19, 107.8, 126.0, 126.4, 128.1, 129.1, 135.9, 140.9, 170.3; IR (thin film) 1654 cm^{-1}; m/z 412 (M^+).

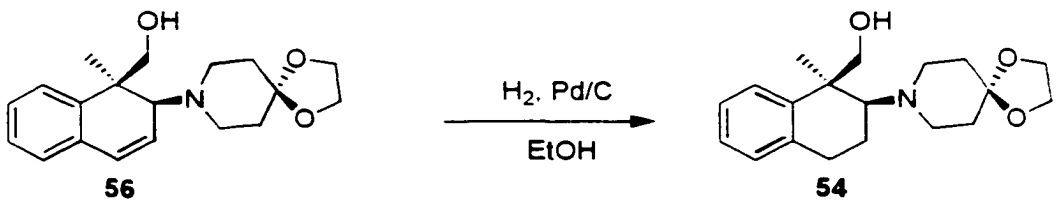


Piperidone. The acetal (0.100 g, 0.25 mmol) was treated with concentrated HCl (5 mL) at 0 °C and then allowed to warm to rt. After 20 min, the mixture was pored into an aqueous NaOH solution (0 °C, NaOH, 3.0 g, water, 40 mL) and stirred for 5 min. The resulting mixture was extracted with 3-15 mL portions of CH_2Cl_2 and dried over $MgSO_4$. Concentration gave 0.0815 g (90%) as a white solid. mp 140-142 °C; $[\alpha]_D$ +176.0 (c 2.7, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 0.91 (s, 9H), 1.81 (s, 3H), 1.98 (m, 1H), 2.2-2.6 (m, 5H), 2.7-3.2 (m, 7H), 3.76 (dd, *J* = 10.2, 7.5, 1H), 3.98 (m, 2H), 7.12 (m, 3H), 7.27 (m, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.5, 26.4, 27.41, 30.91, 34.26, 42.66, 45.55, 51.46, 68.54, 70.73, 75.29, 126.2, 126.6, 128.0, 129.1, 135.6, 140.5, 170.1, 209.9; IR (thin layer) 1654.8, 1715.9 cm^{-1}; *m* / *z* 368 (M^+).

55 **56**

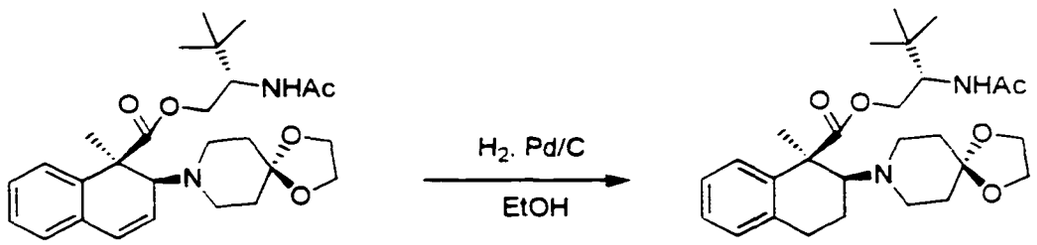
Unsaturated carbinol, 56. To a solution of **55** (0.0601 g, 0.101 mmol) in THF (5 mL, 0 °C), was added LAH (~1M in THF, 0.28 mL, 0..28 mmol). The solution was stirred at 0 °C for 30 min, allowed to reach rt over 1 h, and stirred overnight (12 h). The reaction mixture was added to 15 mL water and extracted with CH_2Cl_2 (2x). The organic layers

were combined, washed with water then brine, and dried over Na_2SO_4. Flash chromatography (EtOAc followed by 10% MeOH/EtOAc) gave 0.037 g (93%) as a clear oil. $[\alpha]_D$ +603.3 (c 1.1, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.07 (s, 3H), 1.60 (bs, 4H), 2.70 (bs, 4H), 3.26 (d, J = 5.7, 1H), 3.86 (s, 4H), 4.02 (d, J = 11.7, 1H), 4.19 (d, J = 11.4, 1H), 5.32 (bs, 1H), 5.91 (dd, J = 9.9, 5.7, 1H), 6.72 (d, J = 9.6, 1H), 7.07 (d, J = 6.9, 1H), 7.27-7.16 (m, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 27.6, 35.4, 40.8, 64.3, 67.0, 68.5, 106.7, 121.3, 124.1, 126.3, 127.6, 128.5, 131.2, 132.4, 141.3; IR (thin layer) 3333(br) cm^{-1}; m/z 315 (M^+).



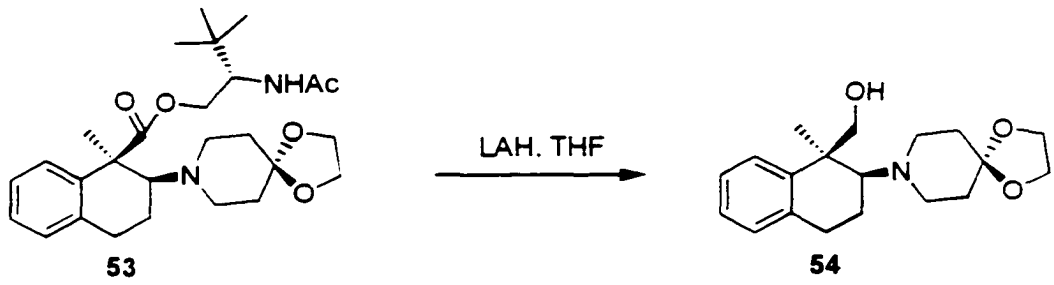
Saturated carbinol, 54. Olefin 56 (0.7123 g, 2.26 mmol) was dissolved in 20 mL EtOH in a pressure tube. To this was added Pd/C (0.0696 g, 10 wt%). The pressure tube was sealed, flushed with 3 portions of H_2, and finally sealed under 40 psi of H_2. The heterogeneous mixture was vigorously stirred for 12 h. The crude product was run through a short plug of silica gel to remove the Pd/C and concentrated under vacuum to yield an amorphous white semi-solid. It was purified *via* flash chromatography (1:1 EtOAc/Hex) to yield 0.5203g (73%) as a white solid. mp 112-114 °C; $[\alpha]_D$ -9.90 (1.0, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.65-1.85 (m, 4H), 2.00-2.20 (m, 2H), 2.65-3.00 (m, 7H), 3.73 (d, J = 11.4, 1H), 3.94 (s, 4H), 4.04 (d, J = 11.1, 1H), 5.57 (s, 1H), 7.02-7.23 (m, 3H), 7.29 (dd, J = 9.9, 0.9, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ

19.9, 25.9, 29.9, 35.9, 42.43, 50.1, 64.4, 69.7, 70.3, 106.8, 126.1, 126.3, 127.3, 128.7, 136.3, 141.7; IR (thin film) 3416(br) cm^{-1}; *m/z* 317 (M^+).



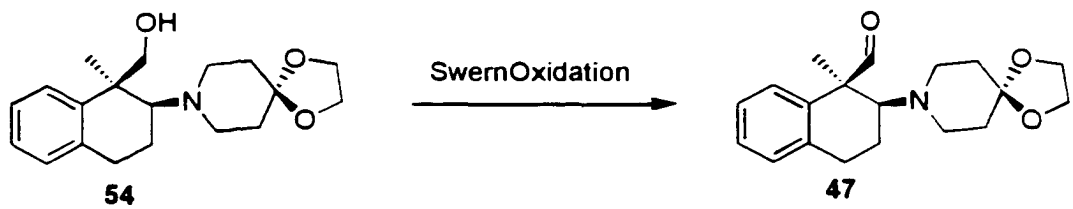
55 **53**

Saturated amido ester, 53. Amido ester **55** (5.521 g, 11.8 mmol) was dissolved in 20 mL EtOH in a pressure tube. To this was added Pd/C (0.5671 g, 10 wt%). The pressure tube was sealed, flushed with 3 portions of H_2, and finally sealed under 20 psi of H_2. The heterogeneous mixture was vigorously stirred for 10 h. The crude product was run through a short plug of silica gel to remove the Pd/C and concentrated under vacuum to yield an oil. Trace impurities were removed *via* flash chromatography (1:1 EtOAc/Hex) to yield 5.327g (96%) as a clear oil. $[\alpha]_D$ 137.4 (2.0, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 0.81 (s, 9H), 1.55-1.75 (m, 7H), 1.83 (s, 3H), 1.95-2.03 (m, 1H), 2.13-2.31 (m, 1H), 2.51-2.62 (m, 2H), 2.67-2.99 (m, 5H), 3.90 (s, 4H), 3.95-4.07 (m, 2H), 4.12-4.18 (m, 1H), 5.19 (d, J = 9.6, 1H), 7.03-7.12 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.8, 23.4, 25.8, 26.8, 30.4, 35.9, 49.4, 51.5, 55.3, 63.4, 64.1, 70.3, 107.3, 126.1, 126.5, 127.4, 129.2, 135.9, 140.4, 169.6, 175.2; IR (thin film) 3304(br), 1720, 1650 cm^{-1};



53 54

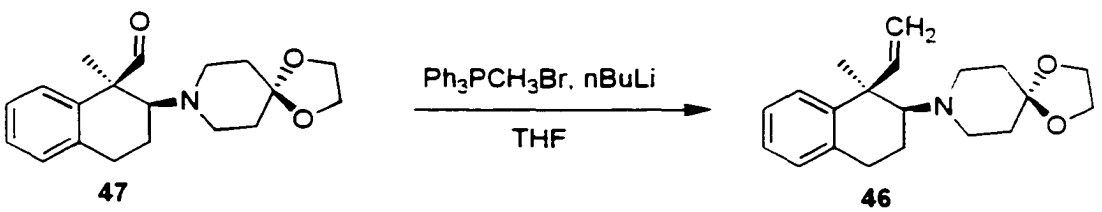
Saturated carbinol, 54. To a solution of LAH (0.8135 g, 21.3 mmol) in THF (75 mL, 0 °C), was added a solution of ester **53** (4.55 g, 9.64 mmol) in THF (10 mL) The solution was stirred at 0 °C for 30 min, allowed to reach rt over 1 h, and stirred overnight (12 h) The reaction mixture was added to 15 mL water and extracted with CH_2Cl_2 (2x). The organic layers were combined, washed with water then brine, and dried over Na_2SO_4. Flash chromatography (EtOAc followed by 10% MeOH/EtOAc) gave 2.87 g (94%) as a white solid. mp 112-114 °C; $[\alpha]_D$ -9.90 (1.0, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.65-1.85 (m, 4H), 2.00-2.20 (m, 2H), 2.65-3.00 (m, 7H), 3.73 (d, *J* = 11.4, 1H), 3.94 (s, 4H), 4.04 (d, *J* = 11.1, 1H), 5.57 (s, 1H), 7.02-7.23 (m, 3H), 7.29 (dd, *J* = 9.9, 0.9, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.9, 25.9, 29.9, 35.9, 42.43, 50.1, 64.4, 69.7, 70.3, 106.8, 126.1, 126.3, 127.3, 128.7, 136.3, 141.7; IR (thin film) 3416(br) cm^{-1}, *m/z* 317 (M^+).



54 47

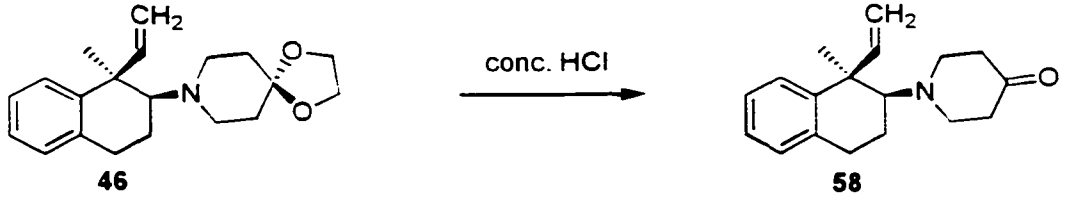
Aldehyde, 47. To a solution of oxalyl chloride (0.060 mL, 0.68 mmol) in CH_2Cl_2 (10 mL, -78 °C) was added DMSO (0.17 mL, 2.41 mmol) slowly. Effervescence was immediate.

The solution was allowed to stir 45 minutes before adding a solution of **54** (0.1626 g, 0.513 mmol) in CH_2Cl_2 (1 mL). The solution was stirred an additional 15 minutes. To this was added dropwise Et_3N (0.25 mL, 1.80 mmol). The solution was stirred for 5 minutes at -78 °C, before allowing it to reach room temperature. Upon warming, the reaction was quenched by the addition of H_2O (2 mL). The heterogeneous mixture was extracted from H_2O with CH_2Cl_2 (2X), washed with brine, dried with Na_2SO_4, and concentrated to yield a white solid. Trace impurities were removed *via* flash chromatography (hexanes/EtOAc) to yield 0.1545g (96%) as a white solid. mp 132.5-134 °C; $[\alpha]_D$ -184.4 (1.1, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.60-1.75 (m, 4H), 2.00-2.25 (m, 2H), 2.57-3.07 (m, 7H), 3.92 (s, 4H), 7.00-7.22 (m, 4H), 9.80 (s, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.7, 22.5, 30.3, 35.6, 49.5, 55.4, 64.3, 70.3, 107.2, 126.5, 127, 129.1, 129.3, 136.6, 137.1, 202.0; IR (thin film) 1715 cm^{-1}; *m/z* 315 (M^+).



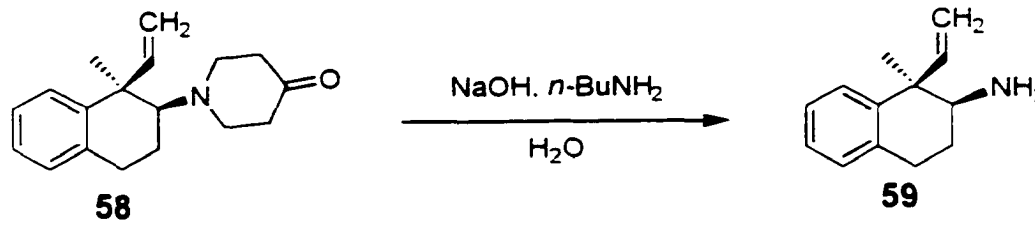
Alkene, 46. To a suspension of Ph_3PCH_3Br (2.38 g, 6.65 mmol) in THF (100 mL, 0 °C) was added *n*-BuLi (2.27M in hexanes, 2.88 mL, 6.55 mmol). The ice bath was removed and the suspension was stirred for 10 min. The suspension went first to a yellow suspension and finally to a homogeneous yellow solution. To this was added aldehyde **47** (1.65 g, 5.24 mmol) in THF (15 mL). The solution was allowed to stir 1 h, before quenching with H_2O (25 mL). The solution was extracted from H_2O with EtOAc (3X),

dried over Na_2SO_4, and concentrated. The crude product was purified *via* flash chromatography (10% EtOAc/Hexanes) to give 1.33 g (81%) as a white solid. mp 93-95 °C; $[\alpha]_D$ -91.88 (1.0, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.70-1.82 (m, 5H), 1.95-2.05 (m, 1H), 2.50-2.66 (m, 3H), 2.83-3.00 (m, 4H), 3.97 (s, 4H), 4.54 (dd, *J* = 17.4, 1.8, 1H), 5.04 (dd, *J* = 10.5, 1.8, 1H), 6.08 (dd, *J* = 17.4, 10.5, 1H), 7.05-7.22 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 19.9, 25.7, 31.4, 35.9, 47.5, 49.9, 64.3, 70.5, 107.9, 114.8, 125.8, 128.7, 129.4, 136.2, 142.9, 145.7; *m/z* 313 (M^+).



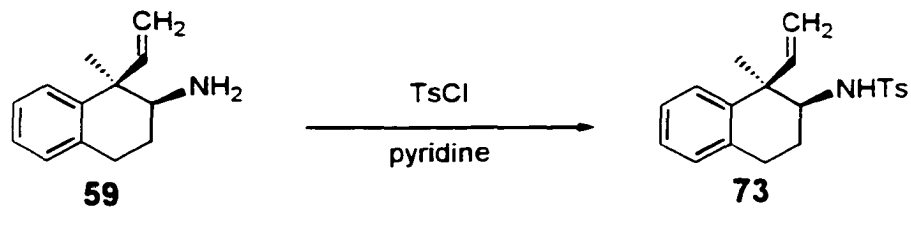
46 **58**

Keto-olefin. 58. Ketal **46** (0.11 g, 0.34 mmol) was treated with concentrated HCl (5 mL) at 0 °C and then allowed to warm to rt. After 25 min, the mixture was poured into an aqueous NaOH solution (0 °C, NaOH, 3.0 g, water, 40 mL) and stirred for 5 min. The resulting mixture was extracted with 3-15 mL portions of CH_2Cl_2 and dried over $MgSO_4$. Concentration gave 0.092 g (100%) as a white solid. mp 68-68.5 °C; $[\alpha]_D$ -108.8 (c 1.0, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.70-1.86 (m, 1H), 1.90-2.03 (m, 1H), 2.35-2.57 (m, 4H), 2.70-3.18 (m, 7H), 4.66 (d, *J* = 17.4, 1H), 5.09 (d, *J* = 10.5, 1H), 6.11 (dd, *J* = 17.4, 10.5, 1H), 7.04-7.22 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 20.2, 25.7, 31.2, 42.4, 47.3, 51.8, 70.5, 115.1, 125.9, 126.0, 128.7, 129.4, 135.8, 142.5, 144.9, 210.1; IR (thin layer) 1715 cm^{-1}; *m/z* 269 (M^+).



58 59

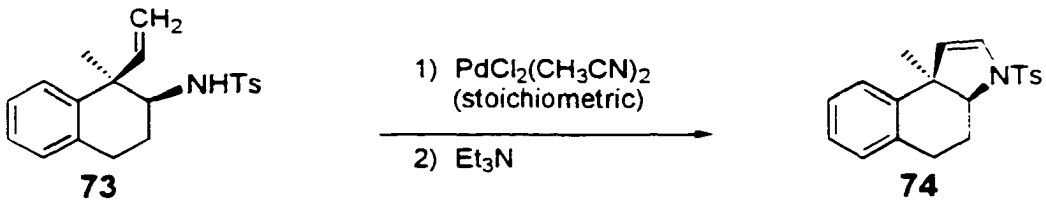
Amino alkene, 59. Piperidone **58** (1.72 g, 6.4 mmol) was placed in a pressure tube. To it was added an aqueous solution of NaOH (NaOH, 2.04 g, water, 100 mL) and *n*-$BuNH_2$ (40 mL, 405 mmol). The tube was flushed with argon and closed with a teflon cap. The mixture was heated to 130 °C. The solution was stirred for 36 h. The solution was concentrated en vacuo to remove the *n*$BuNH_2$. The residue was extracted from water with CH_2Cl_2 (3X), dried over Na_2SO_4, and concentrated to yield a brown oil. Flash chromatography (5% MeOH, EtOAc) gave 0.968g (81%) as a yellow oil. $[\alpha]_D$ -101.2 (c 1.2, CH_2Cl_2); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.25 (bs, 2H), 1.49 (s, 3H), 1.72-1.98 (m, 2H), 2.85-2.95 (m, 3H), 4.93 (d, *J* = 17.4, 1H), 5.20 (d, *J* = 10.8, 1H), 6.05 (dd, *J* = 17.4, 10.8, 1H), 7.07-7.24 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 25.4, 28.6, 28.7, 46.3, 56.8, 115.3, 126.0, 126.1, 129.0, 129.1, 135.9, 142.2, 143.8; IR (thin layer) 3378(br) cm^{-1}; *m/z* 187 (M^+).



59 73

p-Toluenesulfonamide, 73. Amine **59** (0.98 g, 5.2 mmol) was dissolved in pyridine (8.5 mL) and cooled to 0 °C. To this was added *p*-toluenesulfonylchloride (0.99 g, 5.2 mmol).

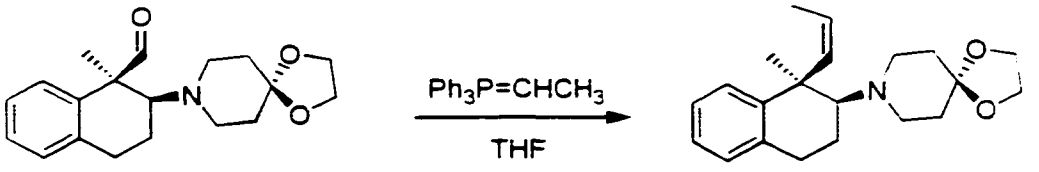
The temperature was maintained at 0 °C for 2 h. The ice bath was removed and the reaction was allowed to stir overnight at room temperature. The crude reaction mixture was added to EtOAc, and washed with 1:1 2N HCl/Brine until washings were acidic. The organic phase was dried over Na_2SO_4. Flash chromatography gave 1.34 g (76%) as a white solid. mp 144-145.2 °C; $[\alpha]_D$ -120.1 (c 1.0, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 1.30 (s, 3H), 1.75-1.81 (m, 2H), 2.44 (s, 3H), 2.78-2.83 (m, 2H), 3.35-3.39 (m, 1H), 4.63 (d, J = 9.3, 1H), 4.91 (dd, J = 17.1, 1.5, 1H), 5.18 (dd, J = 10.5, 2.1, 1H), 5.91 (dd, J = 17.4, 10.5, 1H), 7.01-7.14 (m, 4H), 7.32 (d, J = 8.1, 2H), 7.80 (dd, J = 6.3, 1.5, 2H). ^{13}C NMR (75MHz, $CDCl_3$) δ 21.7, 24.6, 26.9, 29.0, 45.2, 59.1, 116.7, 126.3, 126.4, 127.2, 128.7, 128.9, 129.8, 135.0, 138.3, 141.0, 142.3, 143.4; Anal. Calcd for $C_{20}H_{23}NO_2S$: C 70.35, H 6.79; Found: C 70.28, H 6.83.



73 **74**

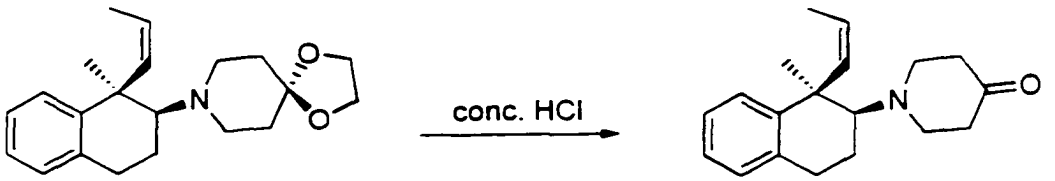
***N*-Tosylenamine, 74.** $PdCl_2(CH_3CN)_2$ (0.013 g, 0.05 mmol) was placed in RBF, and the flask was evacuated and filled with argon several times. THF (2 mL) was added *via* syringe and stirring begun. To this was added amido olefin **73** (0.016 g, 0.047 mmol) dissolved in THF (1 mL). The reaction was stirred for 45 min and then Et_3N (6.5 μL, 0.047 mmol) was added. At 1 h intervals, more Et_3N (6.5 μL, 0.047 mmol) was added to the reaction, and the resulting mixture was stirred for 10 h at room temperature. Flash chromatography gave the tosylenamide as a white solid. ^1H NMR (300MHz, $CDCl_3$) δ

0.91 (s, 3H), 2.00-2.20 (m, 2H), 2.45 (s, 3H), 2.60 (ddd, J = 15.9, 8.1, 3.9, 1H), 2.87 (ddd, J = 15.9, 8.4, 3.9, 1H), 3.58 (dd, J = 6.9, 4.5, 1H), 5.19 (d, J = 4.2, 1H), 6.33 (d, J = 4.2, 1H), 7.05-7.16 (m, 4H), 7.36 (dd, J = 8.4, 0.6, 2H), 7.74 (dd, J = 6.3, 1.8, 2H) m/z 339 (M^+).

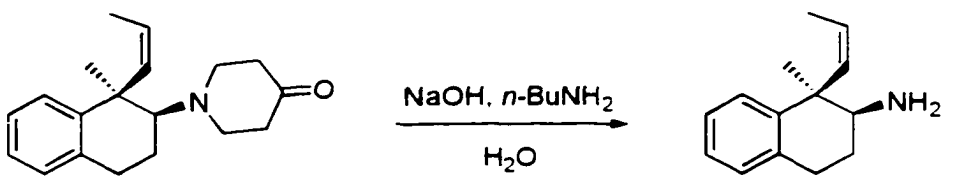


47

1,2-Disubstituted alkene. To a suspension of $Ph_3PCH_2CH_3Br$ (3.53 g, 9.52 mmol) in THF (100 mL, 0 °C) was added *n*-BuLi (2.40 M in hexanes, 3.9 mL, 9.29 mmol). The ice bath was removed and the suspension was stirred for 10 min. The suspension went first to a yellow suspension and finally to a homogeneous yellow solution. To this was added aldehyde **47** (1.52 g, 4.76 mmol) in THF (20 mL). The solution was allowed to stir 20 min at 0 °C, warmed to room temperature, and allowed to stir 20 min, before quenching with H_2O (25 mL). The solution was extracted from H_2O with EtOAc (3X), dried over Na_2SO_4, and concentrated. The crude product was purified *via* flash chromatography (20% EtOAc/Hexanes) to give 1.57 g (99%) as a clear oil. $[\alpha]_D$ -135.9 (1.7, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 0.95 (dd, J = 6.8, 1.2, 3H), 1.59 (s, 3H), 1.71-1.79 (m, 5H), 1.96-2.08 (m, 1H), 2.50-2.63 (m, 3H), 2.88-3.05 (m, 4H), 3.96 (s, 4H), 5.45 (dq, J = 12.3, 6.9, 1H), 5.52 (dd, J = 12.3, 1.5, 1H), 7.04-7.14 (m, 3H), 7.30 (d, J = 7.5, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 13.0, 20.1, 28.7, 31.2, 35.7, 45.9, 49.6, 64.0, 71.7, 107.6, 124.6, 125.4, 125.7, 128.4, 129.1, 135.3, 137.5, 144.7; m/z 327 (M^+).

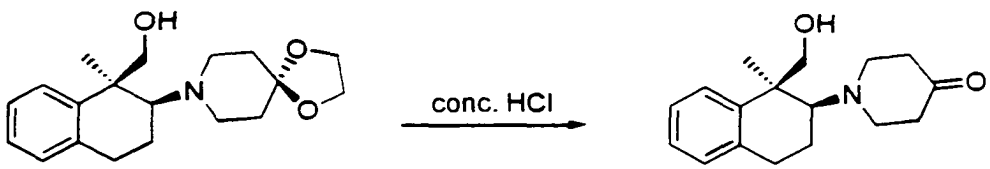


Substituted keto-olefin. The ketal (0.254 g, 0.765 mmol) was dissolved in concentrated HCl (15 mL) at room temperature. The reaction was stirred for 50 minutes and added to a stirred NaOH solution (7.5g NaOH, 100 mL H_2O, 0 °C). The mixture was made very basic with 20% K_2CO_3, and extracted with CH_2Cl_2 (3X). The organic layer was washed with brine and dried over Na_2SO_4. Concentration *en vacuo* afforded pure piperdone (0.213 g, 97%) as a clear oil. $[\alpha]_D$ -154.3 (1.8, CH_2Cl_2); ^1H NMR (300MHz, $CDCl_3$) δ 0.95 (dd, *J* = 5.7, 1.1, 3H), 1.64 (s, 3H), 1.70-1.82 (m, 1H), 1.95-2.05 (m, 1H), 2.40-2.55 (m, 4H), 2.70-3.00 (m, 5H), 3.19-3.30 (m, 2H), 5.49 (dq, *J* = 10.8, 6.6, 1H), 5.55 (dd, *J* 10.8, 0.9, 1H), 7.00-7.20 (m, 3H), 7.31 (dd, *J* = 7.5, 1.8, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 13.4, 20.6, 29.3, 31.3, 42.6, 46.1, 51.9, 71.9, 125.7, 125.9, 126.2, 128.8, 129.4, 135.4, 137.2, 144.5, 210.3; IR (thin film) 1717 cm^{-1}; *m/z* 283 (M^+).



Substituted amino-olefin. The piperidone (0.203 g, 0.78 mmol) was placed in a pressure tube. To it was added an aqueous solution of NaOH (NaOH, 0.25 g, H_2O, 12 mL) and *n*$BuNH_2$ (4.9 mL, 49.7 mmol). The tube was flushed with argon and sealed with a teflon

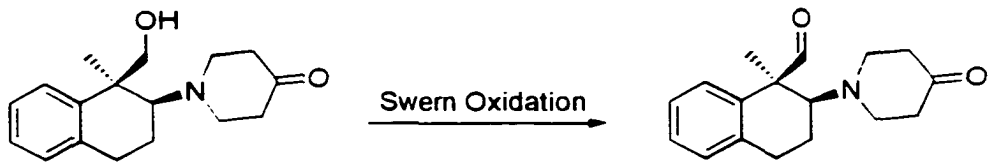
cap The mixture was heated to 130 °C. Upon checking the reaction 24 h later, the temperature had risen to 150 °C. The solution was cooled to 132 °C and stirred an additional 12 h. The solution was concentrated in vacuo to remove the *n*BuNH$_2$. The residue was extracted from water with CH_2Cl_2 (3X), dried over Na_2SO_4, and concentrated to yield a brown oil. Flash chromatography (5% MeOH, EtOAc) gave 0.085g (59%) as a yellow oil. $[\alpha]_D$ -44.3 (c 1.1, CH_2Cl_2); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.17 (dd, *J* 6.9, 1.5, 3H), 1.42 (bs, 2H), 1.52 (s, 3H), 1.77-2.01 (m, 2H), 2.80-3.00 (m, 3H), 5.47 (dq, *J* 12.3, 1.5, 1H), 5.59 (dq, *J* = 12.3, 7.2, 1H), 7.04-7.20(m, 3H), 7.31 (dd, *J* = 6.9, 1.8, 1H); ^{13}C NMR (75MHz, $CDCl_3$) δ 14.3, 27.5, 28.0, 30.0, 45.7, 57.0, 125.6, 126.0, 126.8, 128.8, 129.1, 135.1, 135.8, 143.6; IR (thin layer) 3392(br) cm^{-1}.



56 **61**

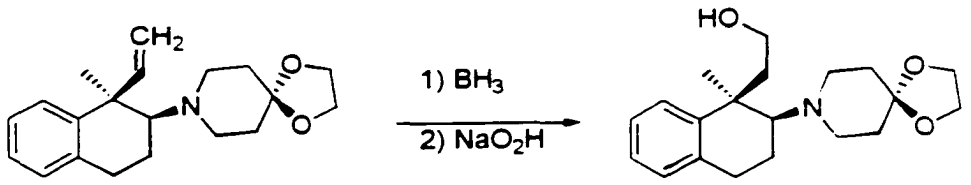
Hydroxyketone, 61. Ketal **56** (1.81 g, 5.8 mmol) was dissolved in concentrated HCl (15 mL) at 0 °C. The solution was allowed to warm to room temperature and stirred for 50 minutes. The solution was made basic by its addition to a stirred solution of 20% KOH (0 °C). The mixture was made very basic with 20% K_2CO_3, and extracted with CH_2Cl_2 (3X). The organic layer was washed with brine and dried over Na_2SO_4. Concentration *en vacuo* afforded 1.54 g (99%) as a clear oil. $[\alpha]_D$ + **610.9** (1.6, CH_2Cl_2); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.10 (s, 3H), 2.20-2.50 (m, 4H), 2.60-2.95 (m, 4H), 3.36 (d, *J* = 6.0, 1H), 4.07 (d, *J* = 11.7, 1H), 4.21 (d, *J* = 11.7, 1H), 4.82 (bs, 1H) 5.86 (dd, *J* = 9.9, 5.7,

1H), 6.72 (d, J = 9.6, 1H), 7.05-7.27 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 27.4, 40.9, 41.7, 48.4, 66.2, 68.2, 120.4, 124.1, 126.5, 127.7, 128.7, 131.6, 131.8, 140.8, 207.5, IR (thin film) 3420 (br), 1714 cm^{-1}.

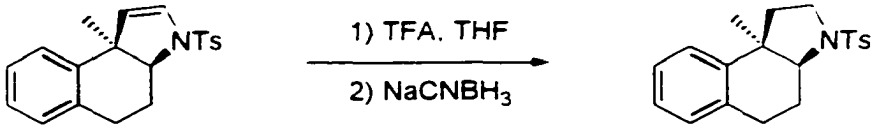


61 **62**

Amino-dicarbonyl compound. 62. To a solution of oxalyl chloride (0.042 mL, 0.48 mmol) in CH_2Cl_2 (10 mL, -78 °C) was added DMSO (0.064 mL, 0.90 mmol) slowly. Effervescence was immediate. The solution was allowed to stir 15 minutes before adding a solution of **61** (0.1012 g, 0.369 mmol) in CH_2Cl_2 (1 mL). The solution was stirred an additional 45 minutes. To this was added dropwise Et_3N (0.19 mL, 1.31 mmol). The solution was stirred for 5 minutes at -78 °C, before allowing it to reach room temperature. Upon warming, the reaction was quenched by the addition of H_2O (2 mL). The heterogeneous mixture was extracted from H_2O with CH_2Cl_2 (2X), washed with brine, dried with Na_2SO_4, and concentrated to yield a white solid. Trace impurities were removed *via* flash chromatography (hexanes/EtOAc) to yield 0.097 g (97%) as a white solid. ^{1}H NMR (300MHz, $CDCl_3$) δ 1.32 (s, 3H), 2.22-2.28 (m, 4H), 2.76-2.82 (m, 4H), 3.63 (d, J = 5.4, 1H), 5.87 (dd, J = 9.9, 5.4, 1H), 6.75 (d, J = 9.9, 1H), 7.18-7.30 (m, 4H), 9.95 (s, 1H).



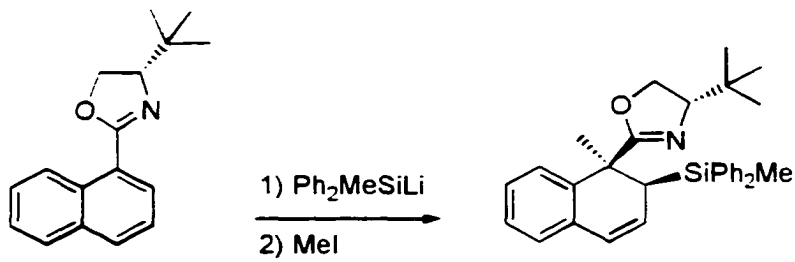
Amino alcohol. To a stirred solution of olefin (0.0512 g, 0.164 mmol) in THF (2 mL, 0 °C) was added BH_3 (1.0M in THF, 0.25 mL, 0.25 mmol). After 1 h at 0 °C, the reaction was warmed to room temperature water was added dropwise until effervescence ceased. To this was added 2M NaOH (0.17 mL) followed by 30% H_2O_2 (0.084 mL). After stirring for 1 h at room temperature, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3X). The organic layers were combined, washed with brine, and dried over Na_2SO_4. Flash chromatography gave the alcohol (0.0324 g, 60%) as a clear oil. ^1H NMR (300MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.63-1.76 (m, 4H), 2.10-2.30 (m, 4H), 2.48-3.00 (m, 7H), 3.78-3.95 (m, 2H), 3.91 (s, 4H), 7.02-7.20 (m, 3H), 7.28 (dd, *J* 8.1, 1.5, 1H); *m/z* 331 (M^+).



74 **75**

***cis*-*N*-Tosylpyrrolidine-fused tetralin, 75.** To a stirred solution of enamide **74** (60 mg, 0.18 mmol) in THF (3 mL) was added TFA (16 μL). The reaction was stirred 3 h. To this was added $NaCNBH_3$ (17 mg, 0.26 mmol), suspended in THF (0.5 mL). The reaction was stirred overnight. The reaction was poured over water and extracted with EtOAc. Flash chromatography gave the saturated sulfonamide (48 mg, 80%) as a white solid. ^1H

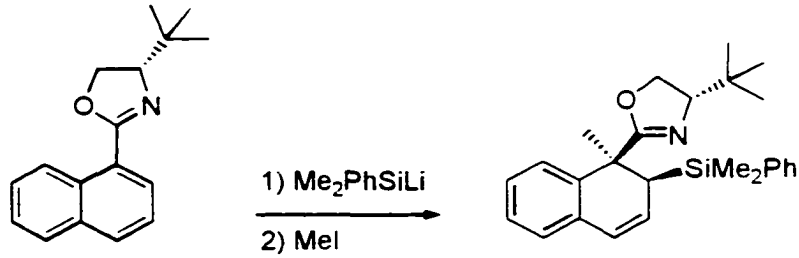
NMR (300MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.73 (m, 1H), 2.00 (m, 2H), 2.23 (m, 1H), 2.46 (s, 3H), 2.80 (m, 2H), 3.31 (m, 2H), 3.46 (dd, *J* = 9.6, 6.1, 1H), 7.12 (m, 4H), 7.35 (d, *J* = 8.1, 2H), 7.74 (d, *J* = 8.1, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ 21.73, 27.58, 27.84, 28.66, 39.27, 45.23, 46.97, 66.70, 126.1, 126.6, 127.2, 127.7, 128.7, 129.8, 134.7, 136.3, 142.1, 143.5; *m/z* 341 (M^+).



34 **83**

Tandem addition product. 83. To a stirred suspension of lithium wire (30 mg, 4.3 mmol) in THF (1 mL) at rt was added chlorodiphenylmethylsilane (160 μL, 0.79 mmol). The flask was sonicated for 5 min to give a very reddish-brown suspension, and was stirred an additional 1.5 h without sonication. The solution was cooled to -78 °C and added dropwise *via* cannula to a stirred solution of naphthyloxazoline **34** (92 mg, 0.36 mmol) in THF (1 mL, -78 °C) and stirred for 19 h. MeI (50 μL, 0.80 mmol) was added *via* syringe and the reaction allowed to warm to -20 °C before quenching with MeOH and concentration *in vacuo*. The residue was partitioned between water and ether (3X), washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (5-20% EtOAc/Hex) gave 86 mg (52%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 3H), 0.75 (s, 3H), 1.53 (s, 3H), 2.73 (dd, *J* = 9.9, 9.9, 1H), 2.90 (dd, *J* = 6.6, 1.2, 1H),

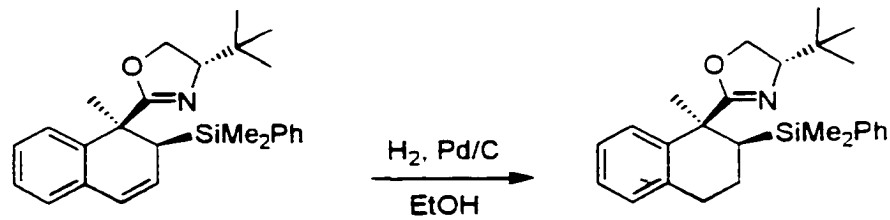
3.17 (dd, J = 10.5, 8.4, 1H), 3.29 (dd, J = 9.9, 8.4, 1H), 5.61 (dd, J = 9.6, 6.6, 1H), 6.34 (d, J = 9.3, 1H), 6.9-7.7 (m, 14H).



34 **84**

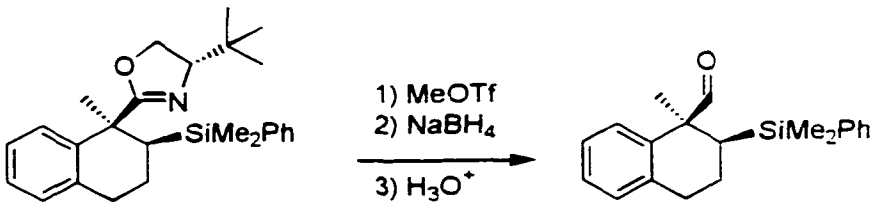
Tandem addition product, 84. To a stirred suspension of lithium wire (1.1 g, 159 mmol) in THF (20 mL) at rt was added chlorodimethylphenylsilane (7.6 mL, 45 mmol). The flask was sonicated for 2 h to give a very reddish-brown suspension, and was stirred an additional 1.5 h without sonication. The solution was added dropwise *via* a very fine cannula over 30 min to a stirred solution of naphthyloxazoline **34** (5.7 g, 23 mmol) in ether (80 mL, -72 °C) and stirred for 87 h. MeI (2.8 mL, 45 mmol) was added *via* syringe and the reaction allowed to warm to -20 °C before quenching with MeOH and concentration *in vacuo*. The residue was partitioned between water and ether (3X), washed with brine, dried over Na_2SO_4, and concentrated. The crude oil was filtered through a plug of silica gel using 10% EtOAc/Hex. The material was recrystallized from ether to give 8.2 g (90%) diastereomerically pure as large cubes. $[\alpha]^{25}_D$ = +309 (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.08 (s, 3H), 0.86 (s, 9H), 1.60 (s, 3H), 2.50 (dd, J = 6.0, 0.9, 1H), 2.84 (dd, J = 10.5, 8.4, 1H), 3.18 (dd, J = 10.5, 8.7, 1H), 3.67 (dd, J = 8.7, 8.4, 1H), 5.90 (dd, J = 9.6, 6.3, 1H), 6.41 (d, J = 9.9, 1H), 6.80-7.50 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.6, -0.7, 26.2, 29.1, 33.6, 37.2, 44.2, 68.0,

75.7, 124.3, 126.3, 126.5, 126.9, 127.3, 127.9, 128.5, 129.6, 132.8, 133.0, 138.9, 140.1, 170.3; IR (thin film) 1654 cm^{-1}; Anal. Calcd for $C_{26}H_{33}NOSi$: C 77.37, H 8.24, N 3.47. Found: C 77.23, H 8.29, N 3.51.



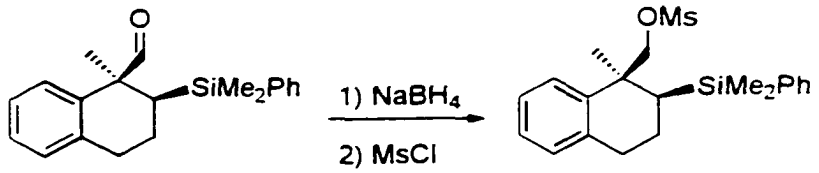
84 **85**

Tetrahydronaphthyloxazoline, 85. A 250 mL flask was charged with dihydronaphthyloxazoline **84** (1.0 g, 2.5 mmol), palladium (100 mg, 10% on carbon), and absolute ethanol (90 mL). The flask was flushed with argon, then H_2, before finally affixing a balloon of H_2. The suspension was stirred overnight, filtered through silica gel (eluting with EtOAc), and concentrated. Column chromatography (2-4% EtOAc/Hex) gave 0.82 g (82%) as an oil. $[\alpha]^{25}_D$ = -142 (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.36 (s, 3H), 0.40 (s, 3H), 0.86 (s, 9H), 1.29 (dd, *J* = 12.9, 2.7, 1H), 1.65 (s, 3H), 1.88 (m, 1H), 2.03 (m, 1H), 2.62 (m, 1H), 2.78 (m, 1H), 3.66 (m, 3H), 6.97-7.60 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -3.5, -0.7, 23.0, 26.3, 31.5, 32.0, 34.0, 35.4, 41.7, 68.4, 75.4, 126.0, 126.0, 127.6, 127.7, 128.9, 129.4, 134.1, 136.8, 139.8, 141.6, 171.2; IR (thin film) 1654 cm^{-1}.



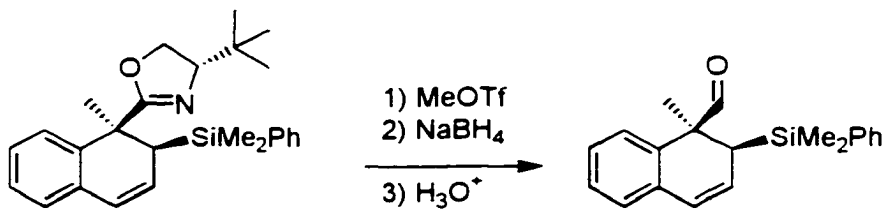
85 **86**

Saturated aldehyde, 86. To a stirred solution of oxazoline **85** (0.64 g, 1.6 mmol) in CH_2Cl_2 (4 mL, 0 °C) was added MeOTf (0.32 mL, 3.2 mmol). The solution was warmed to rt, stirred 6 h, and recooled to 0 °C. To this was added a solution of THF (4 mL), MeOH (1 mL), and $NaBH_4$ (0.3 g, 8 mmol). The ice bath was removed, the suspension stirred 5 min, and the reaction quenched by the cautious addition of saturated NH_4Cl. The mixture was partitioned between ether and brine (3X), washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (2% EtOAc/Hex) gave the oxazolidine (620 mg, 93%) as an oil. The oil was dissolved in THF (20 mL) and water (5 mL), treated with oxalic acid (1.0 g, 11 mmol). The solution was heated at a gentle reflux 13 h, cooled to rt, and concentrated *via* rotary evaporation. The residue was partitioned between water and ether (3X), washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (4% EtOAc/Hex) gave 400 mg (82% over 3 steps) as an oil. $[\alpha]^{25}_D$ = -195 (c = 3.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 3H), 0.39 (s, 3H), 1.33 (dd, *J* = 12.6, 2.4, 1H), 1.40 (s, 3H), 1.75 (m, 1H), 1.98 (m, 1H), 2.78 (m, 1H), 7.10 (m, 4H), 7.45 (m, 5H), 9.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.7, -1.2, 23.0, 25.3, 31.3, 32.8, 52.4, 126.4, 126.7, 127.8, 128.5, 129.1, 129.7, 133.9, 136.7, 138.4, 138.5, 201.5; IR (thin film) 1716 cm^{-1}; Anal. Calcd for $C_{20}H_{24}OSi$: C 77.87, H 7.84; Found: C 77.74, H 7.91.



86 **87**

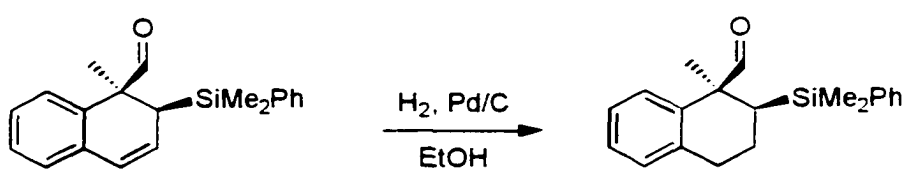
Mesylate, 87. To a solution of aldehyde **86** (25 mg, 0.08 mmol) in EtOH (2 mL, 0 °C) was added $NaBH_4$ (6 mg, 0.1 mmol). The ice bath was removed and the suspension stirred at rt 5 min. The flask was cooled to 0 °C, diluted with ether, and quenched by cautious addition of 1N HCl. The suspension was transferred to a separatory funnel, partitioned between water and ether (2X), dried over Na_2SO_4, and concentrated to give the crude carbinol. This oil was redissolved in CH_2Cl_2 (2 mL), and treated with Et_3N (14 μL, 0.1 mmol), then MsCl (6 μL, 0.08mmol). After 2 h, the reaction was concentrated. Column chromatography gave 14 mg (44%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ 0.44 (s, 3H), 0.46 (s, 3H), 1.33 (s, 3H), 1.89 (m, 3H), 2.53 (s, 3H), 2.76 (m, 2H), 4.26 (d, *J* = 10.2, 1H), 4.31 (d, *J* = 10.2, 1H), 7.0-7.6 (m, 9H).



84 **89**

Unsaturated aldehyde, 89. To a solution of oxazoline **84** (2.03g, 5.03 mmol) in CH_2Cl_2 (2.5 mL) was added MeOTf (1.15 mL, 10.2 mmol) at 0 °C. The ice bath was removed

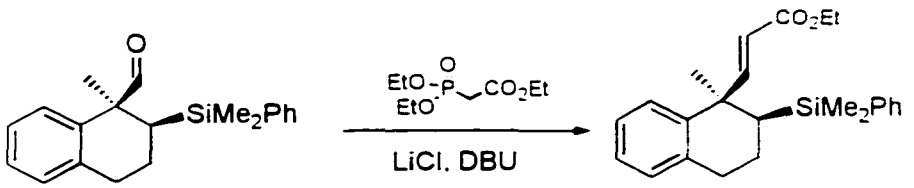
and the solution stirred overnight at rt. This solution was transferred dropwise *via* canula into a 250 mL RBF containing $NaBH_4$ (0.80 g, 21 mmol) in MeOH (5 mL) and THF (20 mL) at 0 °C. There was rapid evolution of gas. Upon completion of addition, the ice bath was removed and stirring was continued 30 min. The solution was concentrated, and the residue partitioned between ether and saturated $NaHCO_3$. The aqueous was washed twice more with ether. The organics were combined, concentrated, and treated with oxalic acid (1.25 g, 14 mmol), THF (30 mL), and water (6 mL). The flask was heated at reflux 4 h, concentrated, and the residue partitioned between ether and water. The aqueous was washed twice more with ether. The organics were combined, dried over Na_2SO_4, and concentrated to give 1.49g (97%) as a white solid. mp 49.9 - 51.5 °C; $[\alpha]^{25}_D$ = −658 (c = 4.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 1.25 (s, 3H), 2.02 (dd, *J* = 6.3, 1.2, 1H), 5.73 (dd, *J* = 9.6, 6.3, 1H), 6.35 (d, *J* = 9.9, 1H), 6.69 (dd, *J* = 7.8, 0.9, 1H), 6.95-7.40 (m, 8H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -2.87, -2.64, 23.3, 36.1, 53.6, 124.4, 125.8, 126.8, 127.8, 127.9, 128.0, 128.8, 129.5, 133.2, 133.7, 135.5, 137.8, 203.4; IR (thin film) 1724 cm^{-1}.



89 **86**

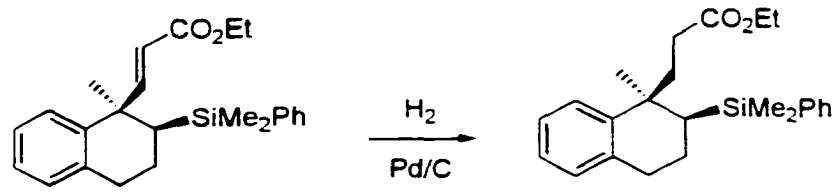
Saturated Aldehyde, 86. A RBF was charged with aldehyde **89** (1.91 g, 6.23 mmol), Pd/C (300 mg, 0.28 mmol, 10%), and EtOH (40 mL) and was purged with hydrogen. A hydrogen balloon attached and the reaction was allowed to stir 10 h. The reaction was

filtered through a pad of silica gel, eluting with EtOAc. Concentration gave 1.88 g (98%) of an oil that matched that prepared above.



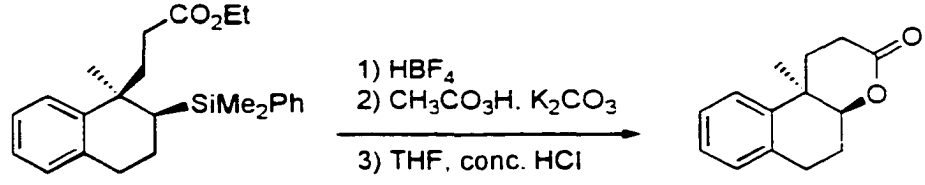
86

α,β-Unsaturated Ester. To a solution of aldehyde **86** (500 mg, 1.62 mmol), LiCl (400 mg, 9.4 mmol), and triethylphosphonoacetate (0.56 mL, 2.8 mmol) in ether (4 mL) and acetonitrile (4 mL) was added DBU (0.42 mL, 2.8 mmol) and the reaction allowed to stir 24 h at rt. The solution was diluted with ether, filtered through celite, and concentrated. Column chromatography (5 - 10% EtOAc / Hexanes) gave 596 mg (97%) as an oil. $[\alpha]_D$ -137 (1.0, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 0.34 (s, 3H), 0.37 (s, 3H), 1.28 (t, *J* 6.9, 3H), 1.32 (dd, *J* = 12.3, 1.8, 1H), 1.39 (s, 3H), 1.63 (dddd, *J* = 23.7, 11.1, 4.5, 2.1, 1H), 1.86 (dddd, *J* = 13.5, 5.1, 3.0, 3.0, 1H), 2.60-2.85 (m, 2H), 4.17 (q, *J* 6.9, 2H), 5.52 (d, *J* = 15.6, 1H), 7.00-7.60 (m, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ -2.70, -1.16, 14.5, 22.1, 29.3, 31.9, 36.1, 43.7, 60.5, 119.0, 126.1, 126.2, 128.0, 128.9, 129.1, 129.4, 134.2, 137.3, 139.4, 141.8, 156.1, 167.0; IR (thin film) 1716 cm^{-1}; HRMS (FAB−) for $C_{24}H_{31}O_2Si$ $(M+1)^-$: Calcd 379.2093, Found 379.2091.



95

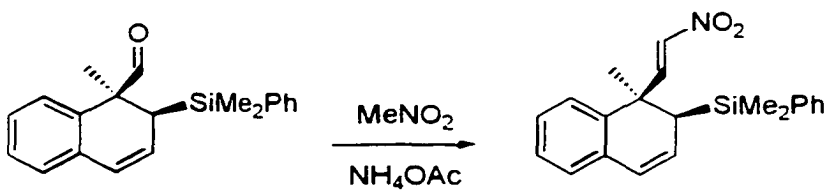
Saturated Ester. 95. A pressure tube was charged with the unsaturated ester (0.60 g, 1.6 mmol), Pd/C (90 mg, 0.09 mmol, 10%), and EtOH (20 mL). The tube was purged with H_2, and pressurized to 80 psi for 22 h. The reaction was filtered through a pad of silica gel, eluting with EtOAc. Concentration gave 0.60 g (100%) of an oil. $[\alpha]_D$ -77.2 (1.1, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 0.42 (s, 3H), 0.44 (s, 3H), 1.16 (t, *J* = 6.9, 3H), 1.30 (s, 3H), 1.31 (dd, *J* 12.3, 3.0, 1H), 1.75 (dddd, *J* = 12.9, 12.9, 10.5, 5.4, 1H), 1.85-2.10 (m, 5H), 2.60-2.90 (m, 2H), 3.97 (q, 2H), 6.95-7.60 (m, 10H); ^{13}C NMR (75MHz, $CDCl_3$) δ -1.72, -0.48, 14.3, 22.6, 31.4, 31.6, 31.6, 36.8, 37.1, 39.7, 60.3, 125.6, 125.8, 126.5, 127.9, 128.9, 129.4, 134.1, 137.1, 139.8, 144.1, 173.9; IR (thin film) 1732 cm^{-1}.



95 **90**

δ-Lactone. 90. To a solution of alkylsilane **95** (1.0 g, 2.63mmol) in CH_2Cl_2 (27 mL, 0 °C) was added HBF_4 (3 mL, 54% in ether). The solution was stirred 15 min at 0 °C and the ice bath was removed and stirring continued overnight. The solution was poured over solid $NaHCO_3$, filtered, and the cake washed with CH_2Cl_2, and concentrated. The crude

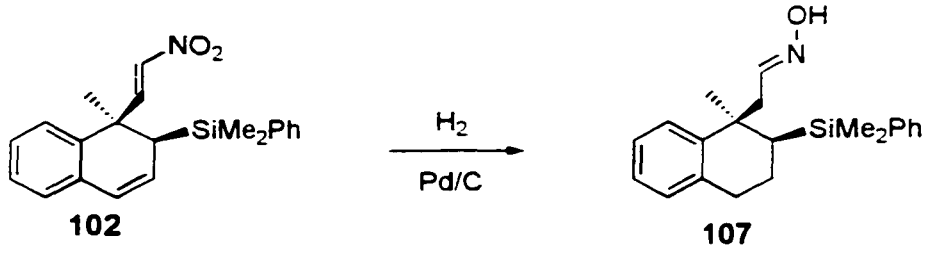
silyl fluoride was treated with K_2CO_3 (6.0 g, 43 mmol), cooled to 0 °C, and treated with CH_3CO_3H (21 mL, 32% in CH_3CO_2H). Effervescence was immediate. After 15 min, the ice bath was removed and stirring continued at rt 9 h. The mixture was poured into water and extracted into ether (3X). The ether layers were combined and back extracted with 20% K_2CO_3 (2X), brine, dried over Na_2SO_4, and concentrated. The crude mixture was redissolved in THF (12 mL), treated with 6 Pasteur pipette drops of conc. HCl, stored in the freezer overnight, and concentrated. Column chromatography (35 → 50% EtOAc/Hex) gave 0.53 g (93%) as a white solid. mp 116 - 118 °C; $[\alpha]_D$ −164 (1.1, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.95-2.25 (m, 4H), 2.33 (ddd, *J* 13.2, 5.7, 4.2, 1H), 2.46 (ddd, *J* = 17.1, 4.8, 3.3, 1H), 2.69 (ddd, *J* = 16.8, 6.0, 2.4, 1H), 3.04 (ddd, *J* = 17.7, 12.3, 6.0, 1H), 4.54 (dd, *J* = 4.5, 1.8, 1H), 7.00-7.30 (m, 4H). ^{13}C NMR (75MHz, $CDCl_3$) δ 24.1, 24.4, 27.9, 30.5, 33.2, 35.8, 84.0, 126.0, 126.7, 127.1, 129.6, 136.0, 138.6, 171.7; IR (thin film) 1714 cm^{-1}; Anal. Calcd for $C_{14}H_{20}O_2 \cdot 1/3H_2O$ C 75.67, H 7.56; Found: C 75.36, H 7.39.



89 **102**

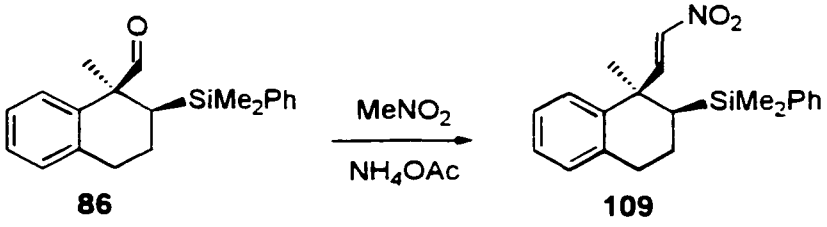
Unsaturated Nitro Olefin, 102. A pressure tube was charged with aldehyde **89** (100 mg, 0.32 mmol), ammonium acetate (100 mg, 1.3 mmol), and nitromethane (2 mL) and purged with argon. A teflon cap was applied, and the reaction was heated at 120 °C for 24 h. The crude was filtered through cotton, concentrated, and the residue partitioned between

brine and ether. The water was twice more extracted with ether. The ethereal was combined, dried over Na_2SO_4, and concentrated to give 114 mg (100%) as an oil. ^1H NMR (300MHz, $CDCl_3$) δ 0.17 (s, 3H), 1.46 (s, 3H), 2.16 (dd, J = 6.0, 0.6, 1H), 5.91 (dd, J = 9.6, 6.3, 1H), 6.49 (d, J = 9.6, 1H), 6.81 (d, J = 7.5, 1H), 7.04 (d, J = 13.5, 1H), 7.10-7.50 (m, 8H), 7.72 (d, J = 13.5, 1H).



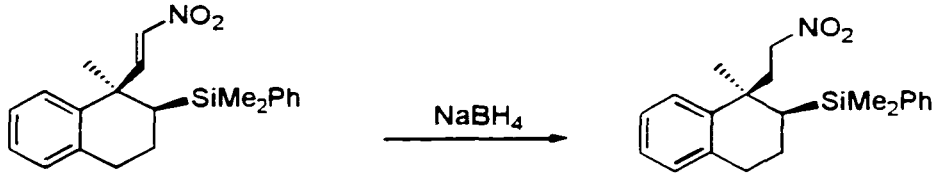
102 107

Oxime, 107. A RBF was charged with nitro olefin **102** (20 mg, 0.06 mmol), Pd/C (27 mg, 10%), and EtOH (4 mL) and purged with hydrogen. A balloon was attached and stirring continued 2 d. The suspension was filtered through silica gel (eluting with EtOAc), and concentrated. Column chromatography (20% EtOAc/Hex) gave 6.6 mg (34%) as an oil. ^1H NMR (300MHz, $CDCl_3$) δ 0.45 (s, 3H), 0.51 (s, 3H), 1.41 (s, 3H), 1.44 (dd, J = 12.6, 3.3, 1H), 1.70-2.00 (m, 2H), 2.65-2.90 (m, 2H), 2.78 (dd, J = 16.5, 6.0, 1H), 2.91 (dd, J = 16.5, 6.0, 1H), 6.61 (dd, J = 5.7, 5.7, 1H), 7.05-7.22 (m, 4H), 7.31-7.38 (m, 3H), 7.57 (bs, 1H), 7.60-7.65 (m, 2H).



86 109

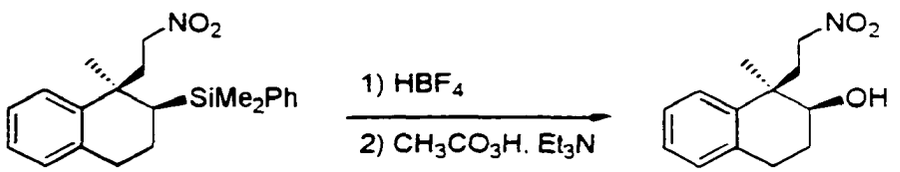
Nitro Olefin, 109. A pressure tube was charged with aldehyde **86** (100 mg, 0.32 mmol), ammonium acetate (100 mg, 1.3 mmol), and nitromethane (2 mL) and purged with argon. A teflon cap was applied, and the reaction was heated at 120 °C for 24 h. The crude was filtered through cotton, concentrated, and the residue partitioned between brine and ether. The water was twice more extracted with ether. The ethereal was combined, dried over Na_2SO_4, and concentrated to give 114 mg (100%) as an oil. $[\alpha]_D$ +155 (3.1, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 0.38 (s, 3H), 0.39 (s, 3H), 1.41 (dd, *J* = 12.6, 1.8, 1H), 1.42 (s, 3H), 1.64 (dddd, *J* = 12.3, 12.3, 11.4, 5.1, 1H), 1.96 (dddd, *J* = 13.5, 5.1, 3.0, 3.0, 1H), 2.65-2.90 (m, 2H), 6.62 (d, *J* = 13.5, 1H), 7.00-7.15 (m, 4H), 7.35-7.40 (m, 3H), 7.42 (d, *J* = 13.2, 1H), 7.50-7.60 (m, 2H); ^{13}C NMR (75MHz, $CDCl_3$) δ -2.27, -1.63, 22.3, 29.2, 31.7, 36.3, 42.3, 126.5, 126.8, 128.1, 128.4, 129.5, 129.7, 134.0, 137.1, 138.3, 138.6, 140.0, 149.6; IR (thin film) 1348, 1523 cm^{-1}; HRMS (FAB+) for $C_{21}H_{26}NO_2Si$ $(M+1)^+$: Calcd 352.1733, Found 352.1728.



109 **111**

Nitroalkane, 111. To a stirred solution of nitro olefin **109** (3.32 g, 9.5 mmol) in acetonitrile (40 mL, 0 °C) was added a solution of $NaBH_4$ (3.0 g, 79 mmol) in water (25 mL) made basic with 10% NaOH in small portions *via* an addition funnel. The pH was monitored with pH paper and was maintained between 3 and 6 by addition of 1N HCl as needed. Upon completion of borohydride addition, the ice bath was removed and the

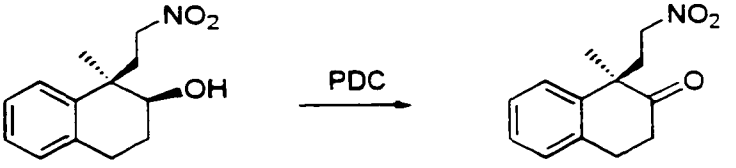
reaction stirred for 4 h at rt. Excess hydride was destroyed by addition of solid NH_4Cl, and the reaction concentrated. The residue was partitioned between ether and water, and the aqueous twice more extracted with ether. The ethereal was washed with brine, dried over Na_2SO_4, and concentrated to give 3.34 g (100%) as an oil. $[\alpha]_D$ -82.0 (2.6, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$) δ 0.47 (s, 3H), 0.52 (s, 3H), 1.34 (dd, *J* = 13.2, 2.7, 1H), 1.38 (s, 3H), 1.60 (dddd, *J* = 13.5, 13.5, 11.1, 6.0, 1H), 2.02 (dddd, *J* = 13.5, 6.3, 3.0, 3.0, 1H), 2.34 (ddd, *J* = 16.5, 11.4, 5.4, 1H), 2.47 (ddd, *J* = 17.4, 11.1, 6.3, 1H), 2.72 (ddd, *J* = 16.8, 10.5, 5.7, 1H), 2.84 (ddd, *J* = 16.8, 5.7, 3.3, 1H), 3.85-4.05 (m, 2H), 7.00-7.65 (m, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ -1.47, -0.76, 22.8, 31.5, 31.8, 36.9, 39.4, 39.5, 73.5, 125.8, 126.3, 126.3, 128.1, 129.4, 129.7, 134.0, 136.9, 138.8, 142.6; IR (thin film) 1379, 1552 cm^{-1}



111 **113**

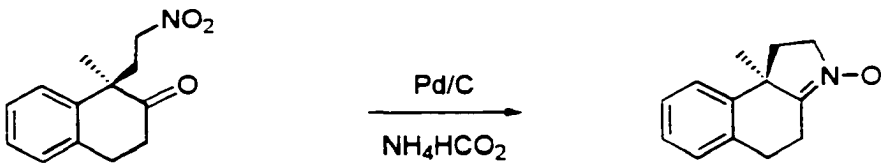
Nitro alcohol, 113. To a stirred solution of nitrosilane **111** (0.50 g, 1.42 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added HBF_4 (2 mL, 54% in ether). The solution was allowed to gradually warm to rt and was stirred overnight. The solution was poured over an excess of solid $NaHCO_3$. The suspension was diluted with CH_2Cl_2, filtered, and concentrated to give the crude silylfluoride. The residue was suspended in CH_3CO_3H (2.5 mL, 32% in CH_3CO_2H) at 0 °C and treated with Et_3N (0.5 mL, 3.59 mmol). The solution was allowed to gradually warm to rt and was stirred overnight. The suspension was

poured into 20% K_2CO_3 and extracted into ether (3X). The ethereal was washed with 20% K_2CO_3 (2X), dried over Na_2SO_4, and concentrated. Column chromatography gave 0.33 g (75%) as an oil. $[\alpha]_D$ +26.4 (1.4, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.80-2.10 (m, 2H), 2.22 (bs, 1H), 2.40 (ddd, *J* = 14.1, 10.2, 6.0, 1H), 2.56 (ddd, *J* 14.1, 10.2, 5.4, 1H), 2.70-3.10 (m, 2H), 3.83 (dd, *J* = 8.1, 3.0, 1H), 4.52 (m, 2H), 7.05-7.30 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 21.6, 22.7, 23.1, 31.6, 36.6, 69.2, 70.0, 121.8, 122.0, 122.2, 124.7, 130.6, 136.5; IR (thin film) 1383, 1549 cm^{-1}.



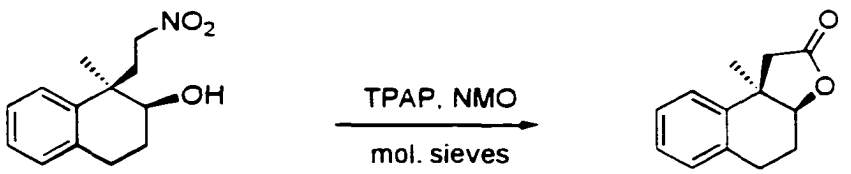
113 **114**

Nitro ketone, 114. To a solution of alcohol **113** (20 mg, 0.085 mmol) in CH_2Cl_2 (1.5 mL) was added PDC (55 mg, 0.15 mmol). After 4 h, another portion of PDC was added (55 mg, 0.15 mmol) was added and stirring continued overnight. The reaction was diluted with ether and filtered through silica gel. Column chromatography gave 7 mg (36%) as an oil. $[\alpha]_D$ −75.5 (1.1, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.47 ddd, *J* = 15.3, 10.2, 5.1, 1H), 2.63 (ddd, *J* = 14.7, 5.7, 5.7, 1H), 2.80-2.95 (m, 2H), 3.00-3.20 (m, 2H), 3.96 (ddd, *J* = 13.2, 10.2, 5.1, 1H), 4.17 (ddd, *J* = 12.9, 10.2, 5.7, 1H), 7.20-7.40 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 28.5, 28.9, 35.7, 37.5, 50.0, 72.0, 126.3, 127.4, 127.8, 128.8, 135.8, 139.7, 212.8; IR (thin film) 1383, 1552, 1712 cm^{-1}.



114 **120**

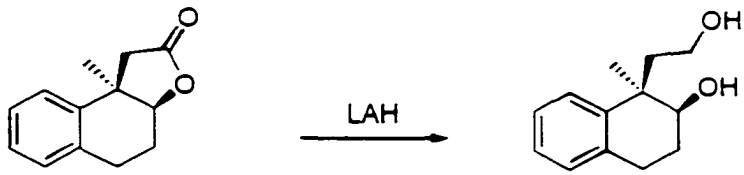
Nitrone, 120. To a stirred solution of nitro ketone **114** (5 mg, 0.020 mmol) in THF/MeOH (1 mL, 1:1) was added NH_4HCO_2 (20 mg, 0.32 mmol) and Pd/C (2 mg, 10%). After stirring overnight, it was diluted with ether (6 mL), filtered through celite, and concentrated. Column chromatography (5% MeOH/CH_2Cl_2) gave 4 mg (93%) as a solid. mp 147-149 °C; $[\alpha]_D$ +99.8 (1.9, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.43 (s, 3H), 2.40-2.50 (m, 2H), 2.70-2.80 (m, 1H), 2.90-3.15 (m, 3H), 3.90-4.00 (m, 1H), 4.25-4.40 (m, 1H), 7.05-7.30 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 21.0, 26.4, 27.3, 34.1, 48.0, 61.4, 124.7, 127.0, 127.5, 128.7, 134.8, 143.1, 151.1; IR (thin film) 1622, 1198 cm^{-1}; Anal. Calcd for $C_{13}H_{15}NO \cdot 1/8H_2O$: C 76.72, H 7.55; Found: C 76.82, H 7.56.



113 **115**

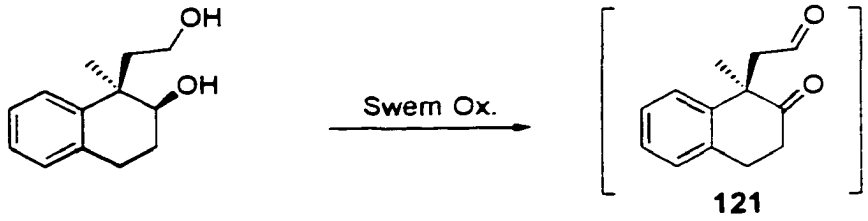
γ-lactone, 115. A RBF was charged with nitro alcohol **113** (18 mg, 0.08 mmol), NMO (18 mg, 0.15 mmol), molecular sieves (45 mg, 3 Å, powdered), and CH_2Cl_2 (0.75 mL). To this was added TPAP (4 mg, 0.01 mmol) at 0 °C. The ice bath was removed, and stirring was continued 30 min. The suspension was diluted with ether and filtered through silica gel to give 14 mg (93%) as a white solid. mp 99.1-101 °C; $[\alpha]_D$ +164 (1.3, $CHCl_3$);

^{1}H NMR (300MHz, $CDCl_3$) δ 1.50 (s, 3H), 2.00-2.20 (m, 2H), 2.70 (ddd, *J* = 16.5, 5.7, 5.7, 1H), 2.73 (d, *J* = 17.1, 1H), 2.81 (d, *J* = 17.1, 1H), 2.93 (ddd, *J* = 16.5, 9.9, 5.7, 1H), 4.54 (dd, *J* = 6.6, 3.3, 1H), 7.00-7.25 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 24.4, 24.8, 28.5, 42.5, 45.1, 85.1, 126.7, 127.2, 127.9, 128.9, 135.0, 139.7, 175.7; IR (thin film) 1780 cm^{-1}; Anal. Calcd for $C_{13}H_{14}O_2$: C 77.20, H 6.98; Found: C 76.93, H 6.95



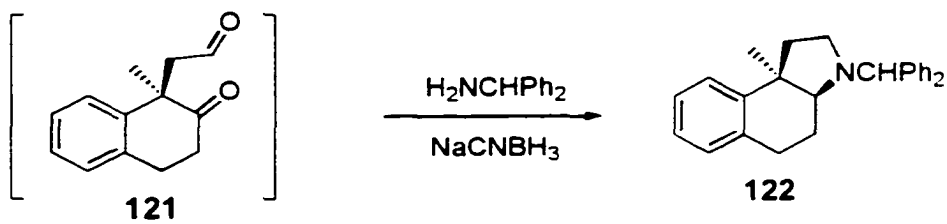
115

1,4-Diol. To a solution of lactone **115** (50 mg, 0.25 mmol) in THF (3 mL) at 0 °C was added LAH (30 mg, 0.79 mmol). After 15 min, the ice bath was removed and stirring was continued for 30 min. The suspension was diluted with THF, and was quenched by dropwise addition of saturated Na_2SO_4 in 20% KOH, until a filterable white solid formed. The suspension was filtered and concentrated. Column chromatography (50% EtOAc/Hex) gave 46 mg (90%) as a white solid. mp 78.8-79.8 °C; $[\alpha]_D$ −12.3 (1.1, $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ 1.32 (s, 3H), 1.84 (ddd, *J* = 15.0, 5.7, 2.4, 1H), 1.95-2.05 (m, 2H), 2.12 (ddd, *J* = 15.3, 9.0, 3.3, 1H), 2.78 (ddd, *J* = 17.4, 6.6, 6.6, 1H), 3.01 (ddd, *J* = 16.8, 6.9, 6.9, 1H), 3.63 (ddd, *J* = 11.1, 6.0, 3.3, 1H), 3.70-3.85 (m, 2H), 4.00-4.50 (bs, 2H), 7.00-7.25 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 26.8, 26.9, 27.1, 41.9, 42.0, 58.8, 73.6, 125.7, 126.2, 126.8, 129.0, 135.2, 144.0; IR (thin film) 3297 (br) cm^{-1}.



121

1,4-Dicarbonyl compound, 121. To a stirred solution of oxalyl chloride (0.38 mL, 0.75 mmol, 2M in CH_2Cl_2) in CH_2Cl_2 (4.5 mL) at -78 °C was added DMSO (0.1 mL, 1.4 mmol). The resulting solution was stirred 15 min and treated with the diol (40 mg, 0.19 mmol) in CH_2Cl_2 (1 mL). The solution was stirred 30 min at -78 °C, allowed to warm to -50 °C in the dewar, and recooled to -78 °C. It was treated with triethylamine (0.3 mL, 2.2 mmol) and stirred 5 min before removing the ice bath and allowing it to reach rt. The solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3X), dried over Na_2SO_4, and concentrated to give 40 mg (100%) as an oil which was used without purification.

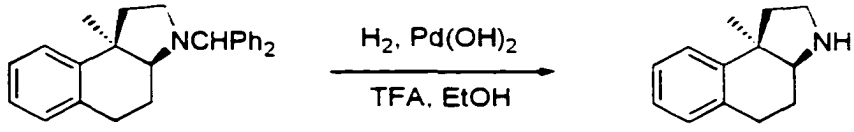


121 122

***cis*-*N*-benzhydryl-pyrrolidine-fused tetralin, 122.** A RBF was charged with 1,4-dicarbonyl compound **121** (40 mg, 0.19 mmol), benzhydrylamine hydrochloride (44 mg, 0.20 mmol), and MeOH (2 mL). The solution was cooled to -78 °C and treated with $NaCNBH_3$ (20 mg, 0.32 mmol). After 1h, an additional portion of $NaCNBH_3$ (20 mg, 0.32 mmol) and the solution was allowed to warm slowly in the dewar to rt overnight.

The suspension was treated with solid $NaHCO_3$ and K_2CO_3 and stirred 15 min. The suspension was diluted with ether, filtered through silica, and concentrated. Column chromatography (2% EtOAc/Hex) gave 49 mg (71%, 2 steps) of a 9:1 mixture of epimers. Column chromatography (100% toluene) gave complete separation of the two diastereomers. **Major (cis)**: $[\alpha]_D$ +3.57 (1.0, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.50-1.75 (m, 2H), 1.85-2.10 (m, 2H), 2.41 (ddd, *J* = 16.2, 9.3, 3.9, 1H), 2.58 (ddd, *J* = 9.3, 6.9, 6.9, 1H), 2.70-2.85 (m, 3H), 4.91 (s, 1H), 6.95-7.50 (m, 9H). ^{13}C NMR (75MHz, $CDCl_3$) δ 24.5, 27.9, 31.0, 40.4, 44.9, 48.7, 67.3, 70.8, 125.2, 126.3, 126.9, 126.9, 127.5, 128.1, 128.2, 128.3, 128.7, 136.7, 142.2, 143.9, 145.8.

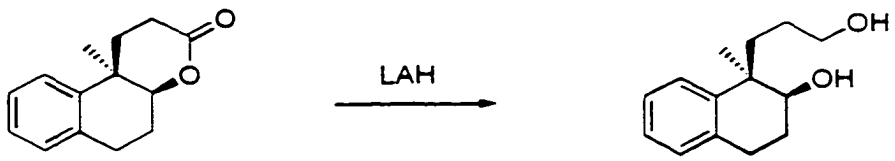
Minor (trans): ^1H NMR (300MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.45-1.65 (m, 2H), 1.76 (ddd, *J* = 11.4, 11.4, 7.8, 1H), 1.96 (ddd, *J* = 11.7, 8.4, 3.0, 1H), 2.46 (ddd, *J* = 11.1, 11.1, 3.3, 1H), 2.57 (dd, *J* = 12.3, 3.6, 1H), 2.71 (ddd, *J* = 18.0, 9.0, 9.0, 1H), 2.87 (dd, *J* = 18.0, 8.1, 1H), 3.19 (ddd, *J* = 9.9, 8.1, 8.1, 1H), 4.76 (s, 1H), 6.95-7.50 (m, 14H); HRMS (FAB+) for $C_{26}H_{27}N$ $(M)^+$: Calcd 353.2144, Found 353.2138.



122 **43**

***cis*-pyrrolidine-fused tetralin, 43.** A RBF was charged with protected aminotetralin **122** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and

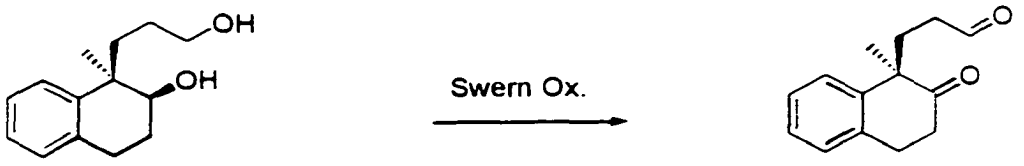
EtOH, filtered, and concentrated. The residue was partitioned between water and ether. The aqueous was washed twice more with ether, dried over Na_2SO_4, and concentrated. Column chromatography (neutral alumina, 1 → 5% MeOH/CH_2Cl_2) 7.7 mg (97%) as an oil. $[\alpha]_D$ +86 (0.4, $CHCl_3$); ^1H NMR (300MHz, C_6D_6) δ 1.16 (s, 3H), 1.60-1.90 (m, 4H), 2.40 (ddd, *J* = 16.2, 6.9, 4.8, 1H), 2.70-3.20 (m, 4H), 4.59 (bs, 1H), 6.80-7.10 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 25.2, 26.5, 29.3, 41.2, 44.2, 45.2, 64.4, 126.2, 126.9, 127.5, 128.8, 135.4, 142.0; IR (thin film) 3322(br) cm^{-1}; HRMS (FAB+) for $C_{13}H_{18}N$ $(M-H)^+$. Calcd 188.1439, Found 188.1437.



90

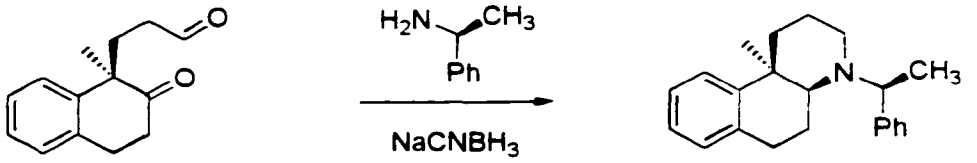
1,5-Diol. To a solution of lactone **90** (50 mg, 0.23 mmol) in THF (3 mL) at 0 °C was added LAH (30 mg, 0.79 mmol). After 15 min, the ice bath was removed and stirring was continued for 30 min. The suspension was diluted with THF, and was quenched by dropwise addition of saturated Na_2SO_4 in 20% KOH, until a filterable white solid formed. The suspension was filtered and concentrated. Column chromatography (50% EtOAc/Hex) gave 49 mg (96%) as a white solid. mp 142-145 °C; $[\alpha]_D$ −17.0 (1.1, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.50-1.70 (m, 2H), 1.70-1.85 (m, 2H), 1.90-2.05 (m, 2H), 2.56 (bs, 2H), 2.75 (ddd, *J* = 17.1, 6.3, 6.3, 1H), 3.00 (ddd, *J* = 17.4, 7.2, 7.2, 1H), 3.56 (m, 2H), 3.85 (dd, *J* = 5.1, 5.1, 1H), 6.95-7.30 (m, 4H); ^{13}C

NMR (75MHz, $CDCl_3$) δ 26.0, 26.4, 27.2, 27.5, 33.4, 41.2, 63.7, 73.3, 125.8, 126.0, 127.2, 129.1, 135.1, 143.2; IR (thin film) 3307 (br) cm^{-1}.



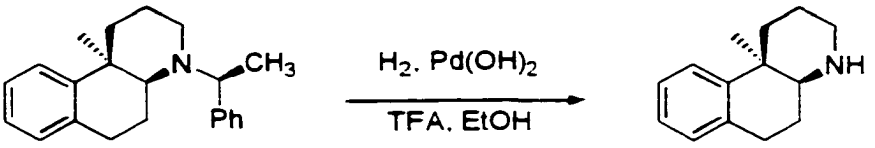
123

1,5-Dicarbonyl compound, 123. To a stirred solution of oxalyl chloride (0.43 mL, 0.85 mmol, 2M in CH_2Cl_2) in CH_2Cl_2 (5 mL) at -78 °C was added DMSO (0.1 mL, 1.4 mmol). The resulting solution was stirred 15 min and treated with the 1,5-diol (60 mg, 0.27 mmol) in CH_2Cl_2 (1 mL). The solution was stirred 30 min at -78 °C, allowed to warm to -50 °C in the dewar, and recooled to -78 °C. It was treated with triethylamine (0.4 mL, 2.9 mmol) and stirred 5 min before removing the ice bath and allowing it to reach rt. The solution was poured into saturated $NaHCO_3$, extracted with CH_2Cl_2 (3X), dried over Na_2SO_4, and concentrated. Column chromatography (20 → 40% EtOAc/Hex) to give 55 mg (93%) as an oil. $[\alpha]_D$ +51.3 (1.6, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.43 (s, 3H), 1.95-2.10 (m, 2H), 2.16 (m, 1H), 2.41 (m, 1H), 2.57 (ddd, J = 15.0, 5.7, 5.7, 1H), 2.74 (ddd, J = 15.0, 8.4, 8.4, 1H), 3.04 (d, J = 5.4, 1H), 3.06 (d, J = 5.4, 1H), 7.10-7.30 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 27.8, 28.7, 31.6, 38.1, 40.2, 51.1, 126.5, 126.8, 127.4, 128.4, 136.0, 141.0, 201.3, 213.9; IR (thin film) 1716 cm^{-1}; HRMS (FAB+) for $C_{13}H_{17}O_2$ $(M+H)^+$: Calcd 217.1229, Found 217.1222.



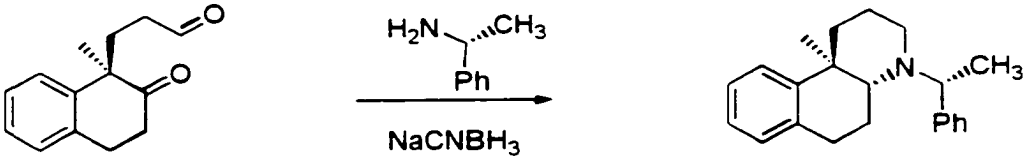
123 **125**

***cis*-*N*-α-methylbenzyl-piperidine-fused tetralin. 125.** A RBF was charged with 1,5-dicarbonyl compound **123** (25 mg, 0.12 mmol), (S)-α-methylbenzylamine hydrochloride (25 mg, 0.15 mmol), and MeOH (1 mL). The solution was cooled to -78 °C and treated with $NaCNBH_3$ (10 mg, 0.16 mmol). After 1h, an additional portion of $NaCNBH_3$ (10 mg, 0.16 mmol) was added and the solution was allowed to warm to rt. The reaction was treated with molecular sieves (50 mg, 3 Å, powdered) and acetic acid (7 μL, 0.12 mmol) and allowed to stir 3 h. The suspension was treated with solid $NaHCO_3$ and K_2CO_3 and stirred 15 min. The suspension was diluted with ether, filtered through silica, and concentrated. Column chromatography (2% EtOAc/Hex) gave 25 mg (71%) as a white solid. mp 97.7-99.5 °C; $[\alpha]_D$ -24.5 (1.4, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.31 (d, *J* = 6.6, 3H), 1.30-1.40 (m, 1H), 1.55-1.75 (m, 2H), 1.67 (s, 3H), 1.80-2.15 (m, 3H), 2.20-2.45 (m, 2H), 2.85 (ddd, *J* = 16.5, 10.8, 5.4, 1H), 2.97 (ddd, *J* = 16.5, 4.8, 4.8, 1H), 3.14 (dd, *J* = 10.8, 2.1, 1H), 3.79 (q, *J* = 6.6, 1H), 7.05-7.50 (m, 9H). ^{13}C NMR (75MHz, $CDCl_3$) δ 16.1, 23.0, 27.0, 29.7, 30.5, 36.4, 38.2, 45.0, 60.0, 60.3, 125.4, 126.1, 126.6, 127.0, 127.2, 128.4, 128.9, 135.3, 147.4, 148.0; HRMS (FAB+) for $C_{22}H_{27}N$ $(M)^+$: Calcd 305.2144, Found 305.2135.



125 **126**

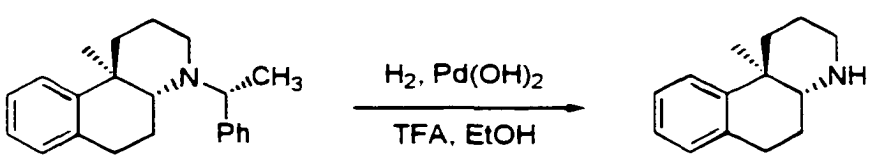
***cis*-piperidine-fused tetralin, 126.** A RBF was charged with protected aminotetralin **125** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and EtOH, filtered, and concentrated. The residue was partitioned between water and ether. The aqueous was washed twice more with ether, dried over Na_2SO_4, and concentrated to give 9.9 mg (100%) as an oil; $[\alpha]_D$ +67 (0.5, $CHCl_3$); ^1H NMR (300MHz, C_6D_6) δ 0.68 (bs, 1H), 1.06 (s, 3H), 1.15-1.35 (m, 3H), 1.47 (dddd, *J* = 13.5, 6.9, 4.5, 2.1, 1H), 1.94 (dddd, *J* = 13.5, 12.0, 6.6, 2.4, 1H), 2.15-2.30 (m, 1H), 2.45-2.60 (m, 3H), 2.70-2.80 (m, 1H), 3.00 (ddd, *J* = 16.8, 12.0, 6.9, 1H), 7.00-7.30 (m, 4H); ^{13}C NMR (75MHz, C_6D_6) δ 23.9, 25.2, 26.3, 30.8, 32.3, 37.5, 37.8, 46.7, 60.4, 125.9, 126.4, 126.7, 130.0, 136.4, 143.4; IR (thin film) 3283(br) cm^{-1}; HRMS (FAB+) for $C_{14}H_{20}N$ $(M+H)^+$ Calcd 202.1596, Found 202.1596.



123 **127**

***trans*-*N*-α-methylbenzyl-piperidine-fused tetralin, 127.** A RBF was charged with 1,5-dicarbonyl compound **123** (25 mg, 0.12 mmol), (R)-α-methylbenzylamine hydrochloride

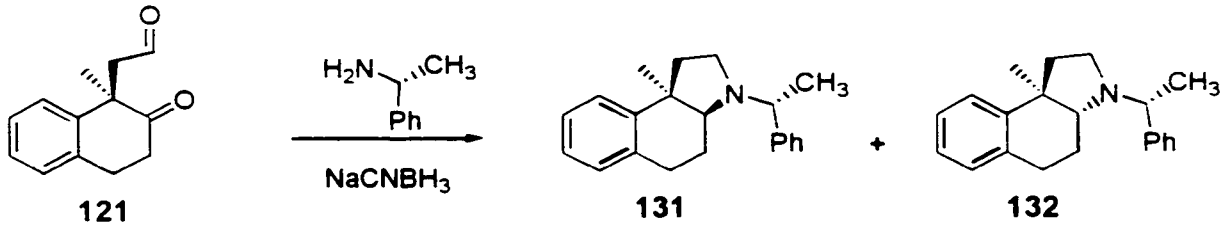
(25 mg, 0.15 mmol), and MeOH (1 mL). The solution was cooled to -78 °C and treated with $NaCNBH_3$ (10 mg, 0.16 mmol). After 1h, an additional portion of $NaCNBH_3$ (10 mg, 0.16 mmol) was added and the solution was allowed to warm to rt. The reaction was treated with molecular sieves (50 mg, 3 Å, powdered) and acetic acid (7 μL, 0.12 mmol) and allowed to stir 4 h. The suspension was treated with solid $NaHCO_3$ and K_2CO_3 and stirred 15 min. The suspension was diluted with ether, filtered through silica, and concentrated. Column chromatography (2% EtOAc/Hex) gave 27 mg (76%) as an oil. $[\alpha]_D$ +39.1 (1.5, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.32 (d, *J* = 6.9, 3H), 1.40 (s, 3H), 1.40-1.55 (m, 2H), 1.65-1.90 (m, 2H), 2.14 (ddd, *J* = 12.3, 12.3, 3.0, 1H), 2.20-2.40 (m, 2H), 2.50-2.60 (m, 1H), 2.63 (dd, *J* = 12.3, 3.3, 1H), 3.02 (d, *J* = 4.8, 1H), 3.05 (d, *J* = 4.8, 1H), 4.45 (q, *J* = 6.9, 1H), 7.10-7.60 (m, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ 9.1, 21.7, 22.7, 23.7, 29.2, 37.9, 38.7, 46.5, 53.7, 64.1, 125.3, 125.6, 125.9, 126.2, 127.8, 128.0, 134.4, 145.6, 147.0; HRMS (FAB+) for $C_{22}H_{28}N$ $(M+H)^+$: Calcd 306.2222, Found 306.2225.



127 **128**

***trans*-piperidine-fused tetralin, 128.** A RBF was charged with protected aminotetralin **127** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and

EtOH, filtered, and concentrated. The residue was partitioned between water and ether. The aqueous was washed twice more with ether, dried over Na_2SO_4, and concentrated to give 9.9 mg (100%) as an oil. $[\alpha]_D$ +116 (1.0, $CHCl_3$); ^1H NMR (300MHz, C_6D_6) δ 0.83 (bs, 1H), 1.22 (s, 3H), 1.20-1.50 (m, 3H), 1.65-1.90 (m, 2H), 2.05-2.15 (m, 1H), 2.35-2.50 (m, 2H), 2.60-2.85 (m, 2H), 2.89 (dd, J = 11.7, 5.1, 1H), 6.90-7.30 (m, 4H); ^{13}C NMR (75MHz, C_6D_6) δ 22.6, 23.9, 26.6, 29.7, 30.7, 37.7, 48.4, 62.0, 125.4, 126.2, 126.5, 129.8, 135.2, 147.4; IR (thin film) 3278(br) cm^{-1}; HRMS (FAB+) for $C_{14}H_{20}N$ $(M+H)^+$: Calcd 202.1596, Found 202.1590.

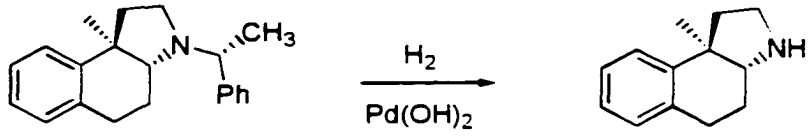


121 **131** **132**

***trans*-*N*-α-methylbenzyl-pyrrolidine-fused tetralin, 132.** A RBF was charged with 1,4-dicarbonyl compound **121** (39 mg, 0.19 mmol), (R)-α-methylbenzylamine hydrochloride (40 mg, 0.20 mmol), and MeOH (2 mL). The solution was cooled to -78 °C and treated with $NaCNBH_3$ (10 mg, 0.16 mmol). After 1h, an additional portion of $NaCNBH_3$ (10 mg, 0.16 mmol) was added and the solution was allowed to warm to rt and stirred overnight. The suspension was treated with solid $NaHCO_3$ and K_2CO_3 and stirred 15 min. The suspension was diluted with ether, filtered through silica, and concentrated. ^1H NMR revealed a 1:1 mixture of epimers. Column chromatography (5% EtOAc/Hex) gave 23 mg (41%) of the *cis* isomer as an oil and then 22 mg (39%) of the *trans* isomer as an oil.

trans: $[\alpha]_D$ +66.6 (1.7, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.34 (d, *J* = 6.6, 3H), 1.85 (dddd, *J* = 11.4, 7.8, 7.8, 7.8, 1H), 1.99 (ddd, *J* = 11.7, 8.4, 3.0, 1H), 2.55-3.10 (m, 5H), 3.88 (q, *J* = 6.6, 1H), 7.00-7.50 (m, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ 16.0, 22.3, 25.2, 27.8, 34.6, 44.6, 46.4, 58.2, 66.7, 125.1, 125.6, 125.8, 126.6, 127.5, 128.2, 128.7, 135.5, 146.4, 147.2; HRMS (FAB+) for $C_{21}H_{26}N$ $(M+H)^+$: Calcd 292.2065, Found 292.2052.

cis: $[\alpha]_D$ +78.9 (1.5, $CHCl_3$); ^1H NMR (300MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.45 (d, *J* = 6.6, 3H), 1.69 (dddd, *J* = 13.2, 9.0, 9.0, 3.9, 1H), 1.80-2.05 (m, 3H), 2.56 (ddd, *J* = 15.6, 9.6, 3.9, 1H), 2.60-2.70 (m, 2H), 2.75-2.90 (m, 2H), 3.89 (q, *J* = 6.6, 1H), 7.00-7.40 (m, 9H); ^{13}C NMR (75MHz, $CDCl_3$) δ 22.8, 26.9, 27.8, 30.9, 40.0, 44.9, 47.9, 60.9, 66.9, 125.2, 126.4, 126.9, 127.6, 128.0, 128.1, 128.1, 128.2, 128.2, 136.9, 143.8, 146.1, HRMS (FAB+) for $C_{21}H_{26}N$ $(M+H)^+$: Calcd 292.2065, Found 292.2055.



132 **133**

***trans*-pyrrolidine-fused tetralin, 133.** A RBF was charged with protected aminotetralin **132** (15 mg, 0.05 mmol), $Pd(OH)_2$ (5 mg, 20% on carbon), TFA (0.2 mL, 2.6 mmol), and EtOH (5 mL). The atmosphere was flushed with hydrogen and a balloon was attached. After 4 h, the suspension was concentrated, made basic with a mixture of 10% NaOH and EtOH, filtered, and concentrated. The residue was partitioned between water and ether. The aqueous was washed twice more with ether, dried over Na_2SO_4, and concentrated to

give 9.6 mg (100%) as an oil; $[\alpha]_D$ +67 (0.5, $CHCl_3$); ^1H NMR (300MHz, C_6D_6) δ 0.93 (s, 3H), 0.97 (bs, 1H), 1.55-1.85 (m, 4H), 2.60-3.05 (m, 4H), 6.95-7.15 (m, 4H); ^{13}C NMR (75MHz, $CDCl_3$) δ 22.4, 22.6, 28.1, 30.5, 36.8, 44.5, 63.7, 125.8, 125.8, 126.1, 129.0, 135.5, 146.2; IR (thin film) 3266(br) cm^{-1}; HRMS (FAB+) for $C_{13}H_{18}N$ $(M-H)^+$ Calcd 188.1439, Found 188.1437.

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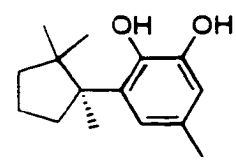
Chapter Two

The Total Synthesis of (-)-Herbertenediol, (-)-Mastigophorene A, and (-)-Mastigophorene B. Combined Utility of Chiral Bicyclic Lactams and Chiral Aryl Oxazolines

A. Herbertenediol, Mastigophorene A, and Mastigophorene B. Isolation, Biological Activity, and Previous Work.

(-)-Herbertenediol (**1**) was first isolated in 1983 from methanolic extracts of the liverwort, *Herberta adunca*, by Matsuo, Yuki, and Nakayama.[1] It has, as key features, a catechol-type diol and a chiral cyclopentane, containing vicinal quaternary carbon centers.

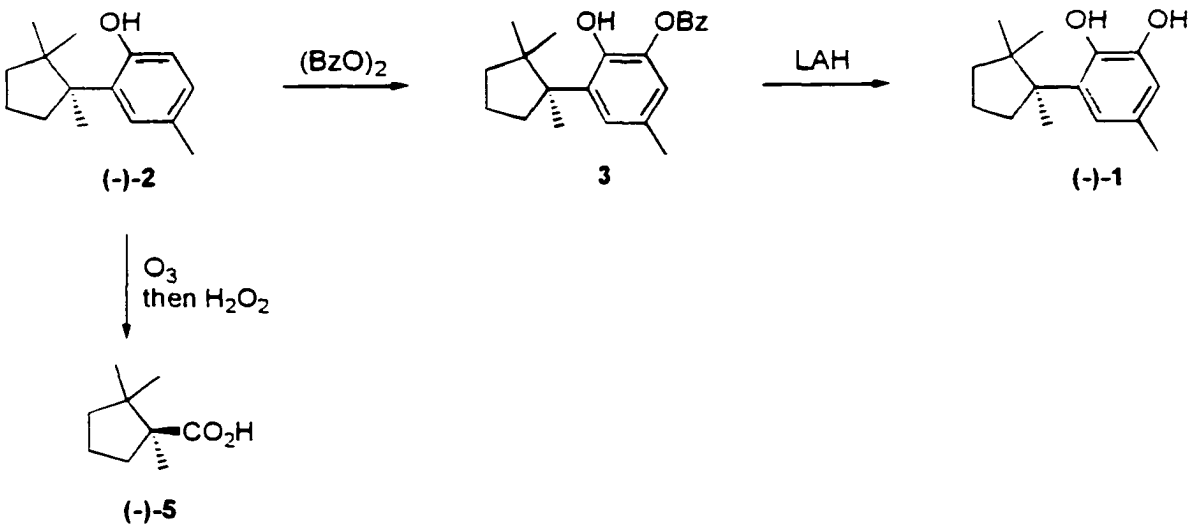


(-)-1

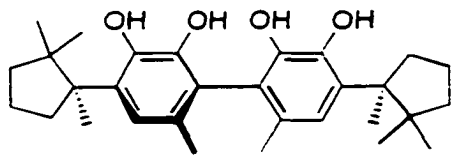
Its gross structure was verified[1] by its synthesis from (-)-α-herbertenol (**2**) and is illustrated in Scheme 1. Benzoyloxylation with benzoyl peroxide, and subsequent reduction, gave material which was in good spectroscopic agreement with **1**. The absolute configuration was assigned on the basis of the degradation of **2** to (-)-camphonanic acid

(5) by ozonolysis with an oxidative decomposition of the ozonide. Later, Fukuyama and coworkers found that herbertenediol possessed potent anti-lipid peroxidation activity,[2] exhibiting 100% inhibition at 1 μg/mL in rat brain homogenates.

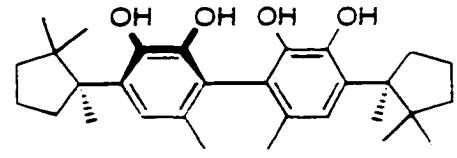
Scheme 1



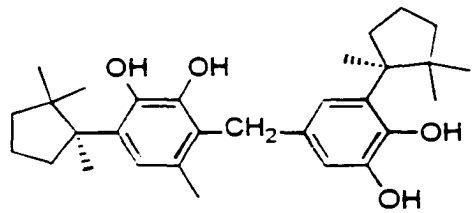
(-)-Herbertenediol was later isolated by Fukuyama and Asakawa from the liverwort, *Mastigophora diclados*.[3] Coexisting with **1**, mastigophorenes A (**6**), B (**7**), C (**8**), and D (**9**) were isolated and found to possess unique dimeric structures of **1**. The gross chemical structures of **6** and **7** were assigned largely on their similarities to herbertenediol. Two key pieces of evidence suggested their constitution. First, each had only one aromatic proton, and second, one of herbertenediol's aromatic methine carbons (δ 113.4) had been replaced with an aromatic quaternary carbon (δ 117.1, for **6** and δ 117.0, for **7**). Spectral non-equivalence of **6** and **7** could then be rationalized as being due to the diastereomeric environment caused by atropisomers about the biaryl axis. The absolute configuration about the biaryl axes of **6** and **7** was clarified by application of the CD exciton chirality rule.



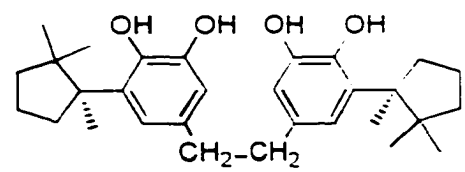
(-)-6



(-)-7



(-)-8

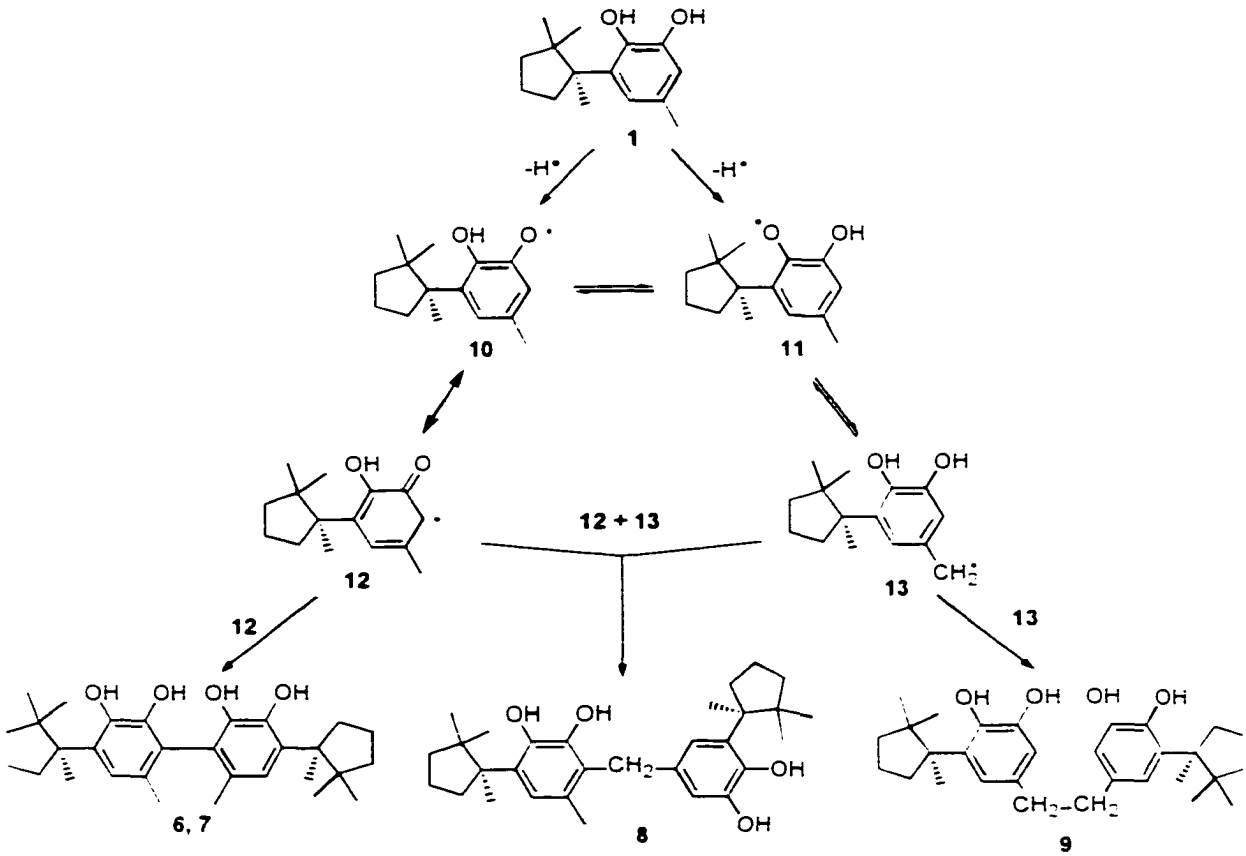


(-)-9

Mastigophorenes A, B, and D were found to exhibit interesting neurotrophic properties at 10^{-5} to 10^{-7} mol/L. At these concentrations, they were found to greatly accelerate neuritic sprouting and network formation in the primary neuritic cell culture derived from the fetal rat hemisphere.[5] In contrast, mastigophorene C suppressed neuritic differentiation.

It has been proposed[5] that all of the mastigophorenes are biosynthesized *via* an oxidative phenolic coupling of coexisting **1**, and is pictured in Scheme 2. Each pathway begins with formation of phenoxy radicals produced by one electron oxidations of herbertenediol. The phenoxy radicals can subsequently interconvert to either **12** or **13**. Mastigophorenes A and B then arise from homocoupling of radical **12**, followed by aromatization. Mastigophorene C may originate from heterocoupling of radical **12** with radical **13**, and mastigophorene D from homocoupling of benzylic radical **13**.

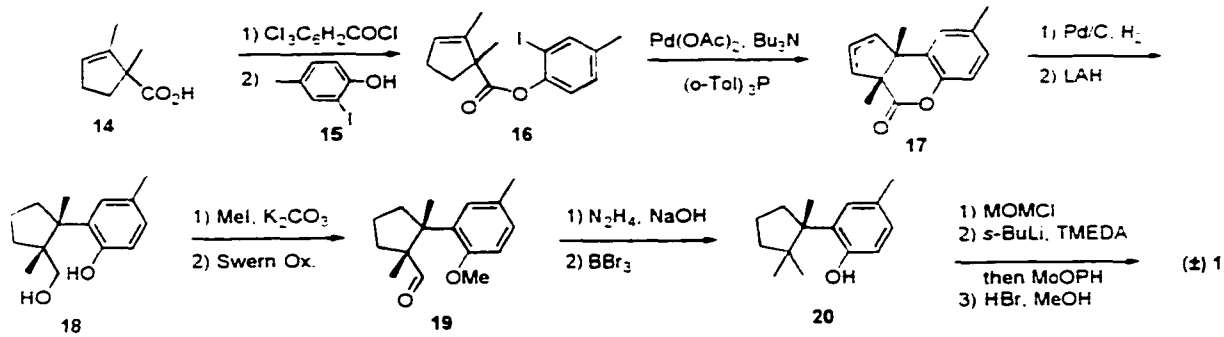
Scheme 2



The only total synthesis of racemic herbertenediol was published by Fukuyama and coworkers in 1996.[2-4] It began with known carboxylic acid **14**, which was coupled to iodo-phenol **15** to give ester **16**. This set the stage for a key intramolecular Heck reaction, setting the vicinal quaternary carbon center in high yield. The olefin was removed by means of hydrogenation and the lactone reduced with LAH to give diol **18**. After protecting the phenol as its methyl ether, the remaining alcohol was oxidized to the aldehyde and reduced to the trimethyl cyclopentane using the Huang-Minlon modification[5] of the Wolff-Kishner[6] reduction. The methyl ether was then replaced with a MOM ether, and the resulting arene *ortho*-metalated, treated with MoOPH, and demethylated with HBr

to complete the synthesis of (±) herbertenediol. The authors report, as a footnote, that acid **14** was prepared in 90% ee, and hence their work constituted a formal synthesis of optically enriched (-)-herbertenediol.

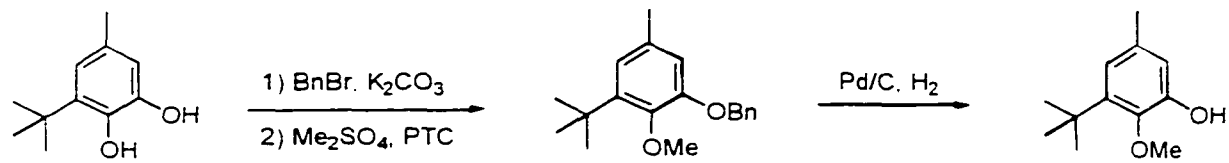
Scheme 3



14 **15** **16** **17** **18** **19** **20**

All work toward the construction of mastigophorenes A and B has been carried out in Bringmann's labs.[7,8] The first such report[7] highlighted their work to access the biaryl axis enantioselectively while working with simplified analogs wherein the chiral cyclopentane has been replaced by more easily accessed *t*-butyl groups. This route began with known diol **21**, immediately protecting the less-hindered hydroxyl as its benzyl ether, while the remaining hydroxyl was protected under phase transfer conditions to give the orthogonally protected diol. Hydrogenolysis liberated phenol **23**, ready for coupling.

Scheme 4

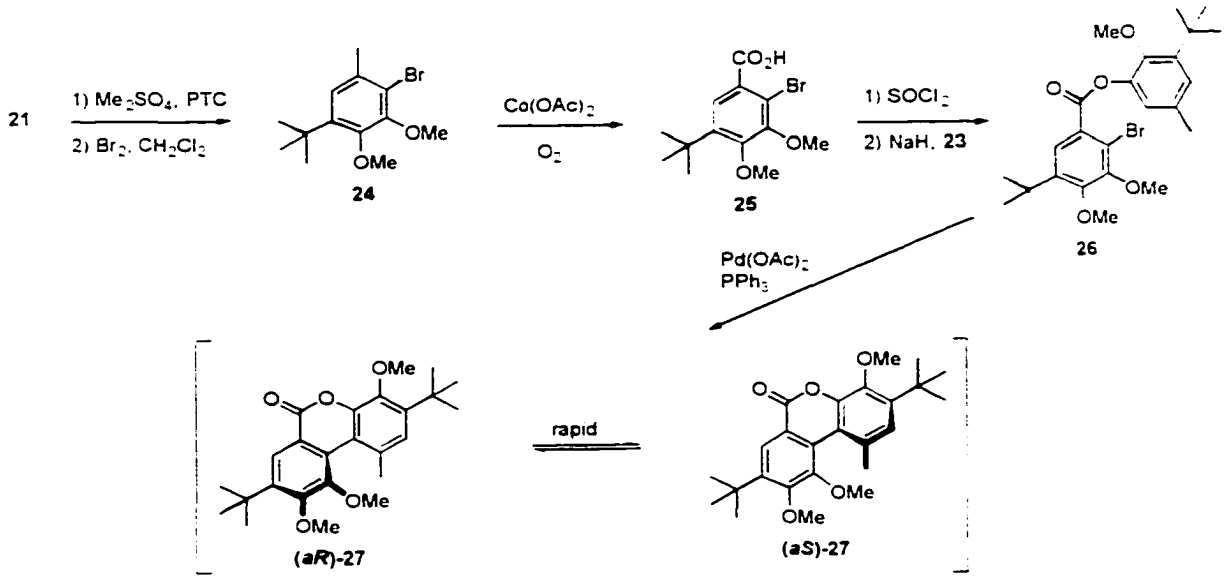


21 **22** **23**

For the other half of the biaryl, they again began with diol **21**. It was exhaustively methylated and then regioselectively brominated. The benzylic methyl group was oxidized

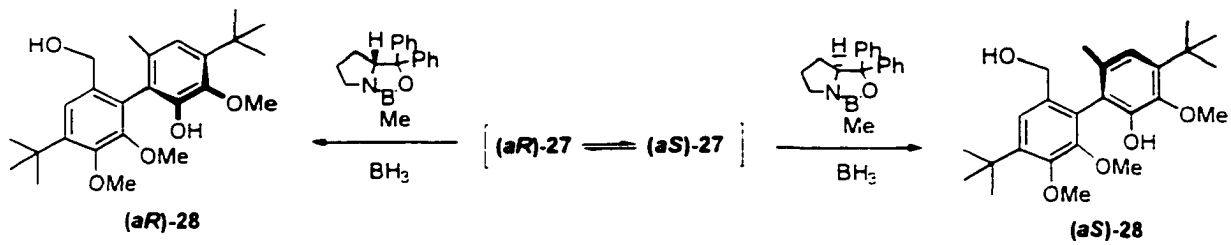
to the benzoic acid and coupled to **23** to give the ester. Treatment of the aryl bromide with Pd(0), induced intramolecular aryl coupling to give lactone **27**

Scheme 5



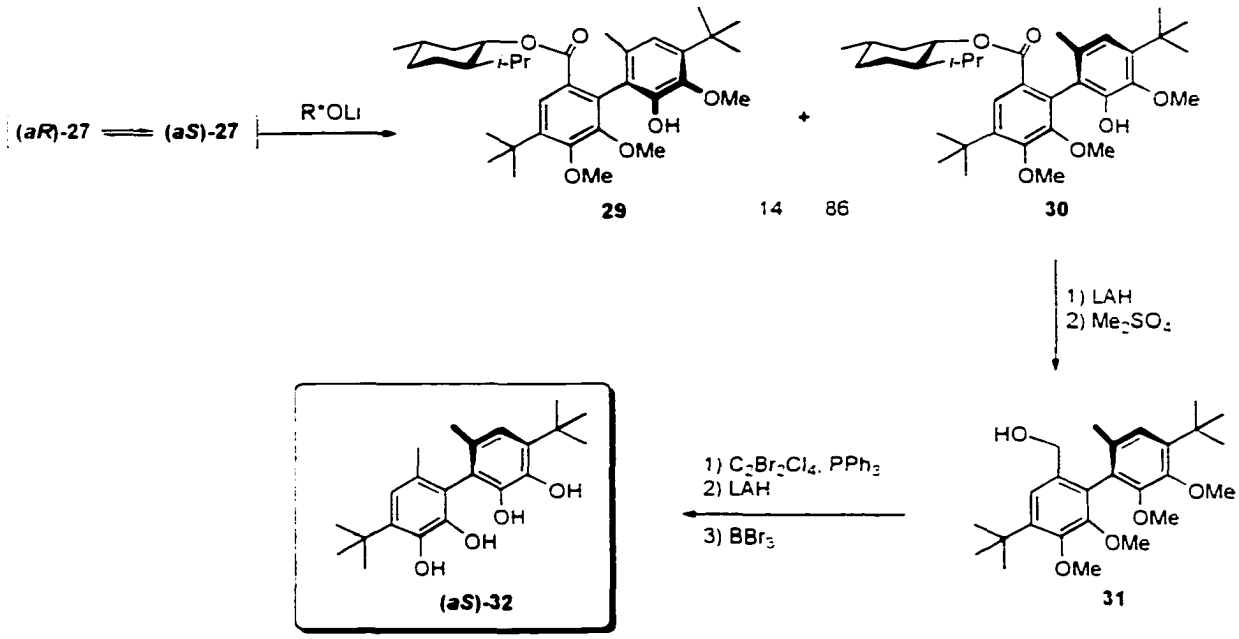
Lactone **27** is stereochemically labile about the biaryl axis, and hence both forms are rapidly interconverted in solution. Attempted reduction of the lactone with Corey's oxazaborolidine catalyst gave rise to good levels of enantioselectivity (~93:7), but as the products were enantiomeric, further enrichment of the enantiomers was difficult. Attempted recrystallization of the crude material, showed increased enantiomeric excesses only in the mother liquor.

Scheme 6



Given the above difficulties, they approached the problem a different way. Instead the authors pursued stereoselective ring opening of **27** with chiral *O*-nucleophiles. Ring opening with 1-(*S*)-menthol gave rise to moderate levels of atroposelection. As the products were diastereomeric they were now separable by simple chromatographic resolutions. Further chemical manipulations culminated in the synthesis of a simplified analog of mastigophorene A ((*aS*)-**32**). Analogous manipulations of stereochemically labile lactone **27** with 1-(*R*)-menthol gave rise to a simplified analog of mastigophorene B ((*aR*)-**32**).

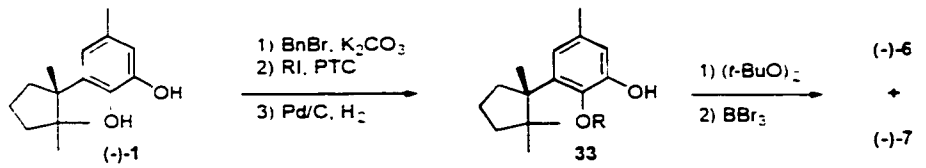
Scheme 7



In a later report, Bringmann *et al.* reported[8] a short synthesis of mastigophorenes A and B by a route which commenced with naturally occurring herbertenediol. This is pictured in Scheme 8. The key step lies in an oxidative phenolic coupling of various mono

protected phenols (**33**). Yields were poor and, not surprisingly, gave very poor levels of atroposelection.

Scheme 8



R	d.r.	yield
Me	40:60	28
Et	50:50	18
i-Pr	---	0

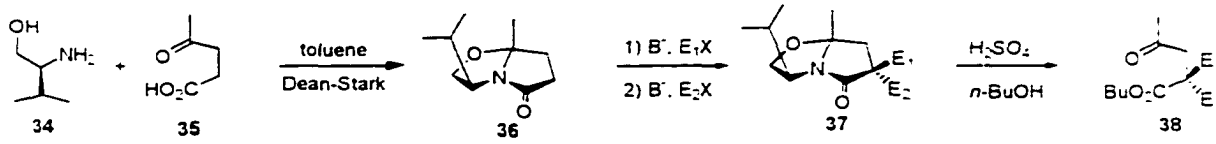
B. Bicyclic Lactams and Their Use in the Preparation of 4-Aryl Cycloalkenones

It should not be surprising that new methods of enantiomeric control have paralleled the growing pressure on the pharmaceutical industry to produce enantiomerically pure products. In order to achieve this mandate, a plethora of asymmetric processes have been developed. Generally speaking, most asymmetric methods capitalize on classical methods for bond construction, but incorporate natural chiral sources such as amino acids or carbohydrates which are covalently or ionically bound to the substrate. One such method that has found widespread success is Meyers' "bicyclic lactam" methodology.[9]

With the first report[10] of a bicyclic lactam in 1984 the foundations were laid for the rich chemistry which followed. In it, an achiral keto acid was condensed with *l*-valinol to afford a single diastereomer of lactam **36**. It was found that treatment of **36** with LDA and electrophiles afforded mono and dialkylated products with high levels of diastereoselectivity. The minor epimers were readily removed by recrystallizations or

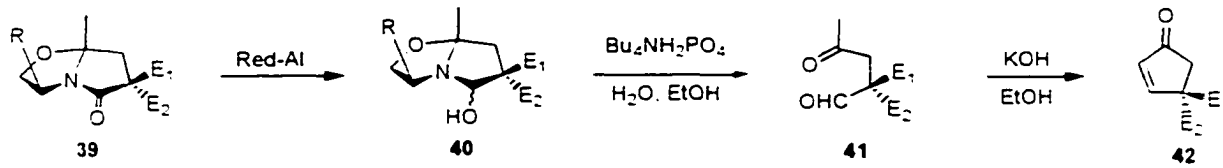
column chromatography to give diastereomerically pure material. Subsequent hydrolysis of the dialkylated products gave optically pure disubstituted keto-esters (**38**).

Scheme 9



Later it was found that the amide of the 5,5-bicyclic lactam may be partially reduced to carbinol amine **40** upon treatment with Red-Al.[11] Hydrolysis of the latter gave rise to keto-aldehydes (**41**) which could be cyclized to the corresponding chiral, non-racemic cyclopentenones (**42**). This is not generally true for the corresponding 5,6-lactams unless a pendant heteroatam can facilitate hydride delivery to carbonyl of the amide.[9] In such cases it becomes possible to construct chiral 4,4-disubstituted cyclohexenones.

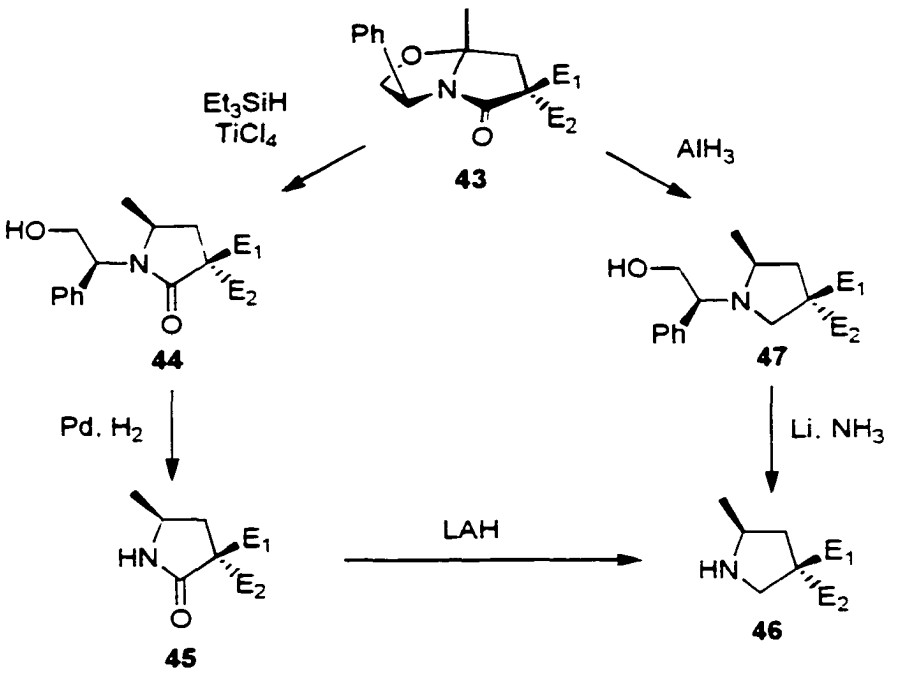
Scheme 10



Another significant advance was realized more recently, upon use of phenylglycinol as the chiral auxiliary. In so doing, it becomes possible to incorporate the nitrogen of the amino alcohol, giving rise to nitrogen heterocycles (pyrrolidines, pyrrolidinones, and piperidines). This work is exemplified by Scheme 11.[9b] Treatment of **43** with triethylsilane in the presence of $TiCl_4$ allows selective reduction of the 'angular' position to give the protected pyrrolidinone.[12] The chiral auxiliary can be cleaved by

hydrogenolysis to afford the unsubstituted pyrrolidinone. This can be further reduced to pyrrolidine **46** upon treatment with LAH. Alternately, the pyrrolidine can be accessed *via* a two step procedure, employing alane (AlH_3) to reduce both the 'angular' position and the amide to afford protected pyrrolidine **47** which can be further reduced by a Li/NH_3 reduction to again afford **46**.

Scheme 11

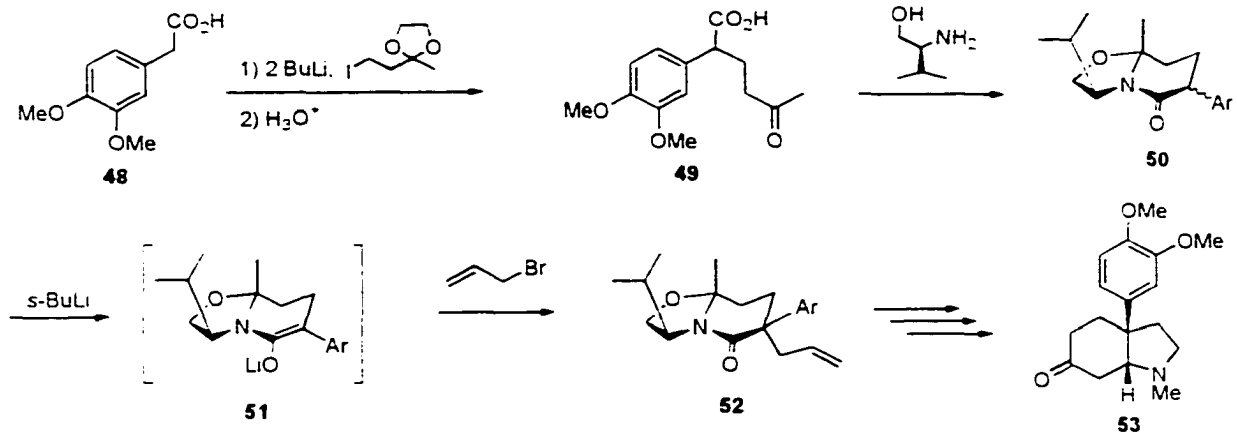


Occasionally, it is not possible to install both groups (E_1, E_2) α to the carbonyl by electrophilic trapping of the enolate. This is most often true when one of the substituents is an aryl group. In these cases, there exists no appropriate electrophilic aryl equivalent. As such it must be incorporated into the keto acid prior to condensation with the amino alcohol.

The first reported example of this type of inclusion of an aryl group was reported in 1985 en route to mesembrine (**53**).[13] The synthesis began with formation of the dianion

of commercially available (3,4-dimethoxyphenyl)acetic acid (**48**) which was quenched with 2-methyl-2-(2-iodoethyl)-1,3-dioxolane. Hydrolysis of the ketal readied the keto acid for condensation with valinol to give the α-aryl bicyclic lactam (**50**) as 3.5 : 1 mix of epimers. However, this mixture was inconsequential as deprotonation of either epimer gives rise to the same enolate (**51**). The enolate was quenched with allyl bromide to afford quaternary bicyclic lactam **52** as a single diastereomer. This process has been termed a 'deracemizing alkylation' since all of the racemic ketoacid is completely utilized in the synthesis.[14] Further chemical manipulations gave mesembrine, **53**.

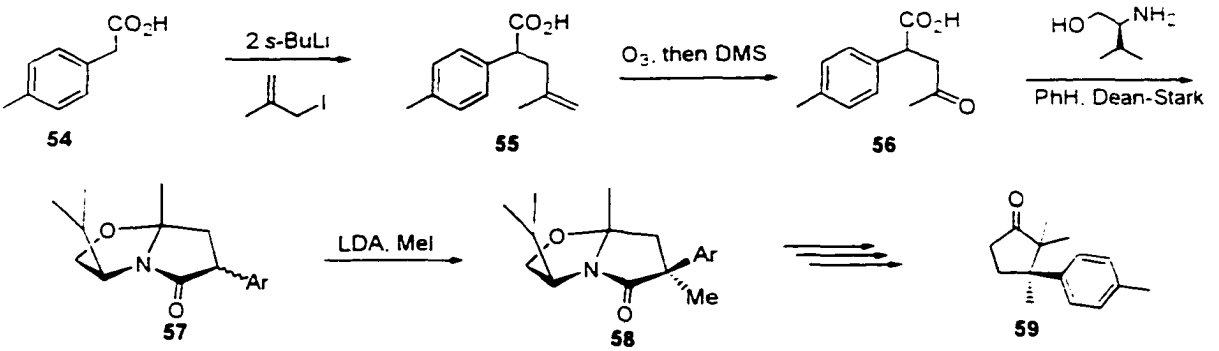
Scheme 12



In 1986, Meyers and Lefker reported the synthesis of (-)-α-cuparenone (**59**).[15] The most significant difference in this work lies in the need to prepare a 5,5-bicyclic lactam rather than the 5,6 lactam seen above. Initial studies attempted to follow the precedent laid by mesembrine, employing 1-bromo-2,2-dimethoxypropane as the electrophile. However, this yielded only starting material, owing to the poor electrophilicity of the bromide. As such, the dianion of **54** was quenched instead with methallyl iodide (Scheme 13). Ozonolysis cleaved the olefin to afford the requisite keto

acid which was condensed with valinol to afford the bicyclic lactam as a mixture of epimers. Once again deprotonation rendered this center planar and alkylation with methyl iodide gave **58** as a 13 : 1 mixture of exo-endo isomers. Recrystallization afforded optically pure **58** which was used to complete the synthesis of α-cuparenone, **59**.

Scheme 13



C. Strategies in Chiral Biaryl Synthesis

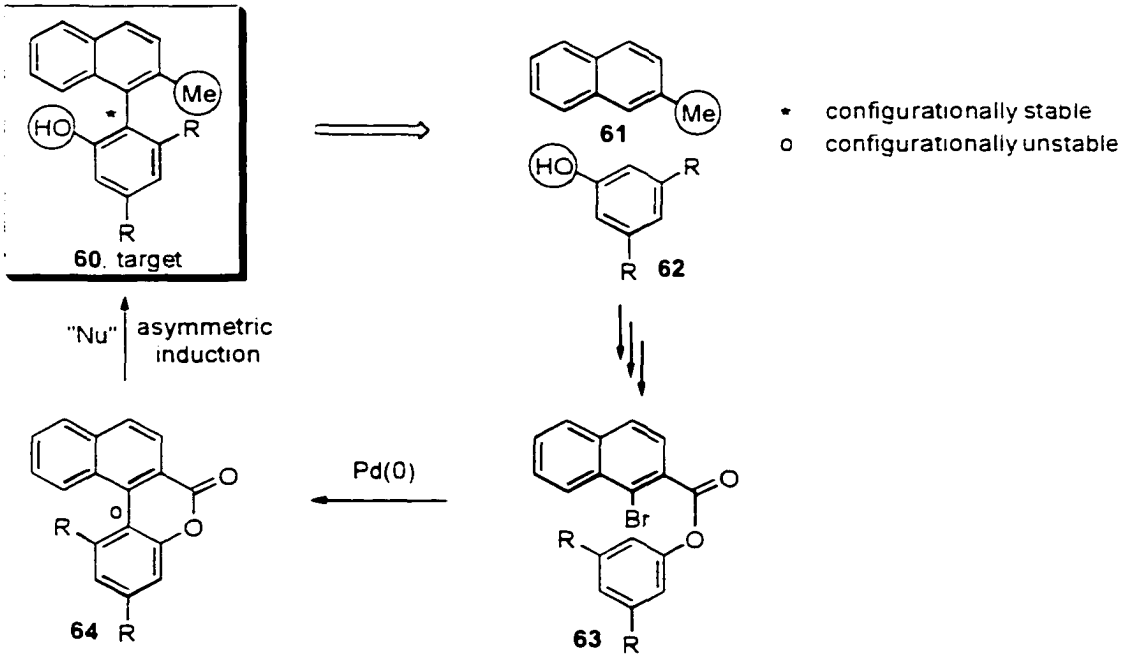
Axially chiral biaryls have been gaining increased notoriety over recent years, and is due in large extent to the growing number of biaryl natural products being isolated. Their biological activities range from antispermatogenic,[16] antimalarial,[17] neurotrophic,[3] and molluscicidal.[18] In addition, stereogenic axes provide rigid molecular frameworks on which to impart chirality into achiral substrates. Among the more notable axially asymmetric reagents are BINOL, BINAP, and BINAL-H. As interest in this class of compounds has grown so have the methods available to access them in an enantioselective fashion. These methods can be divided into several categories: desymmetrization of

prochiral or axially labile substrates, intramolecular atropisomer-selective coupling, and intermolecular atropisomer-selective aryl coupling.[19]

Desymmetrization of Prochiral or Axially Labile Substrates

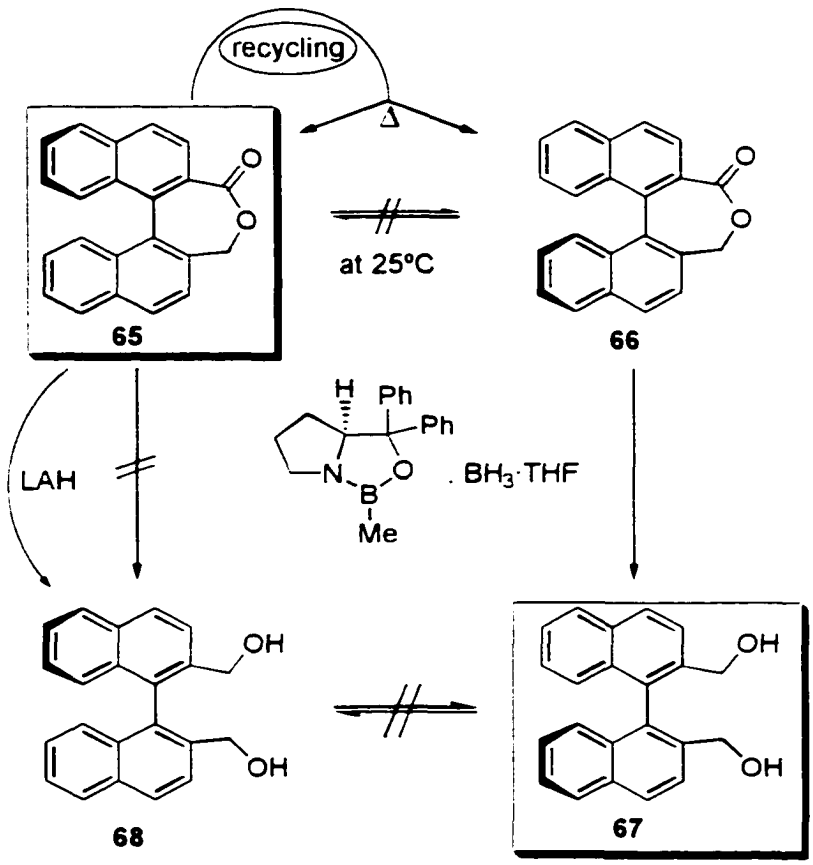
Bringmann[20] has pioneered and developed the use of configurationally unstable δ-lactones of biaryls to a level of generality and usefulness (Scheme 14). It has at its core the formations of a biaryl bond intramolecularly by tethering the two halves by an ester linkage, and once formed, the 6-membered ring renders the biaryl configurationally labile. Thus attack of the lactone with chiral nucleophiles (mainly N^-, O^- and H^-) allows one to perform a dynamic resolution to favor creation of one atropisomer at the expense of another. In so doing, the process of atroposelective biaryl bond formation has been disected into its two discrete parts: C-C biaryl bond formation (racemic) and asymmetric induction at the biaryl axis.

Scheme 14



Two key disadvantages exist within this method. First, when hydride nucleophiles are used to resolve the lactone to the diol, the atropisomers are generally enantiomeric, rendering their further enrichment difficult. Further, the method requires that there be at least one oxygen substituent be present *ortho* to the biaryl axis of the target molecule. An example of this concept has already been described in section 2A, enroute to the synthesis of simplified mastigophorene analogs.

Scheme 15

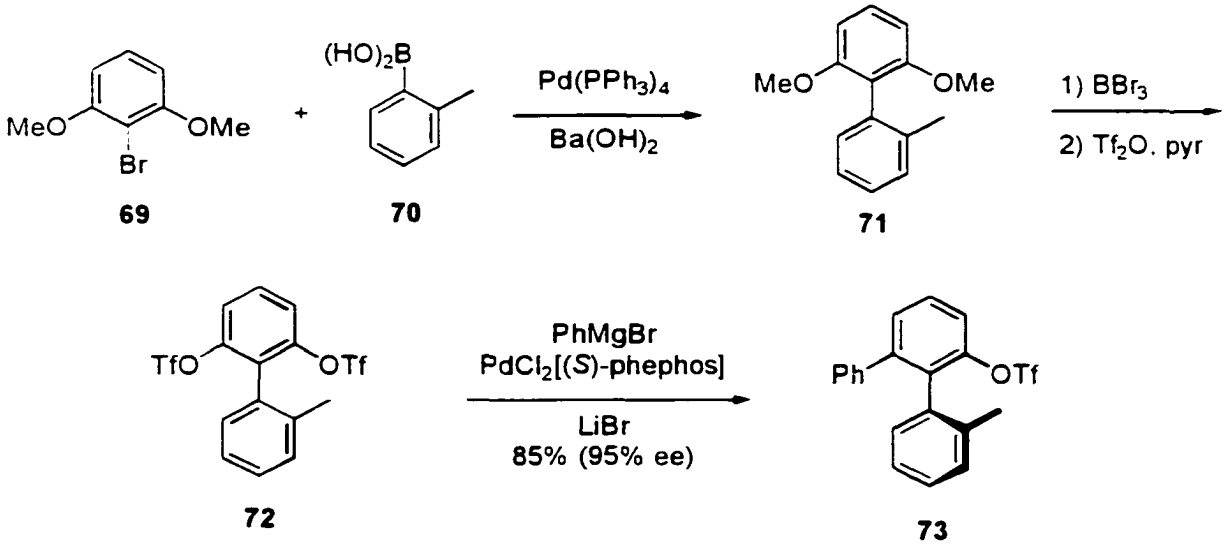


Another derivative of this method has been published based on the concept of non-dynamic resolution (Scheme 15). If one applies the same methods to the synthesis of 7-membered biaryl lactones (**65**, **66**),[21] the products are configurationally stable and

racemize only at elevated temperatures. Reaction with chiral nucleophiles (generally H^-) gives rise to enantiomerically enriched desymmetrized products. This represents a non-dynamic kinetic resolution, where asymmetric induction corresponds to the relative rates of reaction with the chiral nucleophile. As with all non-dynamic kinetic resolutions, the theoretical yield is only 50% conversion. However in this case, the optically enriched starting materials can be taken on in either of two directions. If the enantiomeric diol (**68**) is desired, **65** can be reduced by an achiral reducing agent. Alternately, the material can be recycled by thermal racemization, and again submitted to the kinetic deracemization

A more recent entry into the desymmetrization of biaryls was reported earlier this year by Kamikawa and Hayashi[22] (Scheme 16). The biaryl axis is formed on a 2,6-dimethoxyphenylbromide by means of a Suzuki[23] coupling to give an achiral trisubstituted biaryl, **71**. The methyl ethers are cleaved by the action of BBr_3, and are replaced by triflates, **72**. Palladium-catalyzed Grignard cross-coupling in the presence chiral additives gives good-moderate yields of **73** with high levels of enantiomeric excess

Scheme 16



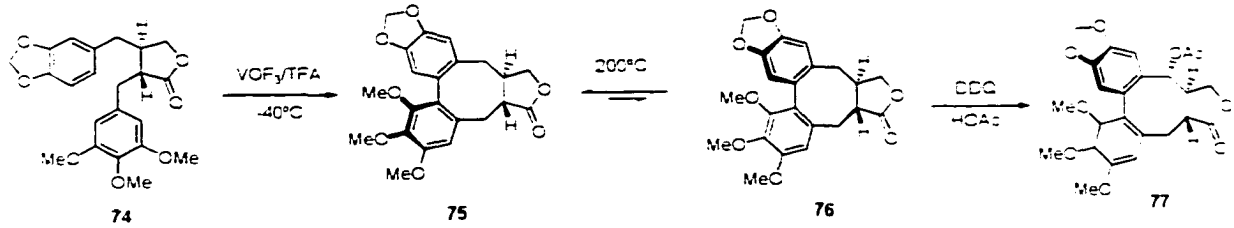
It is of interest to note that the above transformation enjoys such high levels of enantioselection largely because any of the undesired atropisomer that is formed is rapidly consumed under the reaction conditions to give dialkylated material. The method is currently limited to the production of trisubstituted biaryls.

Intramolecular Atropisomer-Selective Coupling

This method relies heavily on the incorporation of chiral, non-racemic templates on which to form the biaryl. The two possible atropisomers are therefore formed from diastereomeric transition states which may favor one product over the other. This category of directed biaryl synthesis can be further divided into two strategies: those that incorporate bridges which are naturally present in the target molecule and those that employ artificial chiral auxiliaries to direct the stereochemical course of reaction.

In general, the former method would appear to be the favored route. When one builds the chiral tether, they are in fact making progress toward the natural product. It is often the defining factor and determines the steric course of coupling (both kinetic and thermodynamic). Koga's synthesis of (-)-steganacin[24] (77) poses an interesting illustration of this concept (Scheme 17). The chiral γ-lactone was constructed with the two pendant arenes tethered. Oxidative coupling using VOF_3 gives solely the unnatural atropisomer as the kinetic product. Heating the product to 200°C induces equilibration of the two atropisomers to a 2:3 ratio in favor of the unwanted isomer. As the atropisomers are diastereomeric, they could be separated, and the minor atropisomer carried through to the final product.

Scheme 17

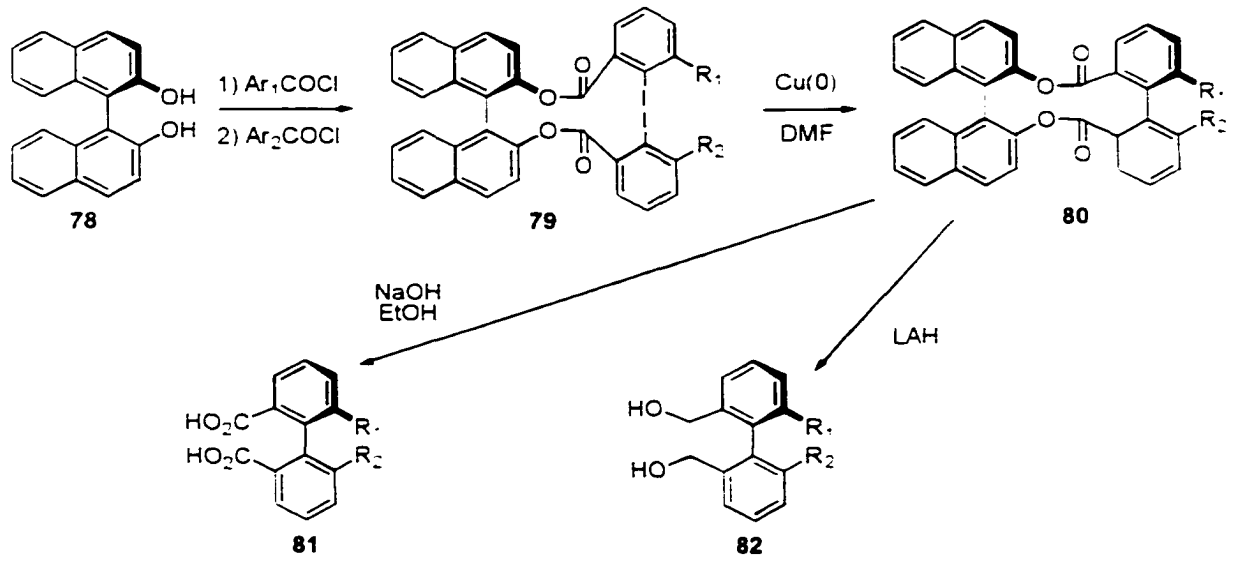


There are several drawbacks to the above method. The first and most significant is its lack of generality. A relatively small percent of chiral biaryls contain a chiral tether and so this strategy can not be considered. Another disadvantage is that this mode of reactivity does not lend itself to tuning. There is no opportunity to modify the chiral environment to favor one atropisomer beyond that which is naturally present in the molecule. Finally, as the above example illustrates, the natural atropisomer is not always the kinetically or thermodynamically favored product.

A much more general and tunable route is to employ an artificial chiral auxiliary. There have been many successful methods of this type reported to date. One of the more general and successful methods is that of Miyano[25] (Scheme 18) wherein BINOL is condensed with two substituted benzoyl chlorides (may be the same or different). Ullmann coupling[26] of the tethered arenes proceeds with complete diastereoselectivity to give, upon cleavage from the chiral auxiliary, the enantiopure dicarboxylic acid (**81**) or diol (**82**). Either enantiomer can be produced *via* selection of the proper enantiomer of BINOL - which obviously needs to be used stoichiometrically. Herein lies the first disadvantage - the stoichiometric use of an expensive diol ($35/g). Further, it suffers from

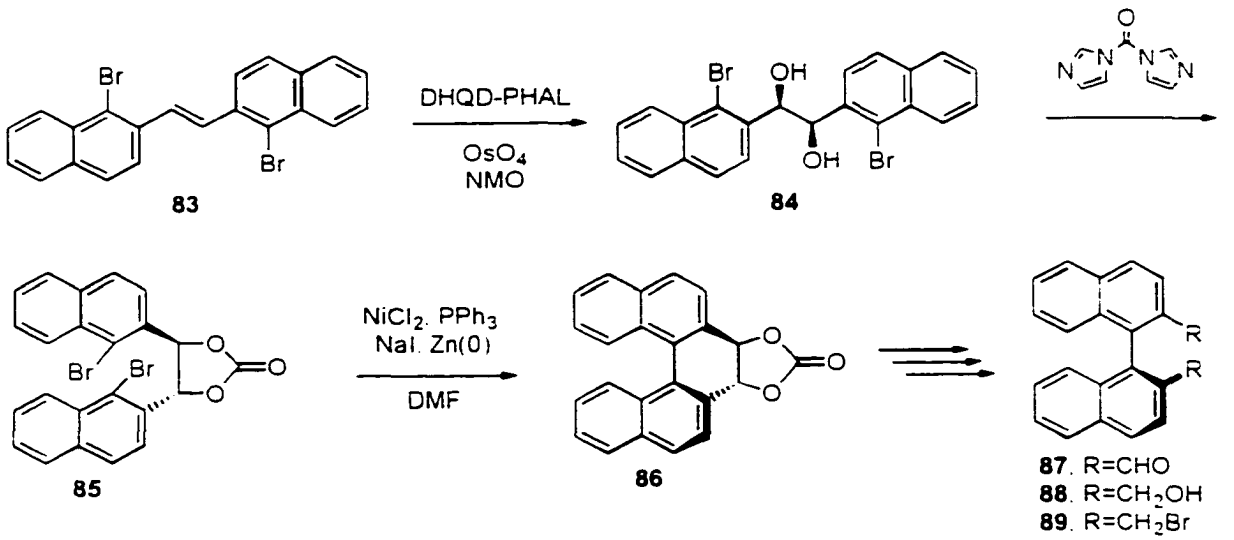
the requirement that the biaryl axis have two identical *ortho* substituents (on opposite arenes).

Scheme 18



Attempts to employ less expensive aliphatic diols (such as 2,3-butanediol, and carbohydrate-derived diols) have generally yielded much lower diastereoselectivity,[27] and offer little more than a way to resolve the enantiomeric products. However, considerably more success has been realized by tethering the two arenes together with an element of *trans*-unsaturation.[28] Asymmetric dihydroxylation and subsequent ring formation (into an acetonide or cyclic carbonate) readies the substrate for biaryl bond formation. This strategy is exemplified by the work of Rawal and is illustrated in Scheme 19. Biaryl coupling under Semmelhack's Ni(0) catalyst system[29] proceeded in poor yield (33%), but occurred with complete diastereoselectivity and could be elaborated to several chiral 1,1'-bi-2-naphthyl products (**87-89**).

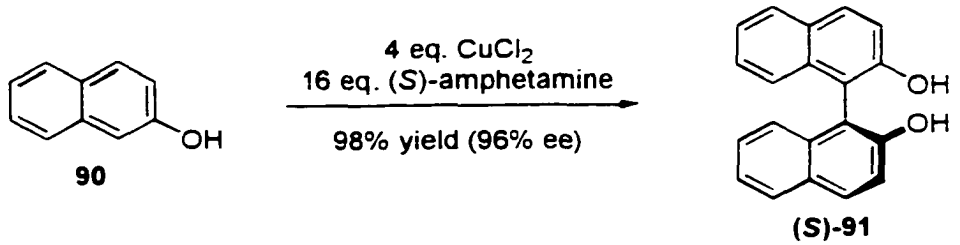
Scheme 19



Intermolecular Atropisomer-Selective Coupling

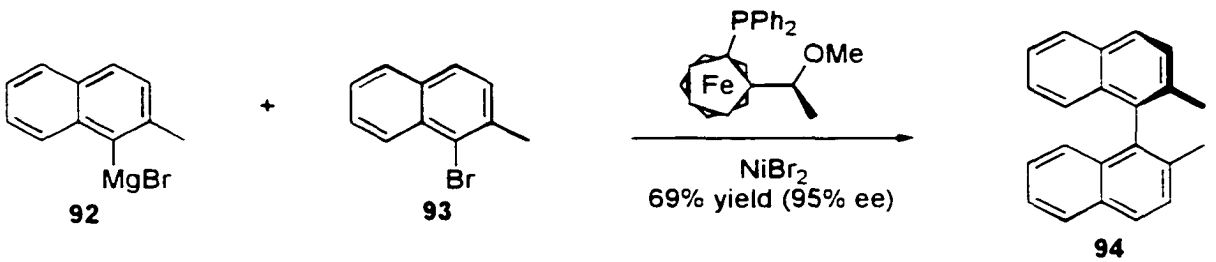
The oldest and still most frequently employed methods rely on generation of the biaryl axis and stereochemical control at that axis in one chemical transformation.[29] This category can be further divided into catalytic methods and chiral auxiliary based methods. Although less general, catalytic methods have had some successes. Brussee's work[30] (Scheme 20), though not strictly catalytic in either copper or chiral amine, seems most appropriately discussed here. Treatment of phenolic substrates in the presence of electrophilic metals gives rise to oxidative dehydrodimerization. In the presence of a chiral ligand, these reactions can be associated by a high degree of enantioselectivity. Thus reaction of 2-naphthol (**90**) with excess $CuCl_2$ and (*S*)-amphetamine gave a quantitative yield of (*S*)-BINOL with an enantiomeric excess of 96%. This reaction represents a special case, specific to 2-naphthol and 9-phenanthrol.[31]

Scheme 20



Another successful catalytic method is that of Hayashi and coworkers [32] The method represents a cross-coupling of an aryl bromide with an aryl Grignard in the presence of a chiral nickel catalyst. The reaction illustrated in Scheme 21 is one of the only reported examples; so it is difficult to determine the generality of the transformation. Attempts to push the reaction to completion were accompanied by lower levels of enantioselection.

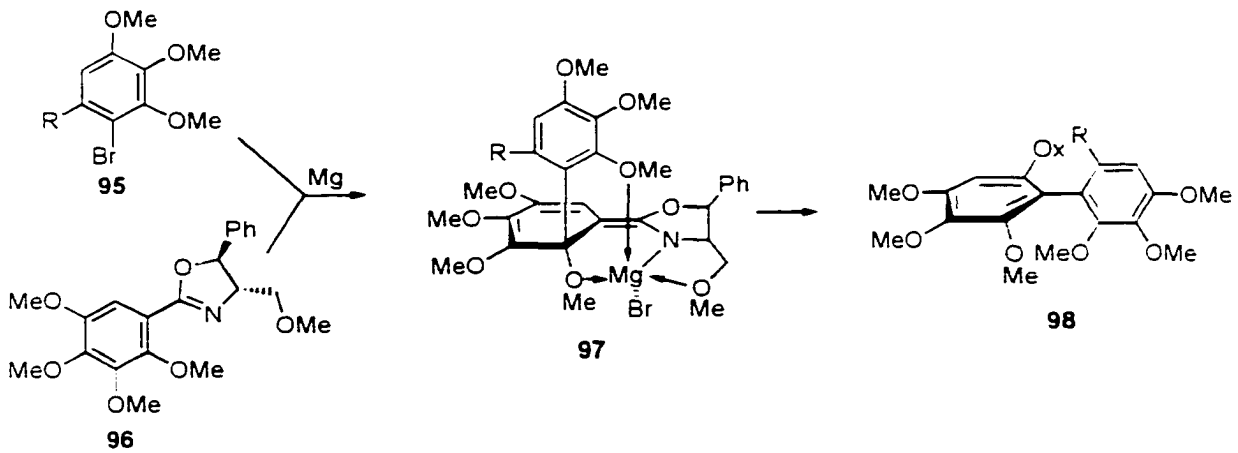
Scheme 21



By far, the most abundant source of examples in the literature are those utilizing the Meyers oxazoline method.[33, 34] This method relies on the conjugate addition of aryl Grignards to aryl oxazolines and was briefly described in 1B. The stereochemistry of the transformation can usually be predicted on the basis of the model shown in Scheme 22. In it, the aryl nucleophile approaches the aryl oxazoline on the face opposite the substituent in the 4-position of the oxazoline. The incoming arene then rotates itself such that the

most Lewis basic substituent in the *ortho* position coordinates to the metal center When methoxide is eliminated, the biaryl axis is fixed in the position shown.

Scheme 22

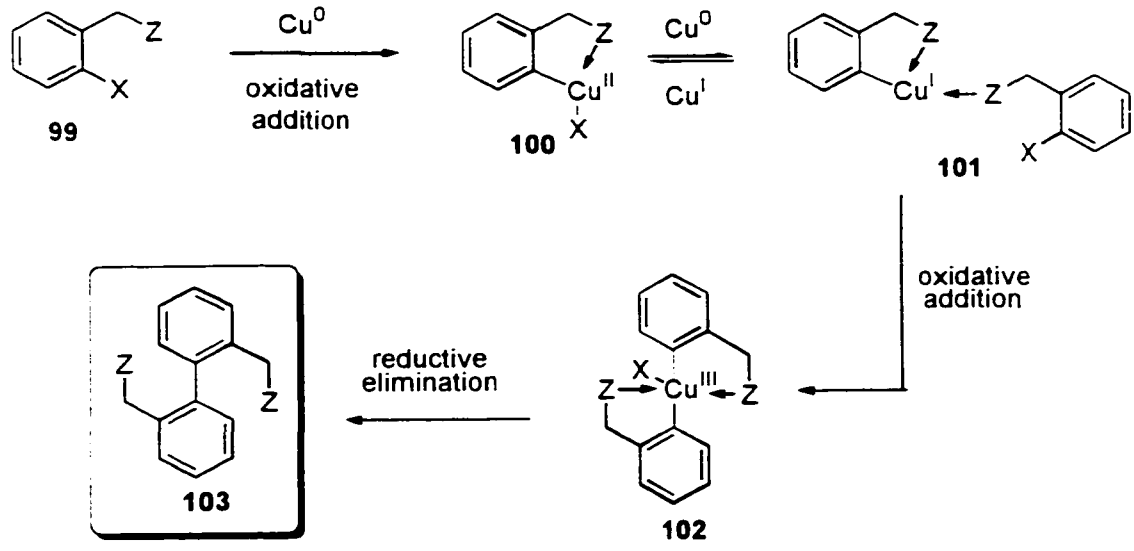


Another oxazoline based method has been pioneered in these labs over the last decade and has slowly replaced the conjugate addition to aryl oxazolines. This procedure is the oxazoline-mediated asymmetric Ullmann coupling.[35] It is instructive to take an initial look at the origins of the Ullmann coupling. The classical Ullmann coupling comprises reactions in which two molecules of aryl halide are condensed in the presence of finely divided elemental copper to form a new aryl-aryl bond with the elimination of copper halide. The classical mechanism[36] is portrayed in Scheme 23, where Z is an electron-donating substituent such as an oxazoline.

The first step is oxidative addition of copper into the aryl-halide bond to form a copper(II) intermediate. This can equilibrate with other, more reduced copper species to generate copper(I) intermediate **100**. This coordinates to the electron-donating substituent on another aryl halide, predisposing the complex to undergo another oxidative

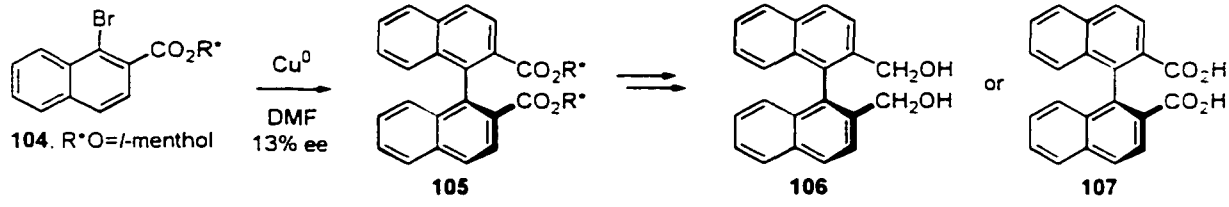
addition, to afford a transient copper(III) species. Reductive elimination, affords homocoupled biaryl **103**.

Scheme 23



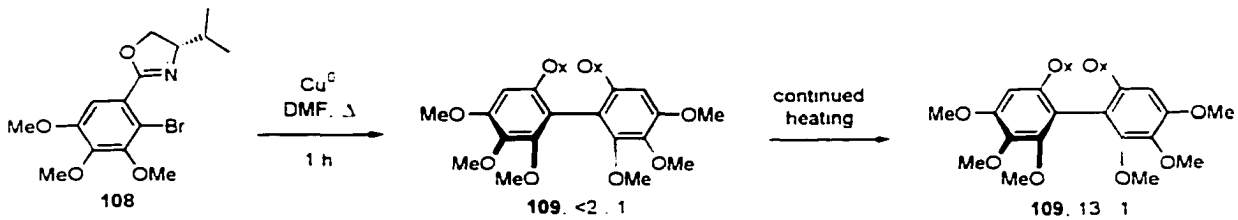
The first intermolecular, asymmetric variant was published by Miyano *et al.*[37] in 1980 (Scheme 24). Chirality was derived *via* esters of chiral alcohols *ortho* to the aryl halide. l-Menthol led to the highest, yet still disappointing, diastereoselectivities, affording the product with only 13% ee. The product was elaborated to either the optically enriched diol **106** or diacid **107** by means of standard chemical manipulations. Although only modest results were secured, the foundation had been laid for more successful ventures.

Scheme 24



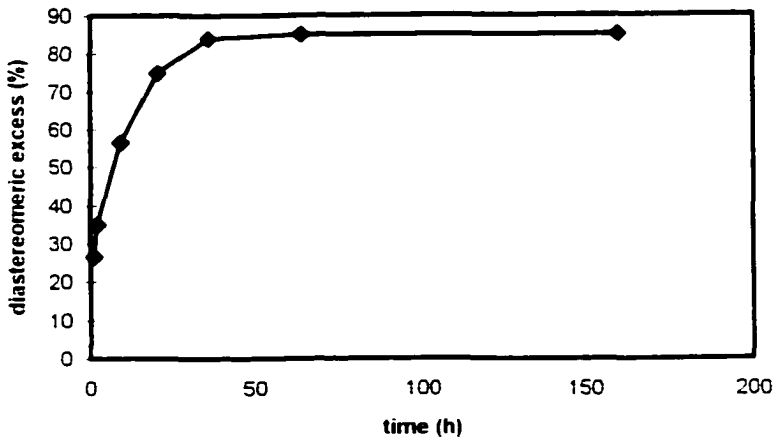
The next such venture was one reported by Nelson and Meyers[35g] in 1993. In it, a chiral aryl oxazoline with an *ortho* bromo substituent was homocoupled to give the chiral biaryl. It is unclear exactly how high selectivity was in the preliminary report, as two resolutions were performed prior to assay (recrystallization, and column chromatography). A detailed account[35e] of the process later appeared which indicated that there was some kinetic preference for one atropisomer over the other (< 2:1) in the initial coupling, but with continued heating the diastereomeric mixture could be improved to 13:1 (Scheme 25).

Scheme 25



It was suggested that Cu(I) and/or Cu(II), liberated from the Ullmann reaction, chelate to the two oxazolines in either of the two possible atropisomers. Therefore the product distribution of the final reaction mixture represents a thermodynamic distribution of the diastereomeric copper complexes. Frequent monitoring of the Ullmann reaction bore this theory out (Figure 1). It was found that the diastereomeric ratio rapidly increased initially, and eventually leveled out to a constant product distribution (~ 13 : 1).

Figure 1: Equilibration of Atropisomers, 109, Over Time



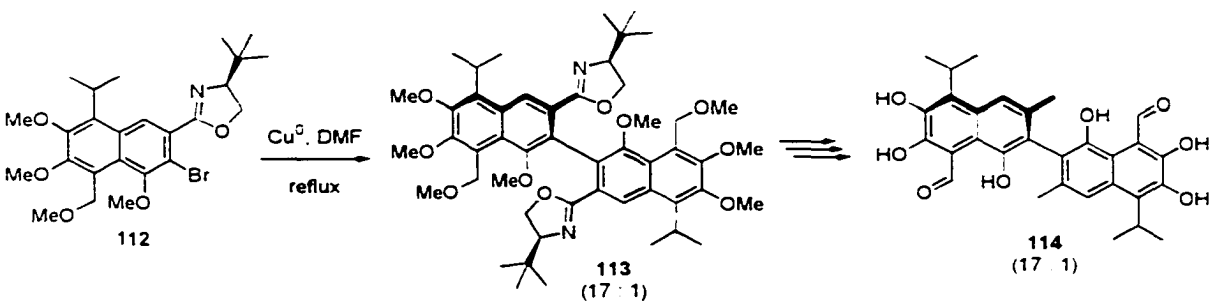
Furthermore, the influence of copper was revealed in subsequent experiments wherein the atropisomers were equilibrated both in the presence and in the absence of copper sources. In certain instances, it was found that equilibration in the absence of copper led to a reversal of atropisomeric selection, favoring what was the minor atropisomer albeit at lower levels of diastereoselection. The notion that copper is tied up with one or both oxazolines is further bolstered by the finding that when the reaction is run in pyridine, the product distribution often mimics that observed in the absence of copper. This would suggest that the oxazoline cannot effectively compete with the excess pyridine for coordination to the copper ions. The model that evolved is that shown in Scheme 26. In it, it is envisioned that the copper coordinates to both oxazolines of the biaryl. One of the atropisomers (**110**) directs each chiral auxiliary toward the other, causing a disfavored steric effect between them. In the other (**111**), the chiral auxiliaries are directed away from one another and the coordinated copper ion, eliminating the steric interaction between them.

Scheme 26

110 **111**

Since it's first conception, a number of publications have extolled the synthetic value of the oxazoline-mediated asymmetric Ullmann reaction. It has been utilized in the synthesis of both natural products, and chiral binaphthyl derivatives. One of the more impressive applications of this powerful method was reported by Willemsen and Meyers[35a,b] *en route* to (*S*)-gossypol (**114**). The key step hinged on the successful 2,2'-binaphthyl biaryl bond formation (**112** → **113**) to create the chiral axis of gossypol. This was effected in high yield (80%) and outstanding levels of diastereomeric excess (17:1), and is illustrated in Scheme 27.

Scheme 27

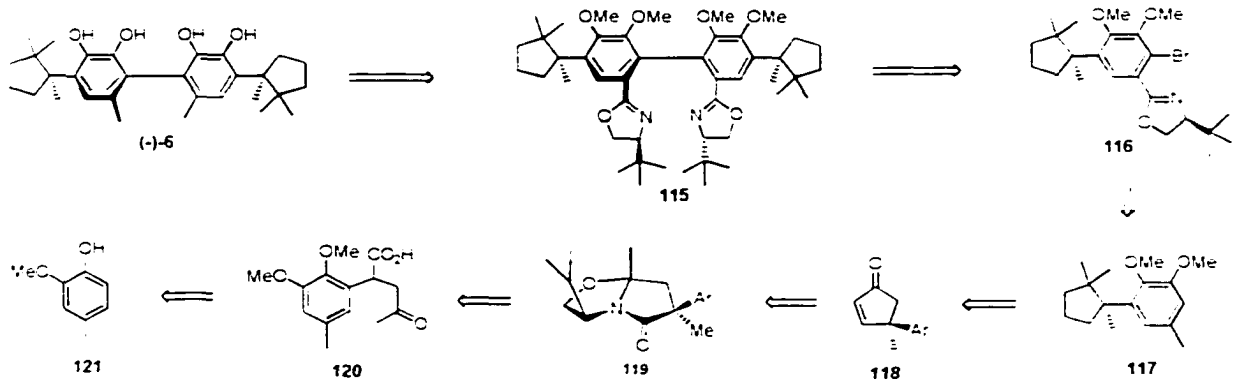


112 **113** (17:1) **114** (17:1)

D. Enantioselective Synthesis of (-)-Herbertenediol, (-)-Mastigophorene A, and (-)-Mastigophorene B

Mastigophorenes A and B were targeted for synthesis as they presented the unique opportunity to extend the Meyers bicyclic lactam methodology[9] to the construction of a chiral cyclopentane containing vicinal quaternary carbon centers as well as to further the understanding of the oxazoline-mediated asymmetric Ullmann coupling,[35] also developed in these laboratories.

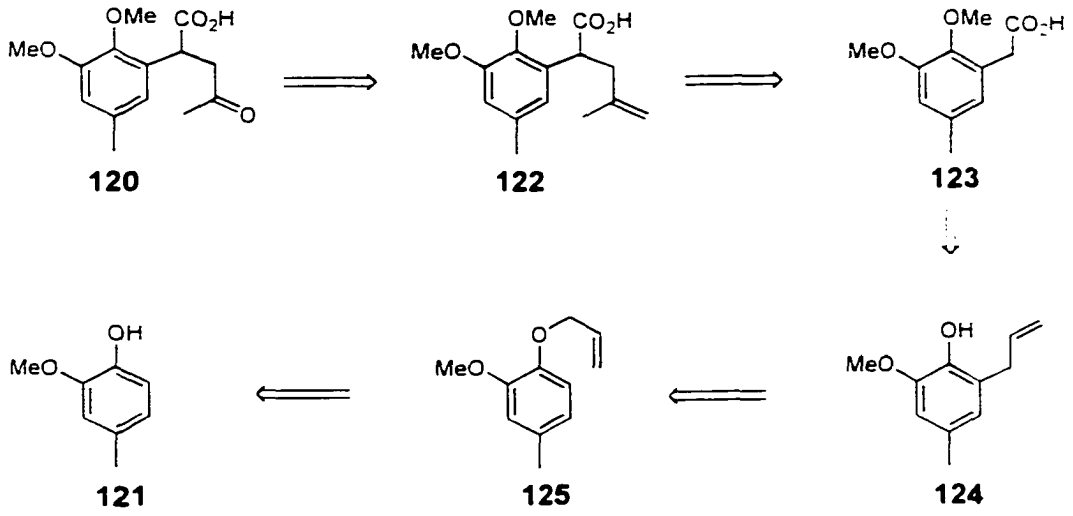
Scheme 28



Our original focus was the synthesis of mastigophorene A, (-)-**6**, (Scheme 28) which we envisioned as arising from the reductive removal of bisoxazoline **115**. This, in turn, would be created *via* an oxazoline-mediated asymmetric Ullmann coupling of arylbromide **116**. The latter could be elaborated from simplified arene **117** by means of straightforward chemical manipulations. The chiral, quaternary carbon-substituted cyclopentane unit of **117** would be derived from chiral cyclopentenone **118** *via* dialkylation and subsequent reduction. The cyclopentenone would arise from chiral, non-racemic bicyclic lactam **119** which would be prepared *via* diastereoselective alkylation of

the bicyclic lactam derived from ketoacid **120**. It was anticipated that ketoacid **120** could be elaborated from commercially available phenol **121**.[38]

Scheme 29

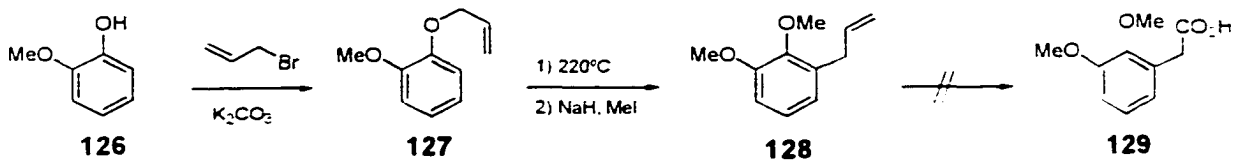


Initially, it was anticipated that the requisite ketoacid could be obtained as portrayed in Scheme 29. The ketoacid would be derived by means of an ozonolysis of alkene **122** which would in turn arise *via* alkylation of the carboxylate dianion of **123**. These two steps are completely analogous to those utilized in Meyers and Lefker's synthesis of α-cuparenone[15] wherein the aryl group used was the simpler *p*-tolyl. The acid would be synthesized by an oxidative cleavage of the olefin in **124**. The requisite allyl group would be installed regioselectively by means of a Claisen rearrangement[39] of **125** which should be readily available from **121**.

It was first deemed desirable to commence model studies of the proposed synthesis which is described in Scheme 30. *o*-Eugenol (**126**) was chosen as an acceptable model, and alkylation of the hydroxyl with allylbromide and subsequent Claisen rearrangement proceeded without event.[39] Etherification of the phenol as its methyl derivative was

effected by treatment with NaH/MeI. Initially, ozonolysis of **128** (with an oxidative work up) seemed most preferable. A number of solvents and conditions were employed, but none were found to be efficacious. It was believed that the electron-rich arene of **128** was suffering oxidation under these conditions.

Scheme 30



126 **127** **128** **129**

Table 1 - Attempts to Oxidize *o*-Allylarene to Carboxylic Acid

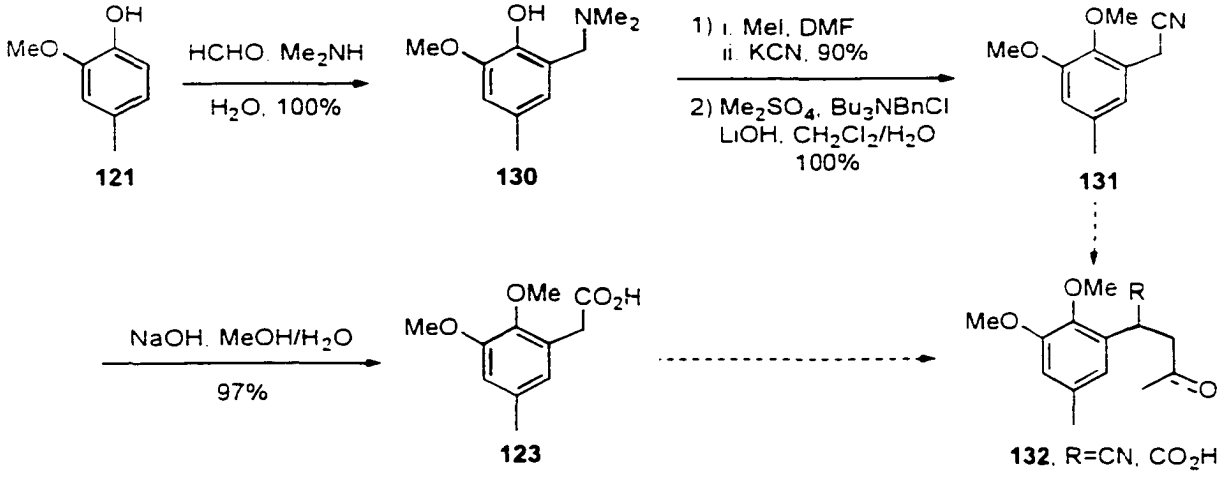
128 **129**

Conditions*	Results
i) O_3, CH_2Cl_2 ii) H_2O_2	Decomposition
i) O_3, MeOH ii) H_2O_2	Decomposition
i) O_3, AcOH ii) H_2O_2	Decomposition
i) O_3, MeOH ii) HCO_2H, H_2O_2	Decomposition
$KMnO_4$, Bu_4NBr, AcOH, CH_2Cl_2/H_2O	Decomposition
Bu_4NMnO_4	Decomposition
$RuCl_3 \cdot H_20$, $NaIO_4$	Some product, mostly decomposition

*Ozone was bubbled into solution at -78°C, using Sudan III as an indicator.

Next a number of permanganate conditions were screened, but again it appeared that oxidation of the aromatic ring was a competitive process. Finally, oxidation with catalytic $RuCl_3$ and $NaIO_4$[40] was attempted. This, too, gave rise to a complex mixture which included (for the first time) traces of what was believed to be the desired product. These are outlined in Table 1. From this work we arrived at two conclusions. First, the above work was not promising enough to apply to the real system upon arrival of the requisite phenol **121**. Secondly, even if we synthesized the necessary substituted phenyl acetic acid **123**, we would not be able to elaborate it using the methallylation/ozonolysis strategy employed earlier by Meyers and Lefker.[15] Consequently this route was abandoned in favor of that shown in Scheme 31.

Scheme 31

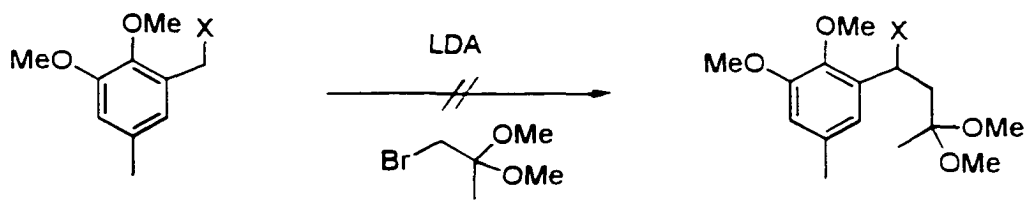


121 **130** **131** **123** **132**, R=CN, CO_2H

Phenol **121** was subjected to Mannich conditions[41] which afforded benzylamine **130** in quantitative yield. It was hoped that quaternization of the benzylic amine could be performed in tandem with methylation of the phenol. However, all attempts to realize this outcome, including formation of the sodium alkoxide prior to addition of methyl iodide,

failed to alkylate the phenol. Therefore, the reactions were performed in a stepwise manner; first forming the quaternary ammonium salt, derived from **130**, and displacing it with potassium cyanide to afford substituted phenylacetonitrile **131** in 90% yield. Alkylation of the hydroxyl to its methyl ether under phase transfer conditions[42] then proceeded in quantitative yield. Basic hydrolysis of nitrile **131** gave phenylacetic acid **123** in 97% yield. It was originally unclear how we would append to **123** or **131** the necessary oxygenated three carbon chain to give **132**. The original retrosynthesis (Scheme 29) envisioned alkylation of the dianion of **123** with methallyl iodide and subsequent ozonolysis in a fashion analogous to the synthesis of α-cuparenone.[15] However, from the above results, it appeared that ozonolysis was a process that would not be amenable to this substrate. As such, initial attempts focused on trapping either **131** or **123** with a bromoacetone equivalent. All efforts utilizing 1-bromo-2,2-dimethoxypropane were unsuccessful owing to its poor electrophilicity (Scheme 32).[43]

Scheme 32



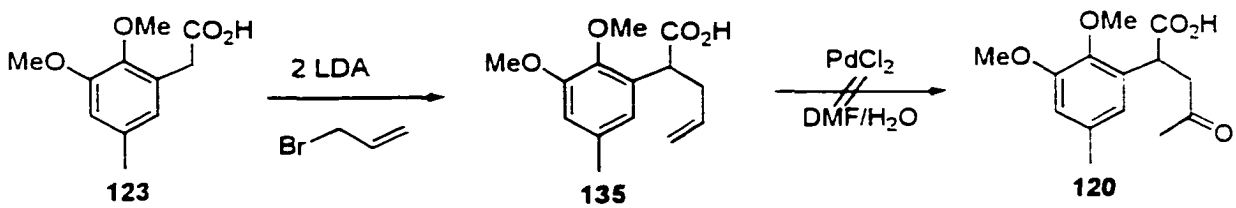
131, X=CN
123, X=CO_2H

133, X=CN
134, X=CO_2H

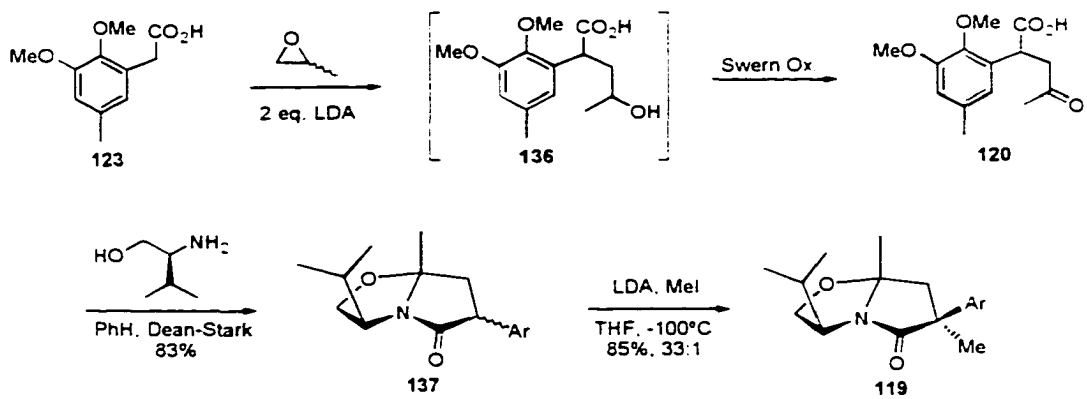
Next, introduction of the three carbon chain required to reach **132** was effected in good yield using allylbromide (Scheme 33). Initial attempts at a Wacker oxidation[44] saw the use of stoichiometric $PdCl_2$ to determine if the chemistry was feasible. There was

rapid consumption of starting material. However much of the olefin was still intact, reconfirming the propensity for the benzene nucleus to undergo oxidation.

Scheme 33



Scheme 34

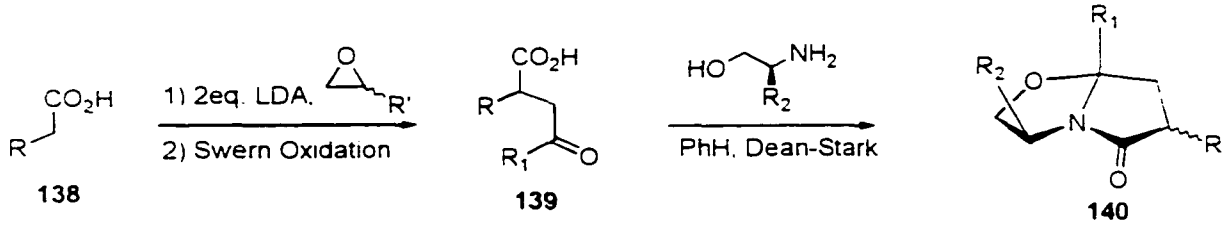


Success was finally realized by trapping the dianion of **123** with (±)-propylene oxide to give γ-hydroxyacid **136** as a 3:2 mixture of diastereomers (Scheme 34).[45] Attempts to isolate this compound gave rise to lactonized products and so it was carried on without purification. The crude hydroxy acid was oxidized under Swern[46] conditions to afford requisite ketoacid **120** (80% over 2 steps). Condensation of **120** with (*S*)-valinol gave an 83% chemical yield of bicyclic lactam **137** as a 3:2 mixture of epimers.[45] As mentioned previously, this mixture was inconsequential as deprotonation of either epimer gives rise to the same enolate and subsequent alkylation of the latter with methyl iodide

gave **119** as a 33:1 mixture of *endo-exo* diastereomers.[45] Recrystallization from heptane afforded the *endo*-alkylated product **119** as a single diastereomer.

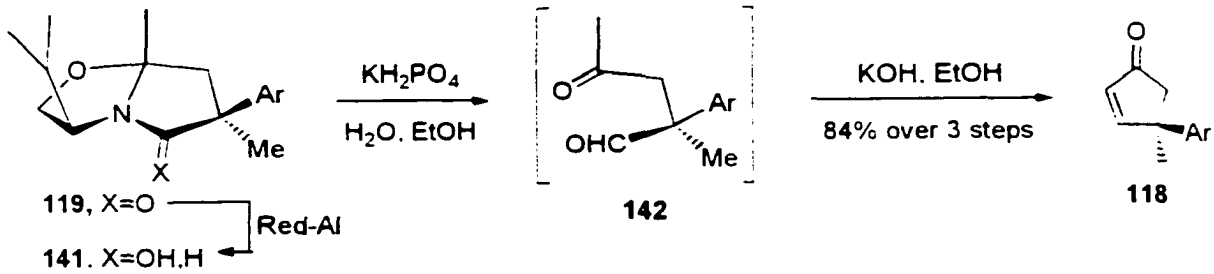
This method of substituted lactam synthesis should prove to be quite general in the synthesis of α-substituted 5,5-bicyclic lactams as the formation of the keto-acid is completely independent of the group desired in the α position (Scheme 35) It also should be noted that this reaction sequence should also allow for the synthesis of lactams with angular groups other than methyl, by use of the appropriately substituted epoxide

Scheme 35



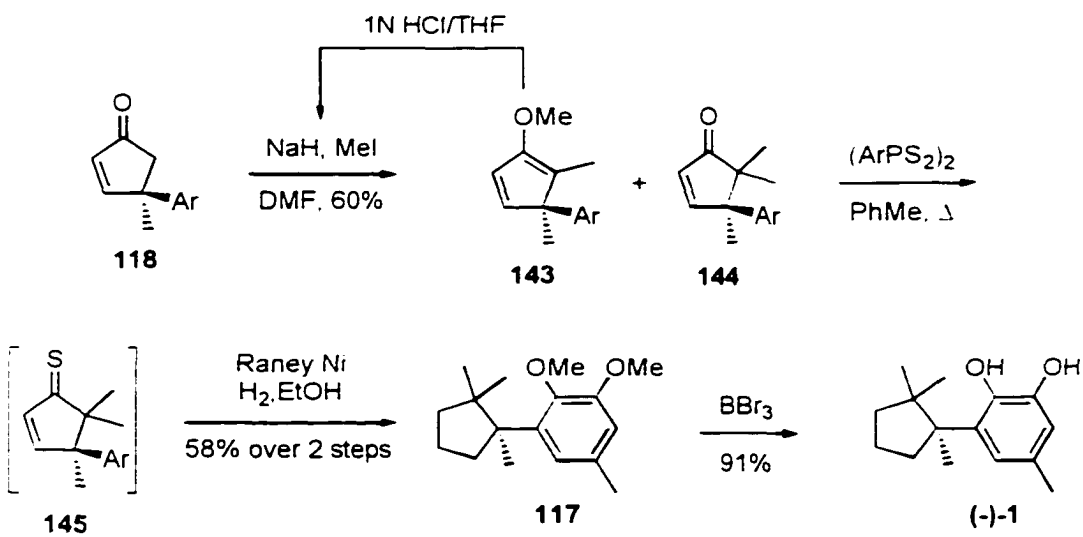
Reduction of bicyclic lactam **119** with Red-Al gave carbinolamine **141**, which on hydrolysis with $Bu_4NH_2PO_4$ (20 equivalents) afforded ketoaldehyde **142** (Scheme 36) Due to the expense of the ammonium phosphate buffer ($209/mol),[38] coupled with the need to hydrolyze sufficient quantities of carbinolamine **141** to allow completion of the synthesis, we screened a number of other buffer solutions in search of a more practical alternative. It was found that similar results could be obtained *via* replacement of $Bu_4NH_2PO_4$ with KH_2PO_4 ($2.11/mol).[38] Unpublished results in this laboratory suggest that this buffer system is widely applicable to other 5,5 and 5,6-bicyclic lactams,[47] yielding the corresponding keto aldehydes in yields consistent with those observed using $Bu_4NH_2PO_4$. Base-induced cyclization of ketoaldehyde **142** afforded chiral cyclopentenone **118** in 84% yield from lactam **119**.

Scheme 36



Attempts to introduce the 5,5-*gem*-dimethyl group into **118** *via* formation of the lithium enolate were unsuccessful, presumably due to steric crowding by the adjacent quaternary carbon center. The use of a bulky base to form the enolate of **118** could be at the crux of the problem. However, deprotonation with the smaller base, NaH, in DMF followed by treatment with MeI allowed formation of the vicinal quaternary carbon center in a 60% yield (Scheme 37). The remainder of material was found to be the methyl enol ether **143**, arising from *C*-alkylation followed by *O*-alkylation. This material was conveniently recycled *via* acid-catalyzed hydrolysis and was resubjected to the previous reaction conditions, thus, improving the yield of **144** to 82% over 2 recycles

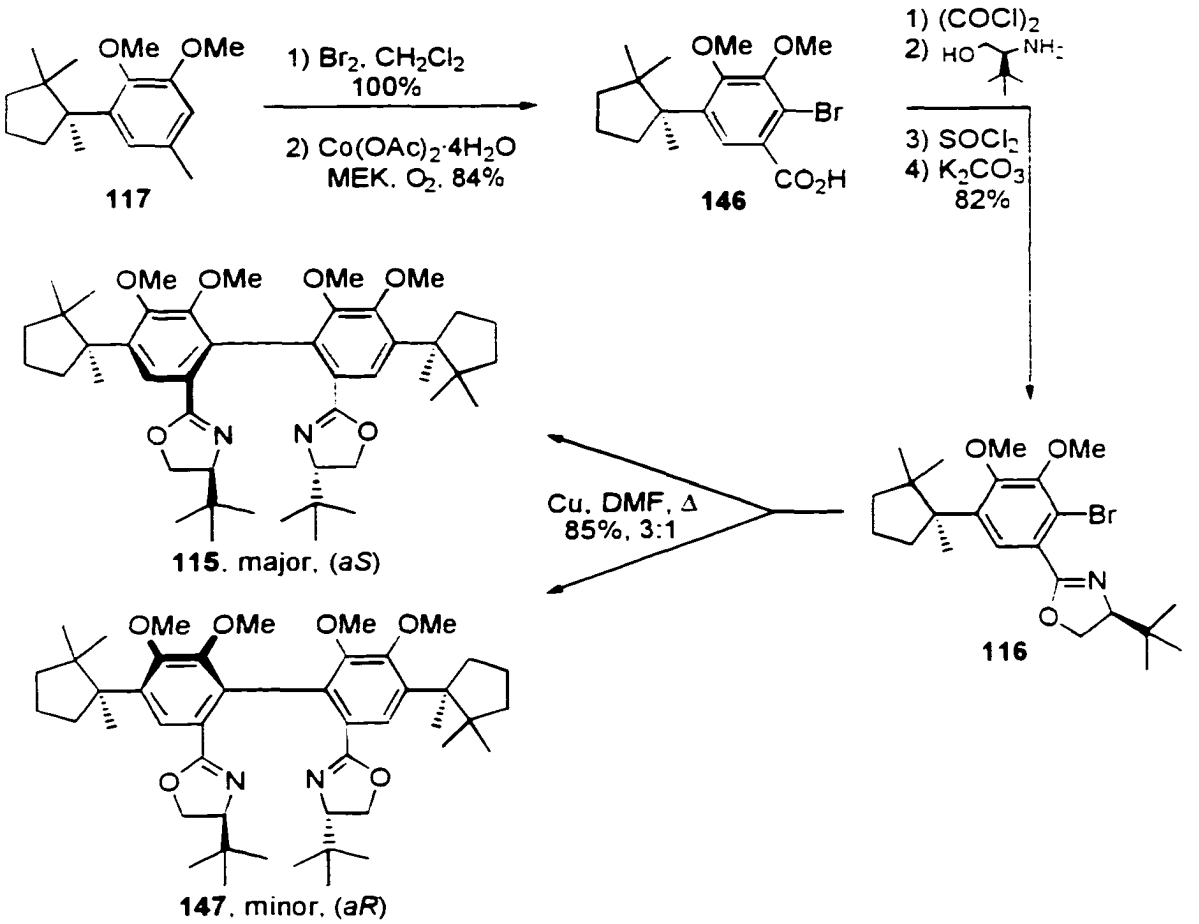
Scheme 37



Attempts to reduce the olefin of **144** and subsequent Wolff-Kishner reduction[10] of the carbonyl group were unsuccessful and is believed to be due to the well-documented steric restraints of hydrazone formation.[48] In addition, attempts to make the sterically demanding ethylene dithioacetal were also fruitless. It was thought that we might bypass this obstacle by replacement of oxygen with a group smaller in size than the hydrazones and dithioketals mentioned above. Therefore, the oxygen was replaced with sulfur, using Belleau's reagent[49] to furnish thiocarbonyl **145**. In view of the instability of thioenones,[50] **145** was utilized immediately by reduction with Raney Ni and H_2. Fortunately, both the sulfur and the olefin were both reduced to afford dimethylherbertenediol (**117**) in 58% yield over 2 steps. Finally, removal of the methyl groups with BBr_3 provided (-)-herbertenediol, (-)-**1**, in 91% yield. The synthetic product was identical in all respects with the natural material and exhibited a rotation of -54 (*c* 1.0, $CHCl_3$), whereas the reported[1] rotation for natural herbertenediol is -47 (*c* 1.4, $CHCl_3$). The structure and optical purity was further established through the subsequent synthesis of mastigophorenes A and B (*vide supra*).

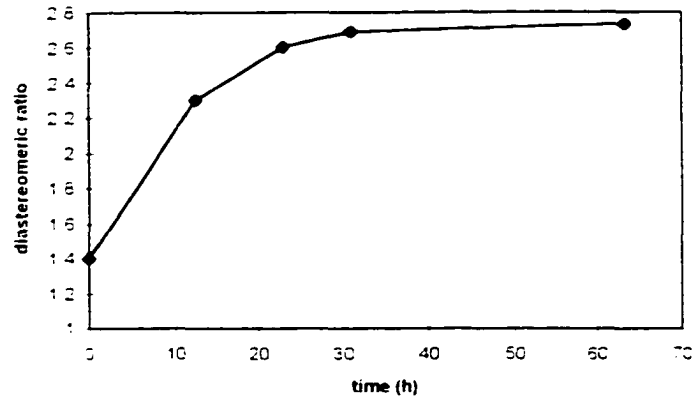
It was now necessary to effect the dimerization of **117** and the establishment of stereochemistry about the newly formed biaryl axis (Scheme 38). Arene **117** was brominated (100%), followed by oxidation[51] to substituted benzoic acid **146** (84%), utilizing conditions similar to those used by Bringmann.[7] The acid was subsequently transformed into the (*S*)-*t*-leucinol derived oxazoline, **116**, in 82% yield under previously described conditions.[52]

Scheme 38



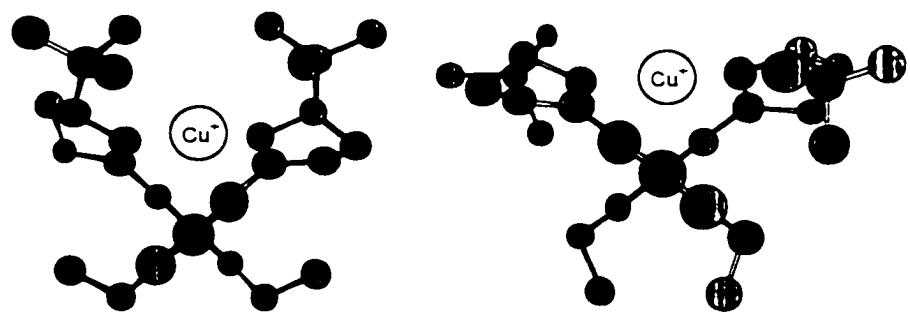
The appropriate aromatic precursor (**116**) was now in hand for the asymmetric Ullmann coupling. Consistent with previous studies,[35c] the early stages of coupling proceeded with little atroposelectivity (**Figure 2**). However, heating the reaction mixture at reflux was accompanied by conversion of **147** to **115** until finally reaching a steady state containing an equilibrium mixture of 3 : 1.[45,53]

Figure 2: Equilibration of Atropisomers, 115 and 147, Over Time



This reaction profile can only be rationalized as a thermodynamic distribution of the two products. One can draw two diastereomeric complexes wherein both of the nitrogens are chelating to copper, each leading to a different atropisomer. The selectivity observed corresponds to the relative stability of initially formed copper complexes **148** and **149** (Figure 3). In complex **148**, the *t*-butyl groups are facing inward, toward one another and the coordinated copper ion. In **149**, the alkyl groups are situated on opposite faces of the molecule, decreasing their steric interaction. Heating the mixture at reflux allows the interconversion of **148** and **149** until an equilibrium is reached.

Figure 3



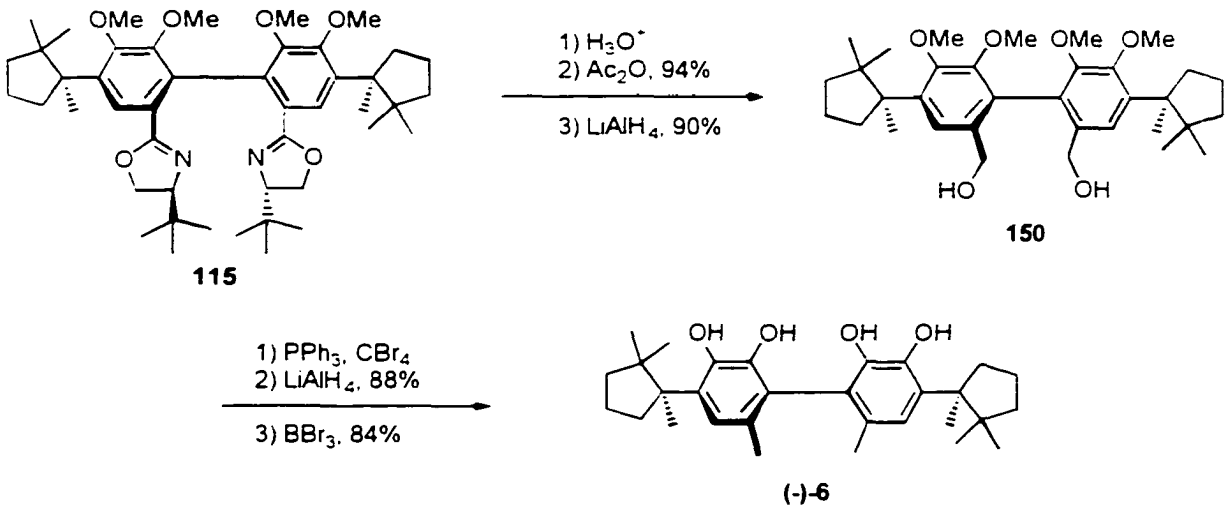
148, Disfavored (→ **147**) **149**, Favored (→ **115**)

All substituents not *ortho* to the biaryl axis have been omitted for clarity

Although **115** and **147** are diastereomers, all attempts to separate them were unsuccessful. However, the propensity for only one of the bisoxazolines to coordinate to copper again became advantageous. If the crude Ullmann coupling was not washed with NH_4OH (to remove coordinated Cu) column chromatography gave **147** (uncomplexed) and **115** as its copper complex, which could then be washed with NH_4OH to release the diastereomerically pure bisoxazoline **115**.

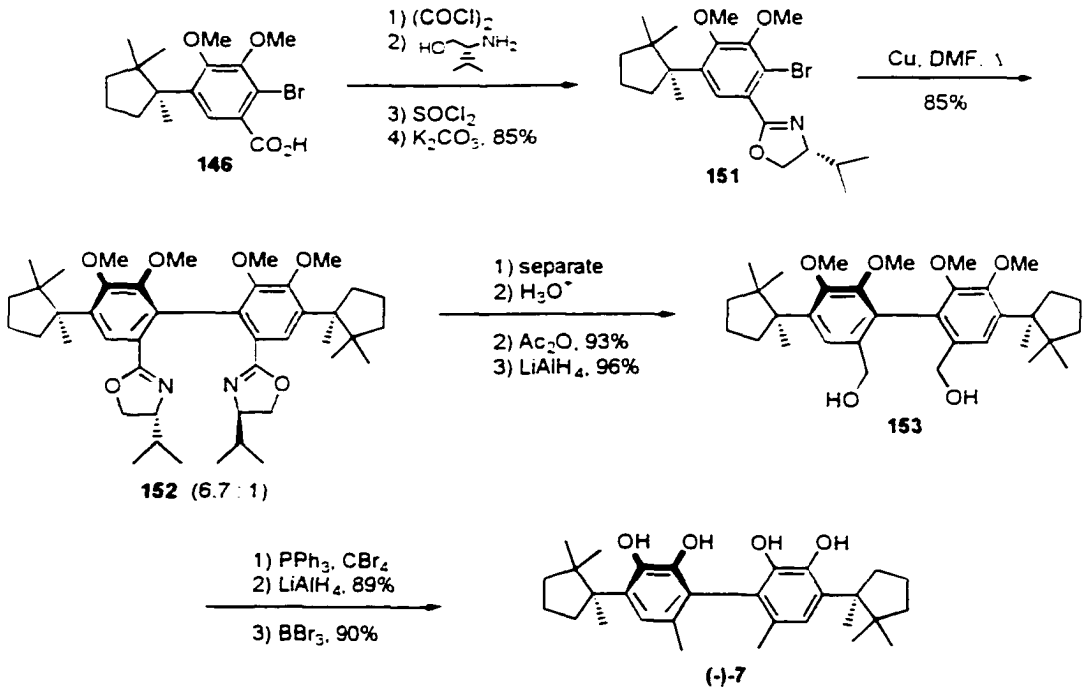
It was now necessary to remove the chiral oxazoline moieties. Acidic hydrolysis to their aminoesters, protection as the bisacetamide (94% over 2 steps), and $LiAlH_4$ reduction (90%) afforded diol **150** (Scheme 39). Conversion to the bromide, followed by displacement with $LiAlH_4$ furnished tetramethylmastigophorene A in 88% over 2 steps. Treatment with BBr_3 allowed clean removal of all methyl groups, providing (-)-mastigophorene A, (-)-**6** - consistent in all respects to the natural product (observed rotation = -68 (c = 0.4, $CHCl_3$); literature[5] = -65 (c = 0.4, $CHCl_3$)).

Scheme 39



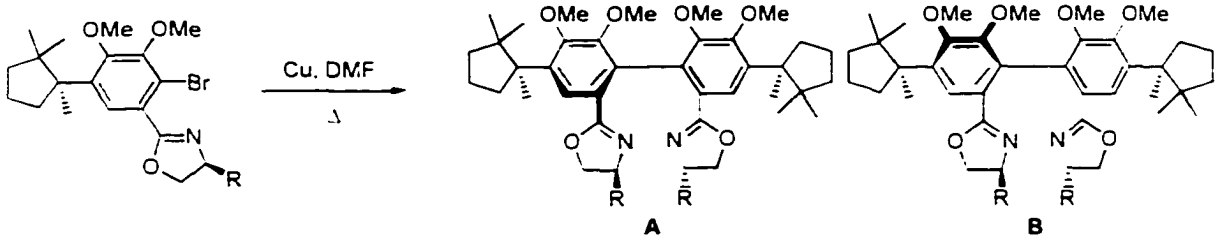
Although mastigophorene B could have been prepared from the minor atropisomer produced above (**147**), it was deemed favorable to construct it from an Ullmann coupling wherein (*S*)-*t*-leucinol has been replaced by another chiral auxiliary. As (*R*)-*t*-leucinol is prohibitively expensive, (*R*)-valinol was chosen despite the fear that this may be accompanied by even lower levels of diastereoselection in the Ullmann coupling. Construction of oxazoline **151** under the same conditions afforded the monomer, ready for coupling (Scheme 40). To our surprise, the Ullmann reaction gave a 6.7 : 1 ratio of atropisomers[45,53] - greater than double the selectivity seen in the *t*-leucinol derived coupling! These were also separable, isolating **152** as its copper complex. Subjection of **152** to the sequence described above gave epimeric mastigophorene B (**7**), identical to the natural product in all respects (observed rotation = -38 (c = 0.35, $CHCl_3$); literature[3] = -39 (c = 0.35, $CHCl_3$)).

Scheme 40



The observation that (*R*)-valinol gave higher diastereoselection than its larger (*S*)-*t*-leucinol counterpart suggested the possibility that the chirality of the cyclopentane rings predisposed the biaryl axis to the (*aR*) configuration. This however was believed to be unlikely due to the distance of the cyclopentanes from the biaryl axis. Alternately, it may be possible that *t*-leucinol is simply too large to give good diastereoselectivity. Referring again to Figure 3, it may be that as the chiral auxiliary gets very large, its interaction with the arene becomes significant, favoring the 'disfavored' atropisomer (**148**).

Table 2 - Effect of Chiral Auxiliary on Atroposelectivity



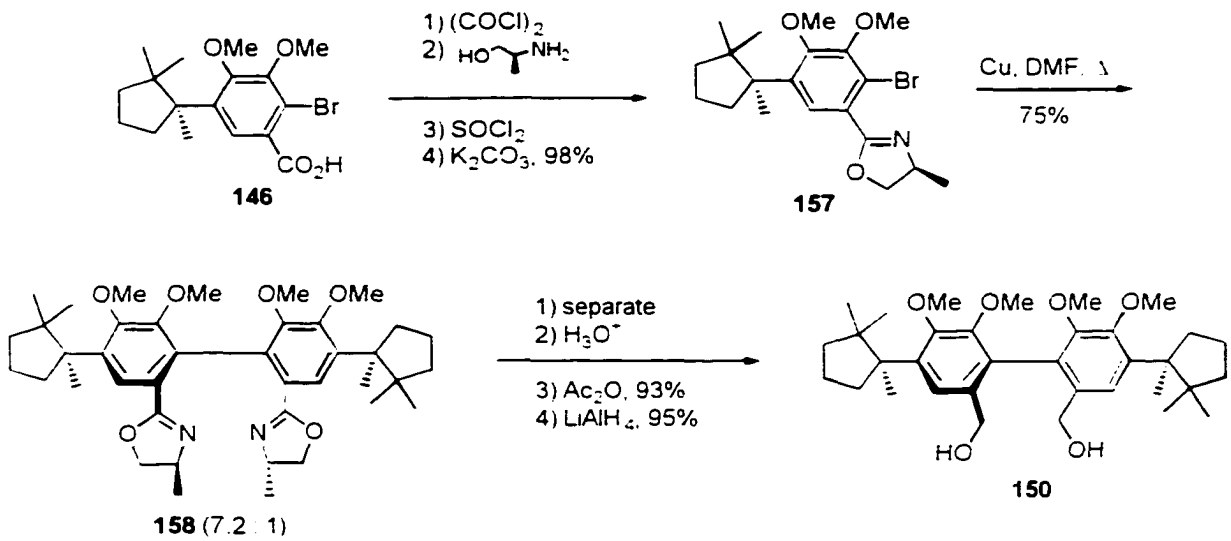
compound	R	*A*-Value of R	ratio of A : B[45]
116	*t*-butyl	>4.5[54a]	3 : 1
154	phenyl	2.9[54b]	4 : 1
155	*i*-propyl	2.1[54c]	6.4 : 1
156	ethyl	1.8[54c]	7.1 : 1
157	methyl	1.8[54c]	7.2 : 1

In order to identify the cause of this anomaly, a number of other chiral auxiliaries were screened (Table 2). It was found that as the size of the chiral auxiliary decreased (*A*-values) the atroposelectivity increased, reaching a maximum of 7.2 : 1 for the (*S*)-alaninol derived oxazoline (**157**). This suggests that even very small alkyl groups in the 4-position

of the oxazoline prevent the formation of complex **148**, and that the *level* of diastereoselection is primarily dependent on minimization of the interaction of the alkyl substituent with the arene in **149**.

Subjection of **158** to the conditions developed above afforded diol **150** (Scheme 41), identical in all respects to that synthesized previously, formally improving the synthesis of mastigophorene A.

Scheme 41

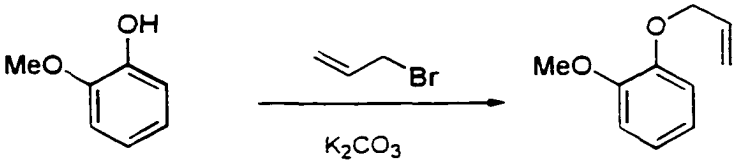


In summary, (-)-herbertenediol, (-)-mastigophorene A, and (-)-mastigophorene B have been synthesized in optically pure form. A non-racemic bicyclic lactam was used to construct a chiral cyclopentane containing vicinal quaternary carbon centers which is common to all of the title compounds. During these studies a more practical method of carbinolamine hydrolysis was developed (KH_2PO_4 *vs.* $Bu_4NH_2PO_4$), reducing the cost to ~1% of the previously employed conditions. An oxazoline-mediated asymmetric Ullmann coupling was then utilized to generate chirality about the biaryl axis of **6** and **7**. An attractive feature of this sequence is the inclusion of the chiral auxiliary into the oxazoline

just prior to the key Ullmann coupling. The benefits bestowed by this aspect of the synthesis are twofold. First, advanced intermediate **146** could be coupled to favor either **6** or 7. Secondly, it allowed for the screening of multiple chiral auxiliaries and the realization that smaller directing groups give higher levels of atroposelection.

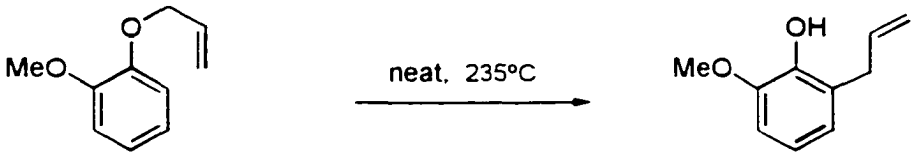
E. Experimental

Thin layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230-400 mesh). All reagents were purchased from Aldrich. All non-aqueous reactions were conducted under an argon atmosphere in oven or flame-dried apparatus. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, Georgia



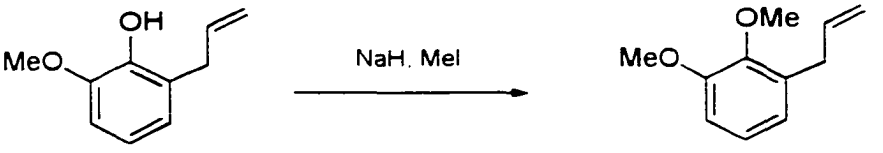
126 **127**

O-Allyl-*o*-eugenol, 127. A RBF was charged with **126** (10.0 g, 81 mmol), allylbromide (10.8 mL, 124 mmol), K_2CO_3 (16.6 g, 120 mmol), and acetone (35 mL). The suspension was heated 24 h at reflux. The suspension was filtered through celite, and concentrated to give 13.1 g (99%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 4.60 (ddd, *J* 5.4, 1.5, 1.5, 2H), 5.26 (dd, *J* = 11.7, 1.5, 1H), 5.38 (dd, *J* = 17.1, 1.5, 1H), 6.07 (ddt, *J* 17.1, 11.7, 5.4, 1H), 6.88 (m, 4H). Spectra are in complete agreement with those previously reported.[39b]



127 **124**

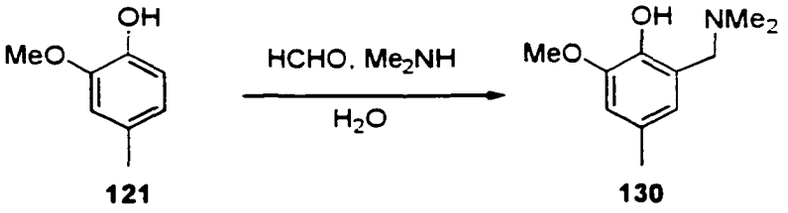
3-Allyl-*o*-eugenol, 124. A reflux condenser was attached to a RBF charged with **127** (5.2 g, 32 mmol). The flask was heated to 235°C in an oil bath and maintained there 1 h. Heat was discontinued, but the flask remained in the oil bath until the temperature reached 100°C at which point the flask was removed from the oil bath and allowed to cool to rt. The oil was dissolved in ether and extracted with 20% NaOH (3X30 mL). The aqueous layers were combined, acidified with conc. HCl, extracted with CH_2Cl_2 (2X), dried over Na_2SO_4, and concentrated to give 3.70 g (71%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (ddd, J = 6.3, 1.5, 1.5, 2H), 3.86 (s, 3H), 5.05 (m, 2H), 5.67 (s, 1H), 5.99 (m, 1H), 6.75 (m, 3H). Spectra are in complete agreement with those previously reported.[39b]



124 **128**

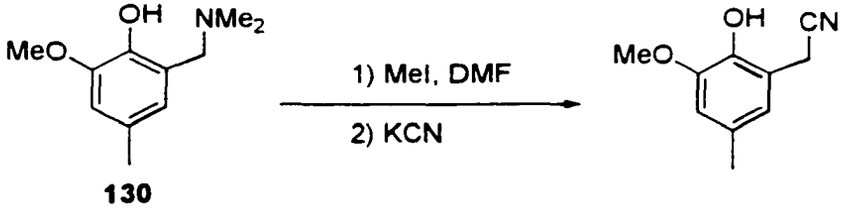
3-Allyl-veratrole, 128. To a cooled (0 °C) solution of **124** (0.20 g, 1.2 mmol) in THF (2 mL) was added NaH (39 mg, 1.5 mmol) in small portions. There was rapid evolution of hydrogen. After stirring 5 min, Me_2SO_4 (0.14 mL, 1.4 mmol) was added and stirring continued 5 min at 0 °C. The ice bath was removed and the reaction was allowed to first reach rt, heated to 65°C for 5 min, and allowed to gradually cool in the oil bath to rt. The oil was partitioned between water and EtOAc. The organic layer was washed twice with 10% KOH, dried over Na_2SO_4, and concentrated to give 0.21g (97%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.41 (d, J = 6.6, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 5.02 (dd, J = 1.5,

1 5, 1H), 5.06 (m, 1H), 5.97 (m, 1H), 6.78 (m, 2H), 6.98 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.2, 55.9, 60.8, 110.6, 115.7, 122.2, 124.0, 134.1, 137.5, 147.2, 153.0



121 **130**

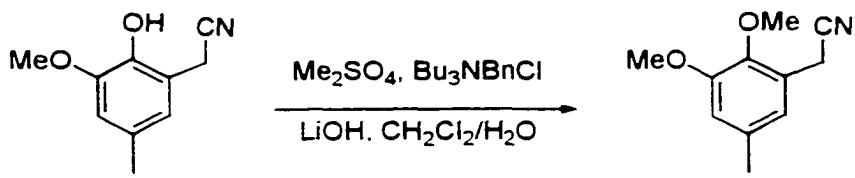
N,N-Dimethyl-2-hydroxy-3-methoxy-5-methylbenzylamine. 130. To a cooled (0 °C) flask charged with **121** (94 g, 725 mmol) was added dimethylamine (40% in H_2O, 102 g, 966 mmol) with stirring. Formaldehyde (37% in H_2O, 64.5 g, 850 mmol) was slowly added, maintaining the temperature below 40 °C. After the addition was complete, the ice bath was removed and the mixture allowed to stir 1.5 h. The mixture was poured into water (500 mL) and made slightly acidic with 1 N HCl. The aqueous phase was extracted with CH_2Cl_2 (3X), dried over Na_2SO_4, and concentrated to give 133 g (100%) of a light oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.29 (s, 6H), 3.57 (s, 2H), 3.83 (s, 3H), 6.36 (d, J = 1.5, 1H), 6.59 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 44.0, 55.4, 62.2, 111.6, 120.3, 121.3, 127.3, 144.4, 147.1.



130

2-Hydroxy-3-methoxy-5-methylphenylacetonitrile. To a stirred solution of **130** (0.20 g, 1 mmol) in DMF (2 mL, 0 °C) was added MeI (140 μL, 2 mmol) in one portion. It was

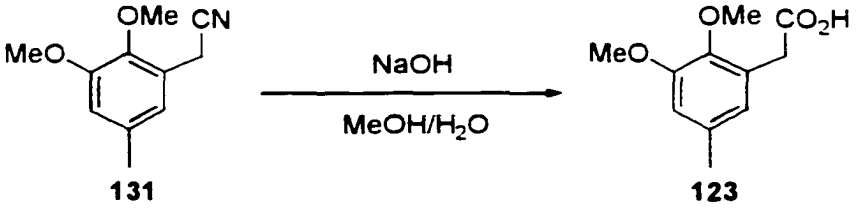
stirred 5 min at 0 °C, 30 min at rt, then recooled to 0 °C. To the crude methiodide was added freshly ground KCN (0.33 g, 5 mmol). It was stirred at 0 °C for 10 min, then at rt for 1 h. The solution was poured into water (10 mL) and extracted into ether (2X) The aqueous phase was acidified and extracted with ether (2X). The organics were combined, washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography gave 0.16 g (90%) as a white solid. mp 45.0-46.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.67 (s, 2H), 3.86 (s, 3H), 5.61 (s, 1H), 6.63 (d, *J* = 1.5, 1H), 6.74 (d, *J* 1.5, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 21.2, 56.2, 111.6, 115.7, 118.2, 121.3, 129.8, 141.1, 146.3; IR (thin film) 3428(br), 2251 cm^{-1}; Anal. Calcd for $C_{10}H_{11}NO_2$: C 67.78, H 6.26; Found: C 67.70, H 6.30.



131

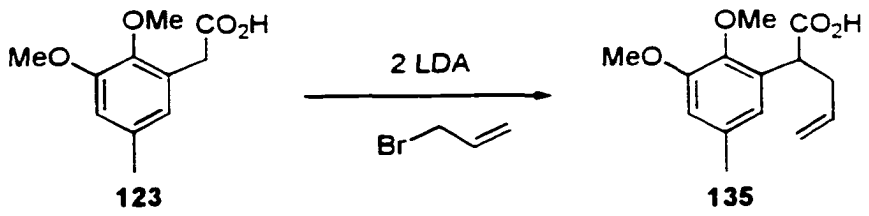
2,3-Dimethoxy-5-methylphenylacetonitrile, 131. A 1 L flask was charged with 2-hydroxy-3-methoxy-5-methylphenylacetonitrile (49.5 g, 283 mmol), $LiOH{\cdot}H_2O$ (17.8 g, 424 mmol), and benzyltributylammonium chloride (17.6 g, 56 mmol). To this was added water (400 mL) and the solution was allowed to stir 1 min. CH_2Cl_2 (400 mL) was added and the heterogeneous mixture stirred 1 min. To this was added Me_2SO_4 (40 mL, 424 mmol) and vigorously stirred 5 min. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2X). The organics were washed with brine, dried over Na_2SO_4, and concentrated. The oil was taken up in EtOAc and filtered through a large pad of silica gel,

eluting with EtOAc to yield 54 g (100%) of 2,3-dimethoxy-5-methylphenylacetonitrile as a light oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.66 (s, 2H), 3.83 (s, 3H), 3.84, (s, 3H), 6.69 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 21.0, 55.5, 60.4, 113.2, 118.2, 121.0, 123.4, 134.1, 144.2, 152.1; IR (thin film) 2251 cm^{-1}



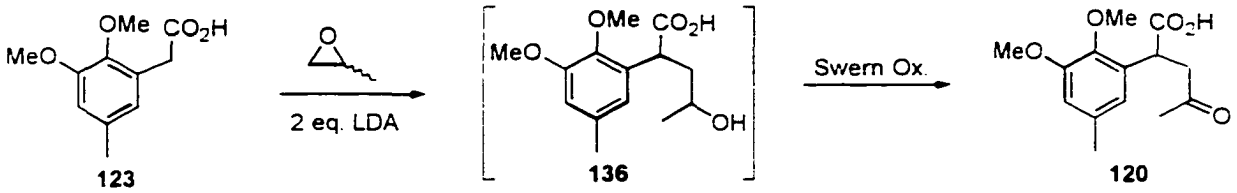
131 **123**

2,3-Dimethoxy-5-methylphenylacetic acid, 123. To a stirred solution of **131** (53.7 g, 281 mmol) in methanol (450 mL) was added aqueous 25% NaOH (125 mL). The mixture was heated at reflux for 24 h, and upon cooling, the solution was concentrated, redissolved in water, extracted with ether (2X), and the ethereal layers discarded. The aqueous phase was acidified with cold conc. HCl and extracted into ether (3X), which was washed with brine, dried over Na_2SO_4, and concentrated to give 57.1 g (97%) of the acid as a white solid. mp 101-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.64 (s, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 6.63 (d, J = 1.5, 1H), 6.67 (d, J = 1.5, 1H), 10.43 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 35.5, 55.6, 60.5, 112.8, 123.0, 127.1, 133.7, 145.0, 152.2, 178.2; IR (thin film) 3000(br), 1698 cm^{-1}; Anal. Calcd for $C_{11}H_{14}O_4$: C 62.85, H 6.71; Found: C 63.05, H 6.65.



123 **135**

2-(2,3-Dimethoxy-5-methylphenyl)-pent-4-ene-oic acid. 135. A stirred solution of diisopropylamine (0.30 mL, 2.1 mmol) in THF (4 mL, 0 °C) was treated with *n*-BuLi (2.19 M in hexanes, 0.96 mL, 2.1 mmol), stirred 30 min, and cooled to -78 °C. To this was added **123** (0.20 g, 0.95 mmol) in THF (1.5 mL) *via* syringe. After 5 min, the ice bath was removed, and the solution was stirred an additional 30 min at rt. The solution was recooled to -78 °C, treated with allylbromide (0.11 mL, 1.3 mmol), and stirred 15 min. The reaction was quenched by addition of water, concentrated, partitioned between water and ether, and the ethereal discarded. The aqueous was made acidic with 1N HCl, extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. Column chromatography (40% EtOAc/hexanes) gave 132 mg (55%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.43 (ddd, *J* = 7.5, 7.5, 7.5, 1H), 2.77 (ddd, *J* = 7.5, 7.5, 7.5, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.08 (dd, *J* = 7.5, 7.5, 1H), 4.96 (dd, *J* = 10.2, 1.8, 1H), 5.04 (dd, *J* = 16.8, 1.8, 1H), 5.71 (m, 1H), 6.63 (s, 1H), 6.66 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 36.6, 44.1, 55.8, 61.0, 112.6, 117.0, 120.4, 131.8, 134.0, 135.5, 144.7, 152.5, 180.0.

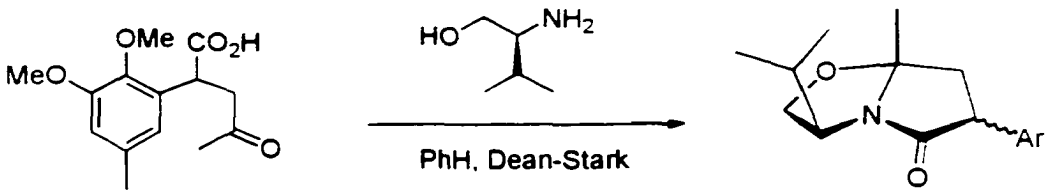


123 **136** **120**

2-(2,3-Dimethoxy-5-methylphenyl)-4-oxopentanoic acid, 120. A stirred solution of diisopropylamine (22 mL, 156 mmol) in THF (350 mL, 0 °C) was treated with *n*-BuLi (2.19 M in hexanes, 68 mL, 148 mmol), stirred 30 min, and cooled to -78 °C. To this was added **123** (15 g, 71 mmol) in THF (100 mL) *via* cannula. The flask was placed in a 0 °C bath and stirred 45 min before recooling to -78 °C. (±)-Propyleneoxide (13.7 mL, 195 mmol) was then added. The flask was placed in a 0 °C bath and stirred overnight, allowing it to reach rt. The mixture was quenched with water and concentrated by rotary evaporation. The crude alcohol was taken up in water, extracted with ether (2X), and the ethereal discarded. The aqueous layer was acidified with conc. HCl and extracted with ether (3X). These organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give a viscous oil. This crude γ-hydroxyacid (**136**) was taken on directly below.

To a stirred solution of oxalyl chloride (6.8 mL, 79 mmol) in CH_2Cl_2 (350 mL, -78 °C) was added DMSO (10 mL, 143 mmol) and allowed to stir 15 min before adding **136** in CH_2Cl_2 (100 mL). The solution was allowed to stir 1 h. To this was added Et_3N (40 mL, 288 mmol), and stirred 5 min. The cold bath was removed and the mixture was allowed to reach rt. It was quenched by addition to water (200 mL) containing NaOH (9 g, 225 mmol), and the layers were separated. The organic layer was washed with 5% NaOH (2X) and the aqueous extracts combined, washed with ether(2X), and the ethereal solutions discarded. The aqueous layer was acidified with cold conc. HCl and extracted into CH_2Cl_2 (3X). These were washed with brine, dried over Na_2SO_4, and concentrated to give 15.3 g (80%) of the ketoacid as a very viscous oil. ^1H NMR (300 MHz, $CDCl_3$) δ

2.01 (s, 3H), 2.15 (s, 3H), 2.44 (dd, J = 18.0, 3.9, 1H), 3.18 (dd, J = 18.0, 9.9, 1H), 3.69 (s, 3H), 3.70 (s, 3H), 4.32 (dd, J = 9.9, 3.9, 1H), 6.46 (d, J = 1.5, 1H), 6.52 (d, J = 1.5, 1H), 10.5 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 30.0, 40.3, 45.9, 55.7, 60.7, 112.8, 120.6, 131.4, 134.1, 144.3, 152.5, 179.2, 206.5; IR (thin film) 3150(br), 1713 cm^{-1}. HRMS (FAB+) for $C_{14}H_{18}O_5$ $(M)^+$: Calcd 266.1154, Found 266.1154.

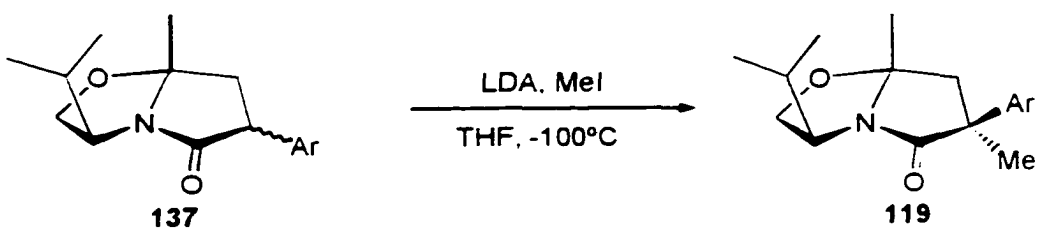


120 **137**

***Exo-Endo*-(2,3-Dimethoxy-5-methylphenyl)bicyclic lactam, 137.** A stirred solution of ketoacid **120** (15.3 g, 57 mmol) and (*S*)-valinol (6.2 g, 60 mmol) in benzene (250 mL) was heated under azeotropic removal of water with a Dean-Stark trap for 16 h. The solution was cooled and concentrated, and the residue was taken up in ether, washed with saturated NH_4Cl, saturated Na_2CO_3, and brine and then dried over $MgSO_4$. The solution was concentrated and filtered through a large pad of silica gel using 40% EtOAc/Hex to yield 15.9 g (84%) of a viscous oil, which was a 3:2 mixture of *exo-endo* epimers. The epimers could be separated by careful chromatography of the mixture. **Major**: $[\alpha]^{25}_D$ = +3.56 (c = 2.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, J = 6.6, 3H), 1.11 (d, J = 6.6, 3H), 1.44 (s, 3H), 1.70 (m, 1H), 2.09 (dd, J = 14.4, 6.3, 1H), 2.24 (s, 3H), 2.66 (dd, J = 13.8, 10.8, 1H), 3.68 (m, 1H), 3.76 (s, 3H), 3.78 (m, 1H), 3.80 (s, 3H), 3.89 (dd, J = 11.1, 6.3, 1H), 4.18 (t, J = 8.1, 1H), 6.50 (d, J = 1.5, 1H), 6.61 (d, J = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 16.5, 16.9, 20.4, 29.6, 36.0, 41.4, 51.1, 55.9, 59.0, 65.8,

94.5, 108.0, 116.8, 129.0, 129.2, 140.0, 147.9, 177.6. IR (thin film) 1712 cm^{-1}. HRMS (EI−) for $C_{19}H_{27}NO_4$ $(M)^-$: Calcd 333.1940, Found 333.1935.

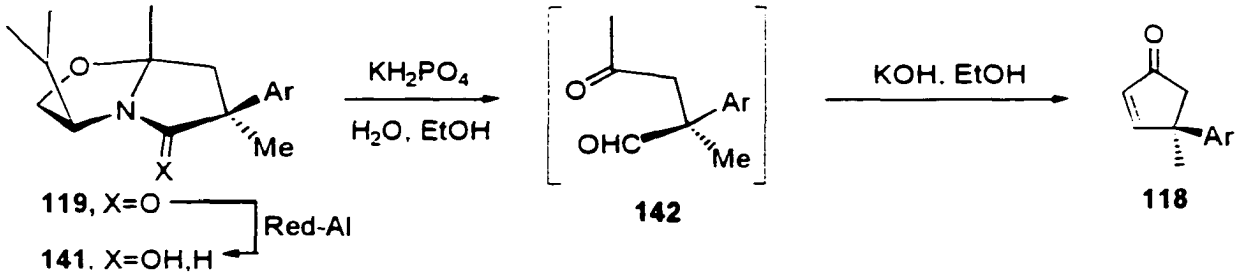
Minor: $[\alpha]^{25}_D$ = +35.9 (c = 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.2, 3H), 1.00 (d, *J* = 6.5, 3H), 1.51 (s, 3H), 1.69 (m, 1H), 2.22 (s, 3H), 2.32 (t, *J* = 11.1, 1H), 2.48 (dd, *J* = 12.9, 8.7, 1H), 3.69 (m, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.89 (dd, *J* = 8.7, 5.4, 1H), 4.19 (m, 2H), 6.49 (s, 1H), 6.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 15.9, 16.8, 20.9, 28.5, 39.3, 41.4, 51.2, 56.2, 57.4, 66.2, 92.6, 108.1, 117.4, 127.1, 129.0, 140.6, 147.7, 173.8; IR (thin film) 1713 cm^{-1}.



***Endo*-Methyl-(2,3-Dimethoxy-5-methylphenyl)bicyclic lactam, 119.** To a stirred solution of diisopropylamine (12.6 mL, 90 mmol) in THF (350 mL, 0 °C) was added *n*-BuLi (2.62 M in hexanes, 33 mL, 86.3 mmol). The solution was stirred 30 min and cooled to -78 °C. To this was added **137** (23 g, 69 mmol) in THF (100 mL) *via* cannula and allowed to stir 1 h. The solution was cooled to -100 °C and MeI (11 mL, 180 mmol) was added dropwise. It was stirred 2 h, quenched by addition of water, and concentrated. The residue, a 33:1 ratio of alkylation epimers, was taken up in 20% EtOAc/Hex and filtered through a large pad of silica gel to give a white solid. This was recrystallized from *n*-heptane to yield 19.7 g (82%) of a white solid as a single diastereomer. The minor diastereomer was isolated by successive recrystallizations of the mother liquor to afford a

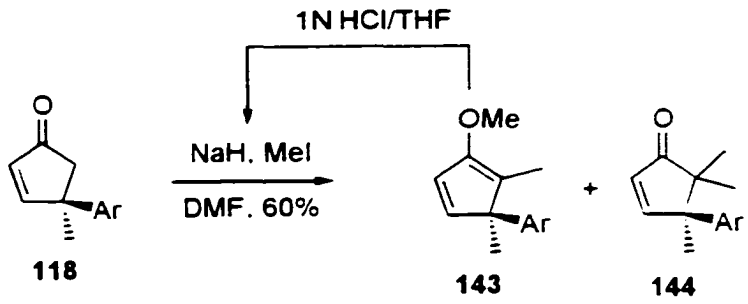
1 : 1 mixture of diastereomers. Careful chromatography of the enriched material then afforded the minor atropisomer. **Major (8)**: mp 109 -110 °C; $[\alpha]^{25}_{D}$ = -46.7 (c = 0.9, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.6, 3H), 1.12 (d, *J* = 6.6, 3H), 1.28 (s, 3H), 1.49 (s, 3H), 1.70 (m, 1H), 2.19 (d, *J* = 13.5, 1H), 2.25 (s, 3H), 2.60 (d, *J* = 13.5, 1H), 3.67 (m, 1H), 3.79 (s, 3H), 3.81 (s, 3H), 4.18 (dd, *J* = 8.7, 7.5, 1H), 6.64 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8, 20.6, 21.2, 24.1, 25.4, 33.8, 48.1, 50.3, 55.2, 59.5, 63.1, 69.9, 97.3, 112.0, 119.6, 132.4, 136.6, 144.0, 152.1, 184.1; IR (thin film) 1711 cm^{-1}; Anal. Calcd for $C_{20}H_{29}NO_4$: C 69.14, H 8.41 N 4.03; Found: C 69.08, H 8.41, N 3.99.

Minor: oil, $[\alpha]^{25}_{D}$ = +64.1 (c = 2.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, *J* 6.6, 3H), 1.05 (d, *J* = 6.6, 3H), 1.55 (s, 3H), 1.67 (s, 3H), 1.70 (m, 1H), 2.07 (d, *J* = 13.2, 1H), 2.28 (s, 3H), 2.62 (d, *J* = 13.2, 1H), 3.76 (s, 3H), 3.78 (s, 3H), 3.82 (m, 1H), 4.29 (dd, *J* = 8.4, 7.8, 1H), 6.65 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 16.1, 17.0, 20.4, 22.6, 29.6, 45.5, 46.5, 51.2, 55.2, 57.4, 66.2, 92.3, 108.6, 115.0, 127.6, 132.1, 139.8, 147.8, 178.2; IR (thin film) 1714 cm^{-1}.



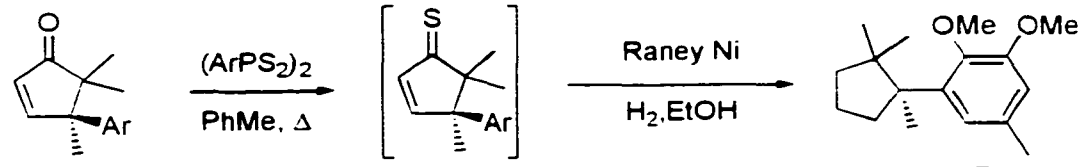
(*S*)-4-(2,3-Dimethoxy-5-methylphenyl)-4-methylcyclopentenone, 118. To a stirred solution of **119** (10 g, 29 mmol) in THF (300 mL, -78 °C) was added Red-Al (65+ wt%,

10 mL, 33 mmol). The mixture was allowed to reach rt and was stirred 24 h and then was quenched by addition of MeOH and concentrated. The residue was taken up in water, extracted with ether (2X), made strongly basic with 20% KOH, and extracted with ether (2X). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated to give the crude carbinolamine (**141**). This was dissolved in 95% EtOH (460 mL) and added to a stirred solution of KH_2PO_4 (78.4 g, 576 mmol) in water (690 mL) and stirred 12 h. The suspension was concentrated, dissolved in water and extracted with ether (3X). The organics were washed with brine, dried over Na_2SO_4, and concentrated to give the crude ketoaldehyde (**142**) as a viscous oil. This was dissolved in absolute EtOH (500 mL), treated with 1M KOH in EtOH (1.5 mL), and heated at reflux 2 h. The solution was cooled, treated with silica gel, and concentrated to adsorb the crude cyclopentenone. Column chromatography (20% EtOAc/Hex) gave 5.95 g (84%) as a colorless oil. $[\alpha]^{25}_D$ = +38.3 (c = 1.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.27 (s, 3H), 2.57 (d, *J* = 18.6, 1H), 2.69 (d, *J* = 18.6, 1H), 3.73 (s, 3H), 3.81 (s, 3H), 6.12 (d, *J* = 6.0, 1H), 6.54 (d, *J* = 1.5, 1H), 6.64 (d, *J* 1.5, 1H), 7.82 (d, *J* 5.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.5, 28.3, 47.3, 51.1, 55.7, 60.5, 112.5, 119.2, 130.6, 133.0, 138.0, 145.1, 153.0, 171.4, 209.8; IR (thin film) 1715 cm^{-1}; Anal. Calcd for $C_{15}H_{18}O_5$: C 73.15, H 7.37; Found: C 72.94, H 7.39.



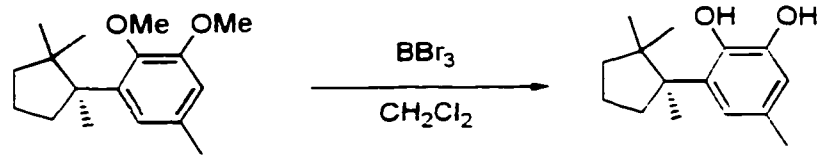
(*S*)-4,5,5-Trimethyl-4-(2,3,dimethoxy-5-methylphenyl)cyclopentenone, 144. To a stirred suspension of NaH (1.78 g, 74 mmol) in DMF (30 mL) was added a solution of cyclopentenone **118** (6.6 g, 26.9 mmol) in DMF (20 mL) *via* cannula. The mixture was placed in a 10 °C bath and MeI (4.4 mL, 70 mmol) was added. The bath was removed and the mixture stirred at rt. The bath was replaced as necessary to maintain a temperature below 40 °C. After the exotherm ceased, the bath was removed and the solution was allowed to stir overnight. The mixture was poured into water (250 mL) and extracted into ether (4X), washed with water, brine, dried over Na_2SO_4, and concentrated to give an oil. The residue was recrystallized from heptane to give 3.96 g (54%) of **144** as a white solid. The mother liquor (**143**) was concentrated and redissolved in 3:1 THF/1 N HCl. After 10 min, the mixture was quenched by addition of $NaHCO_3$ and concentrated. The residue was taken up in water, extracted into ether (3X), washed with brine, dried over Na_2SO_4, and concentrated. This was resubjected to the conditions above, using 1.5 eq NaH and 1.25 eq MeI. Two recycles gave an additional 2.0 g (28%). mp 84.0-85.9 °C; $[\alpha]^{25}_D$ = -79.4 (c = 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.64 (s, 3H), 1.22 (s, 3H), 1.46 (s, 3H), 2.27 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 6.05 (d, *J* = 6.0, 1H), 6.46 (s, 1H), 6.63 (d, *J* = 1.5, 1H), 7.91 (d, *J* = 5.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 21.4, 26.1, 50.9, 54.7, 55.6, 60.3, 112.1, 120.6, 125.8, 132.8, 136.0, 145.3, 152.8, 171.4,

214.6; IR (thin film) 1705 cm^{-1}; Anal. Calcd for $C_{17}H_{22}O_3$: C 74.42, H 8.08. Found: C 74.30, H 8.10.



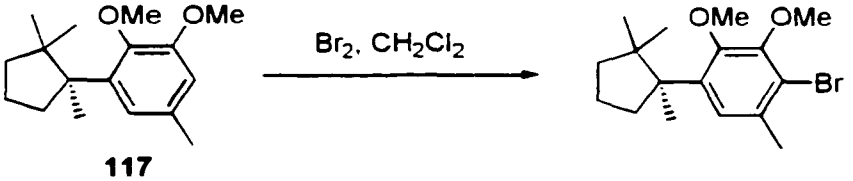
144 145 117

(*S*)-*O,O'*-Dimethylherbertenediol, 117. A flask was charged with cyclopentenone **144** (1.93 g, 7.0 mmol), Belleau's reagent (2.23 g, 4.23 mmol), and toluene (65 mL). The solution was heated to reflux and held there 30 min. The solution was cooled, filtered through Fluorosil, washing with CH_2Cl_2, and concentrated to yield a bright pink oil which was subjected to flash chromatography (5% EtOAc/Hex), taking all pink fractions (**145**). **145** was dissolved in EtOH (75 mL) and Raney Ni was added in portions with stirring until the solution was colorless. A hydrogen balloon was affixed and stirring was continued overnight. The solution was filtered through a pad of silica gel and concentrated. Flash chromatography (4% EtOAc/Hex) gave 1.05 g (58%) as a colorless oil. $[\alpha]^{25}_D$ = -27.0 (c = 1.3, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 (s, 3H), 1.10 (s, 3H), 1.33 (s, 3H), 1.70 (m, 5H), 2.27 (s, 3H), 2.61 (m, 1H), 3.74 (s, 3H), 3.80 (s, 3H), 6.58 (d, *J* = 1.8, 1H), 6.73 (d, *J* = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.8, 24.3, 25.4, 27.0, 39.1, 41.1, 45.1, 51.7, 55.7, 60.5, 111.2, 121.8, 131.7, 140.2, 146.8, 153.2.



117 (-)-1

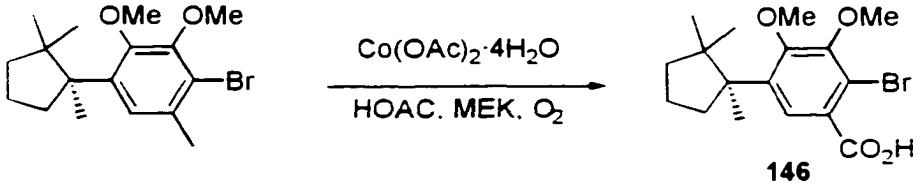
(-)-Herbertenediol, 1. To a stirred solution of **117** (100 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added BBr_3 (1 M in CH_2Cl_2, 1.5 mL, 1.5 mmol). The ice bath was removed, and after 40 min, the solution was poured into 2% $NaHCO_3$, extracted into CH_2Cl_2 (3X), washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (20% EtOAc/Hex) gave 81 mg (91%) as a white crystalline solid mp 89.9-90.5 °C; $[\alpha]^{25}_D$ = -53.8 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.77 (s, 3H), 1.20 (s, 3H), 1.42 (s, 3H), 1.50-1.80 (m, 5H), 2.23 (s, 3H), 2.61 (m, 1H), 5.32 (s, 1H), 5.41 (s, 1H), 6.55 (d, *J* = 1.5, 1H), 6.69 (d, *J* = 1.5, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.3, 23.0, 25.6, 27.0, 39.4, 41.1, 45.0, 51.3, 113.6, 122.1, 128.8, 133.7, 141.1, 143.5; IR (thin film) 3507, 2959, 1300 cm^{-1}; Anal. Calcd for $C_{15}H_{22}O_2$: C 76.88, H 9.46; Found: C 77.08, H 9.60. Spectra are in complete agreement with those previously reported [1]



117

(*S*)-2-Bromo-3,4-dimethoxy-5-(1,2,2-trimethylcyclopentyl)toluene. To a stirred solution of **117** (2.08 g, 7.95 mmol) in CH_2Cl_2 (42 mL, -10 °C) was added bromine (412

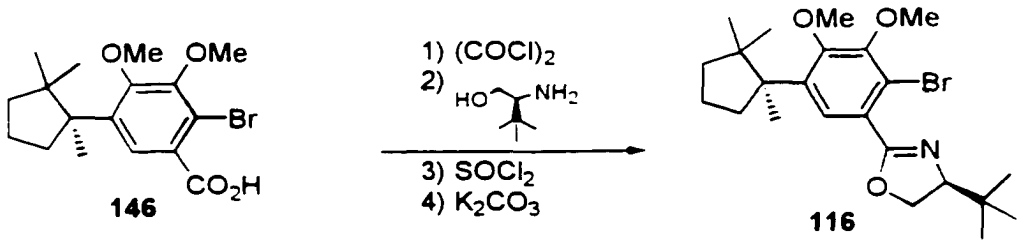
mL, 8.0 mmol) dropwise. After 5 min, the solution was poured into saturated $NaHCO_3$, extracted into CH_2Cl_2 (2X), washed with brine, dried over Na_2SO_4 and concentrated Trace impurities were removed *via* flash chromatography (2% EtOAc/Hex) to give 2.71 g (100%) of (*S*)-1,2,2-Trimethyl-1-(2,3-dimethoxy-4-bromo-5-methylphenyl)cyclopentane as a colorless oil. $[\alpha]^{25}_D$ = -14.5 (c = 1.3, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 1.09 (s, 3H), 1.31 (s, 3H), 1.71 (m, 5H), 2.32 (s, 3H), 2.52 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 6.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.2, 24.2, 25.4, 27.0, 39.3, 41.1, 45.0, 51.7, 59.9, 60.5, 117.7, 125.8, 132.2, 139.9, 150.9, 152.0; HRMS (EI+) for $C_{17}H_{25}NO_2Br$ $(M)^+$: Calcd 340.1038, Found 340.1029; HRMS (EI+) for $C_{23}H_{35}NO_3{}^{81}Br$ $(M)^+$: Calcd 342.1017, Found 342.1016.



146

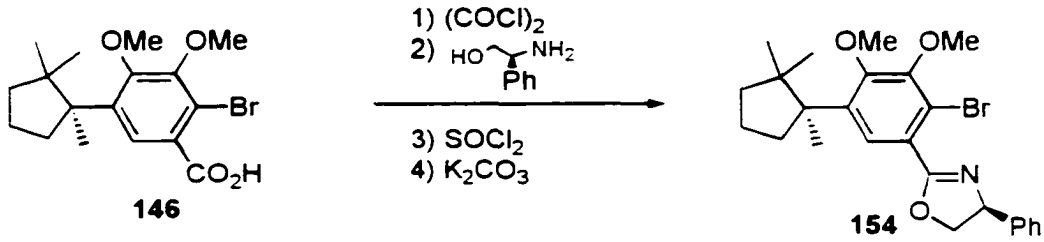
(*S*)-2-Bromo-3,4-dimethoxy-5-(1,2,2-trimethylcyclopentyl)benzoic acid, 146. A pressure tube was charged with (*S*)-1,2,2-trimethyl-1-(2,3-dimethoxy-4-bromo-5-methylphenyl)-cyclopentane (2.70 g, 7.9 mmol), $Co(OAc)_2 \cdot 4H_2O$ (0.66 g, 2.64 mmol), methyl ethyl ketone (2.84 mL, 32 mmol), and glacial acetic acid (25 mL). The tube was sealed, pressurized with oxygen (10 psi) and heated to 110 °C. The pressure was raised to 80 psi and allowed to stir 4 h. The tube was depressurized and poured onto 3 volumes of ice to give a white precipitate. This was filtered to give 2.46 g (84%) of the acid as

crystalline solid. mp 163-165 °C; $[\alpha]^{25}_D$ = -37.3 (c = 1.1, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.12 (s, 3H), 1.34 (s, 3H), 1.75 (m, 5H), 2.52 (m, 1H), 3.80 (s, 3H), 3.89 (s, 3H), 7.84 (s, 1H), 12.35 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 19.2, 20.7, 22.3, 34.8, 36.5, 40.3, 47.2, 55.4, 56.0, 112.6, 120.1, 124.2, 136.0, 147.2, 153.3, 167.3; IR (thin film) 3150(br), 1695 cm^{-1}; Anal. Calcd for $C_{17}H_{23}O_4Br$: C 55.00, H 6.24. Found: C 54.99, H 6.17.

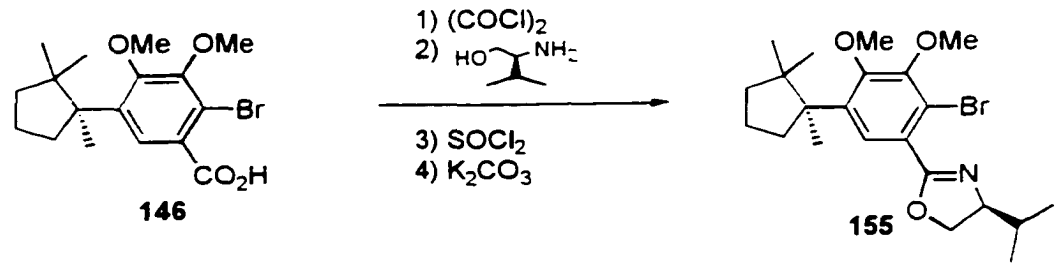


(*S*)-*t*-Leucinol-*o*-bromoaryloxazoline, 116. To a stirred solution of **146** (1.0 g, 2.7 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (0.35 mL, 4.0 mmol), followed by 1 drop of DMF. After 1 h, the solution was concentrated, redissolved in CH_2Cl_2 (10 mL), and cooled to 0 °C. To this was added a solution of (S)-*t*-leucinol (0.38 g, 3.2 mmol) and Et_3N (0.49 mL, 3.5 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed and the mixture was stirred 6 h. The solution was poured into 2% $NaHCO_3$, the layers separated, and extracted twice more with CH_2Cl_2. The organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL), treated with $SOCl_2$ (0.40 mL, 5.4 mmol), and stirred 2 h at rt. The solvent was removed, and the residue dissolved in CH_3CN (10 mL), treated with 20% K_2CO_3, and heated to reflux. After 5h, the heterogeneous mixture was concentrated to remove the

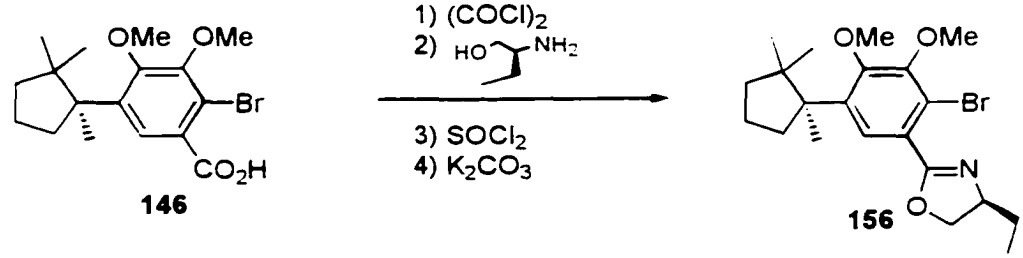
CH_3CN, and extracted with ether (3X). The extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography gave 1.0 g (82%) as a viscous oil. $[\alpha]^{25}_D$ = -79.4 (c = 1.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.97 (s, 9H), 1.09 (s, 3H), 1.31 (s, 3H), 1.68 (m, 5H), 2.49 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 4.05 (dd, *J* = 10.2, 7.8, 1H), 4.21 (dd, *J* = 8.1, 8.1, 1H), 4.33 (dd, *J* = 10.5, 9.0, 1H), 7.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 23.7, 25.4, 26.1, 27.0, 34.1, 39.4, 41.2, 44.8, 51.7, 59.9, 60.5, 68.9, 76.7, 115.7, 124.8, 126.6, 140.6, 151.4, 155.7, 163.0; IR (thin film) 1660 cm^{-1}; HRMS (FAB+) for $C_{23}H_{35}NO_3Br$ $(M+H)^+$: Calcd 452.1800, Found 452.1786; HRMS (FAB+) for $C_{23}H_{35}NO_3{}^{81}Br$ $(M+H)^+$: Calcd 454.1780, Found 454.1775



(*S*)-Phenylglycinol-*o*-bromoaryloxazoline, 154. Prepared from **146** by the same procedure as **116**, using (*S*)-phenylglycinol in place of (*S*)-*t*-leucinol, in 83% yield as a colorless oil. $[\alpha]^{25}_D$ = -35.3 (c = 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 3H), 1.13 (s, 3H), 1.35 (s, 3H), 1.45-1.85 (m, 5H), 2.54 (m, 1H), 3.81 (s, 3H), 3.88 (s, 3H), 4.24 (dd, *J* = 8.4, 8.4, 1H), 4.79 (dd, *J* = 10.2, 8.4, 1H), 5.42 (dd, *J* = 9.9, 8.4, 1H), 7.23-7.38 (m, 5H), 7.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.8, 25.5, 27.2, 39.5, 41.3, 45.0, 51.9, 60.1, 60.6, 70.7, 75.1, 116.0, 124.3, 126.9, 127.0, 127.7, 128.9, 140.9, 142.4, 151.5, 156.1, 164.6; IR (thin film) 1651 cm^{-1}.

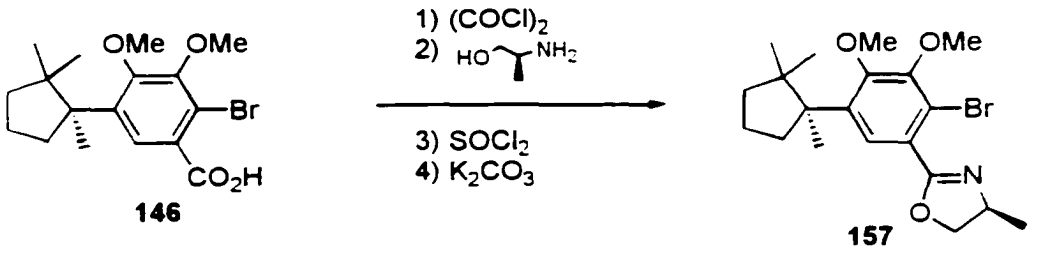


(*S*)-Valinol-*o*-bromoaryloxazoline, 155. Prepared from **146** by the same procedure as **116**, using (*S*)-valinol in place of (*S*)-*t*-leucinol, in 85% yield as a colorless oil $[\alpha]^{25}_{D}$ = -46.6 (c = 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.96 (d, *J* = 7.0, 3H), 1.03 (d, *J* = 6.6, 3H), 1.10 (s, 3H), 1.32 (s, 3H), 1.40-2.00 (m, 6H), 2.48 (m, 1H), 3.78 (s, 3H), 3.84 (s, 3H), 4.13 (m, 2H), 4.39 (dd, *J* = 12.9, 11.4, 1H), 7.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.9, 20.4, 23.6, 25.4, 27.0, 32.7, 39.3, 41.2, 44.8, 51.7, 59.9, 60.4, 70.2, 72.9, 115.7, 124.7, 126.6, 140.6, 151.3, 155.7, 163.0; IR (thin film) 1655 cm^{-1}.

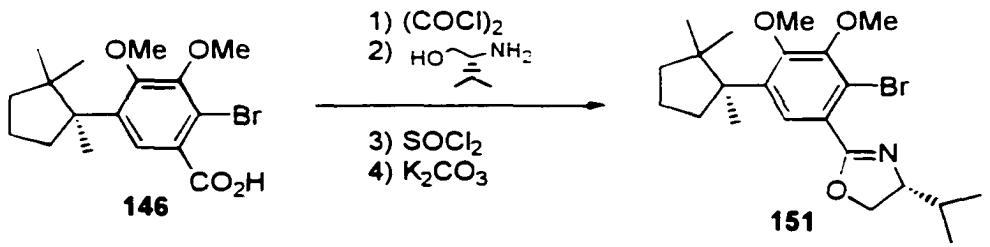


(*S*)-2-Aminobutanol-*o*-bromoaryloxazoline, 156. Prepared from **146** by the same procedure as **116**, using (*S*)-2-aminobutanol in place of (*S*)-*t*-leucinol, in 77% yield as a colorless oil. $[\alpha]^{25}_{D}$ = +1.86 (c = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 1.00 (t, *J* = 7.2, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.40-1.85 (m, 6H), 2.48 (m, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 4.05 (dd, *J* = 7.8, 7.8, 1H), 4.26 (m, 1H), 4.45 (dd, *J* = 8.4, 8.4, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.9, 20.4, 23.7, 25.4, 27.0, 28.6,

39.3, 41.2, 44.8, 51.7, 59.9, 60.4, 68.3, 72.1, 115.7, 124.6, 126.5, 140.6, 151.3, 155.7, 163.1; IR (thin film) 1653 cm^{-1}.

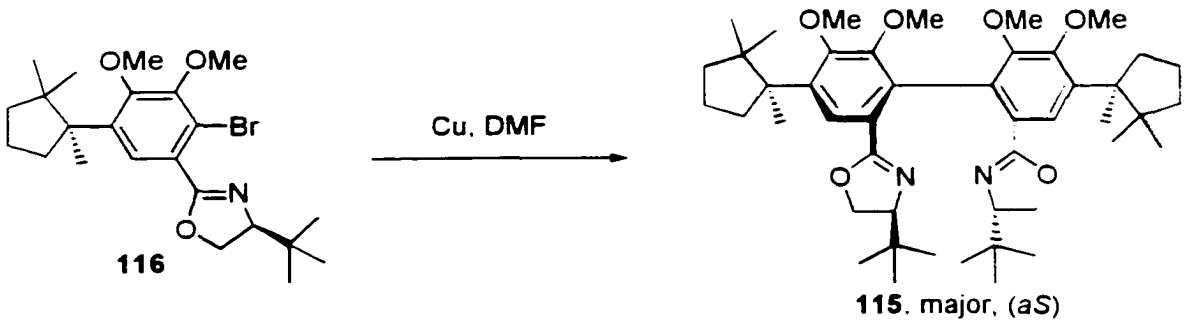


(*S*)-Alaninol-o-bromoarylozazoline, 156. Prepared from **146** by the same procedure as **116**, using (*S*)-alaninol in place of (*S*)-*t*-leucinol, in 98% yield as a colorless oil. $[\alpha]^{25}_D$ = -15.1 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (s, 3H), 1.07 (s, 3H), 1.29 (s, 3H), 1.32 (d, *J* = 6.3, 3H), 1.50-1.80 (m, 5H), 2.48 (m, 1H), 3.75 (s, 3H), 3.81 (s, 3H), 3.91 (dd, *J* = 7.2, 7.2, 1H), 4.38 (m, 1H), 4.45 (dd, *J* = 9.6, 7.8, 1H), 7.39 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.5, 21.6, 23.7, 25.5, 27.1, 39.4, 41.3, 44.8, 51.7, 60.0, 60.5, 62.5, 74.2, 115.8, 124.5, 126.7, 140.7, 151.4, 155.8, 163.1; IR (thin film) 1651 cm^{-1}.



(*R*)-Valinol-*o*-bromoaryloxazoline, 151. Prepared from **146** by the same procedure as **151**, using (*R*)-valinol in place of (*S*)-*t*-leucinol, in 85% yield as a colorless oil. $[\alpha]^{25}_D$ = +7.53 (c = 1.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 3H), 0.95 (d, *J* = 7.0, 3H), 1.03 (d, *J* = 6.9, 3H), 1.10 (s, 3H), 1.31 (s, 3H), 1.40-1.95 (m, 6H), 2.48 (m, 1H),

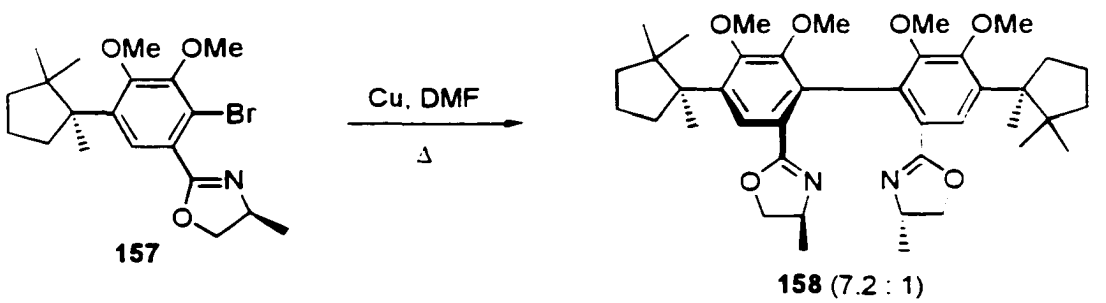
3.77 (s, 3H), 3.84 (s, 3H), 4.13 (m, 2H), 4.38 (dd, J = 12.9, 11.4, 1H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 18.9, 20.4, 23.7, 25.4, 27.0, 32.7, 39.3, 41.2, 44.8, 51.7, 59.9, 60.4, 70.1, 72.9, 115.7, 124.7, 126.5, 140.6, 151.3, 155.7, 162.9; IR (thin film) 1658 cm^{-1}.



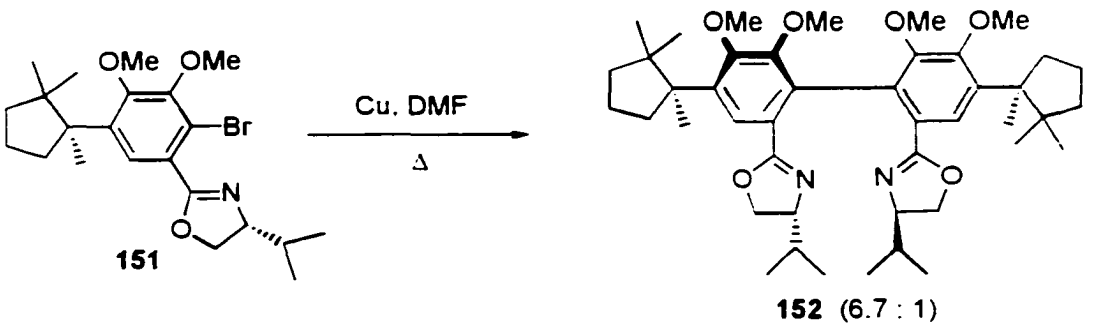
(*S*)-*t*-Leucinol-bisoxazoline, 115. A 10 mL flask with stirbar was charged with **116** (300 mg, 0.66 mmol), freshly activated[55] Cu(150 mg, 2.3 mmol), and DMF (1 mL). The mixture was heated to 95 °C for 8 h and then diluted with DMF (5 mL). A condenser was affixed and the mixture was heated to reflux. After 3 d, the mixture was filtered through cotton to remove excess Cu, poured into water, and extracted into ether (3X). The organics were washed with water (2X), then brine, dried over Na_2SO_4, and concentrated. Flash chromatography (5%-50% EtOAc/Hex) gave the biaryl as its copper complex. This was taken up in ether, washed with NH_4OH (2X), brine, and dried over Na_2SO_4 to yield the 0.158 g (64%) as a single atropisomer. **Major, 115**: $[\alpha]^{25}_D$ = -50.6 (c = 1.1, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 18H), 0.75 (s, 6H), 1.15 (s, 6H), 1.37 (s, 6H), 1.50-1.90 (m, 10H), 2.68 (m, 2H), 3.55 (s, 6H), 3.71 (m, 4H), 3.79 (s, 6H), 3.92 (dd, J = 9.6, 8.1, 2H), 7.76 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6,

24.4, 25.3, 26.1, 27.3, 33.8, 38.9, 41.3, 45.1, 51.7, 59.6, 60.0, 68.1, 76.3, 123.0, 125.2, 131.0, 139.3, 151.3, 154.7, 163.4; IR (thin film) 1655 cm^{-1}. Anal. Calcd for $C_{40}H_{68}N_2O_6$: C 74.16, H 9.20; Found: C 73.92, H 9.31.

Minor, 147: $[\alpha]^{25}_D$ = -13.0 (c = 1.2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (s, 18H), 0.77 (s, 6H), 1.15 (s, 6H), 1.36 (s, 6H), 1.50-1.90 (m, 10H), 2.69 (m, 2H), 3.59 (s, 6H), 3.73 (m, 10H), 3.81 (s, 6H), 3.95 (dd, J = 9.6, 7.8, 2H), 7.59 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.5, 25.5, 26.1, 27.2, 33.8, 39.2, 41.2, 45.1, 51.8, 59.5, 60.1, 67.8, 76.7, 122.1, 125.2, 131.4, 139.3, 151.8, 154.9, 163.0; IR (thin film) 1654 cm^{-1}



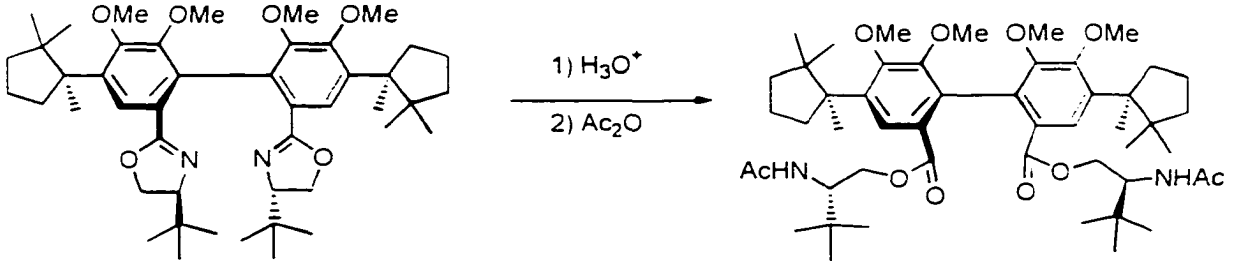
(*S*)-Alaninol-bisoxazoline, 158. Prepared from **157** by the same procedure as **115** in 66% yield as an amorphous solid. **Major**: $[\alpha]^{25}_D$ = -87.9 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.69 (s, 6H), 1.12 (d, 6H), 1.13 (s, 6H), 1.38 (s, 6H), 1.50-1.90 (m, 10H), 2.71 (m, 2H), 3.50 (m, 2H), 3.52 (s, 6H), 3.79 (s, 6H), 4.07 (m, 4H), 7.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 21.4, 24.1, 25.6, 27.3, 39.0, 41.3, 45.2, 51.8, 59.5, 60.1, 62.0, 73.9, 122.8, 125.2, 130.4, 139.7, 151.5, 154.9, 164.3; IR (thin film) 1651 cm^{-1}.



151

152 (6.7 : 1)

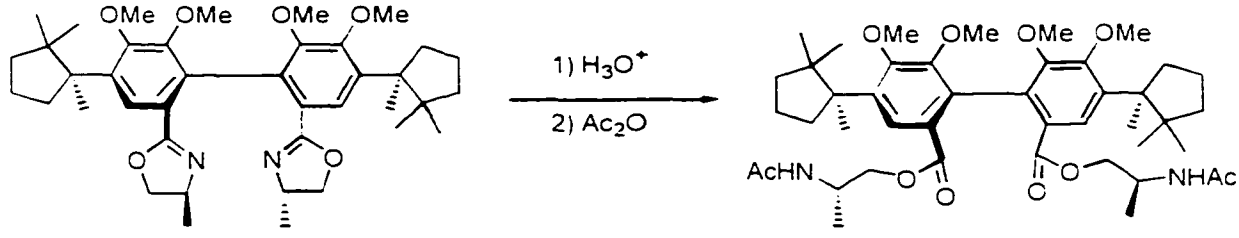
(*R*)-Valinol-bisoxazoline, 152. Prepared from **151** by the same procedure as **115** in 74% yield as an amorphous solid. **Major**: $[\alpha]^{25}_{D}$ = +43.9 (c = 1.3, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (d, *J* = 6.6, 6H), 0.72 (s, 6H), 0.79 (d, *J* = 6.6, 6H), 1.15 (s, 6H), 1.41 (s, 6H), 1.45-1.85 (m, 12H), 2.62 (m, 2H), 3.58 (s, 6H), 3.63 (m, 4H), 3.83 (s, 6H), 3.95 (dd, *J* = 8.7, 7.2, 2H), 7.57 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 19.1, 20.4, 23.5, 25.4, 27.1, 32.8, 39.4, 41.2, 44.7, 51.5, 59.2, 59.9, 69.6, 72.7, 122.3, 124.6, 131.0, 139.1, 151.2, 154.7, 163.4; IR (thin film) 1652 cm^{-1}; Anal. Calcd for $C_{44}H_{64}N_2O_6$: C 73.71, H 9.00, N 3.91; Found: C 73.53, H 9.01, N 3.73.



115

(*S*)-*t*-Leucinol derived bis-acetamide. 115 (95 mg, 0.13 mmol) was dissolved in THF (2 mL) and 1 N HCl (2 mL). The solution was stirred at rt for 3 d. It was poured into saturated $NaHCO_3$ and extracted into ether (3X), washed with brine, dried over Na_2SO_4, and concentrated to give the crude intermediate bisaminoester. The residue was dissolved

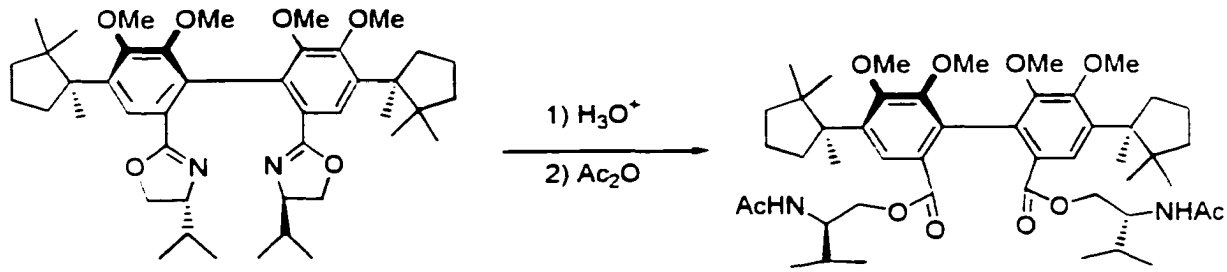
in CH_2Cl_2 (5 mL), and treated with Ac_2O (30 μL, 0.31 mmol), Et_3N (50 μL, 0.35 mmol), and a crystal of DMAP. After stirring 2 h, the solution was poured into saturated $NaHCO_3$, extracted into CH_2Cl_2 (3X), dried over Na_2SO_4, and concentrated. Flash chromatography (50% EtOAc/Hex) gave 0.103 g (94%) of the (*S*)-*t*-Leucinol derived bis-acetamide as an amorphous solid. $[\alpha]^{25}_D$ = -68.5 (c = 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.66 (s, 6H), 0.82 (s, 18H), 1.10 (s, 6H), 1.40 (s, 6H), 1.45-1.85 (m, 10H), 1.87 (s, 6H), 2.58 (m, 2H), 3.33 (s, 6H), 3.80 (s, 6H), 3.94 (m, 4H), 4.27 (m, 2H), 5.75 (d, *J* 9.6, 2H), 7.75 (s, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.5, 23.7, 25.5, 27.0, 27.0, 34.1, 39.4, 41.2, 45.1, 51.9, 55.8, 59.3, 60.2, 63.9, 124.6, 126.2, 131.0, 139.8, 151.0, 156.5, 167.4, 170.0; IR (thin film) 3305(br), 1727, 1660 cm^{-1}.



158

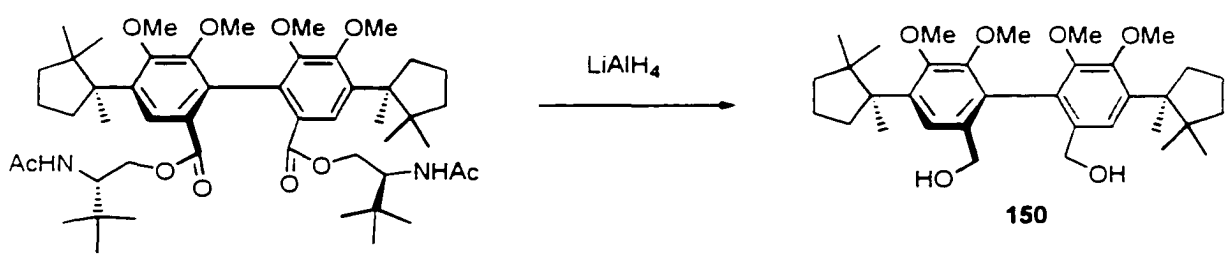
(*S*)-Alaninol derived bis-acetamide. The (*S*)-alaninol derived bis-acetamide was prepared from **158** by the same procedure used to prepare the (*S*)-*t*-leucinol derived bis-acetamide (*en route* to **150**) in 93% yield as an amorphous solid. $[\alpha]^{25}_D$ = -63.1 (c = 3.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 6H), 0.73 (d, *J* = 6.6, 6H), 1.14 (s, 6H), 1.39 (s, 6H), 1.50-1.90 (m, 10H), 1.89 (s, 6H), 2.56 (m, 2H), 3.41 (s, 6H), 3.83 (s, 6H), 3.89 (dd, *J* = 11.1, 4.2, 2H), 4.09 (m, 4H), 5.71 (d, *J* = 7.8, 2H), 7.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4, 20.6, 23.4, 23.7, 25.5, 27.1, 39.7, 41.3, 44.0, 45.0, 52.0, 59.5,

60.2, 68.4, 124.4, 126.7, 131.0, 140.8, 151.1, 156.9, 168.3, 169.7; IR (thin film) 3292(br), 1713, 1657 cm^{-1}.



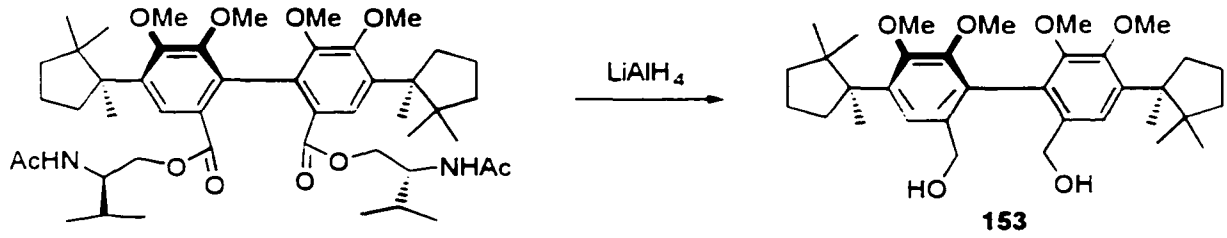
152

(*R*)-Valinol derived bis-acetamide. The (*R*)-valinol derived bis-acetamide was prepared from **152** by the same procedure used to prepare the (*S*)-*t*-leucinol derived bis-acetamide (*en route* to **150**) in 93% yield as an amorphous solid. $[\alpha]^{25}_D$ = +23.5 (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (m, 18H), 1.10 (s, 6H), 1.25-1.90 (m, 12H), 1.35 (s, 6H), 1.88 (s, 6H), 2.69 (m, 2H), 3.41 (s, 6H), 3.75 (m, 2H), 3.78 (s, 6H), 3.95 (dd, *J* 11.7, 3.6, 2H), 4.07 (dd, *J* = 11.4, 5.7, 2H), 5.78 (d, *J* = 9.0, 2H), 7.82 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 19.3, 20.4, 23.3, 24.5, 25.0, 26.9, 29.2, 38.4, 40.8, 45.3, 51.7, 53.5, 59.6, 60.1, 65.2, 123.9, 126.8, 131.2, 140.2, 151.3, 156.7, 167.9, 169.9; IR (thin film) 3305(br), 1726, 1652 cm^{-1}.



150

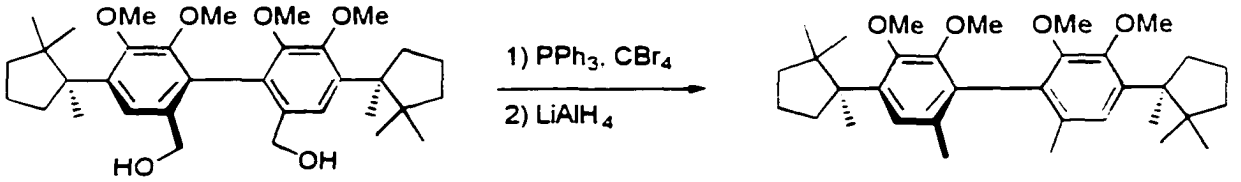
Biaryldiol. 150. To a stirred suspension of $LiAlH_4$ (46 mg, 1.2 mmol) in THF (5 mL, 0 °C) was added the (*S*)-*t*-leucinol derived bis-acetamide (200 mg, 0.23 mmol) The solution was warmed to rt and stirred 2 h. The solution was quenched by addition of MeOH, followed by 20% aq. KOH. The solid was filtered and the eluent was concentrated. Column chromatography (20% EtOAc/Hex) gave 115 mg (90%) of the diol as an amorphous solid. $[\alpha]^{25}_D$ = +71.5 (c = 1.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 6H), 1.14 (s, 6H), 1.43 (s, 6H), 1.45-1.75 (m, 10H), 2.60 (m, 2H), 3.09 (bs, 2H), 3.54 (s, 6H), 3.79 (s, 6H), 4.14 (d, *J* = 11.7, 2H),4.20 (d, *J* = 11.1, 2H), 7.26 (s, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 23.7, 25.6, 27.2, 39.4, 41.3, 45.2, 51.9, 60.0, 60.3, 64.4, 126.2, 127.9, 134.4, 141.2, 150.7, 152.8; IR (thin film) 3362(br) cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_6$: C 73.61, H 9.08; Found: C 73.77, H 9.19.



153

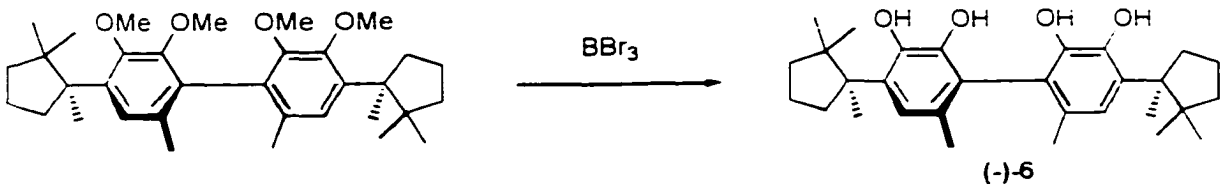
Biaryldiol, 153. Diol **153** was prepared from the (*R*)-valinol derived bis-acetamide by the same procedure used to prepare **150** in 96% yield as an amorphous solid. $[\alpha]^{25}_D$ = -70.2 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.71 (s, 6H), 1.13 (s, 6H), 1.40 (s, 6H), 1.50-1.90 (m, 12H), 2.53 (bs, 2H), 2.80 (m, 2H), 3.55 (s, 6H), 3.78 (s, 6H), 4.22 (bs, 4H), 7.26 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 24.5, 25.2, 27.1, 38.6, 40.8, 45.2,

51.9, 59.9, 60.4, 63.7, 126.1, 128.2, 133.8, 140.7, 150.9, 152.8; IR (thin film) 3289(br) cm^{-1}. Anal. Calcd for $C_{34}H_{50}O_6$: C 73.61, H 9.08; Found: C 73.62, H 9.23.



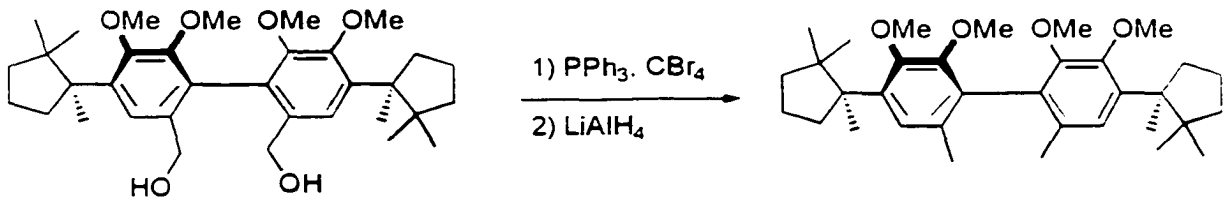
150

Tetramethylmastigophorene A. To a stirred solution of diol **150** (40 mg, 0.072 mmol) in THF (1.5 mL) was added PPh_3 (45 mg, 0.17 mmol) and CBr_4 (60 mg, 0.18 mmol) in one portion. After 30 min, TLC still showed additional starting material, so additional PPh_3 (38 mg, 0.14 mmol) and CBr_4 (48 mg, 0.14 mmol) was added in one portion. After 10 min, the solution was quenched by addition of MeOH, concentrated, and filtered through silica, eluting with CH_2Cl_2. The crude dibromide was dissolved in ether (1.5 mL) and treated with $LiAlH_4$ (1 M in ether, 0.5 mL, 0.5 mmol). The solution was stirred 2 h and quenched by cautious addition of MeOH, then 20% aq. KOH. The white precipitate was filtered. Column chromatography (2% EtOAc/Hex) of the eluent gave 33 mg (88%) of tetramethylmastigophorene A as a crystalline solid. mp 154-156 °C. $[\alpha]^{25}_D$ = −8.68 (c = 1.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 6H), 1.13 (s, 6H), 1.41 (s, 6H), 1.45-1.85 (m, 10H), 1.94 (s, 6H), 2.68 (m, 2H), 3.56 (s, 6H), 3.76 (s, 6H), 6.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 20.7, 24.2, 25.5, 27.1, 39.0, 41.1, 45.2, 51.7, 59.7, 60.2, 125.1, 129.8, 130.7, 139.2, 151.1, 151.3.



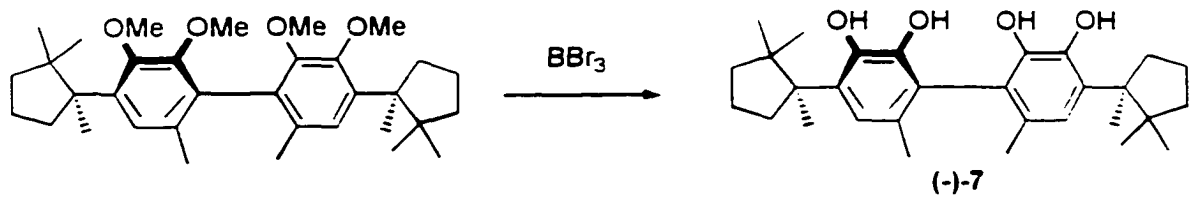
(-)-6

(-)-Mastigophorene A, 6. **6** was prepared from tetramethylmastigophorene A by the action of BBr_3 (10 eq), utilizing the same procedure used to prepare **1** in 84% yield. $[\alpha]^{25}_D$ = -67.6 (c = 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 6H), 1.19 (s, 6H), 1.44 (s, 6H), 1.45-1.85 (m, 10H), 1.92 (s, 6H), 2.67 (m, 2H), 4.69 (s, 2H), 5.56 (s, 2H), 6.84 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3, 20.5, 22.8, 25.6, 27.2, 38.9, 41.2, 45.0, 51.4, 116.9, 122.8, 126.7, 133.9, 140.5, 141.6; IR (thin film) 3526, 2958, 1222 cm^{-1}. Anal. Calcd for $C_{30}H_{42}O_4 \cdot 2/3H_2O$[4]: C 75.27, H 9.12; Found: C 75.60, H 9.08. Spectra are in complete agreement with those previously reported.[3]



153

Tetramethylmastigophorene B. Tetramethylmastigophorene B was prepared from **153** by the same procedure used to prepare tetramethylmastigophorene A (*en route* to **6**) in 89% yield as a crystalline solid. $[\alpha]^{25}_D$ = -26.2 (c = 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.70 (s, 6H), 1.12 (s, 6H), 1.40 (s, 6H), 1.50-1.85 (m, 10H), 1.90 (s, 6H), 2.70 (m, 2H), 3.56 (s, 6H), 3.76 (s, 6H), 6.95 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 20.7, 24.4, 25.5, 27.1, 39.0, 41.1, 45.2, 51.7, 59.7, 60.3, 125.3, 130.0, 130.3, 139.1, 151.1, 151.3.



(-)-7

(-)-Mastigophorene B. 7. 7 was prepared from tetramethylmastigophorene B by the action of BBr_3 (10 eq), utilizing the same procedure used to prepare **1** in 90% yield. $[\alpha]^{25}_D$ = +38.0 (c = 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.79 (s, 6H), 1.21 (s, 6H), 1.47 (s, 6H), 1.50-1.80 (m, 10H), 1.92 (s, 6H), 2.62 (m, 2H), 4.76 (s, 2H), 5.58 (s, 2H), 6.85 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 20.6, 22.6, 25.7, 27.2, 39.2, 41.3, 45.0, 51.4, 117.1, 122.7, 126.8, 133.9, 140.7, 141.6; **IR** (thin film) 3531, 2961, 1226 cm^{-1}. Spectra are in complete agreement with those previously reported.[3]

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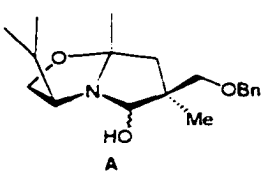
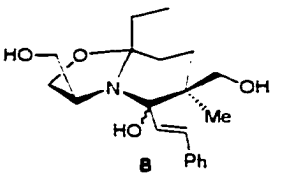
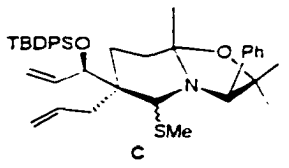
(47) The following substrates (**A-C**) have been hydrolyzed using KH_2PO_3, providing results similar to those observed using $Bu_4NH_2PO_3$.







(48) (a) Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* **1955**, 2056. (b) Barton, D.H.R.; Ives, D.A.J.; Thomas, B.R. *J. Chem. Soc.* **1954**, 903. (c) Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *71*, 3301.

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(53) The stereochemistry about the biaryl axis was assigned by comparison to previous studies of the oxazoline-mediated asymmetric Ullmann coupling.[35] It was not until completion of the syntheses of **2** and **3** that the assignment was verified.

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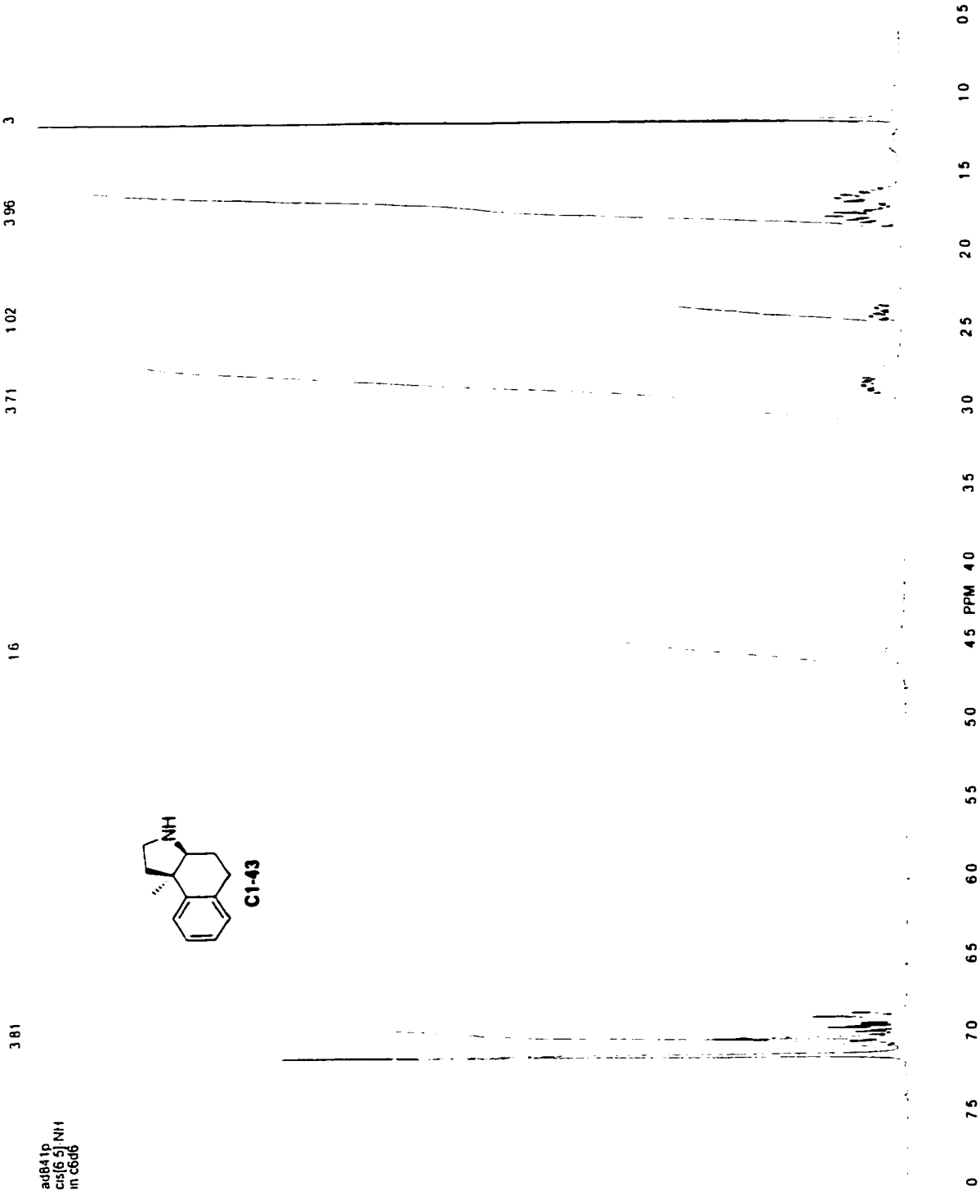
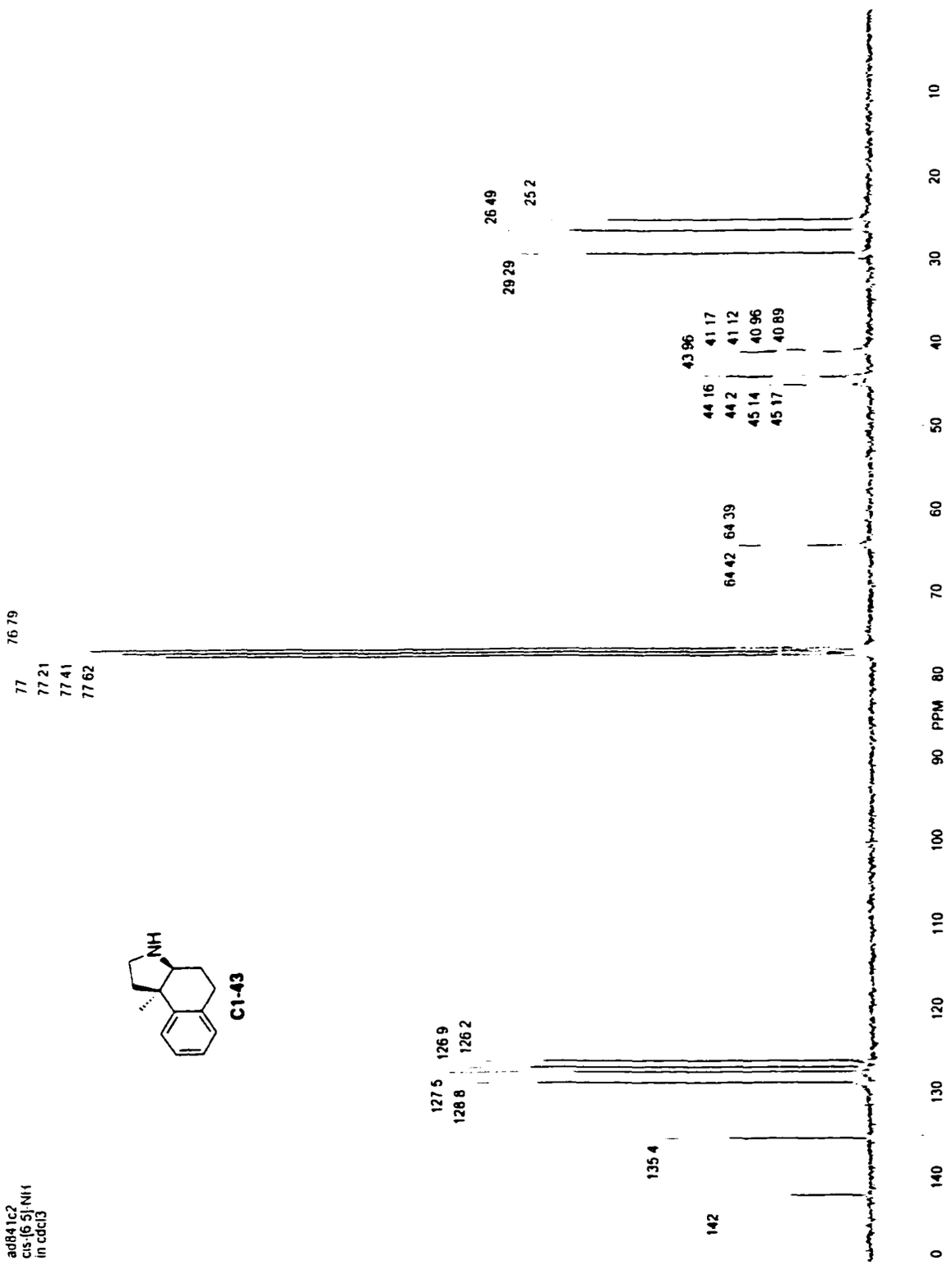
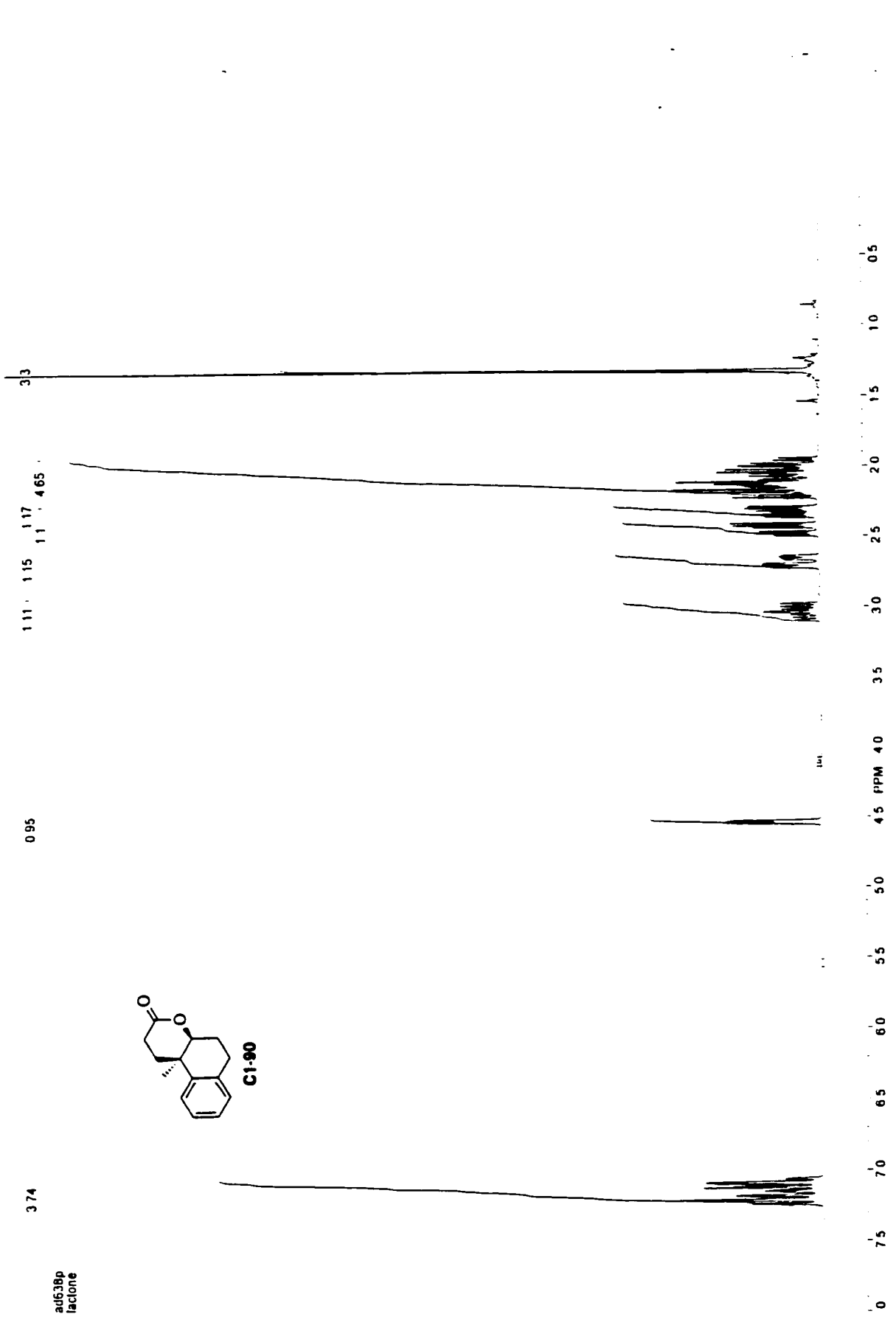
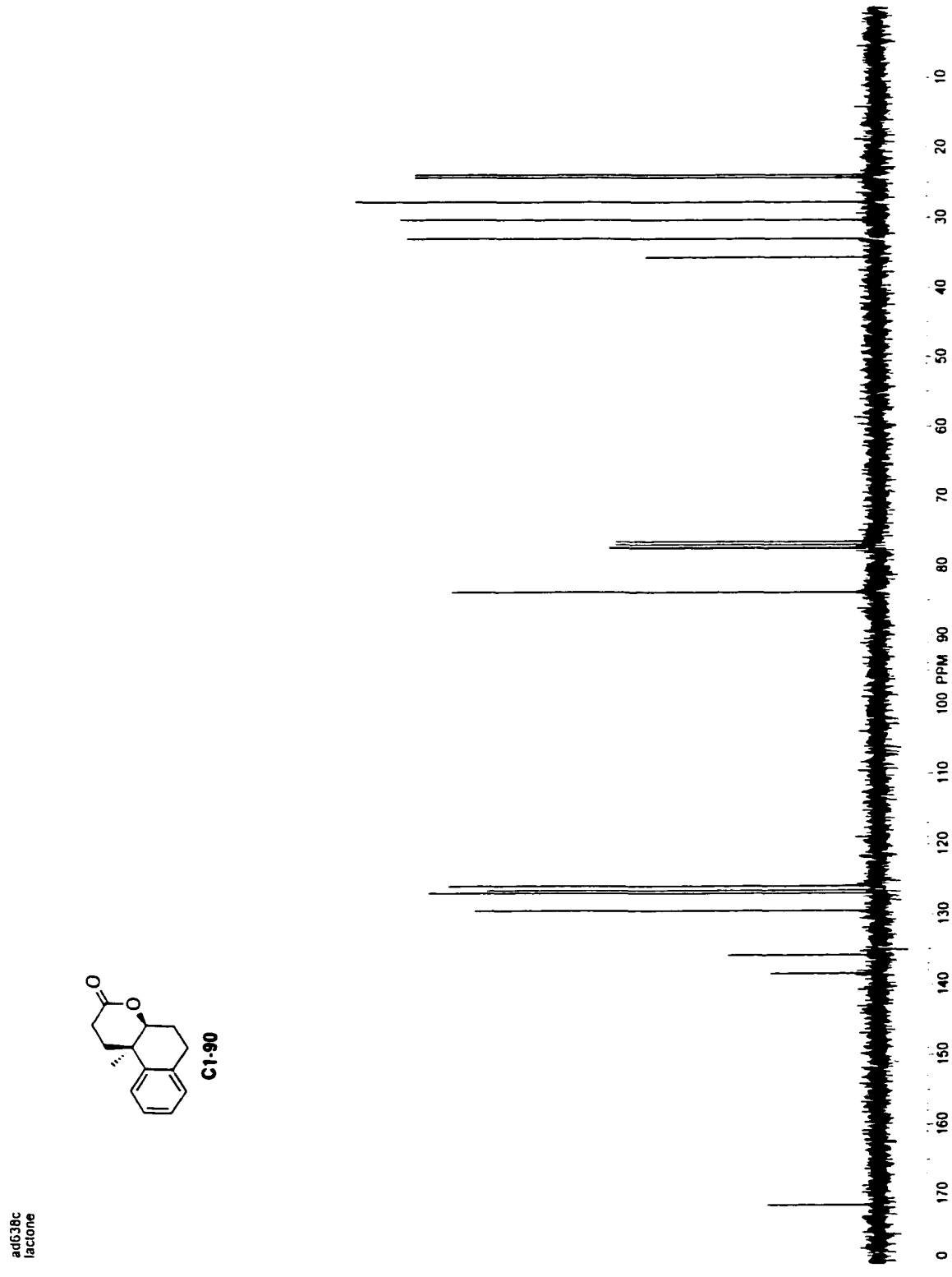
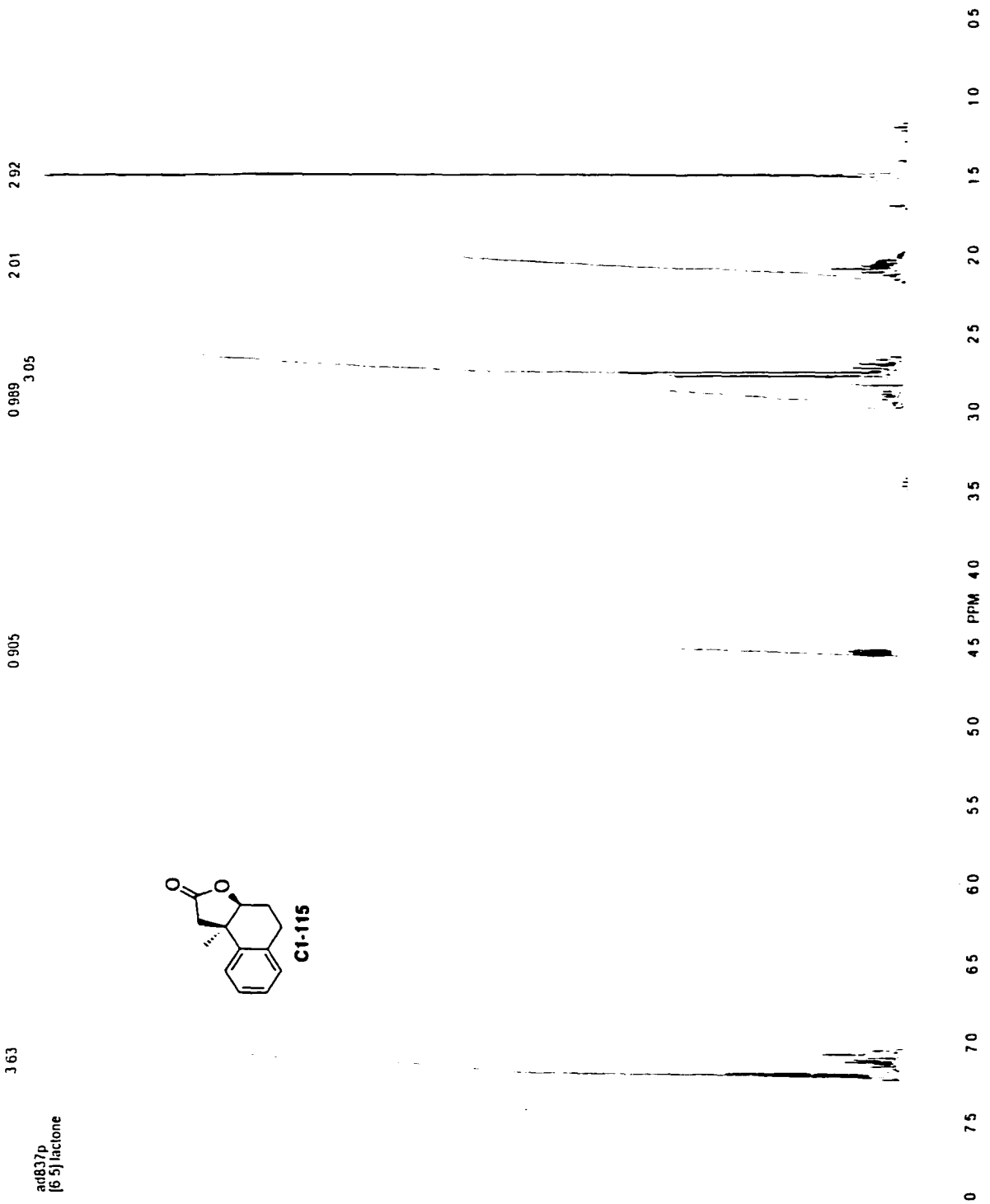
Appendix - Selected ^{1}H and ^{13}C NMR Spectra

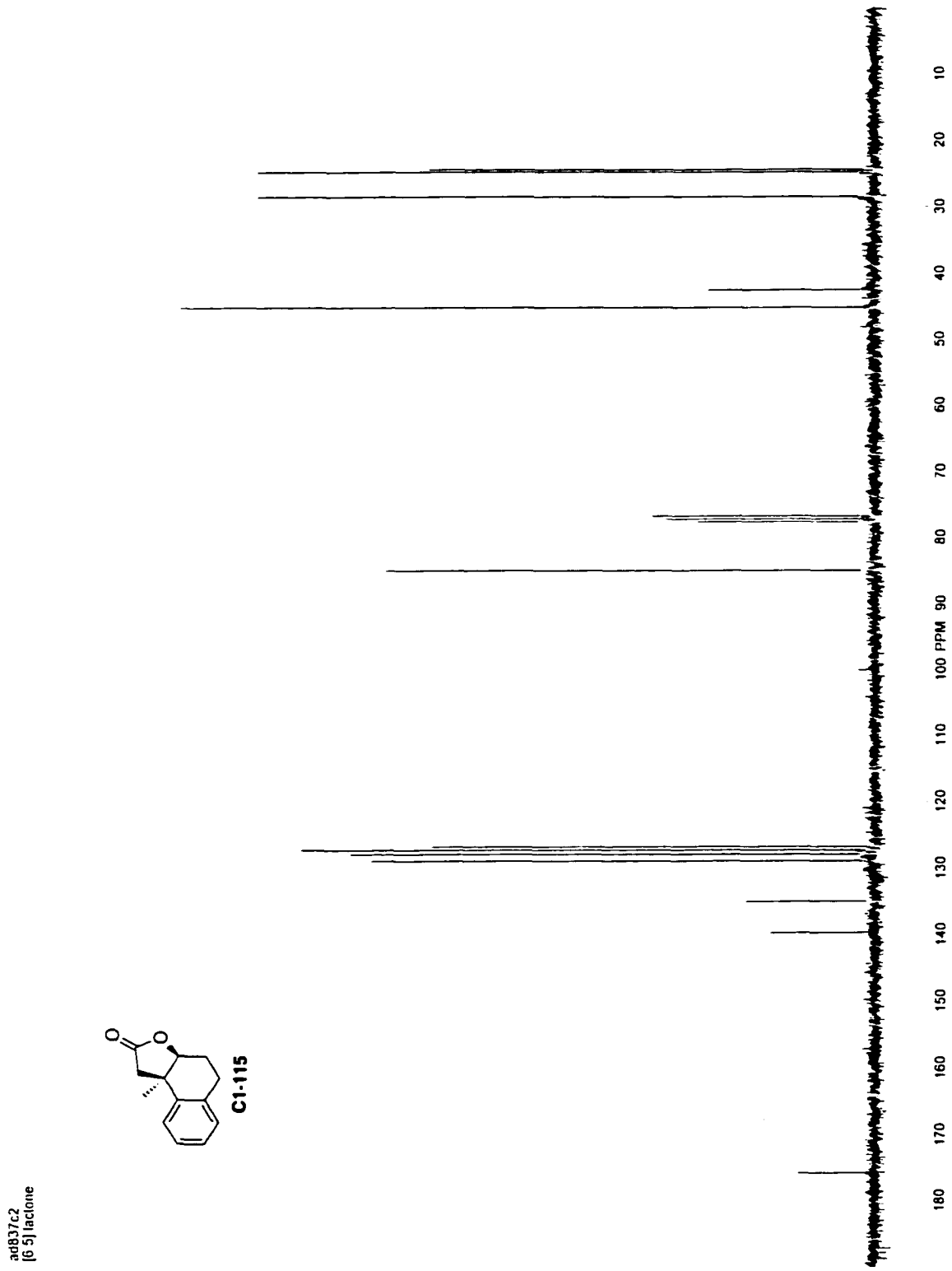


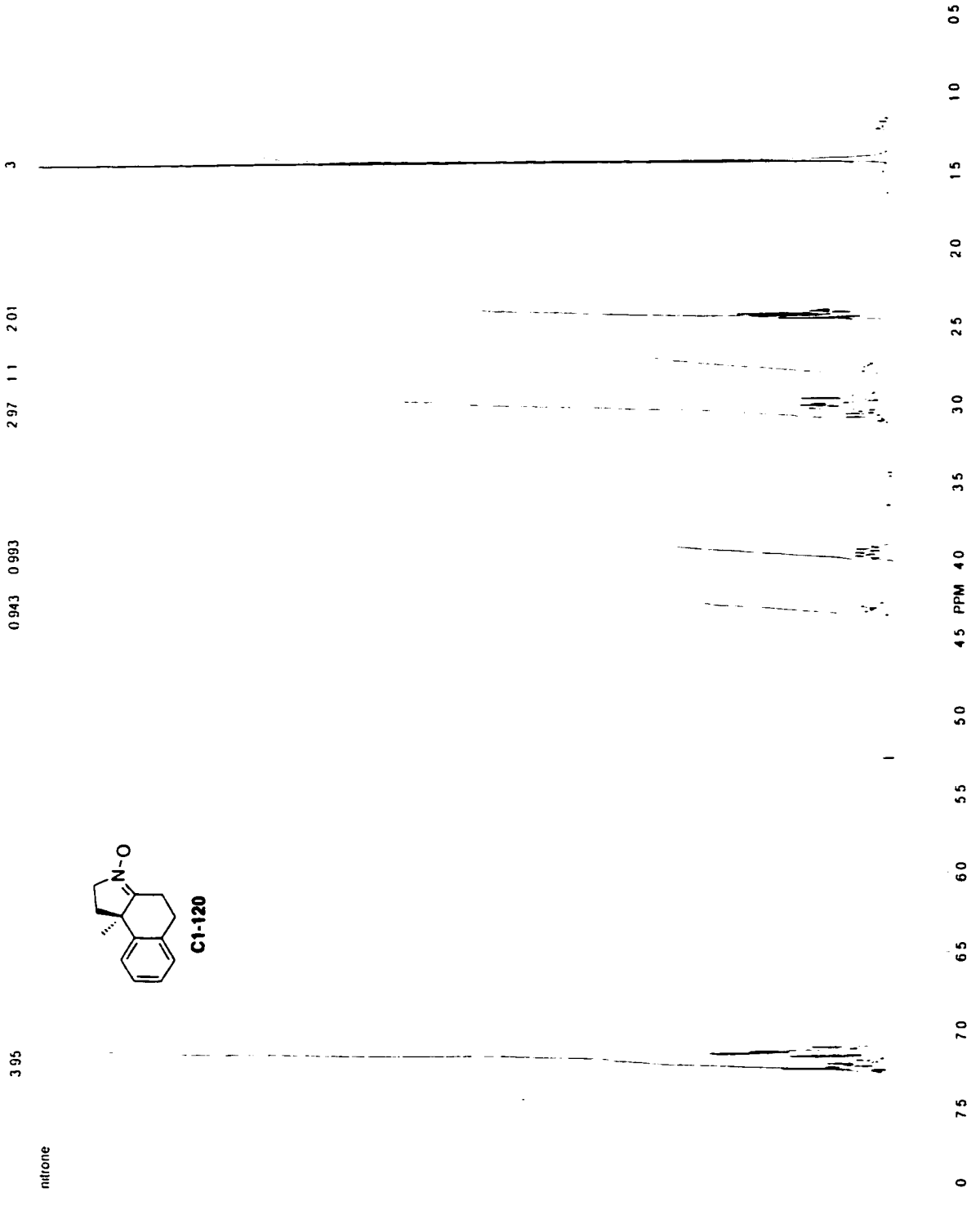


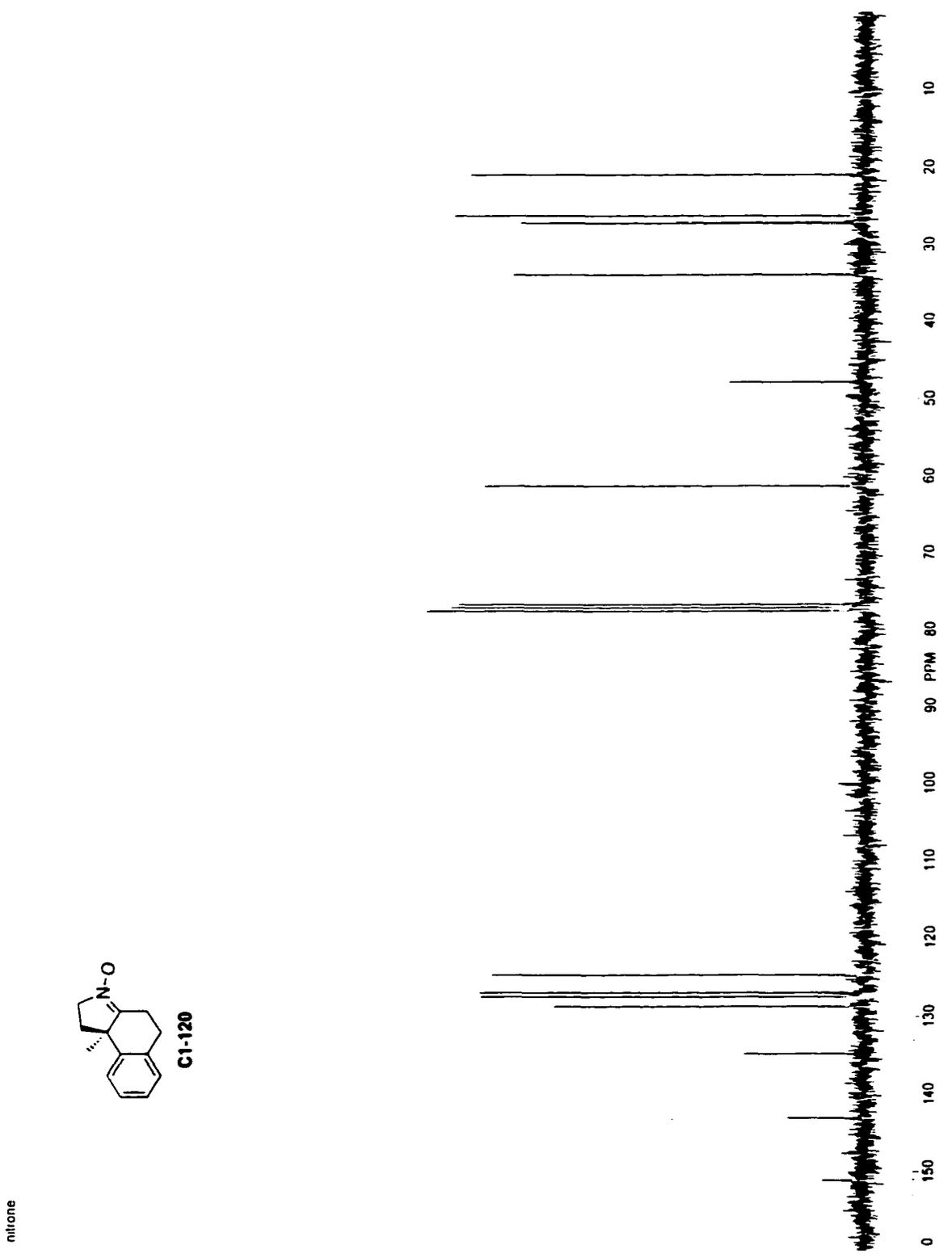


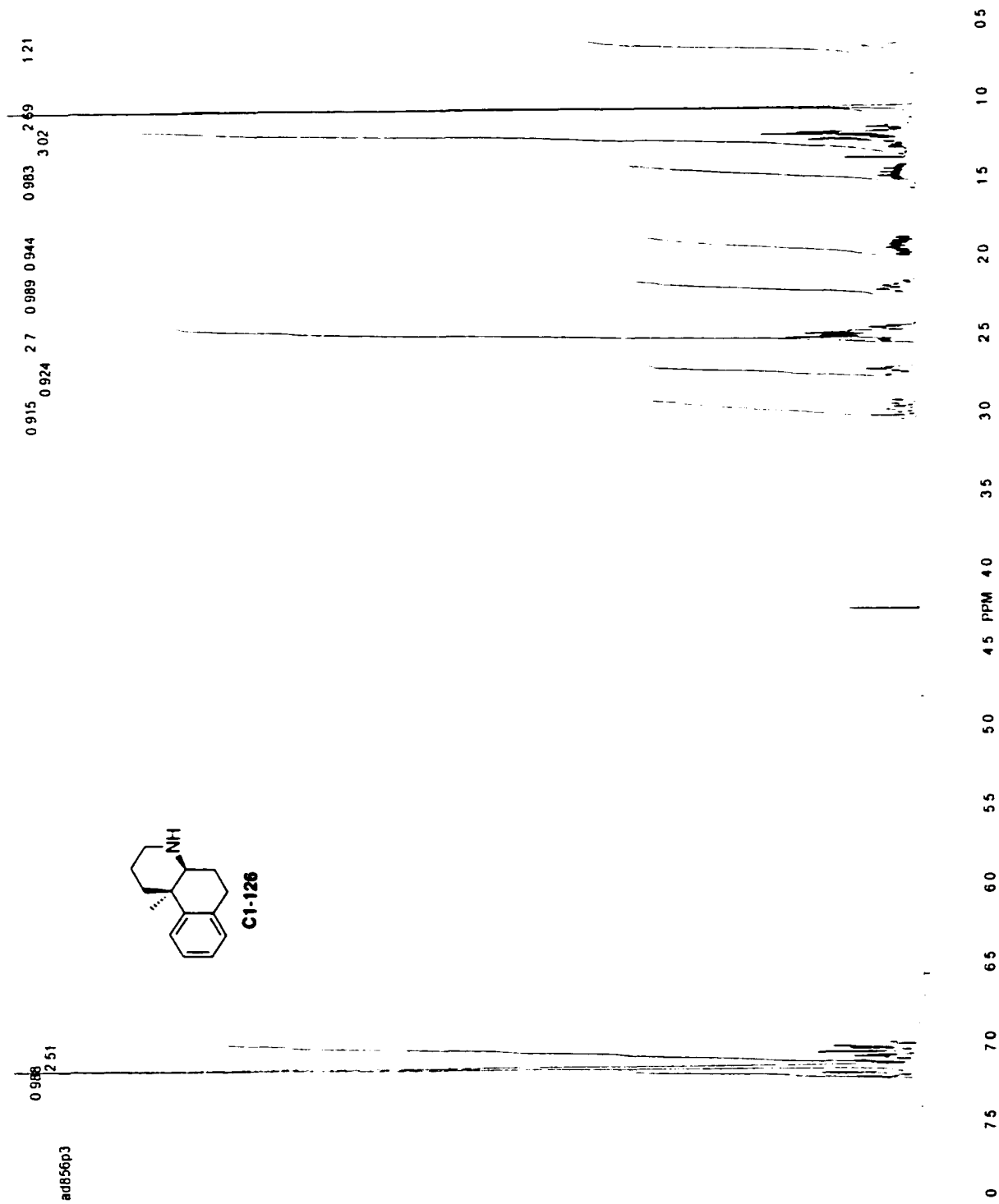


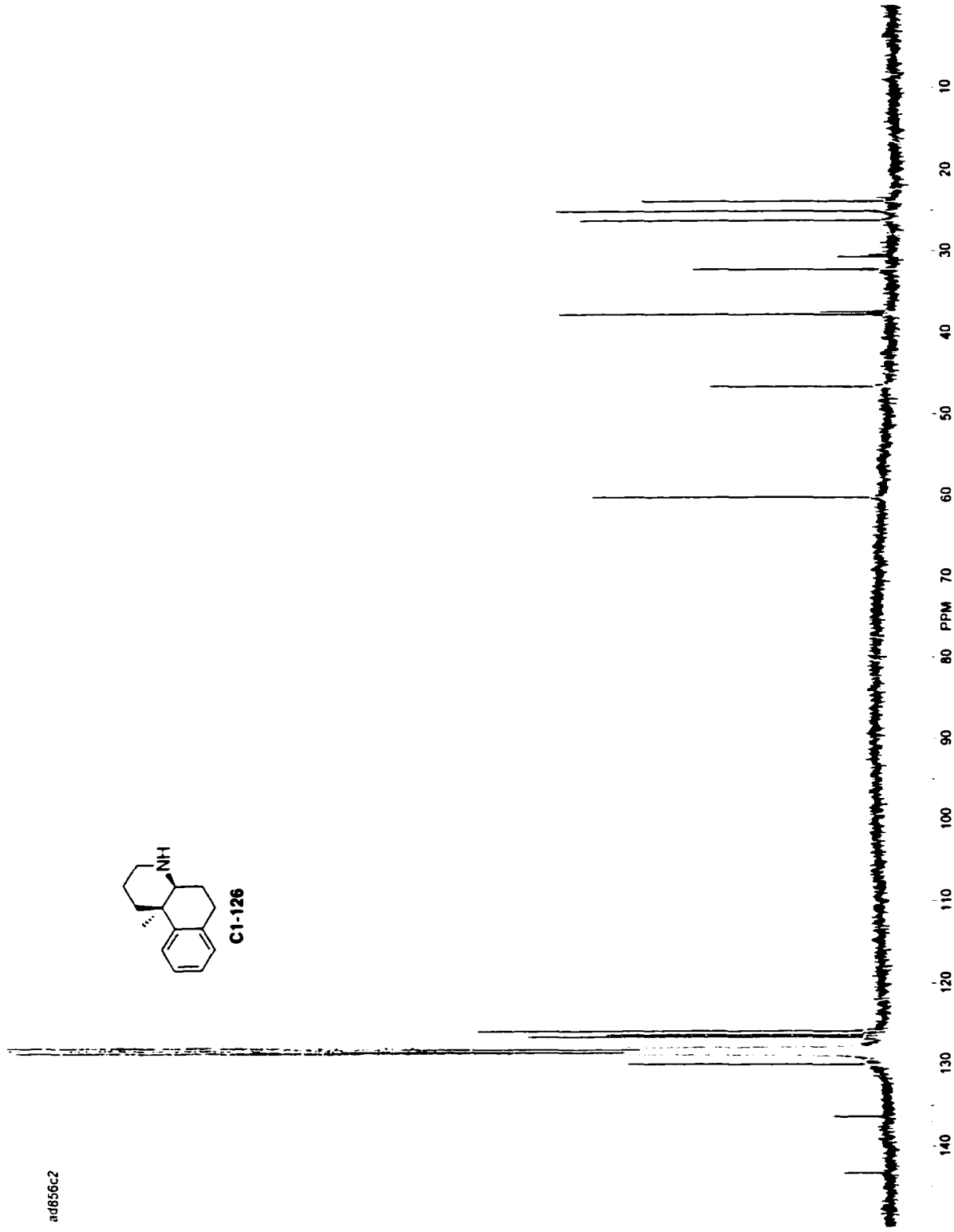


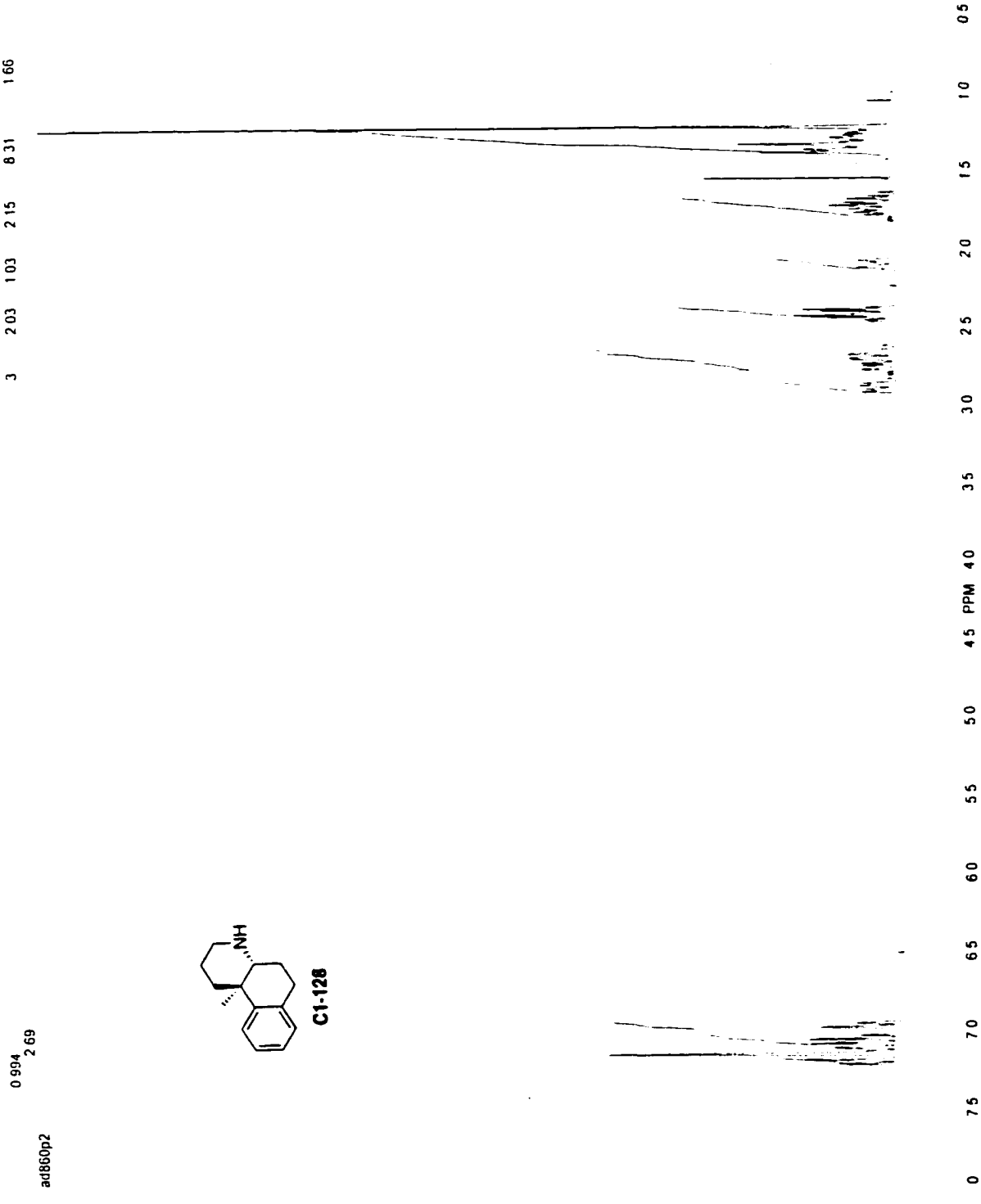


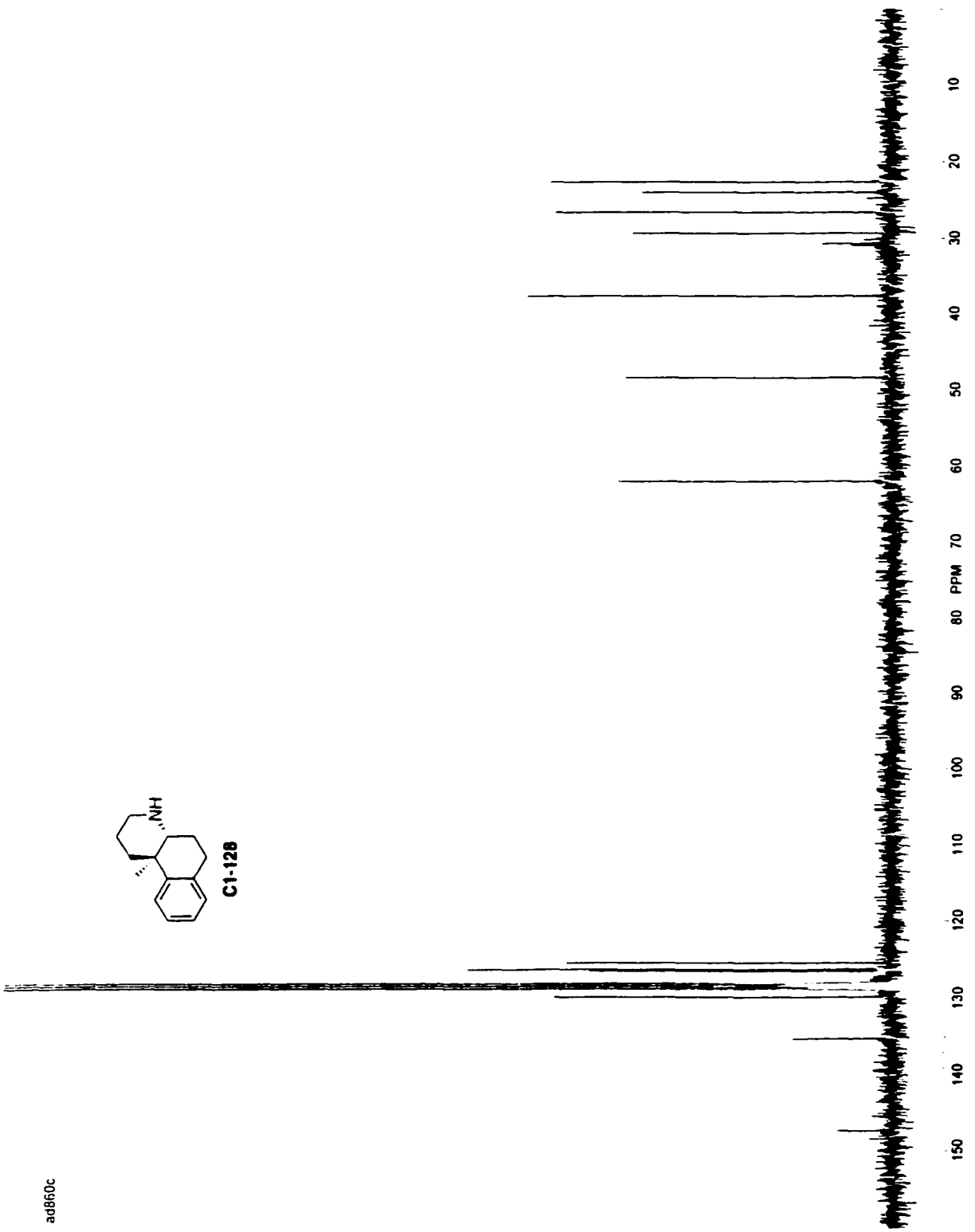


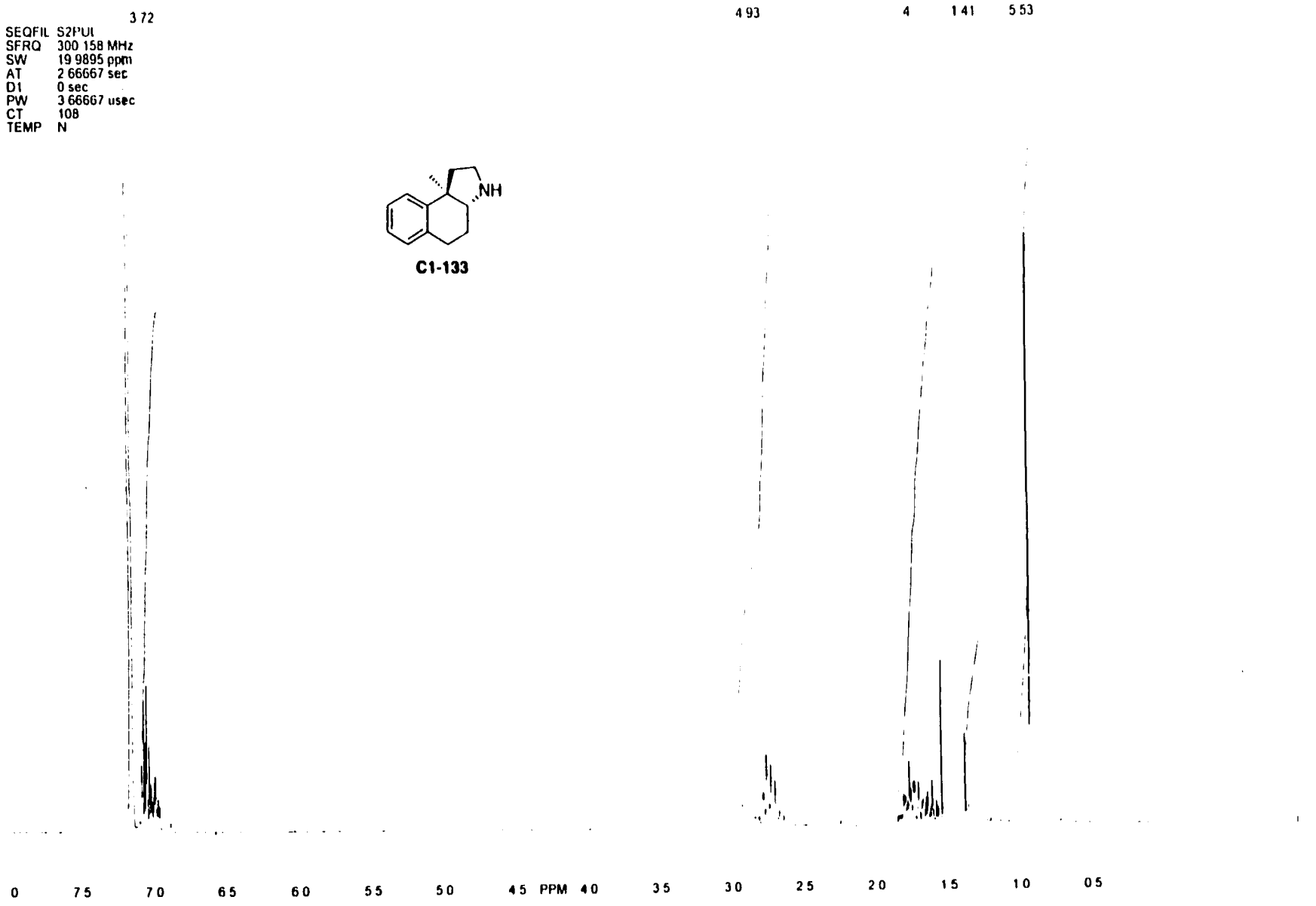


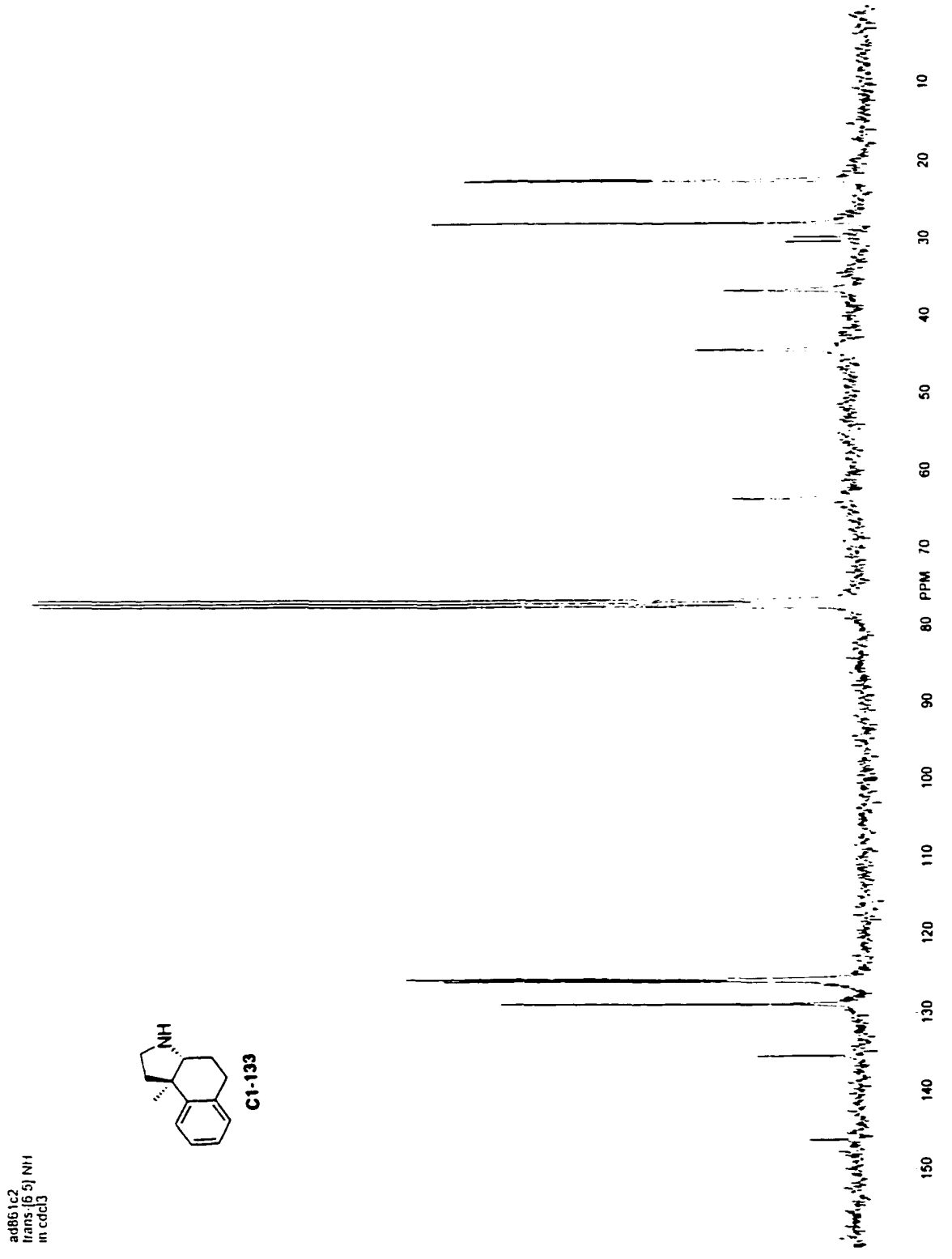


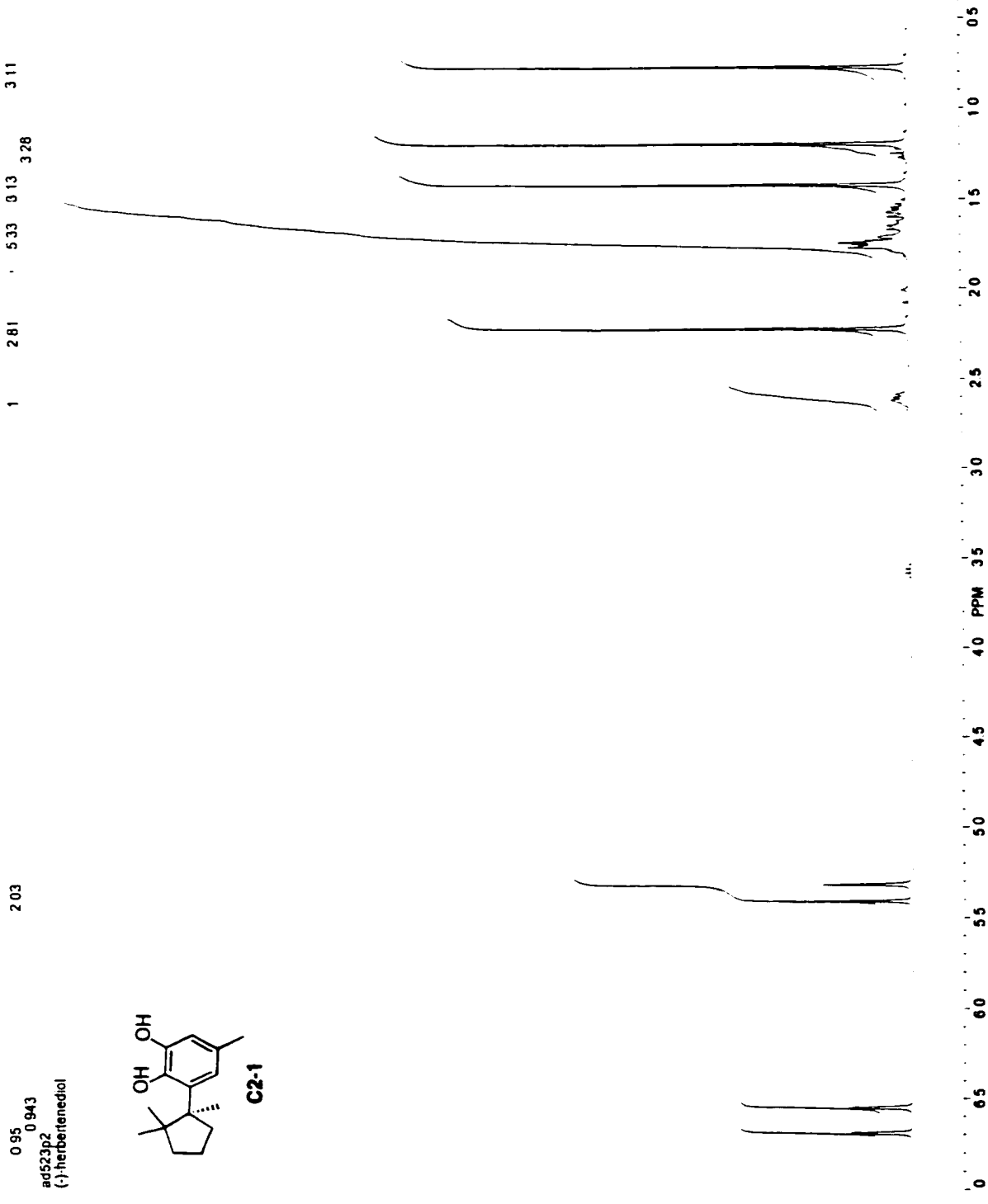




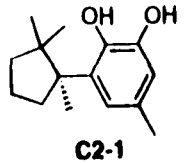




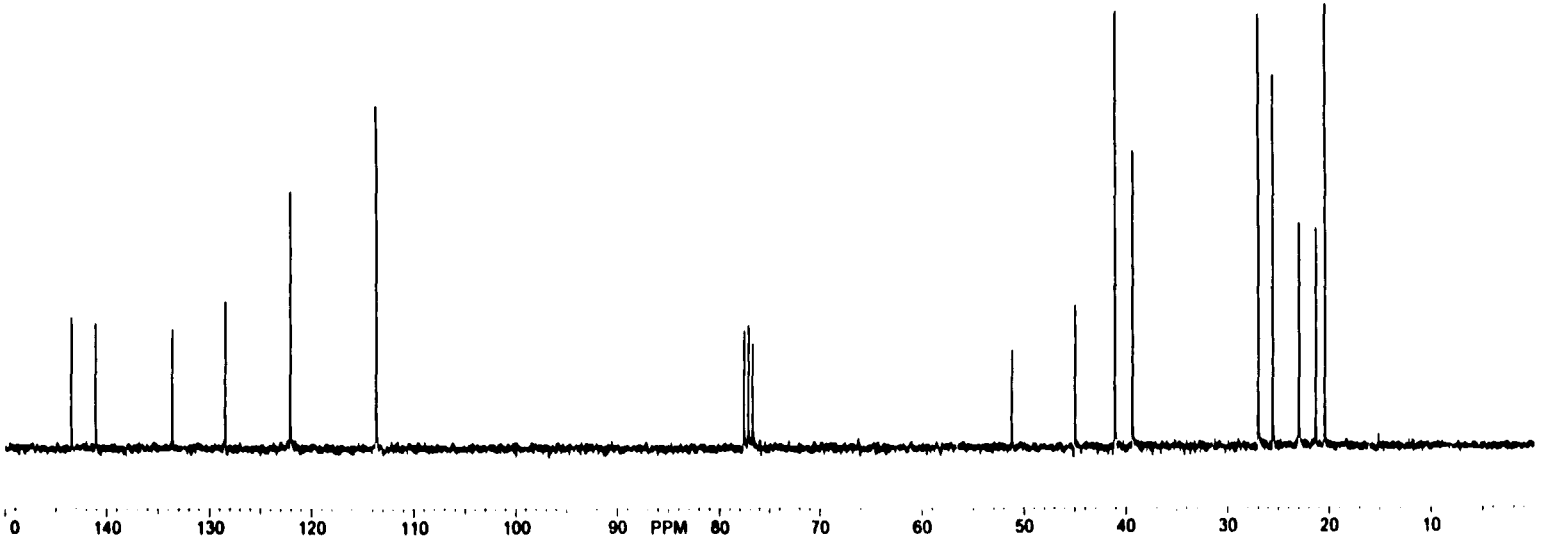


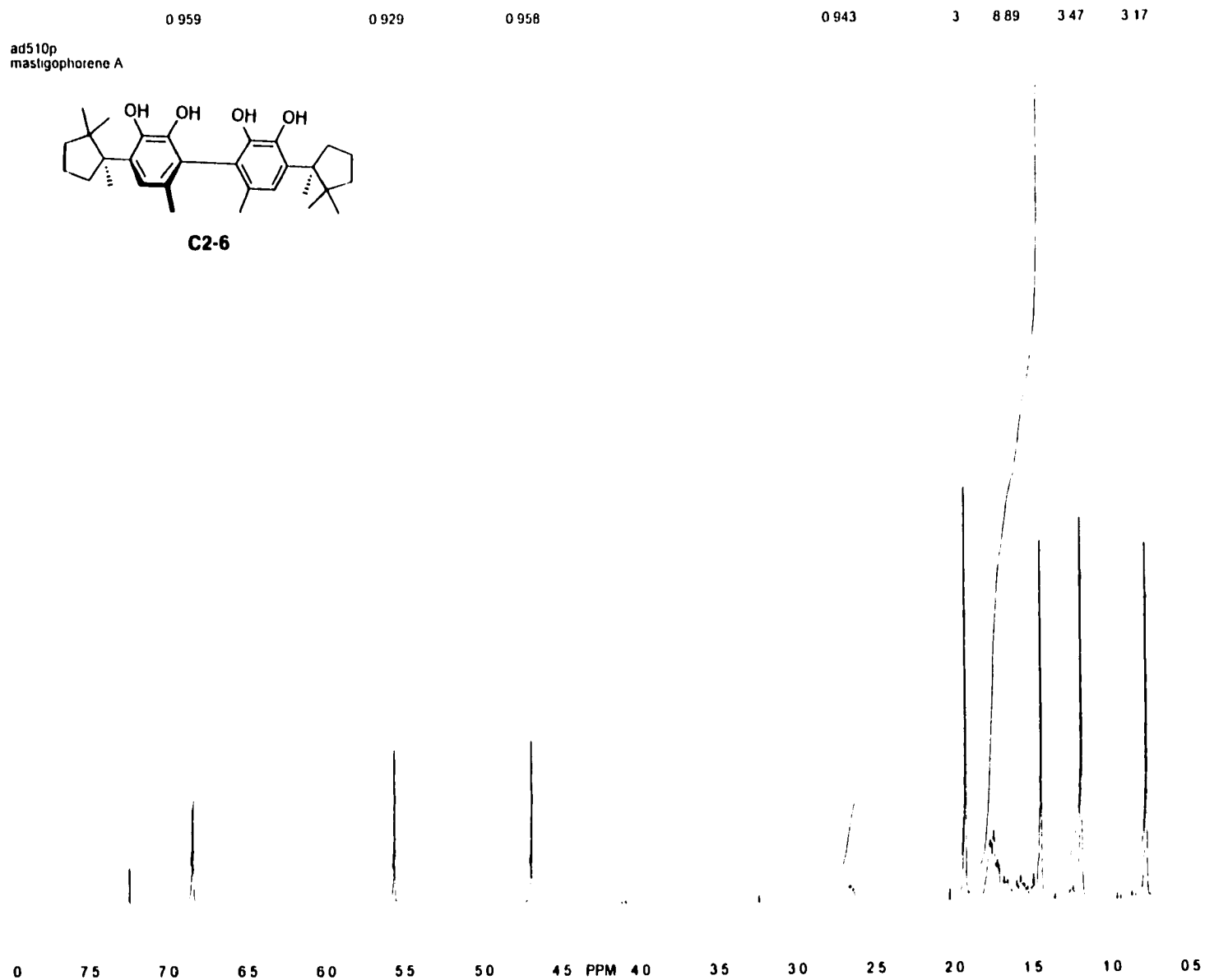


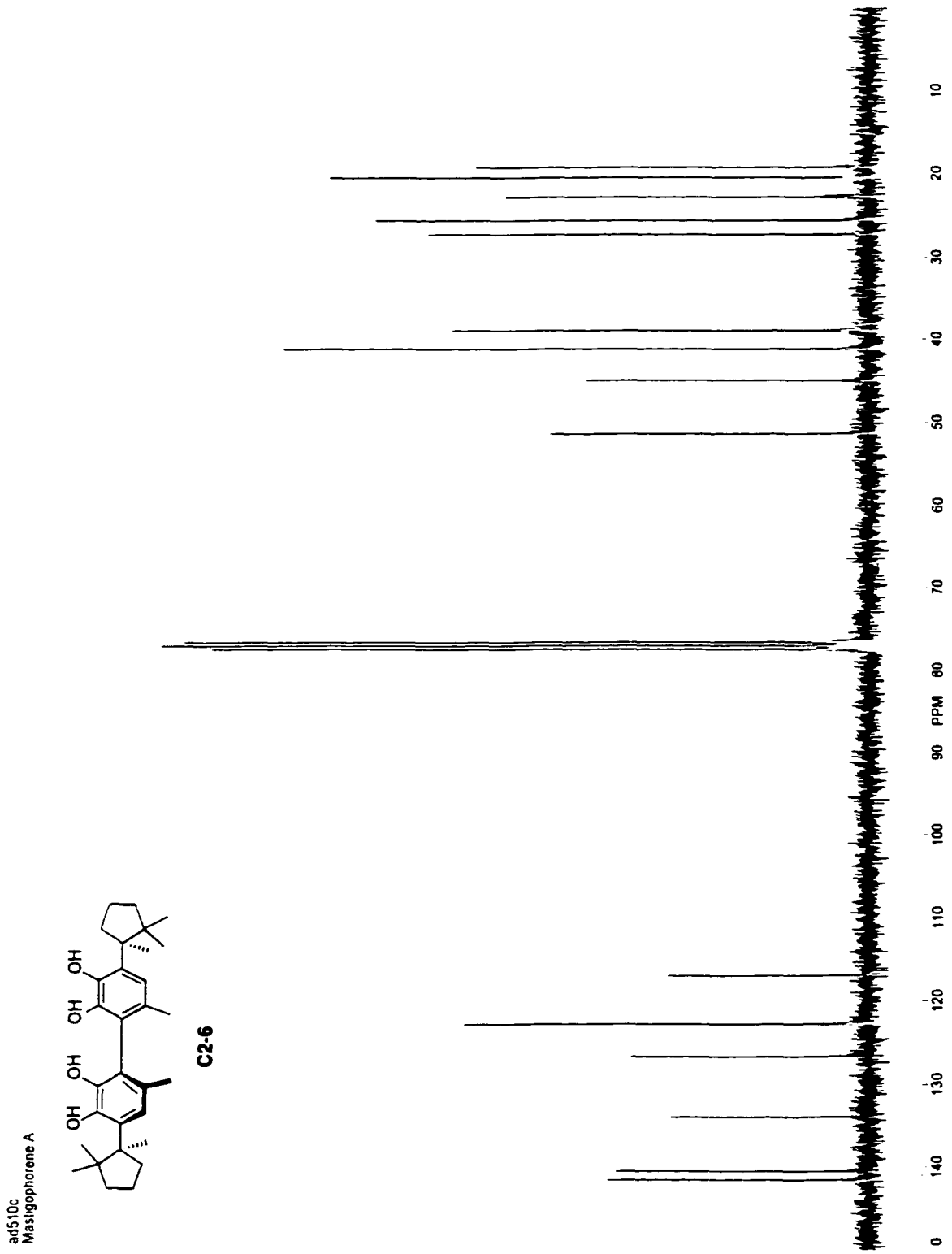
ad523
(-)-herbertenediol

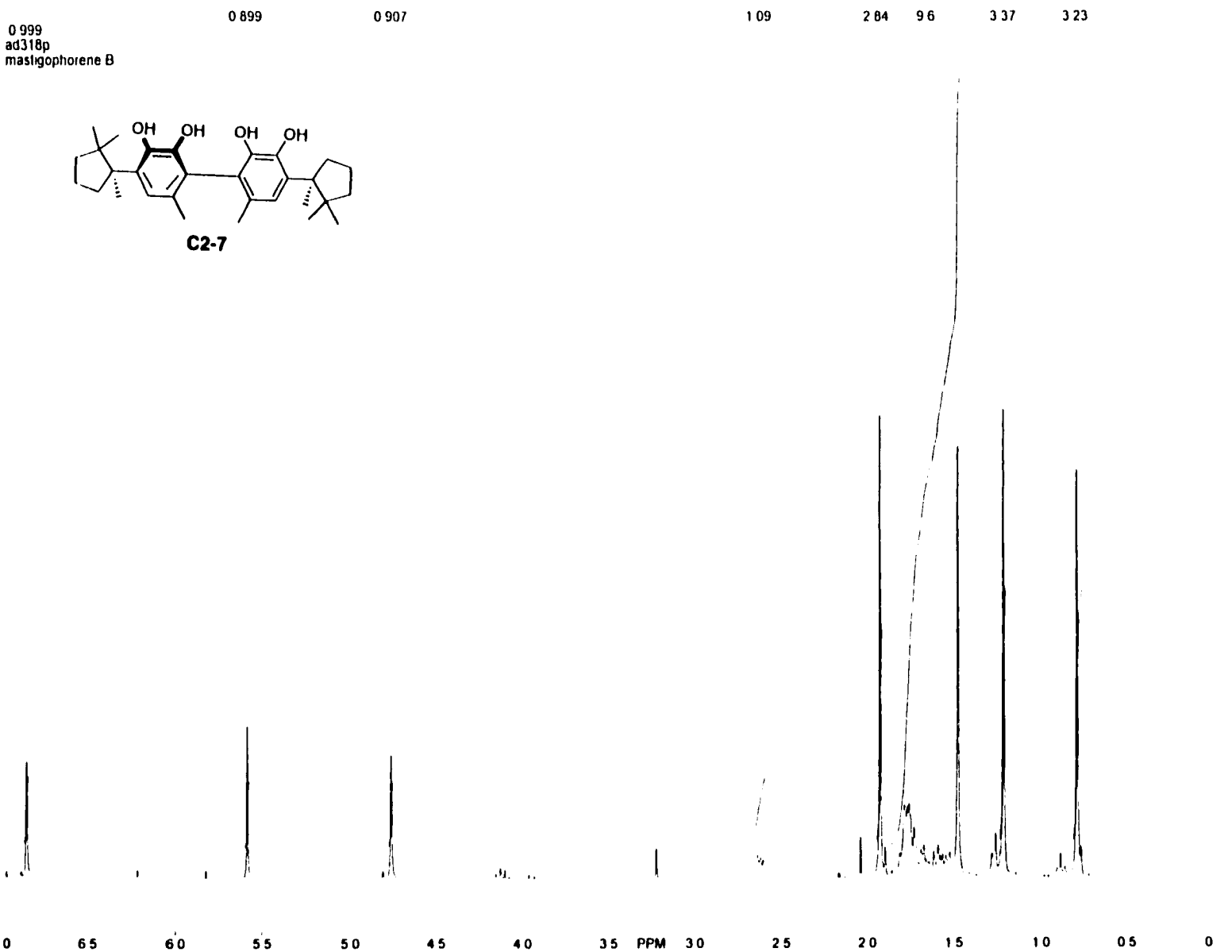


C2-1

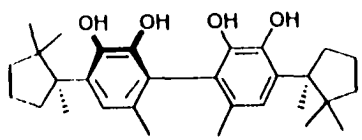








ad518c
mastigophorene B



C2-7