THE UNIVERSITY OF CALGARY

USE OF AN ACETYLENIC SULFONE AS AN ALKENE DIPOLE EQUIVALENT IN THE TOTAL SYNTHESIS OF (±)-PUMILIOTOXIN C

by

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Abstract

Acetylenic sulfones are versatile synthetic reagents that can undergo one or more conjugate additions at the β-position, as well as reactions with one or more electrophiles at the α-position. The sulfone group can be removed reductively at the end of the desired transformations. Thus, acetylenic sulfones act as the synthetic equivalents of dipoles or multipoles.

Based on this behaviour, the synthesis of (±)-pumiliotoxin C, an alkaloid that occurs in the skin secretion of the Panamanian poison-dart frog *Dendrobates pumilio*, was accomplished by sequential Michael addition and α-acylation reactions between an appropriate combination of a β-amino ester and an acetylenic sulfone. The latter functioned as an alkene dipole equivalent in this process.

Thus, 1-(*p*-toluenesulfonyl)-1-pentyne underwent Michael addition with the free primary amine, methyl *cis*-2-amino-*trans*-6-methylcyclohexanecarboxylate, to furnish the correrssponding enamine as a mixture of (E)- and (Z)-isomers in 93% yield. Intramolecular α-acylation of the (E)- and (Z)-enamine mixture was effected with LDA to provide the corresponding enaminone, 4a,5,6,7,8,8a-hexahydro-5-methyl-2-propyl-3-(*p*-tolylsulfonyl)-4-quinolinone. Reduction of its enol triflate derivative by high pressure hydrogenation, followed by reductive desulfonylation of the corresponding N-Cbz derivative with sodium amalgam, afforded (±)-pumiliotoxin C in 46% overall yield from the key intermediate enaminone. 2-Epi-pumiliotoxin C was obtained as a byproduct in 9% overall yield from the enaminone.

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To my Dad

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List of Abbreviations

Ac	acetyl
AIBN	2,2'-azobis(2-methylpropionitrile)
Anal.	Elemental analysis
Ar	aryl
aq.	aqueous
BBEDA	N,N'-bis(benzylidene)ethylenediamine
Bn	benzyl
Boc	tertiary-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
°C	degrees Celsius
cal	calorie
calcd	calculated
cat.	catalytic
Cbz	carbobenzyloxy
cm^{-1}	reciprocal centimeters-wavenumbers
^{13}C NMR	carbon-13 nuclear magnetic resonance
cod	*cis*, *cis*-1,5-cyclooctadiene
COSY	correlation spectroscopy
Cy	cyclohexyl
d	doublet
δ	chemical shift in ppm downfield from tetramethylsilane
dba	dibenzylideneacetone (PhCH=CHCOCH=CHPh)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEAD	diethyl azodicarboxylate
DIBAH	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	ethylene glycol dimethyl ester
DMF	N,N-dimethylforamide

DPPA	diphenylphosphoryl azide
dt	doublet of triplet
E	generalized functional group, normally an electron-withdrawing group
eq.	equivalent or equation
Et	ethyl
g	grams
h	hours
H^+	acid
^1H NMR	proton nuclear magnetic resonance
HMPA	hexamethylphosphoramide
hν	light
HRMS	high resolution mass spectrum
Hz	Hertz
IR	infrared
J	coupling constant
k	kilo
kg	kilograms
L.A.	Lewis acid
LDA	lithium diisopropylamide
LD_{50}	lethal dose
liq.	liquid
lit.	literature
M	molar
m	multiplet
M^+	molecular ion
m/z	mass to charge ratio
Me	methyl
mCPBA	*m*-chloroperoxybenzoic acid
mg	miligrams
MHz	megaHertz
min	minutes
mL	millilitres
μL	microlitres
μg	micrograms
mmol	millimoles

mol	moles
mp	melting point
MS	mass spectrometry
Ms	methanesulfonyl
n-	straight chain
NOE	nuclear Overhauser Effect
Nu	nucleophile
o-	ortho
p.	page
p-	para
Ph	phenyl
PLE	pig liver esterase
PMHS	polymethylhydrosiloxane
pp.	pages
ppm	parts per million
Pr	propyl
py	pyridine
q	quartet
quant.	quantitative
R	generalized alkyl group or substituent
r.t.	room temperature
s	singlet
t	triplet
t-	tertiary
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	*p*-toluenesulfonyl

Chapter One
Introduction

1.1 Dendrobatid alkaloids

1.1.1 Occurrence and structure

In nature, alkaloids are found in a large number of plant and animal species as an immense group of biogenetically diverse families of organic nitrogenous bases.[1] Among the alkaloids so far identified,[2] dendrobatid alkaloids are produced by several species of neotropical frogs of the genera *Phyllobates* and *Dendrobates* (family Dendrobatidae),[2c,2d, 3-5] as well as the Brazilian toad *Melanophryniscus moreirae* (family Bufonidae),[6] the Madagascan frogs *Mantella aurantiaca* and *Mantella madagascariensis* (family Ranidae and subfamily Mantellinae)[6,7] and the Australian frog *Pseudophryne semimarmorata* (family Myobatrachidae).[6,8] In the last two decades, nearly 300 different dendrobatid alkaloids have been detected. The more abundant ones were isolated and characterized, but many others were only given tentative structures based on their gas chromatograms and mass spectra due to their existence in only trace amounts. These alkaloids can be divided into several classes based on their common partial structures (for examples, see Figure 1.1, where compounds listed under each class are those which occur in major amounts in one or more species of the frogs or toad mentioned above). The most complex structures are steroidal alkaloids in the batrachotoxin class produced by a few species of the genus *Phyllobates*. Simpler structures are alkaloids of the pumiliotoxin A class, the decahydroquinoline class, the histrionicotoxin class, the indolizidine class and several other minor classes, afforded by various species of the genus *Dendrobates*, the toad *M. moreirae*, and the frogs *M. aurantiaca, M. madagascariensis* and *P. semimarmorata* .

Figure 1.1: Some examples of dendrobatid alkaloids

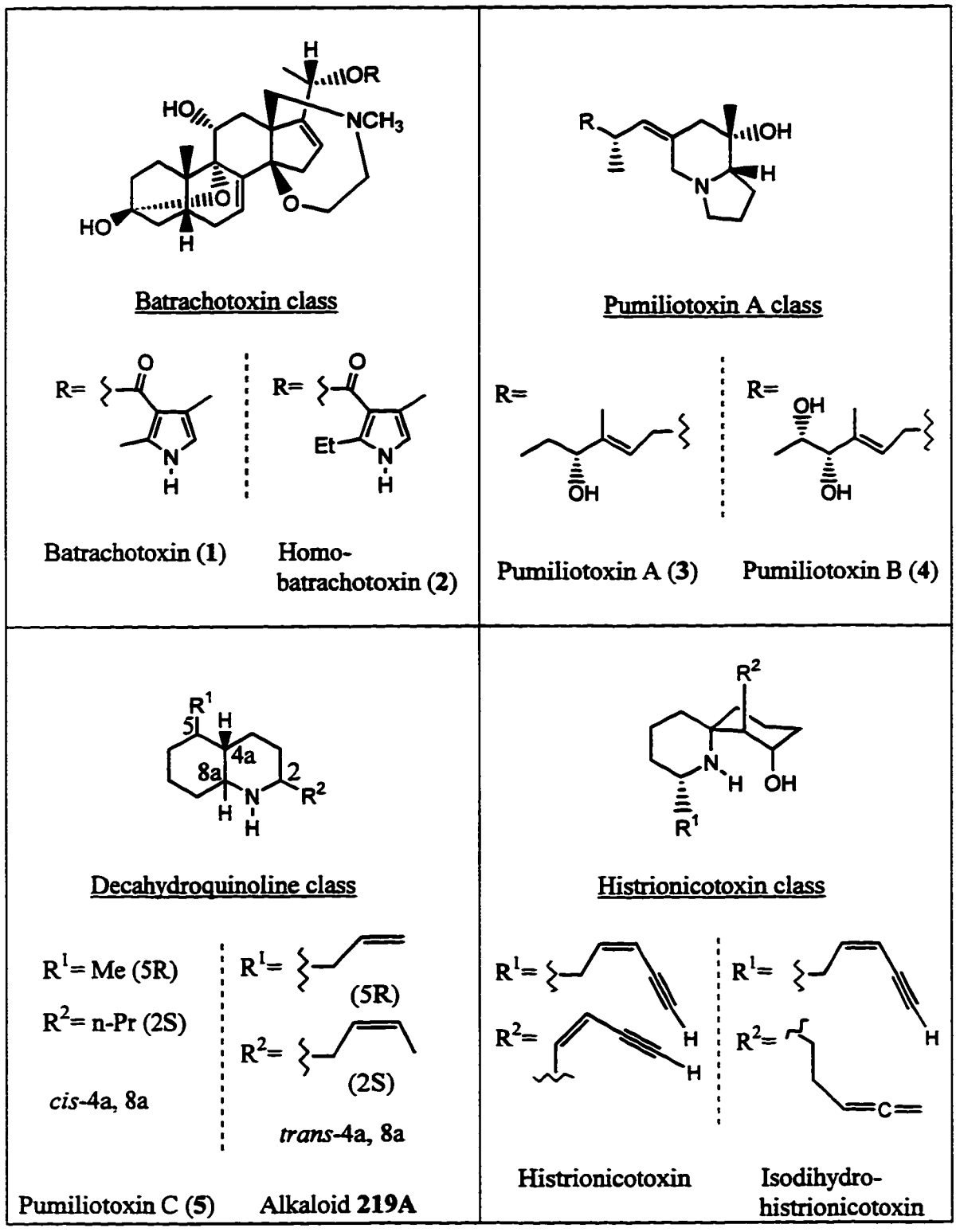
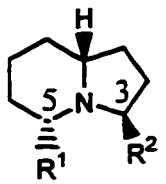
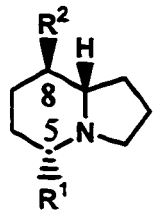


Figure 1.1 (cont'd)



3,5-Disubstituted indolizidine class

R^1= Pr	R^1= $CH_2CH_2CH_2OH$
R^2= Bu	R^2= Bu
Indolizidine **223AB**	Indolizidine **239AB**



5,8-Disubstituted indolizidine class

R^1= $CH_2CH_2CH_2CH{=}CH_2$

R^2= Me

Indolizidine **207A**

1.1.2 Biological activity

As well as their wide variety of structures, these alkaloids possess pharmacological activities of great interest. Many of them serve as toxins for the purpose of chemical self-defense against predation. Therefore, any slight damage to the frog's skin, or even simple contact, results in the release of toxic alkaloids in secretions onto the skin surface.[4a] The most toxic of the dendrobatid alkaloids are batrachotoxin (**1**) and homobatrachotoxin (**2**). These are strong cardiotoxins which cause locomotor and equilibrium difficulties, followed by heavy breathing, violent convulsions, and death in mice when ca. 0.1 μg is injected subcutaneously.[9] The LD_{50} of **1** and **2** in mice was found to be 2~3 μg / kg.[10] These alkaloids are major ingredients of the poison that hunters of the Embera Choco tribe of Colombia use for their blowgun darts.[2b] Other alkaloids produced by various species of the genus *Dendrobates*, the toad *M. moreirae*, and the frogs *M. aurantiaca, M. madagascariensis* and *P. semimarmorata* are less toxic and generally cause only locomotor difficulties and prostration in mice by subcutaneous injection of 50 ~ 100 μg, followed by recovery within a few hours.[4a,4b] Nevertheless pumiliotoxin A (**3**) and pumiliotoxin B (**4**) are capable of causing death in mice within 10 min by subcutaneous injection of 100 μg.[11]

Because of their toxic properties, some of these alkaloids are used as tools for pharmacological studies.[2c,4a,4b] Generally, they have selective effects upon nerve and muscle systems. For example, batrachotoxins **1** and **2** were used to study the function of sodium channels in nerve and muscle because of the ability to selectively increase cell-membrane permeability to sodium ions, which then causes depolarization in a variety of nerves and muscles.[2c,4a,4b,10] In addition, histrionicotoxins have shown their ability to antagonize the conductance changes that normally follow activation of nicotinic receptors by acetylcholine in muscle.[2c,4a,4b,12]

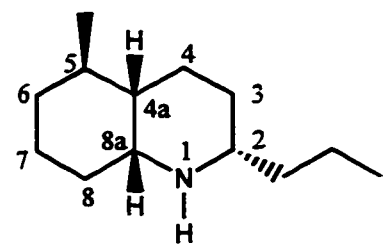
Further potential pharmacological applications of these alkaloids have encouraged new approaches to their syntheses. One compound in particular, pumiliotoxin C (**5**), is the principal subject of this Thesis. Therefore, more detailed background on this compound is presented in section 1.2.1, and a review of previous syntheses of **5** follows in section 1.2.2. Finally, since our synthesis of pumiliotoxin C springs from ongoing studies of acetylenic and other types of unsaturated sulfones that have been under investigation in our laboratory for many years,[13-23] a brief review of relevant aspects of sulfone chemistry reported by our group and others follows in section 1.3.

1.2 Pumiliotoxin C

1.2.1 Background

Pumiliotoxin C (**5**) is a relatively abundant member of the decahydroquinoline class of dendrobatid alkaloids. Major sources of **5** are the species *Dendrobates pumilio*[5c] and *Dendrobates auratus*.[5a,5b] The first isolation of pumiliotoxin C (**5**) from *D. pumilio* and complete structure elucidation of its hydrochloride by ^{1}H NMR spectroscopy and X-ray analysis was done by Witkop et al. in 1969.[24] However, these authors mistakenly assigned the configuration of the unnatural enantiomer, (+)-pumiliotoxin C, to the isolated natural enantiomer. Later, the structure was corrected and the natural (-)-pumiliotoxin C was shown to be (2S,4aS,5R,8aR)-5-methyl-2-*n*-propyl-*cis*-decahydroquinoline (Figure 1.2).[5d]

Figure 1.2 : (-)-Pumiliotoxin C



5

Pumiliotoxin C (**5**) is less toxic than the batrachotoxins **1** and **2**, pumiliotoxin A (**3**) or pumiliotoxin B (**4**). Subcutaneous injection of 100 μg of **5** in mice caused only locomotor difficulties, followed by prostration, with recovery within 1 hour.[4a] This compound, as well as other members of the decahydroquinoline class, act as reversible blockers for the nicotinic acetylcholine receptor-channel.[25,26] Like the histrionicotoxins, these decahydroquinoline alkaloids can be used as tools for pharamacological studies of nerve and muscle systems.

1.2.2 Previous syntheses

Because of the poor availability of even the most abundant dendrobatid alkaloids from natural sources (only 80 mg of pumiliotoxin C (**5**) was isolated from 2540 frogs),[5c] the synthesis of these compounds became essential for pharmacological investigations.

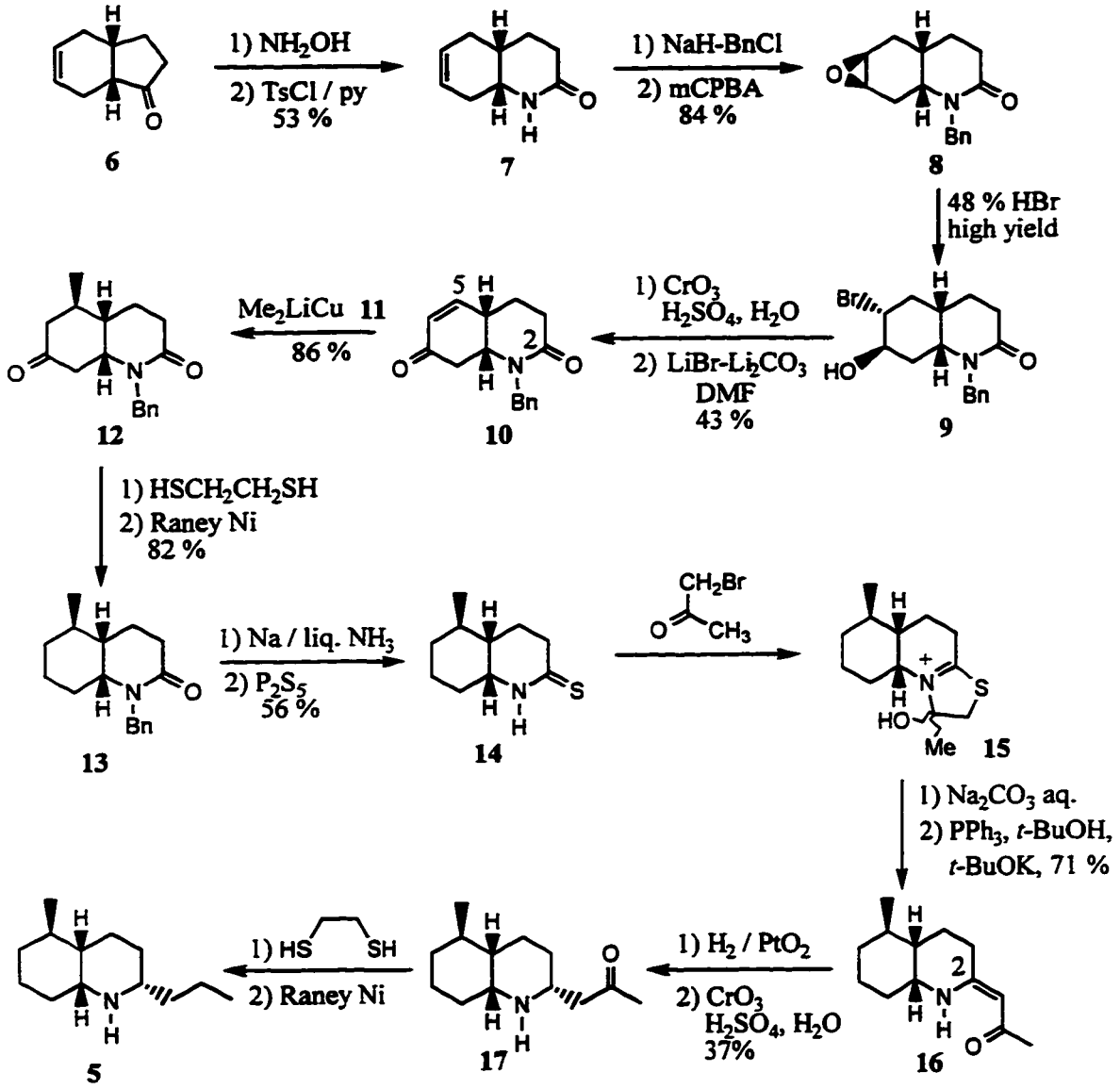
Moreover, the structure of **5** reveals four chiral centers along with an unusual *cis*-fused decahydroquinoline skeleton, which poses a challenge for the synthetic chemist. To date, over two dozen papers regarding the synthesis of pumiliotoxin C (**5**) and closely related compounds have appeared, including both racemic and enantioselective approaches. These are briefly outlined in sections 1.2.2.1-1.2.2.18.

1.2.2.1 Ibuka's synthesis

One of two nearly simultaneous but independent total syntheses of (±)-pumilitoxin C was performed by Ibuka and co-workers in 1975 (Scheme 1.1).[27] Their approach involved preparation of the *cis*-decahydroquinoline derivative **10** from *cis*-tetrahydro-1-indanone (**6**), which was obtained by the Diels-Alder reaction of butadiene and cyclopentenone.[28] This eventually allowed both the introduction of the methyl group at C-5 and hydrogenation at C-2 to occur from the *exo* side to afford the required relative configurations of the four chiral centers of pumiliotoxin C (**5**). *cis*-Octahydroquinolone **7** was obtained by converting *cis*-tetrahydro-1-indanone (**6**) to the oxime, followed by a Beckmann rearrangement. After the benzylation of the lactam **7**, oxidation with mCPBA gave epoxy lactam **8**, which was then treated with 48% hydrobromic acid to afford bromohydrin **9** regioselectively. Jones oxidation and subsequent dehydrobromination furnished α,β-unsaturated ketone **10**, which served as a Michael acceptor of cuprate **11** to give **12** as the sole product. Removal of the ketone carbonyl group by reducing its thioacetal with Raney nickel provided the N-benzylquinolone **13**. Reductive debenzylation and subsequent treatment with phosphorus pentasufide gave thiolactam **14**, which was converted to **16** by the Eschenmoser procedure.[29] Hydrogenation over platinum oxide occurred from the *exo* side to produce the right configuration at C-2 and oxidation of the resulting alcohol afforded the amino ketone **17**. Finally, the thioacetal derived from **17** was reduced with Raney nickel to yield (±)-pumiliotoxin C (**5**), which was characterized as the hydrochloride.

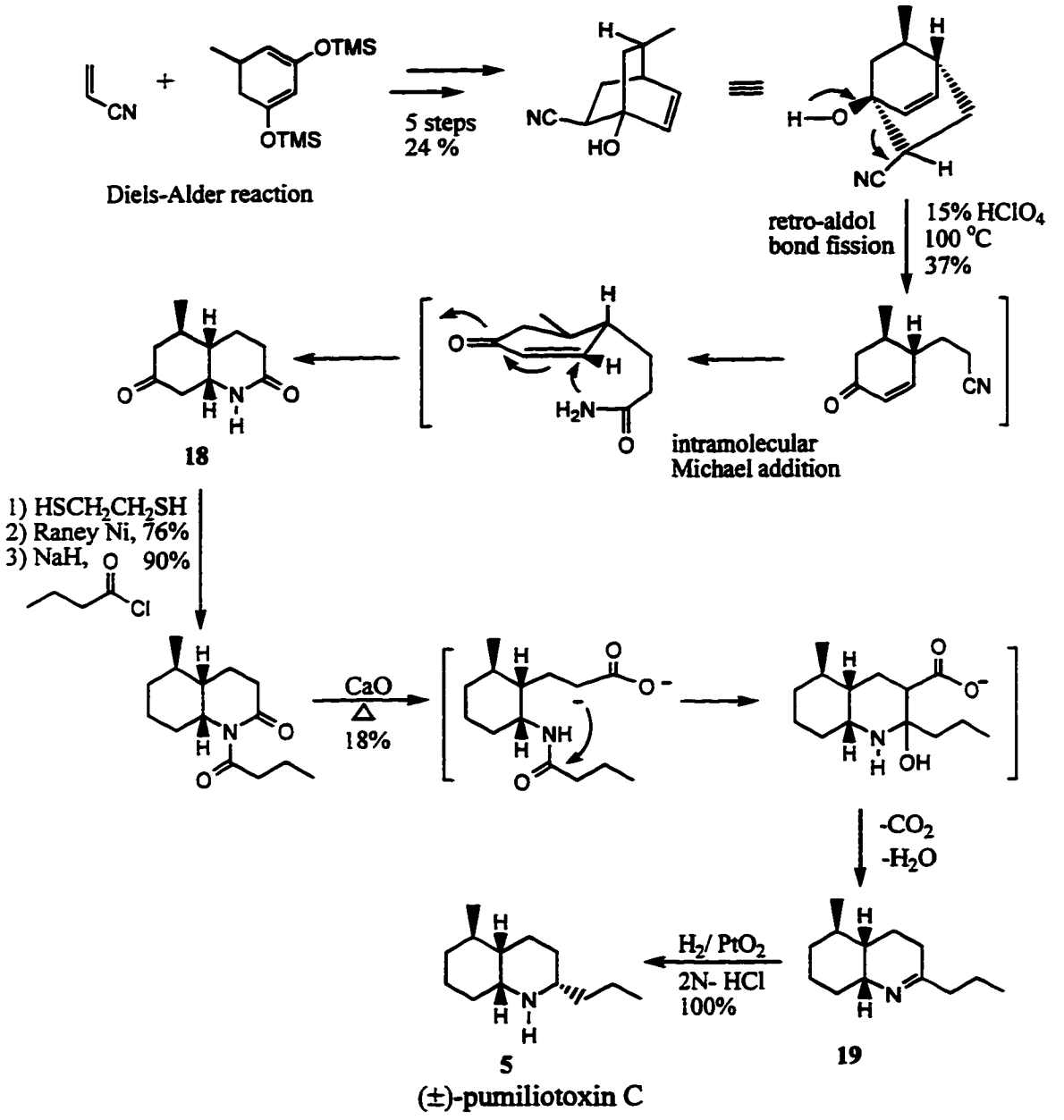
The intermediate **10** is versatile with respect to the extension of this approach to other members of the decahydroquinoline class by using other cuprates to introduce different substituents at C-5. Some disadvantages to this approach are that it is lengthy (2% overall yield of **5**) and relies on a relatively inefficient sequence of steps for the introduction of the *n*-propyl group at C-2 (from **13** to **5**).

Scheme 1.1 : Ibuka's synthesis of (±)-pumiliotoxin C



Later, in 1976[30a] and in 1978,[30b] Ibuka and co-workers reported another method to produce the *cis*-decahydroquinoline derivative **18**, whose three chiral centers had the necessary relative configurations. The method involved successive Diels-Alder reactions using bis(trimethylsilyloxy)dienes (obtained from 5-methyl-1,3-cyclohexadione[31]), retro-aldol bond fission, and intramolecular Michael addition of the corresponding primary amide (Scheme 1.2). The intermediate **18** was then elaborated to (±)-pumiliotoxin C (**5**) in a different manner from **12** in Scheme 1.1. A proposed mechanism for the N-acyl-lactam rearrangement with CaO was reported by Mundy et al.[32]

Scheme 1.2 : Ibuka's alternative synthesis of (±)-pumiliotoxin C

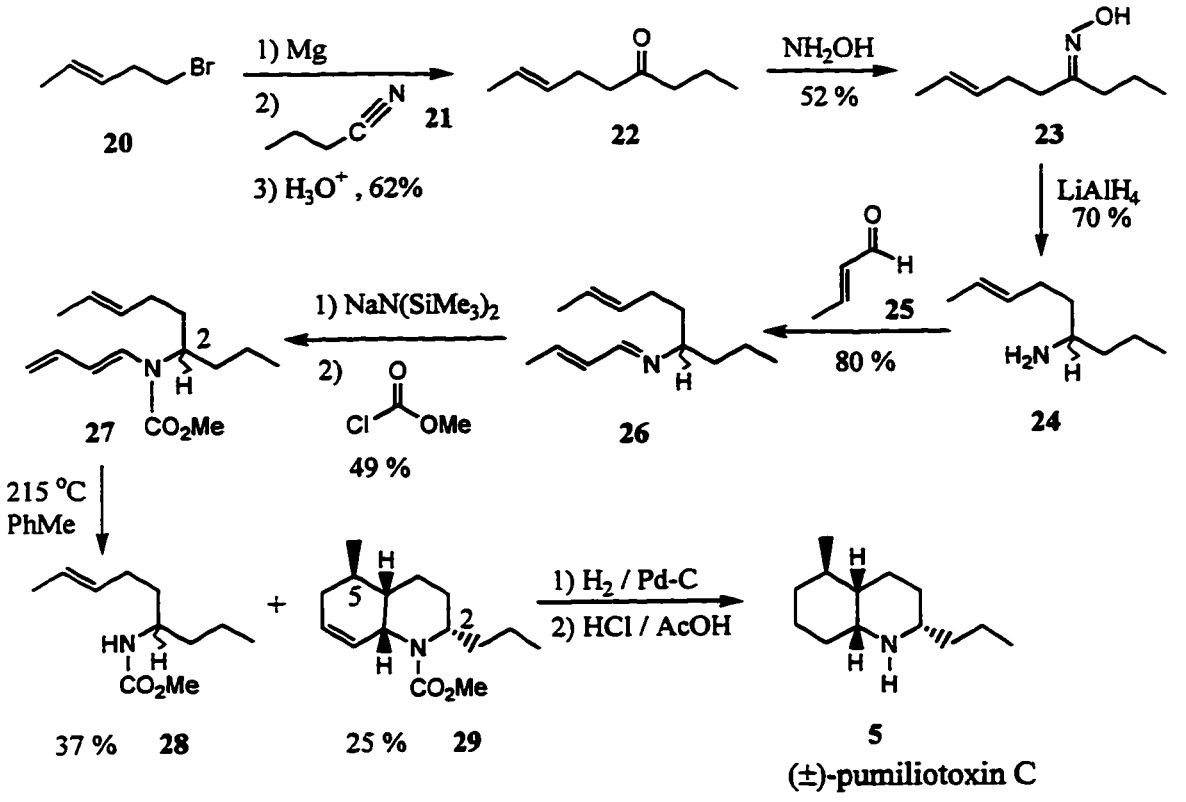


While this synthesis is shorter than their first one in Scheme 1.1, the overall yield (1.1%) of **5** was even lower. The introduction of the *n*-propyl group at C-2 was inefficient, producing the imine **19** in only 18 % yield from its precursor.

1.2.2.2 Oppolzer's synthesis

Oppolzer and co-workers independently reported the other first total synthesis of (±)-pumiliotoxin C in 1975 (Scheme 1.3).[33] The key step was an intramolecular Diels-Alder reaction to construct three chiral centers (from **27** to **29**) whose configurations were largely controlled by the original chiral center at C-2. The Grignard reagent prepared from **20** reacted with butyronitrile **21** to provide the ketone **22** after hydrolysis. Formation of the oxime **23** and subsequent reduction gave the free amine **24** as a racemic mixture, which was condensed with crotonaldehyde **25** to produce the conjugated imine **26**. Treatment with base, followed by quenching with methyl chloroformate, afforded the *trans*-dienamide **27**. Heating of **27** at 215 °C gave the desired *cis*-fused octahydroquinoline **29** in a stereoselective manner, as well as the undesired side product **28**. Finally, hydrogenation of **29** and deprotection of the amine by acid hydrolysis yielded (±)-pumiliotoxin C (**5**).

Scheme 1.3 : Oppolzer's synthesis of (±)-pumiliotoxin C

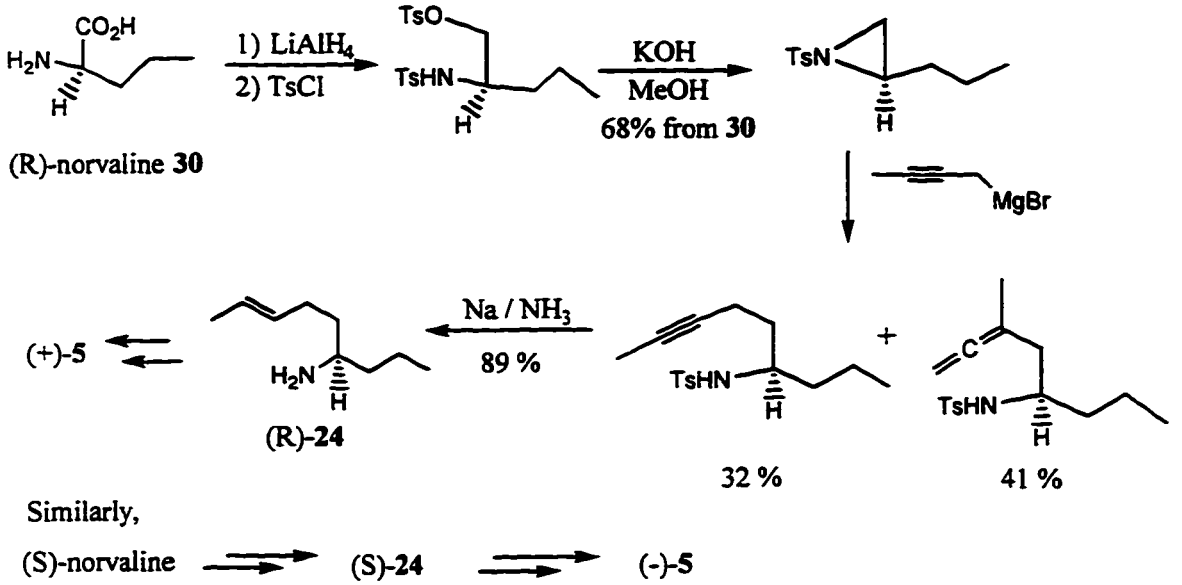


Besides the drawback of the required high temperature, the Diels-Alder reaction gave a poor ratio of the desired **29** to the byproduct **28**. Furthermore, application to other

members of the decahydroquinoline class, which generally have bigger substituents at C-5, would make the Diels-Alder reaction even more difficult because of increased steric hindrance. The overall synthesis is not lengthy, but even so, gives a poor overall yield of **5** (2%).

The first enantioselective synthesis of both (+)- and (-)-pumiliotoxin C, based on a similar synthetic sequence to the one shown in Scheme 1.3, was reported by Oppolzer and Flaskamp in 1977.[34] The choice of either (R)- or (S)-norvaline as a chiral starting material led to (+)- or (-)-pumiliotoxin C, respectively (Scheme 1.4).

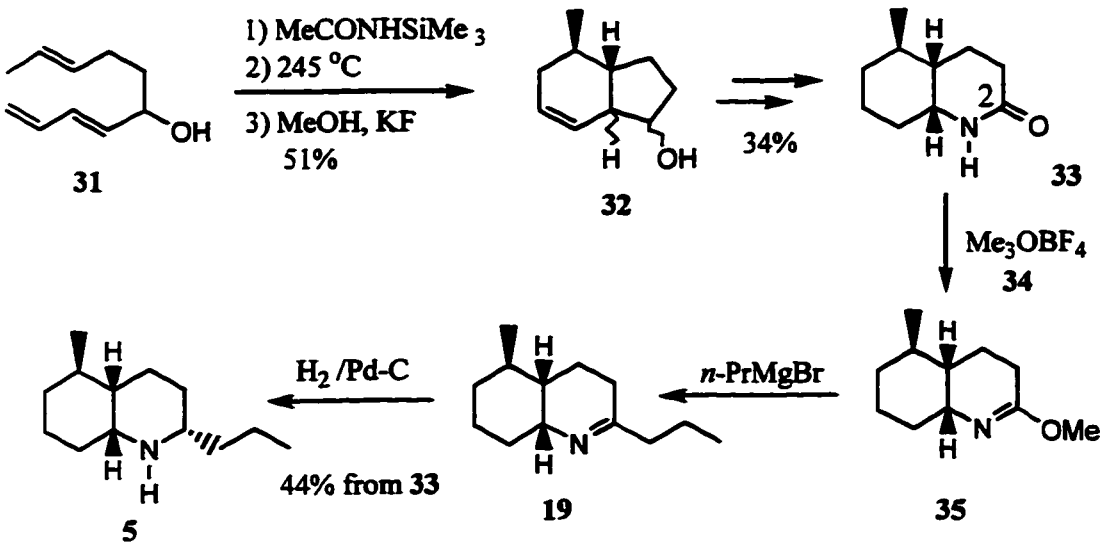
Scheme 1.4 : The first enantioselective synthesis of (+)- or (-)-pumiliotoxin C



In 1977, in contrast to their previous synthesis,[33] Oppolzer and co-workers performed another approach to (±)-pumiliotoxin C by using the three chiral centers formed in a related intramolecular Diels-Alder reaction (from **31** to **32**) to control the stereochemistry of the other chiral center at C-2 (Scheme 1.5).[35] The introduction of the *n*-propyl group at C-2 was successfully carried out from the *exo* side (from **33** to **5**).

Some improvements were observed in the Diels-Alder reaction (51% from **31** to **32** in Scheme 1.5, compared with 25% from **27** to **29** in Scheme 1.3), but the overall yield of **5** was low (4%; **31** was obtained in 54% yield in 2 steps from 4-hexen-1-al). The transformation of **33** to **5** was elegantly performed and several later syntheses all used this method as a reliable means for the introduction of the *n*-propyl substituent (*vide infra*).

Scheme 1.5 : Oppolzer's alternative synthesis of (±)-pumiliotoxin C



1.2.2.3 Habermehl's synthesis

Habermehl and co-workers reported the synthesis of (±)-pumiliotoxin C in 1976 (Scheme 1.6).[36] This approach was based on the procedure previously reported by Parcell and Hauck Jr. for the couplings of 3-bromopropylamine with several enamines.[37] The two key intermediates **37** and **38** were obtained from ethyl 4-methyl-2-oxo-cyclohexanecarboxylate (**36**) and ethyl 3-oxohexanoate, respectively. These were condensed to provide the corresponding mixture of diastereomeric imines **39**. The required configuration of the chiral center at C-4a was obtained as shown in Figure 1.3. Removal of the ester group in **39** and subsequent hydrogenation afforded (±)-pumiliotoxin C (**5**), as well as its C-2 epimer.

This approach is the first convergent synthesis of **5** and gave a 25% overall yield of **5** from **37** and **38**. Although this convergent synthesis is more efficient than the preceding linear ones, and also the ring-closure to from **39** is stereoselective at C-4a, one disadvantage is that nearly half of the material (C-2 epimer of **39**) is wasted.

Scheme 1.6 : Habermehl's synthesis of (±)-pumiliotoxin C

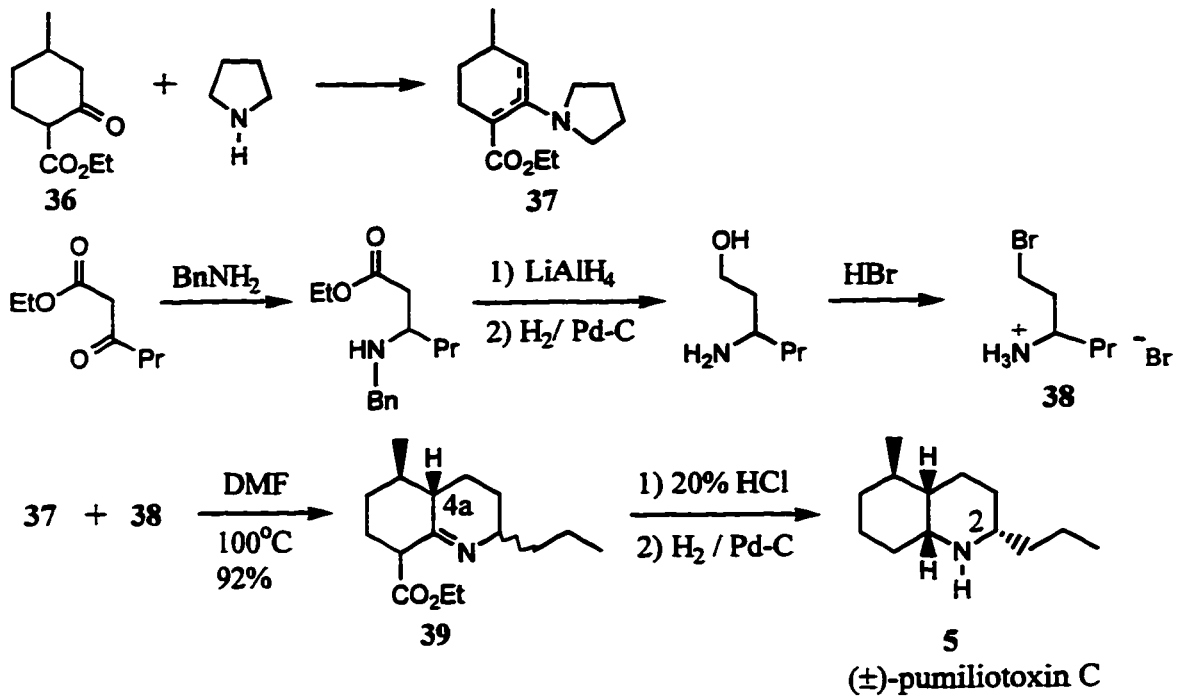
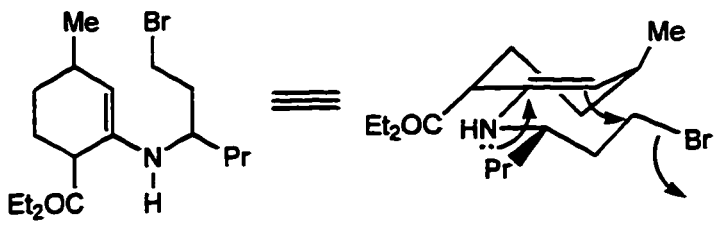


Figure 1.3



Later, in 1977,[38] Habermehl and Andres reported the enantioselective synthesis of **38**, which allowed the eventual enantioselective syntheses of both (+)- and (-)-pumiliotoxin C.

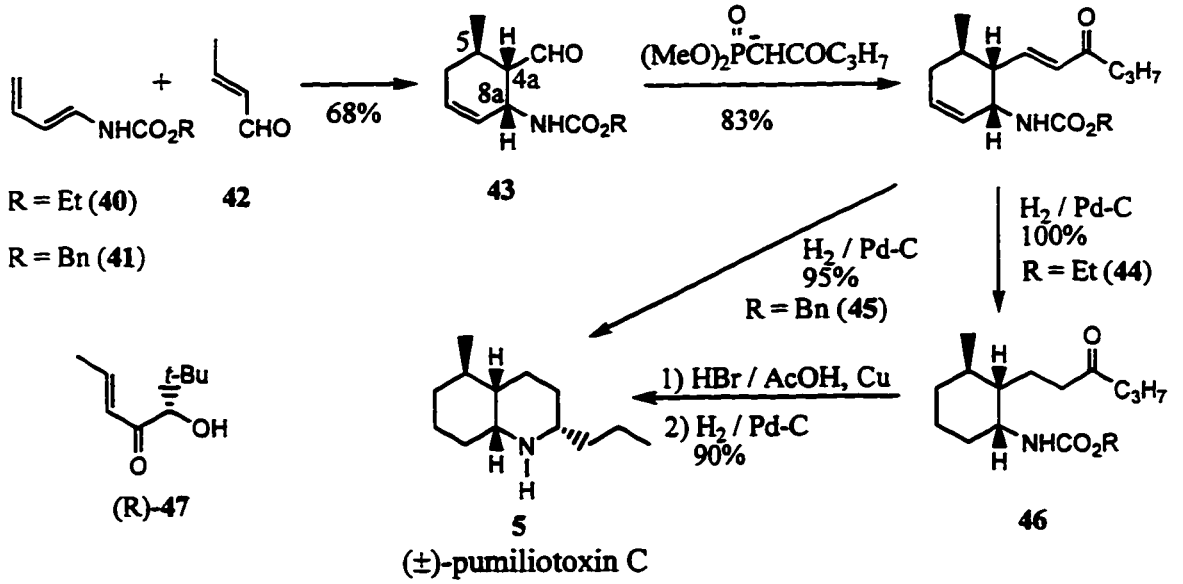
1.2.2.4 Overman's synthesis and Masamune's variation

Overman and Jessup employed a stereoselective Diels-Alder reaction to construct the three chiral centers at the C-5, C-4a, and C-8a (*cis* ring junction) positions in a single step (Scheme 1.7).[39] They coupled a suitable diene (**40**) or (**41**) (**40** and **41** were obtained from *trans*-2,4-pentenoic acid *via* a Curtius rearrangement[40]) with *trans*-crotonaldehyde (**42**) in an *endo* manner to give the desired relative configurations to the newly formed chiral centers. Despite the fact that *trans*-crotonate derivatives typically show low *endo*

stereoselectivities in the Diels-Alder reaction,[41] the successful *endo* cycloaddition was performed with the carbamate **40** as the diene. Further elaboration of the cycloadduct **43** by the Horner-Wadsworth-Emmons procedure gave **44**. Hydrogenation of **44** provided **46** and deprotection of the amine spontaneously led to ring closure to provide the corresponding imine, which was easily hydrogenated from the *exo* side to yield (±)-pumiliotoxin C (**5**). Later, in 1978,[42] Overman and Jessup reported the use of the benzyl carbamate **41**, which allowed the direct conversion of **45** to (±)-pumiliotoxin C (**5**) upon hydrogenation. Use of the chiral dienophile **47** instead of **42** led to the unnatural enantiomer (+)-pumiliotoxin C, as reported by Masamune and co-workers in 1983.[43] Removal of the *t*-Bu group after the Diels-Alder reaction was performed by reduction of the ketone with $LiBH_4$ and subsequent bond fission of the resulting diol with $NaIO_4$ to afford the aldehyde **43**.

The noteworthy point was the use of the Cbz group in **41** (i.e. R=Bn). The removal of the Cbz group, the condensation of the resulting primary amine with the ketone to form the corresponding imine, and reduction of the imine all occurred stereoselectively in a one-pot hydrogenation (from **45** to **5**). This approach proved to be the shortest, most highly stereoselective, and highest yielding (58% overall of **5**) synthesis of (±)-pumiliotoxin C.

Scheme 1.7 : Overman's synthesis of (±)-pumiliotoxin C and Masamune's variation to (+)-pumiliotoxin C



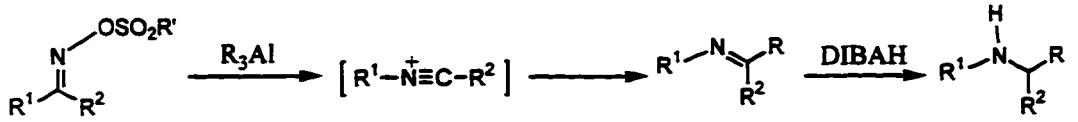
1.2.2.5 Yamamoto's synthesis

Yamamoto and co-workers applied a different strategy to the synthesis of (±)-pumiliotoxin C (**5**) in 1981[44a] and 1983.[44b] This involved a successive Beckmann rearrangement-alkylation sequence mediated by an organoaluminum reagent. The general scheme for this transformation and its specific application to (±)-pumiliotoxin C (**5**) are shown in Scheme 1.8. The starting material **49** was successfully prepared from 4-methyltetrahydroindenone (**48**), which was in turn prepared from 2-methyl cyclohexanone,[45] with the best stereoselectivity obtained by hydrogenation with palladium black in dioxane in the presence of a catalytic amount of propionic acid. The *cis*-fused hexahydroindanone **49** was then converted to **50** by successive treatment with hydroxylamine and *p*-toluenesulfonyl chloride. Subsequent Beckmann rearrangement with tri-*n*-propylaluminum occurred by preferential migration of the group *anti* to the oxime sulfonate to produce the corresponding imine, which was reduced from the *exo* side by DIBAH to yield (±)-pumiliotoxin C (**5**).

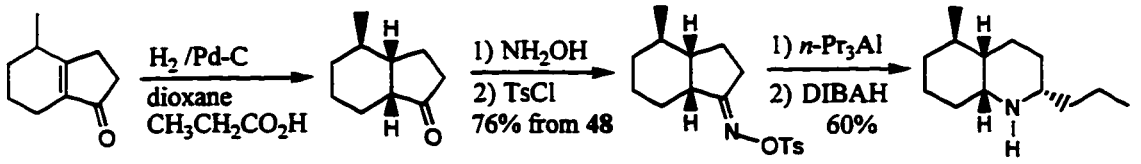
This synthesis is also relatively short, giving the required relative stereochemistry at the four chiral centers in **5**, which was obtained in high yield (46% overall). The use of a variety of other organoaluminum reagents can produce other members of the decahydroquinoline class with different substituents at C-2.

Scheme 1.8 : Yamamoto's synthesis of (±)-pumiliotoxin C

General:



Application to pumiliotoxin C:



48 **49** **50** **5**

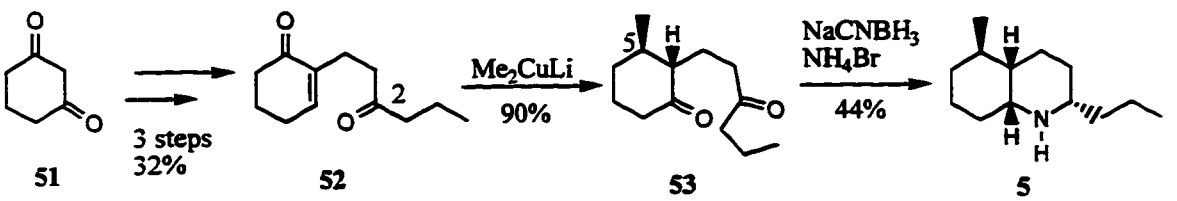
(±)-pumiliotoxin C

1.2.2.6 Abe's synthesis

Abe and co-workers applied reductive aminocyclization to the synthesis of (±)-pumiliotoxin C (**5**) in 1984 (Scheme 1.9).[46] The key intermediate **53** was prepared in four steps from the dione **51**. Treatment of **53** with $NaCNBH_3$ and ammonium bromide furnished the cyclized product, (±)-pumiliotoxin C (**5**). This is similar to the type of intramolecular cyclization approach employed earlier in Overman's procedure in Scheme 1.7.

This synthesis is short, with only 5 steps, but the overall yield of **5** is low (13%). The use of different types of cuprates (at C-5) and substituents on the side chain in **52** (at C-2) can potentially extend the method to the preparation of other members of the decahydroquinoline class.

Scheme 1.9 : Abe's synthesis of (±)-pumiliotoxin C



51 **52** **53** **5** (±)-pumiliotoxin C

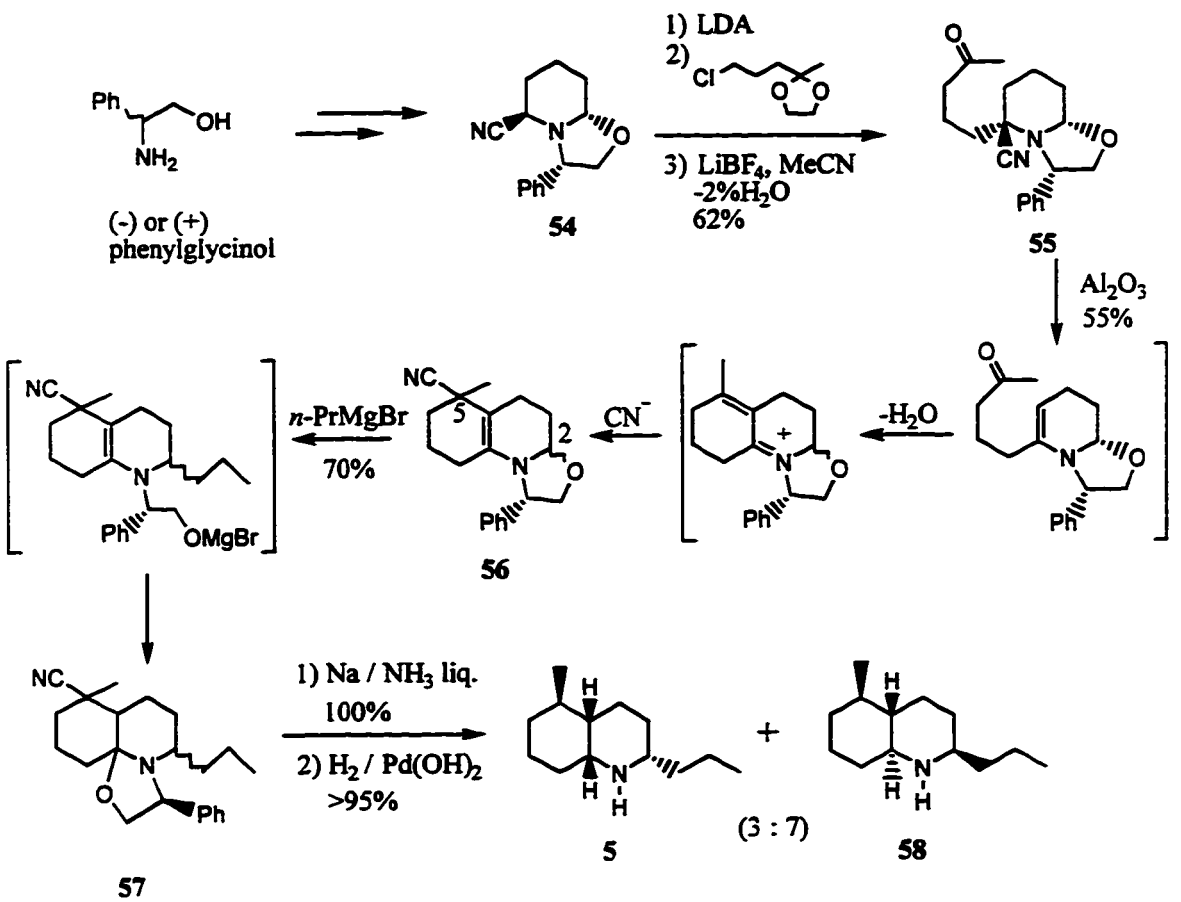
1.2.2.7 Husson's synthesis

Husson and co-workers reported the first enantioselective biomimetic synthesis of (-)-pumiliotoxin C in 1986 (Scheme 1.10).[47a,b] A possible biogenetic pathway from **59** to (-)-pumiliotoxin C (**5**) is shown in Scheme 1.11.[2c] The advanced chiral intermediate (+)-**54**, derived from (+)-phenylglycinol was converted to **55**, which upon treatment with alumina gave the cyclic enamine **56**. The proposed mechanism involved elimination of HCN to provide an enamine, which attacked the carbonyl group to form a conjugated iminium species after dehydration. This iminium salt was then neutralized by CN^- addition at C-5 to give enamine **56**. Treatment of **56** with PrMgBr afforded **57**. Reductive removal of the CN group and the oxazolidine system furnished (-)-pumiliotoxin C (**5**), which was separated from its diastereomer **58** that had been formed as a byproduct. The similar synthesis of (+)-pumiliotoxin C from (-)-phenylglycinol was also completed.[47b]

Thus, both enantiomers of pumiliotoxin C (**5**) were obtainable from the commercially available starting materials, (-)- or (+)-phenylglycinol. A major

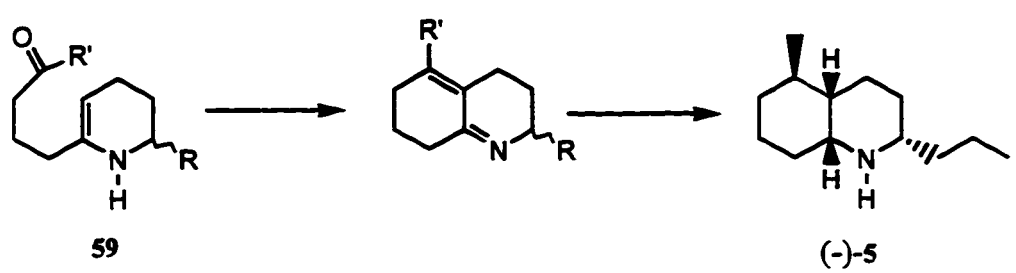
disadvantage of this method is that **55** has the undesired stereochemistry at C-2, where the S_N2 substitution by PrMgBr takes place. Unless epimerization at C-2 was effected by treatment with Al_2O_3 to give **56**, no pumiliotoxin C was obtained with respect to C-2. Furthermore, the stereoselectivity of the two chiral centers at the ring junction was poor. The unfavourable ratio of **5** to **58** imposes severe limitations on the usefulness of this approach (7% overall yield of **5** from **54**).

Scheme 1.10 : Husson's synthesis of (-)-pumiliotoxin C



(-)-pumiliotoxin C

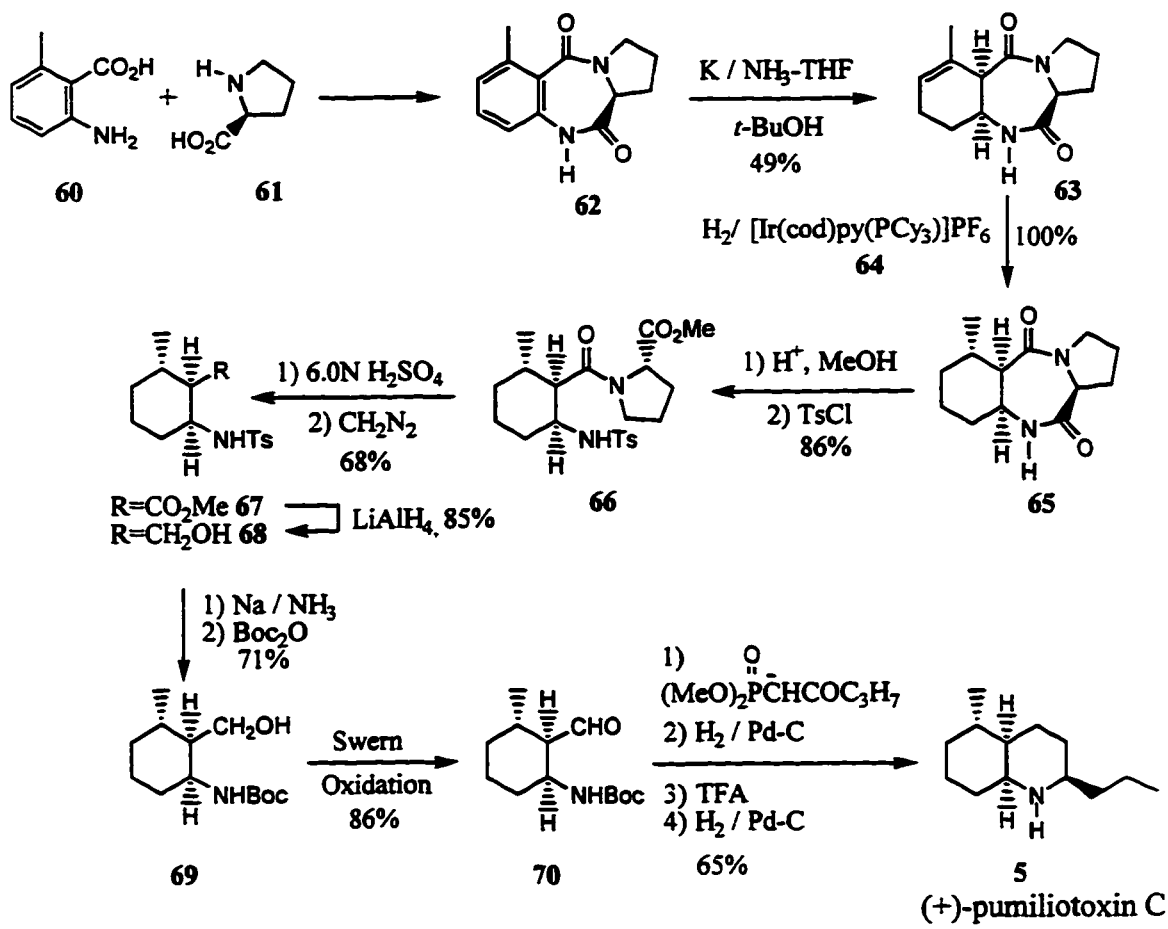
Scheme 1.11 : Possible biogenetic pathway to **5**



1.2.2.8 Schultz's synthesis

Schultz and co-workers reported the enantioselective conversion of anthranilic acid derivatives to chiral cyclohexanes and applied this strategy to the synthesis of the unnatural enantiomer (+)-pumiliotoxin C in 1987 (Scheme 1.12).[48] The key step was the Birch reduction of the chiral anthranilic acid derivative **62**, which was prepared from **60** and L-proline (**61**), to afford **63**. The newly formed *cis*-fused junction in **63** was explained on the basis of molecular modeling results which indicated that the *cis*-isomer is more stable than the *trans*-isomer by ~1.6 kcal / mol. The stereoselective hydrogenation of **63** was performed with the iridium catalyst **64**, whose presumed coordination to a neighboring functional group in **63** provided **65** with 99 : 1 diastereoselectivity. Acid-catalyzed methanolysis, followed by tosylation of the resulting amine, converted **65** to **66**. The amide bond was then cleaved in 6.0 N H_2SO_4 to give a carboxylic acid which was

Scheme 1.12 : Schultz's enantioselective synthesis of (+)-pumiliotoxin C



treated with diazomethane to furnish **67**. Reduction of **67** gave **68**, and reductive cleavage of the tosyl amide, followed by protection with the Boc group, produced **69**. The alcohol **69** was then oxidized to the aldehyde **70**. Further elaboration *via* Overman's procedure (Scheme 1.7) afforded (+)-pumiliotoxin C (**5**).

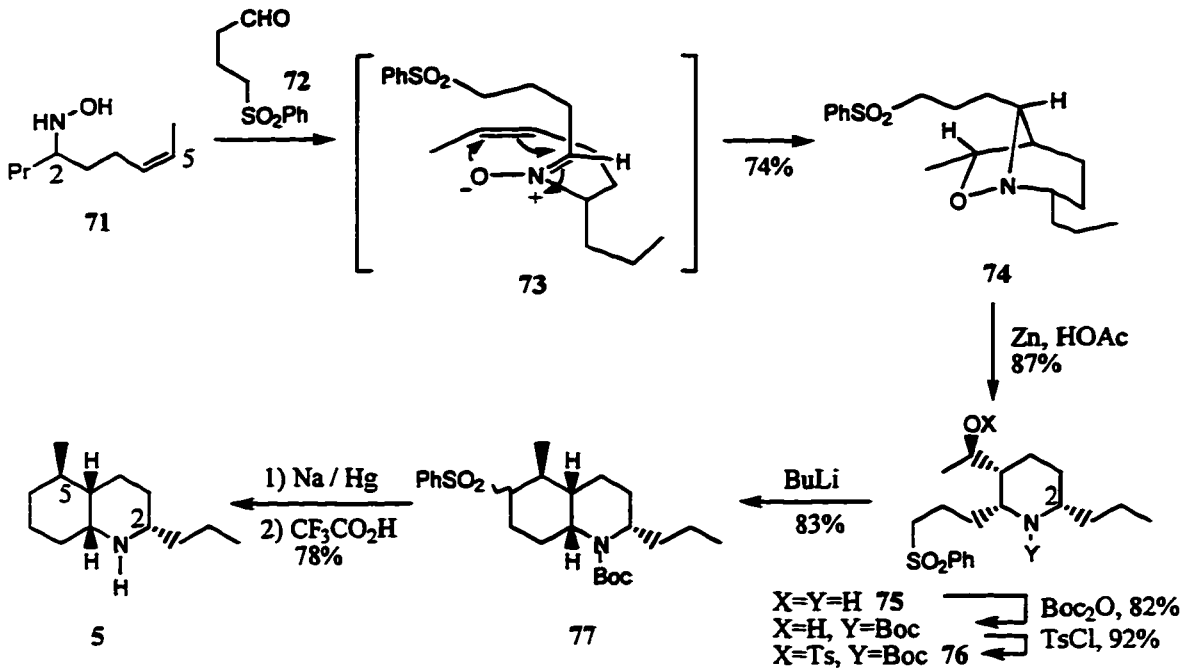
The Birch reduction of **62** gave the desired *cis*-junction of **5** and subsequent hydrogenation with a properly chosen catalyst provided the required relative configuration of the chiral centers at C-5 in **5**. The disadvantage to this synthesis is that it is lengthy (10% overall yield of **5** from **62**). Unluckily, it proved troublesome to handle the Cbz derivative throughout the entire synthesis. The switch to the Boc group in **69** resulted in additional steps in the final conversion of **70** to **5** by Overman's procedure (Scheme 1.7). Finally, the possibility of adapting this approach to the natural (-)-enantiomer of **5** would be limited by the much greater expense of the required unnatural amino acid D-proline.

1.2.2.9 LeBel's synthesis

Based on the idea that preformed piperidines could lead to more complex alkaloid structures, LeBel and co-workers elaborated the advanced intermediate **75** to (±)-pumiliotoxin C in 1989 (Scheme 1.13).[49] Their strategy involved the highly regio- and stereoselective intramolecular [3+2] cycloaddition of nitrone **73**, followed by N-O bond cleavage in **74**, to give the trisubstituted piperidine **75**. Nitrone **73** was in turn obtained by coupling hydroxylamine **71** (**71** was prepared from 2-pentanone in 6 steps) with aldehyde **72** (**72** was prepared from methyl phenyl sulfone in 2 steps) to afford the (Z)-geometric isomer of the C=N bond. Protection of the amine with the Boc group and subsequent tosylation of the hydroxyl group gave **76**, which underwent S_N2 cyclization in the presence of base to afford **77**. Finally, desulfonylation with sodium amalgam and deprotection of the amine with trifluoroacetic acid yielded (±)-pumiliotoxin C (**5**).

This synthesis is versatile with respect to the possible extension to other members of the decahydroquinoline class by changing the nature of the starting material **71**, which contains both of the substituents at C-2 and C-5. The overall approach consists of 14 steps, which is lengthy, but gave a reasonable overall yield (14%). The most remarkable point of this synthesis is that, based on the authors' general experience of obtaining (Z)-geometries in other analogues of **73**, the required relative configuration of the four chiral centers in the target molecules was constructed highly stereoselectively in one pot.

Scheme 1.13 : LeBel's synthesis of (±)-pumiliotoxin C



1.2.2.10 Comins' synthesis

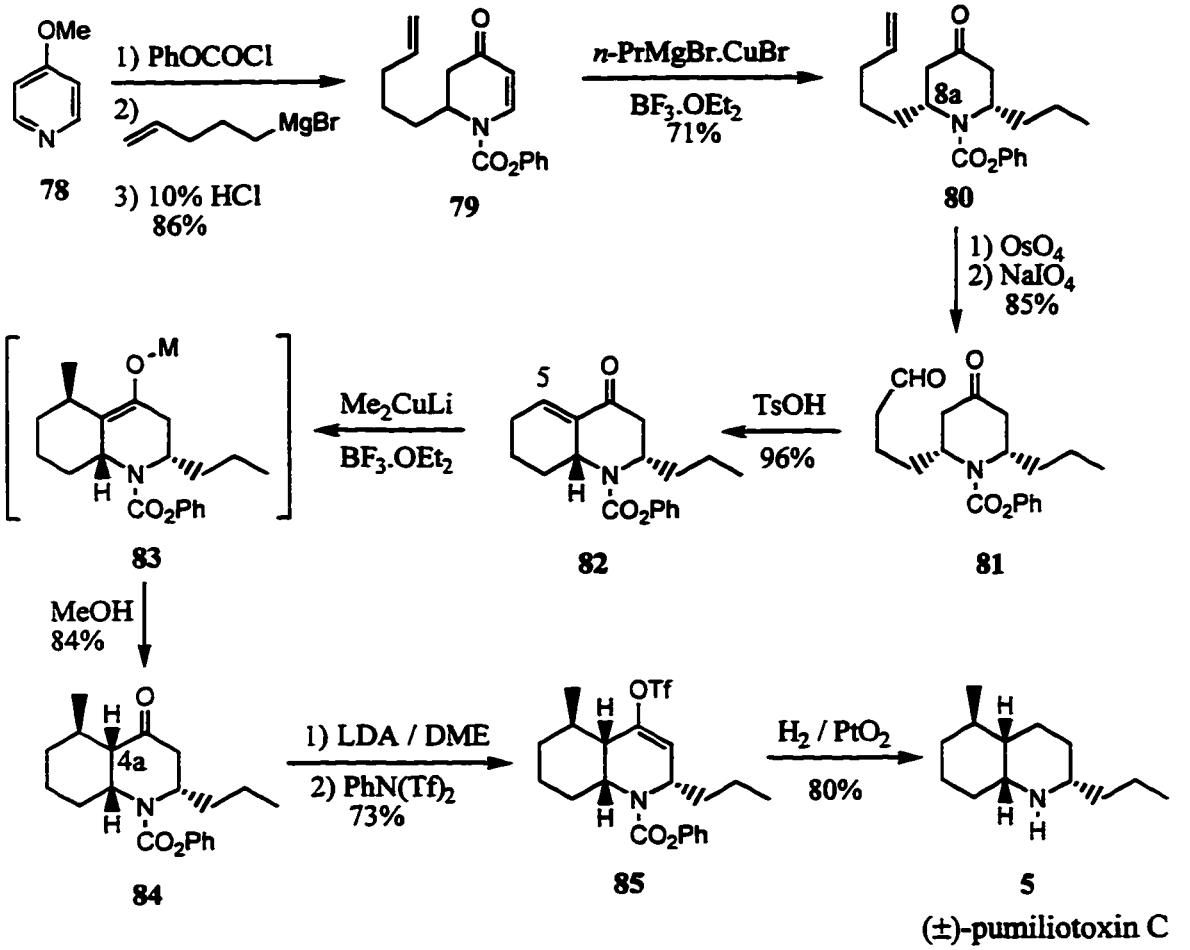
Another piperidine based approach to the synthesis of pumiliotoxin C was reported by Comins and Dehghani in 1991 (Scheme 1.14).[50a] The N-acyldihydropyridone **79** was prepared from 4-methoxypyridine **78**. The copper-mediated Michael addition of *n*-propylmagnesium bromide to **79** gave the *cis*-diastereomer **80** preferentially. Oxidative cleavage of the terminal olefin of **80** with OsO_4 / $NaIO_4$ provided **81**, which on treatment with *p*-toluenesulfonic acid underwent an intramolecular aldol condensation to give the enone **82**. The methyl group was introduced *via* a conjugate addition, giving the correct configuration at C-5, to produce the enolate **83**. Protonation of **83** with methanol afforded **84** with high (97 : 3) stereoselectivity. Finally, formation of vinyl triflate **85** and subsequent hydrogenation over PtO_2, which also reductively reduced the N-phenoxycarbonyl group, yielded (±)-pumiliotoxin C (**5**).

An enantioselective modification of this synthetic sequence was reported by Comins and Dehghani in 1993 and provided natural (-)-Pumiliotoxin C.[50b]

The relative configurations of the four chiral centers in **5** were effectively controlled in this method and a relatively high yield (24% overall) of **5** was obtained in 12 steps. Possible epimerization at C-4a in **84** was avoided by the formation of the kinetic

enolate at the less substituted side. The extension of this method to other members of the decahydroquinoline class is possible by use of other Grignard reagents (from **79** to **80**) and also other cuprates (from **82** to **83**) for introducing different substituents at C-2 and C-5, respectively.

Scheme 1.14 : Comins' synthesis of (±)-pumiliotoxin C



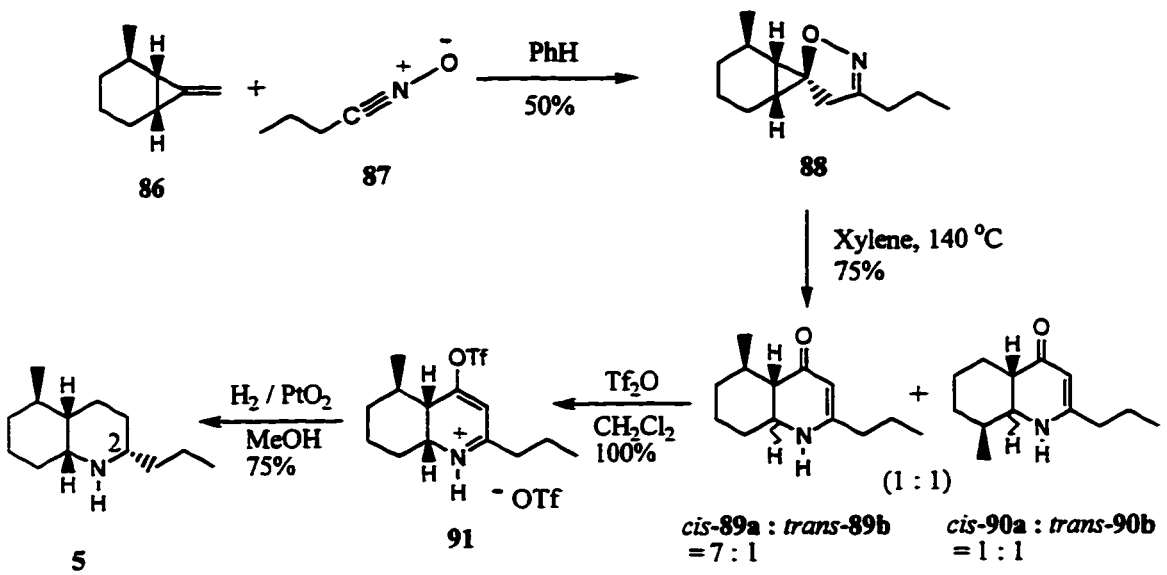
1.2.2.11 Brandi's synthesis

The thermal rearrangement of the spiroisoxazoline **88** was applied to the synthesis of (±)-pumiliotoxin C by Brandi and co-workers in 1992 (Scheme 1.15).[51] The 1,3-dipolar cycloaddition of butyronitrile oxide (**87**), obtained from nitrobutane,[52] to methylenenorcarane **86** (**86** was prepared from 3-methylcyclohexene in 3 steps[53]) afforded the spiroisoxazoline **88** as a single diastereomer. The thermal rearrangement of **88** in refluxing xylene provided a 1 : 1 mixture of regioisomers **89** and **90**. The desired *cis*-**89a** was obtained with good stereoselectivity with respect to the minor *trans*

diastereomer **89b**. The *cis*-**89a** isomer was then treated with triflic anhydride to give **91**, which was hydrogenated over PtO_2 from the *exo* side to yield (±)-pumiliotoxin C (**5**).

The disadvantage to this approach is that the two steps, 1,3-dipolar cycloaddition and thermal rearrangement, proceeded in poor yields and with essentially no regioselectivity, giving only 16% of the desired **89a**. Reduction of the enaminone system was, however, carried out effectively to provide the required stereochemistry at C-2.

Scheme 1.15 : Brandi's synthesis of (±)-pumiliotoxin C



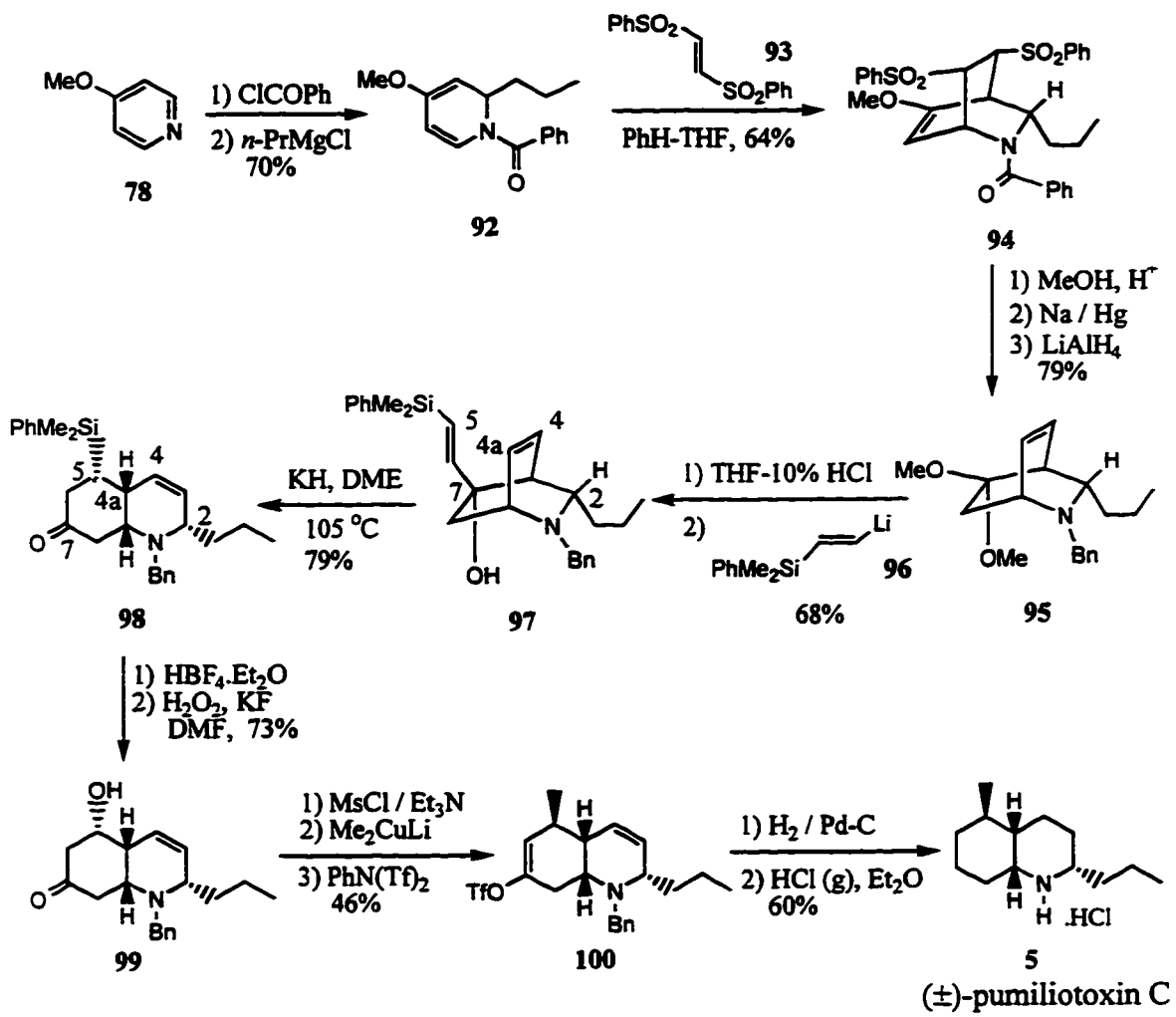
1.2.2.12 Polniaszek's synthesis

Polniaszek and Dillard employed a stereoselective Diels-Alder reaction followed by an anionic oxy-Cope rearrangement in their synthesis of (±)-pumiliotoxin C in 1992 (Scheme 1.16).[54] By following Comins's procedure (Scheme 1.14), **78** was converted to the racemic **92**. The Diels-Alder reaction of **92** with (E)-bis(phenylsulfonyl)ethylene (**93**) gave **94** exclusively so as to minimize steric interactions between the sulfone groups and the methoxy substituent and the N-acyl group. Moreover, approach of the dienophile occurred preferentially from the side away from the propyl group. The bicyclic compound **94** was treated with methanol under acidic conditions to produce the corresponding ketal, which was further elaborated to **95** by successive desulfonylation with sodium amalgam and amide reduction with lithium aluminum hydride. Transformation of the ketal to the ketone was followed by the attack of the vinyllithium **96** from the *exo* side to give **97**. The

carbinol **97** underwent anionic oxy-Cope rearrangement in DME to afford the *cis*-fused **98**. Oxidation of the phenyldimethylsilyl moiety of **98** furnished the hydroxy ketone **99**, which was dehydrated to the enone by treatment with MsCl / Et_3N, followed by DBN. The conjugate addition of lithium dimethylcuprate from the *exo* side, followed by trapping of the enolate with N-phenyltrifluoromethanesulfonimide gave **100**, which was hydrogenated over PtO_2 to yield (±)-pumiliotoxin C (**5**).

The Diels-Alder reaction and Cope rearrangement effectively provided the required relative configurations of the four chiral centers in **5**. However, the overall yield of **5** was low (5%) and the synthesis was lengthy (15 steps).

Scheme 1.16 : Polniaszek's synthesis of (±)-pumiliotoxin C



1.2.2.13 Murahashi's synthesis

Murahashi and co-workers reported a strategy for the synthesis of (-)-pumiliotoxin C based upon the ruthenium-catalyzed hydration of a nitrile under neutral conditions in 1993 (Scheme 1.17).[55] The key step was the transformation of δ-keto nitrile **102**, obtained from (R)-(+)-pulegone **101**, to the enamide **103**. The ruthenium-catalyzed hydration of nitrile **102** to the corresponding primary amide led to spontaneous intramolecular cyclization to provide **103**, after removal of the isopropylidene group by conjugate addition of water to **102** and subsequent retro-aldol reaction. Diastereoselective hydrogenation was carried out over palladium black to give a 98 : 2 mixture of *cis*-**33** and *trans*-**104**. This stereoselectivity was rationalized by assuming the formation of an N-acyliminium ion and hydrogenation from the more accessible *exo* side (Figure 1.4). Further elaboration of **33** to (-)-pumiliotoxin C (**5**) was performed *via* Oppolzer's procedure (Scheme 1.5).

The crucial step (from **102** to **103**) was successfully carried out to afford the lactam **103**. The synthesis of the key intermediate **33** is short (18% from **101** to **103**) and the control of stereochemistry was efficient at both of the new chiral centers at C-4a and C-8a.

Scheme 1.17 : Murahashi's synthesis of (-)-pumiliotoxin C

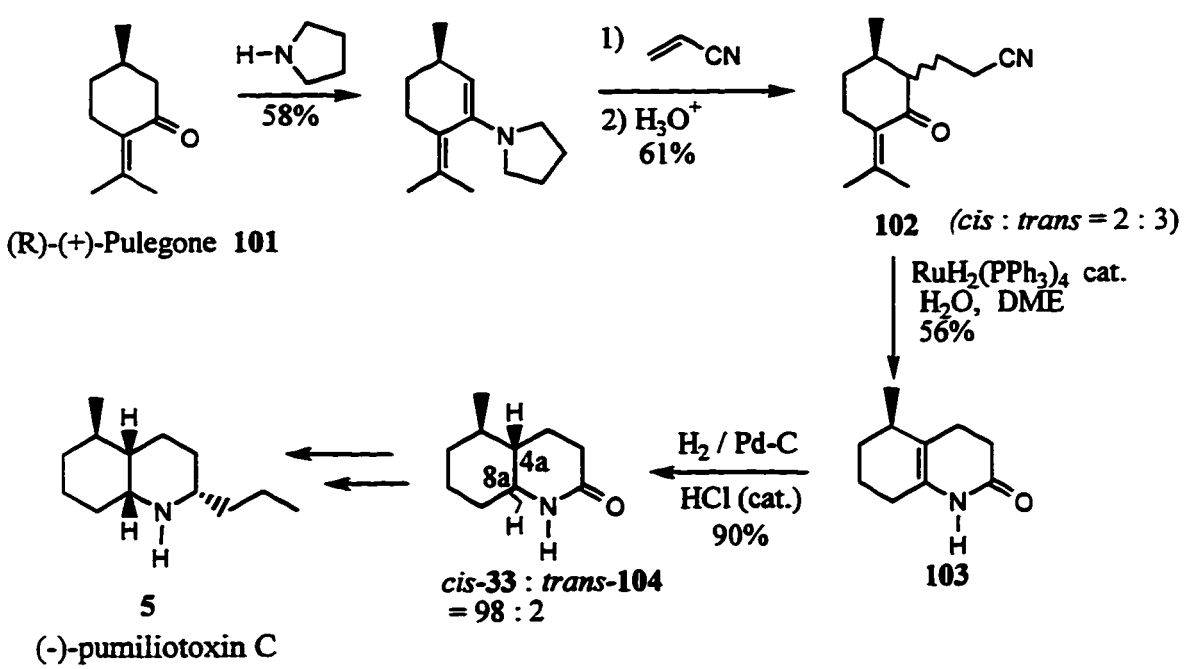
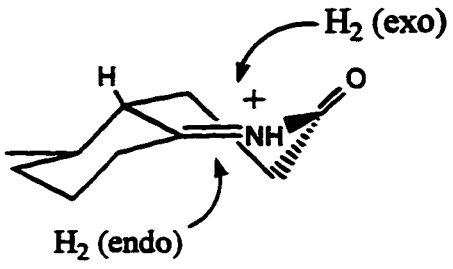


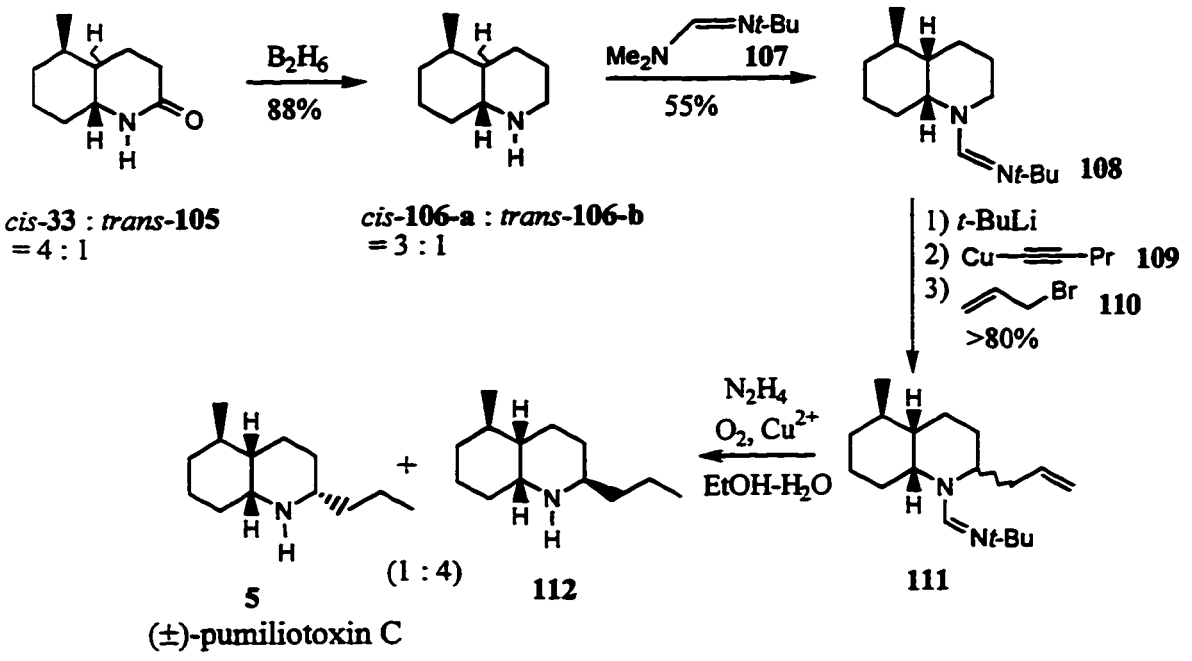
Figure 1.4



1.2.2.14 Meyers' synthesis

Meyers and Milot applied α-alkylation of *trans*- and *cis*-decahydroquinolines to the synthesis of (±)-pumiliotoxin C (**5**) in 1993 (Scheme 1.18).[56] Their general strategy involved the formation of N-Boc and N-formamidine decahydroquinolines, which allowed α-alkylation by successive treatment with bases and electrophiles. Based on Booth's earlier NMR studies,[57] the equilibrium of the conformations of *cis*-decahydroquinolines was predicted to favour **113** when bulky N-substituents such as Boc or formamidine groups were present. Subsequent alkylation at the α-position then preferentially gave **114**, where E is equatorial, as shown in Scheme 1.19. The mixture of *cis* and *trans* bicyclic lactams **33** and **105** was first converted to **106-a** and **106-b** by

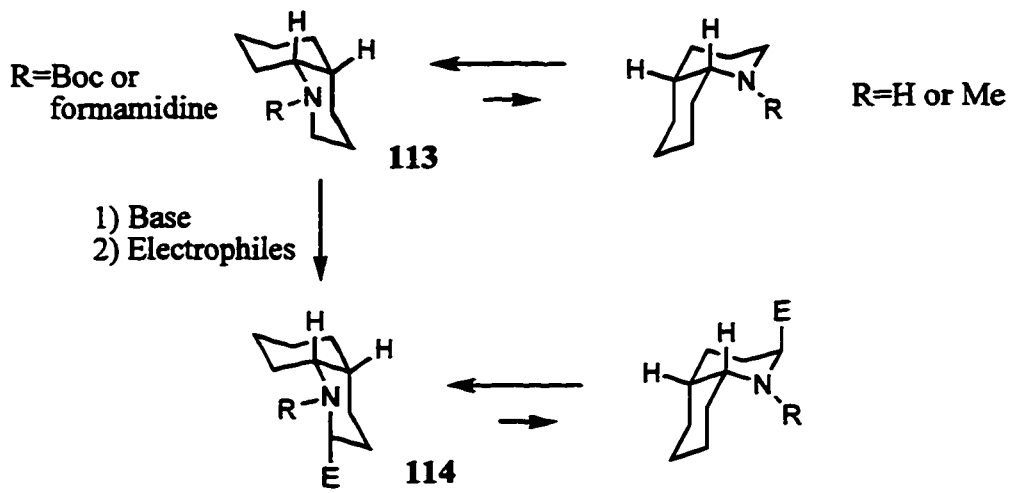
Scheme 1.18 : Meyers' synthesis of (±)-pumiliotoxin C



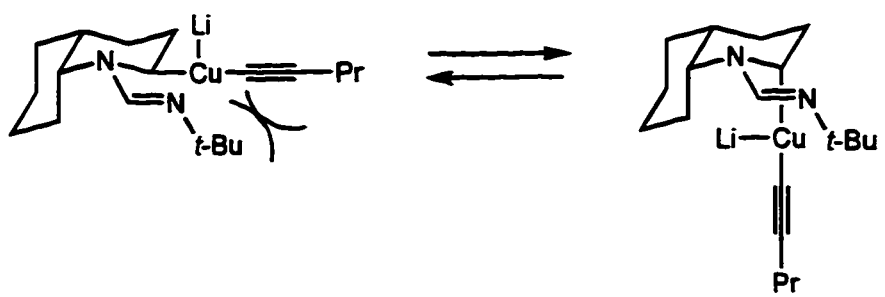
borane reduction, favouring the isomer **106-a** (Scheme 1.18). The thermal exchange of **106-a** with (dimethylamino)formamidine **107** provided **108**. The successive treatment of **108** with base, pentynylcopper **109** (this reagent was used to increase the ratio of axial substituted **111** due to $A^{(1,3)}$ strain as shown in Scheme 1.20), and allyl bromide **110** furnished a C-2 epimeric mixture of **111**, which was further transformed into a 4 : 1 mixture of 2-epi-pumiliotoxin C (**112**) and (±)-pumiliotoxin C (**5**). In the last step, the authors explained that oxygen and trace amounts of Cu^{2+} were needed to oxidize hydrazine to diimide, which was in turn used to reduce the olefin.

The poor stereoselectivity at C-2 limits the value of this approach, especially when it is recalled that the conversion of **33** to **5** had been previously reported by Oppolzer by a much more efficient method (Scheme 1.5).

Scheme 1.19 : Conformational equilibrium of *cis*-decahydroquinolines



Scheme 1.20 : Role of pentynylcopper **109**

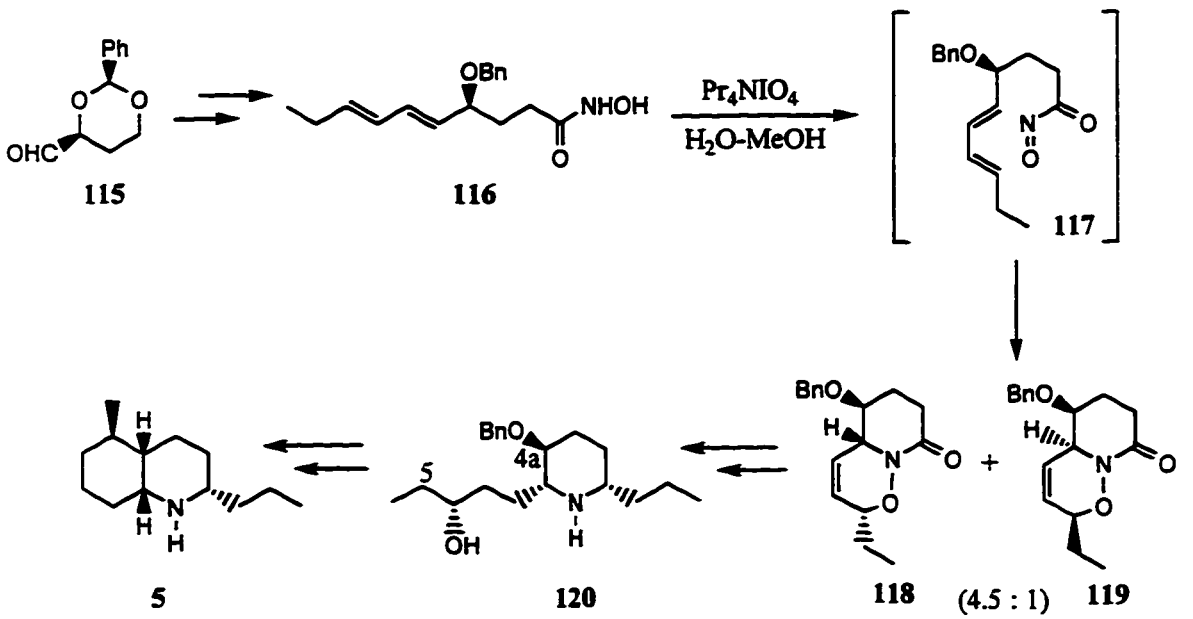


1.2.2.15 Kibayashi's synthesis

Kibayashi and co-workers applied the intramolecular hetero Diels-Alder reaction of a chiral acylnitroso compound to the synthesis of (-)-pumiliotoxin C in 1994[58a] and 1996[58b] (Scheme 1.21). The key intermediate, hydroxamic acid **116**, was obtained from the chiral starting material **115** (**115** was prepared from L-malic acid in 3 steps[59]). Periodate oxidation of **116** in H_2O-MeOH (6 : 1) afforded a 4.5 : 1 mixture of **118** and **119** *via* the intramolecular Diels-Alder reaction of the acylnitroso compound **117** that was generated *in situ*. When this reaction was conducted in chloroform, poor diastereoselectivity (**118** : **119** = 1.4 : 1) was obtained. However, an improved ratio of 4.5 : 1 was achieved under aqueous conditions. The desired **118** was then converted to the trisubstituted piperidine derivative **120**, which was finally elaborated to (-)-pumiliotoxin C (**5**) after many more steps.

The major disadvantage to this approach is that it is very lengthy (23 steps), giving 2 % overall yield of **5**. Elaboration of **120** to **5** turned out to be cumbersome in attempting to close the ring with proper control of the chiral centers at C-4a and C-5.

Scheme 1.21 : Kibayashi's synthesis of (-)-pumiliotoxin C

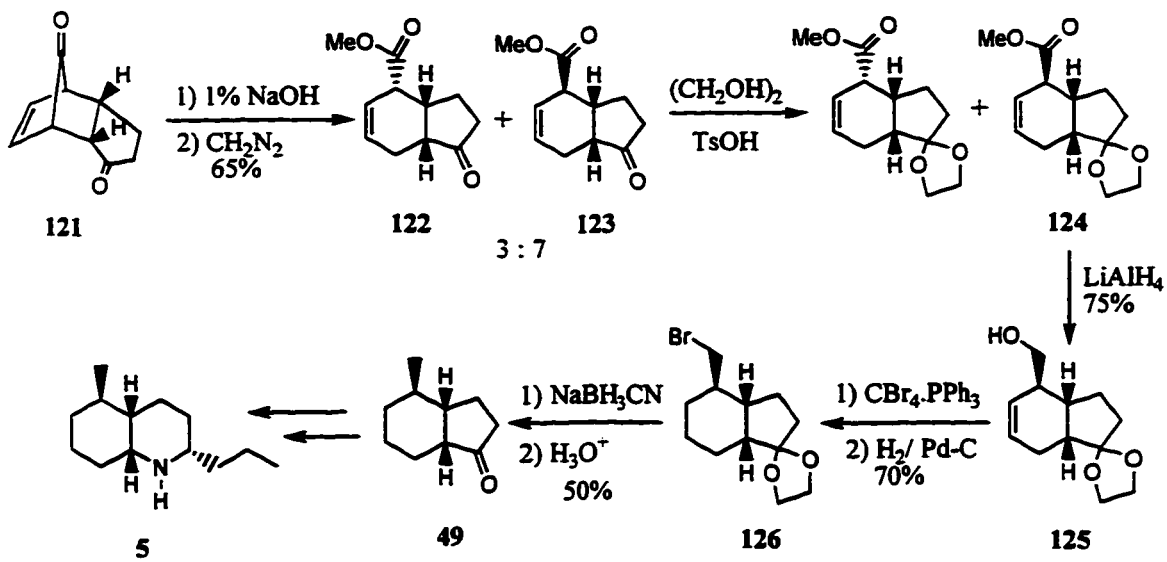


1.2.2.16 Mehta's synthesis

Mehta and Praveen reported the synthesis of (±)-pumiliotoxin C *via* a Haller-Bauer cleavage as the key step in 1995 (Scheme 1.22).[60] A 3 : 7 mixture of *cis*-hydrindanones **122** and **123** was prepared from **121** by Haller-Bauer cleavage conditions using 1% NaOH followed by diazomethane esterification. After ketalization, **124** was reduced to give **125**, which was converted to **126** by sequential bromination and catalytic hydrogenation. Reductive debromination in **126** provided **49**. Further elaboration of **49** to (±)-pumiliotoxin C (**5**) *via* the lactam **33** was performed by Oppolzer's procedure (Scheme 1.5).

The key step of this approach gave a low yield (46%) of the desired **123**, due to epimerization of the ester substituent. Furthermore, the transformation of **123** to the key intermediate **49**, which had been previously elaborated to pumiliotoxin C (**5**) by Oppolzer (Scheme 1.5), was inefficient (26% overall yield). These low yield steps limit the value of this approach.

Scheme 1.22 : Mehta's synthesis of (±)-pumiliotoxin C



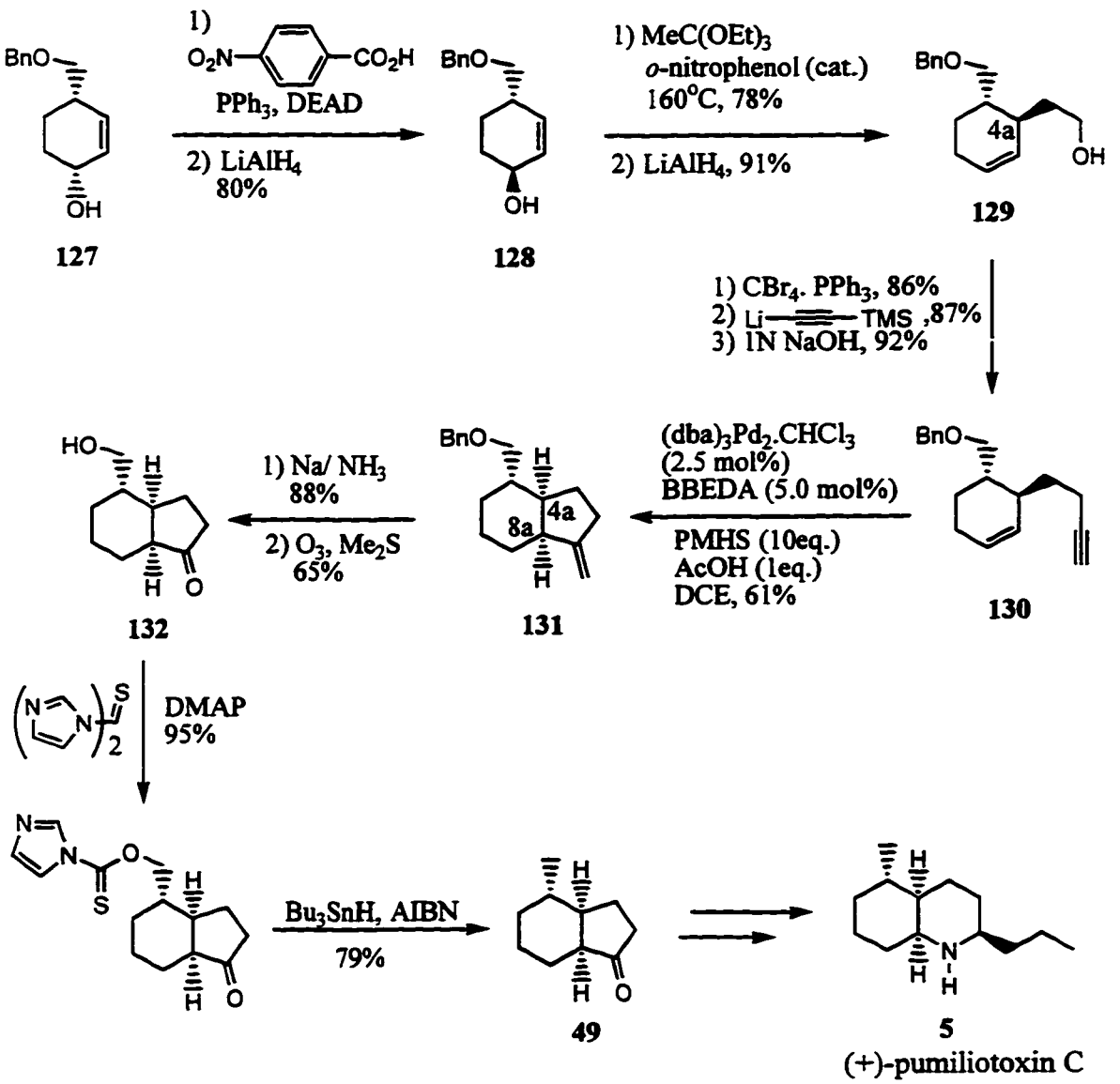
121 122 123 124 125 126 49 5

(±)-pumiliotoxin C

1.2.2.17 Fukumoto's synthesis

The latest synthesis of unnatural (+)-pumiliotoxin C was reported by Fukumoto and co-workers in 1996 (Scheme 1.23).[61] A chiral starting material **127** (**127** was prepared from (S)-3-cyclohexenecarboxylic acid in 5 steps[62]) underwent inversion *via* a Mitsunobu reaction to provide **128**. Thermal Claisen rearrangement of **128** with triethyl orthoacetate afforded the corresponding ester, which was reduced by lithium aluminum hydride to furnish the alcohol **129**. Bromination of **129**, followed by treatment with lithium trimethylsilylacetylide and subsequent desilylation gave the enyne intermediate

Scheme 1.23 : Fukumoto's synthesis of (+)-pumiliotoxin C



130. The palladium-catalyzed reductive cyclization of **130** as the key step of this synthesis provided *cis*-fused **131**. Reductive debenzylation and subsequent ozonolysis afforded *cis*-hydrindanone **132**. Deoxygenation resulted in the formation of **49**, which was then elaborated to (+)-pumiliotoxin C (**5**) by Oppolzer's procedure (Scheme 1.5).

The sterochemical control of the two chiral centers at C-4a and C-8a were effectively performed by Claisen rearrangement and the palladium-catalyzed reductive cyclization, respectively. However, the synthesis is lengthy, giving only 10% of **49**, which still had to be elaborated to **5** by Oppolzer's procedure (Scheme 1.5).

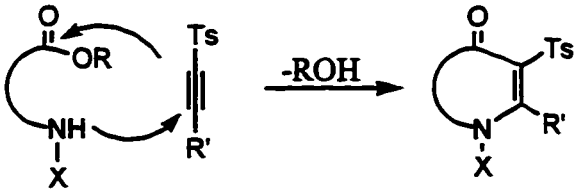
1.2.2.18 Synthesis of related compounds

Preparations of (±)-2-epi-pumiliotoxin C,[36,54,56] (-)-8-epi-pumiliotoxin C,[63] (-)-5-epi-pumiliotoxin C,[58b] and (±)-5-epi-pumiliotoxin C[64] have also been reported.

1.3 A new approach to pumiliotoxin C

Our approach to pumiliotoxin C (**5**) is based upon some novel applications of the chemistry of unsaturated sulfones that have been under investigation in our laboratory for many years.[13-23] In particular, it involves the Michael addition of an amine nucleophile to an acetylenic sulfone, followed by intramolecular acylation of the resulting enamine as the key steps (Scheme 1.24).

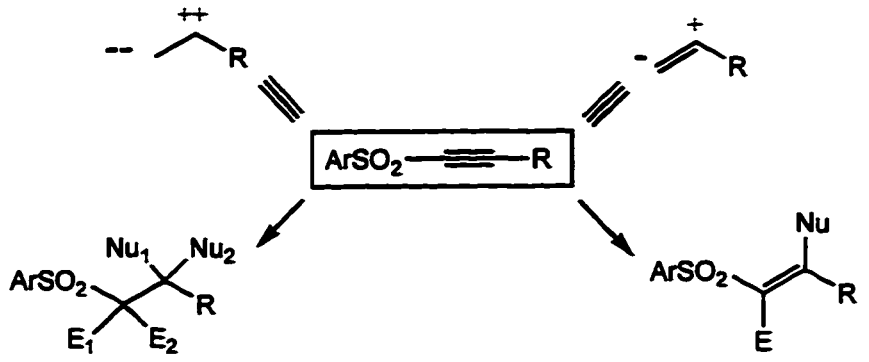
Scheme 1.24 : The key steps of the new approach



X= H, or protecting group

This approach is thus based on the more general hypothesis that an acetylenic sulfone serves as an alkene dipole or alkane multipole equivalent,[22] which has both electrophilic character at the β-position and nucleophilic character at the α-position (Figure 1.5).

Figure 1.5

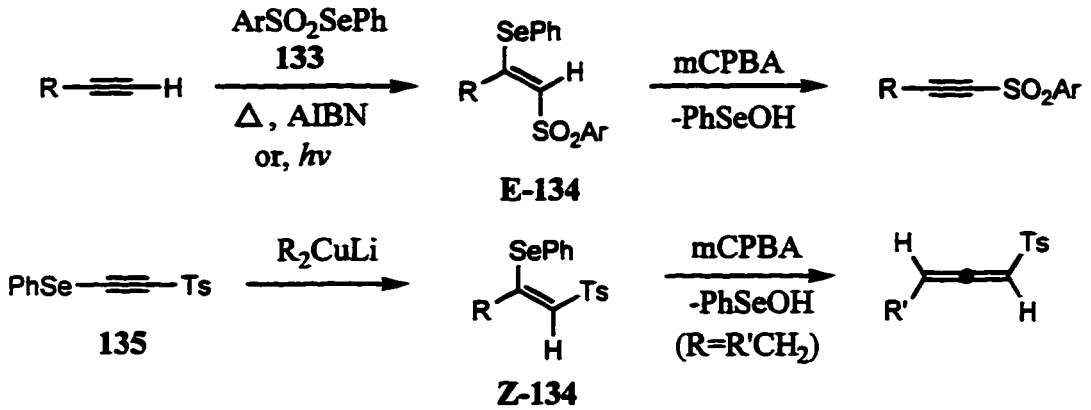


Since our synthesis of pumiliotoxin C resulted from ongoing studies of acetylenic and other types of unsaturated sulfones, a brief review of relevant aspects of sulfone chemistry follows. In general, acetylenic sulfones, together with other types of α,β-unsaturated sulfones such as vinyl and allenic sulfones, have been extensively studied as versatile intermediates in organic synthesis.[65] The main features of these compounds are that they act as Michael acceptors and dienophiles (or other types of 2π components) in cycloaddition reactions. Moreover, both saturated and vinyl sulfones can be deprotonated and alkylated at the α-position. Finally, the disposable sulfone group can be removed by reduction after these transformations are complete. In the following sections 1.3.1-1.3.4 are given brief discussions of the preparation of acetylenic sulfones, Michael additions to them by amine nucleophiles, α-alkylations and acylations that are relevant to our synthesis, and reductive desulfonylation. The outline of the new approach to pumiliotoxin C (**5**) by retrosynthetic analysis follows in section 1.3.5.

1.3.1 Preparation of acetylenic sulfones

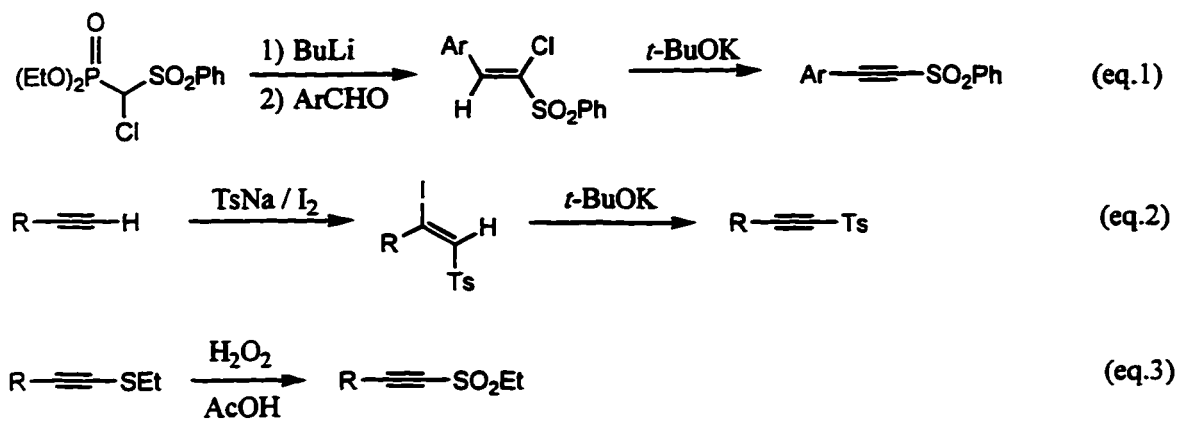
Following a convenient new synthesis of selenosulfonates **133** from the oxidation of sulfonhydrazides with benzeneseleninic acid in 1980,[66] Back and Collins in our laboratory,[14] and independently Kobayashi's group in 1982,[67] applied the free-radical "selenosulfonation" of terminal acetylenes to the preparation of acetylenic sulfones (Scheme 1.25). This method was further extended to the use of **135**, which allows a variety of alkyl groups to be introduced to **134** with cuprates, by Back and Wehrli in 1995.[22] The two methods achieve complementary stereoselectivity and afford acetylenic and allenic sulfones, respectively, after selenoxide *syn*-elimination.

Scheme 1.25 : Preparation of acetylenic and allenic sulfones by selenoxide elimination



Several other methods are also available for the preparation of acetylenic sulfones,[65] and several examples are shown in Scheme 1.26. They are the Horner-Emmons reaction, followed by dehydrochlorination (eq.1),[68] the reactions of acetylenes with TsNa / I_2, followed by dehydroiodination (eq.2),[69] and the oxidation of acetylenic sulfides (eq.3).[70] Acetylenic sulfones are therefore readily available by several convenient methods.

Scheme 1.26 : Some other preparations of acetylenic sulfones

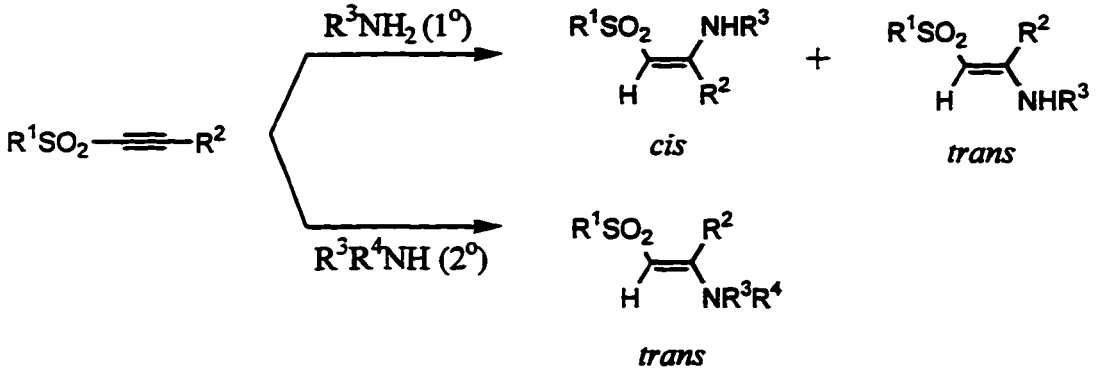


1.3.2 Michael additions of amine nucleophiles to acetylenic sulfones

A series of studies of the additions of amines to acetylenic sulfones were performed by Stirling[71] and Truce[72] in the 1960's and 1970's. The additions of amines occur at the β-position and the stereochemistry of the adducts is controlled by several factors that are summarized below.

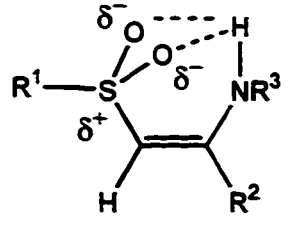
First, the structure of the amine determines to a great extent the stereochemistry of the adducts. Additions of primary (1°) and secondary (2°) amines to substituted acetylenic sulfones provide an equilibrium mixture of *cis* and *trans* adducts, and exclusively the *trans* adducts, respectively (Scheme 1.27).

Scheme 1.27 : Additions of amines to substituted acetylenic sulfones



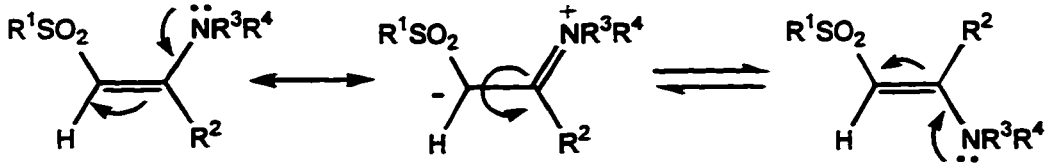
It has been shown that the addition of 1° amines initially occurs in an *anti* manner (sulfone group and amine group are *cis*) to afford the *cis* adduct as the kinetic product. In the case of primary amines, hydrogen bonding between the NH and sulfonyl oxygen atoms stabilizes the *cis* adduct (Figure 1.6). Subsequent equilibration affords mixtures of *cis* and *trans* adducts.

Figure 1.6 : Stabilization of *cis* adduct by hydrogen bonding



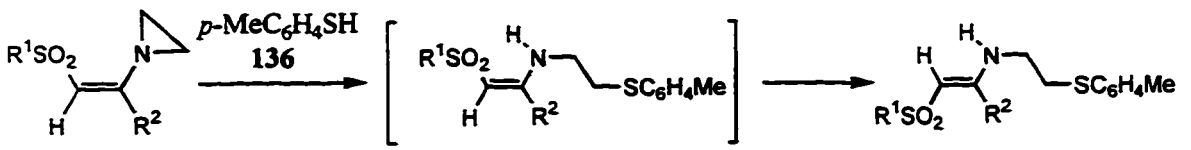
On the other hand, reactions of secondary amines that lack such hydrogen bonding result solely in the formation of the thermodynamically more stable *trans* adducts after isomerization (Scheme 1.28). The greater stability of the *trans* adduct can be explained by dipole cancellation and the absence of non-bonded interactions between the sulfone group and amine group. An NMR study in one case supported the initial formation of the *cis* adduct, whose signals were observed at low temperature, but completely disappeared upon warming to room temperature.

Scheme 1.28 : Isomerization from *cis* to *trans* adduct



One exceptional case was found with ethyleneimine (aziridine), which gave a mixture of *cis* and *trans* adducts, suggesting that despite its secondary structure, complete isomerization was hard to achieve due to the instability of the corresponding strained iminium structure in Scheme 1.28. Relief of this strain by aziridine ring-opening with **136** led to a high yield of the *trans* adduct (Scheme 1.29). This observation also supports the above explanation.

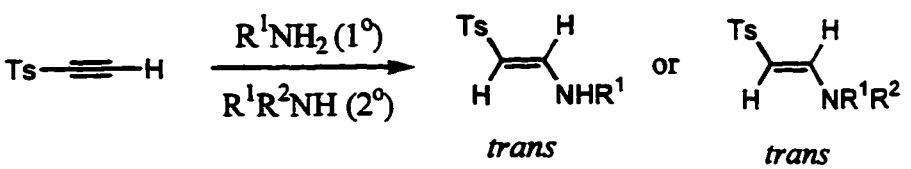
Scheme 1.29



Second, solvents also affect the ratio of *cis* and *trans* adducts between primary amines and acetylenic sulfones. In protic solvents hydrogen bonding between the solvent and the adduct competes with intramolecular hydrogen bonding and leads to higher ratios of *trans* : *cis* adducts, while in aprotic solvents, where solely intramolecular hydrogen bonding is possible, leads to higher *cis* : *trans* ratios.

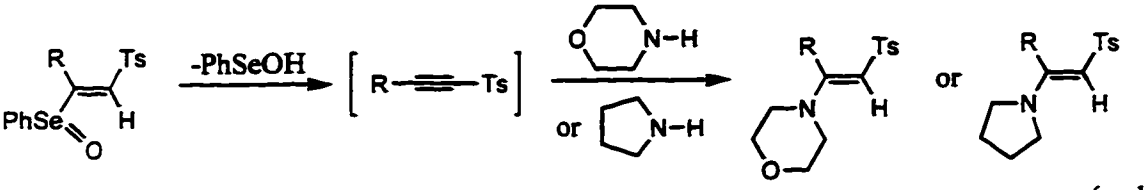
Terminal acetylenes behave in a different manner from substituted ones. Both primary and secondary amines gave exlcusively *trans* adducts, except for aniline and aziridine (Scheme 1.30). Since aniline has an acidic hydrogen for hydrogen bonding with the sulfonyl oxygen atom, it also gave a small amount of the *cis* adduct as well as the major *trans* adduct. Aziridine furnished only the *cis* adduct for the same reason as explained above for substituted acetylenes.

Scheme 1.30 : Additions of amines to terminal acetylenic sulfones

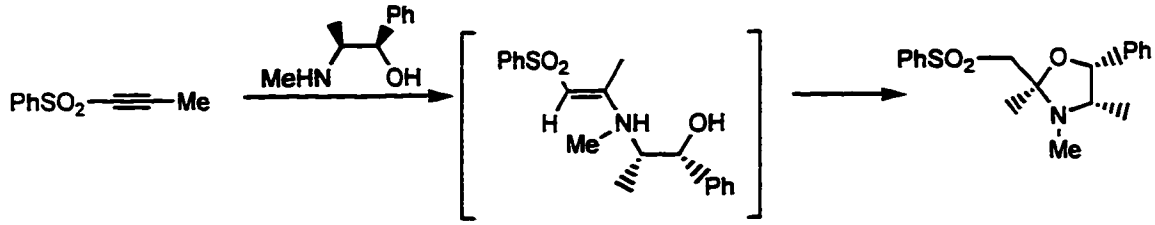


These general features of amine additions to acetylenic sulfones were also observed by Back et al. (eq.1)[17] and Cinquini et al. (eq.2)[73] (Scheme 1.31).

Scheme 1.31



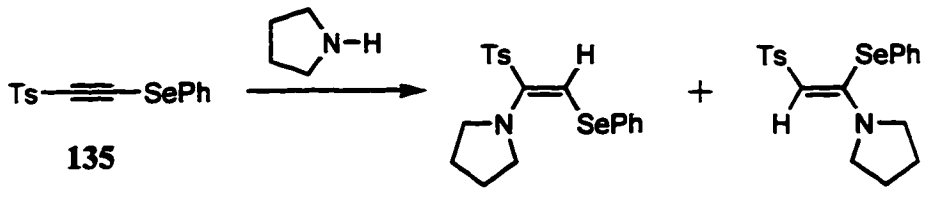
(eq.1)



trans enamine (eq.2)

Recently, Back and Wehrli reported the unexpected *anti*-Michael additions of an amine to the acetylenic sulfone **135**, in which the phenylseleno group clearly had a strong influence on the regiochemistry of the addition (Scheme 1.32).[22]

Scheme 1.32 : Unexpected *anti*-Michael addition



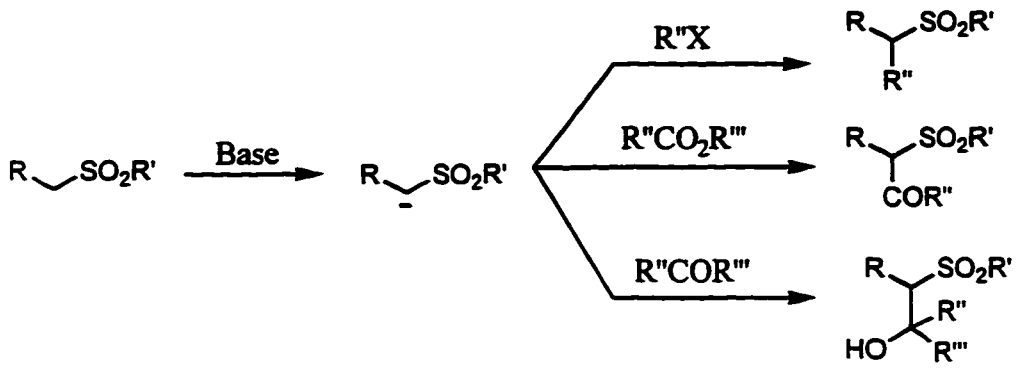
major minor

In conclusion, the regio- and stereochemistry of these additions is controlled by several factors, including the structure of the amine (primary, secondary, or aziridine), the acetylene (terminal or substituted) and the type of solvent.

1.3.3 Sulfone-stabilized carbanions

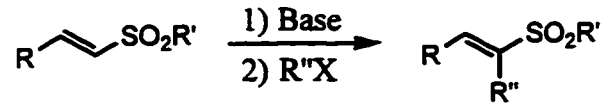
Sulfone-stabilized carbanions have been widely utilized for alkylation, acylation, and addition reactions to carbonyl compounds (Scheme 1.33).[74-76]

Scheme 1.33



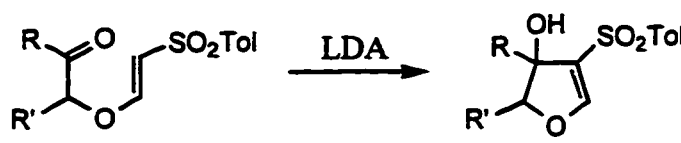
Vinyl sulfones, where carbanions must be formed from deprotonation of sp^2 centers, undergo similar transformations to the above (e.g. Scheme 1.34).[77]

Scheme 1.34



One example of an intramolecular addition to a carbonyl group by a β-oxygen-substituted vinyl sulfone is shown in Scheme 1.35. In this reaction there was a strong kinetic preference for formation of the vinyl carbanion over the alternative ketone enolate, thus making the cyclization possible.[78] Similar cyclizations of β-amino-substituted vinyl sulfones have not yet been reported.

Scheme 1.35



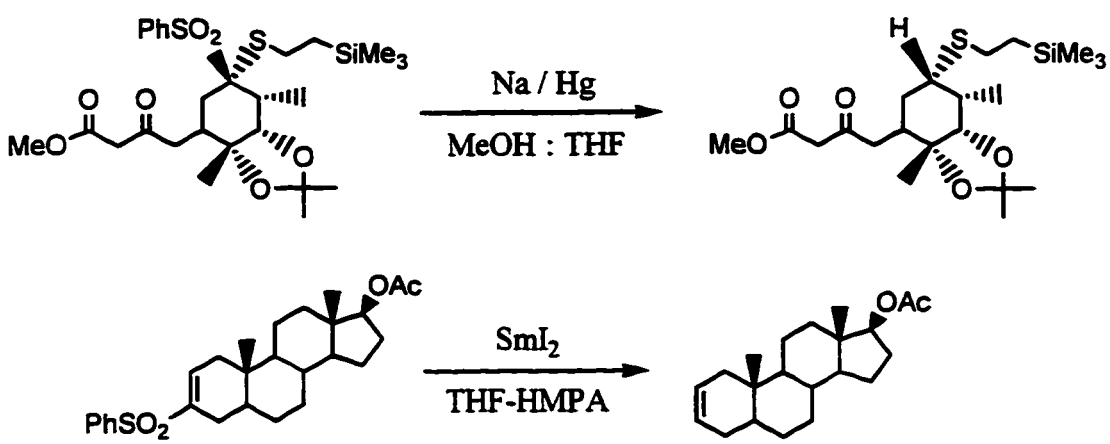
1.3.4 Reductive desulfonylation

As discussed above, sulfones are versatile tools in organic synthesis. However, the removal of the sulfone group is usually required after all other transformations are complete in order to obtain the desired target molecule. Thus, methods for reductive desulfonylation are needed for this purpose.

Among a number of methods established so far,[65a,79] sodium amalgam has been most widely used for the cleavage of aryl sulfones ($ArSO_2$), which are often employed as disposable functional groups in organic transformations.[80] The advantage of this reagent is its mildness that prevents the reduction of certain other functional groups present in the molecule. For example, the ester, ketone, ketal, sulfide, and silyl groups all survived in the reaction shown in Scheme 1.36.[81] Although this reagent is assumed to work in a similar manner to Birch reductions, phenyl groups also survive the desulfonylation conditions.[82] The use of alkali metals in liquid amines generally gives low yields of desulfonylated compounds, and results in competing side reactions such as cleavage of benzyl or allyl groups and reduction of carbonyl groups.[83]

Samarium (II) iodide has also been used as a mild desulfonylating reagent and does not affect acetate groups,[84] where partial or full conversions of ROAc to ROH were observed with sodium amalgam.[82a,85]

Scheme 1.36 : Desulfonylation by sodium amalgam and samarium (II) iodide

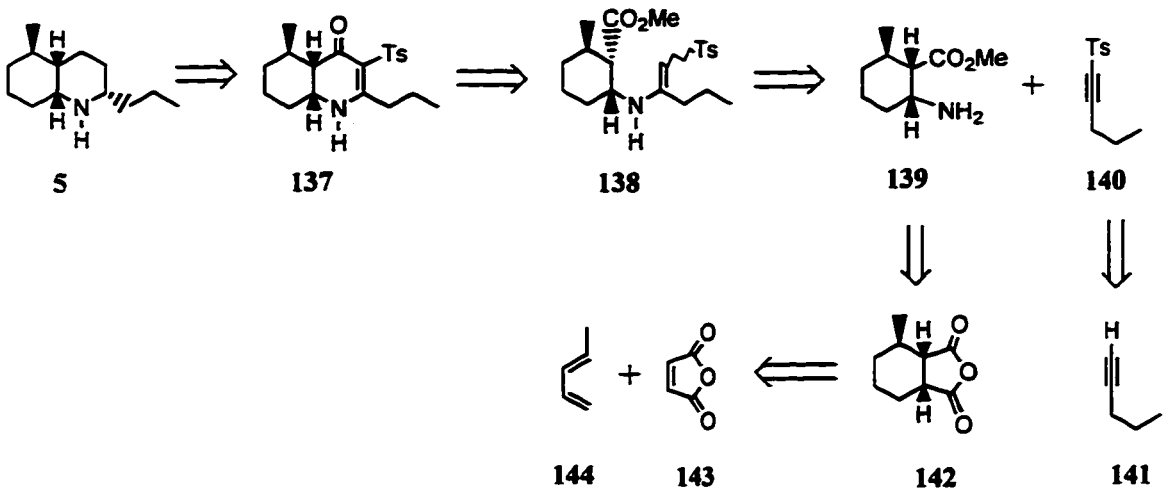


Another mild desulfonylation reagent is magnesium in methanol,[86] but this reagent also reduces carbon-carbon double bonds of α,β-unsaturated esters[87a,b] or imines, and enamines which are conjugated with carbonyl groups or aromatic rings.[87a]

1.3.5 Retrosynthetic analysis of the new approach to pumiliotoxin C

The principal aim of this Thesis was to investigate the possibility of employing the sequential Michael addition and α-acylation of an appropriate combination of a β-functionalized amine and acetylenic sulfone for the preparation of pumiliotoxin C. Our approach is shown retrosynthetically below (Scheme 1.37).

Scheme 1.37 : Retrosynthetic scheme of our approach



The target molecule **5** is obtained from **137** by the *exo*-hydrogenation and removal of the carbonyl and tosyl groups. The enaminone **137** is in turn obtained by intramolecular acylation of **138**, which is in turn obtained by the Michael addition of 1° amine **139** to acetylenic sulfone **140**. The latter two compounds are the key intermediates of this synthesis. The 1° amine **139** can be obtained by modifying the anhydride **142** *via* regioselective alcoholysis to give the corresponding half-ester (or regioselective saponification of the corresponding diester), followed by a Curtius rearrangement to generate the required amino group in **139**. The stereochemistry of the anhydride **142** is ensured by the Diels-Alder reaction of piperylene **143** and maleic anhydride **145**, followed by base-catalyzed epimerization. The other key intermediate **140** is afforded by the "selenosulfonation" of the terminal acetylene **141**, followed by the corresponding selenoxide elimination, using the procedure previously reported by Back and Collins in our laboratory.[14]

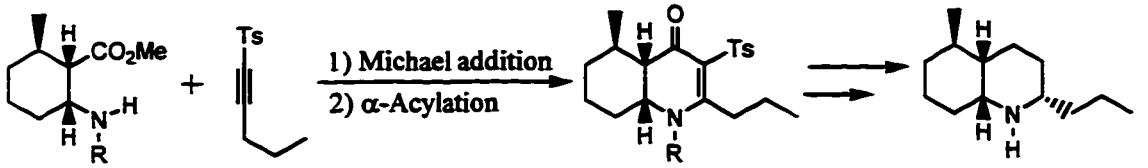
Detailed discussions of the preparation of the two key intermediates **139** and **140**, their coupling and intramolecular cyclization, and the reduction of **137** leading to pumiliotoxin C (**5**) are given in the following chapter.

Chapter Two
Synthesis of (±)-Pumiliotoxin C

2.1 Introduction

As discussed in Chapter One, our synthesis of pumiliotoxin C (**5**) involves the sequential Michael addition and α-acylation of an appropriate combination of β-functionalized amine and acetylenic sulfone as shown in Scheme 2.1.

Scheme 2.1: Key steps of our strategy to pumiliotoxin C

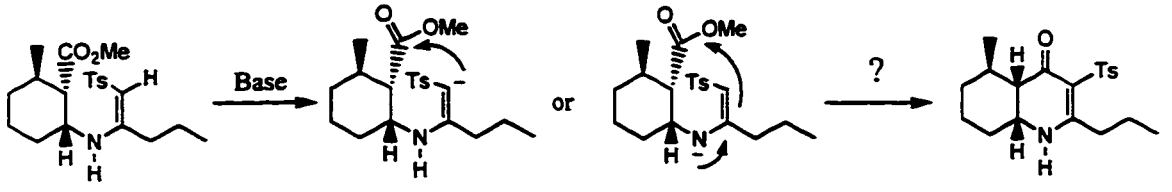


R= H or protecting group **140**

enaminone **137** (R = H)

We attempted three approaches to the above cyclization. First, we investigated if a suitable carbamate (R = CO_2Me) could be converted to its amide anion and added to **140**. Alternatively, the more basic primary amine (R = H) and its N-benzyl derivative (R = CH_2Ph) were also investigated. Based on the studies of Stirling[71] and Truce,[72] the latter was expected to give the corresponding enaminone under base-catalyzed conditions, *via* the exclusive formation of the (E)-enamine as an intermediate. On the other hand, the primary amine would give a mixture of (E)- and (Z)-enamines, in which the (Z)-isomer might not undergo the cyclization, due to strain and steric crowding by the Ts group in the intramolecular acylation step, as shown in Scheme 2.2. Our studies of the preparation and cyclization of the three systems (R = CO_2Me, H, Bn) are described in the following sections.

Scheme 2.2 : α-Acylation of the (Z)-enamine



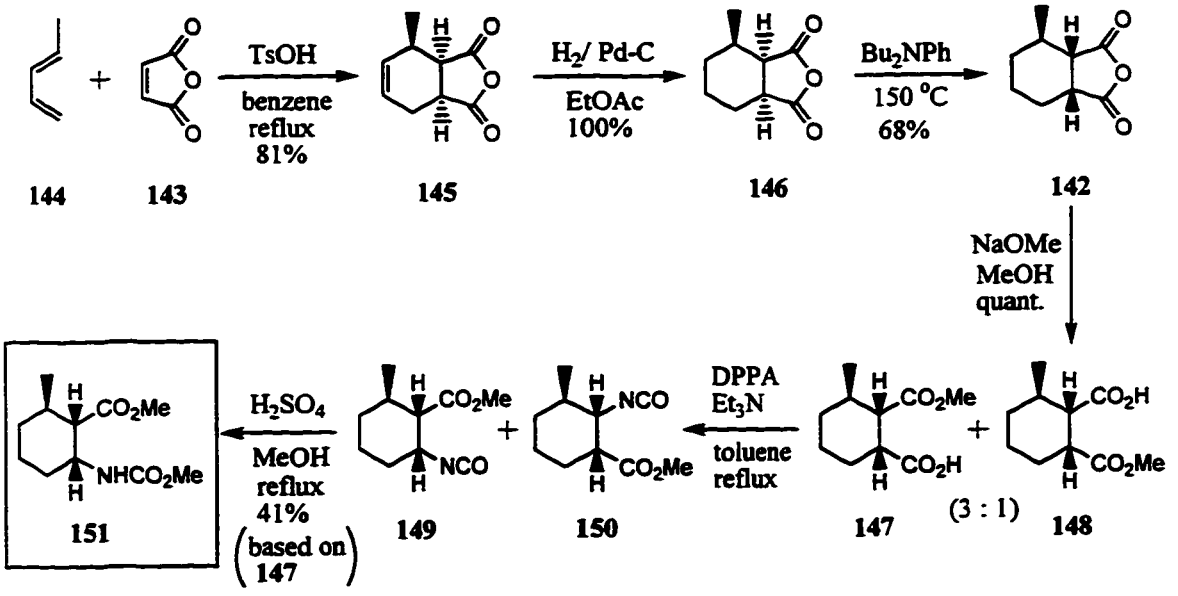
(Z)-enamine

2.2 Attempted addition of carbamate 151 to the acetylenic sulfone 140

2.2.1 Preparation of the carbamate 151

The preparation of the carbamate **151** is shown in Scheme 2.3. Construction of the required relative configurations of the three chiral centers in **151** was performed by Craig's procedure for the synthesis of the cyclic anhydride **142**.[88] First, the Diels-Alder reaction of *trans*-piperylene **144** with maleic anhydride **143** provided the adduct **145**,[89] which was hydrogenated over Pd-C to afford **146**. Then, base-catalyzed epimerization of the two chiral centers α to the carbonyl groups furnished the anhydride **142**.

Scheme 2.3 : Preparation of the carbamate **151**



In order to transform the anhydride **142** to the desired β-amino ester, its regioselective methanolysis was carried out under various conditions to give at best a mixture of half-esters **147** and **148** in the ratio of ca. 3 : 1. The regioisomers could not be separated by either column chromatography or crystallization. This ratio is explained by the preferential attack of the methoxide anion at the equatorial carbonyl group of **142**. The coupling constants of the proton Ha in the NMR spectrum were 10.3 Hz (axial-axial, Ha-Hc) and 7.9 Hz (axial-equatorial, Ha-Hb), indicating that the anhydride **142** has a conformation in which the methyl and one carbonyl group are equatorial and the other carbonyl group is axial (Figure 2.1). Structure determinations of **147** and **148** were tentatively based on the chemical shift of the methyl groups (*CH*$_3$CH), because signals of

protons Hw and Hy and those of protons Hx and Hz overlapped so as to make any distinction between them impossible. The methyl group of **147** (δ 1.06) appeared at higher field than that of **148** (δ 1.08) in the NMR spectrum. This could be due to the effect of the β-substituents that were the ester group (CO_2Me) in **147** and the carboxylic acid (CO_2H) in **148**. Thus, from the supporting data that the methyl group (CH_3CH) of the dimethyl ester **152** (δ 1.03) appeared at higher field than that of the dicarboxylic acid **153** (δ 1.11) (Figure 2.2), **147** was assigned as *trans*-3-methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, 2-methyl ester and **148** as *trans*-3-methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, 1-methyl ester. The assignment was confirmed by the further transformation of the mixture of **147** and **148** as follows.

Figure 2.1 : Methanolysis of **142**

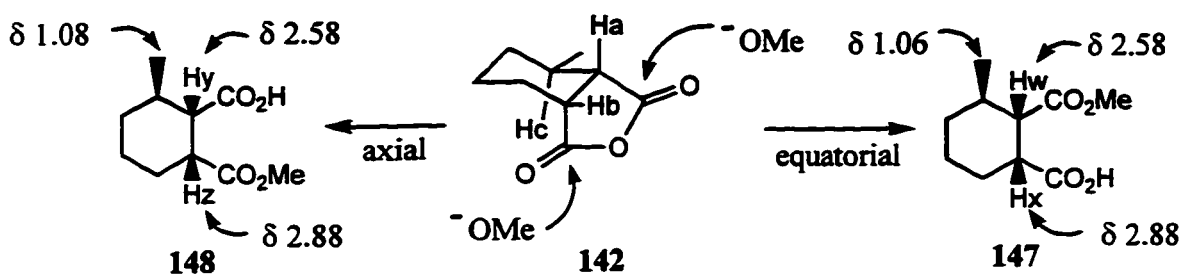
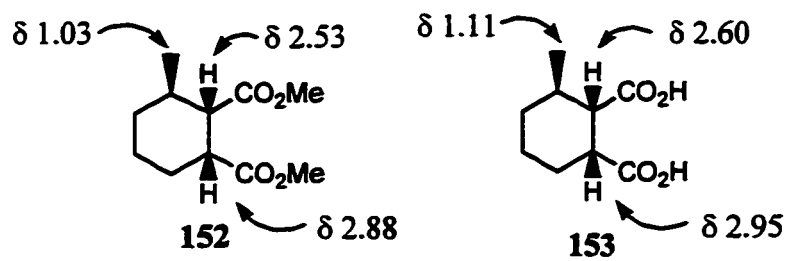


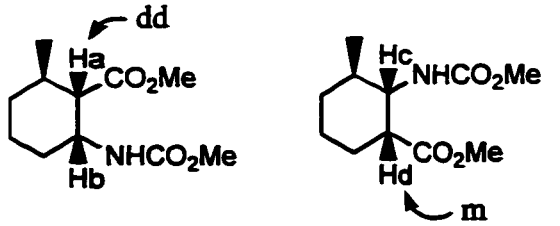
Figure 2.2 : Dimethyl ester **152** and dicarboxylic acid **153**



The mixture of the half-esters **147** and **148** was then subjected to a Curtius rearrangement effected with diphenylphosphoryl azide[90] (DPPA) in the presence of triethylamine to give the corresponding isocyanates **149** and **150**, respectively. The formation of the isocyanates was confirmed by observing the N=C=O absorption (2270 cm^{-1}) in the IR spectrum. Treatment of these isocyanates with water[91] would be expected to afford the desired free β-amino ester **139**. However, in order to avoid possible polymerization by intermolecular amidation between the nucleophilic (NH_2) and electrophilic (CO_2Me) sites in **139**, the isocyanates were converted to less nucleophilic

carbamates by treatment with methanol in the presence of a catalytic amount of sulfuric acid. The separation of **151** from its regioisomer, derived similarly from **148**, was performed by crystallization. The structure of the carbamate **151** was confirmed based on the chemical shift of the proton α to the ester group and its splitting pattern. The signal observed at δ 2.30 was a doublet of doublets (*J*=10.2, 3.8 Hz), suggesting that it is Ha. In the case of the regioisomer of **151**, the proton α to the ester group (Hd) appeared as a multiplet at δ 2.90 (Figure 2.3).

Figure 2.3 : Structures of **151** and its regioisomer

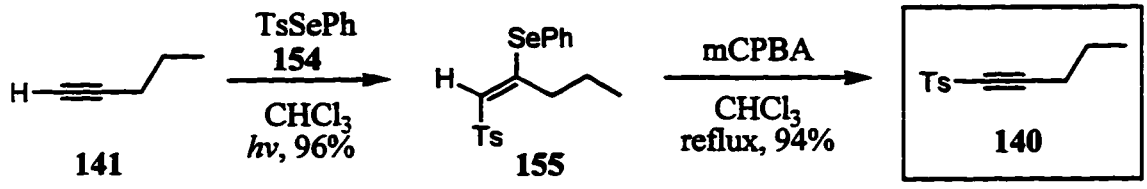


151 regioisomer of **151**

2.2.2 Preparation of the acetylenic sulfone 140

The acetylenic sulfone **140** was prepared by the general procedure of Back and Collins (Scheme 2.4).[14] Commercially available 1-pentyne **141** underwent "selenosulfonation" with *Se*-phenyl *p*-tolueneselenosulfonate **154** to afford β-(phenylseleno)vinyl sulfone **155** as a single stereo- and regioisomer. Oxidation of **155** with mCPBA resulted in a selenoxide *syn*-elimination to furnish the desired acetylenic sulfone **140**, with properties identical to those reported for this product as prepared by a different method elsewhere.[69a]

Scheme 2.4 : Preparation of the acetylenic sulfone **140**

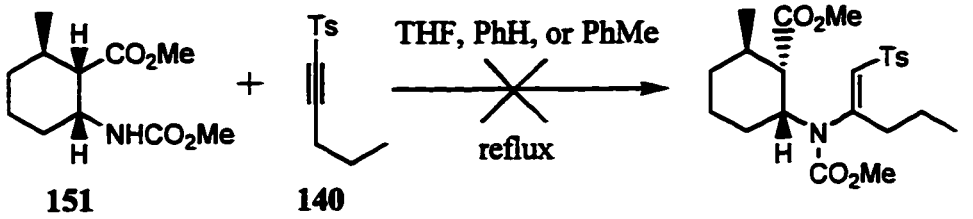


141 **155** **140**

2.2.3 Attempted Michael addition of the carbamate 151 to the acetylenic sulfone 140

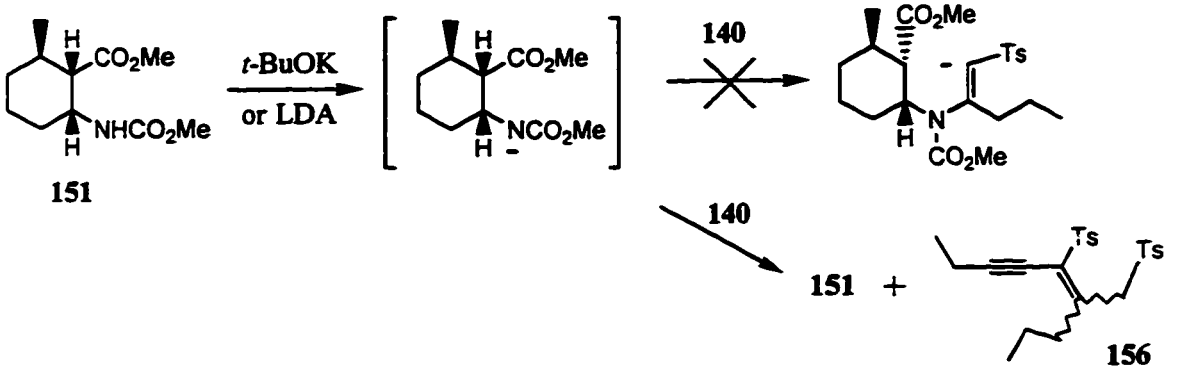
Coupling of the carbamate **151** with the acetylenic sulfone **140** was first attempted without the addition of a base to produce the corresponding amide anion (Scheme 2.5). However, no reaction proceeded in refluxing THF, benzene, or even toluene. This result was not surprising in view of the weak nucleophilicity of **151**.

Scheme 2.5 : Attempted Michael addition of **151** to **140**

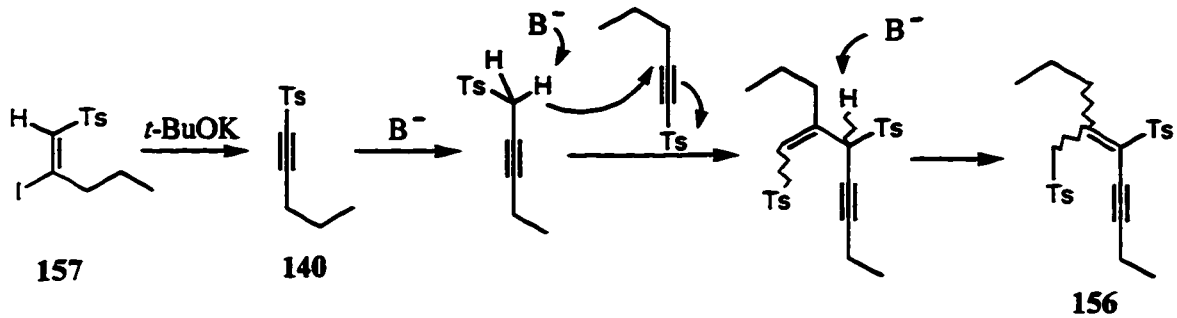


By prior treatment with a sufficiently strong base, however, the carbamate **151** produces a more strongly nucleophilic anion. Unfortunately, the overall reaction resulted in the formation of two dimeric stereoisomers **156** derived form **140**, as well as recovery of the starting material **151** (Scheme 2.6). The similar formation of dimers **156** had been previously reported from (E)-2-iodo-1-tosyl-1-pentene (**157**) by the proposed mechanism shown in Scheme 2.7.[69a]

Scheme 2.6 : Attempted Michael addition of the conjugate base of **151** to **140**



Scheme 2.7 : Proposed mechanism of dimerization of **140**



157 **140** **156**

2.2.4 Conclusion

Michael addition of the carbamate **151** to the acetylenic sulfone **140** did not proceed, even in the presence of an added base to form the corresponding anion of **151**. Instead, dimerization of **140** was observed.

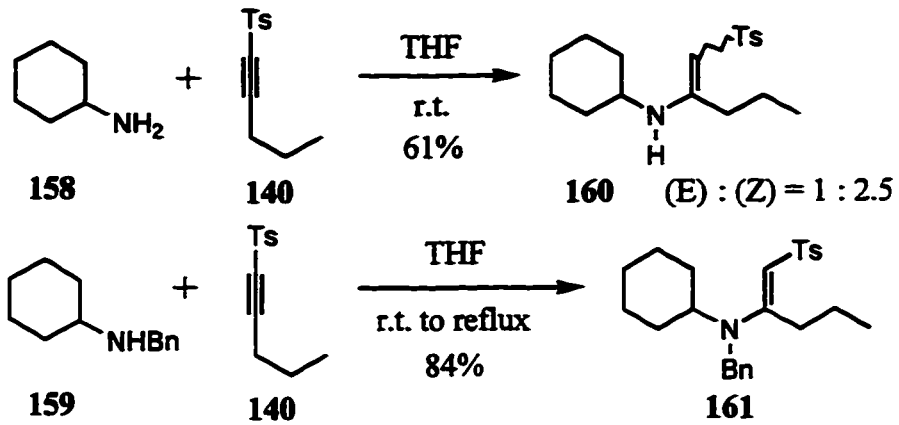
2.3 Reaction of primary amine 139 and its benzyl derivative 163 with the acetylenic sulfone 140

2.3.1 Model study

The failure of the Michael addition of the carbamate **151** to the acetylenic sulfone **140** led us to investigate the use of β-amino esters that lack the delocalizing carbamate group. Since the β-amino ester required for our synthesis of pumiliotoxin C is a cyclohexylamine derivative, a model study was first carried out with cyclohexylamine (**158**) itself, and with N-benzylcyclohexylamine (**159**). Both amines gave the expected products as a mixture of (E)- and (Z)-stereoisomers **160** from **158**, and exclusively as the (E)-isomer **161** from **159** (Scheme 2.8). The stereochemistry was as predicted on the basis of discussion presented in section 1.3.2. In the NMR spectra of these products, two and one vinyl signals were observed as singlets for **160** (δ 4.99-**E** and 4.51-**Z**) and **161** (δ 4.93), respectively, suggesting that they are enamines. In NOE experiments with **160**, 3.0 % enhancement of the signal of the allylic protons was observed when the vinyl signal of the (Z)-isomer was irradiated. Also, 16.4 % enhancement of the CHN signal was observed by irradiation of the vinyl signal of the (E)-isomer. The compound **161** was tentatively assigned as an (E)-enamine based on the comparison of the chemical shift of

its vinyl signal (δ 4.93) with that of the (E)- (δ 4.99) and (Z)- (δ 4.51) isomers of **160**. The IR, ^{13}C NMR, and mass spectra of **160** and **161** also suggested the structures shown.

Scheme 2.8 : Model study for Michael addition of free amines to **140**



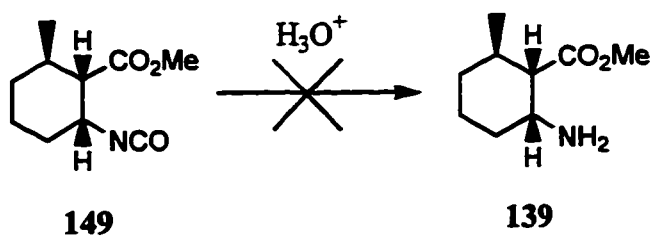
The success of the model reactions therefore prompted an investigation of the required primary amine **139** and its N-benzyl derivative **163**, where the as yet unprecedented α-acylation of the resulting β-amino substituted vinyl sulfones might lead to the desired cyclized products.

2.3.2 Preparation of amines 139 and 163

2.3.2.1 Attempted hydrolysis of isocyanate 149

Free amines (RNH_2) are generally obtained from isocyanates (RNCO) by hydrolysis.[90,91] Therefore, our first attempt to prepare **139** was the acid-catalyzed hydrolysis of **149** (Scheme 2.9), which had been obtained as an inseparable mixture with its regioisomer **150** (see Scheme 2.3).

Scheme 2.9 : Attempted hydrolysis of the isocyanate **149**



149 **139**

Several attempts were made by changing the acidity, temperature and time of the reaction, but clean **139** was not obtained. In neutral or weakly acidic conditions (2-10% HCl), some starting material was recovered along with complex mixture of products that could not be identified with certainty. In more strongly acidic conditions (5-10% H_2SO_4), all of the starting material was consumed, but again the products were formed as complex mixtures.

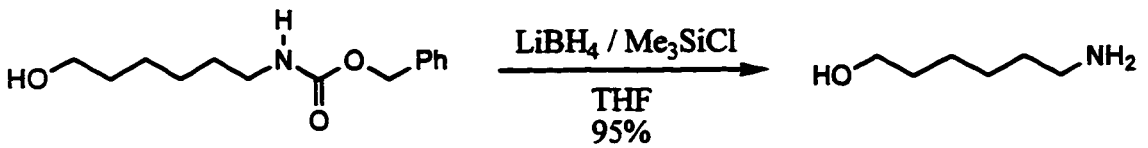
It seems probable that the amine **139** was actually formed by hydrolysis of the isocyanate, but competing polymerization also occurred during the reaction. When hydrolysis under neutral conditions was attempted, starting material persisted and the products that gradually formed were again obtained as complex mixtures. Thus, no optimum conditions could be found for the clean acid-catalyzed hydrolysis of **149** to **139**. Basic conditions with NaOH were not attempted in order not to affect the ester group.

2.3.2.2 Attempted reduction of the carbamate 151

Our next attempt to prepare **139** was the selective reduction of **151**. Generally, the reduction of carbamates by diborane or $LiAlH_4$ affords the corresponding methylamines,[92] but Giannis and Sandhoff reported the use of $LiBH_4$ / Me_3SiCl in THF, from which they suggested the formation of BH_3-THF complex *in situ*, for the reduction of a carbamate to furnish a primary amine (Scheme 2.10).[93]

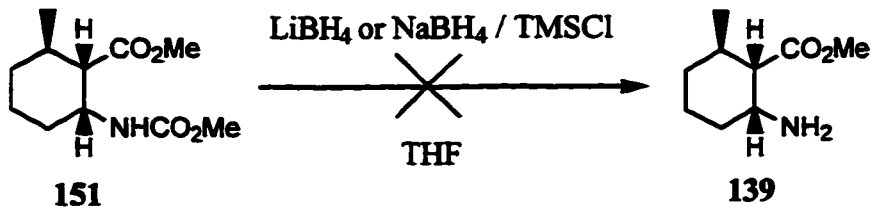
Scheme 2.10 : Reduction of carbamates

$$R_2NCO_2Me \xrightarrow[LiAlH_4]{B_2H_6 \text{ or}} R_2NMe$$



Since the carbamate **151** has two carbonyl groups (ester and carbamate), the reduction has to be carried out chemoselectively. The selective reduction of the carbamate over the ester moiety was expected, because the carbonyl oxygen atom of the carbamate group is more electron-rich than that of the ester group, resulting in preferential attack upon the electrophilic borane (Scheme 2.11). However, neither the use of $LiBH_4$ nor $NaBH_4$ with Me_3SiCl gave any reduced products and only starting material was recovered (>80%).

Scheme 2.11 : Reduction of **151**

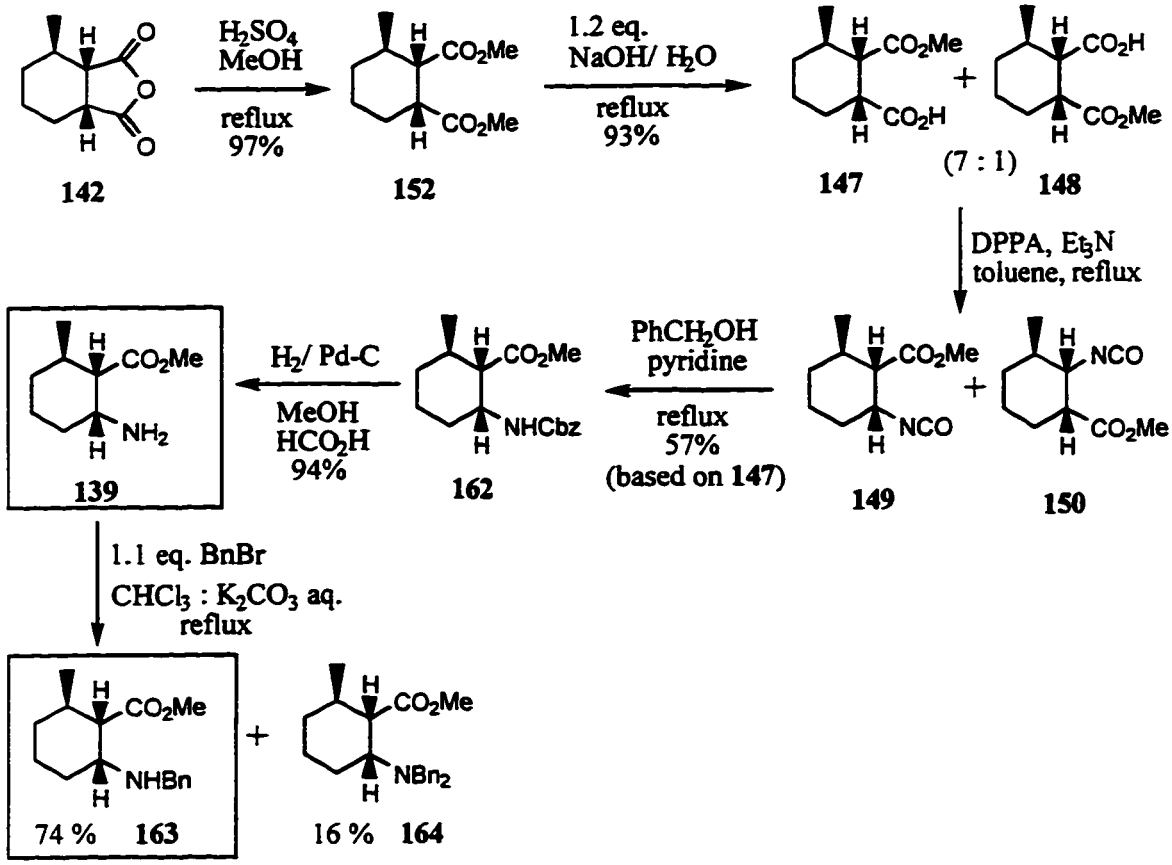


151 **139**

2.3.2.3 Hydrogenolysis of the Cbz derivative 162

The Carbobenzyloxy (Cbz) group is one of the most widely used protecting groups for amines because of the ease of removal by acid-catalyzed hydrolysis or hydrogenolysis.[94a] The use of the Cbz group provides the advantage that when it is removed, basic conditions are not required so as not to affect the ester group. Preparation of the Cbz derivative **162** and its hydrogenolysis to the desired free amine **139** are shown in Scheme 2.12. Moreover, during this phase of the project, a more regioselective

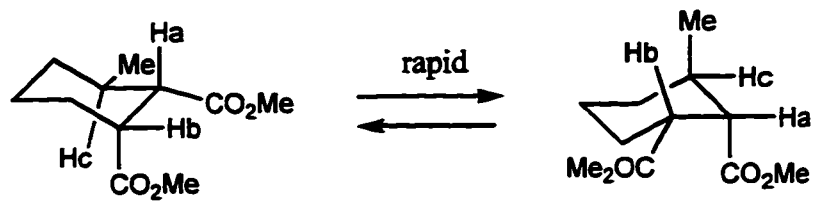
Scheme 2.12 : Preparation of amines **139** and **163**



preparation of the half-ester **147** was developed

The anhydride **142** was prepared in the previously described manner as shown in Scheme 2.3. It will be recalled that methanolysis of **142** gave the half-esters **147** and **148** in the ratio of ca. 3 : 1. This ratio was improved to ca. 7 : 1 by selective saponification of the corresponding diester **152**. This improved selectivity can be explained as follows. First, hydrolysis of axial esters gives more crowded tetrahedral intermediates, so that equatorial esters should be hydrolyzed preferentially. According to molecular modeling (the energies of the two chair conformations of **152** were obtained at the STO-3G *ab initio* level with Spartan), the conformer **152a** is more stable than **152b** by 2.59 kcal / mol. Therefore, the major product should be the undesired regioisomer **148**. Fortunately, this was not so, indicating that **152b** had reacted preferentially. In the NMR spectrum, the presumably more stable conformer **152a** (where the methyl group as well as one ester substituent are equatorial) should show a diaxial coupling of ca. 10-13 Hz between Ha and Hc. On the other hand, the diequatorial coupling of Ha and Hc in **152b** would be expected to have a much smaller value of 2-5 Hz.[94b] However, the observed coupling of 7.2 Hz, which is intermediate between the expected value for **152a** and **152b**, suggests rapid interconversion of **152a** and **152b** on the NMR time scale (Figure 2.4).

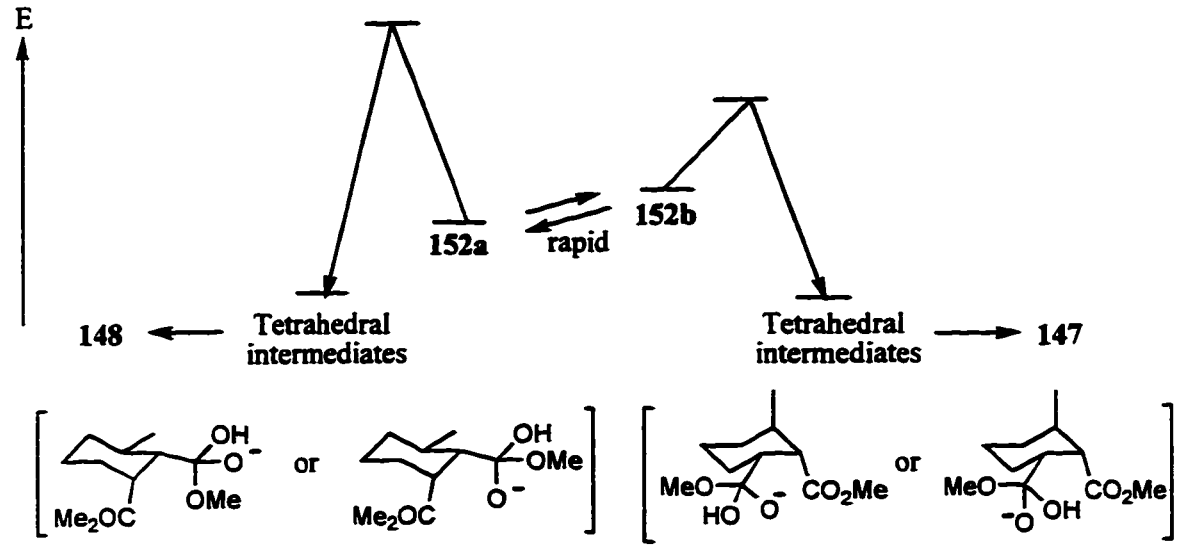
Figure 2.4 : Interconversion of **152a** and **152b**



152a **152b**

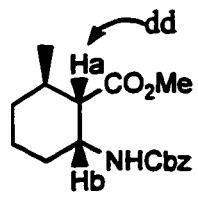
Thus, a possible explanation for the preferential formation of **147** over **148** is that hydrolysis of the equatorial ester in **152b** is kinetically favoured over hydrolysis of the equatorial ester of **152a**, even though the latter is more stable. The proposed overall reaction scheme can be described in the following energy diagram (Figure 2.5), where the saponification of **152** is rationalized by the Curtin-Hammett principle.[95]

Figure 2.5 : Possible reaction diagram of the selective saponification of **152**

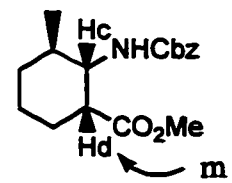


The 7 : 1 mixture of half-esters **147** and **148** was then subjected to a Curtius rearrangement effected with DPPA[90] in the presence of triethylamine to provide the corresponding isocyanates **149** and **150**, respectively. Treatment of the mixture of **149** and **150** with benzyl alcohol in pyridine afforded the Cbz derivative **162**, which was separated from its regioisomer, derived similarly from **148**, by column chromatography. The structure of the Cbz-protected amine **162** was confirmed based on the chemical shift of the proton α to the ester group and its splitting pattern. The signal observed at δ 2.30 was a doublet of doublets (J= 10.1, 3.6 Hz), suggesting that it is Ha. In the case of the regioisomer of **162**, the proton α to the ester group (Hd) appeared as a multiplet at δ 2.90 (Figure 2.6).

Figure 2.6 : Structures of **162** and its regioisomer



162



regioisomer of **162**

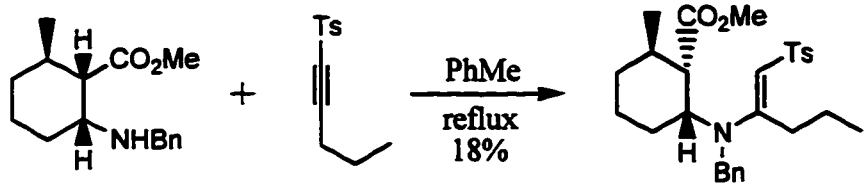
Next, deprotection of the Cbz group of **162** was performed by hydrogenolysis with Pd-C in ether or methanol. In both cases isolation of the free amine was precluded by competing polymerization. Successful deprotection of the Cbz group to afford the amine **139** was eventually achieved by the addition of formic acid to the methanol solution of **162**. The use of formic acid forms the amine salt RNH_3^+ which suppresses polymerization. Thus, after completion of the reaction, the methanol solution was evaporated *in vacuo*, the residue was made basic with 1.0 N NaOH and the free amine was rapidly extracted with ether. The ether was then carefully evaporated *in vacuo* without heating to furnish **139** as a colourless oil in 94 % yield. After this experiment had been completed, the synthesis of **139** was reported by Davies and Bhalay *via* a different approach.[96]

Finally, the N-benzyl derivative **163** was prepared by treatment of **139** under standard conditions[97] with benzyl bromide in refluxing $CHCl_3$: K_2CO_3 - H_2O.

2.3.3 Michael addition of amines 163, 166 and 139 to the acetylenic sulfone 140

The Michael addition of the N-benzylamine **163** to the acetylenic sulfone **140** afforded exclusively the (E)-isomer **165** (Scheme 2.13), but in no more than 18% yield under a variety of conditions.

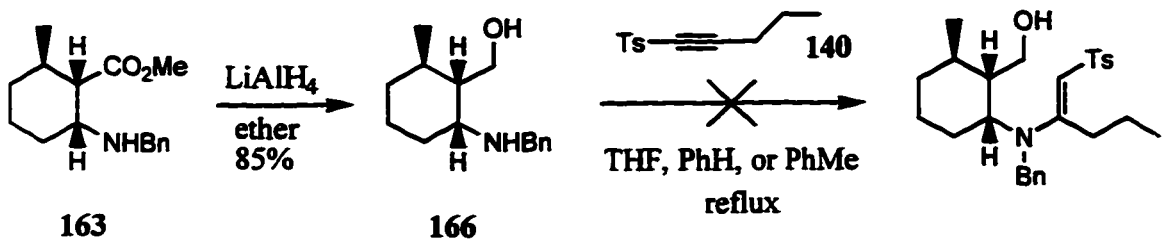
Scheme 2.13 : Michael addition of **163** to **140**



163 **140** **165**

Similarly, **163** was reduced to its hydroxymethyl derivative **166**, but attempts to couple it with **140** again failed to proceed in refluxing THF, benzene, or even toluene (Scheme 2.14). Since N-benzylcyclohexylamine (**159**) underwent Michael addition smoothly in the model study in Scheme 2.8, one of the possible reasons that **163** and **166** failed to undergo Michael addition in high yield may be their relatively greater steric hindrance due to the ester or hydroxymethyl substituents, respectively.

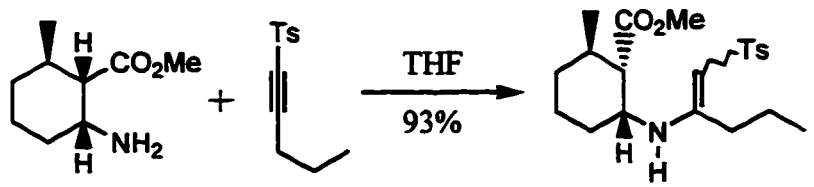
Scheme 2.14 : Preparation of **166** and its attempted Michael addition to **140**



163 **166**

The Michael addition of the primary amine **139** to the acetylenic sulfone **140** afforded a mixture of (E)- and (Z)-isomer in the ratio of ca. 1 : 2.5 in high yield (Scheme 2.15).

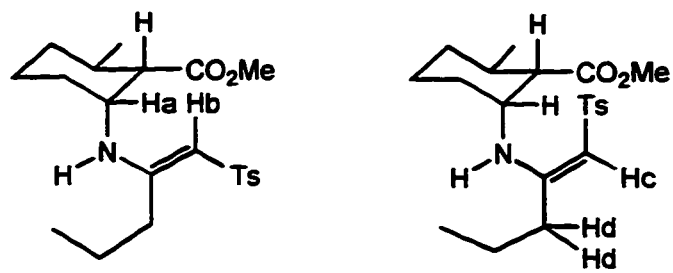
Scheme 2.15 : Michael addition of **139** to **140**



139 **140** **138** (E) : (Z) = 1 : 2.5

The geometry of **138** was determined based on an NOE experiment. In the (E)-isomer, an NOE of 19.4 % (Ha) was observed when the vinylic Hb was irradiated, while in the (Z)-isomer, an NOE of 3.4 % (Hd) was observed when the vinylic Hc was irradiated. (Figure 2.7).

Figure 2.7 : NOE experiment of **138**



(E)-isomer of **138** (Z)-isomer of **138**

2.3.4 Conclusion

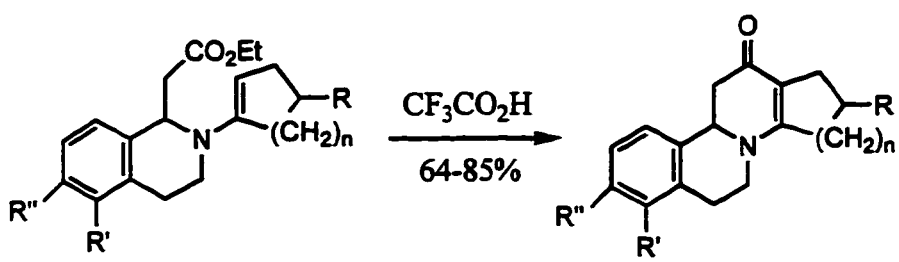
In the model study, both cyclohexylamine (**158**) and N-benzylcyclohexylamine (**159**) smoothly underwent Michael addition to the acetylenic sulfone **140** to afford the corresponding enamines. Unfortunately, the bulkier N-benzyl β-amino ester **163** failed to undergo a similarly efficient Michael addition, giving only 18 % yield of the product **165**. Furthermore, the hydroxymethyl derivative **166** failed to undergo any Michael addition to **140** at all. Consequently, the plan to use secondary amines to obtain exclusively the (E)-isomer of the desired adduct had to be abandoned. We therefore turned our attention to the use of the primary amine **139**, which had afforded a high yield of the enamine sulfone **138** as an (E), (Z) mixture. It will also be recalled that some concern remained regarding the possibility of cyclizing the (Z)-isomer of **138** (see Scheme 2.2), which was the major stereoisomer of the addition. Nevertheless, with **138** in hand, we investigated the subsequent cyclization of the (E), (Z) mixture.

2.4 Intramolecular cyclization of 138

2.4.1 Introduction

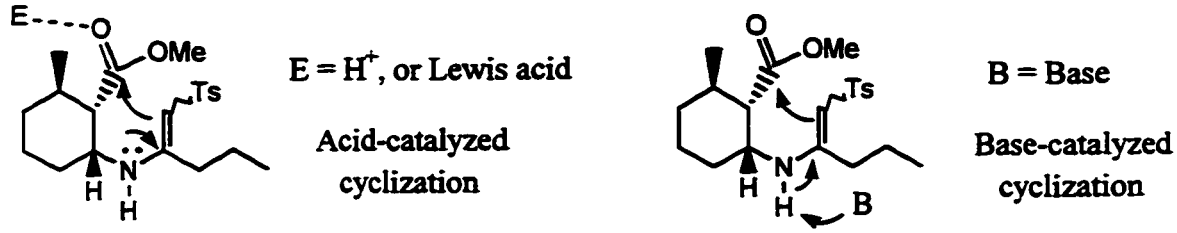
Acylations of enamines at the β-carbon are usually performed with acid chlorides or anhydrides,[98] but several successful intramolecular cyclizations of β-enamino esters to form six-membered rings have been reported (e.g. Scheme 2.16).[99] However, the α-acylations of β-amino substituted vinyl sulfones have not yet been reported.

Scheme 2.16 : Cyclization of β-enamino esters



When the Michael addition of **139** to **140** shown in Scheme 2.15 was conducted in refluxing THF, benzene, or toluene, the further intramolecular cyclization did not occur. Therefore, the use of either acid or base catalysts appeared necessary (Figure 2.8).

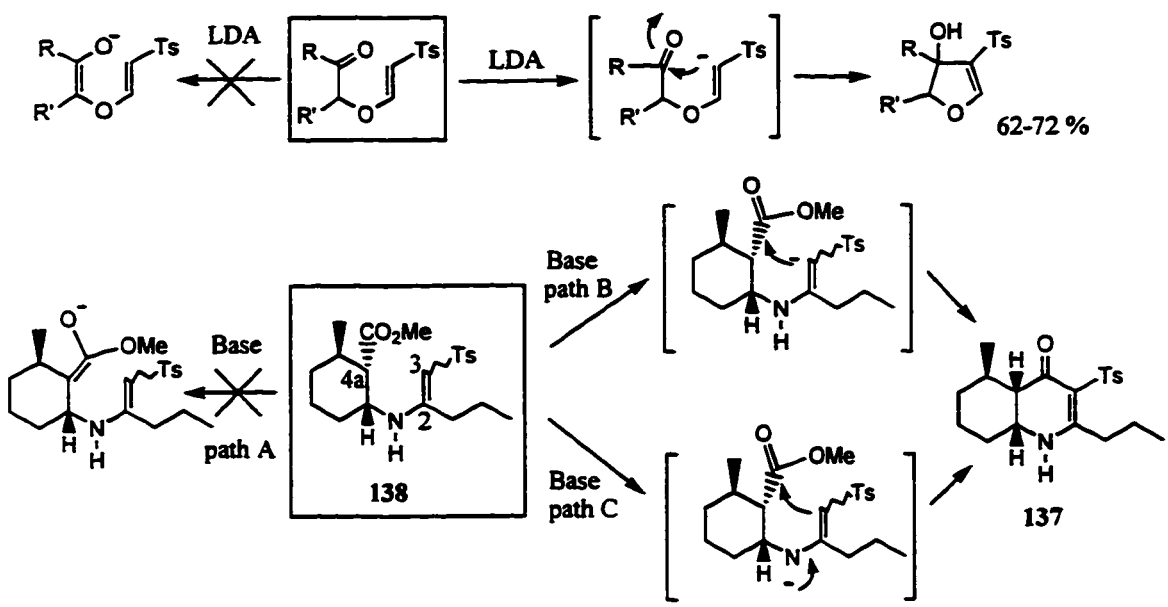
Figure 2.8 : Acid or base-catalyzed intramolecular cyclization of **138**



The cyclization was first attempted in the presence of *p*-toluenesulfonic acid. However, cyclization was not observed and hydrolysis of the enamine function occurred. We therefore investigated base catalysis.

Three protons in **138** are relatively acidic and must be considered in the base-catalyzed approach. They are the amino proton and the protons α to the sulfone and carbonyl groups. Previously, it will be recalled that the β-oxy-substituted vinyl sulfone shown in Scheme 1.35 and below in Scheme 2.17 underwent similar ring closure.[78] In that case, there was a kinetic preference for the formation of the vinyl carbanion over the alternative ketone enolate. In the case of **138**, a stronger kinetic preference for the corresponding vinyl carbanion (path B) over the alternative ester enolate (path A) is expected because the α-protons of esters (pKa 24.5) are less acidic than those of ketones (pKa 19-20).[100] This is required not only for the cyclization to succeed, but also to avoid possible epimerization of C-4a (Scheme 2.17).

Scheme 2.17 : Cyclization of β-oxy and β-amino substituted vinyl sulfones

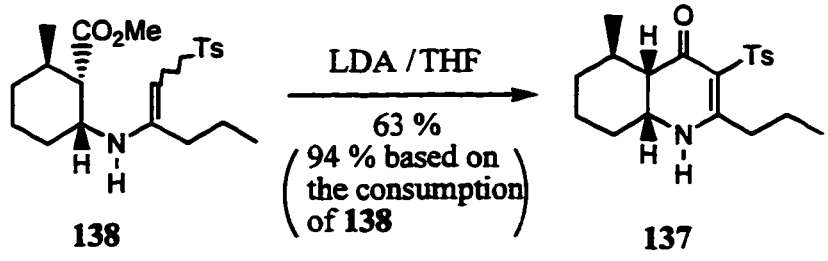


Moreover, N-deprotonation must also be considered (path C), since a relatively stable anion is formed, subject to resonance and the electron-withdrawing effect of the sulfone group. As discussed in Scheme 2.2, if the reaction proceeds *via* path B, the (Z)-isomer of **138** can't undergo ring-closure, which could result in a poor yield of **137**, since the (E) : (Z) ratio of **138** is ca. 1 : 2.5. On the other hand, if the reaction proceeds *via* path C, free rotation of the C-2, C-3 bond becomes possible (as in Scheme 1.28), permitting (E) $\rightleftharpoons$ (Z) equilibration so that a high yield of **137** is obtainable.

2.4.2 Base-catalyzed cyclization

Our base-catalyzed approach to **137** is shown in Scheme 2.18. The enamine sulfone **138** was added to 1~1.2 equivalents of LDA in THF and the mixture was stirred at various temperatures (-78°C to reflux). The THF was evaporated and the residue was washed with H_2O, and **137** was extracted with ether. However, loss of product was significant during this aqueous work-up. Therefore, after the evaporation of the THF, the crude material was chromatographed directly and an improved yield of **137** was obtained.

Scheme 2.18 : Base-catalyzed cyclization of **138**



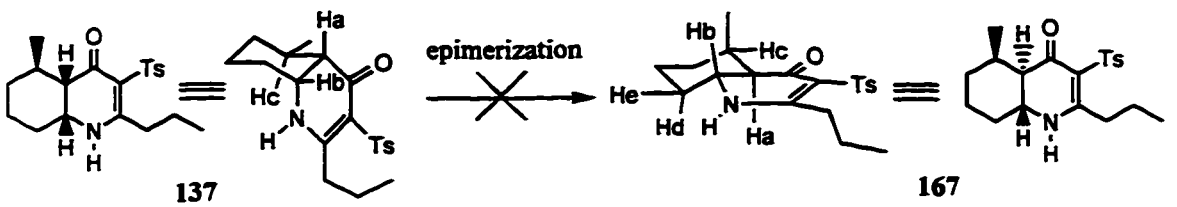
138 **137**

Significant amounts of unreacted **138** were also recovered (33%). NMR analysis of this material indicated that it had the same (E) - (Z) ratio of 1 : 2.5 as the original starting material. Since it is unlikely that the two isomers would be consumed at equal rates, we conclude that (E) $\rightleftharpoons$ (Z) equilibration occurs during the reaction, as would be consistent with path C in Scheme 2.17.

Thus, although we tentatively favoured path C, we could not rule out the possibility that the basic conditions had also caused epimerization at the chiral center α to the carbonyl group in the product (Scheme 2.19). Careful structural characterization was therefore necessary. In case epimerization had happened to form **167**, the proton Hb would appear as a broad multiplet (or a doublet of doublets of doublets) due to the two large axial-axial couplings (Hb-Ha and Hb-Hd). However, only a relatively narrow

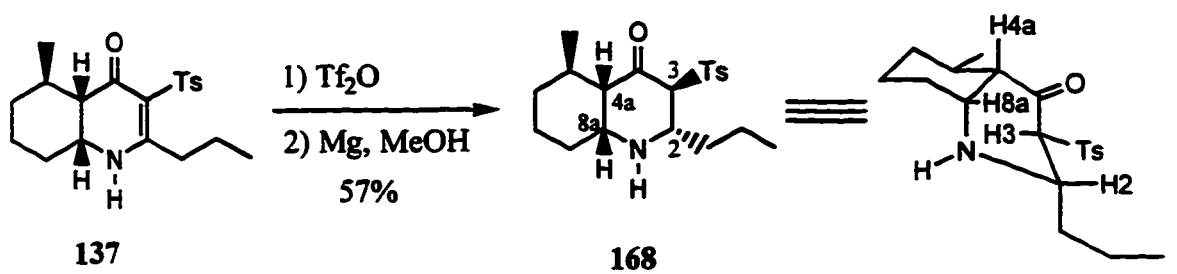
multiplet at δ 3.81 was observed for Hb in the ^{1}H NMR spectrum (width at half-height = 10 Hz), indicating that Hb is in an equatorial position as in **137**. The NMR spectrum also supported the presumption of an axial Ha, since it appeared as a doublet of doublets at δ 1.73 with J=10.5, 3.8 Hz, consistent with the required axial-axial and axial-equatorial couplings with vicinal protons. However, the latter observation alone does not permit a distinction to be made between **137** and **167**.

Scheme 2.19 : Conformations of **137** and **169**



Further evidence that epimerization had not occurred in **137** was obtained by its reduction to compound **168** (Scheme 2.20), the preparation of which is discussed in more detail in section 2.5. In the COSY experiment of **168**, the correlations between H4a-H8a and H2-H3 were observed, where the proton H4a (a doublet of doublets at δ 2.22, J= 9.4, 4.3 Hz, consistent with axial-axial and axial-equatorial couplings with vicinal protons) is axially positioned. In corroborating NOE experiments, an NOE of 6.1 % (H8a) was observed when H2 was irradiated, suggesting their *cis*-1,3 relationship. Also, an NOE of 12.0 % (H4a) was observed when H8a was irradiated, which indicated their *cis*-1,2 relationship. No NOE was observed between H2-H3 since they have a *trans* diaxial relationship. If epimerization had occurred, then as seen with **167** in Scheme 2.19, the stereochemical relationship for H4a-H8a would become *trans* diaxial, which would no longer be expected to show an NOE. Therefore, it can be concluded that epimerization at the chiral center α to the carbonyl group in **137** had not occurred during the base-

Scheme 2.20 : Preparation of **168**



catalyzed cyclization of **138**. This was ultimately confirmed by the preparation of pumiliotoxin C from **137**, where the *cis*-fused rings remained intact.

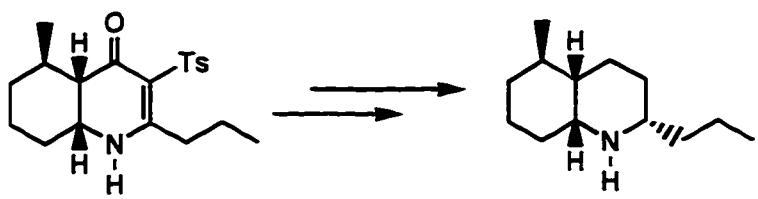
2.4.3 Conclusion

The base-catalyzed cyclization of the β-amino substituted vinyl sulfone **138** was accomplished without causing epimerization of the chiral center α to the carbonyl group. It is proposed that the reaction proceeds by abstraction of the amino proton and that the resulting conjugated anion undergoes free rotation of the C-2, C-3 bond prior to the cyclization.

2.5 Reduction of the enaminone 137 to (±)-pumiliotoxin C (5)

Finally, reduction of the keto, sulfone and carbon-carbon double bond of the enaminone **137** would provide the target molecule, pumiliotoxin C (**5**) (Scheme 2.21).

Scheme 2.21: Reduction of **137** to pumiliotoxin C (**5**)

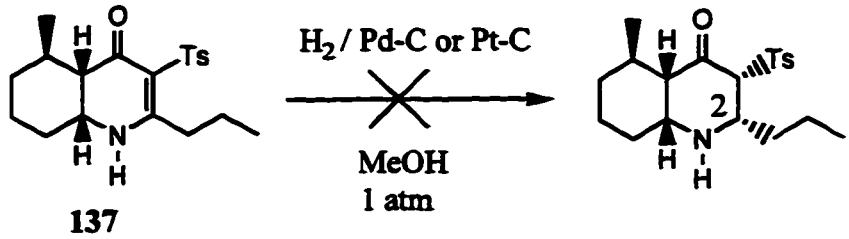


137 pumiliotoxin C (**5**)

2.5.1 Attempted reduction of the carbon-carbon double bond

The enaminone **137** is a *cis*-decahydroquinoline derivative, so that preferential reduction of the double bond from the less hindered *exo* side was expected to give the required stereochemistry to the new chiral center at C-2. Numerous examples of *exo*-selectivity in the reactions of related bicyclic intermediates were shown in Chapter One. Our first attempt was hydrogenation at atmospheric pressure (Scheme 2.22). However, use of Pd-C or Pt-C as a catalyst resulted in only the recovery of the starting material. Formic acid was added to Pd-C in MeOH, but again no reaction occurred.

Scheme 2.22 : Attempted hydrogenation of **137**



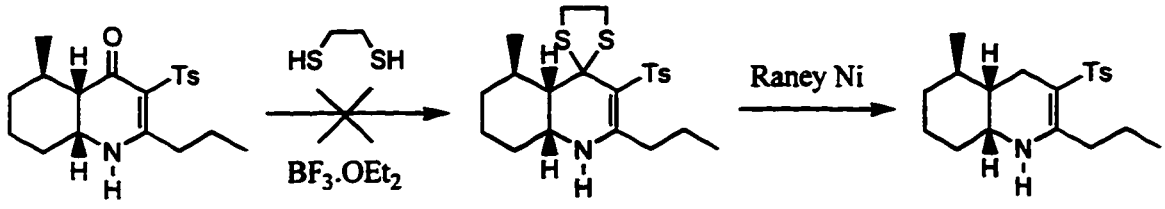
137

Another attempt to reduce the double bond was based on the use of the combination of $NiCl_2$ and $NaBH_4$ in MeOH.[101] In this method, the resulting nickel boride serves as a hydrogenation catalyst, but still no reduction was accomplished and the starting material was recovered.

2.5.2 Attempted reduction of the carbonyl group

The failure of the reduction of the carbon-carbon double bond could be attributed to the highly conjugated enaminone system. Therefore, removal of the carbonyl group was attempted by the formation of its thioacetal, which in turn could be reductively cleaved by Raney Ni (Scheme 2.23).[102] Several different conditions were examined for thioacetal formation, using boron trifluoride as a catalyst, but only unreacted starting material was recovered.

Scheme 2.23 : Attempted formation of a thioacetal of **137**



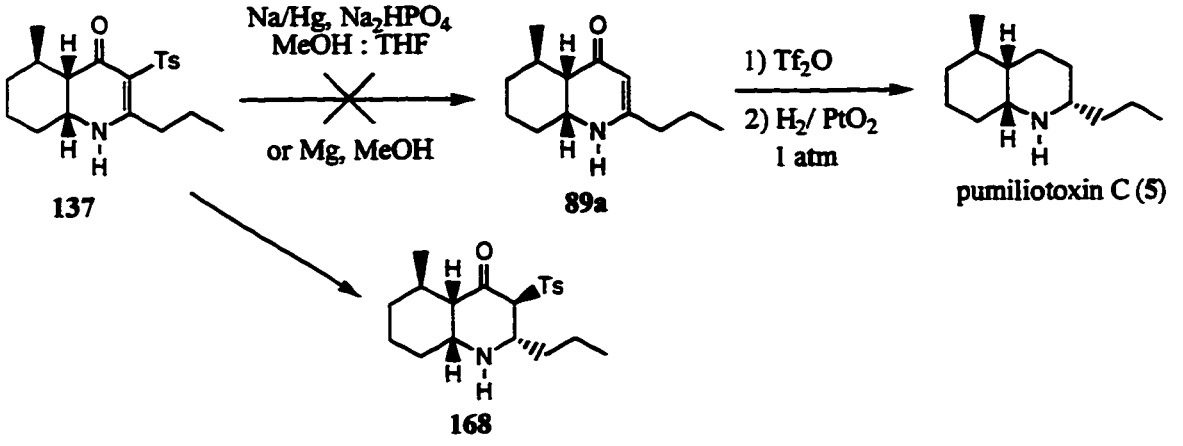
137

2.5.3 Attempted reductive desulfonylation

It will be recalled that **89a**, a compound analogous to **137**, but lacking the sulfone group had been previously transformed to pumiliotoxin C (**5**) by Brandi et al.[51] (see Scheme 2.24) Therefore, our next attempt to reduce the enaminone **137** was the prior reductive removal of the sulfone group, the success of which would lead to a formal synthesis of pumiliotoxin C by Brandi's procedure. Use of sodium amalgam[80] or

magnesium in methanol[86] as a desulfonylating reagent, however, resulted in the formation of complex mixtures, affording only small amounts of a product tentatively identified as **168**, whose complete purification could not be achieved. Formation of **168** was caused by the preferential reduction of the carbon-carbon double bond instead of the C-Ts bond. Evidence for its structure was based on its NMR spectrum, which was described earlier in section 2.4.2.

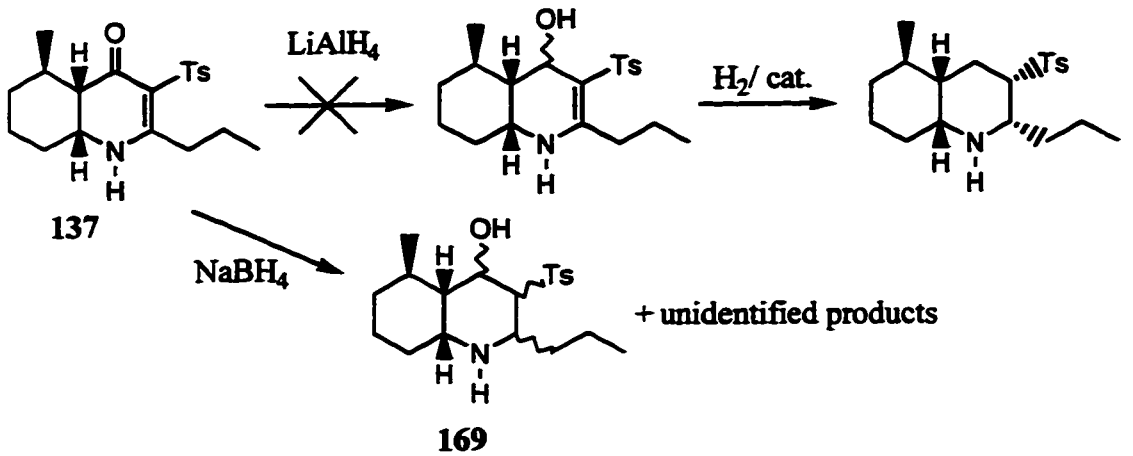
Scheme 2.24 : Attempted reductive desulfonylation of **137**



2.5.4 Reduction of 137 with $LiAlH_4$ and $NaBH_4$

Treatment of **137** with $LiAlH_4$ was expected to provide the corresponding allylic alcohol, which in turn could be hydrogenated to cleave both the hydroxyl group and reduce the double bond.[103] Similarly $NaBH_4$ might reduce the carbon-carbon double bond as well as the carbonyl group.[104] However, the use of these hydride reagents gave complex mixtures which could not be separated. The reaction with $NaBH_4$ proved more tractable, and the principal products were tentatively identified as the various stereoisomers of **169** (Scheme 2.25), whose complex signals of C*H*N and C*H*Ts protons appearred at δ 4.5 - 2.6 in the ^1H NMR spectrum, and the presence of a hydroxyl group (3492 cm^{-1}) and the absence of a carbonyl absorption were observed in the IR spectrum.

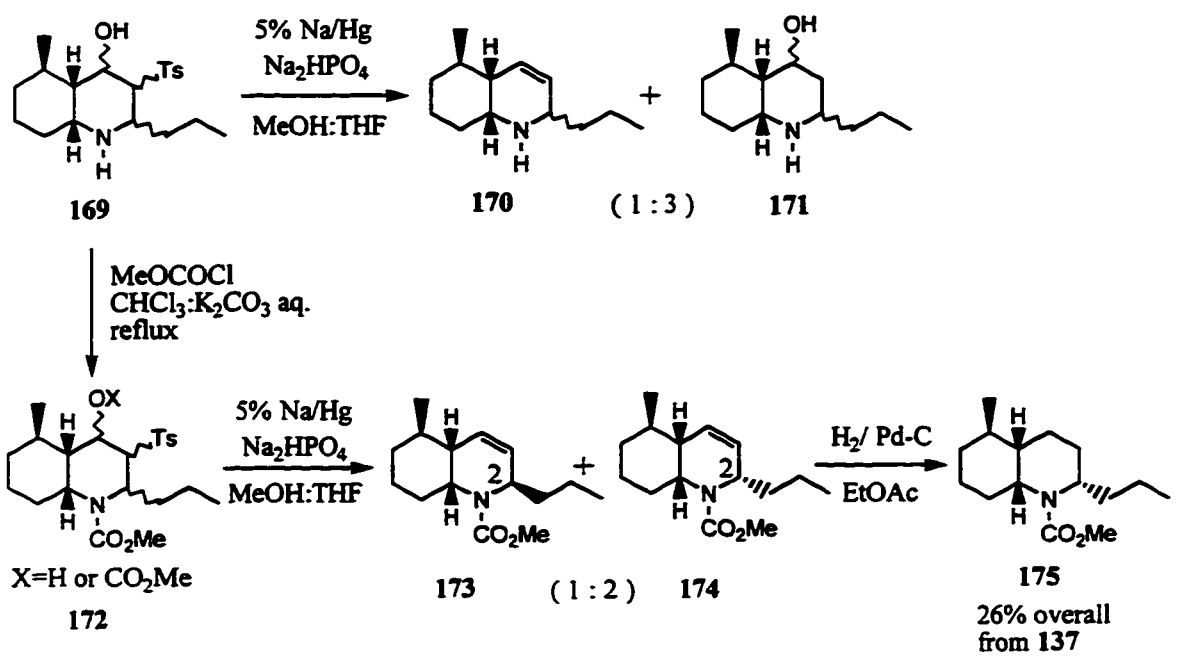
Scheme 2.25 : Reduction of **137** with $LiAlH_4$ and $NaBH_4$



137 169

Several further transformations of **169** were performed (Scheme 2.26). These included reductive elimination of TsOH or of alcohol derivatives of **169**. Such processes are well known in conjunction with the Julia olefination reaction.[105] First, reductive desulfonylation of **169** with Na / Hg provided an inseparable mixture of **170** and **171** in the ratio of ca. 1 : 3 based on NMR integration (vinyl signals of **170** and C*H*OH signal of **171**). Reductive desulfonylation was also attempted with carbamate **172**, which afforded an inseparable mixture of **173** and **174** in the ratio of ca. 1 : 2, based on NMR integration

Scheme 2.26 : Further transformation of **169**



169 170 (1 : 3) 171

X=H or CO_2Me

172 173 (1 : 2) 174 175

26% overall from **137**

of the methoxy signals. It was concluded the major isomer was **174**, because its methoxy signal appeared at the same chemical shift as that of the closely related compound obtained from the treatment of **177** (*vide infra* in Scheme 2.29) with methyl chloroformate. The structural determination of **173** and **174** was tentatively based on the ^{1}H NMR spectrum, in which the signals of the Ts group and *CH*OH proton were no longer observed, and instead the signals of vinyl protons were observed. This mixture was then subjected to hydrogenation to furnish **175** in 26% overall yield from **137**, separated from its 2-epi-diastereomer, similarly derived from **173**. The latter minor isomer could not be isolated in pure form. The preparation of carbamate **175** had been previously reported by Oppolzer (see Scheme 1.3), but spectral data were not provided. Since the NMR spectrum of **175** was identical to that of the product obtained from **177** and methyl chloroformate, followed by desulfonylation in a later experiment (as in Scheme 2.29, where MeOCOCl was used instead of CbzCl), **175** was identified as the N-methoxycarbonyl derivative of pumiliotoxin C.

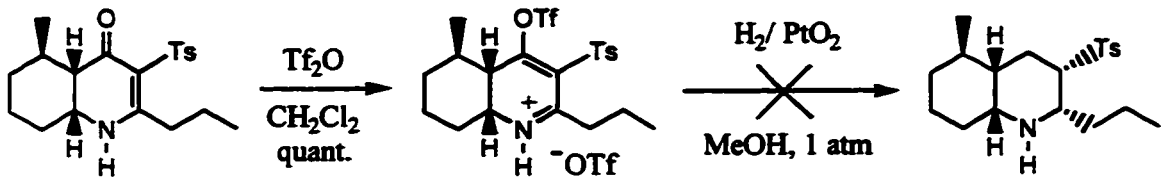
Since the conversion of **137** to **174** suffered from poor stereoselectivity with respect to the chiral center at C-2, the overall yield of **175** by this route was low (26% from **137**) and would require an additional deprotection step in order to obtain pumiliotoxin C. The complex mixtures and difficulties in separating the intermediates associated with this route encouraged us to seek a more efficient approach.

2.5.5 Preparation and reduction of the enol triflate 176 and subsequent desulfonylation to (±)-pumiliotoxin C (5)

Use of triflic anhydride to prepare the corresponding enol triflate[106] from the enaminone **89a** was reported by Brandi et al., who then reduced the triflate to afford (±)-pumiliotoxin C (**5**) in 75% yield (Scheme 1.15 and 2.24).[51] The difference between their structure **89a** and our **137** is the presence of the sulfone group in the latter. In section 2.5.3, the reductive desulfonylation of **137** had been attempted, but the desired **89a** was not obtained. Therefore, preparation of the enol triflate, followed by hydrogenation, was examined in the presence of the sulfone group in **137**.

The enaminone **137** was treated with triflic anhydride in refluxing CH_2Cl_2 and gave a quantitative yield of the corresponding enol triflate **176**, which was not further purified. The same conditions as employed by Brandi (25 mol % of PtO_2, MeOH, 1 atm, 48 h)[51] were first investigated for the reduction of the enol triflate **176** (Scheme 2.27). However, no reaction proceeded at atmospheric pressure and only unreacted starting material was recovered.

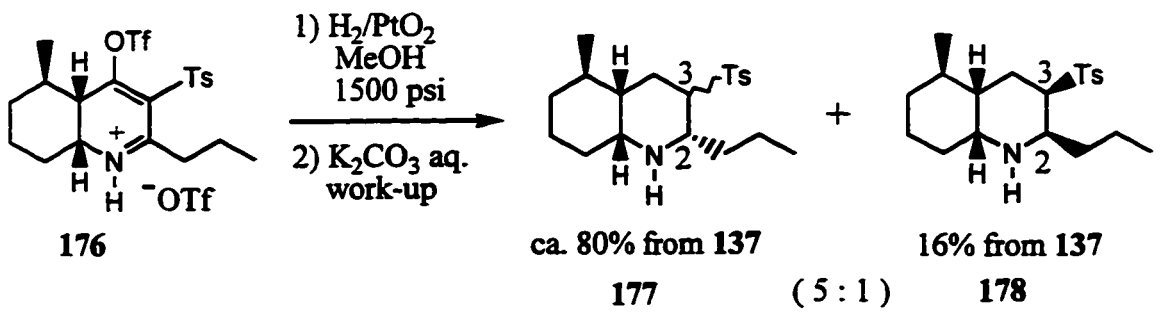
Scheme 2.27 : Preparation of the enol triflate **176** and its attempted reduction



The failure of the hydrogenation at 1 atm is probably caused by steric hindrance by the bulky sulfone group that blocks the approach of the catalyst to **176**. Thus, reductive desulfonylation of **176** was attempted by Mg / MeOH[86] (Scheme 2.20), but the product obtained was again **168** as in Scheme 2.24.

Our next attempt was the use of high pressure for the hydrogenation of **176**, which was conducted in a 50 mL Parr reactor. The best conditions that were found consistently provided a 5 : 1 ratio of **177** and **178**, where the former product was obtained as an inseparable mixture of C-3 epimers and the latter as a single diastereomer (Scheme 2.28). Compound **177** also contained small amounts of unidentified impurities which could not be separated at this stage.

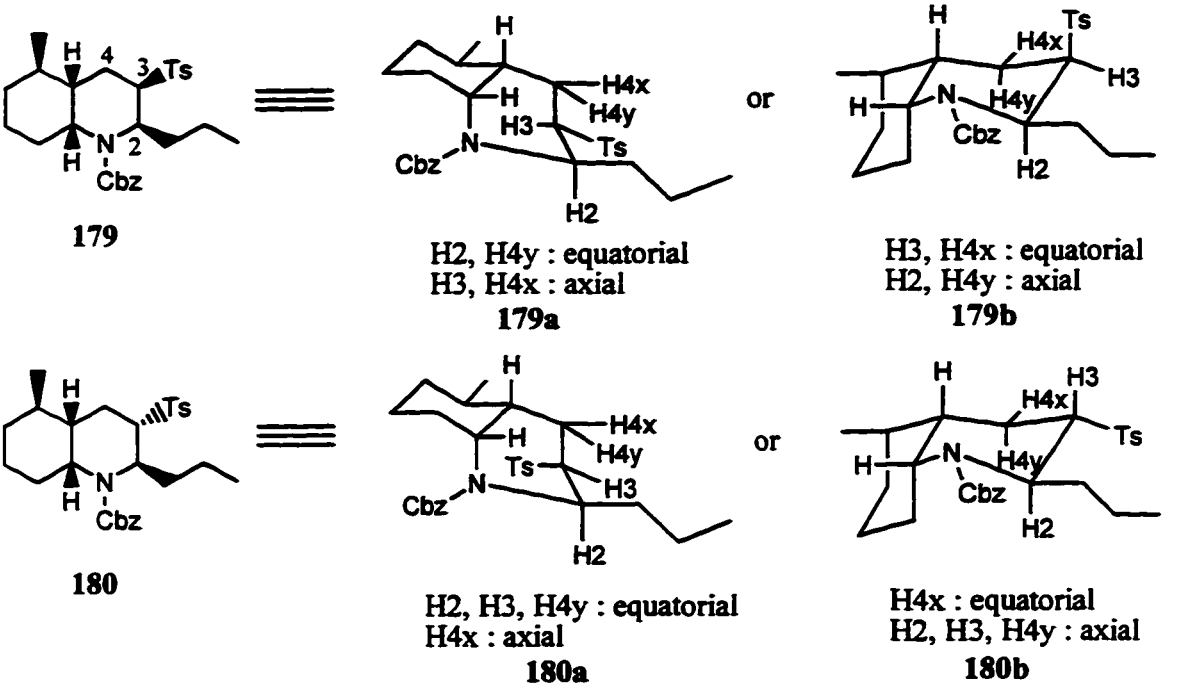
Scheme 2.28 : High pressure hydrogenation of **176**



The stereochemistry at C-2 of **177** and **178** was eventually confirmed by converting the crude mixture of **177** to pumiliotoxin C, and the pure isomer **178** to 2-epi-pumiliotoxin C. The sulfone group in **178** was tentatively assigned as an *exo* substituent by NMR analysis of its N-Cbz derivative **179**, which was prepared by treatment with CbzCl in $CHCl_3$: K_2CO_3 - H_2O. The four conformations of **179** and of the corresponding C-3 *endo* sulfone **180** are shown in Figure 2.9. In the COSY spectrum of **179**, a correlation was observed between H2 at δ 4.58 and H3 at δ 3.48. In an NOE experiment, an NOE of 15.0 % (H2) was observed when H3 was irradiated, suggesting that they do not have a *trans* diaxial relationship, which excludes **180b**. In the Homo decoupling experiment, irradiation of the

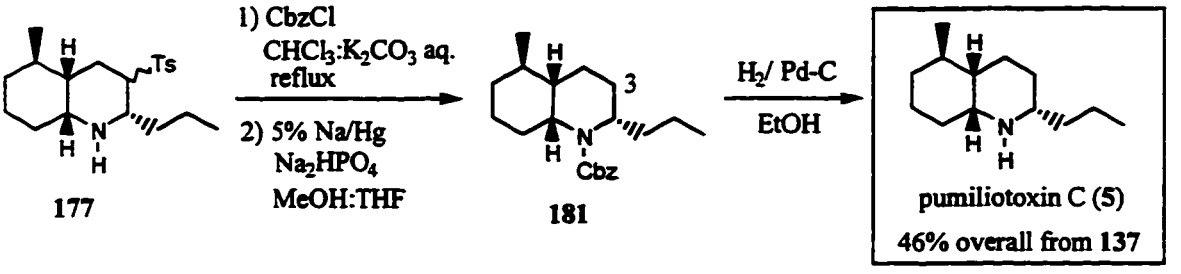
signal of H2 collapsed the signal of H3 to a doublet of doublets, J= 11.3, 8.3 Hz with H4x and H4y, indicating that H3 has an axial-axial and an axial-equatorial relationships with H4x and H4y. Only the conformation **179a** satisfies all of these spectral data.

Figure 2.9 : Conformations of **179** and **180**



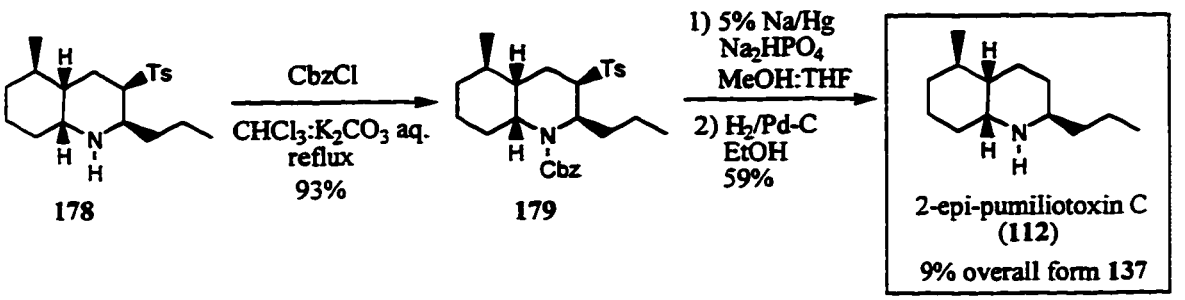
The crude hydrogenated product **177** was then subjected to reductive desulfonylation to afford the target molecule. However, the use of Na / Hg was inefficient, providing pumiliotoxin C (**5**) in only 17% overall yield from the enaminone **137**. The use of an alternative mild desulfonylating reagent, SmI_2, also proved fruitless, giving no reaction. This problem was overcome by protecting the amine moiety in **177** as the Cbz derivative (Scheme 2.29).

Scheme 2.29 : Desulfonylation of N-Cbz derivative to (±)-pumiliotoxin C (**5**)



Thus, treatment of **177** with CbzCl in $CHCl_3$: K_2CO_3 - H_2O furnished the corresponding N-Cbz derivative, which underwent reductive desulfonylation with sodium amalgam smoothly to give **181**. In the NMR spectrum of crude **181**, small signals of vinyl protons were observed. We tentatively attribute this to the existence of small amounts of C-4 hydroxy epimers in the inseparable mixture of C-3 epimers of **177**. Thus, carbon-carbon double bond formation at C-3 was caused by reductive elimination of TsOH with Na / Hg. Finally, hydrogenolysis of the N-Cbz group and simultaneous hydrogenation of the double bond of the impurities over Pd-C afforded pumiliotoxin C (**5**) in 46 % overall yield from the enaminone **137**. Similarly, **178** was converted to 2-epi-pumiliotoxin C (**112**) in 9 % overall yield form **137** (Scheme 2.30).

Scheme 2.30 : Desulfonylation of N-Cbz derivative to 2-epi-pumiliotoxin C (**112**)



The IR, NMR, and mass spectra of (±)-pumiliotoxin C (**5**) and (±)-2-epi-pumiliotoxin C (**112**) were in close agreement with the literature.[44b,56,60] The hydrochloride of **5** also showed a similar melting point range to those reported in the literature.[33,42, 44b, 49, 50b, 54, 60]

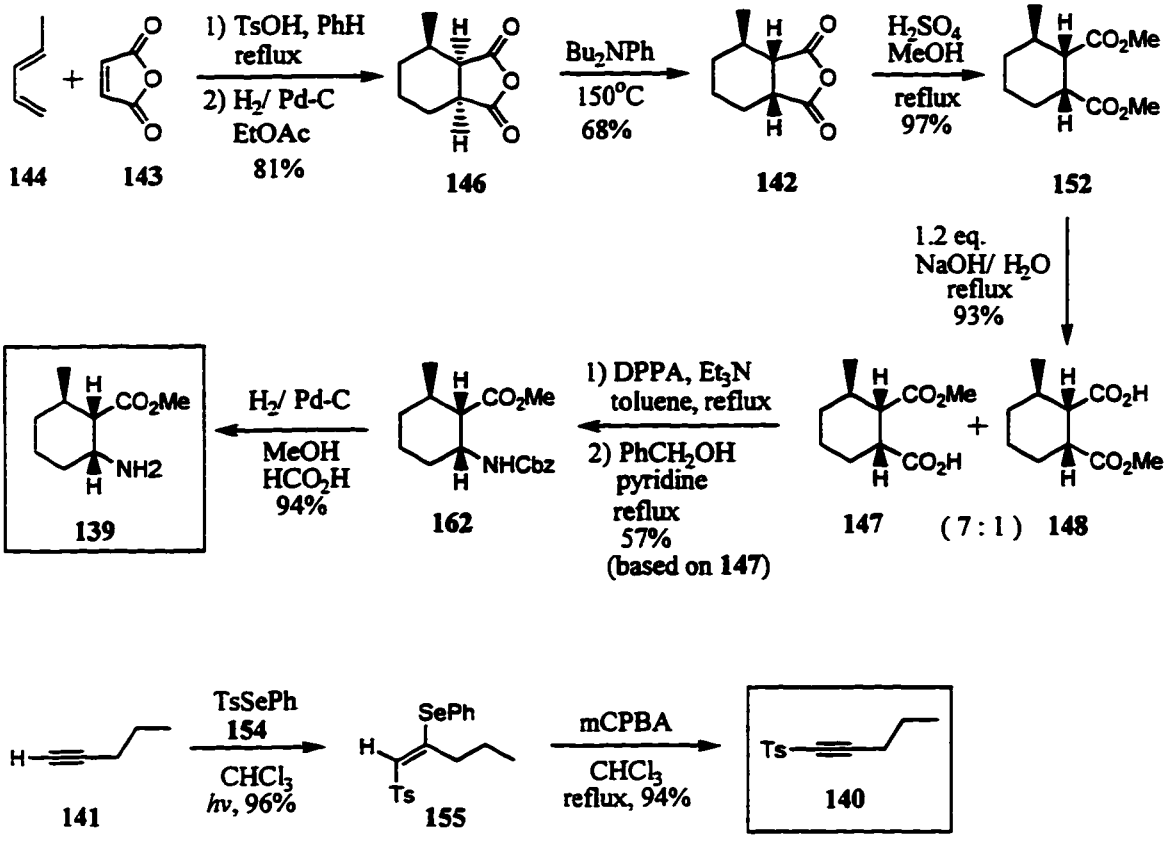
2.5.6 Conclusion

Among several approaches attempted for the reduction of the enaminone **137** to pumiliotoxin C (**5**), the best route was found to comprise the following sequence: (i) preparation of the enol triflate **176**, (ii) high pressure hydrogenation of **176**, (iii) protection of the amine with a Cbz group, (iv) desulfonylation and finally (v) hydrogenolysis. By this method, a 46% overall yield of (±)-pumiliotoxin C (**5**) form **137** was obtained as well as a 9% overall yield of (±)-2-epi-pumiliotoxin C (**112**) from **137**.

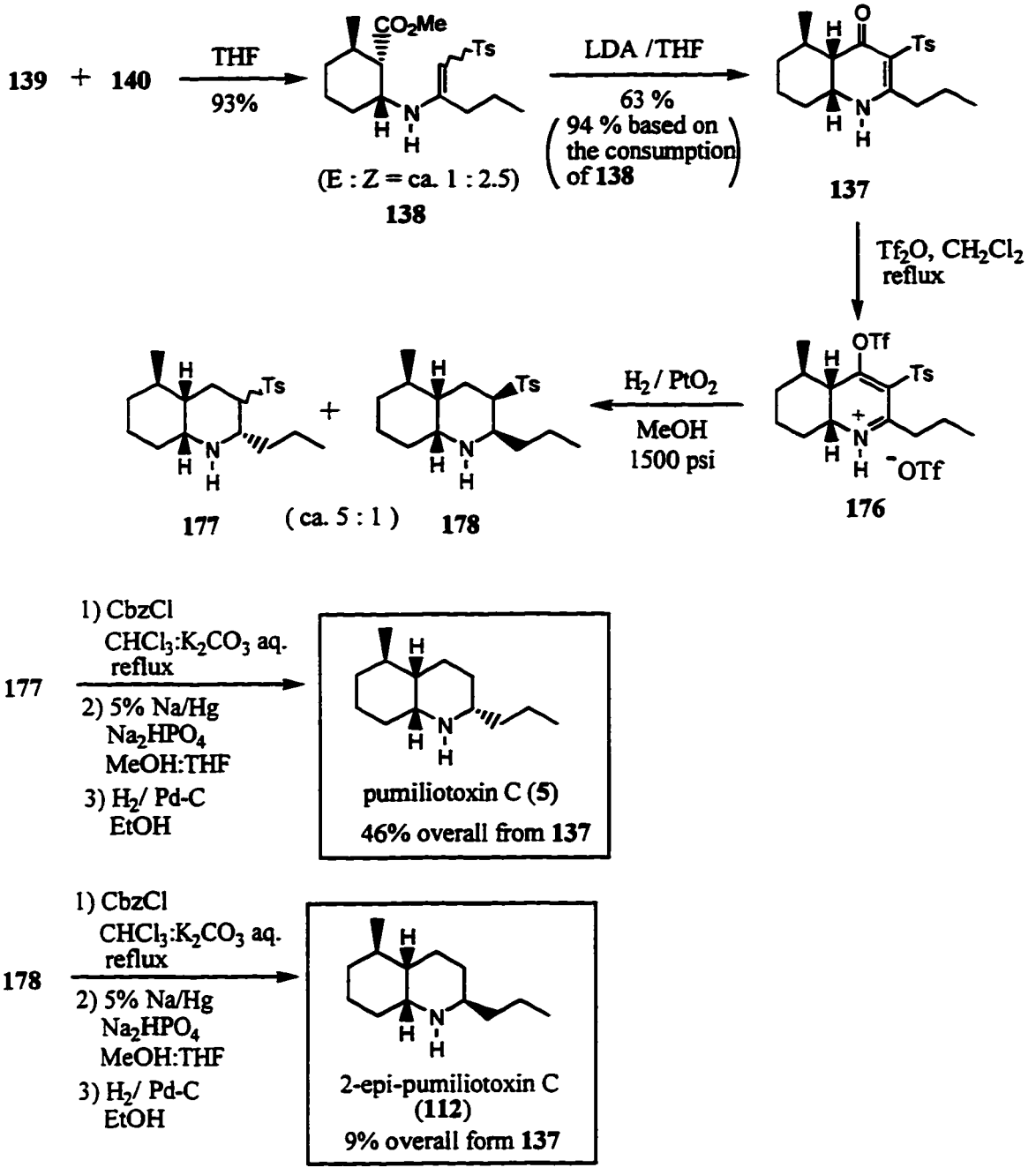
2.6 Overall conclusion and future work

Our synthetic sequences for the preparation of pumiliotoxin C (**5**) are summarized in Scheme 2.31. The cyclic anhydride **142** was prepared by the Diels-Alder cycloaddition of piperylene (**144**) with maleic anhydride (**143**), followed by hydrogenation to **146**, and base-catalyzed epimerization to **142**. The selective partial saponification of the diester **152** afforded the half esters **147** and **148** in the ratio of 7 : 1. This mixture was then subjected to a Curtius rearrangement effected with DPPA and the resulting isocyanates were trapped *in situ* with benzyl alcohol to afford the Cbz-protected amine **162**, which was separated from the regioisomer derived similarly from **148**. Finally, hydrogenolysis produced the desired amino ester **139**. The other key intermediate **140** was prepared by the selenosulfonation of 1-pentyne (**141**), followed by selenoxide elimination. The conjugate addition of **139** to **140** in THF afforded a 2.5 : 1 mixture of (Z)- and (E)-isomers of **138**. Ring-closure was effected by treatment with LDA to provide the enaminone **137**. Hydrogenation of the corresponding enol triflate **176** occurred

Scheme 2.31 : Overall scheme of our synthesis of (±)-pumiliotoxin C (**5**)



Scheme 2.31 (cont'd)



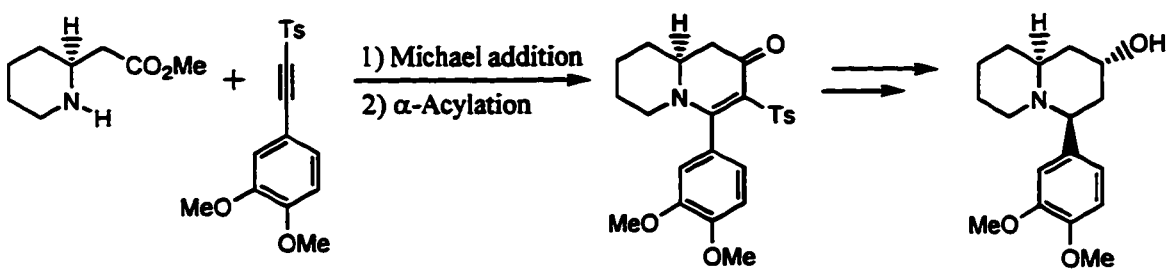
stereoselectively from the *exo* side, producing the C-2 epimers **177** and **178** in the ratio of ca. 5 : 1. The desired C-2 isomer **177** was obtained as an inseparable mixture of C-3 epimers, whereas the 2-epi derivative **178**, which was separated chromatographically from **177**, was a single C-3 stereoisomer. Reductive desulfonylation of the Cbz derivative of **177** with 5% sodium amalgam, followed by hydrogenolysis of the Cbz group, afforded

(±)-pumiliotoxin C (**5**) in 46% overall yield from enaminone **137**. Similarly, the N-Cbz derivative of **178** gave (±)-2-epi-pumiliotoxin C (**112**) in 9% overall yield from **137**.

The success of the present synthesis of pumiliotoxin C (**5**) proves that enaminones obtained by the sequential Michael addition and α-acylation of an appropriate combination of β-functionalized amine and acetylenic sulfone are synthetically useful intermediates. Compared with several previous syntheses of pumiliotoxin C, our convergent synthesis gave a reasonably good overall yield of **5** (40%) from the two key intermediates, β-amino ester **139** and acetylenic sulfone **140**. These intermediates were in turn prepared in 50% yield in 4 steps from the known dimethyl ester **152**, and in 90% yield in 2 steps from 1-pentyne (**141**), respectively. If one takes into account that most of the previous syntheses were linear and gave only ~10% yield of **5**, this synthesis turns out to be of comparable efficiency to the highest yielding literature syntheses of Habermehl (25%),[36] Overman (58%),[42] Yamamoto (46%),[44] and Comins (24%).[50] Our synthesis of (±)-pumiliotoxin C was recently published in Tetrahedron Letters.[107]

Future work related to this synthesis includes the investigation of the PLE-catalyzed enantioselective synthesis of **5**. Since we have a potential substrate, racemic dimethyl ester **152**, enantioselective preparation of **147** through kinetic resolution may be possible, even though the other enantiomer will be wasted. Furthermore, more detailed studies of the intramolecular cyclization of other amines with acetylenic sulfones will extend our strategy to the preparation of a variety of different alkaloids. One such example is lasubine II (**182**), an arylquinolizidine alkaloid isolated from Lythraceous plants (Scheme 2.32).

Scheme 2.32 : Preparation of lasubine II



lasubine II (**182**)

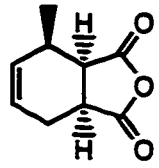
Chapter Three
Experimental Section

3.1 General Comments

Melting points were determined on an A.H. Thomas hot-stage apparatus and are uncorrected. IR spectra were recorded on a Mattson 4030 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker ACE 200 or a Bruker AM 400 spectrometer, with deuteriochloroform as the solvent, and either chloroform or tetramethylsilane as the internal standard. Assignment of signals as CH_3, CH_2, CH, or C, where so indicated in ^{13}C NMR spectra, was performed by DEPT experiments. Elemental analyses and mass spectra were obtained by Ms. D. Fox and Ms. Q. Wu at the University of Calgary. Analytical TLC was carried out with aluminum sheets coated with Merck silica gel 60 F-254, and the spots visualized with UV light, by spraying with a 2% ceric sulfate solution in 12% aqueous sulfuric acid, or by dipping in 10% ammonium molybdate solution in aqueous sulfuric acid, followed by heating for several seconds. Flash chromatography was performed using Merck silica gel, 230-400 mesh unless otherwise indicated. Photolyses were carried out in a Rayonet RMR-500 reactor equipped with four 254 nm lamps. The high pressure hydrogenation reactions were performed in a Parr microreactor, 50 mL, model 4592.

Piperylene was used as a mixture of *cis* and *trans* isomers (30 : 70 by NMR integration) with the assumption that the *trans* isomer would react preferentially in Diels-Alder reactions. The benzyl chloroformate contained 7% of benzyl chloride, as determined by NMR spectroscopy. mCPBA was purified by washing with a pH 7.5 phosphate buffer and was assumed to be 100% pure.[108] Dry diisopropylamine was obtained by distillation from calcium hydride. All other reagents were obtained from commercial sources and were used without further purification. Anhydrous THF and methylene chloride were obtained by distillation from lithium aluminum hydride and phosphorus pentoxide, respectively.

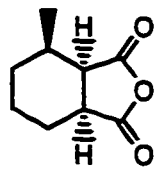
3.2 *cis*-3-Methyl-4-cyclohexene-*cis*,*cis*-1,2-dicarboxylic anhydride (145)



145

Compound **145** was prepared by the procedure of Frank, Emmick, and Johnson; spectral data for **145** were not given in the literature.[89] A solution of piperylene (**144**) (30 mL, 0.30 mol), *p*-toluenesulfonic acid (183 mg, 1.06 mmol), and maleic anhydride (**143**) (15.0 g, 0.153 mol) in 75 mL of benzene was refluxed for 22.5 h. The benzene was evaporated and the resulting black solid was washed with ether. Recrystallization of the crude material from hexanes gave 20.6 g (81%) of **145** as colourless needles: mp 60-61°C (lit.[89] 61°C); IR (KBr) 1839 (C=O), 1767 (C=O), 1630 (C=C), 1335, 1215, 1069, 920 cm^{-1}; ^1H NMR (200 MHz) δ 6.05-5.90 (m, 1H, vinylic H), 5.90-5.80 (m, 1H, vinylic H), 3.44 (ddd, *J*= 9.7, 7.5, 2.3 Hz, 1H), 3.29 (dd, *J*= 9.7, 6.6 Hz, 1H), 2.74 (ddd, *J*= 15.8, 6.3, 2.3 Hz, 1H), 2.62-2.42 (m, 1H), 2.32-2.17 (m, 1H), 1.38 (d, *J*= 7.4 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 174.5 (C=O), 171.7 (C=O), 134.6, 127.0, 44.8, 40.6, 29.5, 23.4, 16.3.

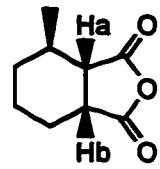
3.3 *cis*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic anhydride (146)



146

Compound **146** was prepared by the procedures of Craig,[88a] or Bussert, Greenlee, Derfer, and Boord;[88b] spectral data for **146** were not given in the literature.[88a,b] A solution of the adduct **145** (20.6 g, 0.124 mol) in 50 mL of ethyl acetate was hydrogenated for 49 h over 10% palladium on charcoal (198 mg) at room temperature and at atmospheric pressure. Removal of the catalyst by filtration through Celite and evaporation of the solvent afforded 20.7 g (100%) of **146** as a pale yellow oil: IR (film) 1855 (C=O), 1788 (C=O), 1218, 902 cm^{-1}; ^1H NMR (200 MHz) δ 3.23-3.00 (m, 2H), 2.15-1.88 (m, 2H), 1.87-1.15 (m, 5H), 1.28 (d, *J*= 7.1 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 173.0 (C=O), 171.3 (C=O), 44.9, 40.9, 28.5, 28.4, 23.8, 20.5, 17.5.

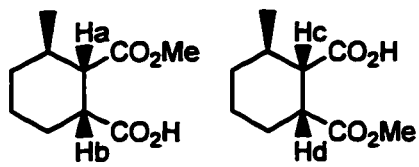
3.4 *trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic anhydride (142)



142

Compound **142** was prepared by the procedure of Craig; spectral data for **142** was not given in the literature.[88a] The adduct **146** (20.0 g, 0.119 mol) was divided into four fractions (5.0 g, 0.030 mol each) and N,N-dibutylaniline (0.50 mL, 2.2 mmol) was added to each of them. Each fraction was heated at 140 - 150°C for 44 h under a nitrogen atmosphere, the fractions were combined, diluted with ether, washed with 10% HCl solution, and dried over $MgSO_4$. The ether was evaporated and crystallization of the resulting pale yellow oil from hexanes afforded 13.5 g (68%) of **142** as flat colourless crystals: mp 64-67°C (lit.[88a] 70°C); IR (KBr) 1847 (C=O), 1777 (C=O), 1216, 922, 887 cm^{-1}; ^1H NMR (200 MHz) δ 3.27 (m, 1H, Hb), 2.61 (dd, *J*= 10.3, 7.9 Hz, 1H, Ha), 2.32-2.15 (m, 1H), 1.82-1.49 (m, 4H), 1.46-1.22 (m, 1H), 1.18 (d, *J*= 6.5 Hz, 3H, Me), 1.16-0.92 (m, 1H); ^{13}C NMR (50 MHz) δ 172.9 (C=O), 171.8 (C=O), 47.3, 40.7, 32.7, 31.3, 21.4, 21.2, 19.8.

3.5 *trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, 2-methyl ester (147) and *trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, 1-methyl ester (148) *via* methanolysis of anhydride 142

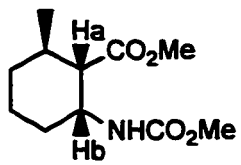


147 **148**

A solution of **142** (2.563 g, 15.26 mmol) in 50 mL of 1 M MeONa-MeOH was stirred at room temperature for 20 min, treated with 10% HCl solution to make the solution strongly acidic, and the product was extracted with ether and dried over $MgSO_4$. The solvent was evaporated and 3.269 g (quantitative yield) of an inseparable mixture of **147** and **148** (3 : 1 ratio by NMR integration) was obtained as a yellow oil. The mixture had the following properties: IR (film) 3500-2600 (broad, CO_2H), 1736 (ester C=O), 1705 (carboxylic acid C=O), 1246, 1204, 1161 cm^{-1}; ^1H NMR (200 MHz) δ 11.51 (br m, 1H,

CO_2H, **147** and **148**), 3.68 (s, 3H, OMe, **147**), 3.67 (s, 3H, OMe, **148**), 2.88 (m, 1H, Hb and Hd), 2.58 (dd, *J*= 6.4, 4.6 Hz, 1H, Ha and Hc), 2.48-2.21 (m, 1H, **147** and **148**), 2.08-1.83 (m, 1H, **147** and **148**), 1.83-1.30 (m, 4H, **147** and **148**), 1.29-1.13 (m, 1H, **147** and **148**), 1.08 (d, *J*= 6.7 Hz, 3H, Me, **148**), 1.06 (d, *J*= 6.9 Hz, 3H, Me, **147**); ^{13}C NMR (100 MHz) δ 180.5 (C=O, **147**), 179.8 (C=O, **148**), 174.3 (C=O, **148**), 173.9 (C=O, **147**), 51.5 (OMe, **147** and **148**), 49.2 (CH, **148**), 48.9 (CH, **147**), 40.1 (CH, **148**), 40.0 (CH, **147**), 31.0 (CH_2, **148**), 30.7 (CH_2, **147**), 29.4 (CH, **147**), 29.2 (CH, **148**), 26.0 (CH_2, **148**), 25.7 (CH_2, **147**), 20.3 (CH_2, **148**), 20.2 (CH_2, **147**), 19.7 (CH_3, **148**), 19.6 (CH_3, **147**); mass spectrum, *m/z* (relative intensity, %) 200 (M^+, 0.72), 182 (M^+-H_2O, 10), 168 (M^+-MeOH, 15), 154 (25), 122 (37), 96 (68), 95 (100), 81 (94), 67 (52), 55 (50), 41 (56). Exact mass calcd for $C_{10}H_{16}O_4$-H_2O: 182.0942. Found: 182.0954.

3.6 Methyl *cis*-2-[N-(methoxycarbonyl)amino]-*trans*-6-methylcyclohexanecarboxylate (151)



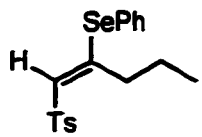
151

The isocyanates derived from **147** and **148** were prepared by the general procedure of Shioiri, Ninomiya, and Yamada.[90] A solution of DPPA (5.00 mL, 23.2 mmol), triethylamine (3.30 mL, 23.7 mmol), and a mixture of **147** and **148** (3 : 1 ratio, 4.65 g, 23.3 mmol) in 300 mL of toluene was refluxed for 5 h. The solution was diluted with benzene, washed with saturated K_2CO_3 solution, and dried over $MgSO_4$. The solvent was evaporated and 4.17 g (91%) of the corresponding mixture of isocyanates **149** and **150** was obtained as a yellow oil, which was used without further purification in the next step: IR (film) 2270 (N=C=O), 1736 (ester C=O) cm^{-1}.

A solution of the isocyanates **149** and **150** (4.17 g, 21.2 mmol) and a catalytic amount (ca. 0.2 mL) of concentrated H_2SO_4 in 70 mL of methanol was refluxed for 1 h. The methanol was evaporated and the residue was triturated with ether and the aqueous layer was made basic with saturated K_2CO_3 solution. The ether layer was separated and dried over $MgSO_4$. The ether was evaporated and 4.32 g of the crude product was obtained. In order to separate pure **151** from its regioisomer derived from **148**, repetitive crystallization from hexanes was carried out to give 1.62 g (41% based on the amount of **147** in the starting material) of **151** as a white solid: mp 59-61°C; IR (KBr) 3368 (NH), 1724 (ester C=O),

1711 (carbamate C=O), 1531, 1241 cm^{-1}; ^1H NMR (200 MHz) δ 5.20 (m, 1H, NH), 4.12 (m, 1H, Hb), 3.68 (s, 3H, CCO_2Me), 3.64 (s, 3H, NCO_2Me), 2.30 (dd, *J*= 10.2, 3.8 Hz, 1H, Ha), 2.40-1.35 (m, 6H), 1.17-0.99 (m, 1H), 0.93 (d, *J*= 6.5 Hz, 3H, Me); COSY (400 MHz) correlations were observed between (i) NH (δ 5.20) - Hb (δ 4.12), and (ii) Hb (δ 4.12) - Ha (δ 2.30). ^{13}C NMR (50 MHz) δ 173.7 (*C*C=O), 156.3 (*N*C=O), 52.4 (CH), 51.8 (OMe), 51.5 (OMe), 47.7 (CH), 32.3 (CH_2), 30.1 (CH_2), 29.0 (CH), 20.1 (CH_3), 19.7 (CH_2); mass spectrum, *m/z* (relative intensity, %) 229 (M^+, 27), 197 (M^+-MeOH, 84), 169 (80), 114 (100), 95 (78). Anal. calcd for $C_{11}H_{19}O_4N$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.37; H, 8.29; N, 6.02.

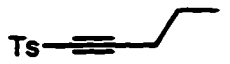
3.7 (E)-2-(Phenylseleno)-1-(*p*-tolylsulfonyl)-1-pentene (155)



155

Compound **155** was prepared by the general procedure of Back, Lai, and Muralidharan.[14] A solution of *Se*-phenyl *p*-tolueneselenosulfonate **154** (3.02 g, 9.68 mmol) and 1-pentyne **141** (1.60 mL, 16.3 mmol) in 8.0 mL of chloroform in a 10 mm diameter glass tube was placed inside a water-cooled condenser for the purpose of avoiding 1-pentyne evaporation during the reaction. The mixture was irradiated at 254 nm for 4 h. The chloroform was evaporated and chromatography with 10% ethyl acetate - hexanes afforded 3.52 g (96%) of **155** as a single regio- and stereoisomer in the form of a pale green oil. An analytical sample was obtained by crystallization from hexanes to give cubic crystals: mp 50-52°C; IR (KBr) 1564, 1304, 1272, 1139, 1079, 811, 749 cm^{-1}; ^1H NMR (200 MHz) δ 7.68 (d, *J*= 8.3 Hz, 2H, Ar), 7.55-7.26 (complex, 7H, Ar), 5.86 (s, 1H, vinylic H), 2.84 (br t, *J*= 7.8 Hz, 2H, allylic H), 2.42 (s, 3H, Me), 1.64 (sextet, *J*= 7.5 Hz, 2H, CH_2CH_3), 0.96 (t, *J*= 7.3 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 160.9 (C), 143.7 (C), 139.5 (C), 136.6 (2 CH), 129.9 (2 CH), 129.7 (CH), 129.6 (2 CH), 126.8 (2 CH), 125.9 (C), 123.9 (CH), 34.8 (CH_2), 23.3 (CH_2), 21.4 (CH_3), 13.6 (CH_3); mass spectrum, *m/z* (relative intensity, %) 380 (M^+ ^{80}Se, 14), 248 (10), 223 (19), 183 (16), 157 (69), 155 (39), 139 (33), 91 (100). Anal. calcd for $C_{18}H_{20}O_2SSe$: C, 56.99; H, 5.30. Found: C, 56.99; H, 5.34.

3.8 1-(*p*-Tolylsulfonyl)-1-pentyne (140)



140

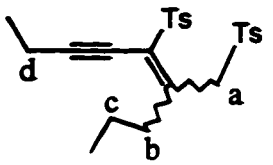
Compound **140** had been synthesized previously in a different manner by Iwata, Morioka, Kobayashi, Asada, Kinoshita, and Inomata.[69a] Its preparation from **155** was accomplished by the general procedure of Back, Collins, and Kerr.[14] A solution of mCPBA (3.204 g, 18.57 mmol) and **155** (3.49 g, 9.18 mmol) in 100 mL of chloroform was refluxed for 7 h, washed with saturated K_2CO_3 solution, and dried over $MgSO_4$. The chloroform was evaporated and chromatography with 10% ethyl acetate - hexanes afforded 1.917 g (94%) of **140** as a red oil: IR (film) 2199 (C≡C), 1327, 1156, 678 cm^{-1}; ^1H NMR (200 MHz) δ 7.88 (d, *J*= 8.3 Hz, 2H, Ar), 7.36 (d, *J*= 8.6 Hz, 2H, Ar), 2.46 (s, 3H, Me), 2.33 (t, *J*= 7.0 Hz, 2H, propargylic H), 1.58 (sextet, *J*= 7.3 Hz, 2H, CH_2CH_3), 0.96 (t, *J*= 7.3 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 144.8, 138.9, 129.5, 126.6, 96.8, 78.2, 21.2, 20.3, 20.2, 12.9; mass spectrum, *m/z* (relative intensity, %) 222 (M^+, 90), 139 (100), 129 (49), 107 (64), 91 (62), 65 (50).

Spectral data for **140** were reported in the literature[69a]: IR (neat) 2940, 2920, 2850, 2180, 1585, 1440, 1320, 1300, 1280, 1170, 1150, 1080, 1010, 985, 870, 805, 700, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.88 (d, *J*= 8.1 Hz, 2H), 7.36 (d, *J*= 8.1 Hz, 2H), 2.46 (s, 3H), 2.33 (t, *J*= 7.1 Hz, 2H), 1.58 (sextet, *J*= 7.1 Hz, 2H), 0.96 (t, *J*= 7.1 Hz, 3H); mass spectrum, *m/z* (relative intensity, %) 224 (M^++2, 5.6), 223 (M^++1, 15.0), 222 (M^+, 100.0), 201 (21.3), 143 (33.0), 139 (73.0), 129 (38.6), 107 (33.4), 91 (21.6), 85 (20.1).

3.9 Attempted Michael addition of 151 to 140

A solution of **151** (119 mg, 0.520 mmol) and **140** (114 mg, 0.514 mmol) in 7.0 mL of THF was stirred at room temperature for 18 h and then refluxed for 4 h. The THF was evaporated and the ^1H NMR spectrum of the crude material showed no reaction. The solvent was evaporated and replaced by 7.0 mL of benzene and the mixture was refluxed for 20 h. Again, no reaction was observed. Finally, the mixture was refluxed in 7.0 mL of toluene for 22.5 h. The toluene was evaporated *in vacuo* and both starting materials were recovered by chromatography (>80%).

3.10 Attempted base-catalyzed Michael addition of 151 to 140. Formation of 156



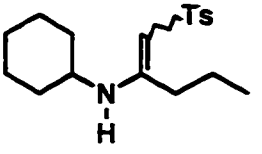
156

To a solution of **151** (102 mg, 0.445 mmol) in 9.0 mL of THF was added *t*-BuOK (50 mg, 0.446 mmol) and the resulting mixture was stirred at room temperature for 20 min in a nitrogen atmosphere. Then a solution of **140** (107 mg, 0.482 mmol) in 8.0 mL of THF was added and the mixture was stirred at room temperature for another 1 h. The THF was evaporated. The residue was triturated with ether and washed with NaCl solution. The ether layer separated and was dried over $MgSO_4$. The ether was evaporated and chromatography with ethyl acetate : hexanes = 1 : 2 gave two dimers **156** (29 mg, 27% - Rf = 0.48 and 33 mg, 31% - Rf = 0.37 with ethyl acetate : hexanes = 1 : 2 by TLC), derived from **140**, and unreacted **151** (70%). Dimer with Rf = 0.48: IR (film) 2215 (C≡C), 1596 (C=C), 1317, 1144, 672 cm^{-1}; ^1H NMR (200 MHz) δ 7.91 (d, *J*= 8.5 Hz, 2H, Ar), 7.87 (d, *J*= 8.5 Hz, 2H, Ar), 7.39 (d, *J*= 8.0 Hz, 2H, Ar), 7.31 (d, *J*= 8.1 Hz, 2H, Ar), 4.90 (s, 2H, Ha), 2.70 (t, *J*= 7.8 Hz, 2H, Hb), 2.47 (s, 3H, Me), 2.44 (s, 3H, Me), 2.28 (q, *J*= 7.5 Hz, 2H, Hd), 1.57 (sextet, *J*= 7.5 Hz, 2H, Hc), 1.04 (t, *J*= 7.5 Hz, 3H, Me), 0.93 (t, *J*= 7.3 Hz, 3H, Me); mass spectrum, *m/z* (relative intensity, %) 444 (M^+, 2), 289 (M^+-Ts, 27), 139 (67), 91 (100). Dimer with Rf = 0.37: IR (film) 2215 (C≡C), 1596 (C=C), 1317, 1141, 676 cm^{-1}; ^1H NMR (200 MHz) δ 7.71 (d, *J*= 8.3 Hz, 2H, Ar), 7.58 (d, *J*= 8.3 Hz, 2H, Ar), 7.33 (d, *J*= 8.0 Hz, 2H, Ar), 7.11 (d, *J*= 8.4 Hz, 2H, Ar), 4.18 (s, 2H, Ha), 3.02 (t, *J*= 8.0 Hz, 2H, Hb), 2.49 (s, 3H, Me), 2.38 (s, 3H, Me), 2.02 (q, *J*= 7.5 Hz, 2H, Hd), 1.57 (sextet, *J*= 7.5 Hz, 2H, Hc), 1.02 (t, *J*= 7.3 Hz, 3H, Me), 0.91 (t, *J*= 7.5 Hz, 3H, Me); mass spectrum, *m/z* (relative intensity, %) 444 (M^+, 2), 289 (M^+-Ts, 47), 139 (100), 91 (88).

Spectral data for **156** were reported in the literature[69a]: IR (neat) 3020, 2960, 2920, 2880, 2200, 1585, 1480, 1450, 1395, 1310, 1290, 1280, 1240, 1140, 1075, 800, 720, 690 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 446 (M^++2, 0.16), 445 (M^++1, 0.34), 444 (M^+, 1.17), 289 (43.14), 225 (4.04), 139 (100.00), 133 (24.74), 105 (10.34), 91 (10.79). One of the dimers: ^1H NMR ($CDCl_3$) δ 7.90 (d, *J*= 8.1 Hz, 2H), 7.86 (d, *J*= 8.1 Hz, 2H), 7.38 (d, *J*= 8.1 Hz, 2H), 7.30 (d, *J*= 8.1 Hz, 2H), 4.90 (s, 2H), 2.70 (t, *J*= 7.3 Hz, 2H), 2.47 (s, 3H), 2.43 (s, 3H), 2.27 (q, *J*= 7.3 Hz, 2H), 1.57 (sextet, *J*= 7.3 Hz, 2H), 1.04 (t, *J*= 7.3 Hz, 3H), 0.94 (t, *J*= 7.3 Hz, 3H). The other dimer: ^1H NMR ($CDCl_3$) δ 7.69 (d, *J*= 8.1 Hz,

2H), 7.57 (d, *J*= 8.1 Hz, 2H), 7.34 (d, *J*= 8.1 Hz, 2H), 7.11 (d, *J*= 8.1 Hz, 2H), 4.17 (s, 2H), 3.03 (t, *J*= 7.3 Hz, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 2.01 (q, *J*= 7.3 Hz, 2H), 1.57 (sextet, *J*= 7.3 Hz, 2H), 1.04 (t, *J*= 7.3 Hz, 3H), 0.90 (t, *J*= 7.3 Hz, 3H, Me).

3.11 (Z)- and (E)-2-(Cyclohexylamino)-1-(*p*-tolylsulfonyl)-1-pentene (160)

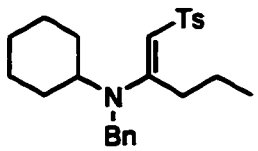


160

A solution of cyclohexylamine (**158**) (110 μL, 0.961 mmol) and acetylenic sulfone **140** (185 mg, 0.833 mmol) in 2.0 mL of THF was stirred at room temperature for 5 h and concentrated *in vacuo*. The crude material was chromatographed over neutral alumina (activated, 80-200 mesh) with ethyl acetate : hexanes = 1 : 10 to give an oil, which solidified at room temperature to afford 163 mg (61%) of an inseparable mixture of (Z)- and (E)-enamines **160** (2.5 : 1 ratio by NMR integration) as cubic crystals: mp 106-109°C. The unseparated mixture of (Z)- and (E)-enamines was characterized. The assignment of signals in the ^{1}H and ^{13}C NMR spectra is tentative: IR (KBr) 3354 (NH), 1576, 1533, 1273, 1136, 1078 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.75 (d, *J*= 8.2 Hz, 2H, Ar, **E**), 7.72 (d, *J*= 8.1 Hz, 2H, Ar, **Z**), 7.24 (d, *J*= 7.9 Hz, 4H, Ar, **E** and **Z**), 4.99 (s, 1H, vinylic H, **E**), 4.51 (s, 1H, vinylic H, **Z**), 4.29 (br d, 1H, NH, **E**), 3.22 (m, 1H, CHN, **Z**), 3.08 (m, 1H, CHN, **E**), 2.45 (t, *J*=7.9 Hz, 2H, allylic H, **E**), 2.38 (s, 3H, Me, **Z**), 2.09 (t, *J*= 7.7 Hz, 2H, allylic H, **Z**), 1.49 (sextet, *J*= 7.6 Hz, 2H, CH_2CH_3, **Z**), 1.42 (sextet, 2H, CH_2CH_3, **E**, overlapping with the sextet of the (Z)-isomer), 0.90 (t, *J*= 7.4 Hz, 3H, Me, **Z**) 0.85 (t, *J*= 7.4 Hz, 3H, Me, **E**); COSY (400 MHz) correlations were observed between (i) allylic CH_2 (δ 2.09, **Z**) - CH_2CH_3 (δ 1.49, **Z**), (ii) NH (δ 4.29, **E**) - CHN (δ 3.08, **E**), (iii) allylic CH_2 (δ 2.45, **E**) - CH_2CH_3 (δ 1.42, **E**), and (iv) CH_2CH_3 (δ 1.42, **E**) - CH_3 (δ 0.85, **E**). NOE (400 MHz) (i) 3.0% enhancement of the signal at δ 2.09 (allylic CH_2, **Z**) was observed when vinylic H (δ 4.51, **Z**) was irradiated, (ii) 16.4% enhancement of the signal at δ 3.08 (CHN, **E**) was observed when vinylic H (δ 4.99, **E**) was irradiated. ^{13}C NMR (100 MHz) δ 159.5 (NC=C, **Z**), 158.7 (NC=C, **E**), 143.5 (C), 142.6 (C), 142.2 (C), 141.8 (C), 129.2 (2 CH, **E** and **Z**), 126.0 (2 CH, **E**), 125.4 (2 CH, **Z**), 91.3 (CH, **E**), 87.6 (CH, **Z**), 51.2 (CH, **E** and **Z**), 34.6 (CH_2, **E**), 34.4 (CH_2, **Z**), 33.4 (CH_2, **E**), 31.9 (CH_2, **Z**), 25.4 (CH_2, **E**), 25.2 (CH_2, **Z**), 24.6 (CH_2, **E** and **Z**), 22.1 (CH_2, **E**), 21.5 (CH_2, **Z**), 21.3 (CH_3, **E** and **Z**), 13.6 (CH_3, **E** and **Z**); mass spectrum, *m/z* (relative intensity, %) 321 (M^+, 29),

278 (M^+-Pr, 13), 240 (80), 212 (74), 166 (M^+-Ts, 100), 138 (67), 91 (84), 84 (85), 41 (89). Exact mass calcd for $C_{18}H_{27}O_2NS$: 321.1763. Found: 321.1790.

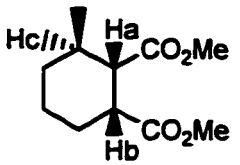
3.12 (E)-2-(N-Cyclohexyl-N-benzylamino)-1-(*p*-tolylsulfonyl)-1-pentene (161)



161

A solution of N-benzylcyclohexylamine (**159**) (272 mg, 1.44 mmol) and acetylenic sulfone **140** (308 mg, 1.39 mmol) in 5.0 mL of THF was stirred for 24 h at room temperature and then refluxed for 4.5 h. The THF was evaporated and chromatography over neutral alumina (activated, 80-200 mesh) with 10% ethyl acetate - hexanes afforded 479 mg (84%) of **161** as a single regio- and stereoisomer in the form of a yellow oil: IR (film) 1543, 1279, 1131, 1079 cm^{-1}; ^1H NMR (200 MHz) δ 7.49 (d, *J*= 8.2 Hz, 2H, Ar), 7.35-7.02 (complex, 7H), 4.93 (s, 1H, vinylic H), 4.36 (s, 2H, CH_2Ph), 3.60 (m, 1H, CHN), 2.63 (br t, *J*= 8.3 Hz, 2H, allylic H), 2.39 (s, 3H, Me), 1.89-1.57 (m, 5H), 1.56-1.17 (m, 6H), 1.16-0.98 (m, 1H), 0.90 (t, *J*= 7.3 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 160.4 (C), 143.4 (C), 141.5 (C), 137.1 (C), 128.9 (2 CH), 128.4 (2 CH), 126.7 (CH), 125.9 (2 CH), 125.8 (2 CH), 96.4 (CH), 57.9 (CH), 47.7 (CH_2), 31.3 (2 CH_2), 29.7 (CH_2), 25.7 (2 CH_2), 25.0 (CH_2), 22.1 (CH_2), 21.2 (CH_3), 14.0 (CH_3); mass spectrum, *m/z* (relative intensity, %) 411 (M^+, 1.4), 256 (M^+-Ts, 100), 91 (89). Exact mass calcd for $C_{25}H_{33}O_2NS$: 411.2232. Found: 411.2227.

3.13 *trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, dimethyl ester (152)

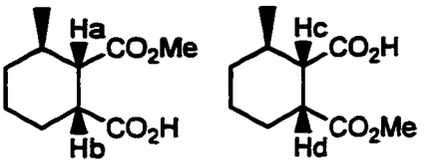


152

Dimethyl ester **152** had been previously synthesized by Kawasaki and Matsumura.[109] A solution of the adduct **142** (7.759 g, 46.18 mmol) and a catalytic amount (0.2 - 0.3 mL) of concentrated H_2SO_4 in 150 mL of methanol was refluxed for 36 h. The methanol was evaporated and the residue was triturated with ether and washed with saturated K_2CO_3

solution. The ether layer was separated and dried over $MgSO_4$. The ether was evaporated and 9.585 g (97%) of **152** was obtained as a yellow oil: IR (film) 1739 (C=O), 1200, 1160 cm^{-1} (lit.[108] 1740 cm^{-1}); ^1H NMR (200 MHz) δ 3.67 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.88 (dt, *J*= 6.9, 4.4 Hz, 1H, Hb), 2.53 (dd, *J*= 7.2, 4.6Hz, 1H, Ha), 2.40-2.20 (m, 1H, Hc), 2.05-1.85 (m, 1H), 1.80-1.45 (m, 4H), 1.25-1.08 (m, 1H), 1.03 (d, *J*= 6.8 Hz, 3H, Me). Homo decoupling (400 MHz) (i) irradiation of the Ha signal at δ 2.53 collapsed the Hb signal at δ 2.88 to dd, *J*= 6.9, 4.3 Hz, (ii) irradiation of the Hb signal at δ 2.88 collapsed the Ha signal at δ 2.53 to d, *J*= 7.2 Hz, (iii) irradiation of the Hc signal at δ 2.40 - 2.20 collapsed the signals at δ 2.53 (Ha) and 1.03 (Me) to a broad singlet and singlet, respectively. ^{13}C NMR (50 MHz) δ 173.8 (C=O), 173.4 (C=O), 51.0 (2 CH_3), 49.3 (CH), 40.1 (CH), 31.1 (CH_2), 29.1 (CH), 25.9 (CH_2), 20.1 (CH_2), 19.5 (CH_3); mass spectrum, *m/z* (relative intensity, %) 214 (M^+, 0.9), 182 (M^+-MeOH, 10), 154 (26), 95 (49), 40 (100). Exact mass calcd for $C_{12}H_{18}O_4$: 214.1205. Found: 214.1213.

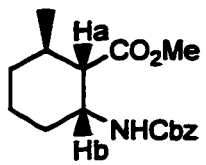
3.14 *trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, 2-methyl ester (147) and *trans*-3-Methylcyclohexane-*cis*,*cis*-1,2-dicarboxylic acid, 1-methyl ester (148) *via* selective saponification of dimethyl ester 152



147 **148**

Dimethyl ester **152** (18.32 g, 85.61 mmol) and NaOH (4.08 g, 102 mmol) were refluxed for 4 h in 200 mL of water. After it was cooled to room temperature, the reaction mixture was acidified with 10% HCl solution, extracted with ether, and dried over $MgSO_4$. The ether was evaporated and 15.85 g (93%) of an inseparable mixture of **147** and **148** (7 : 1 ratio by NMR integration) was obtained as a yellow oil. The properties of the mixture, except for the ratio, were as described in section 3.5.

3.15 Methyl *cis*-2-[N-(carbobenzyloxy)amino]-*trans*-6-methylcyclohexane-carboxylate (162)

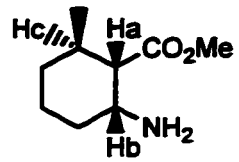


162

The Curtius rearrangement of **147** and **148** was carried out by the general procedure of Shioiri, Ninomiya, and Yamada.[90] A solution of DPPA (3.40 mL, 15.8 mmol), triethylamine (2.20 mL, 15.8 mmol), and a mixture of **147** and **148** (7 : 1 ratio, 3.152 g, 15.76 mmol) in 60 mL of toluene was refluxed for 5 h. The solution was diluted with benzene, washed quickly with saturated K_2CO_3 solution, and dried over $MgSO_4$. The solvent was evaporated and 2.745 g (88%) of the corresponding mixture of isocyanates **149** and **150** was obtained as a yellow oil, which was used without further purification in the next step: IR (film) 2270 (N=C=O), 1736 (ester C=O) cm^{-1}.

A solution of the isocyanates **149** and **150** (2.745 g, 13.93 mmol), and benzyl alcohol (2.20 mL, 21.3 mmol) in 3.0 mL of pyridine was refluxed for 20 min. Evaporation of the pyridine and removal of excess benzyl alcohol by Kugelrohr distillation gave a crude product (4.0 g), which was chromatographed over neutral alumina (activated, 80-200 mesh) and then silica-gel (elution with 10% ethyl acetate - hexanes) to afford 2.383 g (57 % overall based on **147**) of **162** as a pale green oil: IR (film) 3364, 3345, 1729 (ester and carbamate C=O), 1235 cm^{-1}; ^1H NMR (200 MHz) δ 7.37-7.30 (br s, 5H, Ar), 5.30 (m, 1H, NH), 5.08 (s, 2H, CH_2Ph), 4.16 (m, 1H, Hb), 3.63 (s, 3H, OMe), 2.30 (dd, J= 10.1, 3.6 Hz, 1H, Ha), 2.08-1.83 (m, 2H), 1.83-1.50 (m, 4H), 1.15-1.00 (m, 1H), 0.94 (d, J= 6.5 Hz, 3H, Me); COSY (400 MHz) correlations were observed between (i) NH (δ 5.30) - Hb (δ 4.16), and (ii) Hb (δ 4.16) - Ha (δ 2.30). Homo decoupling (200 MHz) irradiation of the Hb signal at δ 4.16 collapsed the Ha signal at δ 2.30 to d, J= 9.8 Hz. ^{13}C NMR (100 MHz) δ 173.3 (C=O), 155.4 (C), 136.4 (C), 128.0 (2 CH), 127.6 (3 CH), 66.1 (CH_2), 52.1 (CH), 51.1 (CH_3), 47.5 (CH), 32.0 (CH_2), 29.8 (CH_2), 28.6 (CH), 19.9 (CH_3), 19.5 (CH_2); mass spectrum, *m/z* (relative intensity, %) 305 (M^+,4), 170 (M^+-Cbz, 20), 108 (17), 91 (100). Exact mass calcd for $C_{17}H_{23}O_4N$: 305.1627. Found: 305.1623.

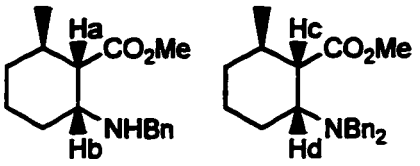
3.16 Methyl *cis*-2-amino-*trans*-6-methylcyclohexanecarboxylate (139)



139

Compound **139** had been synthesized previously in a different manner by Davies and Bhalay; spectral data for **139** were not given in the literature.[96] A solution of N-Cbz amino ester **162** (4.931 g, 16.17 mmol) and formic acid (1.2 mL) in 30 mL of methanol was hydrogenated for 19 h over 10% palladium on charcoal (420 mg) at room temperature and at atmospheric pressure. The catalyst was removed by filtration through Celite and the solvent was evaporated. The residue was triturated with ether and the aqueous layer was made basic with 1.0 N NaOH solution. The ether layer was separated and dried over $MgSO_4$. The ether was evaporated carefully without heating and 2.609 g (94%) of **139** was obtained as a colourless oil: IR (film) 3439, 3386, 3312, 1729 (C=O), 1193, 1153 cm^{-1}; ^1H NMR (200 MHz) δ 3.68 (s, 3H, OMe), 3.32 (m, 1H, Hb), 2.17 (dd, *J*= 11.1, 3.1 Hz, 1H, Ha), 2.05-1.80 (m, 1H, Hc), 1.80-1.40 (m, 5H), 1.37 (br s, 2H, NH_2-exchangeable with D_2O), 1.07-0.91 (m, 1H), 0.88 (d, *J*= 6.3 Hz, 3H, Me). Homo decoupling (400 MHz, $CDCl_3$-D_2O) (i) irradiation of the Hb signal at δ 3.32 collapsed the Ha signal at δ 2.17 to d, *J*= 11.1 Hz, (ii) irradiation of the Hc signal at δ 2.05-1.80 collapsed the signals at δ 2.17 (Ha) and δ 0.88 (Me) to a broad singlet and singlet, respectively. ^{13}C NMR (50 MHz) δ 174.1 (C=O), 54.4 (CH), 50.4 (CH_3), 47.4 (CH), 33.2 (CH_2), 32.3 (CH_2), 26.8 (CH), 19.9 (CH_3), 18.5 (CH_2); mass spectrum, *m/z* (relative intensity, %) 171 (M^+,4), 97 (20), 70 (23), 56 (100). Exact mass calcd for $C_9H_{17}O_2N$: 171.1259. Found: 171.1257.

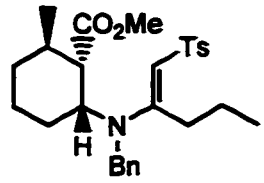
3.17 Methyl *cis*-2-(benzylamino)-*trans*-6-methylcyclohexanecarboxylate (163) and its N,N-dibenzyl derivative 164



163 **164**

Compound **163** was prepared by a procedure similar to one reported by Yamazaki and Kibayashi.[97] A mixture of the amino ester **139** (538 mg, 3.15 mmol) and benzyl bromide (450 μL, 3.78 mmol) in 6.0 mL of a 1 : 1 mixture of chloroform and saturated K_2CO_3 solution was refluxed for 5 h. The organic layer was separated and dried over $MgSO_4$. The chloroform was evaporated and chromatography of the residue with 25% ethyl acetate - hexanes afforded 604 mg (73%) of monobenzylamine **163** and 150 mg (14%) of dibenzylamine **164** as yellow oils: Compound **163**: IR (film) 3338 (NH), 1729 (C=O), 1456, 1162 cm^{-1}; ^1H NMR (200 MHz) δ 7.38-7.16 (br s, 5H, Ar), 3.84 (d, *J*= 13.5 Hz, 1H, *CH*Ph), 3.64 (s, 3H, OMe), 3.62 (d, *J*= 13.6 Hz, 1H, *CH*Ph), 3.10 (m, 1H, Hb), 2.22 (dd, *J*= 10.9, 3.5 Hz, 1H, Ha), 2.18-1.20 (m, 7H), 1.09-0.95 (m, 1H), 0.89 (d, *J*= 6.2 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 174.5 (C=O), 140.6 (C), 127.9 (2 CH), 127.8 (2 CH), 126.4 (CH), 54.0 (CH), 52.9 (CH), 50.8 (CH_3 and CH_2), 33.5 (CH_2), 28.0 (CH and CH_2), 20.6 (CH_3), 19.1 (CH_2); mass spectrum, *m/z* (relative intensity, %) 261 (M^+, 5), 230 (M^+-OMe, 5), 218 (14), 146 (81), 106 (64), 91 (100). Exact mass calcd for $C_{16}H_{23}O_2N$: 261.1728. Found: 261.1721. Compound **164**: IR (film) 1732 (C=O), 1444, 1158, 743, 698 cm^{-1}; ^1H NMR (400 MHz) δ 7.34-7.12 (complex, 10H, Ar), 3.75 (d, *J*= 13.7 Hz, 2H, *CH*Ph), 3.63 (s, 3H, OMe), 3.55 (d, *J*= 13.7 Hz, 2H, *CH*Ph), 3.08 (m, 1H, Hd), 2.55 (t, *J*= 5.5 Hz, 1H, Hc), 2.22-1.89 (m, 3H), 1.71-1.42 (m, 3H), 1.12-1.03 (m, 1H), 0.81 (d, *J*= 6.8 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 175.2 (C=O), 140.4 (2 C), 128.7 (4 CH), 128.0 (4 CH), 126.6 (2 CH), 55.2 (2 CH_2), 53.6 (CH), 51.1 (CH_3), 50.5 (CH), 31.1 (CH), 29.3 (CH_2), 23.7 (CH_2), 21.6 (CH_2), 20.2 (CH_3); mass spectrum, *m/z* (relative intensity, %) 351 (M^+, 20), 320 (M^+-OMe, 2), 260 (M^+-CH_2Ph, 12), 236 (51), 132 (13), 91 (100). Exact mass calcd for $C_{23}H_{29}O_2N$: 351.2198. Found: 351.2225.

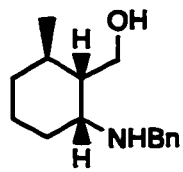
3.18 Methyl *cis*-2-{N-benzyl-N-[2-(1-*p*-tolylsulfonyl)-1-pentenyl]}amino-*trans*-6-methylcyclohexanecarboxylate (165)



165

A mixture of amine **163** (30 mg, 0.11 mmol) and acetylenic sulfone **140** (25 mg, 0.11 mmol) in 4.0 mL of toluene was refluxed for 18 h and concentrated *in vacuo*. The crude material contained starting materials and a complex mixture of unidentified products, which was chromatographed over neutral alumina (activated, 80-200 mesh) with 25% ethyl acetate - hexanes to afford 10 mg (18 %) of **165** as a yellow oil: IR (film) 1728 (C=O), 1546, 1456, 1280, 1131, 1079, 729 cm^{-1}; ^1H NMR (200 MHz) δ 7.53 (br d, *J*= 7.5 Hz, 2H, Ar), 7.32-7.12 (complex, 5H, Ar), 6.98 (br d, *J*= 6.6 Hz, 2H, Ar), 5.02 (s, 1H, vinylic H), 4.56 (d, *J*= 17.9 Hz, 1H, *CH*Ph), 4.32 (d, *J*= 17.8 Hz, 1H, *CH*Ph), 4.10 (m, 1H, CHN), 3.55 (s, 3H, OMe), 3.12 (m, 1H, allylic H), 2.79 (m, 1H, allylic H), 2.40 (s, 3H, Me), 2.38-1.20 (m, 10H), 1.15 (d, *J*= 7.2 Hz, 3H, Me), 0.86 (t, *J*= 7.3 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 174.1 (C=O), 160.2, 143.3, 141.9, 138.0, 129.1, 128.6, 126.8, 126.2, 125.6, 98.4, 54.0, 51.6, 48.6, 31.8, 30.1, 29.7, 27.2, 26.8, 22.4, 21.4, 20.9, 18.9, 14.1; mass spectrum, *m/z* (relative intensity, %) 483 (M^+, 1.8), 452 (M^+-OMe, 1.6), 328 (M^+-Ts, 81), 238 (14), 91 (100). Exact mass calcd for $C_{28}H_{37}O_4NS$: 483.2443. Found: 483.2457.

3.19 N-Benzyl-*cis*-2-(hydroxymethyl)-*trans*-3-methylcyclohexylamine (166)



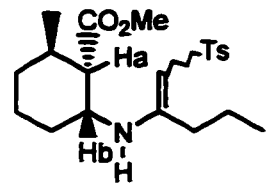
166

A solution of amino ester **163** (205 mg, 0.785 mmol) in 2.0 mL of anhydrous ether was added dropwise by syringe to a suspension of lithium aluminum hydride (140 mg, 3.68 mmol) in 3.0 mL of anhydrous ether. The resulting mixture was stirred for 7 h at room temperature under a nitrogen atmosphere. Excess lithium aluminum hydride was decomposed by adding water cautiously and the resulting white precipitate was removed by filtration. The filtrate was extracted repeatedly with ether, and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and 156 mg (85%) of **166** was obtained as a yellow oil: IR (film) 3321 (NH and OH), 1453, 1090, 741, 698 cm^{-1}; ^1H NMR (200 MHz) δ 7.41-7.21 (br s, 5H, Ar), 4.00-3.65 (complex, 4H, CH_2OH and CH_2Ph), 3.07 (m, 1H, CHN), 2.06-1.95 (m, 1H), 1.85-1.31 (m, 6H), 1.27-1.00 (m, 2H), 0.97 (d, J= 6.3 Hz, 3H, Me); ^{13}C NMR (50 MHz) δ 139.5 (C), 128.4 (2 CH), 128.2 (2 CH), 127.0 (CH), 65.0 (CH_2), 57.8 (CH), 51.6 (CH_2), 47.2 (CH), 33.9 (CH_2), 27.6 (CH_2), 27.4 (CH), 20.1 (CH_2), 19.7 (CH_3); mass spectrum, *m/z* (relative intensity, %) 233 (M^+, 25), 190 (24), 146 (80), 106 (34), 91 (100). Exact mass calcd for $C_{15}H_{23}ON$: 233.1779. Found: 233.1762.

3.20 Attempted Michael addition of 166 to 140

A solution of **166** (156 mg, 0.670 mmol) and **140** (151 mg, 0.680 mmol) in 4.0 mL of THF was refluxed for 7 h and the solvent was evaporated. The ^1H NMR spectrum of the crude material showed no reaction. The solvent was evaporated and replaced by 4.0 mL of benzene and the mixture was refluxed for 19 h. Again no reaction was observed. Finally, the mixture was refluxed in 4.0 mL of toluene for 20 h. The solvent was evaporated and both starting materials were recovered by chromatography (>80%).

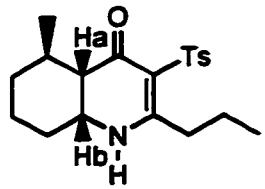
3.21 Methyl *cis*-2-{N-[2-(1-*p*-tolylsulfonyl)-1-pentenyl]}amino-*trans*-6-methyl-cyclohexanecarboxylate (138)



138

A solution of amino ester **139** (151 mg, 0.883 mmol) and acetylenic sulfone **140** (197 mg, 0.887 mmol) in 5.0 mL of THF was stirred for 21 h at room temperature. The THF was evaporated and chromatography over neutral alumina (activated, 80-200 mesh) with 10% ethyl acetate - hexanes afforded 324 mg (93%) of **138** as a mixture of (E)- and (Z)-isomers (1 : 2.5 ratio by NMR integration), in the form of a red oil. An analytical sample was obtained by crystallization from ether to give a white powder with the same (E) : (Z) ratio: mp 83-87°C. The assignment of signals in the ^{1}H NMR spectrum is tentative: IR (KBr) 3321 (NH), 1735 (C=O), 1599, 1274, 1127, 1078 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.90 (br d, *J*= 10.2 Hz, 1H, NH, **Z**), 7.81 (d, *J*= 8.2 Hz, 2H, Ar, **Z**), 7.76 (d, *J*= 8.2 Hz, 2H, Ar, **E**), 7.28 (d, *J*= 7.4 Hz, 2H, Ar, **Z**), 7.26 (d, *J*= 7.7 Hz, 2H, Ar, **E**), 4.99 (s, 1H, vinylic H, **E**), 4.54 (s, 1H, vinylic H, **Z**), 4.72 (m, 1H, NH, **E**), 4.00 (m, 1H, Hb, **Z**), 3.75 (m, 1H, Hb, **E**), 3.64 (s, 3H, OMe, **E**), 3.60 (s, 3H, OMe, **Z**), 2.60-2.45 (m, 2H, allylic H, **E**), 2.41 (s, 3H, Me, **E** and **Z**), 2.34 (dd, *J*=10.7, 3.9 Hz, Ha, **E**), 2.26 (dd, *J*=11.4, 3.7 Hz, 1H, Ha, **Z**), 2.18-1.30 (m, 12H, **E** and **Z**), 2.02 (dt, *J*=7.1, 1.5 Hz, 2H, allylic H, **Z**), 0.98 (d, *J*=6.3Hz, 3H, Me, **Z**), 0.93 (d, *J*=6.5Hz, 3H, Me, **E**), 0.87 (t, *J*=7.3Hz, 3H, Me, **E** and **Z**); COSY (400 MHz) correlations were observed between (i) Hb (δ 4.00, **Z**) - Ha (δ 2.26, **Z**), (ii) NH (δ 4.72, **E**) - Hb (δ 3.75, **E**), and (iii) Hb (δ 3.75, **E**) - Ha (δ 2.34, **E**). NOE (400 MHz) (i) 3.4% enhancement of the signal at δ 2.02 (allylic CH_2, **Z**) was observed when vinylic H (δ 4.54, **Z**) was irradiated, (ii) 19.4% enhancement of the signal at δ 3.75 (CHN, **E**) was observed when vinylic H (δ 4.99, **E**) was irradiated; mass spectrum, *m/z* (relative intensity, %) 393 (M^+, 7), 362 (M^+-OMe, 5), 301 (7), 238 (M^+-Ts, 93), 95 (69), 91 (65), 83 (100). Anal. calcd for $C_{21}H_{31}O_4NS$: C, 64.12;H, 7.89; N,3.56. Found: C, 63.84; H, 7.79; N, 3.44.

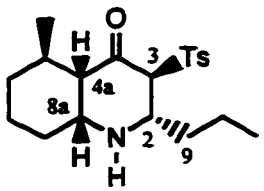
3.22 4a,5,6,7,8,8a-Hexahydro-5-methyl-2-propyl-3-(*p*-tolylsulfonyl)-4-quinolinone (137)



137

n-Butyllithium (1.44 mmol) was added to a solution of diisopropylamine (200 μL, 1.43 mmol) in 2.0 mL of THF and the resulting solution was stirred for 20 min at -78°C. A solution of compound **138** (488 mg, 1.24 mmol) in 5.0 mL of THF was added and the resulting mixture was stirred for another 1.25 h at -78°C, then for 20 min at room temperature, and finally was refluxed for 1 h. The THF was evaporated and chromatography over neutral alumina (activated, 80-200 mesh) with 10% ethyl acetate - hexanes, followed by ethyl acetate : methanol = 2 : 1, afforded 162 mg (33%) of unreacted **138** as a red oil and 280 mg (63%; 94% based on the amount of **138** consumed) of **137** as a pale yellow solid, respectively. Recrystallization from methanol gave **137** as colourless needles: mp 224-226°C; IR (KBr) 3283 (NH), 1657 (C=O), 1548, 1515, 1281, 1148, 1132, 672 cm^{-1}; ^1H NMR (400 MHz) δ 7.88 (d, *J*= 8.1 Hz, 2H, Ar), 7.23 (d, *J*= 8.0 Hz, 2H, Ar), 5.48 (m, 1H, NH), 3.81 (m, 1H, Hb), 3.19 (dt, *J*= 13.3 Hz, 7.7Hz, 1H, allylic H), 2.79 (dt, *J*= 13.3, 7.7 Hz, 1H, allylic H), 2.38 (s, 3H, Me), 1.98-1.78 (m, 3H), 1.73 (dd, *J*= 10.5, 3.8 Hz, 1H, Ha), 1.78-1.50 (m, 5H), 1.09 (t, *J*= 7.3 Hz, 3H, Me), 1.02-0.76 (m, 1H), 0.64 (d, *J*= 6.5 Hz, 3H, Me); COSY (400 MHz) correlations were observed between (i) Hb (δ 3.81) - Ha (δ 1.73), and (ii) allylic H (δ 3.19) - allylic H (δ 2.79). mass spectrum, *m/z* (relative intensity, %) 361 (M^+, 2), 360 (M^+-1, 3), 296 (100), 269 (71), 228 (49), 190 (54), 91 (66), 41 (44). Anal. calcd for $C_{20}H_{27}O_3NS$: C, 66.48; H, 7.48; N, 3.88. Found: C, 66.33; H, 7.44; N, 3.95.

3.23 4-Oxo-3-(*p*-tolylsulfonyl)pumiliotoxin C (168)



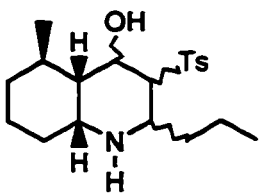
168

The triflate salt **176** was prepared by the general procedure of Brandi, Cordero, Goti and Guarna.[51] A solution of **137** (202 mg, 0.560 mmol) and triflic anhydride (95 μL, 0.56 mmol) in 12 mL of dichloromethane was refluxed for 18 h. The solvent was evaporated and 351 mg (97%) of **176** was obtained as a white solid: ^{1}H NMR (400 MHz) δ 9.55 (br m, 1H, NH), 7.73 (d, *J*= 8.4 Hz, 2H, Ar), 7.46 (d, *J*= 8.0 Hz, 2H, Ar), 4.06 (m, 1H, CHN), 2.78 (m, 2H, N=CCH$_2$), 2.51 (s, 3H, Me), 2.33 (dd, *J*= 10.7, 4.8 Hz, 1H, CHC=C), 1.90-1.74 (m, 3H), 1.73-1.48 (m, 5H), 1.11 (d, *J*= 6.7 Hz, 3H, Me), 1.18-1.06 (m, 1H), 0.98 (t, *J*= 7.2 Hz, 3H, Me).

A mixture of magnesium turnings (347 mg, 14.3 mg-atoms) and 18 mL of methanol was warmed to 40-50°C. When hydrogen evolution commenced, triflate salt **176** (152 mg, 0.24 mmol) was added and the resulting mixture was allowed to cool to room temperature and stirred for additional 18.5 h. The solvent was evaporated and the residue was triturated with chloroform and washed with saturated K_2CO_3 solution. The chloroform layer was separated and dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was chromatographed with ethyl acetate : hexanes = 1 : 3 to afford 49 mg (57%) of **168** as an oil. Crystallization from hexanes gave **168** as a pale yellow solid: mp 102-109°C. The product showed initial signals in the ^{1}H NMR spectrum attributed to the keto structure **168**. However, new signals attributed to its corresponding enol form gradually appeared, making assignments difficult. They are tentatively made as follows: Keto strucutre: IR (KBr) 3465 (NH), 1701 (C=O), 1456, 1337, 1144, 1086, 746 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.82 (d, *J*= 8.3 Hz, 2H, Ar), 7.33 (d, *J*= 8.1 Hz, 2H, Ar), 3.97 (d, *J*= 8.4 Hz, 1H, H3), 3.58 (m, 1H, H2), 3.25 (m, 1H, H8a), 2.44 (s, 3H, Me), 2.22 (dd, *J*= 9.4, 4.3 Hz, 1H, H4a), 2.19-2.08 (m, 1H), 2.07-1.94 (m, 1H), 1.89-1.79 (m, 1H), 1.76-1.38 (m, 9H), 0.99 (t, *J*= 7.4 Hz, 3H, Me), 0.66 (d, *J*= 6.7 Hz, 3H, Me); COSY (400 MHz) correlations were observed between (i) H3 (δ 3.97) - H2 (δ 3.58), (ii) H8a (δ 3.25) - H4a (δ 2.22), and (iii) H2 (δ 3.58) - H9 (δ 1.89-1.79). NOE (400 MHz) (i) 6.1% enhancement of the signal at δ 3.25 (H8a) was observed when H2 (δ 3.58) was irradiated, (ii) 6.0% enhancement of the signal at δ 3.58 (H2) was observed when H8a (δ 3.25) was irradiated, (iii) 12.0%

enhancement of the signal at δ 2.22 (H4a) was observed when H8a (δ 3.25) was irradiated. Homo decoupling (400 MHz) (i) irradiation of the signal at δ 1.89-1.79 (H9) collapsed the H2 signal at δ 3.58 to br d, J= 8.5 Hz, (ii) irradiation of the signal at δ 3.58 (H2) collapsed the H3 signal at δ 3.97 to a singlet, (iii) irradiation of the signal at δ 3.25 (H8a) collapsed the H4a signal at δ 2.22 to d, J= 9.5 Hz, (iv) irradiation of the signal at δ 3.97 (H3) collapsed the H2 signal at δ 3.58 to dd, J= 7.8, 3.7 Hz. Enol structure: ^{1}H NMR (400 MHz) δ 7.82 (d, J= 8.3 Hz, 2H, Ar), 7.38 (d, J= 8.0 Hz, 2H, Ar), 3.75 (t, J= 7.6 Hz, 1H, H2), 3.65 (s, 1H, OH), 3.19 (m, 1H, H8a), 2.47 (s, 3H, Me), 0.90 (d, J= 6.6 Hz, 3H, Me), 0.75 (t, J= 7.3 Hz, 3H, Me); mass spectrum, *m/z* (relative intensity, %) 363 (M^+, 3), 320 (M^+-Pr, 50), 296 (45), 208 (M^+-Ts, 38), 164 (34), 138 (80), 91 (100), 41 (78). Exact mass calcd for $C_{20}H_{29}O_3NS$: 363.1868. Found: 363.1870.

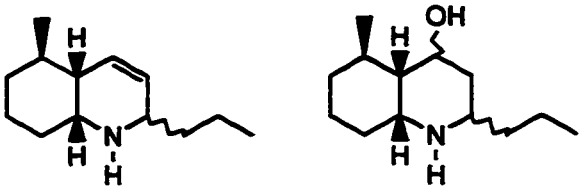
3.24 Preparation of 169 by reduction of 137 with $NaBH_4$



169

A mixture of **137** (44 mg, 0.12 mmol) and $NaBH_4$ (275 mg, 7.28 mmol) in 6.0 mL of ethanol was refluxed for 1.5 h and concentrated *in vacuo*. The residue was triturated with dichloromethane and washed with 1.0 N NaOH. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and 45 mg of **169** were obtained as an inseparable mixture of the various stereoisomers in the form of a yellow oil. Assignment of signals in the NMR spectra could not be done: IR (film) 3492 (OH), 1598, 1456, 1288, 1140, 669 cm^{-1}.

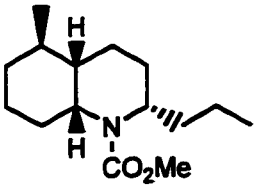
3.25 Preparation of 170 and 171 by desulfonylation of 169



170 **171**

A mixture of **169** (45 mg), Na_2HPO_4 (79 mg, 0.56 mmol) and 5% sodium amalgam (3.96 g, 8.61 mg-atoms of Na) in 4.0 mL of a 1 : 1 mixture of methanol and THF was stirred at room temperature for 19.5 h and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was triturated with dichloromethane and washed with 1.0 N NaOH.. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and chromatography with elution with methanol (only one spot was observed by TLC) gave 11 mg of an inseparable mixture of **170** and **171** as an oil. Assignment of signals in the ^1H NMR spectrum is tentative: ^1H NMR (200 MHz) δ 5.99 (br d, *J*= 10.8 Hz, 1H, vinylic H, **170**), 5.59 (br d, *J*= 10.8 Hz, 1H, vinylic H, **170**), 3.82 (dt, *J*= 12.1, 4.2 Hz, 1H, *CH*OH, **171**).

3.26 N-(Methoxycarbonyl)pumiliotoxin C (175) *via* reduction of 137 with $NaBH_4$



175

Compound **175** was previously synthesized by Oppolzer in 1975, but spectral data were not given in the literature.[33] A solution of **169** (22 mg), obtained as described in section 3.24, and methyl chloroformate (150 μL, 1.94 mmol) in 2.0 mL of a 4 : 1 mixture of chloroform and saturated K_2CO_3 solution was refluxed for 2 h. The organic layer was separated and dried over $MgSO_4$. The solvent and excess methyl chloroformate were evaporated and 25 mg of **172** was obtained as an oil, which was then dissolved in 3.0 mL of a 1 : 1 mixture of methanol and THF. To this solution were added Na_2HPO_4 (32 mg, 0.23 mmol) and 5% sodium amalgam (2.328 g, 5.061 mg-atoms of Na). The resulting mixture was stirred at room temperature for 2 h and filtered through Celite. The filtrate

was concentrated *in vacuo* and the residue was triturated with dichloromethane and washed with saturated K_2CO_3 solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and 15 mg of an inseparable mixture of **173** and **174** (1 : 2 ratio by NMR integration) was obtained as an oil: ^{1}H NMR (200 MHz) δ 5.71 (dt, *J*= 10.3, 3.0 Hz, 1H, vinylic H, **174**), 5.50 (br d, *J*= 10.3 Hz, 1H, vinylic H, **174**), 5.05 (br d, *J*= 3.7 Hz, 1H, vinylic H, **173**), 4.97 (br s, 1H, vinylic H, **173**), 3.72 (s, 3H, OMe, **174**), 3.69 (s, 3H, OMe, **173**).

Finally, the mixture of **173** and **174** (15 mg) was hydrogenated over 10% palladium on charcoal (13 mg) in 3.0 mL of ethyl acetate for 17.5 h at room temperature and at atmospheric pressure. The catalyst was removed by filtration through Celite. The filtrate was concentrated *in vacuo* and chromatography with 2% ethyl acetate - hexanes gave 4 mg (26% overall from **137**) of **175** as an oil. The stereoisomer derived similarly from **173** could not be isolated. Compound **175**: IR (film) 1697 (C=O), 1445, 1405, 1358, 1309, 1094, 766 cm^{-1}; ^{1}H NMR (400 MHz) δ 4.22 (m, 1H, CHN), 4.05 (m, 1H, CHN), 3.67 (s, 3H, OMe), 1.92-1.17 (m, 16H), 1.06 (d, *J*= 7.3 Hz, 3H, Me), 0.90 (t, *J*= 7.3 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 156.6 (C=O), 52.2 (CH_3), 50.4 (CH), 49.7 (CH), 42.1 (CH), 37.7 (CH_2), 34.5 (CH), 28.5 (CH_2), 28.1 (CH_2), 26.7 (CH_2), 21.3 (CH_2), 20.6 (CH_2), 20.3 (CH_2), 19.3 (CH_3), 14.0 (CH_3); mass spectrum, *m/z* (relative intensity, %) 253 (M^+, 2), 251 (M^+-2, 4), 238 (M^+-Me, 39), 210 (M^+-Pr, 100), 135 (77), 109 (82), 67 (56), 55 (67), 41 (52). Exact mass calcd for $C_{15}H_{27}O_2N$: 253.2042. Found: 253.2037.

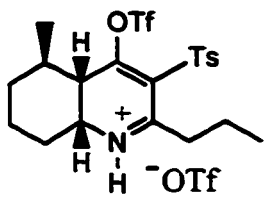
3.27 N-(Methoxycarbonyl)pumiliotoxin C (175) *via* triflate salt 176

This reaction was carried out in order to confirm that the product obtained in section 3.26 was the N-methoxycarbonyl derivative of pumiliotoxin C. The enaminone **137** (101 mg, 0.280 mmol) was converted to **177** (98 mg) by the manner described in section 3.28. A mixture of **177** (98 mg) and methyl chloroformate (400 μL, 5.18 mmol) in 2.0 mL of a 4 : 1 mixture of chloroform and saturated K_2CO_3 solution was refluxed for 3 h, and the organic layer was separated and dried over $MgSO_4$. The solvent and excess methyl chloroformate were evaporated *in vacuo* to furnish the N-methoxycarbonyl derivative of **177** (99 mg) as an oil, which was then dissolved in 6.0 mL of a 1 : 1 mixture of methanol and THF. To this solution were added Na_2HPO_4 (140 mg, 0.986 mmol) and 5% sodium amalgam (9.80 g, 21.3 mg-atoms of Na). The resulting mixture was stirred at room temperature for 3 h and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was triturated with dichloromethane and washed with saturated K_2CO_3 solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent

was evaporated and the desulfonylated products (82 mg) were obtained as an oil, which was hydrogenated over 10% palladium on charcoal (25 mg) in 4.0 mL of methanol for 25 h (initial heating was needed to dissolve the desulfonylated products) at room temperature and at atmospheric pressure. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The crude material was chromatographed with 2% ethyl acetate - hexanes to afford 31 mg (44% overall from **137**) of **175** as an oil. The properties of **175** were as described in section 3.26.

3.28 (±)-Pumiliotoxin C (5)

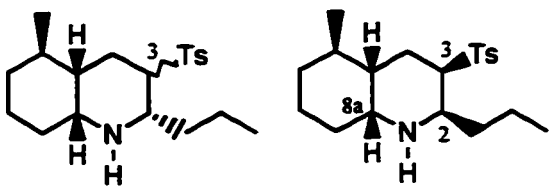
(1) Preparation of triflate salt **176**



176

A solution of **137** (101 mg, 0.280 mmol) and triflic anhydride (70 μL, 0.42 mmol) in 3.0 mL of dichloromethane was refluxed under an argon atmosphere for 18 h and concentrated *in vacuo* to afford **176** as a white solid (173 mg), which was used in the next step without further purification.

(2) Hydrogenation of **176** to **177** and **178**

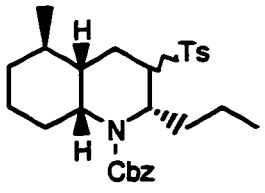


177 **178**

A solution of the triflate salt **176** (173 mg) in 6.0 mL of methanol was hydrogenated over PtO_2 (104 mg, 0.458 mmol) at 1500 psi for 6 days (144 h). The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The residue was triturated with dichloromethane and washed with saturated K_2CO_3 solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed. Elution with ethyl acetate : hexanes = 1 : 5

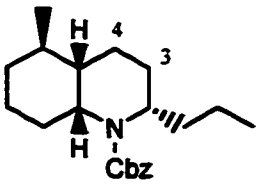
(Rf = 0.75 with ethyl acetate : hexanes = 1 : 3 by TLC) gave one of the C-3 epimers of **177**, containing some inseparable impurities (1st fraction). Then, elution with ethyl acetate : hexanes = 1 : 3 gave **178** (Rf = 0.65, same solvent) as a single diastereomer (16 mg) (2nd fraction). Finally, elution with ethyl acetate provided the other C-3 epimer of **177** (Rf = 0.50 - 0.25, tailing spot, same solvent), containing some inseparable impurities (3rd fraction). The 1st and 3rd fractions were combined (81mg) and this mixture was used directly in the next step. The compound **178** was crystallized from hexanes to provide colourless needles: mp 115-117°C; IR (film) 1291, 1145, 1084 cm^{-1}; ^1H NMR (400 MHz) δ 7.75 (d, *J*= 8.1 Hz, 2H, Ar), 7.33 (d, *J*= 8.1 Hz, 2H, Ar), 3.52 (dt, *J*= 11.4, 3.7 Hz, 1H, H2), 3.38 (dt, *J*= 12.5, 4.0 Hz, 1H, H3), 3.03 (m, 1H, H8a), 2.43 (s, 3H, Me), 2.08-1.85 (m, 3H), 1.75-1.21 (m, 11H), 0.96 (t, *J*= 7.3 Hz, 3H, Me), 0.91-0.82 (m, 1H), 0.47 (d, *J*= 6.3 Hz, 3H, Me); COSY (400 MHz) correlations were observed between H2 (δ 3.52) - H3 (δ 3.38). ^{13}C NMR (100 MHz) δ 144.2 (C), 136.1 (C), 129.6 (2 CH), 128.3 (2 CH), 60.9 (CH), 52.1 (CH), 46.3 (CH), 42.3 (CH), 35.2 (CH_2), 32.2 (CH_2), 27.4 (CH and CH_2), 22.5 (CH_2), 21.6 (CH_3), 20.8 (CH_2), 19.2 (CH_3), 19.1 (CH_2), 13.9 (CH_3); mass spectrum, *m/z* (relative intensity, %) 349 (M^+, 2.6), 306 (M^+-Pr, 100), 194 (M^+-Ts, 55), 151 (70), 91 (69), 72 (65), 41 (51). Exact mass calcd for $C_{20}H_{31}O_2NS$: 349.2075. Found: 349.2049.

(3) N-Protection of **177**



A mixture of **177** (81 mg) and benzyl chloroformate (350 μL, ca. 2.31 mmol) in 2.0 mL of a 4 : 1 mixture of chloroform and saturated K_2CO_3 solution was refluxed for 3 h, and the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed with 5% ethyl acetate - hexanes to remove excess benzyl chloroformate, and then with ethyl acetate to afford the N-Cbz derivative of **177** (113 mg) as an oil.

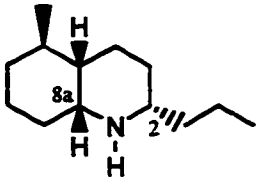
(4) Desulfonylation of N-Cbz derivative of **177** to **181**



181

A mixture of the N-Cbz derivative of **177** (113 mg) , Na_2HPO_4 (141 mg, 0.993 mmol) and 5% sodium amalgam (10.2 g, 22.2 mg-atoms of Na) in 6.0 mL of a 1 : 1 mixture of methanol and THF was stirred at room temperature for 5 h, filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was triturated with dichloromethane and washed with saturated K_2CO_3 solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed. Elution with ethyl acetate gave **181** (69 mg) as an oil, containing a small amount of unseparated impurities as evidenced by ^{1}H NMR (200 MHz) signals at δ 5.71 (dt, *J*= 10.5, 3.0 Hz, 1H, vinylic H), 5.51 (br d, *J*= 10.3 Hz, 1H, vinylic H). The crude mixture was used directly in the next step.

(5) Hydrogenolysis of **181** to **5**



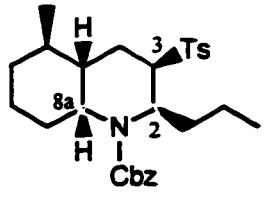
5

A mixture of **181** (69 mg) and 10% palladium on charcoal (20 mg) in 3.0 mL of ethanol (initial gentle heating was needed to dissolve **181**) was hydrogenated at room temperature and at atmospheric pressure for 6 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The residue was triturated with chloroform and washed with saturated K_2CO_3 solution. The chloroform layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed with 5% triethylamine - hexanes to afford (±)-pumiliotoxin C (**5**) (25 mg, 46% overall from **137**) as a pale yellow oil. An analytical sample of the hydrochloride was prepared and crystallized from 2-propanol to give **5**-HCl as colourless needles: 5-hydrochloride: mp 242-245°C (sealed capillary; lit.[33] 245°C, lit.[42] 243-244°C, lit.[44b] 241-243°C, lit.[49]

231-233°C, lit.[50b] 237-239°C, lit.[54] 238-239°C, lit.[60] 235-238°C); ^{1}H NMR (400 MHz) δ 9.60 (m, 1H, NH), 8.30 (m, 1H, NH), 3.33 (m, 1H, H8a), 3.00 (m, 1H, H2), 2.55-2.30 (m, 2H), 2.23-1.95 (m, 4H), 1.92-1.84 (br d, 1H), 1.83-1.75 (br d, 1H), 1.72-1.35 (m, 6H), 1.32-1.20 (m, 1H), 1.04-0.95 (m, 1H), 0.92 (t, *J*= 7.4 Hz, 3H, Me), 0.90 (d, *J*= 6.2 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 60.1, 58.0, 40.9, 34.8, 34.3, 29.1, 27.2, 25.2, 23.1, 20.6, 19.7, 19.1, 13.7. 5-free base: IR (film) 3300 (NH), 2917, 2860, 2809, 1452, 1374, 1354, 1313, 1117, 1089, 753 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.87-2.83 (m, 1H, H8a), 2.58-2.50 (m, 1H, H2), 2.00-1.80 (m, 2H), 1.75-0.88 (m, 15H), 0.91 (t, *J*= 6.9 Hz, 3H, Me), 0.85 (d, *J*= 6.6 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 57.8, 56.0, 42.6, 39.6, 35.9, 33.3, 27.4, 27.2, 27.0, 21.2, 19.9, 19.1, 14.3; mass spectrum, *m/z* (relative intensity, %) 195 (M^+, 4), 194 (M^+-1, 8), 166 (M^+-CH_2CH_3, 60), 152 (100).

The following IR, NMR, mass spectra for **5**-HCl and **5**-free base were reported in the literature: 5-hydrochloride: ^{1}H NMR[60] ($CDCl_3$, 200 MHz) δ 9.6 (br s, 1H), 8.3 (br s, 1H), 3.32-3.30 (br d, 1H), 3.12-2.90 (m, 1H), 2.61-1.10 (m, 13H), 0.94-0.92 (t, *J*= 6.8 Hz, 3H), 0.92-0.90 (d, *J*= 6.8 Hz, 3H); ^{13}C NMR[60] ($CDCl_3$, 50 MHz) δ 60.1, 58.0, 40.9, 34.9, 34.4, 29.1, 27.3, 25.2, 23.2, 20.7, 19.7, 19.1, 13.7. 5-free base: IR[56] (film) 2926, 2863, 2796, 1448, 1376, 1312, 1123, 1094, 1078, 755, 650 cm^{-1}; ^{1}H NMR[56] ($CDCl_3$, 300 MHz) δ 2.85-2.83 (m, 1H, H8a), 2.55-2.49 (large m, 1H, H2), 2.00-1.80 (m, 2H), 1.70-0.87 (m, 18H), 0.84-0.82 (d, *J*= 6.6 Hz, 3H, Me); ^{13}C NMR[56] ($CDCl_3$, 75 MHz) δ 57.7, 56.0, 42.6, 39.8, 36.0, 33.5, 27.4 (overlapping, CH and CH_2), 27.1, 21.2, 19.9, 19.2, 14.3; mass spectrum,[44b] *m/z* (relative intensity, %) 195 (M^+, 6), 152 (100).

3.29 N-(Carbobenzyloxy)-3-(*p*-tolylsulfonyl)-2-epi-pumiliotoxin C (179)

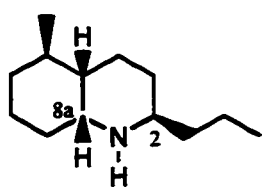


179

A solution of **178** (31 mg, 0.089 mmol) and benzyl chloroformate (30 μL, ca. 0.21 mmol) in 1.0 mL of a 4 : 1 mixture of chloroform and saturated K_2CO_3 solution was refluxed for 2 h, and the organic layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed with ethyl acetate : hexanes = 1 : 5 to afford 40 mg (93%) of **179** as a gum: IR (film) 1691 (C=O), 1403, 1321, 1275, 1147 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.77 (d, *J*= 8.2 Hz, 2H, Ar), 7.40-7.27 (complex, 7H, Ar),

5.14 (d, *J*= 12.4 Hz, 1H, *CH*Ph), 5.09 (d, *J*= 12.4 Hz, 1H, *CH*Ph), 4.58 (m, 1H, H2), 3.93 (dt, *J*= 11.7, 4.2 Hz, 1H, H8a), 3.48 (ddd, *J*= 11.5, 8.1, 3.6 Hz, 1H, H3), 2.46 (s, 3H, Me), 2.32-2.21 (m, 1H), 2.20-1.92 (m, 3H), 1.84-1.60 (m, 2H), 1.58-1.18 (m, 7H), 1.04 (d, *J*= 7.3 Hz, 3H, Me), 0.92-0.82 (m, 1H), 0.86 (t, *J*= 7.0 Hz, 3H, Me); COSY (400 MHz) correlations were observed between H2 (δ 4.58) - H3 (δ 3.48). NOE (400 MHz) (i) 9.6% enhancement of the signal at δ 3.48 (H3) was observed when H2 (δ 4.58) was irradiated, (ii) 15.0% enhancement of the signal at δ 4.58 (H2) was observed when H3 (δ 3.48) was irradiated. Homo decoupling (400 MHz) (i) irradiation of the signal at δ 3.48 (H3) collapsed the H2 signal at δ 4.58 to dd, *J*= 8.1, 4.5 Hz, (ii) irradiation of the signal at δ 4.58 (H2) collapsed the H3 signal at δ 3.48 to dd, *J*= 11.3, 8.3 Hz. ^{13}C NMR (100 MHz) δ 155.4 (C=O), 144.8 (C), 136.5 (C), 135.9 (C), 130.0 (2 CH), 128.4 (2 CH), 128.3 (2 CH), 128.0 (CH), 127.9 (2 CH), 67.0 (CH_2), 61.4 (CH), 50.6 (CH), 50.1 (CH), 36.1 (CH_2), 35.9 (CH), 32.2 (CH), 29.6 (CH_2), 26.0 (CH_2), 21.6 (CH_3), 21.0 (CH_2), 19.9 (CH_2), 19.3 (CH_2), 19.1 (CH_3), 14.2 (CH_3); mass spectrum, *m/z* (relative intensity, %) 483 (M^+, 0.6), 440 (M^+-Pr, 34), 396 (88), 241 (73), 91 (100). The product was used directly in the next step.

3.30 2-epi-Pumiliotoxin C (112)



112

A mixture of **179** (38 mg, 0.079 mmol), Na_2HPO_4 (46 mg, 0.32 mmol) and 5% sodium amalgam (3.61g, 7.85 mg-atoms of Na) in 2.0 mL of a 1 : 1 mixture of methanol and THF was stirred at room temperature for 3 h, filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was triturated with dichloromethane and washed with saturated K_2CO_3 solution. The dichloromethane layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed. Elution with ethyl acetate : hexanes = 1 : 10 gave 23 mg (88%) of N-Cbz-2-epi-pumiliotoxin C as an oil: IR (film) 1688 (C=O), 1407, 1318, 1101 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.31-7.28 (complex, 5H, Ar), 5.20 (d, *J*= 12.6 Hz, 1H, *CH*Ph), 5.11 (d, *J*= 12.6 Hz, 1H, *CH*Ph), 3.98 (dt, *J*= 12.1, 4.4 Hz, 1H, H8a), 3.82 (m, 1H, H2), 2.02-1.18 (m,

15H), 1.06 (d, *J*= 7.3 Hz, 3H, Me), 0.98-0.93 (m, 1H), 0.89 (t, *J*= 7.3 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 155.6 (C=O), 137.3 (C), 128.3 (2 CH), 127.7 (3 CH), 66.4 (CH_2), 51.4 (CH), 50.4 (CH), 37.5 (CH_2), 36.5 (CH), 33.1 (CH), 29.8 (CH_2), 25.9 (CH_2), 22.6 (CH_2), 20.3 (CH_2), 19.9 (CH_2), 19.7 (CH_2), 19.0 (CH_3), 14.0 (CH_3); mass spectrum, *m/z* (relative intensity, %) 329 (M^+, 9), 286 (M^+-Pr, 89), 242 (93), 194 (M^+-Cbz, 24), 177 (50), 150 (48), 91 (100). Exact mass calcd for $C_{21}H_{31}O_2N$: 329.2355. Found: 329.2366.

A solution of N-Cbz-2-epi-pumiliotoxin C (20 mg, 0.061 mmol) in 2.0 mL of ethanol was hydrogenated over 10% palladium on charcoal (10 mg) at room temperature and at atmospheric pressure for 4 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo*. The residue was triturated with chloroform and washed with saturated K_2CO_3 solution. The chloroform layer was separated and dried over $MgSO_4$. The solvent was evaporated and the crude material was chromatographed with 5% Et_3N - hexanes to afford (±)-2-epi-pumiliotoxin C (**112**) (8 mg, 67%; 9% overall from **137**) as a yellow oil; IR (film) 3276 (NH), 2928, 2863, 1455, 1375, 1145, 1080, 742 cm^{-1}; ^1H NMR (400 MHz) δ 3.15-3.10 (dt, *J*= 10.5, 4.1 Hz, 1H, H8a), 2.84-2.75 (m, 1H, H2), 1.90-1.01 (m, 17H), 1.00-0.99 (d, *J*= 7.2 Hz, 3H, Me), 0.91 (t, *J*= 7.0 Hz, 3H, Me); ^{13}C NMR (100 MHz) δ 50.0, 49.5, 42.0, 38.4, 32.5, 31.6, 29.7, 28.4, 25.3, 20.5, 19.4, 19.3, 14.2; mass spectrum, *m/z* (relative intensity, %) 195 (M^+, 1.6), 194 (M^+-1, 3), 166 (M^+-CH_2CH_3, 5), 152 (M^+-Pr, 100).

The following IR and NMR spectra for **112** were reported in the literature[56]: IR (film) 3280, 2926, 2869, 1463, 1376, 1360, 1303, 1206, 1131, 1079, 971, 943, 865, 742, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.13-3.07 (dt, *J*= 10.5, 4.3 Hz, 1H, H8a), 2.81-2.75 (m, 1H, H2),1.89-1.01 (m, 17H), 1.00-0.97 (d, *J*= 7.2 Hz, 3H), 0.92-0.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 49.9 (CH), 49.4 (CH), 42.0 (CH), 38.5 (br, CH_2), 32.5 (br, CH), 31.5 (br, CH_2), 28.5 (br, CH_2), 25.3 (br, CH_2), 20.5 (CH_2), 19.3 (CH_3), 19.2 (CH_2), 14.2 (CH_3).

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