Intramolecular Propargylic Barbier Reactions for the Stereoselective Synthesis of Natural Products

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To My Family

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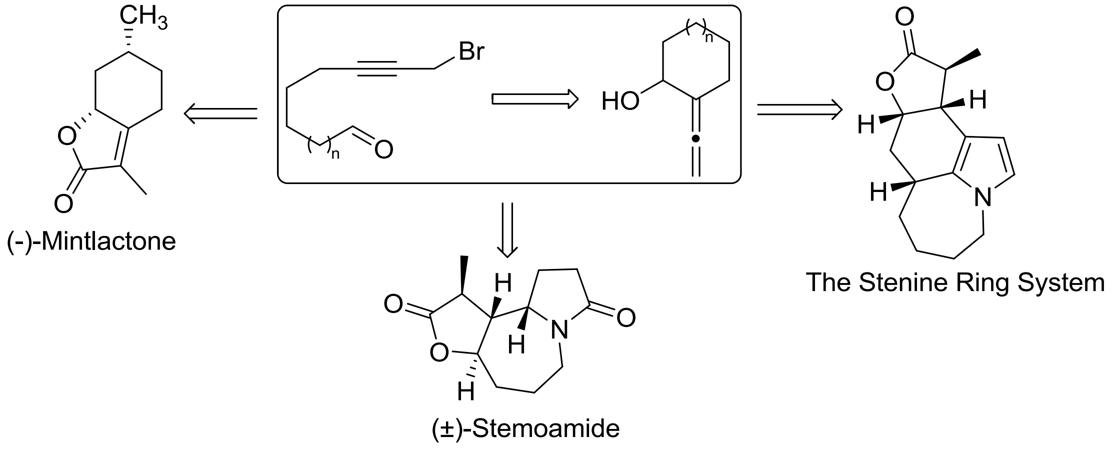
Abstract

This thesis describes the implementation of the intramolecular Barbier reaction in the diastereoselective synthesis of butenolide natural products. The first chapter provides a brief overview of the intramolecular and intermolecular propargylic Barbier reaction together with regioselective and stereoselective challenges.

The second chapter discusses a concise route to (-)-mintlactone starting from propargyl alcohol*via* a highly diastereoselective intramolecular propargylicBarbier reaction.

The third and fourth chapters describe the extension of this methodology to synthesize the Stemona alkaloids. The third chapter describes an efficient way to construct the seven-membered azepine ringin a synthesis of (±)-stemoamide starting from succinimide.The fourth chapter describes the construction of basic stenine ring system starting from pyrroleemploying an asymmetric organocatalyzed cyclization, Sonogashira coupling, a diastereoselectiveintramolecular propargylic Barbier reaction, and diastereoselectivealkene reduction. In addition, we also disclose a new strategy tocontrol the electron density of the pyrrole nucleus by using the trifluoromethyl ketone as anelectron withdrawing group.



Publications arising from this thesis

1. “Synthesis of the Stenine Ring System from Pyrrole”, S. Sridhar and Roderick W. Bates, *J. Org. Chem.***2011**, *76,* 5026.
2. “A Synthesis of (±)-Stemoamide using the Intramolecular Propargylic Barbier Reaction”, S. Sridhar and Roderick W. Bates, *Synlett* **2009**, *12*, 1979.
3. “A Synthesis of(-)-Mintlactone”, S. Sridhar and Roderick W. Bates, *J. Org. Chem.* **2008**, *73*, 8104.

Abbreviations

Å	angstrom
Ac	acetyl
AlBN	azobisisobutyronitrile
Ar	aryl
aq.	aqueous
Bn	benzyl
br.	broad
^{t}Bu	*tert*-butyl
cat.	catalytic
d	doublet
DHP	dihydropyran
DMI	1,2-dimethylimidazole
DMP	Dess-Martin periodinane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dr	diastereoisomeric ratio
ee	enantiomeric excess
eq.	molar equivalents
Et	ethyl
EWG	electron withdrawing group
FC	Friedel–Crafts
FDPP	pentafluorophenyl diphenylphosphinate
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectroscopy
HMQC	Heteronuclear Multiple-Quantum Correlation

IR	infrared
J	coupling constant
L	unspecified ligand
LDA	lithium diisopropylamide
KHMDS	potassium bis(trimethylsilyl)amide
M	Metal
m	multiplet
Me	methyl
NBS	*n*-bromosuccinimide
NMR	nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
p	para
PPTS	pyridinium *p*-toluenesulfonate
PS-PPTS	polymer supported pyridinium *p*-toluenesulfonate
TsOH	4-Methylbenzenesulfonic acid
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
^{i}Pr	*iso* propyl
psi	pounds per square inch
Py	pyridine
R	unspecified carbon substituent
RT	room temperature
s	singlet
t	triplet
T	temperature
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	tetrahydrofuran

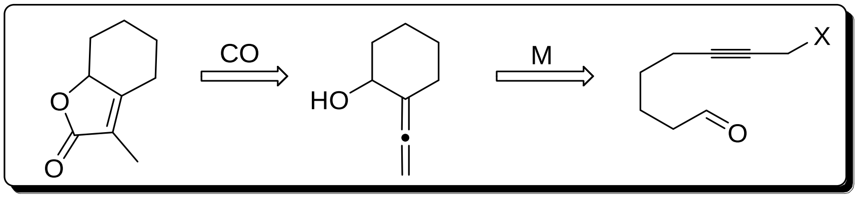
THP	tetrahydropyranyl
TMS	trimethylsilyl
q	quartet
quin	quintet

Chapter 1

The Propargylic Barbier Reaction

1.1. Introduction

The butenolide moiety is widespread amongst natural products. In addition, many natural products contain oxidised or reduced butenolides.A number of methods have been reportedfor the stereoselective synthesis of butenolides.[1,2]One way to synthesize butenolides is by the cyclocarbonylation of allenic alcohols (**Scheme 1.1**).[3] Allenic alcohols would be obtained by the Barbier reaction between propargylic halides and aldehydes.[4]



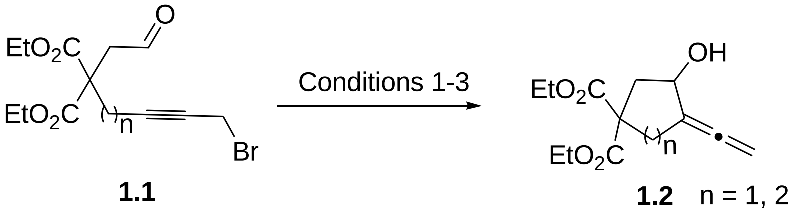
X = Br, Cl, I
Metal: In, Zn, Sn or its salt ($SnCl_2$)

Scheme 1.1

The Barbier reaction is similar to the well known Grignard reaction. However, the Barbier reaction is a one-pot synthesis, whereas the Grignard reaction is a two step process.[5]Thus, the Barbier reaction is operationally simpler and, in many case, the need for the careful exclusion of oxygen and water is unnecessary. The regioselectivity and stereoselectivity of the intermolecular propargylic Barbier reaction between the aldehydes or ketones and propargylic halides have been studied well. However, to the best of our knowledge, there are only two reports of such an intramolecular transformation, neither addressing stereochemical issues.[6,7] Our particular interest is the stereoselective synthesis of butenolides employing the diastereoselective intramolecular propargylic Barbier reaction as a key step. In this chapter, we will briefly review the synthesis of allenic alcohols *via* the intermolecular and the intramolecular propargylic Barbier reaction and its synthetic applications. In addition, the regioselectivity of the intermolecular propargylic Barbier reaction will be discussed.

1.2. Intramolecular propargylic Barbier reaction

Allenic alcohols are the exclusive products in the intramolecular propargylic Barbier reaction. Saicic *et al.* was first cr39edited with the formation of cyclic allenols by the employment of the intramolecular propargylic Barbier reaction, in 2002 (**Scheme 1.2**).6 In this work, they demonstrated the formation of five and six membered rings (**1.2**) from bromo-aldehydes (**1.1**), *via* the use of zinc or indium. Under Luche conditions,[8] using zinc in the presence of ammonium chloride, the five membered allenic alcohol (**1.2**) was obtained as the exclusive product in a moderate yield of 52% within 2 hours (**Table 1.1**, entry1). However, under the same conditions, the six membered allenic alcohol was obtained in a low yield of 35% with excess zinc (entry 2). When indium was employed for this transformation a moderate improvement in yield was observed (44%) after 5 days (entry 3).

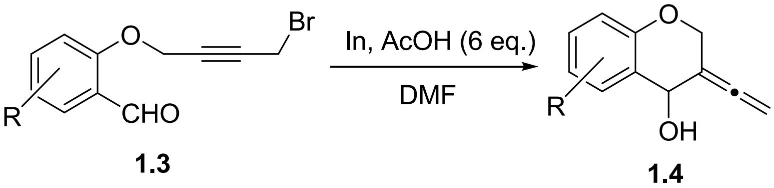


Scheme 1.2

Table 1.1

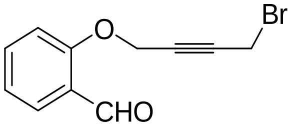
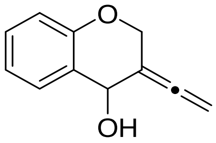
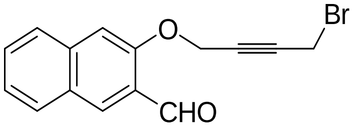
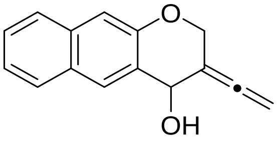
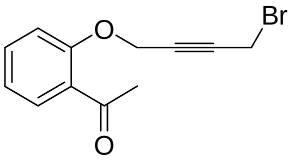
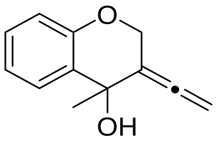
Entry	Conditions	n	Time	Yield/%
1	Zn, NH_4Cl, THF, RT	1	3 h	54
2	Zn (excess), NH_4Cl, THF, RT	2	8 h	35
3	In, THF-H_2O, RT	2	5 days	44

Following this work, Cha *et al*. demonstrated the synthesis of chromane derivatives (**1.4**) from bromo-aldehydes (**1.3**) *via* an indium mediated intramolecular propargylic Barbier reaction (**Scheme 1.3**).7 Their initial attempts for cyclisation using indium in THF, DMF, EtOH and CH_2Cl_2 failed. The cyclisation occurred with the combination of indium and acids such as AcOH, TsOH or 6 M HCl in moderate to good yields. Among these acids, acetic acid (6 eq.) was found to be the best acid additive for the cyclisation in DMF.



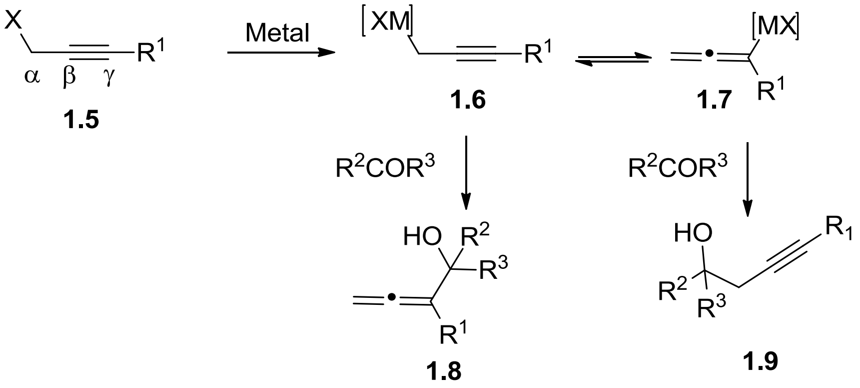
Scheme 1.3

Table 1.2.

Entry	Reactant	Product	Yield/%
1			92
2			62
3			68

1.3. Intermolecular propargylic Barbier reaction

It is difficult to obtain the allenic alcohol exclusively over the propargylic alcohol in the intermolecular propargylic Barbier reaction. This is due to the metallotropic rearrangement between the propargylic organometallic (**1.6**) and the allenic intermediates (**1.7**) which would form after the metal insertion with propargyl halides (**1.5**) (**Scheme 1.4**).[9] However, the exact mechanism is not known. It is believed that the allenylmetalintermediates (**1.7**) would lead to the acetylenic products (**1.9**) and the propargylmetal intermediates (**1.6**) would give the allenic adducts (**1.8**). In general, the regioselectivity is highly dependent on the nature of substituents in the propargyl halides. The unsubstituted propargylic halides and *α*-substituted propargylic halides preferentially give the acetylenic products (**1.9**). Conversely, the *γ*-substituted propargylic halides readily give the allenic alcohols (**1.8**) as the major product. The regioselectivity could also be affected by steric and electronic properties of the carbonyl compounds, solvents and the metals used.

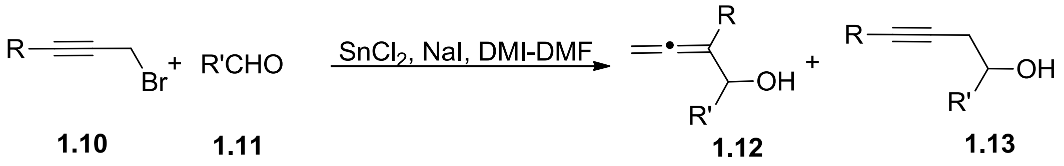


Metal: Cd, Pb, In, Zn, Sn or its salt ($SnCl_2$)
X: Cl, Br, I

Scheme 1.4. Possible mechanism and regioselectivity for intermolecular propargylic Barbier reaction.

1.3.1. Reaction mediated by tin and its salt

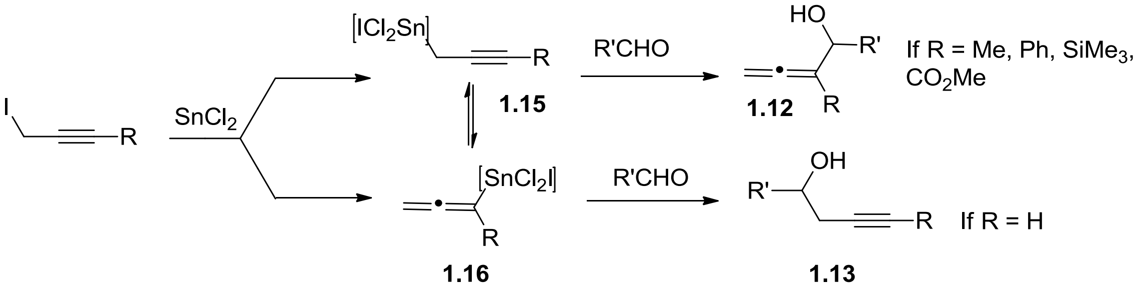
In 1981, Mukaiyama demonstrated the highly regioselective synthesis of allenols utilizing $SnCl_2$ in the presence of NaI (**Scheme 1.5**).[10] In this reaction, the regioselectivity was controlled by the *γ*-substituted propargyl halides (**Table 1.3**). A mixture of allenic (**1.12**) and propargylic alcohol (**1.13**) were obtained with the unsubstituted propargyl halides (**1.10**). Although the exact mechanism is not clear, they postulated that a mixture of propargyl(dihaloiodo)stannane (**1.15**) and allenyl(dihaloiodo)stannane (**1.16**) are formed by the S_N2 and S_N2'attack of stannous chloride to the unsubstituted propargyl iodide, which subsequently reacted with the aldehyde to give the allenol and propargyl alcoholrespectively (**Scheme 1.6**). On the other hand, the allenic alcohols were the predominant products with the *γ*-substituted propargyl halides (**1.10**). They reasoned that the predominant S_N2 attack would be favored over S_N2', due to the steric repulsion between *γ*-substituent and the (dihaloiodo)stannane functionality.



Scheme 1.5.

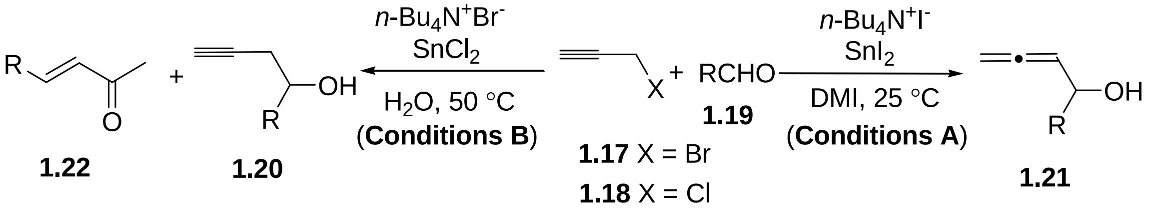
Table 1.3.

Entry	R	R^1CHO	Yield (**1.12**+**1.13**)/%	Ratio of **1.12**/**1.13**
1	H	PhCHO	98	48:52
2	CH_3	PhCHO	79	97:3
3	CH_3	$PhCH(CH_3)CHO$	75	92:8
4	$SiMe_3$	$PhCH_2CH_2CHO$	70	100:0
5	$SiMe_3$	PhCHO	67	60:40
5	CO_2Me	PhCHO	55	100:0
6	CO_2Me	$PhCH_2CH_2CHO$	60	97:3



Scheme 1.6.

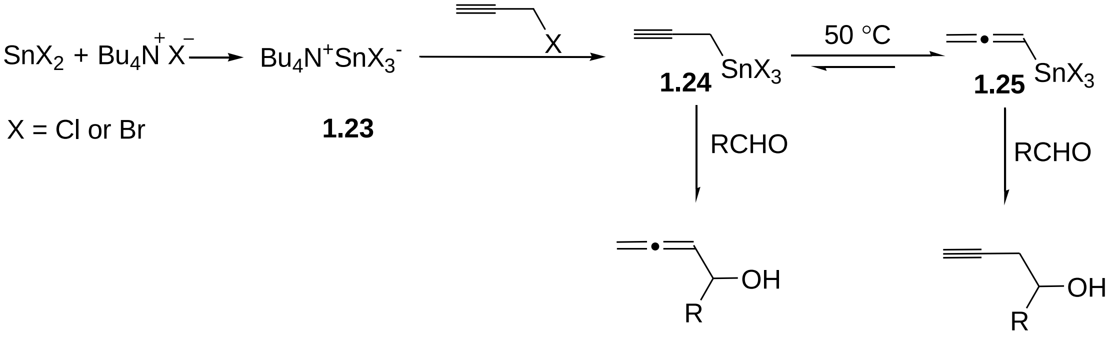
In 1998, Masuyama *et al.* reported that the regioselectivity could be controlled by the Lewis acidity of tin, the reaction temperature and the solvent (**Scheme 1.7**).[11] The reaction of propargyl bromides (**1.17**) and aldehydes (**1.19**) with $SnCl_2$ in the presence of*n*-$Bu_4N^+Br^-$ at 50 °C in water, furnished the propargyl alcohols (**1.20**) as the major product (**Table 1.4**, entries 1-3) (**Conditions B**). Interestingly, treatment of aldehydes (**1.19**) with propargyl chlorides (**1.18**) with SnI_2 in the presence of *n*-$Bu_4N^+I^-$ at 25 °C in DMI provided the allenols (**1.21**) as the major product (entries 4-6) (**Conditions A**). They reasoned that under conditions A, prop-2-ynyltriiodotin (**1.24**) was first formed at 25 °C, which subsequently proceeded *via*γ-addition to the aldehyde without isomerising to propa-1,3-dienyltriiodotin (**1.25**), yielding the allenol (**1.21**) (**Scheme 1.8**). However, at higher temperature (50 °C), isomerisation would take place to form the propa-1,3-dienyltriiodotin complex (**1.25**), which would react with the aldehyde to provide the propargyl alcohol (**1.20**). Under Conditions B, a rearranged product enones (**1.22**) were obtained in 4-14% yields, which could come from the hydration of allenols (**1.21**) (**Scheme 1.9**).



Scheme 1.7.

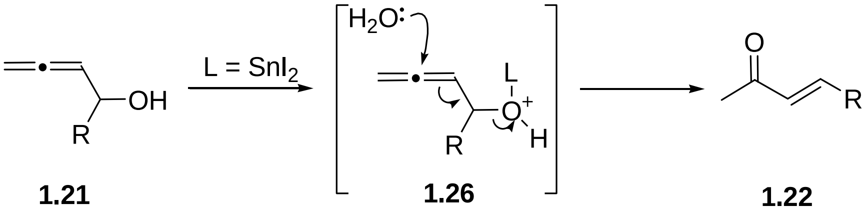
Table 1.4.

Entry	RCHO	Conditions	Yield (**1.21**+**1.20**)/%	Ratio of **1.20**/**1.21**
1	PhCHO	B	72	100:0
2	4-CNC_6H_4	B	77	100:0
3	4-OMeC_6H_4	B	62	100:0
4	PhCHO	A	78	4:96
5	4-CNC6H_4	A	62	2:98
6	4-OMeC6H_4	A	50	5:95



1.21 **1.20**

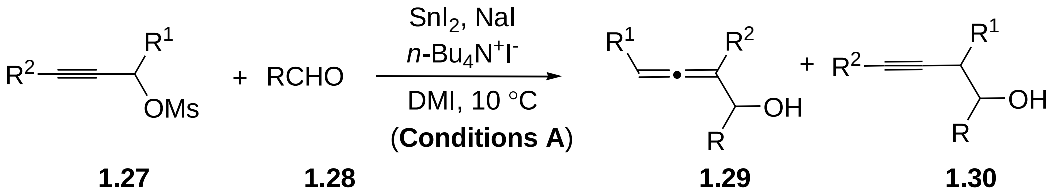
Scheme 1.8.



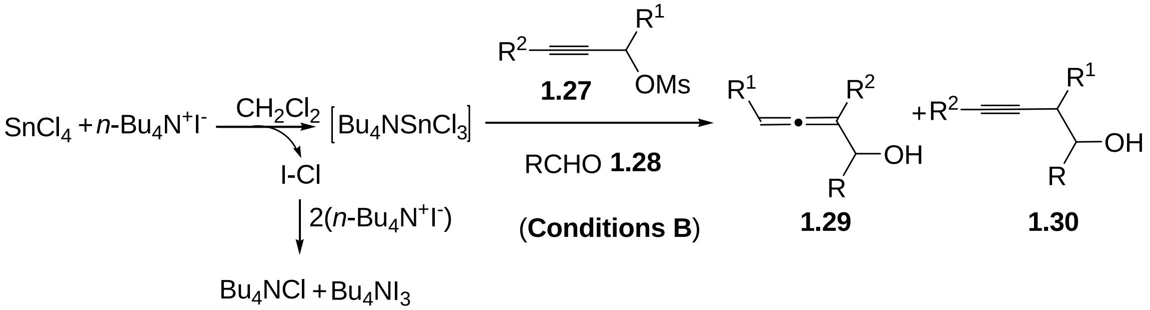
1.21 **1.26** **1.22**

Scheme 1.9.

In 2000, Masuyama *et al.* further demonstrated the Barbier reaction with the highly substituted propargyl mesylates in the presence of SnI_2/*n*-Bu_4NI in DMI (**Scheme 1.10**, Conditions A).[12]In this study, they revealed that the γ-substituted propargyl mesylates (**1.27**) preferentially gave the allenol products (**1.29**) and α-substituted propargyl mesylates (**1.27**) selectively gave the propargyl alcohols (**1.30**). For this transformation, they also employed $SnCl_4$/*n*-Bu_4NI in CH_2Cl_2 (**Scheme 1.11**, Conditions B).[13] In this reaction tin(II) species were prepared *in situ* by the reduction of tin(IV) chloride with *n*-Bu_4NI.



Scheme 1.10.

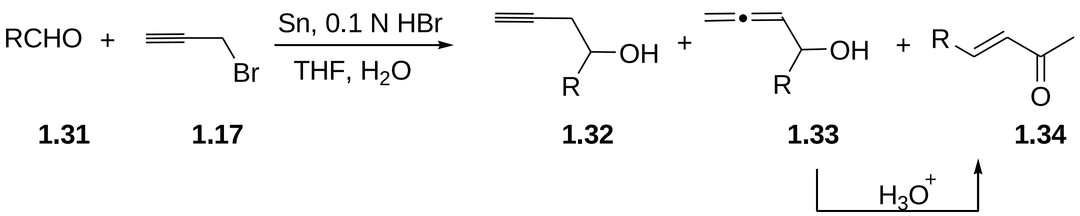


Scheme 1.11.

Table 1.5

Entry	RCHO	Conditions	R^1	R^2	Yield (**1.29**+**1.30**)/%	Ratio of **1.29**/**1.30**
1	PhCHO	A	H	CH_3	58	100:0
2	PhCHO	A	H	C_6H_5	81	100:0
3	PhCHO	A	CH_3	H	71	12:88
4	PhCHO	A	Pr	H	66	2:98
5	PhCHO	B	H	C_6H_5	33	91:9
6	PhCHO	B	CH_3	H	70	2:98
7	4-ClC_6H_5CHO	B	H	CH_3	34	99:1

In 1990, Wu *et al*. showed that the propargyl Barbier reaction could proceed using tin in the presence of 0.1 N HBr (**Scheme 1.12**).[14] Treatment of aldehydes (**1.31**) with propargyl bromide (**1.17**) and tin in the presence of 0.1 N HBr, furnished a mixture of propargylic alcohols (**1.32**) and allenols (**1.33**) and enones (**1.34**). In this work, they studied aromatic aldehydes (**1.31**) having electron withdrawing and electron donating groups at different positions. The allenic alcohols (**1.33**) were stable when an electron-withdrawing group (NO_2) was present in the aromatic aldehyde or an electron donating group was in the *meta* position in the aromatic aldehydes, or in simple aliphatic aldehydes (**Table 1.6**, entries 2-5). On the other hand, when electron-donating groups were present, (especially in *para* position) in the aromatic aldehydes (OH, OCH_3, CH_3) the allenic alcohols (**1.33**) rearranged to the corresponding *α,β*-enones (**1.34**) (entry 1).



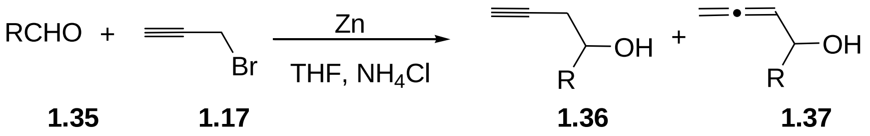
Scheme 1.12.

Table 1.6.

Entry	RCHO	Yield (**1.32**+**1.33**+**1.34**)/%	Ratio of **1.32**/**1.33**/**1.34**
1	*p*-OHC_6H_4CHO	52	52 : 0 : 48
2	PhCHO	57	55 : 30 : 15
3	*m*-OHC_6H_4CHO	58	47 : 41 : 12
4	*p*-$NO_2C_6H_4CHO$	50	41 : 59 : 0
5	*n*-C_4H_9CHO	56	57 : 43 : 0

1.3.2. Reaction mediated by zinc

In 1995, Yavari and Riazikermanicontrolled the regioselectivity of unsubstituted propargyl bromide employing zinc under Luche's conditions8 (**Scheme 1.13**).[15] Treatment of propargyl bromide (**1.17**) with aldehydes (**1.35**) in the presence of zinc in a mixtureofsaturated aqueous NH_4Cl-THF (2:5) afforded the corresponding homopropargylic alcohols (**1.36**) in moderate to high yields together with small amounts of the allenic alcohols (**1.37**) (**Table 1.7**, entries 1-3).

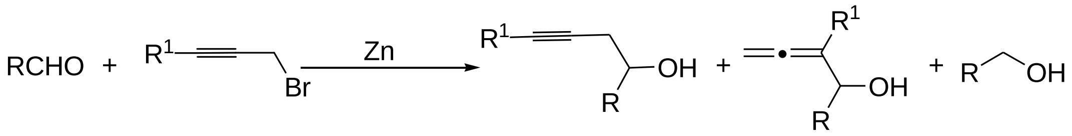


Scheme 1.13.

Table 1.7.

Entry	RCHO	Yield (**1.36**+**1.37**)/%	Ratio of **1.36**/**1.37**
1	PhCHO	68	89:11
2	*p*-$CH_3OC_6H_4CHO$	55	95:5
3	*o*-OHC_6H_4CHO	69	98:2

Later, Bieber *et al.* carried out a more detailed study of zinc mediated reactions in the presence mild acids and under basic conditions (**Scheme 1.14**).[16] The reaction between benzaldehydeand the propargyl bromide (**1.17**) in the presence of zinc in saturated NH_4Cl solution provided the propargylic alcohol in 15% yield together with 18% of the benzyl alcohol (**1.42**) (**Table 1.8**, entry 1). The best yield (85%) was achieved in a solvent mixture of saturated calcium chloride containing 10% of ammonium chloride and THF as a co-solvent (entry 2). In contrast, a γ-substituted propargyl bromide (1-bromobut-2-yne) furnished the allenol as the major product, along with a considerable amount of propargylic alcohol (entries 3, 4). This same alkyne gave exclusively the allenic product with benzaldehyde in the presence tin salts (**Scheme 1.5**). Interestingly, under the same conditions Jogi and Maeorg controlled the regioselectivity by simply changing the reactants.[17] The coupling of 1-bromo-2-nonyne propargylic bromide with *n*-butanalin the presence of zinc gave the allenic alcohol as the exclusive product in modest yield (entry 5).



1.38 **1.39** **1.40** **1.41** **1.42**

Scheme 1.14.

Table 1.8.

Entry	RCHO	R^1	Conditions	Yield/% **1.40**	**1.41**	**1.42**
1	C_6H_5CHO	H	NH_4Cl	15	1	18
2	C_6H_5CHO	H	$CaCl_2/NH_4Cl$/ THF	85	3	0
3	C_6H_5CHO	CH_3	NH_4Cl	19	53	0
4	C_6H_5CHO	CH_3	K_2HPO_4	28	40	0
5	$CH_3(CH_2)_2CHO$	$CH_3(CH_2)_5$	NH_4Cl/THF	0	47	0

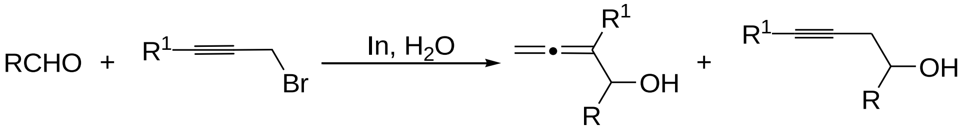
1.3.3. Reaction mediated by Indium

In 1991, Chan and Li first reported that the indium could effect the allylation of aldehydes and ketones in water at room without any promoters, whereas zinc and tin needed some promoters (acid) to carry out the Barbier reactions.[18]They reasoned that the first ionization potential of indium is much lower than zinc, tin and magnesium and has a similar value to the more reactive metals (Li, Na) (**Table 1.9**). However, in some cases the replacement of water with dilute hydrochloric acid (0.1 N) or acetic acid as additive in organic solvents increases the rate and the efficiency of indium.6’[20]

Table 1.9.

Metal	In	Mg	Zn	Sn	Li	Na
First ionization potential (eV)	5.79	7.65	9.39	7.43	5.39	5.12

Later, in 1995 Chan and Isaac demonstrated the regioselective allenylation employing indium in aqueous medium (**Scheme 1.15**).[19] In this work, they examined the effect of *γ*-substituents of the propargyl bromide. The indium mediated coupling with aliphatic or aryl aldehydes (**1.43**) with the propargyl bromide (**1.17**) in water mainly gave the propargylic alcohols (**1.46**) in good yields (**Table 1.10**, entry 1). Interestingly, when the propargyl bromide is *γ*-substituted with Me or Ph or $SiMe_3$ or $SiMe_2Ph$, allenic alcohols (**1.46**) were observed predominantly or exclusively in good yields (entries 2-6). In this method, no reduction or rearranged product (enone) was observed.



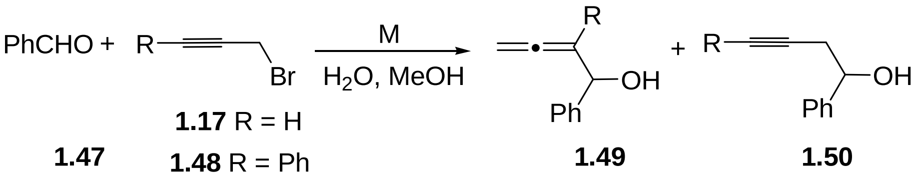
1.43 **1.44** **1.45** **1.46**

Scheme 1.15.

Table 1.10.

Entry	Aldehydes	R^1	Yield (**1.45**+**1.46**)/%	Ratio of **1.45**/**1.46**
1	$CH_3(CH_2)_7CHO$	H	97	12:88
2	$CH_3(CH_2)_7CHO$	Ph	89	95:5
3	HCHO	Ph	94	99:1
4	1-Naphthaldehyde	Me	98	100:0
5	PhCHO	$SiMe_3$	60	80:20
6	1-Naphthaldehyde	$SiMe_2Ph$	60	80:20

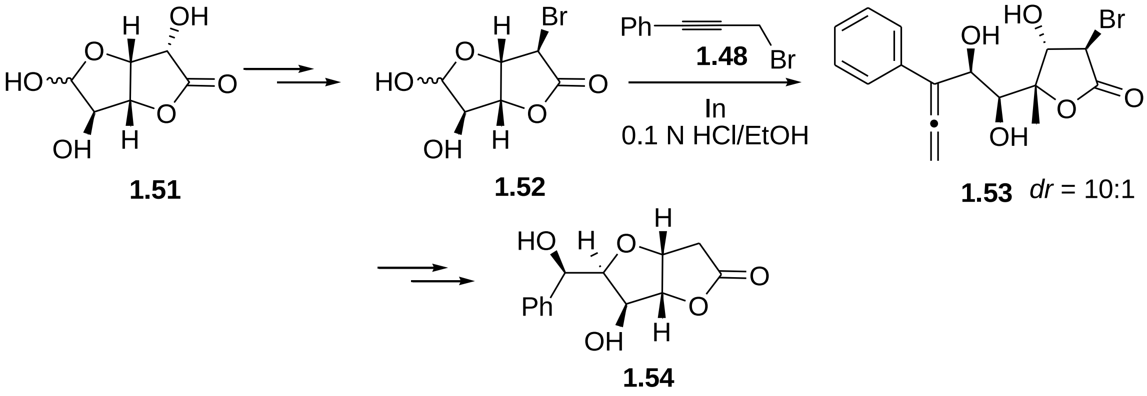
Li *et al*. accomplished the total synthesis of (+)-goniofufurone (**1.54**) employing the intermolecular propargylic Barbier reaction as a key step (**Scheme 1.17**).[20] The reaction between benzaldehyde (**1.47**) and propargyl bromide (**1.17**) furnished a mixture of allenic alcohol (**1.49**) and propargylic alcohol (**1.50**) in different ratios with different metals (**Scheme 1.16**) (**Table 1.11**, entries 1-4). However, the reaction of γ-substituted propargyl bromides with an aliphatic or an aromatic substituent with aldehydes furnished the allenol as the major products or exclusive products (entry 5). Based on this result, the diastereoselective allenation was studied (**Scheme 1.17**). The key intermediate hydroxy-lactone (**1.52**) was derived from D-glucorono-6,3-lactone (**1.51**) in 4 steps. Coupling between the phenyl propargyl bromide (**1.48**) and hydroxy-lactone (**1.52**) furnished the allenol (**1.53**) in a low yield of 32% and good diastereoselectivity (10:1). Based on Paquette's work the diastereoselectivity was rationalized by a chelation control model in which allenation occurred from the less hindered face of the aldehyde complex (**Scheme 1.18**). Subsequent manipulation of allenol (**1.53**) provided (+)-goniofufurone (**1.54**).



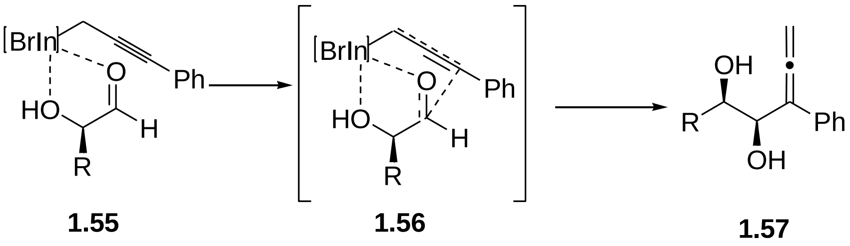
Scheme 1.16.

Table 1.11.

Entry	Metal	R	Yield (**1.49**+**1.50**)/%	Ratio of **1.49**/**1.50**
1	In	H	85	33:67
2	Sn	H	60	17:83
3	Zn	H	64	25:75
4	Cd	H	60	50:50
5	In	Ph	69	100:0

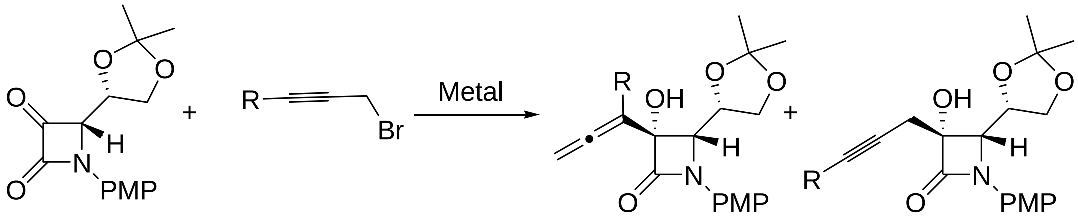


Scheme 1.17.



Scheme 1.18.

Alcaide*et al.* reported the metal-mediated Barbier reactions of azetidine-2,3-diones (**1.58**) with different substituted propargyl bromides (**1.59**) and different metals (**Scheme 1.19**).[21] The reactions of 2,3-azetidinedione (**1.58**)with propargyl bromides bearing a methyl or phenyl substituent at *γ* position, in the presence of In or Sn provided the allenic alcohol as the exclusive product with high diastereoselectivity (**Table 1.12**, entries 1, 2, 5). Whereas, under the same conditions, phenyl propargyl bromide (**1.48**) employing zinc gave a mixture of allenic and propargylic products in a ratio of 4:1 (entry 3). Interestingly, replacing saturated NH_4Cl with water using zinc gave the allenic product as a sole product but in low yield (entry 4). Alcaide*et al*. further extended this methodology to the synthesis of highly functionalized pyrroles (**1.63**) (**Scheme 1.20**).[22]

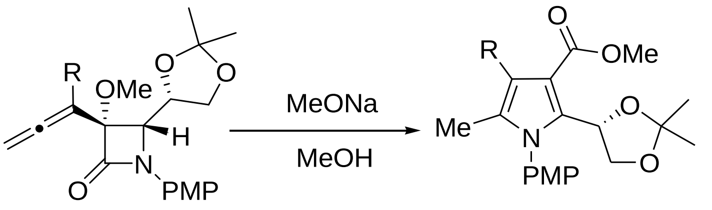


1.58 **1.59** **1.60** **1.61**

Scheme 1.19.

Table 1.12.

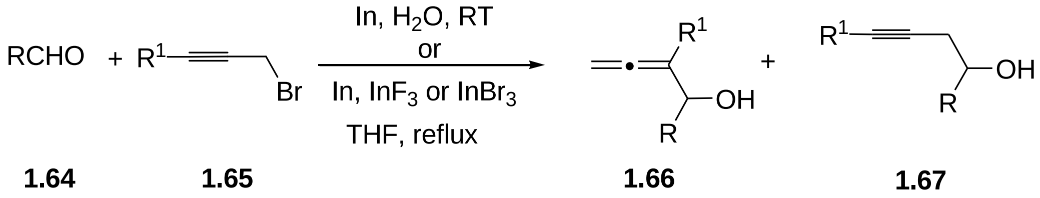
Entry	R	Conditions	Yield**1.60**+**1.61**/%	Ration of **1.60**/**1.61**
1	Ph	In, THF/NH_4Cl (Sat.)	76	100: 0
2	Ph	Sn, THF/NH_4Cl (Sat.)	75	100: 0
3	Ph	Zn, THF/NH_4Cl (Sat.)	71	80:20
4	Ph	Zn, THF/H_2O	16	100:0
5	Me	Zn, THF/NH_4Cl (Sat.)	59	100:0



1.62 **1.63**

Scheme 1.20.

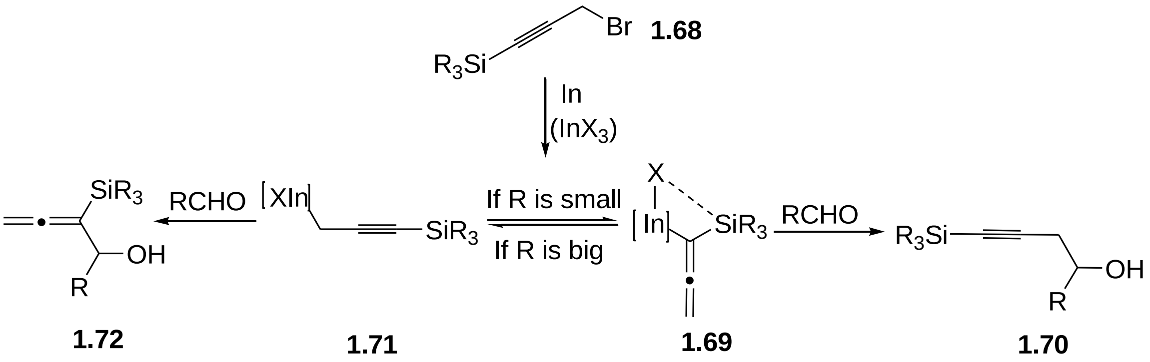
Employing indium, Loh and Li developed a general strategy to obtain either the allenolsor the propargylic alcohols by simply changing the reaction conditions (**Scheme 1.21**).[23] When the reactions were carried out between the silyl substituted propargyl bromides (**1.65**) and aldehydes (**1.64**) at reflux in tetrahydrofuran in the presence of 2 eq. of indium and 0.1 eq. of indium(III) bromide or 0.1 equivalent indium(III) fluoride, the regioselectivity was biased towards the propargylic alcohols (**1.67**) (**Table 1.13**, entries 1, 3). In contrast, under same conditions phenyl propargyl bromide (**1.48**) furnished the allenic alcohol as the major product (**5**) (entry 2). However, the allenic compounds were obtained in excellent selectivity in the presence of indium with the bulky trialkylsilyl propargyl bromides (**1.65**) in aqueous medium (entries 4, 5). They speculated that,the coordination between silicon and the halide of indium would favour the complex (**1.69**), which subsequently reacts with the aldehyde to give the propargylic alcohols (**1.70**) (**Scheme 1.22**). On the other hand, in an aqueous medium, such coordination would be less favoured due to the bulky silicon and complex (**1.71**) would form, which further reacts with the aldehyde to provide the allenic alcohol (**1.72**).



Scheme 1.21.

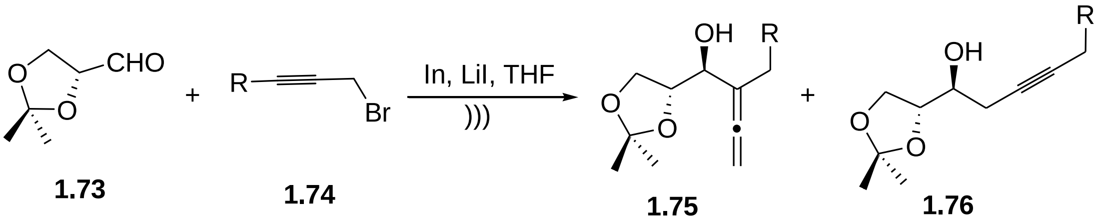
Table 1.13.

Entry	Aldehydes	R^1	Conditions	Yield (**1.66**+**1.67**)/%	Ratio of **1.66**/**1.67**
1	$CH_3(CH_2)_7CHO$	TMS	In, $InBr_3$, reflux	95	1:99
2	$CH_3(CH_2)_7CHO$	Ph	In, $InBr_3$, reflux	65	88:12
3	PhCHO	TMS	In, $InBr_3$, reflux	92	1:99
4	PhCHO	TBDPS	In, RT, H_2O	55	96:4
5	PhCHO	TIPS	In, RT, H_2O	59	96:4



Scheme 1.22.

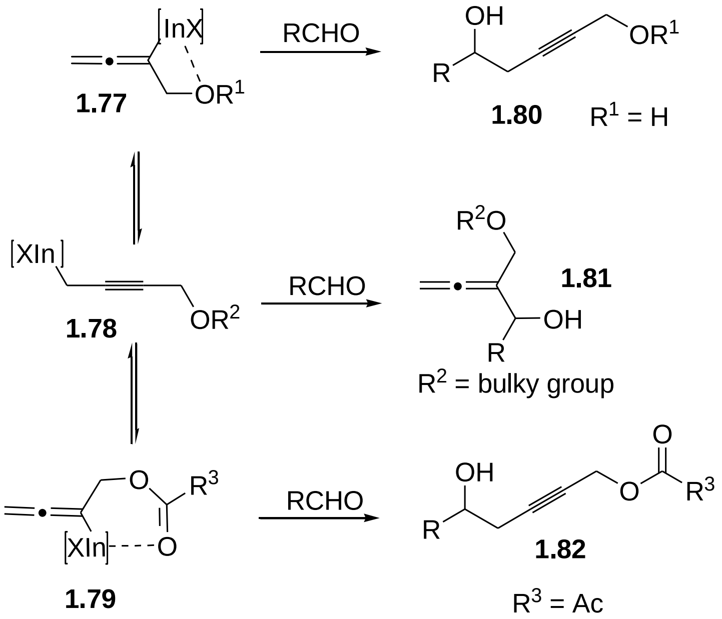
Recently, Schmid *et al.* studied the regioselectivity of indium mediated allenylation of 2,3-*O*-isopropylidene-D-glyceraldehyde (**1.73**) with hydroxy protected groups on 4-bromo-2-butyn-1-ol (**1.74**) (**Scheme 1.23**).[24]Under ultrasonic conditions, in the presence of indium (0.55 eq.) and lithium iodide the reaction was shown to proceed well and give a mixture of propargylic alcohols and allenic alcohols in good to moderate yields (**Table 1.14**, entries 1-5). Interestingly, *via* the Felkin-Anh model, high diastereoselectivity (96:4) was observed with the allenylation, whereas the propargylation gave a mixture of diastereomers (4:1 or 2:1). They hypothesized that the regioselectivity was controlled by chelation between the indium and oxygen (**Scheme 1.24**). The absence of chelation and the use of bulky protecting groups preferentially give the allenic alcohol *via* intermediate (**1.78**). However, the presence of chelating groups (OH, OAc) favoured the propargylic alcohols *via* intermediates **1.77** or **1.79**. The application of this methodology was further demonstrated in the stereoselective total synthesis of 1-deoxy-D-ribulose (**1.85**) and D-erythro-2-pentulose (**1.86**) (**Scheme 1.25**).



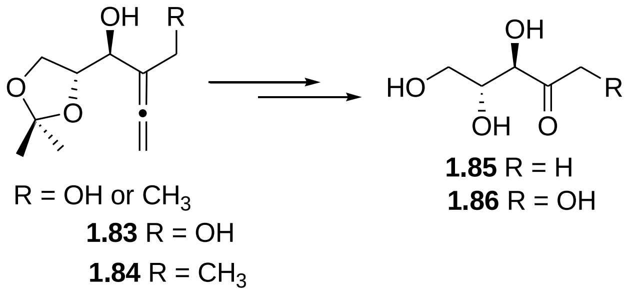
Scheme 1.23.

Table 1.14.

Entry	R	Yield **1.73**+**1.76**/%	Ratio of **1.75**/**1.76**
1	CH_2OCH_2OBn	69	78:22
2	CH_2OH	70	28:72
3	CH_2OAc	70	45:55
4	$CH_2OTBDPS$	48	67:33
5	CH_3	75	98:2



Scheme 1.24.

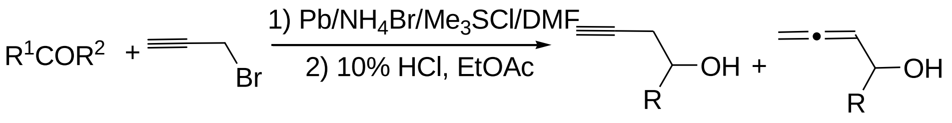


Scheme 1.25.

1.3.4. Reaction mediated by other metals

In 1986, Torii *et al.*reported the lead promoted Barbier reaction with the combination of Bu_4NBr and Me_3SiCl in DMF (**Scheme 1.26**).[25] Treatment of propargyl bromide (**1.17**) with various aldehydes (**1.87**) furnished a mixture of the allenols and the propargyl alcohols (**Table 1.15**, entries 1-3). However, no reaction was observed with ketones (entry 4). When Bu_4NBr was replaced with other salts such as NaBr, KBr,

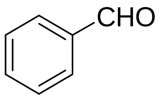
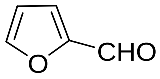
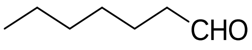
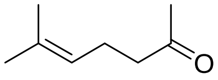
$MgBr_2$, the yields of **1.88** and **1.89** were reduced. The exact role of Bu_4NBr is unclear, however they speculated that Bu_4NBr effects the generation of an active organo-lead reagent.



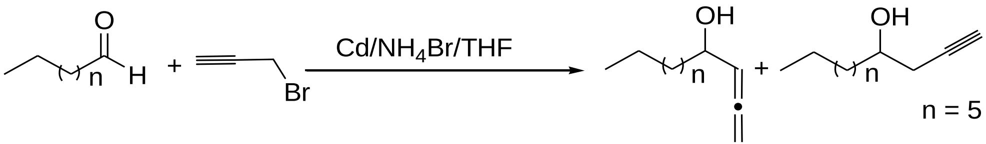
1.87 **1.17** **1.88** **1.89**

Scheme 1.26.

Table 1.15.

Entry	R^1COR^2	Yield **1.88**+**1.89**/%	Ratio of **1.88**/**1.89**
1		95	4:1
2		83	9:1
3		90	2.3:1
4		0	0

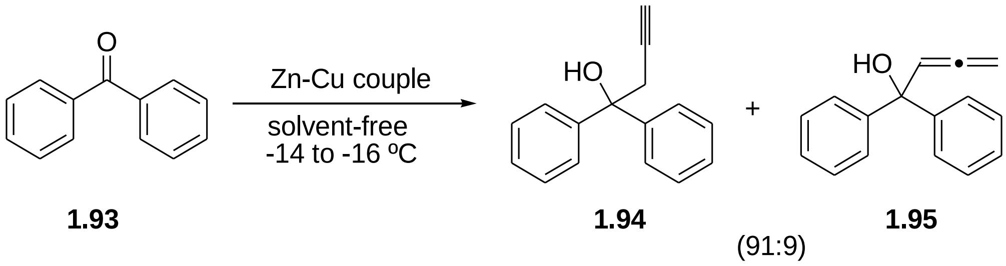
In 1992, Sandhu *et al*. reported the cadmium mediated Barbier reaction.[26] In the presence of Bu_4NBr, the propargyl Barbier reaction was shown to proceed, furnishing a mixture of propargylic and allenic alcohols in a 2:1ratio (**scheme 1.27**).



1.90 **1.17** **1.91** **1.92**

Scheme 1.27.

Huang *et al.* disclosed solvent free conditions for the propargyl Barbier reaction employing a Zn-Cu couple (**Scheme 1.28**).[27] In this method, the reaction between the aldehydes and ketones gave propargylic alcohols as the exclusive product in moderate to excellent yields. However, when the reaction was carried with benzophenone (**1.93**), a mixture of propargylic (**1.94**) and allenic alcohols (**1.95**) wereobserved in a ratio of 91:9 in 91% yield.



Scheme 1.28.

1.4. Conclusion

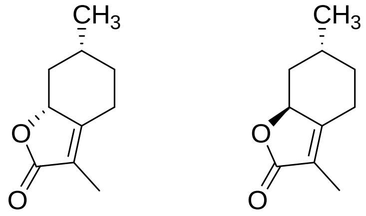
The foregoing sections have briefly reviewed the intramolecular and intermolecular propargylic Barbier reaction with different metals and its synthetic applications. In the intermolecular propargylic Barbier reaction the regioselectivity is controlled by the *γ*-substituent of the propargyl halides and the reagents employed. In particular, the unsubstituted propargylic halides and *α*-substituted propargylic halides preferentially give the propargylic alcohols as the major product. The *γ*-substituted propargylic halides favours the formation of the allenic alcohols. It is worth noting that there are only two reports of the intramolecular propargylic Barbier reaction, neither addresses the stereochemical issues. The following chapters will discuss our effort in the synthetic application of diastereoselective intramolecular propargylic Barbier reaction in total synthesis, with special emphasis on diastereoselectivity.

Chapter 2

A Synthesis of (-)-Mintlactone

2.1. Introduction

To test the concept of diastereoselective intramolecular propargylic Barbier reaction in total synthesis, the simplest butenolide natural products (-)-mintlactone (**2.1**)and its diastereomer, (+)-isomintlactone (**2.2**),were selected as the appropriate target molecules (**Figure 2.1**). Both monoterpenic molecules (**2.1** and **2.2**) are suitable targets, which raises the issue of diastereoselectivity during cyclization. In 1968, Muraki first isolated (-)-mintlactone (**2.1**) from the oil of *M. cardiac, M. arvensis* and*M. piperita L.*[28] Subsequently, in 1980, Takahashi *et al.* isolated (+)-isomintlactone (**2.2**) from *M. piperita L*. (peppermint oil) and determined the relative and absolute configurations of these two lactones by chemical synthesis from (+)-menthofuran.[29] Peppermint oil is used as a flavoring agent in cosmetics, medicine and food.[30,31]



2.1 **2.2**

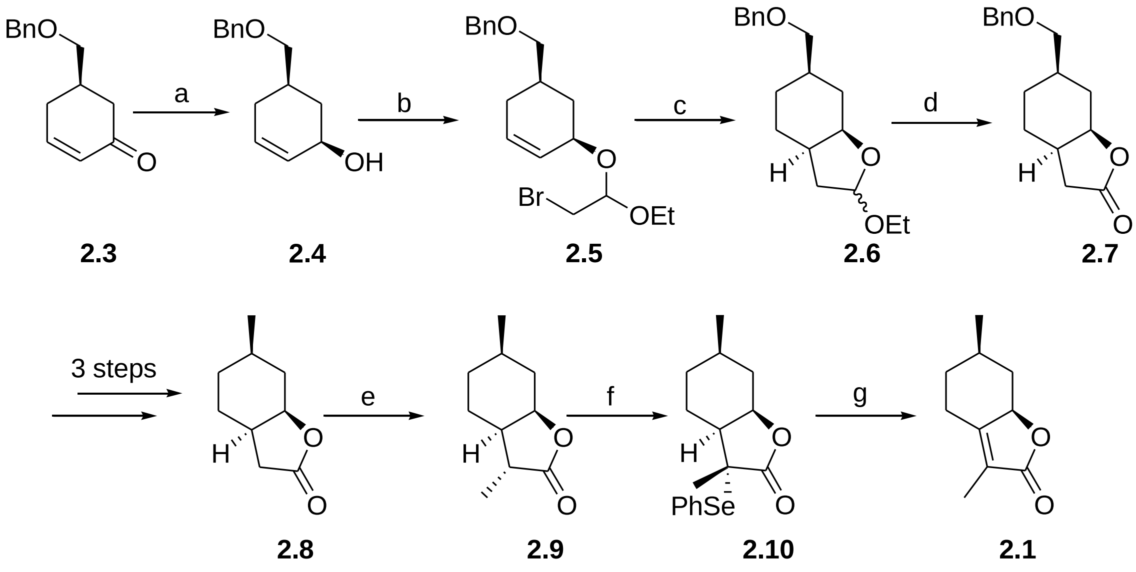
Figure 2.1

2.2. Selected previous total synthesis of (+)-and (-)-mintlactone

Interestingly, before its isolation, the first synthesis of (-)-mintlactone (**2.1**) was achieved from (+)-menthofuran, by Foote *et al*. in 1967.[33a] Since then a number of syntheses has been published.[32,33] The following sub-sections will give a brief overview of selected total syntheses of mintlactone.

2.2.1. Carda's approach

In 1991, Carda and Marco described the first total synthesis of (-)-mintlactone (**2.1**).[33e] Their synthesis began with the diastereoselective reduction of enone (**2.3**), which furnished the alcohol (**2.4**) in good *ee* (95%) and excellent yield of 98% (**Scheme 2.1**). Subsequent treatment with NBS in ethyl vinyl ether as a solvent afforded the key intermediate bromo-alkene (**2.5**) in 90% yield. The bromo-alkene (**2.5**) was subjected to homolytic reductive ring closure with Bu_3SnH to give lactol (**2.6**) in 93% yield and subsequent oxidation with Jones reagent yielded the benzyl-lactone (**2.7**). Further manipulation of the benzyl-lactone (**2.7**) led to the methyl-lactone (**2.8**). Methylation of the lactone (**2.8**) followed by selenylation afforded the selenyl-lactone (**2.10**), which underwent oxidative elimination in the presence of H_2O_2, to provide (-)-mintlactone (**2.1**) in 82% yield. The key feature of this synthesis demonstrated the stereoselective free radical ring closure of bromo-alkene (**2.5**) to construct the bicyclic system.

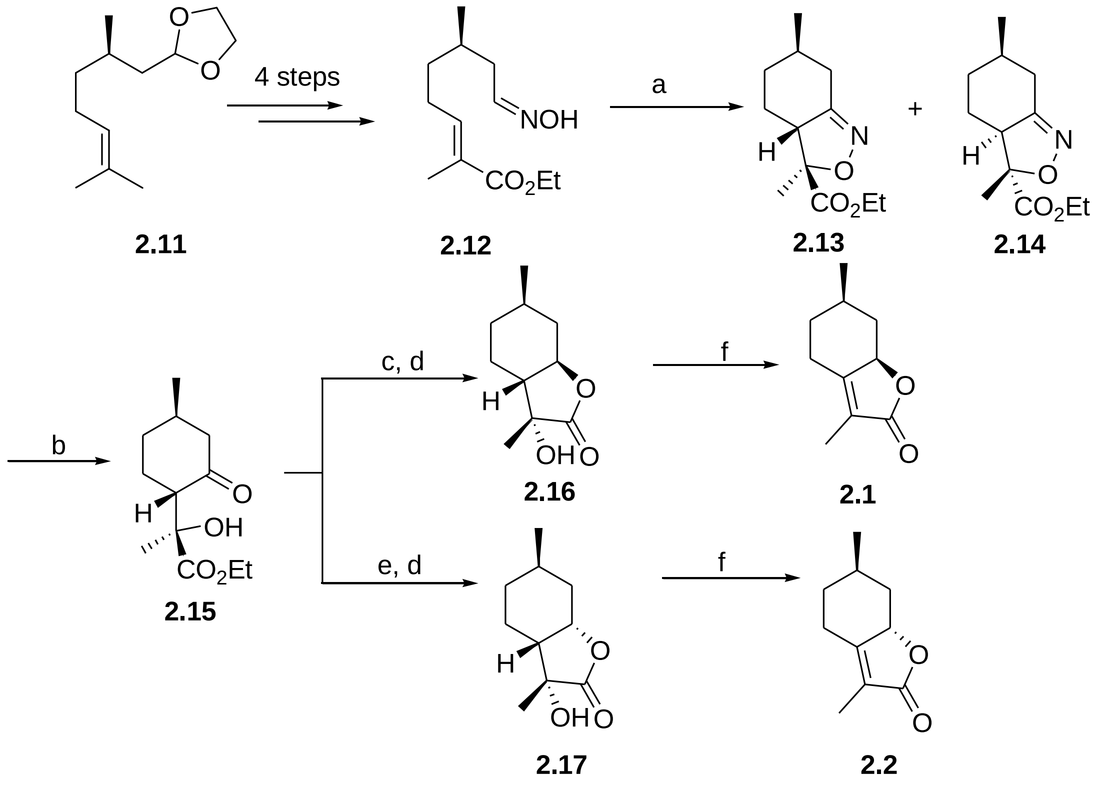


Scheme 2.1. Selected steps from Carda's synthesis of (-)-mintlactone

Reagent and conditions: a) $NaBH_4$, $CeCl_3$, EtOH, 0 °C, 98%; b) NBS, $EtOCH=CH_2$, -40 °C, 90%; c) Bu_3SnH, AIBN, benzene, reflux, 93%; d) CrO_3, H_2SO_4, acetone, 0 °C, 92%; e) LDA, HMPA, MeI, THF, -78 °C to -50 °C, 60%; f) LDA, HMPA, PhSeCl, THF, -78 °C to -50 °C, 40%; g) H_2O_2, THF, CH_3COOH, 0 °C, 82%.

2.2.2. Shishido's approach

In 1992, Shishido *et al*. completed the synthesis of (-)-mintlactone and(+)-*iso*-mintlactone (**Scheme 2.2**).[33f] The key step in this synthesis was an intramolecular [3+2] cycloaddition reaction. The key intermediate (**2.12**) was derived from (+)-citronellal (**2.1**) in four steps. Treatment of oxime (**2.12**) with 7% aqueous sodium hypochlorite in dichloromethane at room temperature afforded the isoxazolines (**2.13**) and (**2.14**) in a ratio of 20:1 in 84% yield. The major isomer (**2.13**) was subjected to reductive hydrolysis to give hydroxy-ketone (**2.15**) in 81% yield. Employing triacetoxyborohydride, the diastereoselective hydride reduction of (**2.15**) was carried out in a MeCN-AcOH mixture and subsequent lactonization furnished the hydroxy-lactone (**2.16**). Subsequent dehydration provided (-)-mintlactone (**2.1**) in 92% yield.For the diastereoselective synthesis of (+)-isomintlactone (**2.2**), Shishido *et al*. employed zinc borohydride as the reducing agent. Treatment of (**2.15**)with zinc borohydride in etherat 0 °C for 5 minutes and subsequent acid treatment afforded the diastereoisomeric lactones (**2.16**) and (**2.17**) in a ratio of 1:6 in 47% yield. Dehydration of the lactone (**2.17**) furnished the (+)-isomintlactone (**2.2**) in good yield. The contrasting behavior of the two hydride reagent gives the two stereoisomers. While the use of zinc borohydride leads to the expected equatorial attack, the reduction by triacetoxy borohydride is directed by the nearby alcohol group. This direction is possible because of facile alcohol-acetate exchange at boron. The key aspect of Shishido's approach is the implementation of the intramolecular [3+2] cycloaddition to construct the bicyclic system.

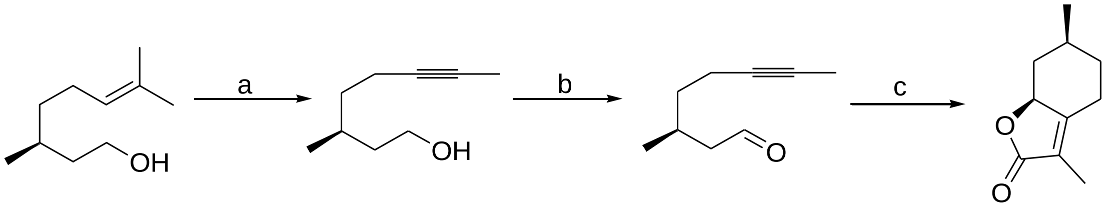


Scheme 2.2. Selected steps from Shishido's synthesis of (+)-and (-)-mintlactone

Reagent and conditions: a) 7% aqueous NaOCl, CH_2Cl_2, RT, 84%; b) H_2, Raney Ni, $B(OMe)_3$, $MeOH-H_2O$, RT, 81%; c) $Me_4NBH(OAc)_3$, MeCN-AcOH, -40 °C to RT; d) *p*-TsOH, CH_2Cl_2, RT, 88%; e) $Zn(BH_4)_2$, diethyl ether, 0 °C, then (d) 47%; f) $POCl_3$, pyridine, RT, 92%.

2.2.3. Zhai's approach

In 2009, Zhai *et al*. elegantly synthesized (+)-mintlactone (**2.1**) in three steps starting from (-)-citronellol (**2.18**) (**Scheme 2.3**).[33p] They employed an intramolecular hetero Pauson-Khand reaction as a key reaction. Treatment of (+)-citronellol (**2.18**) with nitrous acid furnished the alkyne (**2.19**) in a low yield of 26%.[34] Subsequent oxidation with PCC provided the less stable aldehyde (**2.20**) in 68% yield. The aldehyde (**2.20**) was subjected to a hetero-Pauson-Khand reaction in the presence of freshly prepared $Mo(CO)_3(DMF)_3$ in THF, which provided (+) mintlactone (**2.1**) in 39% yield and good diastereoselectivity (12:1).[35] Although the key Pauson-Khand reaction resulted in low yield, the bicyclic system (**2.1**) was constructed in single step with good diastereoselectivity, and, overall this is a remarkably short synthesis of (+)-mintlactone.



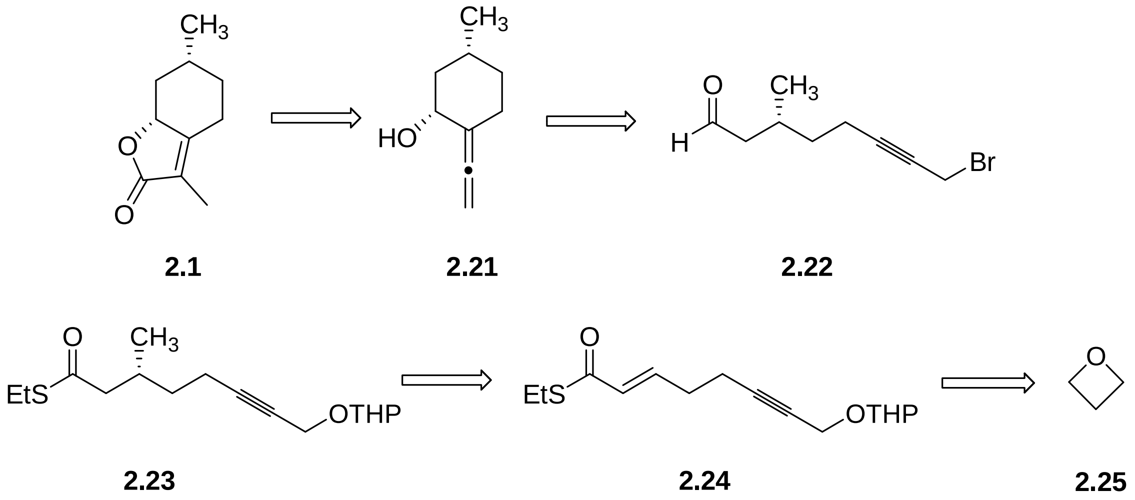
2.18 **2.19** **2.20** **2.1**

Scheme 2.3. Zhai's synthesis of (+)-mintlactone

Reagent and conditions: $NaNO_2$, CH_3COOH, H_2O, 0 °C to 60 °C, 26%; b) PCC, CH_2Cl_2, RT, 68%; c) $Mo(CO)_3(DMF)_3$,THF, RT, 39%.

2.3. Retrosynthesis analysis of (-)-mintlactone (2.1)

A simple retrosynthetic analysis of (-)-mintlactone (**2.1**)is illustrated in **Scheme 2.4**. The final step of our synthesis would be the cyclocarbonylation of allenol (**2.21**) under Takahashi’s conditions.3 The allenol (**2.21**) would be synthesized by the unexplored diastereoselective intramolecular propargylic Barbier reaction of aldehyde (**2.22**). Functional groups modification of methyl-thioester (**2.23**) would give the Barbier precursor (**2.22**). The methyl-thioester (**2.23**) could be prepared by an asymmetric Michael addition to unsaturated thioester (**2.24**). The unsaturated thioester (**2.24**) could be obtained from oxetane (**2.25**).

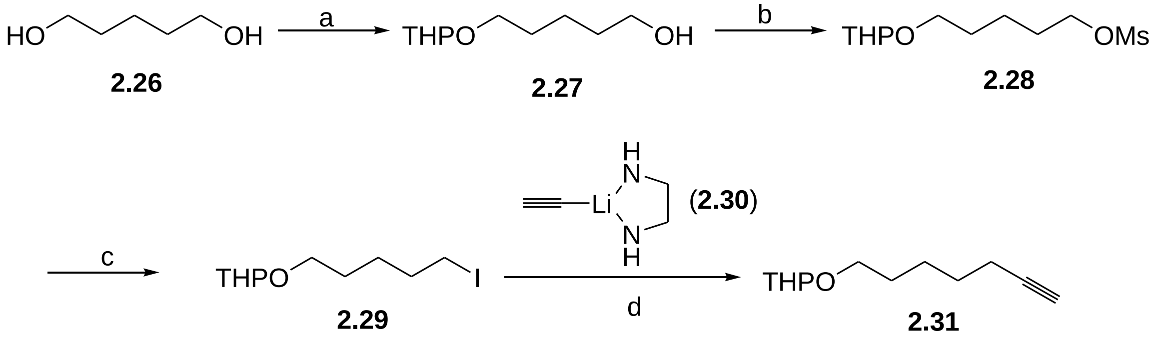


Scheme 2.4.

2.4. Results and discussion

2.4.1. Synthesis of Barbier precursor (2.36)

Before proceeding to the synthesis of (-)-mintlactone (**2.1**), a model study was carried out for the formation of six membered allenol (**2.37**) employing intramolecular propargylic Barbier reaction with different metals under various conditions. Barbier precursor (**2.36**) was prepared by the following standard reactions (**Scheme 2.5, 2.6**). Our model study commenced with the mono protection of pentane-1,5-diol (**2.26**) (**Scheme 2.5**). Treatment of 3,4-dihydro-2*H*-pyran with excess pentane-1,5-diol (**2.26**) in the presence of PPTS, furnished the mono protected THP-alcohol (**2.27**) in 60% yield after purification.[36] Unfortunately, in our hands the mono protection of pentane-1,5-diol in the presence of aqueous $NaHSO_4$, under Nishiguchi'sconditions, gave a low yield of 10%.[37] The IR showed the presence of a hydroxy group at 3431 cm^{-1}and the ^{1}H NMR displayed the acetal proton of the THP functionality at 4.57 ppm as a triplet with a coupling constant of 3.5 Hz.

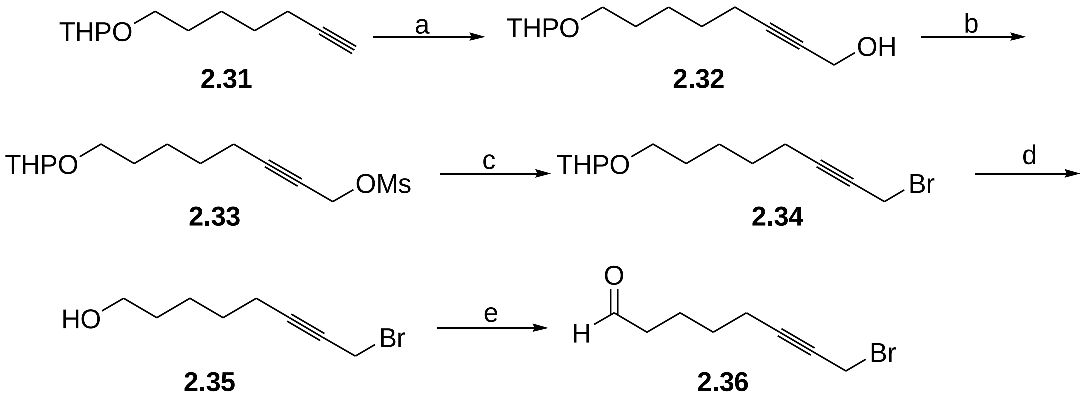


Scheme 2.5.

Reagent and conditions: a) Dihydropyran, PPTS, CH_2Cl_2, RT, 12 h, 60%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 99%; c) NaI, $NaHCO_3$, acetone, reflux, 14 h, 90%; d) DMSO, RT, 4 h, 80%.

Treatment of THP-alcohol (**2.27**) with methanesulfonyl chloride in the presence of triethylamine in dry dichloromethane at 0 °C, provided THP-mesylate (**2.28**) in quantitative yield(**Scheme 2.5**). The formation of THP-mesylate (**2.28**) was confirmed from the IR spectrum, which showed the absence of the hydroxyl group and the presence characteristic sulfonyl absorption bands at 1354 cm^{-1} and 1175 cm^{-1}.Displacement of the methanesulfonate of (**2.28**) was then carried out with the sodium iodide in acetone at reflux using the Finkelstein reaction.[38]A moderate yield (50%) of THP-iodide (**2.29**) was isolated after purification. We believe that the moderate yield is due to the formation of HI in the reaction, which may hydrolyse the THP ether. Interestingly, the yield was increased to 90% with the addition of a buffer,$NaHCO_{3,}$to the reaction mixture. The IR spectrum showed the disappearance of the sulfonyl functionality and the ^{13}C NMR displayed the iodo attached methylene carbon at 6.8 ppm, which confirmed the product formation. The extremely high field chemical shift is highly characteristic of iodides. The THP-iodide (**2.29**) was converted to the THP-alkyne (**2.31**) using lithium acetylenide-ethylenediamine complex (**2.30**) in a good yield of 80%. The IR displayed the presence of the alkyne stretch at 2116 cm^{-1} and the alkyne C-H stretch at 3296 cm^{-1} which confirmed the product formation.

The alkyne (**2.31**)was deprotonated with *n*-BuLi in THF at -78 °C and treated with paraformaldehyde to furnish the THP-propargyl alcohol (**2.32**) in 75% yield after purification (**Scheme 2.6**). The formation of desired product was clearly identifiable from the presence of OH band at 3383 cm^{-1} in the IR spectrum and the ^{1}H NMR spectrum showed the hydroxy attached methylene protons at 4.24 ppm as a broad singlet. The propargylic alcohol (**2.32**) was converted to the mesylate (**2.33**) under the previous conditions (**Scheme 2.5**) and subsequent treatment with the lithium bromide in THF yielded the bromide (**2.35**) in a yield of 80%. The IR displayed the absence of the sulfonyl functionality and the ^{1}H NMR spectrum showed the bromo attached methylene protons at 3.92 ppm as a triplet with a coupling constant of 2.3 Hz.



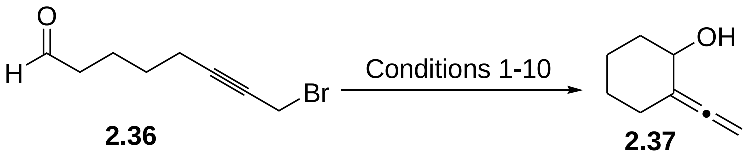
Scheme 2.6.

Reagent and conditions: a) *n*-BuLi, $(CH_2O)_n$, THF, -78 °C to RT, 5 h, 75%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; c) LiBr, THF, RT, 80%; d) Amberlyst-15, MeOH, 90%; e) DMP, CH_2Cl_2, 80%.

Deprotection of the THP ether of bromide (**2.34**) was then carried out with Amberlyst-15 in methanol, which afforded the alcohol (**2.35**) in a good yield of 90%. The IR spectrum showed the presence of OH functionality at 3431 cm^{-1} and the ^{1}H NMR spectrum displayed the absence of the THP group. Although oxidation of the alcohol (**2.35**) failed under Ley's conditions,[39] use of IBX under Santagostino's conditions in DMSO provided the bromo-aldehyde (**2.36**) in a moderate yield of 20%.[40]Finally, a good yield (80%) of bromo-aldehyde (**2.36**) was obtained employing the Dess-Martin periodinane as the oxidant.[41] The IR spectrum showed the disappearance of the broad OH band and the appearance of an aldehyde band at 1722 cm^{-1}. The ^{1}H NMR spectrum also displayed the characteristic aldehyde peak at 9.77 ppm as a triplet with a coupling constant of 1.5 Hz, which confirmed the product formation.

2.4.2. Synthesis of six memebered allenol (2.37)

With the bromoaldehyde (**2.36**) in hand, we began our investigation of the intramolecular propargylic Barbier reaction (**Scheme 2.7**). To understand the effect of a metal on cyclisation we studied different metals as well as different solvents to form the six membered ring allene (**2.37**) (**Table 2.1**). Treatment of bromo-aldehyde (**2.36**) with indium in H_2O or under sonication or THF/NH_4Cl furnished the allenol (**2.37**) as the exclusive product in moderate yields (entries 1-3). The corresponding propargylic alcohol was not observed in the crude ^1H NMR analysis. When the reaction was carried out in methanol and neat conditions no reaction occurred and only recovery of starting material was achieved (entries 4, 5). Under Luche's conditions,8 treatment of bromo-aldehyde (**2.36**) with zinc provided allenol (**2.37**) in 45% yield (entry 6). The reaction with tin resulted in low yields of 0-10% (entries 7-9). Furthermore, a moderate yield (50%) was observed under Mukaiyama's conditions[10] in the presence of $SnCl_2$ and NaI in dry DMF (commercial) at room temperature (entry 10). The IR spectrum showed the characteristic allene band at 1960 cm^{-1} and broad OH band at 3391 cm^{-1}. The ^{13}C NMR displayed the central allene quaternary carbon at 200.5 ppm, which confirmed the product formation.

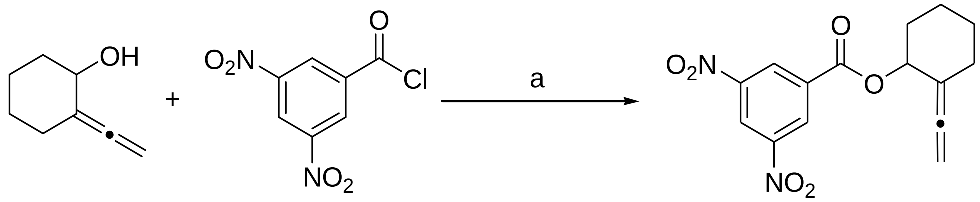


Scheme 2.7.

Table 2.1.

Entry	Solvent	Metal	Conditions	Time/h	Yield %
1	H_2O	In	RT	16	50
2	H_2O	In	)))	1	15
3	THF/NH_4Cl	In	RT	10	40
4	Methanol	In	RT	12	0
5	Neat	In	RT	12	0
6	THF/NH_4Cl	Zn	RT	2	45
7	THF	Sn	RT	10	0
8	H_2O	Sn	RT	16	10
9	THF	Sn	)))	1	10
10	DMF	$SnCl_2$/NaI	RT	14	50

In order to confirm the formation of the six memered allene motif by X-ray crystallography studies, the allenol (**2.37**) was converted to its dinitrobenzoate derivative (**2.39**) (**Scheme 2.8**). Treatment of allenol (**2.37**) with *m*-dinitrobenzoyl chloride (**2.38**) in the presence of DMAP furnished the nitro-allene (**2.39**) in 80% yield. The IR spectrum showed the disappearance of the OH band and the ^{1}H NMR spectrum displayed the three aromatic protons at 9.22 ppm (1H, t, J = 2.1Hz) and 9.17 ppm (2H, d, J = 2.1 Hz). The structure was unambiguously revealed by X-ray crystallography[42] (**Figure 2.2**).



2.37 **2.38** **2.39**

Scheme 2.8.

Reagent and conditions: DMAP, Et_3N, CH_2Cl_2, RT, 4 h, 80%.

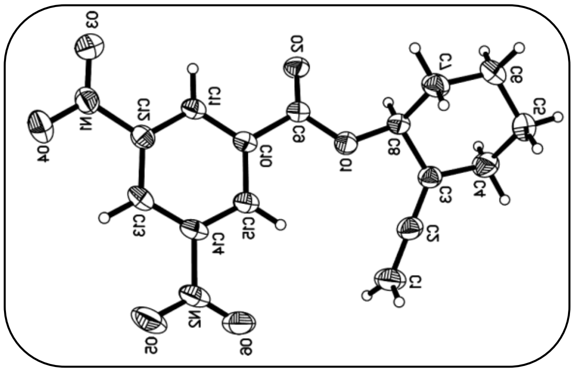
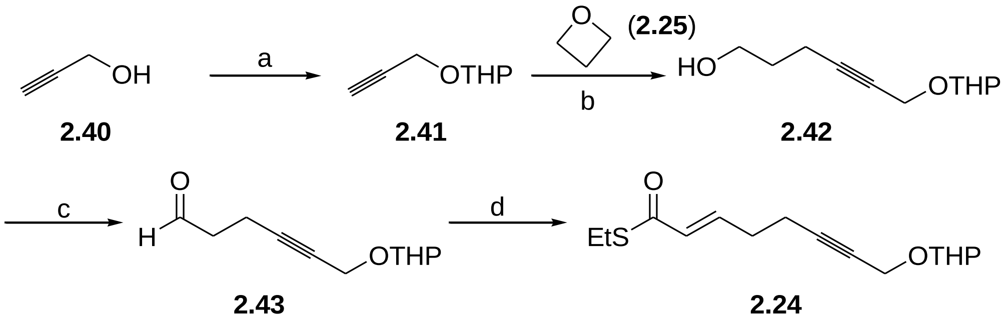


Figure 2.2 The X-ray structure of nitro-allenol (**2.39**)

By screening different metals and different conditions, we found that indium,zincand stannous chlorideare good reagents for the cyclisation. The investigation of diastereoselective intramolecular propargylic Barbier reaction in (-)-mintlactone (**2.1**) synthesis will be discussed in the following sections.

2.4.3. Synthesis of α,β-unsaturated ester (2.24)

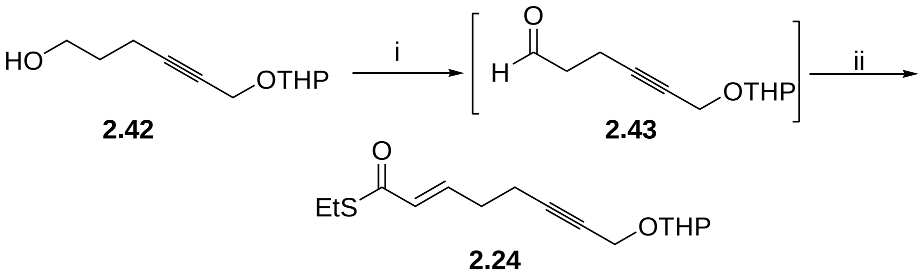
Encouraged by the model study results, we decided to investigate the synthesis of (-)-mintlactone (**2.1**). Our synthesis commenced with the protection of propargyl alcohol (**Scheme 2.9**). Treatment of propargyl alcohol (**2.40**) with 3,4-dihydro-2*H*-pyran in the presence of Amberlyst-15 in dichloromethaneafforded the THP-alkyne (**2.41**) in 82% yield after distillation. We then required a three carbon electrophilic fragment. Oxetane (**2.25**) was chosen over a protected 3-halo propanol, both for atom economy and to avoid a deprotection step. While epoxides are very common in organic synthesis, oxetane, the homologous functionality, is rarely used. The ring opening of oxetane (**2.25**) was carried out under Ganem's conditions.[43] Treatment of the lithium derivative of the THP ether of propargyl alcohol (**2.41**) with oxetane (**2.25**) in the presence of $BF_3{\cdot}OEt_2$ in THF at -78 °C, furnished the alcohol (**2.42**) in 75% yield after purification. The IR spectrum showed the characteristic alkyne band at 2226 cm^{-1} and a broad band at 3402 cm^{-1} for the OH functionality. The ^1H NMR spectrum displayed a triplet at 4.78 ppm with a coupling constant of 3.1 Hz for the acetal proton of the THP functionality, which confirmed our desired product. Subsequently, oxidation proceeded smoothly with the Dess-Martin periodinane in the presence of $NaHCO_3$ buffer in dichloromethane to give aldehyde (**2.43**) in a yield of 76%. Here the basic buffer was used to minimize THP ether hydrolysis. The formation of aldehyde (**2.43**) was identified by the disappearance of the alcohol functionality in the IR spectrum and the appearance of characteristic aldehyde group at 9.77 ppm as a singlet in the ^1H NMR spectrum.



Scheme 2.9.

Reagent and conditions: a) DHP, Amberlyst-15, CH_2Cl_2, RT, 20 h, 82%; b) *n*-BuLi, $BF_3 \cdot OEt_2$, THF, -78 °C, 1 h, 75%; c) DMP, CH_2Cl_2, $NaHCO_3$, RT, 2 h, 76%; d) $Ph_3P{=}CHCOSEt$ (**2.44**), CH_2Cl_2, 0 °C, 2 h, 85%.

The reactionbetween aldehyde (**2.43**) and thioester ylid (**2.44**)[44]in dichloromethane at 0 °Cgave the *trans* isomer (**2.24**) over the *cis* isomer ofalkene in a ratio of 95:5 (**Scheme 2.9**). After careful column chromatography the desired *trans* alkene (**2.24**) was isolated in 85% yield. The IR spectrum showed a band at 1672 cm^{-1} for the thioester functionality and the ^1H NMR displayed a doublet at 6.14 ppm for the *α*-alkene proton with a *trans* coupling constant of 15.4 Hz, which confirmed the desired *trans* thioester (**2.24**). Since the oxidation and the Wittig reaction are clean, we then investigated the one-pot synthesis of thioester (**2.24**) from the alcohol (**2.42**) under Barrett'sconditions (**Scheme 2.10**).[45]Oxidation of alcohol (**2.42**) was carried out using the Dess-Martin periodinane in dichloromethane followed by a Wittig reaction with thioester ylid (**2.44**)[44] in the same pot, which furnished the *trans* alkene (**2.24**) in 71% yield after purification.

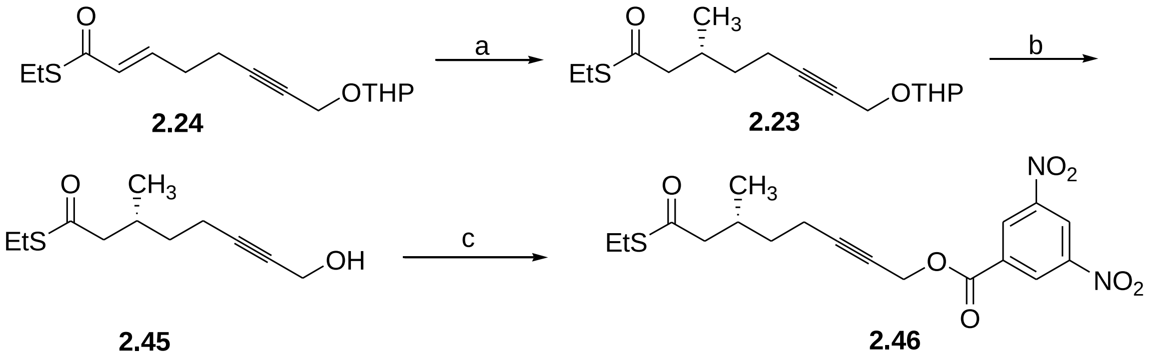


Scheme 2.10.

Reagent and conditions: i. DMP, $NaHCO_3$, CH_2Cl_2, RT, 3 h, ii. $Ph_3P{=}CHCOSEt$ (**2.44**), RT, 14 h, 71%.

2.4.4. Asymmetric Michael addition

In order to install the methyl group, we employed Feringa's asymmetric conjugateaddition methodology(**Scheme 2.11**).[46] Treatment of *trans* thioester (**2.24**) with MeMgBr in the presence of CuI (1 mol%) and *R*-Tol-BINAP (1.4 mol%) in *t*-BuOMe at -70 °C, furnished the *β*-methyl-thioester (**2.23**) in excellent yield of 84%.[47] The formation of product (**2.23**) was identified by the ^1H NMR spectrum, which showed the absence of alkene protons and the presence of doublet at 0.93 ppm with a coupling constant of 6.6 Hz indicative of the methyl protons. The enantiomeric excess was determined by chiral HPLC analysis of the 3,5-dinitrobenzoate derivative (**2.46**) of the propargyl alcohol (**2.45**) (**Scheme 2.11**). A derivative had to be prepared because of the need for a chromophore for the detection of the HPLC. The THP groupof (**2.23**) was removed with the use of Amberlyst-15 in methanol, to afford the alcohol (**2.45**) in quantitative yield. Subsequently, alcohol (**2.45**) was treated with 3,5-dinitrobenzoyl chloride in the presence of DMAP in dichloromethane, which furnished the dinitrobenzoate derivative (**2.46**) in 81% yield. The *ee* was found to be 94% (appendix page 276). The (*R*)-absolute configuration was assigned based on the work of Feringa and later confirmed by conversion to the natural product.

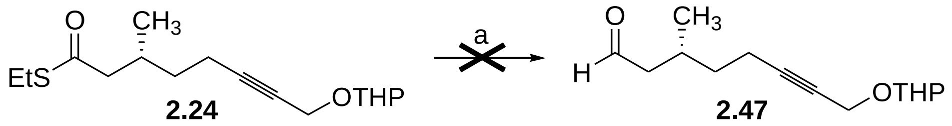


Scheme 2.11.

Reagent and conditions: a) MeMgBr, CuI (1 mol%), *R*-Tol-BINAP (1.4 mol%), *t*-BuOMe, - 70 °C, 84%; b) Amberlyst-15, CH_3OH, RT, 99%; c) 3,5-dinitrobenzoyl chloride, DMAP, CH_2Cl_2, RT, 81%.

2.4.5. Attempted synthesis of aldehyde (2.47)

Encouraged by the asymmetric Michel reaction, we then attempted to convert *β*-methyl-thioester (**2.24**) into the aldehyde (**2.47**) using Fukuyama's protocol (**Scheme 2.12**).[48] Unfortunately, treatment of *β*-methylthioester (**2.24**) with Et_3SiH in the presence of Pd in acetone failed and resulted in a complex mixture. The crude ^1H NMR spectrum revealed a small alkene peak, due to competing alkyne reduction. Attempts to prevent the alkyne reduction by adding triethylamine also resulted in a complex mixture.[49] Disappointing with this result, we decide to investigate an alternative route, which involved the reduction of the thioester in later stage using DIBAL-H (**Scheme 2.13**).

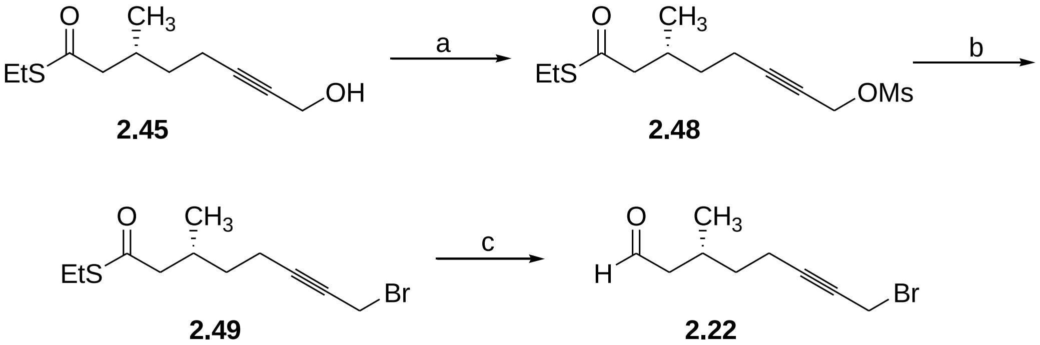


Scheme 2.12.

Reagent and conditions: a) Et_3SiH, Pd/C, CH_3COCH_3.

2.4.6. Synthesis of bromo-aldehyde (2.49)

To continue the synthesis alcohol (**2.45**) was converted into the bromide (**2.49**) *via* the mesylate (**2.48**). The alcohol (**2.45**) was treated with methanesulfonyl chloride in the presence of triethylamine in dry dichloromethane at 0°C, which afforded the methanesulfonate (**2.48**) in quantitative yield without purification (**Scheme 2.13**). The formation of methanesulfonate (**2.48**) was clearly identifiable from the IR spectrum, which showed the characteristic sulfonyl absorption bands at 1359 and 1174 cm^{-1}. The ^1H NMR spectra showed a singlet at 3.10 pm for the sulfonyl methyl group, which confirmed the product formation.



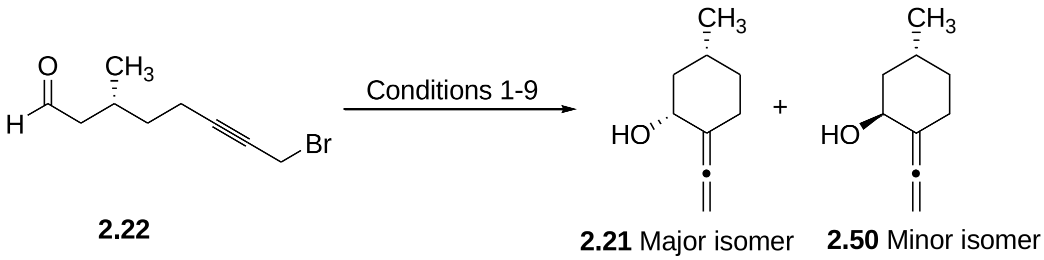
Scheme 2.13.

Reagent and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; b) LiBr, THF, RT, 86%; c) DIBAL-H, CH_2Cl_2, - 78 °C, 10 minutes, 92%.

Displacement of the methanesulfonate of (**2.48**) with lithium bromide was then carried out in THF, which afforded the bromide (**2.49**) in 86% yield after purification (**Scheme 2.13**). The formation of our desired product was identified by the disappearance of characteristic sulfonyl bands in the IR spectrum and the appearance of a triplet at 3.9 ppm with a coupling constant of 2.3 Hz, indicative of the bromo attached methylene protons.The bromide (**2.49**) was treated with DIBAL-H in dry dichloromethane at - 78 °C, to afford the bromo-aldehyde (**2.22**) in excellent yield of 92%. The disappearance of the thioester band at 1681 cm^{-1}in the IR spectrum and the^{1}H NMR displayed a triplet at 9.76 ppm with a coupling constant of 2.0 Hz for the aldehyde group, which confirmed the formation of our desired product. It was gratifying that there was no reduction of the reactive propargylic bromide.

2.4.7. Synthesis of allenol (2.21)

With the bromoaldehyde (**2.22**) in hand, the diastereoselective intramolecular propargylic Barbier cyclisation was investigated (**Scheme 2.14**). Based on our model study, we were particularly interested in employing Zn, In or $SnCl_2$ for cyclisation. Our initial trial with zinc in the presence of NH_4Cl in THF at room temperature under Luche's conditions,8 gave an inseparable mixture of allenol isomers (**2.21**and **2.50**) in a low yield of 36% and quite modest diastereoselectivity (75:25) as judged by the ^{1}H NMR analysis(**Table 2.4**, entry 1). Employingindium in a water-DMF mixture (4:1) at room temperature furnished the allenol (**2.21**) as a single diastereomer (≥95:5) in a moderate yield of 47% (entry 2). On the other hand, clean cyclisation was observed upon treatment with tin(II) chloride in the presence sodium iodide in dry DMF (commercial) at room temperature or 0 °C under Mukaiyama's conditions (entries 3, 4).[10] A single isomer of *cis* allenol (**2.21**) was isolated in 45-52% yield after purification. Since, tin(II) chloride gave the cleanest conversion to the desired allenol and the highest yield, our efforts were focused on optimizing this reaction.



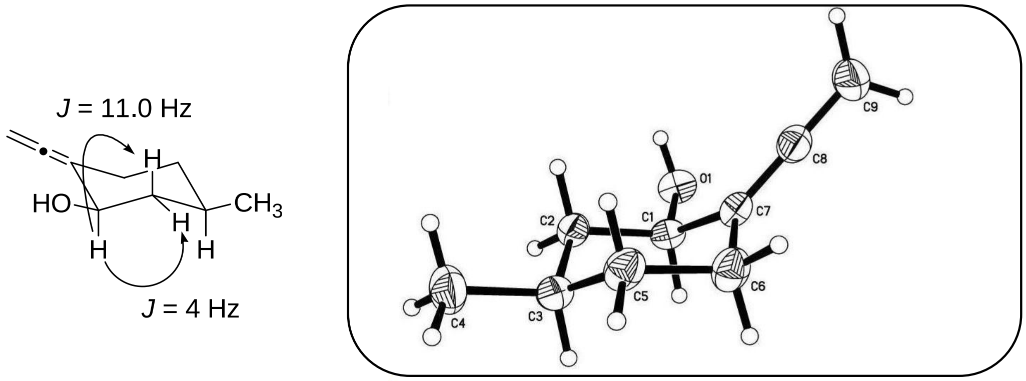
Scheme 2.14.

Table 2.4.

Entry	Conditions	Time/ hr	T/ °C	Yield/%	dr
1	Zn, NH_4Cl	12	RT	36	75:25
2	In, H_2O, DMF	24	RT	47	≥95:5
3	$SnCl_2$, NaI, DMF(dry commercial available)	16	RT	45	≥95:5
4	$SnCl_2$, NaI, DMF(dry commercial available)	24	0	52	≥95:5
5	$SnCl_2$, NaI, DMF (dry)	48	0	13	≥95:5
6	$SnCl_2$, NaI, DMF, H_2O	56	-10	75	≥95:5
7	$Sn(BF_4)_2$, NaI, DMF, H_2O	48	-10	10	≥95:5
8	$Sn(O_2C_8H_{15})_2$, NaI, DMF, H_2O	48	-10	24	≥95:5
9	SnI_2, NaI, DMF, H_2O	12	-10	0	-

Due to an initial concern about the possibility of moisture present in the commercial “anhydrous” DMF, we examined the use of carefully dried DMF (distilled from CaH_2 under reduced pressure). To our surprise, for the reaction in anhydrous DMF, the yield was reduced to 13% but without changing the diastereoselectivity (entry 5). Interestingly, addition of water (12.5% with respect to DMF) to the above conditions at -10 °C resulted in an enhanced yield of 75% and excellent diastereoselectivity (entry 6). Based on Masuyama’s report, we believe that the role of water is to form the more reactive hydroxy tin intermediates (**II** and **III**, **Scheme 2.15**) in the reaction mixture.[50,51,52] We also examined other sources of the tin(II) reagent for the cyclisation. However, the use of tin(II) tetrafluoroborate (aq.) or tin(II) 2-ethylhexanoate resulted in low yields (10- 24%, entries 7-8). Furthermore when tin(II) iodide was employed, no reaction was observed (entry 9).

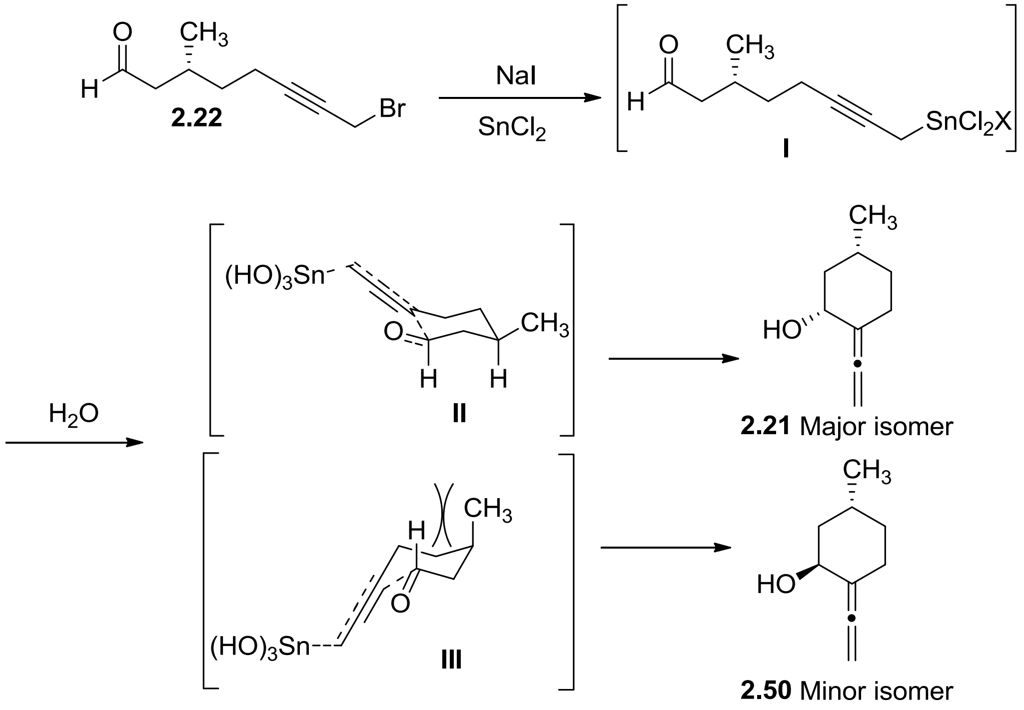
The ^{1}H NMR and ^{13}C NMR of allenol (**2.21**) are given in the appendix (page 278). The formation of allenol (**2.21**)was confirmed from the appearance of characteristic allene absorption band at 1956 cm^{-1} and a broad band at 3325 cm^{-1} indicative of the hydroxy group in the IR spectrum. This was further supported by the characteristic peak for the central allene carbon at 199.6 ppm in the ^{13}C NMR spectrum. The stereochemistry of the allenol product was assigned based upon the observation of coupling constants of 11 and 4.3 Hz for the proton α to the hydroxyl group, after decoupling of the allenic protons, to simplify the spectrum. These coupling constants are consistent with the alcohol group and, presumably, the methyl group being equatorial. The 11 Hz coupling can be assigned to be $J_{\text{ax-ax}}$, while the 4.3 Hz coupling can be $J_{\text{ax-eq}}$ (**Figure 2.3**). This assignment was subsequently confirmed by X-ray crystallography[42] (**Figure 2.3**). We were pleased to find that the allenol (**2.21**) itself could be crystallized, despite its low melting point, and there was no need to prepare crystalline derivatives.



Coupling constants X-ray structure

Figure 2.3 Coupling constants and X-ray crystallography of allenol (**2.21**)

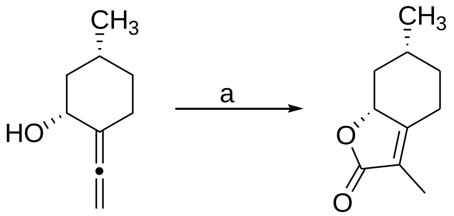
A possible mechanism for the formation of the *trans* and *cis* allenol isomer involves the six-membered chair transition states **II** and **III** (**Scheme 2.15**). In cyclic chair transition state **II** less steric interaction between the carbonyl and hydrogen would give the *cis* allenol (**2.21**) as a major isomer. But, in transition state **III**, due to the 1,3 interaction between the hydrogen and methyl, which leads to the *trans* allenol (**2.50**) as a minor isomer.



Scheme 2.15.

2.4.8. Synthesis of (-)-mintlactone (2.1)

To complete the synthesis, cyclocarbonylation was carried out under Takahashi's conditions (**Scheme 2.16**).3The allenic alcohol (**2.21**) was treated with triruthenium dodecacarbonyl and triethylamine under a pressure of 100 psi of CO. A yield of 83% of mintlactone (**2.1**) was obtained by using only 2 mol% of $Ru_3(CO)_{12}$. The ^{1}H NMR and ^{13}C NMR of mintlactone (**2.1**) are shown in the appendix (page 279). The spectroscopic data (^{1}H and ^{13}C NMR) were in good agreement with that reported (**Table 2.5**).[33h] An optical rotation of -59.2 (*c* =2.4, $CHCl_3$) was measured for the synthetic material [lit.[33a,33h] -51.8 (*c* =10, EtOH), -57 (*c* =2.4, $CHCl_3$)].

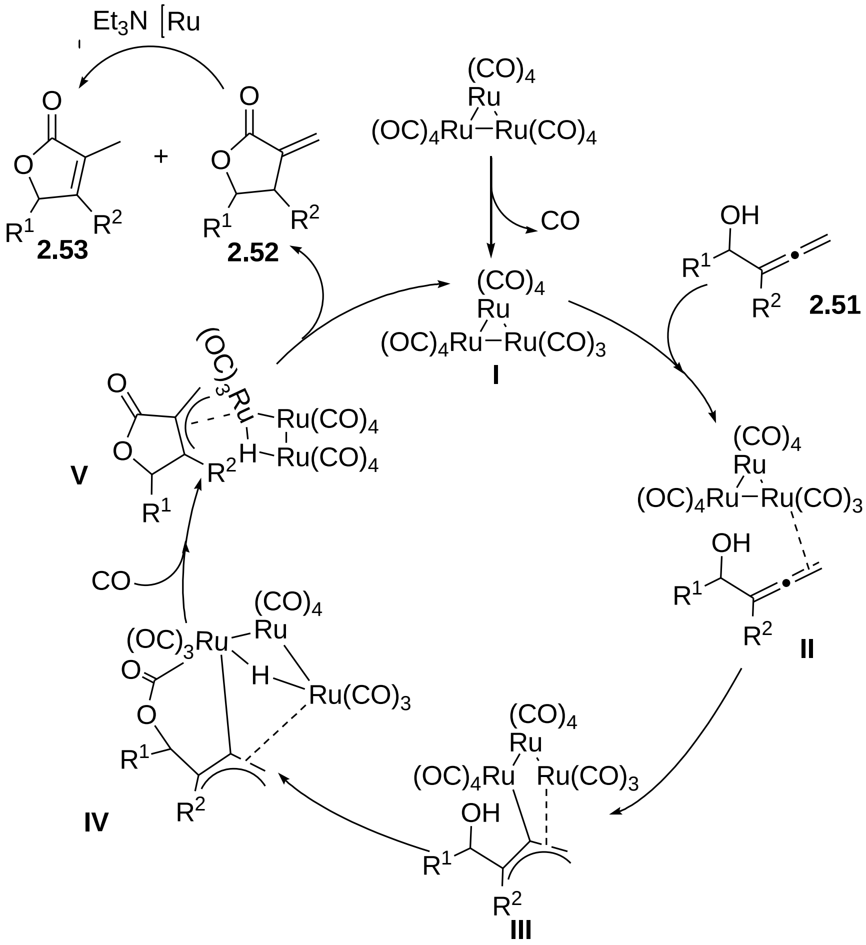


2.21 **2.1**

Scheme 2.16.

Reagents and conditions: a) $Ru_3(CO)_{12}$, Et_3N, CO (100 psi), dioxane, 100 °C, 14 h, 83%.

Takahashi's proposed mechanism starts with the dissociation of carbon monoxide from $Ru_3(CO)_{12}$ giving the active ruthenium complex (**I**) (**Scheme 2.17**).3[c]Subsequent coordination with the allene (**2.51**) forms the complex (**II**) and further transformation affords the π-allyl species (**III**). An intramolecular hydroxy attack would form the metallacycle intermediate (**IV**) which undergoes reductive elimination to give the intermediate (**V**).Then internal hydrogen transfer would lead to the formation of (**2.52**) and (**2.53**). Finally, isomerization of (**2.52**) could occur in the presence of NEt_3 and the Ru catalyst to afford the more stable lactone (**2.53**).



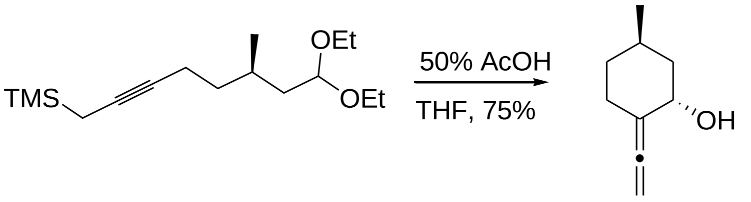
Scheme 2.17. Takahashi's mechanism for carbonylation

Table 2.5 Compared physical and spectral data for (-)-mintlactone

	Literature[33h]	Our synthetic data
Optical rotation	-57 (c = 2.4, $CHCl_3$)	-59.2 (c = 2.4, $CHCl_3$)
^1H NMR	200 MHz, $CDCl_3$	300 MHz, $CDCl_3$
	4.66 (1H, dd, J = 11.0, 6.0 Hz).	4.60 (1H, dd, J = 11.0, 6.0 Hz)
	2.8 (1H, ddd, J = 14.0, 4.6, 1.9 Hz)	2.77 (1H, ddd, J = 14.2, 4.3, 1.8 Hz)
	2.45 (1H, m)	2.43-2.35 (1H, m)
	2.25 (1H, m)	2.17 (1H, td, J = 13.7, 5.4 Hz)
	2.00 (1H m)	1.95-1.85(1H, m)
	1.8 (3H, t, J = 1.4 Hz)	1.78 (3H, t, J = 1.4 Hz)
	1.75 (1H, m)	1.76-1.62 (1H, m)
	1.1-1.5 (2H ,m)	1.09-0.86 (2H, m)
	1.00 (3H, d, J = 6.5 Hz)	0.98 (3H, d, J = 6.6 Hz)
^{13}C NMR	50 MHz, $CDCl_3$	75.4 MHz, $CDCl_3$
	174.86	174.9
	162.62	162.4
	119.85	119.6
	80.24	80.0
	42.27	42.0
	34.82	34.6
	29.19	29.8
	25.75	25.5
	21.45	21.2
	8.38	8.2

2.5. Conclusion

In summary, we have successfully demonstrated the first diastereoselective intramolecular propargylic Barbier reaction in total synthesis with remarkably high diastereoselectivity. The synthesis of (-)-mintlactone has been achieved in 13 steps starting from simple non chiral starting materials oxetane and propargyl alcohol, in an overall yield of 17.3%. Interestingly, after the completion and publication of our synthesis of (-)-mintlactone, Tsubuki *et al*. reported an analogous of (+)-*iso*-mintlactone using a propargyl silane in place of propargyl bromide, prior to the final cyclocarbonylation (**Scheme 2.18**).[33n] No reason was offered for the opposite stereochemical outcome of the reaction.*



2.54 **2.50** Trans allenol

Scheme 2.18.

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*A similar selectivity was observed in (±)-stemoamide synthesis by Ran Hong *et. al*[59h.]

Chapter 3

A Synthesis of (±)-Stemoamide

3.1. Introduction

Having successfully accomplished a highly stereoselective synthesis of (-)-mintlactone (**2.1**), our attention turned to the synthesis of some of the butenolides of the *Stemona* alkaloids, by employing the intramolecular propargylic Barbier reaction as the key step. Extracts of plants of the *Stemona* family have long been employed in traditional Chinese and Japanese medicine to treat respiratory disorders such as asthma, bronchitis, petusis and tuberculosis. The root extracts of these plants can have potent antifeedant, repellent and some insecticidal activities.[53] For example they are active against *Bombyx mori* (silkworm larvae). In 1934, tuberostemonine was the first alkaloid isolated from *Stemona tuberosa* and *Stemona sessifolia* roots in the *Stemona* family.[54] Since then, about 139 alkaloids have been isolated.

Pilli has organised the *Stemona* alkaloids into eight different groups based on the nucleus present in the alkaloid (**Figure 3.1**).[55,58a]The pyrrolo[1,2-a]azepine nucleus is common to six groups: stenine (**I**), stemoamide (**II**), tuberostemospironine (**III**), stemonamine (**IV**), parvistemoline (**V**), stemofoline (**VI**) and the pyrido[1,2-a]azepine nucleus is present in stemocurtisine (**VII**) (**Figure 3.1**). Finally, a miscellaneous group of alkaloids is classified by the absence of these two nuclei, which arise from oxidation or rearrangement processes.[56]

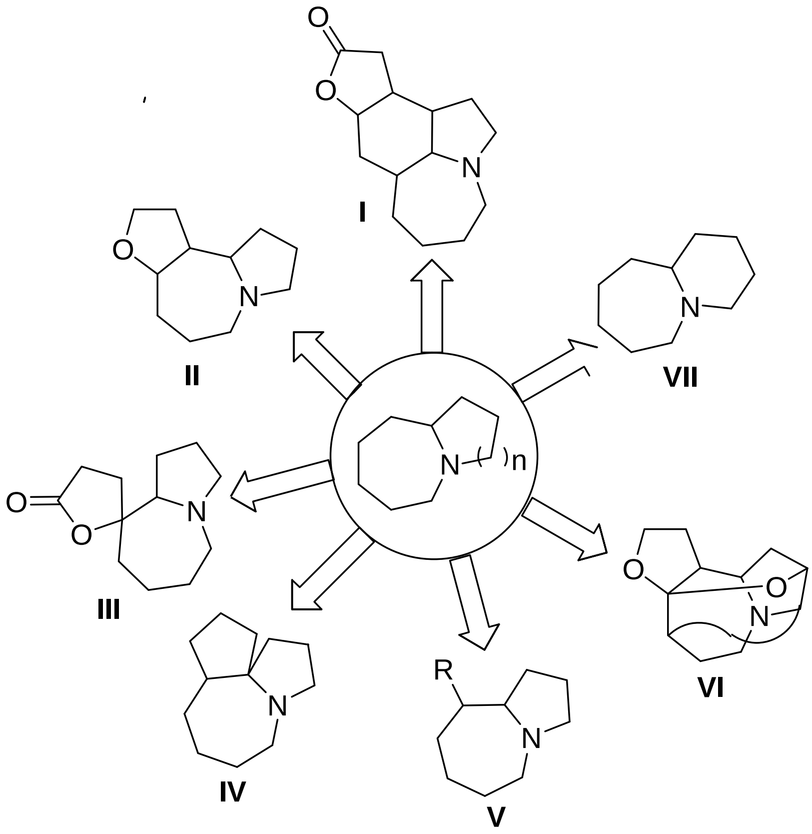
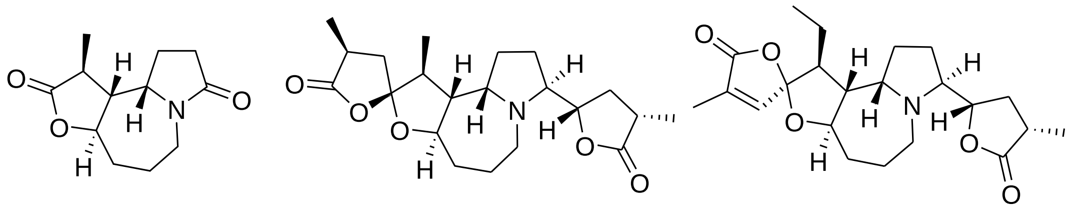


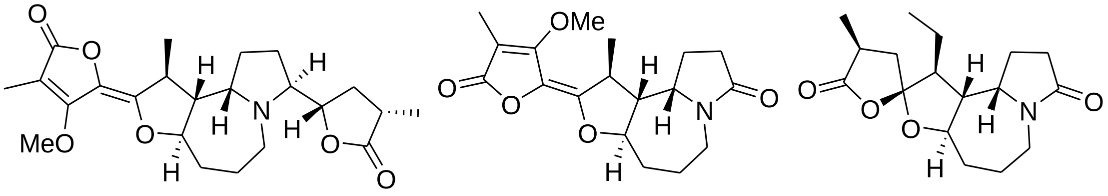
Figure 3.1 Stemona alkaloid groups

3.1.1. Stemoamide group

Alkaloids in this group are represented by the basic skeletal structure of stemoamide (**3.1**) (**Figure 3.2**) with the tricyclic 2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine unit. Selected examples of stemoamide group alkaloids are shown in figure 3.2. In 1992, Xu and co-workers isolated (-)-stemoamide (**3.1**) from*Stemona tuberose*.[57] Among the polycyclic alkaloids, (-)-stemoamide incorporates a simple structural unit with an azepine unit, and a butyrolactone with four contiguous sterogenic centres in a tricyclic core. Due to the architectural features stemoamide (**3.1**) makes an interesting target molecule for the intramolecular propargylic Barbier reaction.



Stemoamide **3.1** Dihydrostemoninine **3.2** Stemonine **3.3**



Isoprotostemonine **3.4** Protostemonaide **3.5** Sessilifoliamide **3.6**

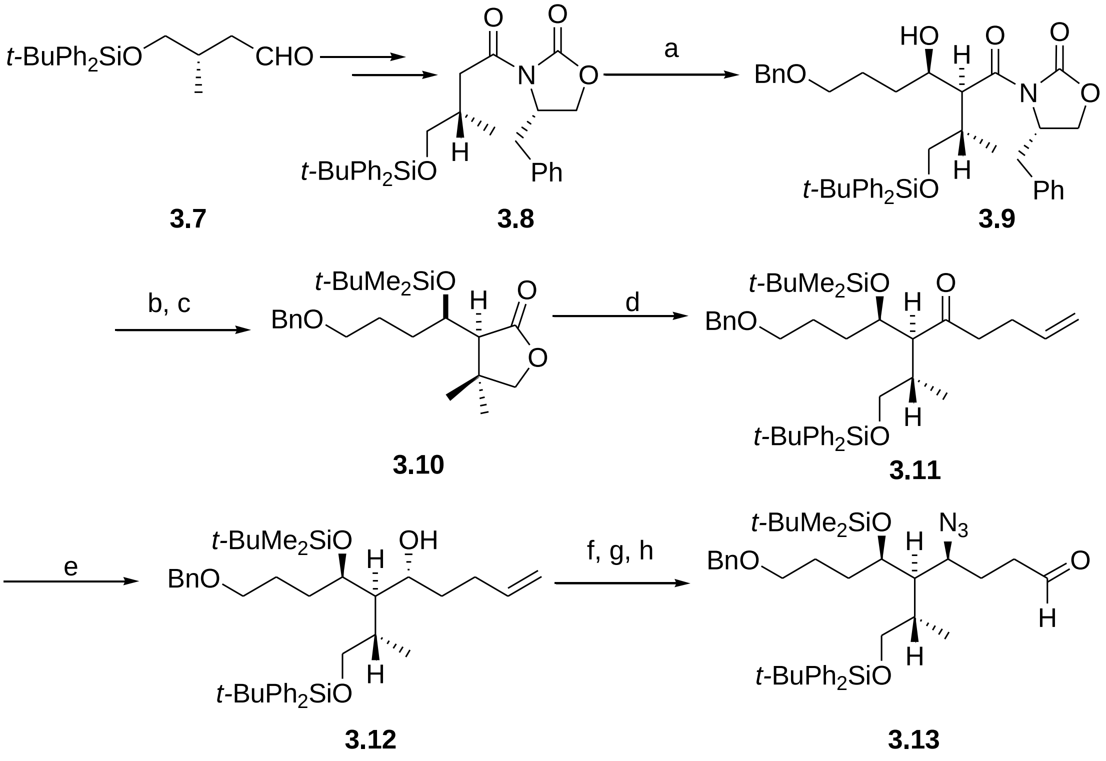
Figure 3.2 Selected examples of the stemoamide alkaloids

3.2. Previous selected total synthesis of stemoamide

Over the past two decades since the isolation of stemoamide (**3.1**), a number of formal and total syntheses have been reported using a wide variety of synthetic methods.[58,59]The following sub-sections will provide a brief overview of the selected total synthesis of stemoamide (**3.1**) and will hopefully highlight the different routes utilised to achieve the synthesis of this natural product.

3.2.1. Williams' approach

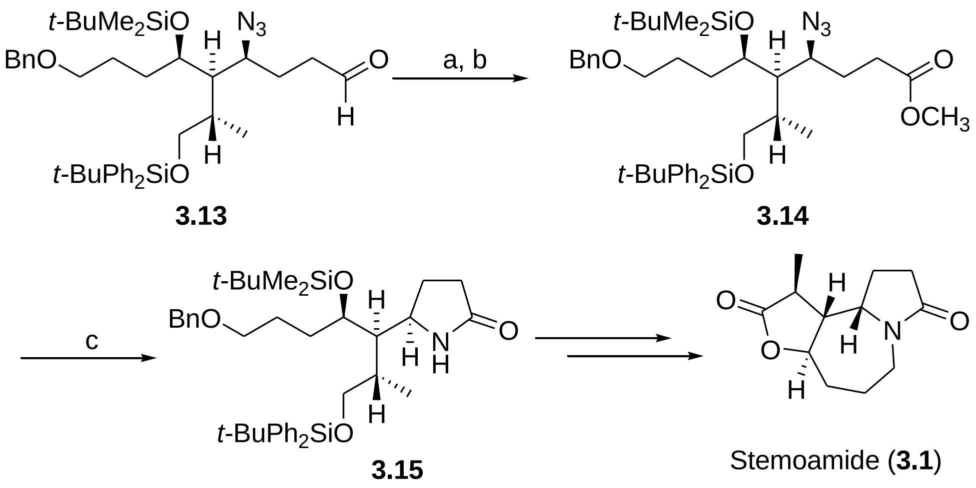
In 1994, Williams' group accomplished the first total synthesis of (-)-stemoamide (**3.1**).[59a] Their strategy demonstrated the use of an asymmetric aldol reaction together with selective 1,3-acyclic diol formation. Williams' total synthesis commenced with the readily available (*R*)-(-)-methyl-3-hydroxy-2-methylpropionate (**3.7**) (**Scheme3.1**). The asymmetric aldol reaction between the chiral imide (**3.8**) and 4-benzyloxybutanal afforded the *syn*-aldol derivative (**3.9**) in 88% yield. Removal of the silyl ether, followed by cyclisation under basic conditions lead to a butyrolactone, and subsequent protection of the alcohol yielded TBS ether (**3.10**) in 97% yield.



Scheme 3.1 Selected steps from Williams' synthesis of (-)-stemoamide

Reagents and conditions: a) *n*-Bu_2BOTf, CH_2Cl_2, -78 °C, 1 h, then Et_3N, 4-benzyloxybutanal, - 78 °C to 0 °C, 1 h, 88%; b) 48% aq. HF, CH_3CN, RT, 20 min, then $NaHCO_3$ (0.9 M, 0.7 eq), K_2CO_3 (18 eq), 2 h, 82%; c) *t*-$BuMe_2SiOTf$, collidine, CH_2Cl_2, -78 °C to RT, 97%; d) 4-Iodo-1-butene, *t*-BuLi, Et_2O, -100 °C, 45 min, then **3.10**, -100 °C to -78 °C, then *t*-$BuMe_2SiOTf$, collidine, CH_2Cl_2, -78 °C to RT 2.5 h, 78% ; e) $LiEt_3BH$, THF,- 78 °C to RT 1.5 h; f) MsCl, pyridine, RT, 12 h, 96%; g) NaN_3, HMPA, RT, 9 h; g) O_3, CH_2Cl_2/CH_3OH, - 78 °C, then Me_2S, -78 °C to RT 3 h, 49% (two steps yield).

The condensation of the lactone (**3.10**) with the Grignard reagent derived from 4-bromo-1-butene was the problematic step in their synthesis (**Scheme 3.1**). Various side reactions were observed such as Wurtz coupling and reduction of the primary halide. In order to prevent side reactions, a modified procedure reported by Bailey and Negishi was employed.[60,61] At a very low temperature (-100 ºC) use of 4-lithio-butene in diethyl ether provided the alcohol, which was protected as its TBS ether in the same pot, affording the ketone (**3.11**) in 78% yield. The ketone (**3.11**) was reduced by treatment with super hydride® to afford the 1,3-*anti*-diol (**3.12**) as the exclusive product in 91% yield. The stereoselective formation of the 1,3-*anti*-diol is generated *via* a Felkin-Anh hydride addition.The alcohol (**3.12**) was converted into an azide *via* a **mesylate**, followed by ozonolysis of the double bond, which afforded the azido aldehyde (**3.13**).



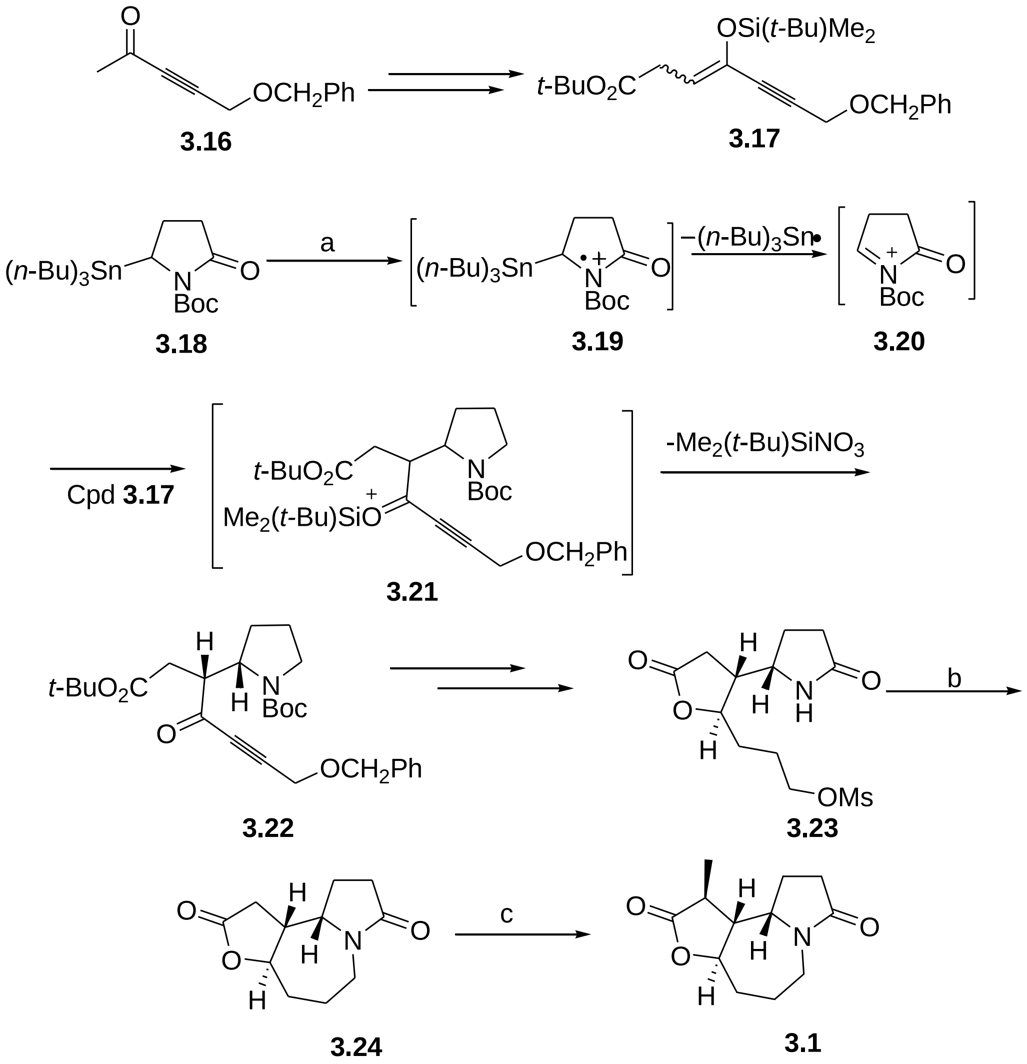
Scheme 3.2. Selected steps from Williams' synthesis of (-)-stemoamide

Reagents and conditions: a) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, CH_3CN, *t*-BuOH, H_2O, 2-methyl-2-butene, 0 °C, 30 min; b) CH_2N_2, Et_2O, 0 °C, 15 min, 96% from aldehyde (**3.13**); c) PPh_3, THF/H_2O, reflux, 48 h, 87%.

Oxidation of the aldehyde (**3.13**), followed by esterification of the resulting carboxlic acid furnished the methyl ester (**3.14**) (**Scheme 3.2**). Under mild conditions, the azide was reduced to an amine and *in situ* cyclization lead to lactam (**3.15**). Further manipulation of the lactam (**3.15**) provided (-)-stemoamide (**3.1**). Thus, the first total synthesis was completed with a longest linear sequence of 24 steps with an overall yield of 1%. However, multiple protection and deprotection diminished the efficiency of the synthesis.

3.2.2. Narasaka's approach

Narasaka and Kohno described an outstanding linear approach to (±)-stemoamide in 12 steps (**Scheme 3.3**).[59b] The key step of their approach demonstrated an oxidative coupling reaction between silyl enol ethers and the stannyl derivatives. The key intermediate silyl ether (**3.17**) was prepared from acetylenic ketone (**3.16**) in 4 steps. In the presence of CAN, oxidation of stannyl pyrrolidine (**3.18**) gives the radical cation (**3.19**) and subsequent cleavage of the stannyl functionality afforded an acyliminium ion (**3.20**) which further reacted with the silyl enol ether (**3.17**) furnishing a diastereomeric mixture (4:1) of the alkyne ketones (**3.22**) in 65% yield. Further manipulation of the ketone (**3.22**) provided amide (**3.23**). Under high-dilution conditions, treatment of amide (**3.23**) with NaH in THF furnished the tricyclic lactone (**3.24**) in 62% yield. The synthesis was completed by treatment of lactone (**3.24**) with methyl iodide in the presence of LDA. Methylation from the less hindered β-face stereoselectively gave (±)-stemoamide (**3.1**) in 59% yield. The key feature of Narasaka's synthesis is the efficient and novel coupling reaction to construct the carbon skeleton and the stereoselective methylation of the lactone (**3.24**).



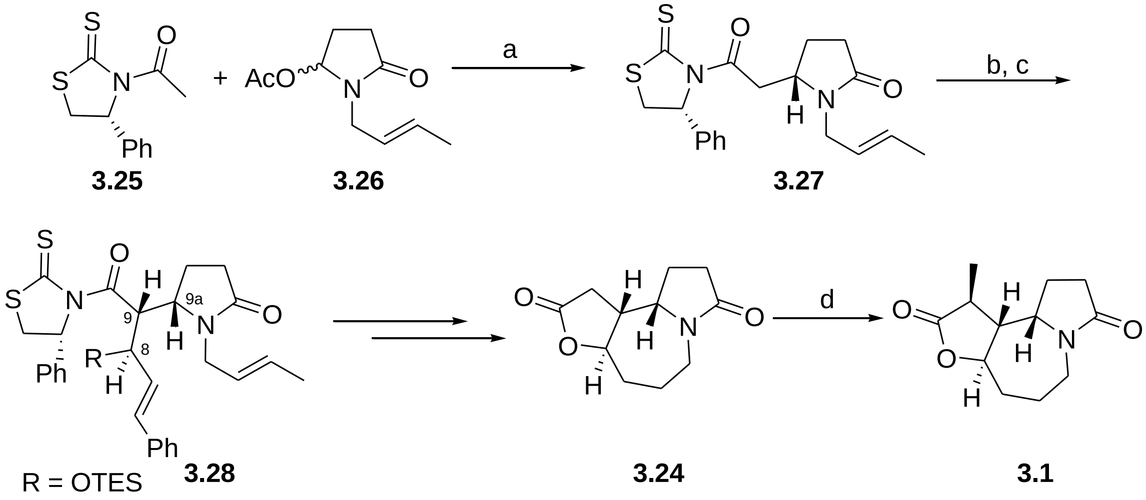
Scheme 3.3. Selected steps from Narasaka’ssynthesis of (±)-stemoamide

Reagents and conditions: a) $(NH_4)_2Ce(NO_3)_6$ (CAN), molecular sieves, EtCN, - 45 °C, 65%; b) NaH, THF, RT, 62%; c) LDA, MeI, THF, -78 °C to RT, 59%.

3.2.3. Olivo’s approach

Olivo’s efficient route commenced with the diastereoselective addition of a titanium enolate of (**3.25**) to the iminium ion formed from 5-acetoxy pyrrolidinone

(**3.26**), which afforded the thiazolidinethione (**3.27**) with the necessary configuration at C9a in 92% yield (**Scheme 3.4**).[59c] Subsequent treatment of thiazolidinethione (**3.27**) with cinnamaldehyde provided aldol product (**3.28**) with the required configurations at C-8 and C-9 in 74% yield. After several steps, including a ring closing metathesis to form azepine ring, the lactone (**3.24**) was methylated, employing Narasaka's conditions to give (-)-stemoamide (**3.1**) in a yield of 70%. The total synthesis was accomplished in 11 steps with an overall yield of 14%. The key feature of Olivo's synthesis is the use of a chiral auxiliary to install the correct stereocenters in the molecule (C8, C9, and C9a).

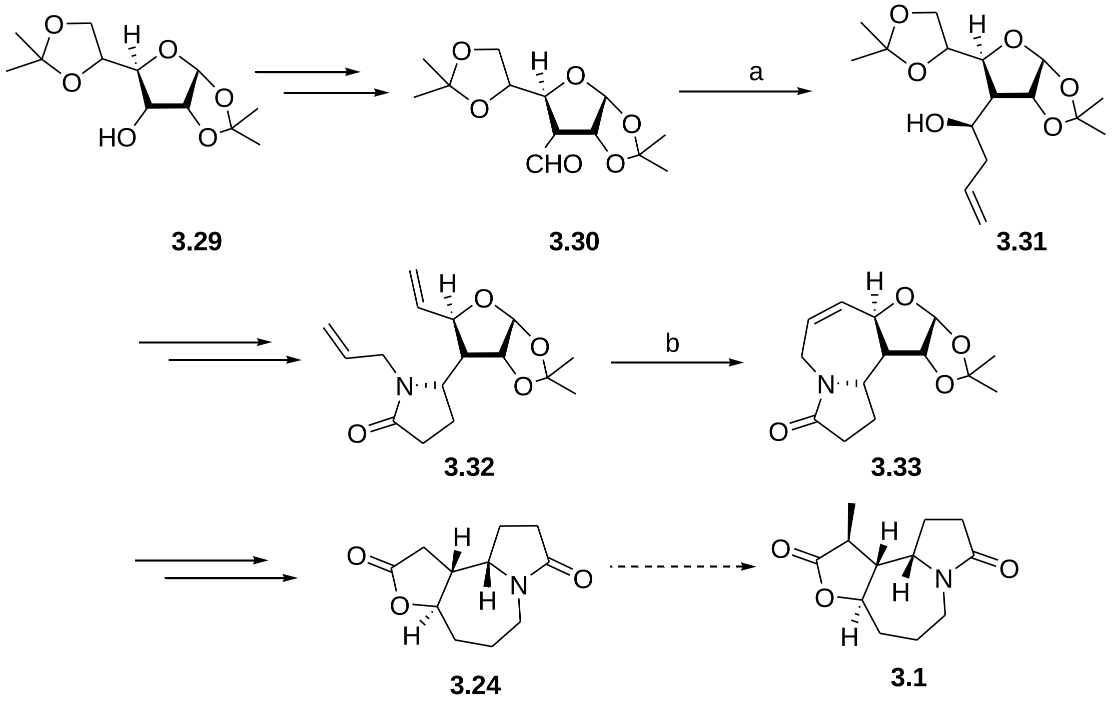


Scheme 3.4. Selected steps from Olivo's synthesis of (-)-stemoamide

Reagents and conditions: a) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, -78 °C to 0 °C, 6 h, 92%; b) cinnamaldehyde, cat. $MgBr_2{\cdot}OEt_2$, TMSCl, Et_3N, EtOAc, RT, 36 h, 74%; c) TESOTf, 2,6-lutidine, -78 °C to RT, 14 h, 99%; d) LHMDS, MeI, THF, -78 °C, 2 h, 70%.

3.2.4. Gurjar's approach

Gurjar and Srivasa Reddy reported a carbohydrate based formal synthesis of (-)-stemoamide (**3.1**) (**Scheme 3.5**).[59d] Their strategy involves the stereocontrolled synthesis of the 2-pyrrolidinone derivative at C-9 (C-3 position of D-glucose) and ring-closing metathesis (RCM). The key intermediate aldehyde (**3.30**) was prepared from D-glucose diacetonide (**3.29**) in three steps. The aldehyde (**3.30**) was treated with the allyl bromide in the presence of zinc under Barbier conditions, which furnished the alcohol (**3.31**) as a single isomer in 81% yield. Further manipulation of the alcohol (**3.31**) provided alkene (**3.32**), which was subjected to ring-closing metathesis to give amide (**3.33**). After several steps the amide (**3.33**) was converted into the butenolide (**3.24**), which is a precursor to (-)-stemoamide (**3.1**). The key concept of the synthesis is the stereocontrolled allylation under Barbier conditions. However, a formal synthesis was achieved by employing a total of 22 steps, which diminished the efficiency of the synthesis.

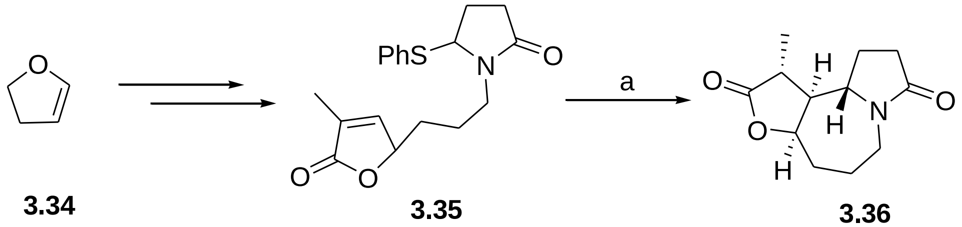


Scheme 3.5. Selected steps from Gurjar’s synthesisof (-)-stemoamide

Reagents and conditions: a) allyl bromide, Zn, sat. NH_4Cl, THF, 30 min, 81%.; b) Grubbs' catalyst, CH_2Cl_2, reflux, 12 h, 83%.

3.2.5. Cossy's approach

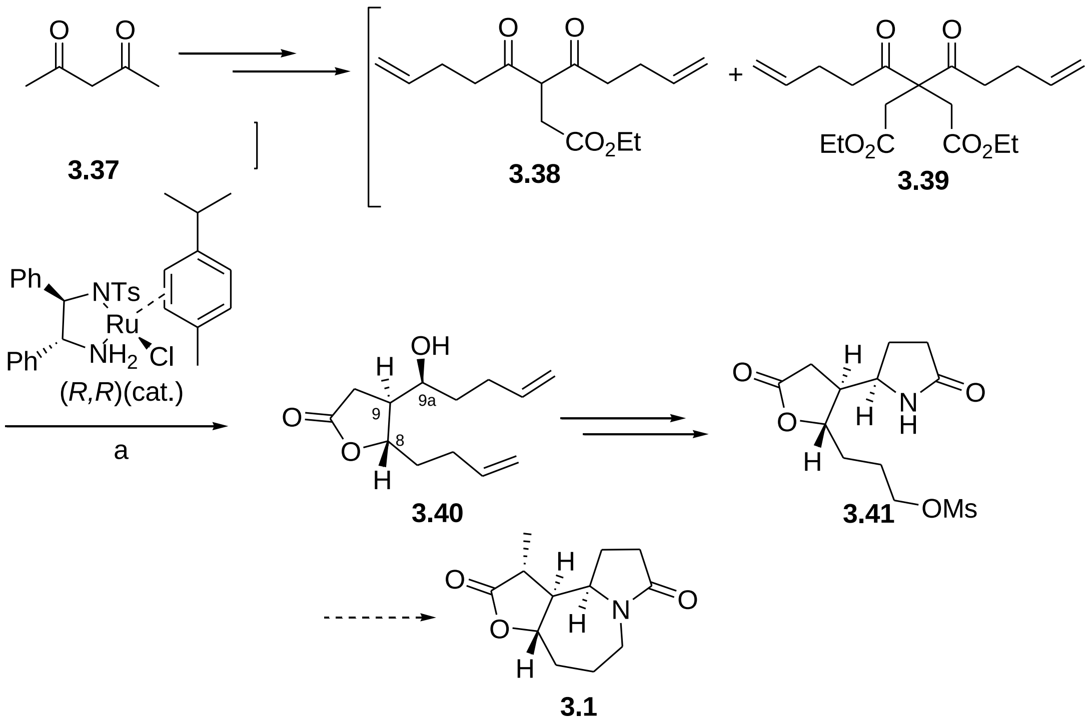
Cossy *et al.* reported a formal synthesis of (+)-stemoamide (**3.1**) and (±)-9,10-bis-epi-stemoamide (**3.36**).[59k,l,m] In their approach towards the construction of the azepine ring in (±)-9,10-bis-epi-stemoamide (**3.36**), they employed a 7-*exo-trig* atom-transfer cyclization (**Scheme 3.6**). The key intermediate lactone (**3.35**) was prepared from 2,3-dihydrofuran (**3.34**) in 9 steps. Treatment of lactone (**3.35**) with Bu_3SnH in benzene provided tricyclic (±)-9,10-bis-*epi*-stemoamide (**3.36**) as a single isomer in 20% yield.



Scheme 3.6. Selected steps from Cossy's synthesis of (±)-9,10-bis-epi-stemoamide

Reagents and conditions: a) Bu_3SnH, AIBN, benzene, 80 °C, 20%.

In their second approach they utilized a reductive desymmetrization of a *γ*-1,3-diketone in order to control the stereocenters (C8, C9, and C9a) of (+)-stemoamide (**3.1**) (**Scheme 3.7**). An inseparable mixture of di and mono alkylated diketoester (**3.38/3.39**) was derived from 2,4-pentanedione (**3.37**). The mixture of isomers (**3.38/3.39**) was treated with Noyori's catalyst[62] under hydrogen transfer conditions (HCO_2H, Et_3N), which provided lactone (**3.40**) after six days in 48% yield, with 4:1 diastereoselectivity. Further manipulation of the lactone (**3.40**) provided Narasaka's intermediate, the mesylate (**3.41**), which is a known precursor to (+)-stemoamide (**3.1**).



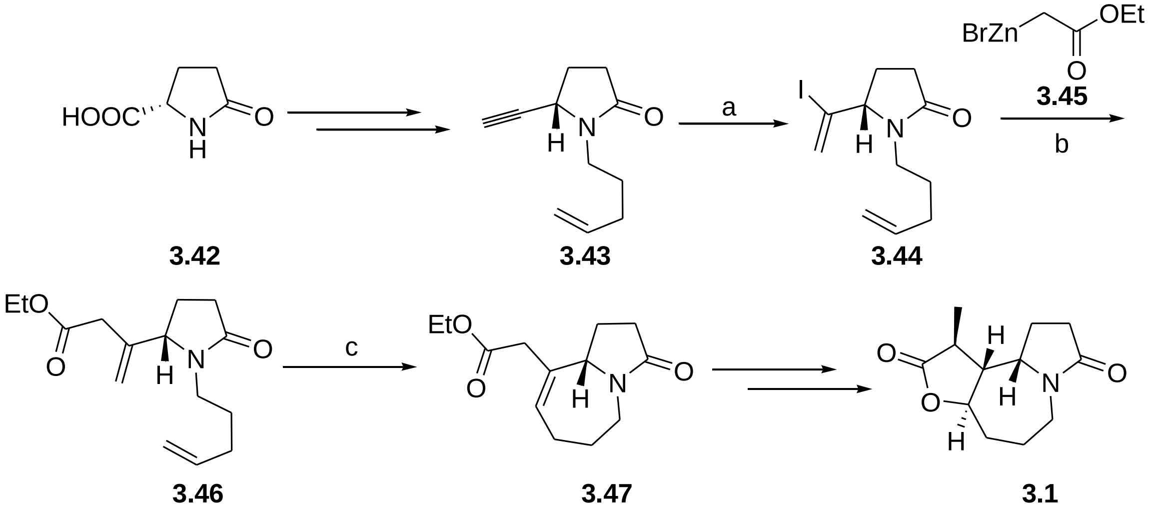
Scheme 3.7. Selected steps from Cossy's synthesis of (+)-stemoamide

Reagents and conditions: a) HCO_2H, Et_3N, RT, 6 days, 48%.

The highlight of both of Cossy's both approaches is the use of simple starting materials to construct the stemoamide (**3.1**). Although in the radical approach the key radical reaction resulted in low yield, excellent diastereoselectivity was achieved with the control of the three of the four streocenteres.

3.2.6. Somfai's approach

Somfai and co-workers described a stereocontrolled total synthesis of (-)-stemoamide in 2007 (**Scheme 3.8**).[59e] The key enyne intermediate (**3.43**) was derived from (-)-pyroglutamic acid (**3.42)**. A chemoslective iodoboration of the alkyne in the presence of the alkene was achieved, using *B*-I-9-BBN at low temperature to afford the vinyliodide (**3.44**). Negishi cross coupling of the vinyliodide (**3.44**) with a Reformatsky nucleophile (**3.45**) provided diene (**3.46**). On subsequent treatment of diene intermediate (**3.46**) with Grubbs 2nd generation catalyst, metathesis proceeded smoothly, to give alkene (**3.47**) in 92% yield. Further manipulation of the alkene (**3.47**) provided the lactone which was methylated, employing Narasaka's conditions to give (-)-stemoamide (**3.1**).The highlight of the synthesis is the sp^2–sp^3 Negishi cross coupling to form the C-C bond and selective iodoboration.

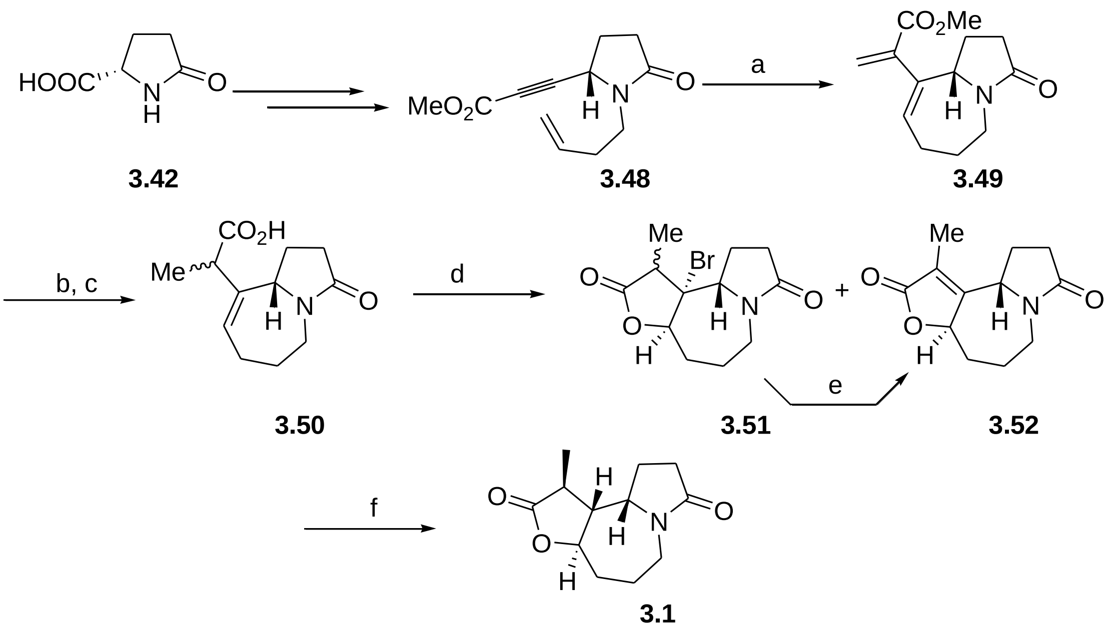


Scheme 3.8. Selected steps from Somfai'ssynthesis of (-)-stemoamide

Reagents and conditions: a) *B*-I-9-BBN, CH_2Cl_2/Hexane, - 20 °C, 72%; b) $Pd(PPh_3)_4$, THF/DMPU, 50 °C, 78%; c) 5 mol% of Grubbs' 2nd generation, CH_2Cl_2, 40 °C, 92%.

3.2.7. Mori's approach

In 1996, Mori and Kinoshita reported an elegant method for the synthesis of (-)-stemoamide (**3.1**) (**Scheme 3.9**).[59f] Their strategy demonstrated an intramolecular enyne metathesis and the stereoselective reduction of the butenolide. The key intermediate enyne (**3.48**) was derived from (-)-pyroglutamic acid (**3.42**) in 8 steps. On treatment of the enyne intermediate (**3.48**) with Grubbs' 1st generation catalyst, ene-yne metathesis proceeded smoothly, to afford the diene (**3.49**) in 87% yield. The regioselective reduction of the α,β-double bond and subsequent hydrolysis of the ester furnished the unsaturated carboxylic acid (**3.50**). Bromolactonization of the unsaturated carboxylic acid (**3.50**) in the presence of Al_2O_3, proceeded *via* 5-*endo-trig* cyclisation, and provided bromolactone (**3.51)** and butenolide (**3.52**) in yields of 25% and 31% respectively. Under basic conditions, the bromolactone (**3.51**) was converted into the butenolide (**3.51**). Employing Jacobi's method,[63] the stereoselective reduction of the butenolide (**3.52**) was achieved with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ successfully providing (-)-stemoamide (**3.1**) in 48% yield. The key feature of Mori's approach is the first use of enyne metathesis in natural product synthesis.

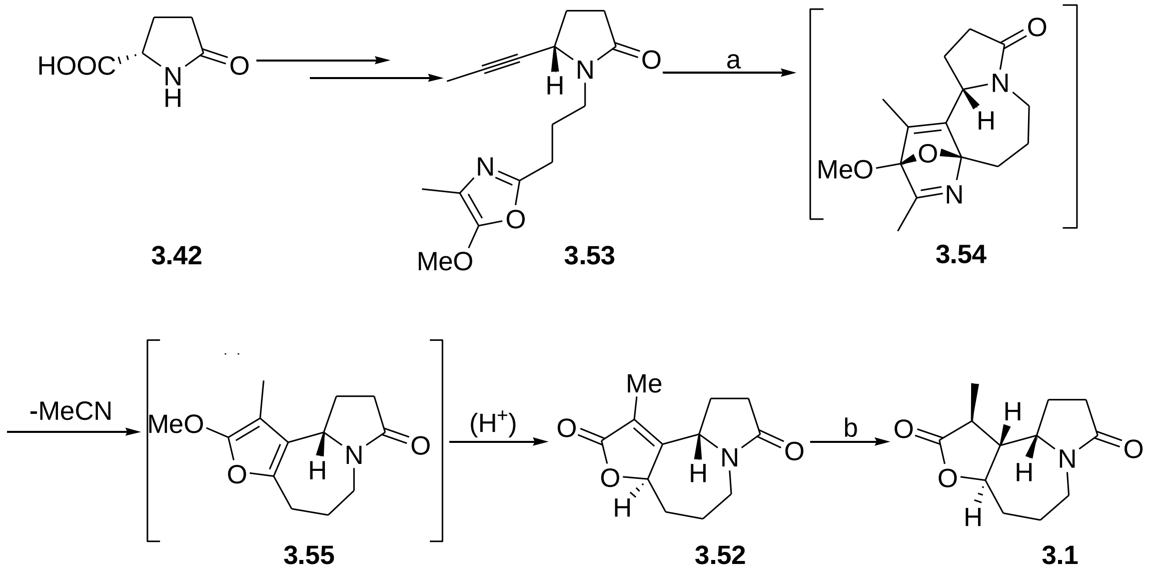


Scheme 3.9. Selected steps from Mori’s synthesis of (-)-stemoamide

Reagents and conditions: a) 4 mol% of Grubbs' 1st generation, CH_2Cl_2, RT, 87%; b) $NaBH_4$, MeOH, 0 °C to RT, 2 h, 85%; c) NaOH, MeOH/H_2O, 0 °C, 7 h; d) $CuBr_2$ on Al_2O_3, $CHCl_3$, 65°C, 60 h; e) Et_3N, EtOAc, RT, 14 h, 50% ; f) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, -30 °C, 1.6 h, 48%.

3.2.8. Jacobi’s approach

Jacobi and Lee described an exceptional method for the synthesis of (-)-stemoamide in 9 steps with an overall yield of 4% (**Scheme 3.10**).[59g]Their strategy demonstrated an elegant intramolecular (Diels-Alder)-(*retro*-Diels-Alder) reaction. The key intermediate, alkyne oxazole (**3.53**), was efficiently prepared from (-)-pyroglutamic acid (**3.42**) in 7 steps. At a very high temperature (182 °C) in diethylbenzene, the intramolecular [4+2] cycloaddition of the oxazole and the alkyne and tandem retro-cycloaddition, proceeded to give the butenolide (**3.52**) in 53% yield. Subsequently, butenolide (**3.52**) was reduced with the nickel boride catalyst derived from $NaBH_4$ and $NiCl_2$ to give (-)-stemoamide (**3.1**) in 73% yield. The key aspect of this synthesis is the implementation of an intramolecular Diels-Alder reaction to construct the entire skeleton in a single step.



3.42 **3.53** **3.54**

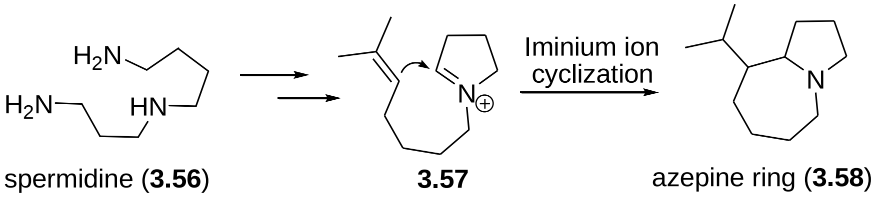
3.55 **3.52** **3.1**

Scheme 3.10. Selected steps from Jacobi's synthesis of (-)-stemoamide

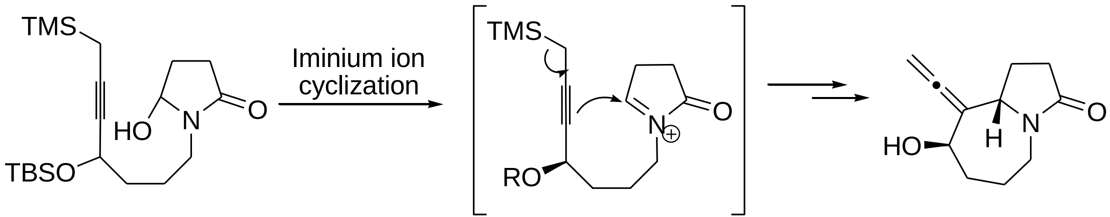
Reagents and conditions: a) Diethylbenzene, 182 °C, 53%; b) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH, - 30 °C, 1.6 h, 73%.

3.2.9. Ran Hong'sapproach

During the writing of this thesis, Hong *et al*. described a biomimetic approach to (±)-stemoamide (**3.1**) in 8 steps (**Scheme 3.13**).[59h] In 2004, Seger *et al.,*[64] proposed that the azepine ring (**3.58**) formation was *via* a iminium-ion (**3.57**) from a putative precursor spermidine (**3.56**) (**Scheme 3.11**). Based on this proposal, Hong *et al*. demonstrated the formation of the azepine (**3.61**) through intramolecular cyclization of the propargylsilane (**3.59**) with an iminium ion (**3.60**) (**Scheme 3.12**).



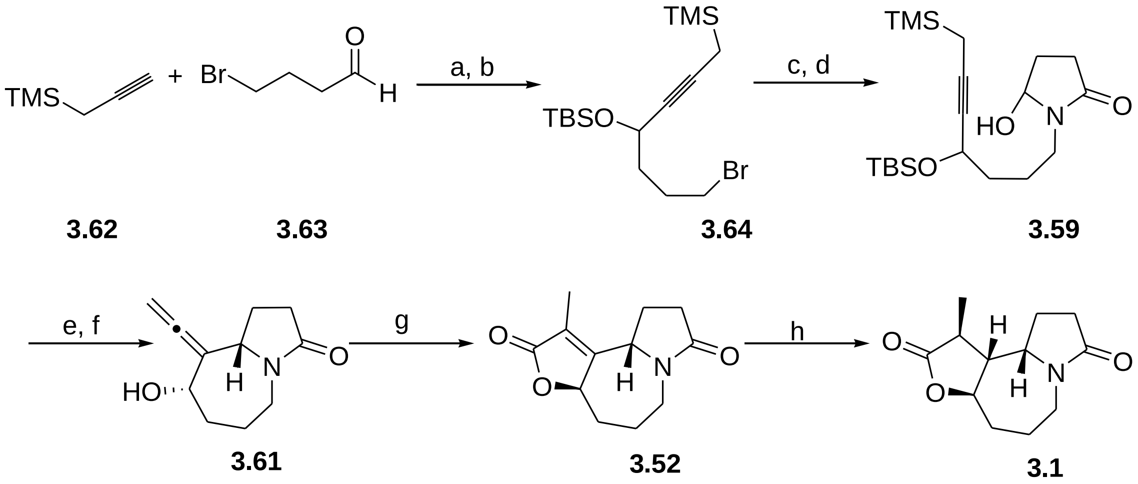
Scheme 3.11. Seger's biosynthesis from spermidine



3.59 **3.60** **3.61**

Scheme3.12. Hong's biomimetic approach to (±)-stemoamide

The lithium derivative of propargyl trimethylsilane (**3.62**) reacted with bromoaldehyde (**3.63**) to give the propargyl alcohol, which was subsequently protected as a TBS ether (**3.64**) (**Scheme 3.13**). Succinimide (**3.65**) was reacted with TBS ether (**3.64**) in the presence of NaH, to furnish the imide, and subsequent reduction of the imide with $NaBH_4$ afforded the hemiaminal (**3.59**) in good yield. Treatment of hemiaminal (**3.59**) with anhydrous $FeCl_3$ in toluene, afforded the alcohol in a yield of 86% with 3:1 diastereoselectivity. Subsequent deprotection furnished the allenol (**3.61**) in 96% yield. By comparison with the ^{1}H NMR data of our allenol (**3.66**) and X-ray crystallography of their allenol (**3.61**), the stereochemistry of the major diastereomer of was found to be *cis*, which was the opposite to that of the natural product. Serendipitously, under Takahashi's conditions,[3] treatment of allenol (**3.61**) with triruthenium dodecacarbonyl in triethylamine as solvent under a pressure of 147 psi of CO, resulted in epimerization of the *cis* allenic alcohol (**3.61**) through *β*-hydride elimination, which gave the *trans* butenolide (**3.52**) in 83% yield, which corresponded to the natural product.

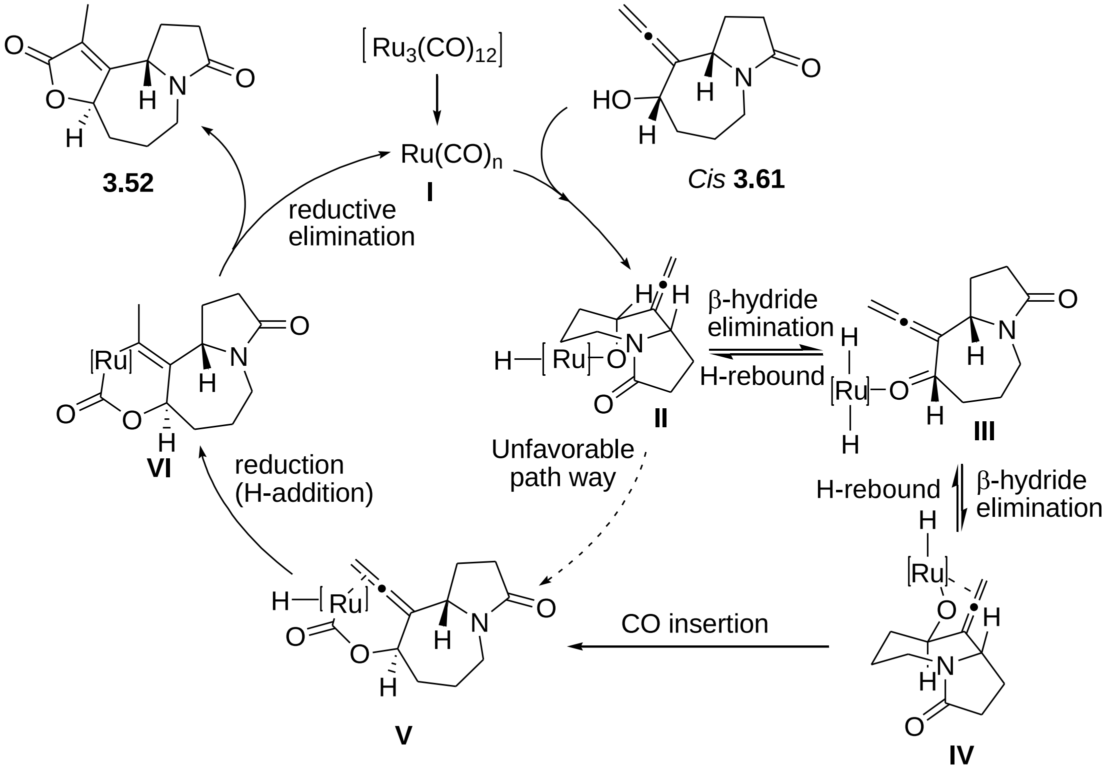


Scheme 3.13. Hong's synthesis of (±)-stemoamide

Reagents and conditions: a) *n*-BuLi, THF, -78 °C, 93%; b) TBSCl, DBU, CH_2Cl_2, RT, 87%; c) succinimide (**3.65**), K_2CO_3, DMF, RT; d) $NaBH_4$, EtOH, 0 °C, 93% (two steps); e) $FeCl_3$, toluene, 0 °C, 86%; f) TBAF, THF, 96%; g) [$Ru_3(CO)_{12}$], CO (147 psi), Et_3N, 81%; h) $NaBH_4$, $NiCl_2$, MeOH, 74%.

Hong proposed a mechanism for his observation in the carbonylation step (**Scheme 3.14**). The first step of the reaction is the coordination of the ruthenium complex with hydroxyl group to afford the *cis* complex (**II**) which is in contrast with the original mechanism proposed by Takahashi (**Scheme 2.17**, chapter 2).3 Due to the weak interaction between the allene moiety and the metal centre in the *cis* complex, *β*-hydride elimination is favoured to give the ketone intermediate (**III**). Subsequent H-rebound leads to the corresponding *trans* complex (**IV**), which has a favourable conformation to promote CO insertion followed by reductive elimination giving the *trans* butenolide

(**3.52**). However, in this proposed mechanism the exact role of triethyl amine is unclear. It may also be noted that Takahashi proposed that the ruthenium remains trinuclear.3

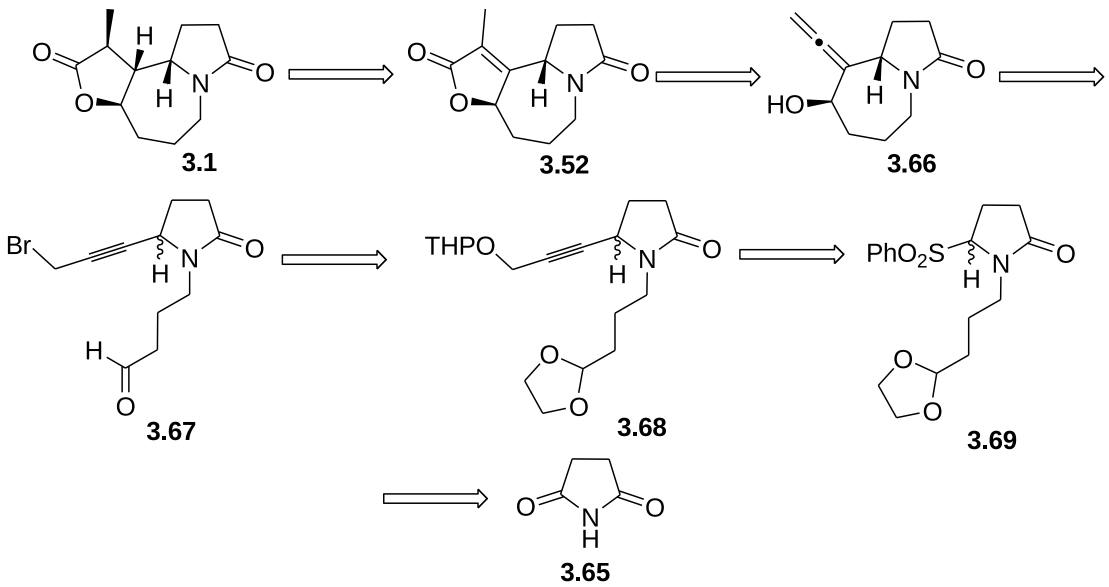


Scheme 3.14. Hong's proposed mechanism for carbonylation

Finally, employing Jacobi's method,[63] the stereoselective reduction of the butenolide (**3.52**) was achieved providing (±)-stemoamide (**3.1**) in 74% yield (**Scheme 3.13**). The highlight of the synthesis is the biomimetic approach and the synthesis was achieved employing 8 steps and overall yield of 37%. However, only the azepine formation can be claimed to be biomimetic, although, biosynthetically, the iminium ion is intercepted by an alkene, not a propargylsilane.

3.3. Retrosynthesis analysis of (±)-stemoamide

In chapter 2, we had demonstrated a highly diastereoselective synthesis of (-)-mintlactone (**2.1**), through the implementation of an intramolecular propargylic Barbier reaction as the key step. To further demonstrate the versatility of this methodology, (±)-stemoamide (**3.1**) was chosen as a suitable target molecule. Our retrosynthetic analysis of (±)-stemoamide is depicted in **Scheme 3.15**. By employing Jacobi's protocol, the stereoselective reduction of the butenolide (**3.52**) to (±)-stemoamide (**3.1**), would be the final step for our synthesis.[63,59g]Thus, our retrosynthetic plan for (±)-stemoamide (**3.1**) involves forming the butenolide (**3.52**) by the Barbier-cyclocarbonylation sequence. The main challenge in the synthesis is the stereoselective formation of the azepine moiety (**3.66**), which would be constructed by the intramolecular propargylic Barbier reaction. The Barbier precursor (**3.67**) would be synthesised from propargyl dioxolane (**3.68**), by means of a series of functional group transformations. Propargyl dioxolane (**3.68**) could be prepared from sulfone (**3.69**) under the conditions described by Ley *et al*.[73] For studies in the racemic series, the iminium ion precursor sulfone (**3.69**)will be prepared from succinimide (**3.65**).

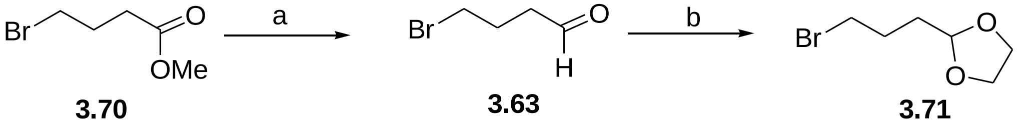


Scheme 3.15. Retrosynthetic analysis of (±)-stemoamide

3.4. Results and discussion

3.4.1. Synthesis of bromo-dioxolane (3.71)

Our initial plan was the synthesis of the Barbier precursor, which is the bromoaldehyde (**3.67**) (**Scheme 3.27**). This was constructed starting with commercially available succinimde (**3.65**). The required side chain unit bromo-dioxolane (**3.71**)was efficiently prepared from the methyl-4-bromobutanoate (**3.70**) (**Scheme 3.16).** Treatment of methyl-4-bromobutanoate (**3.70**) with DIBAL-H in dry dichloromethane at a carefully controlled temperature (-78 °C) provided 4-bromobutanal (**3.63**)in a yield of 84%, which was used without further purification.[65] Careful temperature control of the reaction conditions was required, during addition of DIBAL-H, in order to prevent over reduction of the ester to the alcohol.



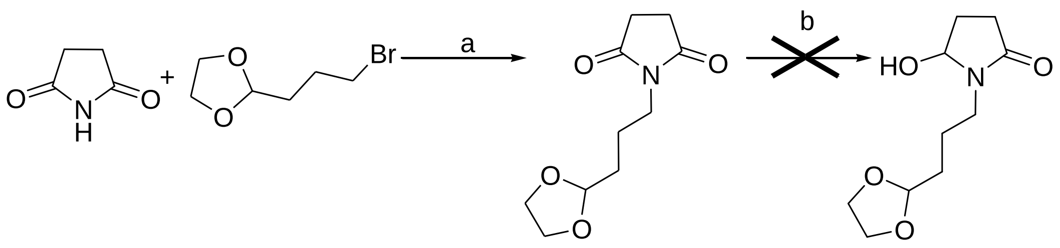
Scheme 3.16.

Reagents and conditions: a) DIBAL-H (1.3 eq.), dichloromethane, -78 °C, 10 mins., 84%; b) 1,2-ethylene glycol (3 eq.), *p*-TsOH, toluene, reflux, 1.5 hours, 73%.

In the presence of *p*-TsOH, 4-bromobutanal (**3.63**)was protected as its 1,3-dioxolane, by reaction with ethylene glycol in toluene at reflux, using a Dean-Stark apparatus, to afford the bromo-dioxolane (**3.71**) in 73% yield after purification (**Scheme 3.16**). In the ^{1}H NMR spectra, the disappearance of the aldehyde peak at 9.81 ppm and the appearance of the acetal proton at 4.9 ppm and multiplet between 3.98-3.81 ppm for the dioxolane methylene protons confirmed the formation of the bromo-dioxolane (**3.71**).

3.4.2. Attempted synthesis of ethyllactam (3.73)

Initially, we planned to synthesize the hydroxylactam (**3.73**), by an *N*-alkylation/reduction sequence, but it was unsuccessful (**Scheme 3.17**). Our initial *N*-alkylation was carried out by treatment of succinimde (**3.65**) withbromo-dioxolane (**3.71**) in the presence of sodium hydride in DMF at room temperature to provide the imide (**3.72**) in 78% yield, which was used without further purification. The presence of strong absorption band at 1701 cm^{-1} for the carbonyl group in the IR spectrum and in the ^{1}H NMR spectrum, the appearance of a triplet at 4.79 ppm (1H, t, J = 4.0 Hz), indicated the acetal proton and a singlet displayed at 2.62 ppm (4H) for the succinimide protons confirmed the product formation. Attempts to reduce the imide (**3.72**) were not successful. Using Speckamp's method,[66] treatment of imide (**3.72**) with $NaBH_4$ in ethanol in the presence of 2 N HCl at -10 °C, no reaction was observed. When the temperature was increased to room temperature, a complex mixture was isolated along with some starting imide (**3.72**). We attribute this to over reduction of the amide or cleavage of the acid sensitive dioxolane under the acidic conditions.

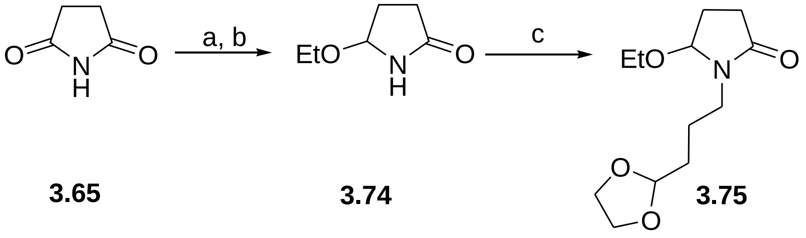


3.65 **3.71** **3.72** **3.73**

Scheme 3.17.

Reagents and conditions: a) NaH, DMF, RT, 78%; b) $NaBH_4$ (1 eq.), ethanol, -10 °C.

We then turned our attention to an alternative sequence, reduction followed by *N*-alkylation (**Scheme 3.18**). Regioselective reduction of succinimide (**3.65**) was achieved with an excess of sodium borohydride in ethanol at -5 °C under Speckamp's conitions.[66] At regular intervals of 15 minutes, 5 drops of 2N HCl were added to the reaction mixture. Addition of 2 N HCl is to form a reactive di-borane species.[67] After 5 hours stirring at the same temperature, the reaction mixture was acidified to pH ~ 2 with 2 N HCl, followed by basic workup, and lactam (**3.74**) was obtained in 61% yield in a one-pot reaction.



3.65 **3.74** **3.75**

Scheme 3.18.

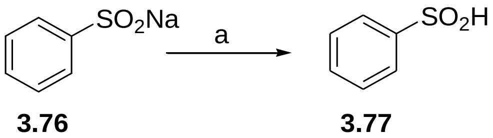
Reagents and conditions: a) $NaBH_4$ (1.5 eq.), ethanol, -5 °C, 5 h; b) 2N HCl, 2 h, 61% (two steps) c) cpd-**3.71,** *n*-BuLi, THF-DMSO, - 78 °C to RT, 18 h.

Treatment of lactam (**3.74**) withbromodioxolane (**3.71**) in the presence of sodium hydride in DMF at room temperature providedthe amide (**3.75**), in a moderate yield of

60% after purification, along with both starting materials. In order to improve the yield, the procedure was modified.[68] Efficient *N*-alkylation was cleanly achieved in a yield of 92% by deprotonation using *n*-BuLi in THF, followed by alkylation with the bromodioxolane in DMSO to afford the lactam (**3.75**) which was used without purification. The use of the highly polar solvent DMSO was to enhance the rate of the reaction by encouraging coordination of the lithium salt.*N*-Alkylation was confirmed from the loss of the broad NH band in the IR spectrum. The ^{1}H NMR spectrum displayed a triplet at 4.87 ppm (J = 4.2 Hz) corresponding to the aminal proton, while the ^{13}C NMR spectrum displayed the presence of a quaternary carbonyl carbon at 174.9 ppm.

3.4.3. Synthesis of sulfone (3.69)

In order to generate an iminium ion under mild conditions in the presence of the acid sensitive dioxane, it was necessary to replace the ethoxy group with a good leaving group such as sulfonyl (**Scheme 3.19**). Initially, preparing the sulfone (**3.69**) in good yield was found to be a difficult task. Several reaction conditions were screened, including the amount of benzenesulfinic acid, the temperature and the time (**Table 3.1**). Benzenesulfinic acid is unstable. Hence, the required benzenesulfinic acid (**3.77**) was freshly prepared by acidification of sodium benzenesufinate (**3.76**) (**Scheme 3.19**).[69]

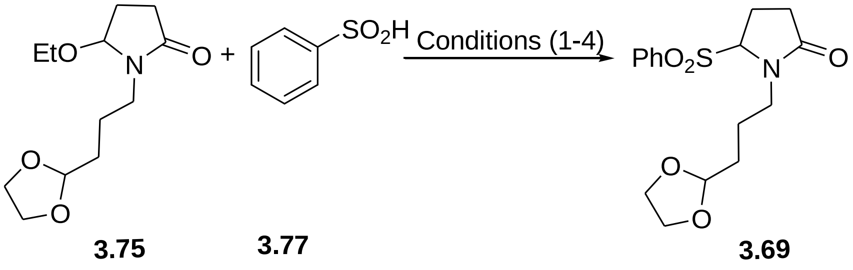


Scheme 3.19.

Reagents and conditions: a) 2 N HCl, RT, 2 h, 99%.

The ethoxy group of lactam (**3.75**) was substituted by sulfinate using benzenesulfinic acid (**3.77**) in the presence of $CaCl_2$ in dry dichloromethane at room temperature, affording the sulfone (**3.69**) in only a low yield of 41% after 3 hours, along with 20% of starting material after purification (**Scheme 3.20**) (**Table 3.1**, entry 1). The ^{1}H NMR spectrum of the sulfone (**3.69**) displayed a doublet of doublets at 4.75 ppm (1H, J = 7.0, 1.0 Hz) for the aminal proton. A multiplet was observed between 7.89–7.55 ppm for the five aromatic protons. In the IR spectrum, the presence of characteristic absorption bands for the sulfinyl group at 1303 and 1131 cm^{-1} confirmed the product formation.

It was thought that increasing the reaction time would improve the yield of sulfone. However, when the reaction time was prolonged to 24 hours, only 20% of product was obtained with remaining material decomposing (entry 2). Increasing the amount of benzenesulfinic acid (**3.69**) (2.5 eq.) resulted in a low yield of 26% (entry 3). Lowering of the temperature to 0 °C, under the same conditions, afforded the sulfone (**3.69**) in a very low yield of 10% (entry 4).



3.75 **3.77** **3.69**

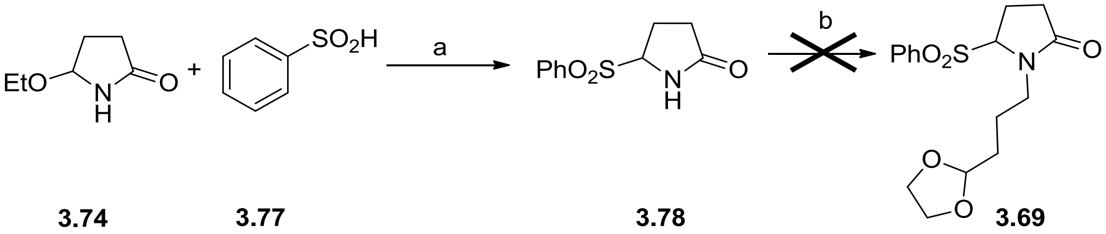
Scheme3.20.

Table 3.1.

Entry	Conditions	Time/h	Temp/°C	Yield/%
1	Cpd -**3.77**(1.3 eq), $CaCl_2$, CH_2Cl_2	3	RT	41
2	Cpd-**3.77**(1.3 eq), $CaCl_2$, CH_2Cl_2	24	RT	20
3	Cpd-**3.77** (2.5 eq), $CaCl_2$, CH_2Cl_2	2	RT	26
4	Cpd-**3.77** (1.3 eq), $CaCl_2$, CH_2Cl_2	16	0	10

Upon careful analysis of the crude ^{1}H NMR spectrum, a peak at 9.71 ppm indicative of a minute amount of aldehyde was observed. We attribute this to the deprotection of dioxolane group. Based on our results and spectroscopic data, we initially believed that the acid sensitive dioxolane group may not be stable under the acidic conditions (benzenesulfinic acid $pK_a = 3.5$).[70]

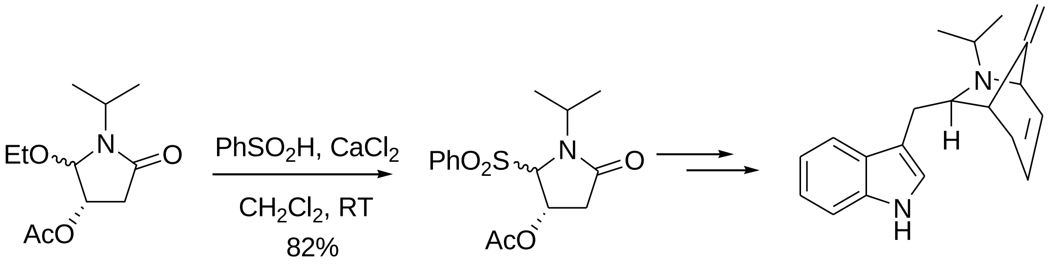
As a result, the alternative sequence, sulfonation followed by *N*-alkylation was then investigated (**Scheme 3.21**). The amide (**3.41**) was treated with benzenesulfinic acid (**3.77**) in the presence of $CaCl_2$ in dry dichloromethane at room temperature, affording the sulfone-amide (**3.78**) in moderate yield of 55% yield after 5 hours. In contrast, the *N*-alkylation of sulfone-amide (**3.78**) with bromodioxolane (**3.71**) under same conditions used to prepare the lactam (**3.75**) (**Scheme 3.17**), failed and only gave a complex mixture of unidentifiable compounds.



Scheme 3.21.

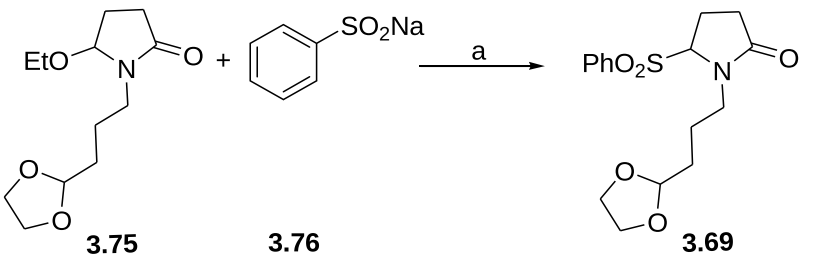
Reagents and conditions: a) $CaCl_2$, CH_2Cl_2, 5 h, 55%; b) bromodioxolane (**3.71**), *n*-BuLi, THF-DMSO, - 78 °C to RT, 18 h.

A careful search of literature precedents in sulfone chemistry, with special interest in natural product synthesis, was therefore made. Fortunately, it revealed that a synthesis of (-)-peduncularine (**3.81**) by Martin, who specifically states that the importance of the "quality" of the benzenesulfinic acid was essential to the success or failure of the reaction (**Scheme 3.22**).[71]



Scheme 3.22. Martin's synthesis of (-)-peduncularine

Encouraged by Martin's report, we decided to use the pure form of benzenesulfinic acid (**3.77**) in our reactions. One way to obtain a pure form of the benzenesulfinic acid (**3.77**) is to recrystallize the benzenesulfinic acid (**3.77**). Another method is to generate the acid *in situ* from its sodium salt (**3.73**).The *in situ* preparation was considered to be more practical and more convenient and, therefore, was chosen.



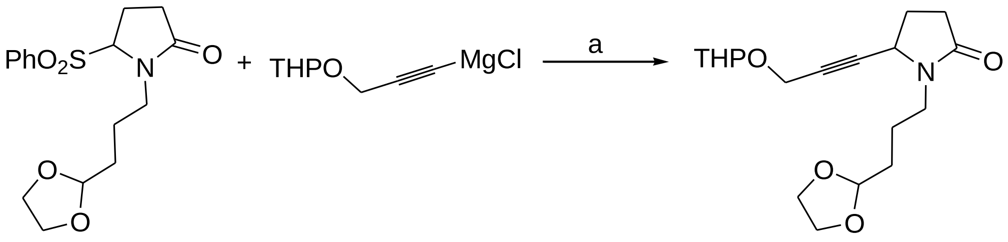
Scheme 3.23.

Reagents and conditions: a) TFA, $MgSO_4$, CH_2Cl_2, 5 h, RT, 92%.

To our delight, substitution was cleanly achieved with excellent yield, according to the method of Moeller(**Scheme 3.23**).[72] Treatment of ethyl-lactam (**3.75**) with sodium benzenesufinate (**3.76**) in the presence of TFA and magnesium sulfate in dry dichloromethane at room temperature, afforded the sulfone (**3.69**) in 92% yield, which was used without further purification.

3.4.4. Synthesis of propargyldioxolane (3.68)

Proceeding forward, displacement of sulfinate by the acetylide anion of the THP ether of propargylic alcohol was then carried out according to the method of Ley *et al* (**Scheme 3.24**).[73] Treatment of the iminium ion precursor sulfone (**3.69**) with the acetylenic Grignard (**3.82**) derived from *i*-PrMgCl and zinc bromide in THF, furnished the alkyne-dioxolane (**3.68**)in 72% yield after purification. In the ^{1}H NMR spectrum, the appearance of a broad singlet at 4.73 ppm indicate the acetal proton of the THP ether. Furthermore the ^{13}C NMR spectrum showed the presence of alkynyl carbons of the alkyne at 83.4 and 81.2 ppm, thus confirming the product formation.



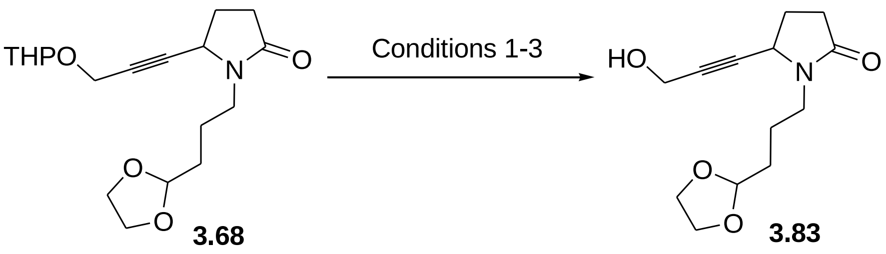
3.69 **3.82** **3.68**

Scheme 3.24.

Reagents and conditions: a) *i*-PrMgCl, $ZnBr_2$, THF, 0 °C to RT, 4 h, 72%.

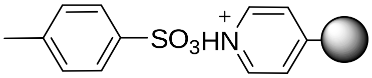
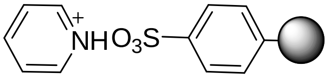
3.4.5. Selective deprotection of THP ether

From this point, a series of functional group transformations set the stage for the intramolecular Barbier reaction (**Scheme 3.28**). Under mild conditions, employing Roy's method, the THP ether of (**3.68**) was selectively removed in the presence of the dioxolane (**Scheme 3.25**).[74] Selective deprotectionof (**3.68**) proceeded smoothly in the presence of pyridinium *p*-toluenesulfonate (PPTS) in dry methanol to afford the alcohol-dioxolane (**3.83**) in a moderate 60% yield (entry 1). In the IR spectrum, the presence of a broad bandat 3398 cm^{-1} indicated the presence of the OH functionality, while in the ^1H NMR spectrum, the appearance of a triplet at 4.83 ppm (1H, t, $J = 4.0$ Hz) for the acetal proton with a mulptiplet at 3.95-3.73 ppm indicative of the dioxolane protons, which further confirmed the formation of our desired product.



Scheme 3.25.

Table 3.2.

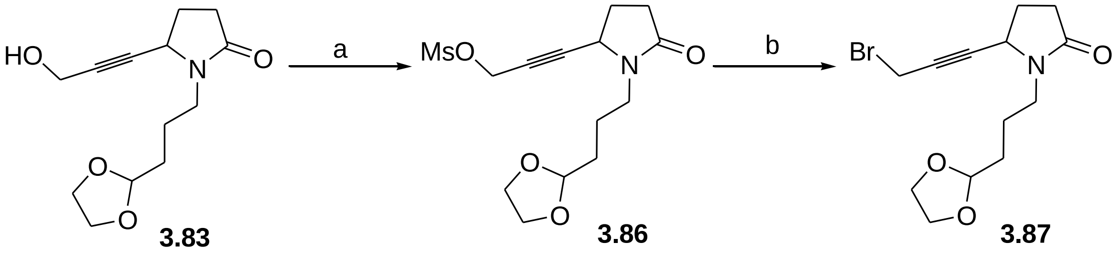
Entry	Conditions	Time (h)	Yield (%)
1	PPTS, CH$_3$OH	10	60
2	 [PS-PPTS (**A**) (**3.84**)], CH$_3$OH	8	99
3	 [PS-PPTS (**B**) (**3.85**)], CH$_3$OH	10	0[a]

a: starting material recovered.

Although the reaction was very clean by TLC, the yield was moderate. In part, this was due to the hydrophilic nature of the propargyl alcohol-dioxolane (**3.83**), which rendered it difficult to isolate. when employing an aqueous work up. In order to improve the yield, we decide to use a solid supported resin as a method to simplify the workup procedure.[75] The advantage of using the resin is to avoid an aqueous workup as simple filtration can remove the resin. A polymer supported version of PS-PPTS (**A**) (**3.84**) was prepared by treatment of poly-4-vinyl pyridine with *p*-TsOH in dichloromethane. To our delight, treatment of alkyne-dioxolane (**3.68**) with PPTS resin (**A**) (**3.84**) in anhydrous methanol at room temperature cleanly furnished the propargyl alcohol-dioxolane (**3.83**) in quantitative yield. Curiously, the alternative polymer supported resin PS-PPTS (**B**) (**3.85**) prepared from amberlyst-15 and pyridine was found to be non reactive. Treatment of alkyne-dioxolane with resin (**3.85**) in dry methanol at room temperature gave no product and only starting material was recovered.

3.4.6. Synthesis of bromoaldehyde (3.67)

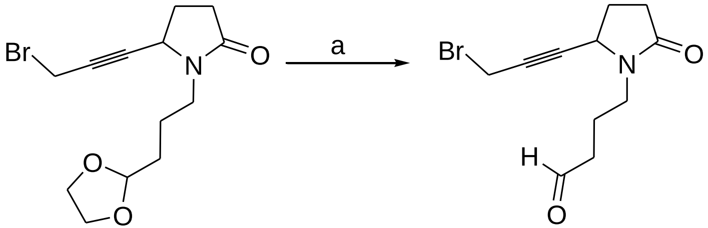
The propargyl alcohol-dioxolane (**3.83**) was treated with methanesulfonyl chloride in the presence of triethylamine in dry dichloromethane at 0 °C to provide mesylate (**3.86**) in quantitative yield (**Scheme 3.26**). Formation of the methanesulfonyl-dioxolane (**3.86**) was confirmed from the IR spectrum with the absence of the broad absorption band at 3468 cm^{-1} for the hydroxyl group and the presence of the sulfonyl characteristic absorption bands at 1349 and 1169 cm^{-1}. In the ^{1}H NMR spectra, a singlet was observed for the sulfonyl methyl group at 3.0 pm, which confirmed the formation of product.



Scheme 3.26.

Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; b) LiBr, THF, RT, 99%.

Displacement of the methanesulfonate of (**3.86**) with lithium bromide in THF proceeded smoothly to afford the bromo-dioxolane (**3.87**) in quantitative yield and it was subjected to the next step without purification (S**cheme 3.26**). The ^{1}H NMR spectrum displayed the absence of methane sulfonyl group at 3.0 ppm and the presence of a doublet at 3.90 ppm (2H, *J* = 1.9 Hz) for the bromo attached methylene protons, which confirmed the formation of our desired product (**3.67**).



3.87 **3.67**

Scheme 3.27.

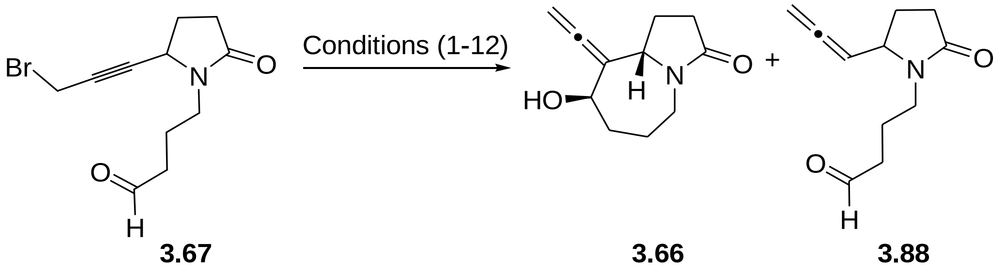
Reagents and conditions: a) *p*-TsOH, Acetone-THF, RT, 47% over four steps.

Subsequent hydrolysis of the bromo-dioxolane (**3.87**) in the presence of *p*-TsOH in an acetone-water mixture resulted in the formation of the bromo-aldehyde (**3.67**) in an overall yield of 47% from propargyl-dioxolane (**3.68**) (**Scheme 3.27**). The formation of bromoaldehyde (**3.67**)was recognized from a singlet peak at 9.76 ppm for the aldehyde proton in the ^{1}H NMR spectrum and the presence of the aldehyde carbonyl peak at 201.7 ppm in the ^{13}C NMR spectra.

3.4.7. Synthesis of allenol (3.66)

With the bromo-aldehyde (**3.67**) in hand, our investigation continued with the key intramolecular Barbier reaction to construct the seven membered ring. The use of zinc, indium, bismuth, and stannous chloride all led to the formation of the desired allenol (**3.66**)with one of the two possible diastereomers predominating (**Scheme 3.28**). Employing Mukaiyama's conditions,[10] the bromo-aldehyde (**3.67**) was treated with stannous chloride in the presence of sodium iodide in wet DMF at 0 °C, providing the allenol (**3.66)** in a good yield of 80% (**Table 3.3**, entry 1) and in modest diastereoselectivity (80:20) as judged by the ^{1}H NMR analysis. These same conditions had proved to be optimum in our synthesis of (-)-mintlactone. Furthermore, lowering the reaction temperature to -10 °C, resulted in a decreased yield only with no significant change in diastereoselectivity (80:20) (entry 2).

Under Luche conditions,8treatment of bromoaldehyde (**3.67**) with zinc in the presence of NH_4Cl (sat.) in THF gave an excellent *dr* (95:5) but a low yield of 14% (entry 3).The ^{1}H NMR and ^{13}C NMR spectrum of the allenol (**3.66**) are shown inappendix (page 280). The formation of the allenol (**3.66**)was observed from the disappearance of the aldehyde group at 1717 cm^{-1} and the appearance of characteristic absorption band at 1954 cm^{-1}, indicating the allene group and a broad band at 3377 cm^{-1} for the hydroxyl group in the IR spectrum. This was further supported by the appearance of a triplet at 5.11 ppm (2H, t, *J* = 1.7 Hz) for the terminal protons of the allene in the ^{1}H NMR spectrumand characteristic peak for the central allene carbon at 203.7 ppm in the ^{13}C NMR spectrum.



Scheme 3.28.

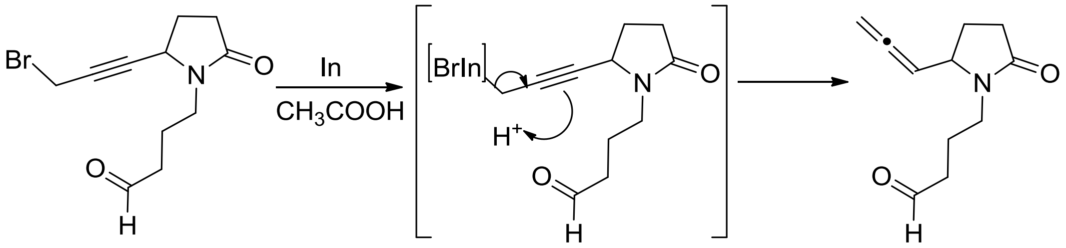
Table 3.3.

Entry	Conditions	Time/hr	T (°C)	Yield/%	dr
1	$SnCl_2$, NaI, DMF, H_2O^a	18	0	81	80:20
2	$SnCl_2$, NaI, DMF, H_2O^a	18	-10	60	80:20
3	Zn, NH_4Cl	12	0	14	≥95:5
4	Bi, DMF or DMF, H_2O^a	18	RT	0	-
5	Bi, DMF, AcOH, $H_2O^{a,b}$	20	RT	22	86:14
6	In, THF	20	RT	34	≥95:5
7	In, THF, AcOH, $H_2O^{a,b}$	12	0	70	91:9
8	In, THF, AcOH, $H_2O^{a,b}$	24	-20	82	94:6
9	In, THF, AcOH, $H_2O^{a\ b}$	24	-40	0	-
10	In, AcOH, $H_2O^{c,d}$	12	-5	50	≥95:5
11	In, DMF	16	RT	53	91:9
12	In, DMF, H_2O^e	16	RT	51	91:9

[a] DMF-H_2O or THF-H_2O = 8:1; [b] AcOH (4 eq.); [c] AcOH-H_2O = 4:1; [d] 20 % of allene-aldehyde (**3.88**) isolated; [e] DMF-H_2O = 1:8.

The use of indium was considered to be the best for the cyclisation reaction. Treatment of bomoaldehyde (**3.67**) with indium in THF at RT, gave an excellent dr (95:5), but a low yield of 14% (entry 6). Gratifyinglyusing Kang's conditions, with the addition of acetic acid in wet THF (5 eq.) at 0 °C, resulted in an increased yield of 73% with excellent *dr* (91:9) (entry 7).7 The optimum conditions for cyclisation were found to be the use of indium in the presence of acetic acid in wet THF at -20 °C, which resulted in an increased yield of 82% with excellent *dr* (94:6) (entry 8). On the other hand, further lowering of the temperature to -40°C, caused failure of the cyclisation and 30% of the starting material was recovered (entry 9). The reaction using indium in water or DMF, under the same conditions, resulted in a low yield only, but good *dr* (91:9) (entries 11, 12). Surprisingly, Kang *et. al.,* did not mention the importance of acetic acid in the intramolecular Barbier reaction.7We speculate that the role of acetic acid is to accelerate the reaction rate by a combination of protonation of the aldehyde carbonyl, coordination to indium and also to remove the oxide layer (80-100 angstroms) present on the indium surface.[76,77]

It was interesting to find that by replacing THF with acetic acid at -5 °C, gave excellent diastereoselectivity (95:5) (entry 10). However, only a moderate yield of 50% was achieved, concurrent with the formation of the allene-aldehyde (**3.88**) in 20% yield. The ^{1}H and ^{13}C NMR spectrum of the allene-aldehyde (**3.88**) are shown in figure 3.3. The allene-aldehyde (**3.88**) was identified from the appearance of the aldehyde group at 1714 cm^{-1} and a characteristic absorption band at 1956 cm^{-1}indicative of the allene functionality in the IR spectrum. In the ^{1}H NMR spectra, the assignment was further supported by the presence of a singlet at 9.76 ppm for the aldehyde and apparent quartet at 5.0 ppm (1H, *J* = 6.6 Hz) for the internal proton of the allene. The ^{13}C NMR spectra also proved this with the distinguishing peak for the centre carbon of the allene moiety at 209.0 ppm and peak at 201.5 ppm corresponded to the carbonyl carbon of the aldehyde. The formation of the allene-aldehyde (**3.88**) presumably is due to protonation of the organoindium intermediate (**Scheme 3.29**). This compound could also be isolated from some runs using zinc in a yield of 2%. The isolation of this by-product (**3.88**) indicated us that too much acid makes the protonation competitive with cyclisation.



3.67 **3.88**

Scheme 3.29. Possible mechanism for the formation of allene-aldehyde (**3.88**)

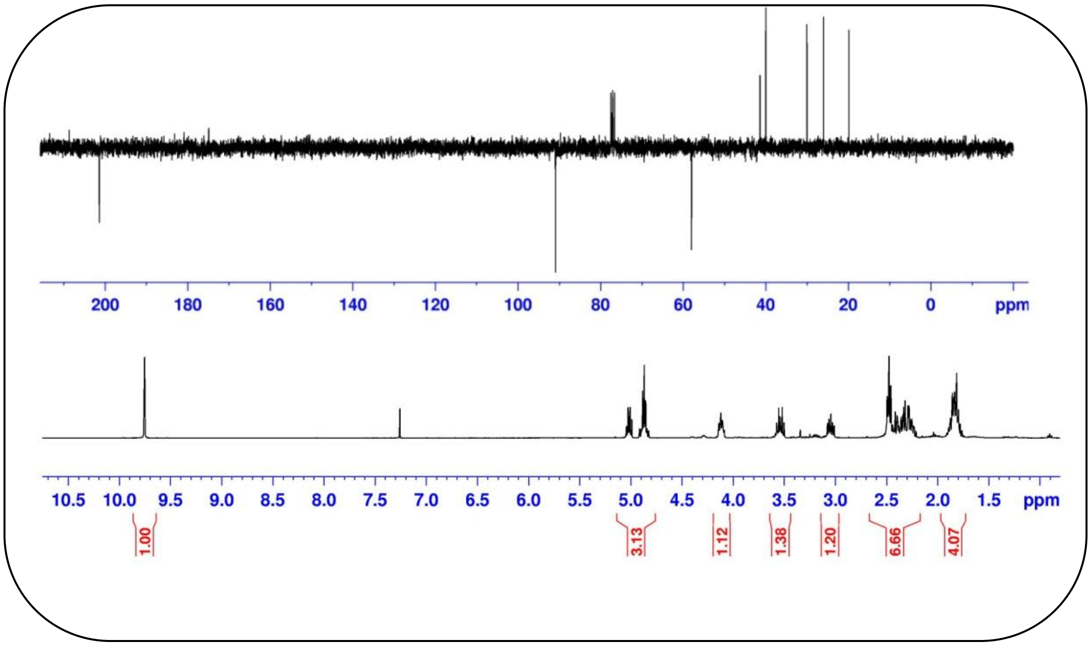


Figure 3.3 ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C (100 MHz, PENDANT, $CDCl_3$) NMR of allene-aldehyde (**3.88)**

Based on NOESY experiment we were unable to determine the relative stereochemistry. Fortunately, we were able to grow a single crystal of the major isomer. The X-ray crystallography[42] revealed that the relative stereochemistry of the two methyne protons is *trans*, which corresponds to the natural product (**Figure 3.4).**

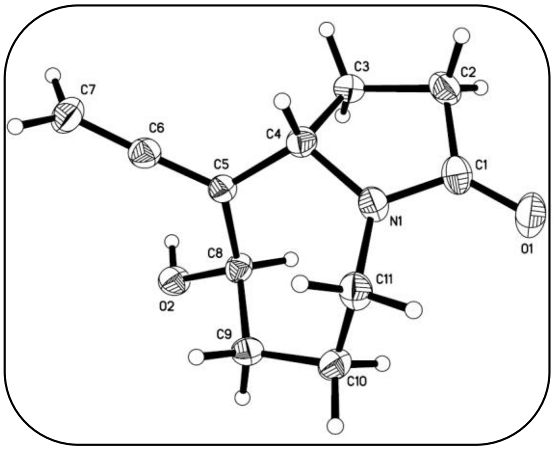
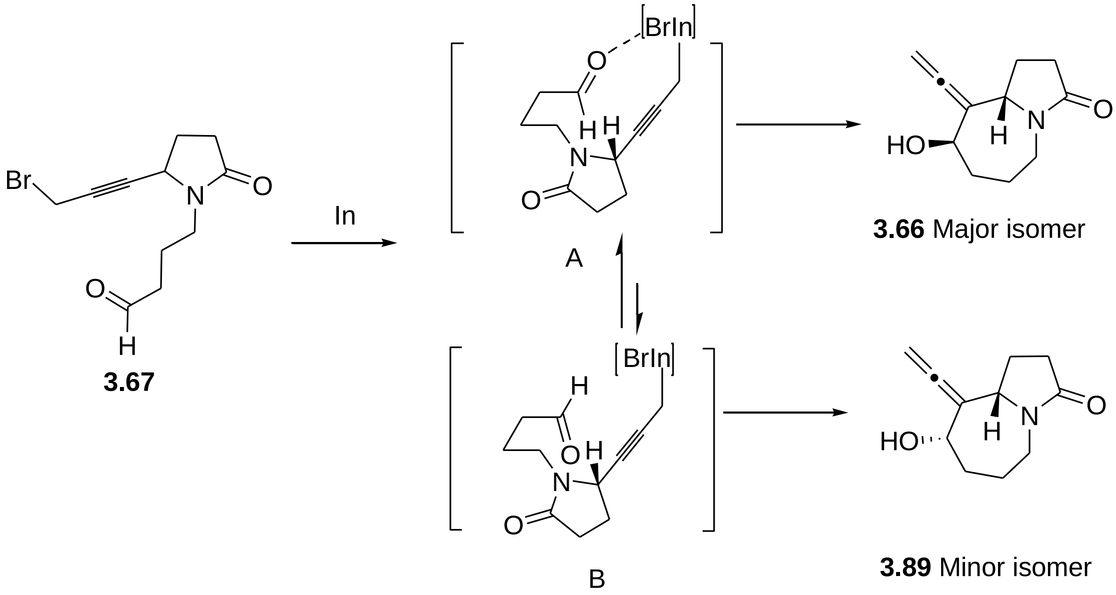


Figure 3.4 The X-ray structure of allenol **3.66**



Scheme 3.30. Rationale for *trans* selectivity in cyclisation

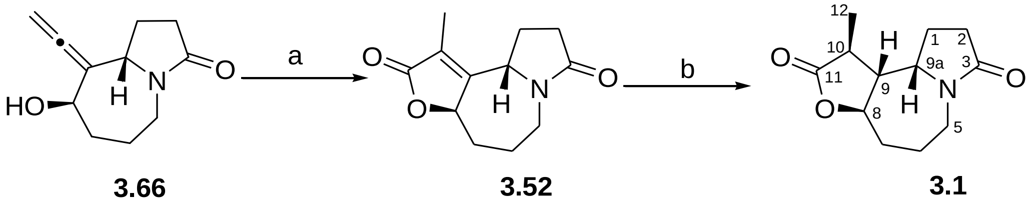
A possible mechanism for the formation of the *trans* and *cis* allenol isomer is shown in **Scheme 3.30**. Based on the work of Paquette and Andino, we speculate that the stereo selectivity is controlled by the oxophilic coordination of the indium atom to the carbonyl oxygen.[78] In a reaction mixture, two reasonable transition states **A** and **B** are possible. In a closed transition state **A**, coordination of the indium atom to the carbonyl oxygen is possible, which leads to *trans* allenol as a major isomer. In an open transition state **B**, the weak interaction between the indium atom and the carbonyl oxygen, would result in the *cis* allenol as a minor product. However, such intramolecular coordination in an alkyne system(**A** and **B**) is questionable.

3.4.8. Synthesis of (±)-stemoamide (3.1)

The final steps to complete the synthesis of the natural product (**3.1**) are illustrated in **Scheme 3.31**.Employing Takahashi's conditions,3 treatment of allenic alcohol (**3.66**)with triruthenium dodecacarbonyl in the presence of triethylamine under a pressure of 100 psi of CO, afforded the butenolide (**3.52**) in a yield of 81% without any epimerization. This is in contrast with Ran Hong's result.[59h] In the IR spectrum, the disappearance of the characteristic peak of the allene and hydroxyl group and the appearance of peak at 1745 cm^{-1} indicated the carbonyl group. The ^1H NMR spectra, showed a ddq at 4.86 ppm (1H, *J* = 11.6, 1.7 & 1.7 Hz) which was indentified as the oxygen attached methine proton. The ^{13}C NMR spectra displayed a peak at 174.1 ppm for the carbonyl group and peaks at 164.8 and 123.7 indicative of the two alkene carbons.

The synthesis was completed by the asymmetric reduction of the double bond, employing Jacobi's method.[58g,59f,63]Treatment of butenolide (**3.52**) with $NaBH_4$ in the presence of $NiCl_2$ at -30 °C, in methanol, provided (±)-stemoamide(**3.1**) and its epimer

(**3.90**) in a ratio of 6:1. After recrytallisation from EtOAc, (±)-stemoamide(**3.1**) was obtained in a yield of 55%. The ^{1}H NMR and ^{13}C NMR spectrum of (±)-stemoamide (**3.1**) are given in appendix (page 281).The spectroscopic data (^{1}H and ^{13}C NMR) of our synthetic material are in good agreement with that reported previously (**Table 3.4**) and further unambiguously characterised by X-Ray crystallography[42] (**Figure 3.5**).



Scheme 3.31. Synthesis of (±)-stemoamide

Reagents and conditions: a) $Ru_3(CO)_{12}$, Et_3N, CO (100 psi), dioxane, 100 °C, 14 h, 81%; b) $NaBH_4$, $NiCl_2$, MeOH, - 30 °C, 55%.

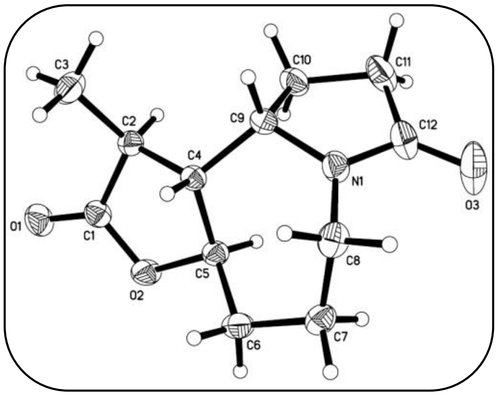
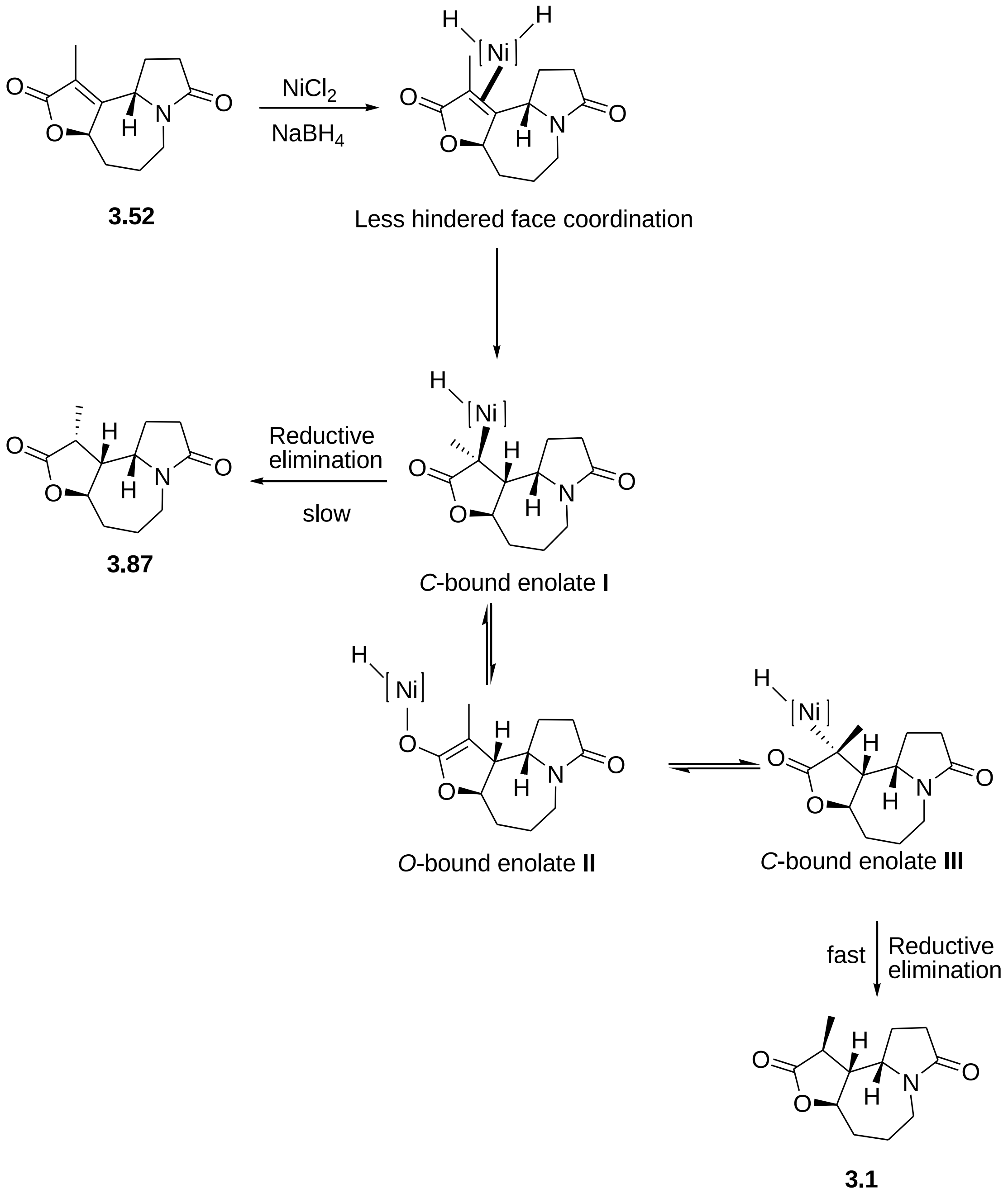


Figure 3.5. The X-ray structure of (±)-stemoamide(**3.1**)

Although, Jacobi and Mori did not provide the actual mechanism for the stereoselective reduction, we believe that the reaction is unlikely to be nickel catalysed reduction with *insitu* generated hydrogen as *trans* addition of H_2 is observed. We suggest that it proceeds as follows (**Scheme 3.32**). In this reaction, due to the steric constraint, hydride is delivered from a nickel atom coordinated to the less hindered *β*-face to give the stable *C*-bound enolate **I**.The *C*-bound enolate **I** is in equilibrium with the diastereoisomeric *C*-bound enolate **III***via* the *O*-bound enolate **II**. The slow rate of the reductive elimination of the more stable *C*-bound enolate **I** leads to faster reductive elimination from *C*-bound enolate **III**, yielding (±)-stemoamide (**3.1**). However, the exact structure of the Ni species is not known.



Scheme 3.32. Possible mechanism for asymmetric reduction

Table 3.4. Compared physical and spectral data for (±)-stemoamide

	Literature[59b]	Our synthetic data
Melting point	184–185 °C	180-182 °C
^{1}H NMR	400 MHz ($CDCl_3$)	500 MHz ($CDCl_3$)
	4.26 (1H, dt, *J* = 10.3, 2.9 Hz) 4.17-4.11 (1H, m) 4.01 (1H, dt, *J* = 10.7, 6.4 Hz) 2.76 -2.65 (1H, m) 2.60 (1H, dq, *J* = 12.4, 6.8 Hz) 2.45 2.36 (4H, m) 2.13-2.07 (1H, m) 1.90-1.83 (1H, m) 1.73 (1H, quin, *J* = 10.7 Hz) 1.56-1.46 (2H, m) 1.30 (3H, d, *J* = 6.8 Hz)	4.19 (1H, dt, *J* = 10.5, 2.7 Hz) 4.18-4.09 (1H, m) 3.99 (1H, dt, *J* = 10.5, 6.4 Hz) 2.72-2.62 (1H, m) 2.61-2.54 (1H, m) 2.43-2.34 (4H, m) 2.08-1.98 (1H, m) 1.88-1.82 (1H, m) 1.72 (1H, quin, *J* = 10.7 Hz) 1.58-1.43 (2H, m) 1.27 (3H, d, *J* = 6.9 Hz)
^{13}C NMR	100 MHz ($CDCl_3$)	125 MHz ($CDCl_3$)
	177.2 174.0 77.4 55.8 52.7 40.0 37.2 34.8 30.6 25.5 22.1 13.9	177.4 (C-3) 174.0(C-11) 77.6 (C-8) 55.8 (C-9a) 52.7 (C-9) 40.2 (C-5) 37.3 (C-10) 34.8 (C-2) 30.6 (C-1) 25.6 (C-7) 22.6 (C-6) 14.1 (C-12)

3.5. Conclusion

In summary, the synthesis of (±)-stemoamide has been achieved in 12 steps started from readily available succinimide, in an overall yield of 6%. In an efficient way, the seven member azepine moiety of stemoamide was constructed stereoselectively with the use of the intramolecular propargylic Barbier reaction. Once again, the key intramolecular propargylic Barbier reaction proceeds in excellent diastereoselectivity and corresponds to that of the natural product.

Chapter 4

Synthesis of the Stenine Ring System from Pyrrole

4.1. Introduction

Encouraged by the (±)-stemoamide synthesis and to further demonstrate the viability of our intramolecular propargylic Barbier reaction for the synthesis of complex butenolides, tetracyclic pyrrole (**4.1**) which possesses the basic ring system (ABCD rings) of stenine (**4.2**), was chosen as a target molecule (**Figure 1**). The basic tetracyclic (**4.1**) skeleton is shared with other stenine group alkaloids such as tuberostemonine (**4.3**), tuberostemonine A (**4.4**) and didehydrotuberostemonine (**4.5**). In 1996, Uyeo *et al.* isolated stenine (**4.2**) from *Stemona tuberose* along with tuberostemonine.[79] In the same year, Uyeo *et al.* also established the stereochemistry and absolute configuration of stenine (**4.2**) by its chemical conversion to tuberostemonine (**4.3**).[80] The absolute configuration of tuberostemonine methobromide salt was revealed by X-ray diffraction studies.

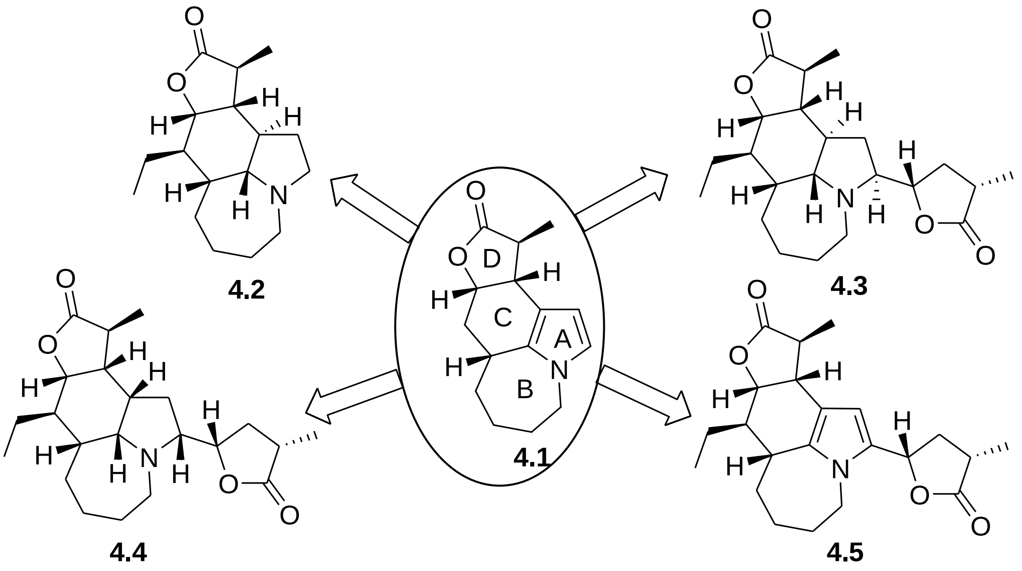


Figure 4.1. Tetracyclic pyrrole (**4.1**) and the stenine group of alkaloids

The alkaloids from the Stenine group are structurally represented by the tetracyclicfuro[2,3-*h*]pyrrolo[3,2,1-*jk*][1]benzazepin-10(*2H*)-one nucleus (chapter 3, **Figure 3.1**). Stenine (**4.2**) contains a pyrrolidine, a seven membered azepine ring, a cyclohexane ring embedded with a butyrolactone and seven contiguous stereogenic centers.

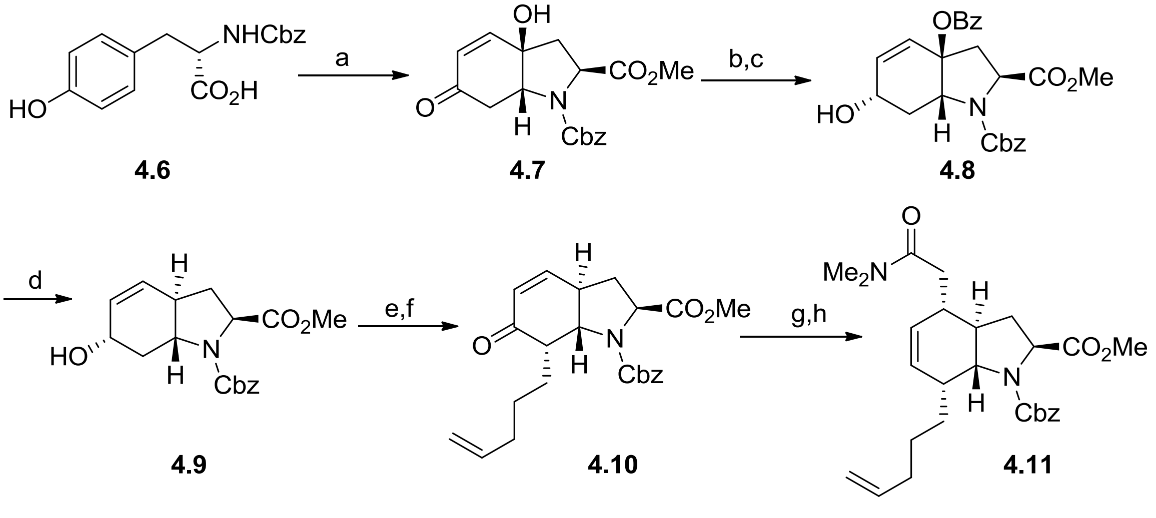
4.2. Selected previous total synthesis of stenine

Due to the structural and stereochemical challenges, stenine makes an attractive target for the synthetic chemist. Stenine (**4.2**) has been the subject of a number of syntheses[81] and related studies.[82] To date, Wipf *et al.* and Morimoto *et al.* have reported the asymmetric total synthesis of stenine.[81f,81d] This following sub-section will give a brief review of the Wipf asymmetric synthesis and Aubé's expeditious total synthesis of (±) stenine (**4.2**).

4.2.1. Wipf's approach

In 1995, the Wipf group accomplished the first enantioselective total synthesis of (-)-stenine starting from L-tyrosine.[81f] One of the key transformations in their synthesis was the oxidative cyclisation of L-tyrosine (**Scheme 4.1**). Treatment of L-tryosine (**4.6**) with iodobenzene diacetate furnished bicycle (**4.7**) as a singlediastereoisomer in a moderate yield of 54%. Benzoylation of the alcohol and subsequent reduction with

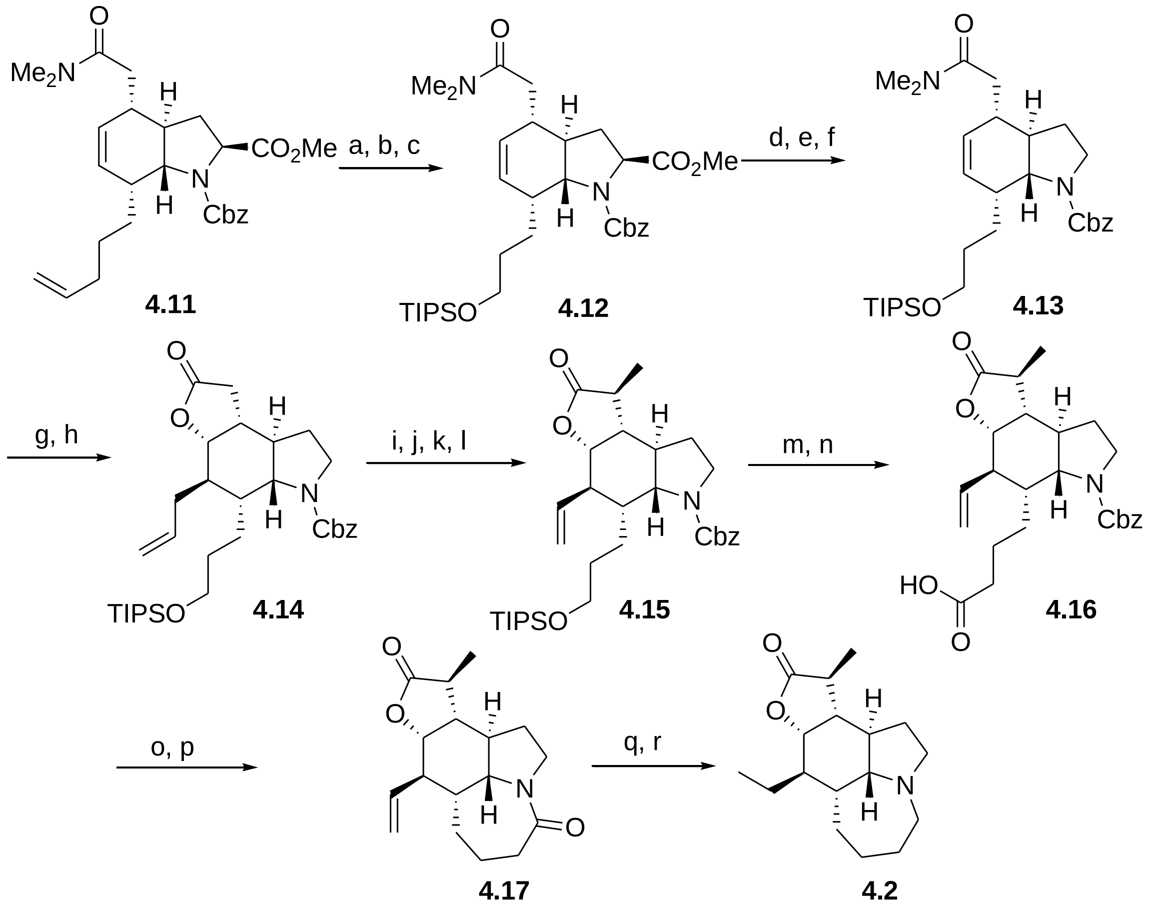
$NaBH_4$ in the presence of $CeCl_3$ gave the equatorial alcohol (**4.8**) in 89% yield and as a single diastereoisomer.



Scheme 4.1.

Reagent and conditions: a) $PhI(OAc)_2$, $NaHCO_3$, CH_3OH, 54%; b) Bz_2O, Et_3N, CH_2Cl_2. 99%; c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, CH_3OH, 89%; d) $Pd_2(dba)_3{\cdot}CHCl_3$, Bu_3P, HCO_2H/Et_3N, 60 °C, THF, 68%; e) TPAP, NMO, CH_2Cl_2, 90%; f) KHMDS, -80 °C, $HC{=}CH(CH_2)_3OTf$, toluene, 46%; g) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, THF, CH_3OH, 91%; h) $H_3CC(OMe)_2NMe_2$, 130 °C, 77%.

Reduction was carried out *via* a π-allylpalladium complex in order to convert the *cis* fused indolone (**4.8**) into the required *trans* fused indolone (**4.9**) (**Scheme 4.1**). Oxidation of the allylic alcohol, followed by alkylation with 4-pentenyl-1-triflate provided the desired *α*-alkylated enone (**4.10**) in 46% yield. The moderate yield in this transformation was caused by competitive *O*-alkylation. The enone (**4.10**) was again reduced with $NaBH_4$ in the presence of $CeCl_3$ togive the alcohol, which was subjected to Eschenmoser-Claisen rearrangement to furnish *γ,δ*-unsaturated amide (**4.11**) in 77% yield.



Scheme 4.2.

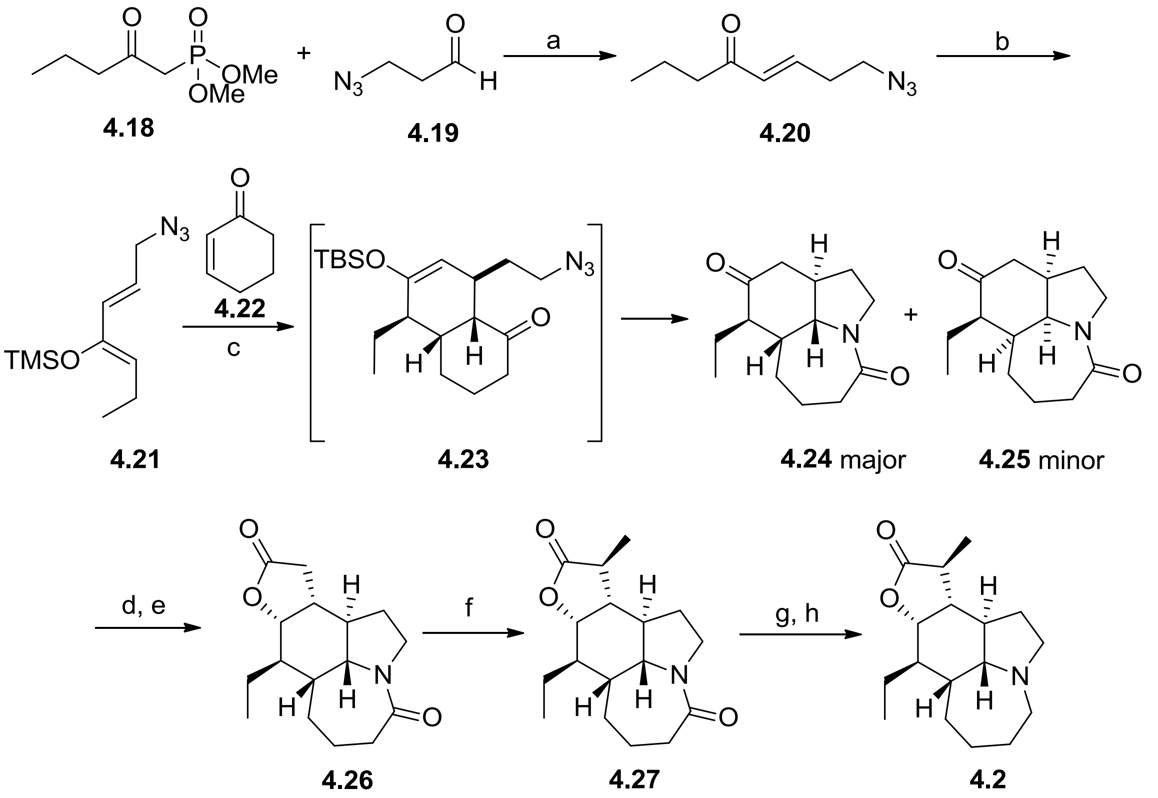
Reagent and conditions: a) AD-mix-*β*; $NaIO_4$, *t*-BuOH, 82%; b) $NaBH_4$, CH_3OH, 93%; c) TIPS-Cl, DMAP, CH_2Cl_2, 76%; d) LiOH, THF, H_2O, 90%; e) $PhOPOCl_2$, Et_3N, PhSeH, THF, 79%; f) Bu_3SnH, AIBN, 130 °C, 70%; g) I_2, pH:5.5, THF, 85%; h) Allyl-$SnBu_3$ AIBN, 77%; i) LDA·HMPA, MeI, 87%; j) OsO_4, $NaIO_4$, THF, H_2O, *t*-BuOH; k) $NaBH_4$, THF, CH_3OH, 63%; l) *o*-$(NO_2)C_6H_4SeCN$, Bu_3P, H_2O_2, THF, 54%; m) HF, MeCN; n) CH_2Cl_2, DMP, H_2O, $NaClO_2$; o) $Pd(OH)_2$, H_2, CH_3OH; p) FDPP, CH_2Cl_2 71%; q) Lawesson's reagent, CH_2Cl_2, 93%; r) Raney-Ni, EtOH, 73%.

Interestingly, the external alkene of (**4.11**) was selectively cleaved in the presence of the cyclohexene ring with AD-mix-*β*, followed by sodium periodate cleavage of the resulting diol to provide the aldehyde in 82% yield (**Scheme 4.2**).[83] The aldehyde was reduced with sodium borohydride and silylation of the primary alcohol furnished the triisopropylsilyl ether (**4.12**) in 76% yield. Subsequent functional group manipulation resulted in the formation of amide (**4.13**) in moderate yield. A careful study was carried out during iodolactonization of (**4.13**), in which the pH of the reaction medium was adjusted to minimize silyl ether hydrolysis. The resulting lactone was subjected to Keck allylation in neat allyltributylstannane to give alkene (**4.14**) in 77% yield.

Methylation of alkene (**4.14**) from the sterically more accessible face furnished the methylated lactone in 87% yield (**Scheme 4.2**). Subsequently, the methylated lactone was subjected to Lemieux-Johnson oxidation,[84] reduction with $NaBH_4$ and a Grieco elimination[85] sequence to provide tricycle (**4.15**) in a yield of 54%. This sequence was employed in order to remove the one carbon from the allyl group so that it can later form the ethyl substituent. After the desilyation of (**4.15**) with HF, the resulting alcohol was converted into acid (**4.16**) with the use of the Dess-Martin periodinane and sodium chlorite. The double bond was hydrogenated and cyclized in the presence of pentafluorophenyl diphenylphosphate at room temperature to afford lactam (**4.17**) in 23% yield. Employing Lawesson's reagent, the amide was converted into a thioamide. Desulfurization with Raney nickel provided (-)-stenine (**4.2**). Thus the first asymmetric total synthesis was completed in a linear sequence of 26 steps and an overall yield of 1.1%. The key concept of this synthesis is the use of substrate control starting from L-tyrosine.

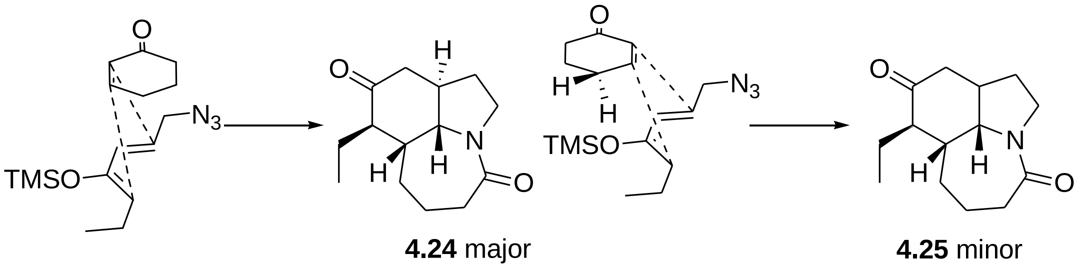
4.2.2. Aubé's approach

In 2005, Aubé and Zeng reported an elegant synthesis of (±)-stenine (**4.2**). Their strategy demonstrated the utility of the Diels-Alder and Schmidt reactions (**Scheme 4.3**).[81b] Horner-Wadsworth-Emmons reagent (**4.18**) was treated with aldehyde (**4.19**) in the presence of sodium hydride to afford the enone (**4.20**), which was converted to the corresponding trimethylsilyloxy diene (**4.21**). The reaction between trimethylsilyloxy diene (**4.21**) and cyclohexenone (**4.22**) in the presence of $SnCl_4$, provided a 3:1 mixture of Diels-Alder/Schmidt products **4.24** and **4.25**. Based on Corey's report, Aube speculated that *exo*-selectivity is favoured because the *endo*-transition state encounters steric interactions between one of the γ protons and the dienophile (**Scheme 4.4)**.[86] Alkylation followed by a reduction sequence provided lactone (**4.26**). Methylation from the sterically less hindered face furnished the methylated lactone (**4.27**) in 79% yield. By employing Wipf's strategy, the methylated lactone (**4.27**) was converted into a thioamide and subsequent desulfurization provided (±)-stenine (**4.2**) in a yield of 89%. Thus the expeditious total synthesis was completed in 9 steps from commercial available starting materials and 14% overall yield. The highlight of this synthesis is the implementation of Diels-Alder and Schmidt reactions to construct the three rings (A, B and C) of stenine in a single step.



Scheme 4.3.

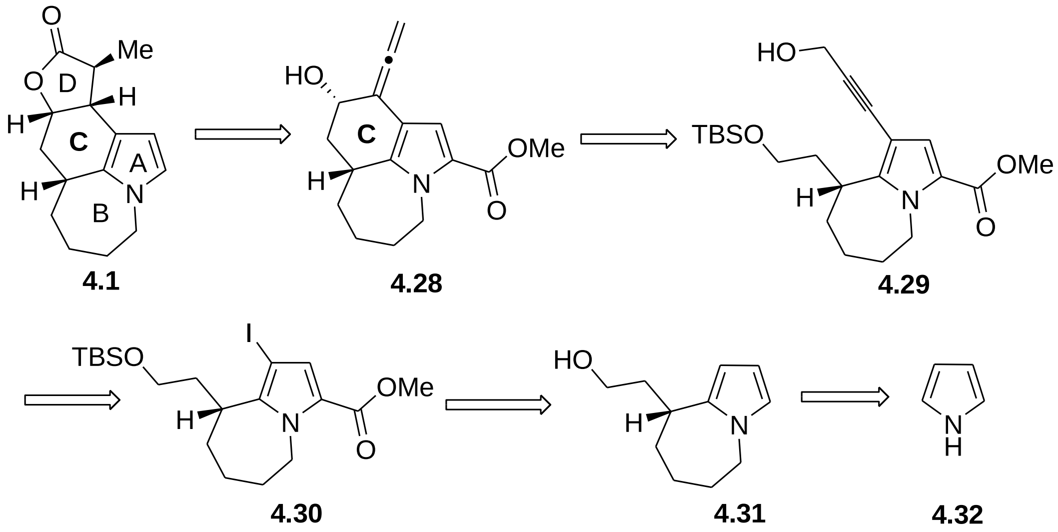
Reagent and conditions: a) NaH, THF, 92%; b) TMSOTf, Et_3N, diethyl ether, 95%; c) $SnCl_4$, CH_2Cl_2,70%; d) LiHDMS, $BrCH_2CO_2Me$, THF, 73%; e) $NaBH_4$, MeOH, 64%; f) LiHMDS, MeI, THF, 79%; g) Lawesson's reagent, CH_2Cl_2, 93%; h) Raney-Ni, EtOH, 89%.



Scheme 4.4. Possible mechanism for Aubé's Diels-Alder reaction

4.3. Retrosynthesis analysis of tetracyclic pyrrole (4.1)

Our retrosynthetic analysis of tetracyclic pyrrole (**4.1**)is shown in **Scheme 4.5**. The initial effort would focus on construction of the basic skeleton of stenine **(4.1)** without the ethyl group at this stage. Based on our previous synthesis of stemoamide (**3.1**), it was anticipated that tetracyclic pyrrole (**4.1**) could be obtained by the carbonylation and the stereoselective reduction of allenol (**4.28**). However, in this case reduction of butenolide would be more difficult, because it is conjugated with the pyrrole. The central unit of the stenine system, the cyclohexane (**C** ring) could be synthesized from our intramolecular propargylic Barbier reaction. The challenge in our synthesis is to set the stage for the key Barbier reaction, which was expected to require pyrrole methyl ester (**4.29**). We anticipated that the alkyne would be installed by Sonogashira reaction of iodo-pyrrole (**4.30**). The azepine unit (**4.31**) will be constructed from pyrrole (**4.32**) employing the intramolecular Michael cyclisation. Pyrrole (**4.32**) is a suitable choice of starting material for our synthesis, in which substitution could be directed to the *N, α,* and *β* positions by the judicious choice of conditions.[87]


O
Me
O
D
H
H
C
A
H
N
B
4.1
HO
C
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4.28
HO
TBSO
OMe
H
N
O
4.29
I
TBSO
OMe
H
N
O
4.30
HO
H
N
4.31
N
H
4.32

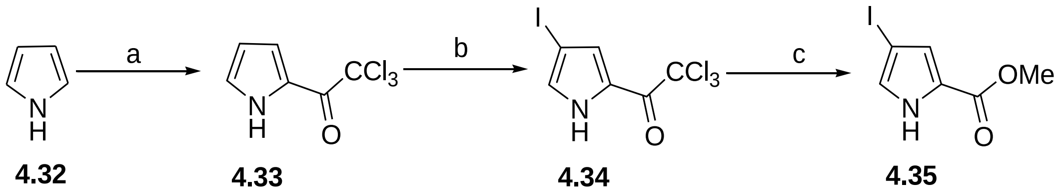
Scheme 4.5.

4.4. Results and discussion

4.4.1. Attempted synthesis of azepine unit (4.41)

Our initial plan was to set the stage for the Sonogashira coupling in the azepine motif of the pyrrole ring. Two different sequences were subsequently investigated to synthesize the Sonogashira precursor. The first sequence involved Friedel-Crafts/electrophilic substitution followed by construction of azepine motif by the intramolecular Michael cyclisation. Alternatively, the azepine motif was constructed by Banwell's protocol,[88] followed by Friedel-Crafts/electrophilic substitution.

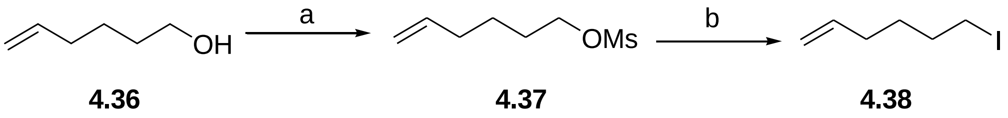
Our synthesis began with preparation of iodo-ester (**4.35**) from pyrrole (**4.32**) employing Belanger's procedure (**Scheme 4.6**).[89] Friedel-Crafts acylation of the pyrrole (**4.32**) with freshly prepared trichloacetyl chloride in diethyl ether cleanly gave the trichloroacetyl-pyrrole (**4.33**) in 93% yield. Subsequently, regioselective iodination at C-4 position was achieved with the use of iodine monochloride in dichloromethane, to afford iodo-pyrrole (**4.34**) in a yield of 90%. It is worth noting that, based on ^{1}H NMR data (coupling constants), the regioselectivity of iodination is difficult to assign, because 3-bond coupling and 4-bond coupling are both in the range of 3.5-1.3 Hz. However this structure was previously confirmed by X-ray crystallography.[90] Methanolysis was then carried out by treatment of iodo-pyrrole (**4.34**) with sodium methoxide in methanol, giving the iodo methyl ester (**4.35**) in 70% yield.



Scheme 4.6. Synthesis of iodo-methyl ester

Reagents and conditions: a) $ClCOCCl_3$, diethyl ether, RT, 3 h, 93%; b) ICl, CH_2Cl_2, RT, 16 h, 90%; c) $NaOCH_3$, CH_3OH, RT, 5 h, 70%.

With the iodo methyl ester (**4.35)** in hand, the requisite side chain unit iodo-hexene (**4.38**) was prepared from 5-hexen-1-ol (**4.36**) *via* its mesylate (**Scheme 4.7**). Treatment of 5-hexen-1-ol (**4.36**) with triethylamine and methanesulfonyl chloride in dry dichloromethane at 0 °C, furnished the hexene-mesylate (**4.37**) in quantitative yield. Displacement of the methanesulfonate of (**4.37**) was carried out with sodium iodide in acetone at reflux, using the Finkelstein reaction to give iodo-hexene (**4.38**)[91] in 86% yield.

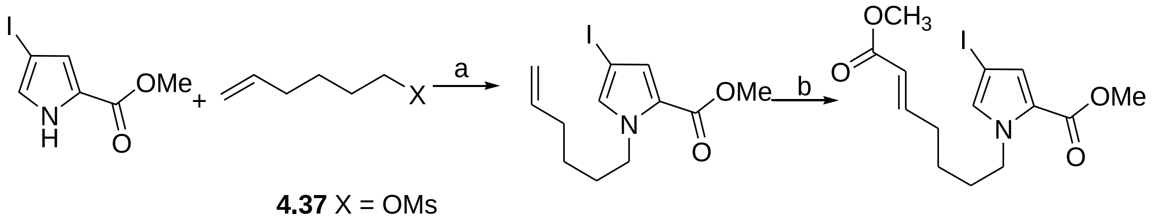


Scheme 4.7. Synthesis of 6-Iodo-1-hexene

Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 99%; b) NaI, acetone, reflux, 4 h, 86%.

N-Alkylation of the sodium salt of iodo methyl ester (**4.35**) with iodo-hexene (**4.38**) proceeded smoothly in THF at 50 °C to furnish the *N*-alkylated pyrrole (**4.39**) in 83% yield after purification (**Scheme 4.8**). Conversely, when *N*-alkylation was carried out with hexene-methanesulfonate (**4.37**) under the same conditions, *N*-alkylated pyrrole (**4.39**) was isolated in a modest yield of 50%. In order to improve the yield, the procedure was modified by increasing the temperature to 65 °C under the same conditions with a prolonged reaction time of 28 hours. This resulted in a good yield of 80% after purification. The absence of the NH peak in the IR spectrum and the presence of two doublets at 5.06 ppm (1H, d, *J* = 17.0 Hz) and 4.96 ppm (1H, d, *J* = 9.2 Hz) in the ^{1}H NMRspectrum was indicative of the terminal vinyl protons, which confirmed the *N*-alkylation product (**4.39**).

Cross-metathesis of *N*-alkylated methyl pyrrole (**4.39**) with methyl acrylate was then carried out with Grubbs' catalyst (**Scheme 4.8**). On treatment of *N*-alkylated methoxy pyrrole (**4.39**) with methyl acrylate in the presence of the 2nd generation Grubbs catalyst in dichloromethane at 40 °C, metathesis proceeded smoothly, to give methoxy-alkene (**4.40**) in 80% yield. The ^{1}H NMR spectrum of alkene (**4.40**) showed a singlet at 3.72 ppm for the aliphatic methoxy group and a doublet of triplet at 6.92 ppm (1H, *J* = 15.9, 7.0 Hz) and 5.81 ppm (1H, *J* = 15.6, 1.5 Hz) with the *trans* coupling constant (~16 Hz) indicative of the *trans* alkene protons, which confirmed the *trans* product formation.

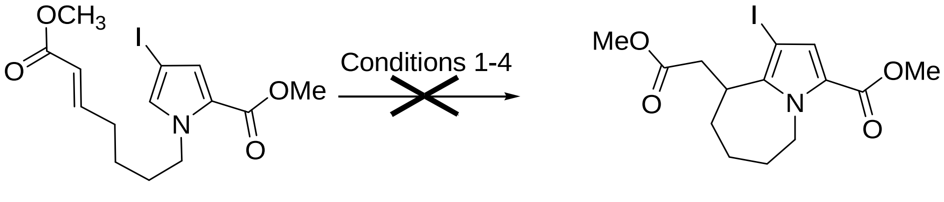


4.35 **4.37** X = OMs **4.38** X = I **4.39** **4.40**

Scheme 4.8. Synthesis of *trans* alkene

Reagents and conditions: a) NaH, THF, 65 °C, 28 h, 80%; b) methyl acrylate, Grubbs (II) catalyst, CH_2Cl_2, 40 °C, 14 h, 80%.

The next task was to construct the seven membered pyrrole-azepine motif (**4.41**), from *tran*s alkene (**4.40**) by employing the intramolecular Michael addition (**Scheme 4.9**). Unfortunately, all attempts failed to induce cyclisation under various conditions (**Table 4.1**). Treatment of *tran*s pyrrole-alkene (**4.40**) with a mild Lewis acid, $BF_3{\cdot}OEt_2$, in dichloromethane at room temperature, gave no product and only starting material was recovered. Similarly, the use of forcing conditions, refluxing dichloromethane or dichloroethane, was unsuccessful and resulted in only recovery of the starting material (entries 2 and 3). Furthermore, under Banwell's conditions,[92] decomposition of the starting material was observed in the presence of strong Lewis acid $AlCl_3$ at room temperature (entry 4).



4.40 **4.41**

Scheme 4.9. Attempts to form azepine ring

Table 4.1.

Entry	Conditions	Time/h	T/°C	Comment
1	$BF_3.OEt_2$, dichloromethane	18	RT	Starting material recovered
2	$BF_3.OEt_2$, dichloromethane	18	40	Starting material recovered
3	$BF_3.OEt_2$, 1,2-dichloroethane	12	80	Starting material recovered
4	$AlCl_3$, dichloromethane	18	RT	Starting material decomposed

On the basis these results, we speculate that the electron withdrawing group at the C-2 position of the pyrrole ring, would decrease the nucleophilicity of the carbon at C-5. Since the cyclisation reaction failed, an alternative sequence was investigated in reverse order, the intramolecular Michael cyclisation followed by Friedel-Crafts and electrophilic substitution. In order to construct the azepine moiety in an asymmetric manner, MacMillan's organocatalyst was employed according to the method of Banwell.[88]

4.4.2. Preparation of MacMillan's catalyst

In 2000, a remarkable strategy for organocatalysis was developed by Macmillan in his pioneering work.[93] The imidazolidinone-based catalysts (**Figure 4.2**)[94]have been used in asymmetric reactions such as1,3-dipolar cycloadditions, Friedel-Crafts alkylations, *α*-chlorinations, *α*-fluorinations and intramolecular Michael reactions.[95]

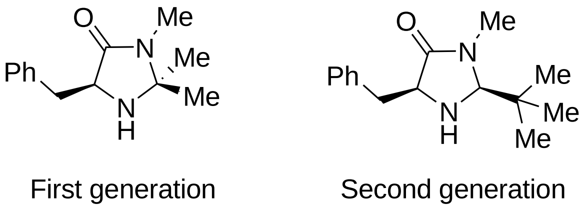
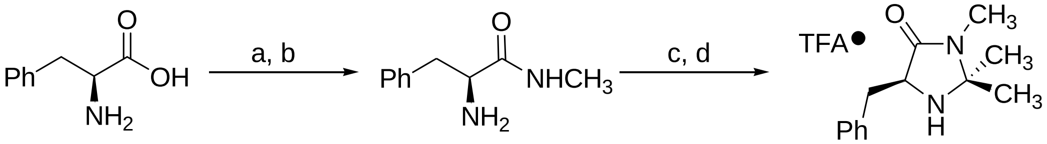


Figure 4.2. MacMillan's catalyst

The requisite first generation catalyst was easily prepared from (*S*)-phenylalanine (**4.42**) following MacMillan's procedure (**Scheme 4.10**).Esterification of (*S*)-phenylalanine (**4.42**) with methanol in the presence of thionyl chloride provided the methyl ester hydrochloride.[96] Amidation of the methyl ester hydrochloride with methyl amine resulted in the formation of methyl amide (**4.43**), which was subjected to a condensation reaction with acetone, furnishing the cyclic amine. Subsequent treatment of the cyclic amine with trifluoroacetic acid provided (*S*)-MacMillan's amine salt (**4.44**).[93]



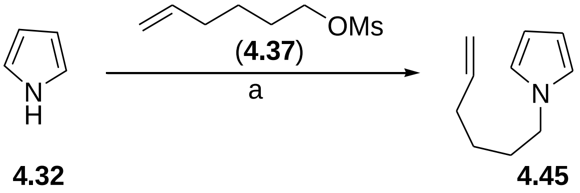
4.42 **4.43** **4.44**

Scheme 4.10. Preparation of MacMillan's catalyst

Reagent and conditions: a) MeOH, $SOCl_2$, RT, 14 h; b) $MeNH_2$, RT, 12 h; c) CH_3COCH_3, MeOH, *p*-TsOH, RT; d) TFA, RT, 65% (four steps overall yield).

4.4.3. Synthesis of aldehyde (4.46)

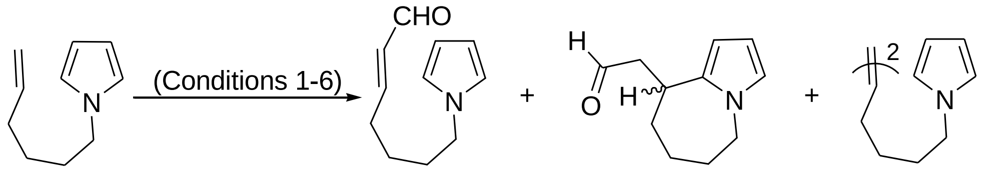
With the MacMillan catalyst (**4.44**) in hand, *N*-alkylation was then carried out according to the method of Heaney and Ley.[97] Treatment of pyrrole (**4.32**) with hexene-mesylate (**4.37**) in the presence of powdered sodium hydroxide in DMSO cleanly furnished the *N*-alkylated pyrrole (**4.45**) in 87% yield after purification (**Scheme 4.11**). In order to get a higher yield, after the addition of hexene-mesylate (**4.37**) at 0 °C, the reaction mixture should warm to room temperature gradually. In contrast, *N*-alkylation in THF under the condition optimized to prepare the methoxy pyrrole (**4.39**) (**Scheme 4.8**) resulted in a low yield of 20%. We reasoned that the starting materials (**4.35** and **4.32**) have different electronic properties. The pyrrole (**4.32**) is an electron rich material compared to the methyl ester (**4.35**). The formation of *N*-alkylated pyrrole (**4.45**) was clearly indicated by the absence of the NH peak in the IR spectrum and the appearance of two broad doublets at 5.0 ppm (1H, *J* = 19.0 Hz) and 4.96 ppm (1H, *J* = 11.4 Hz) in the ^{1}H NMR spectrum indicative of the terminal vinyl protons.



Scheme 4.11. *N*-alkylation of pyrrole

Reagent and conditions : a) NaOH, DMSO, 0 °C to RT, 14 h, 87%

Cross-metathesis of *N*-alkylated pyrrole (**4.45**) with crotonaldehyde was then carried out (**Scheme 4.12**). Initial attempts with the use of 5 mol% Grubbs 2nd generation catalyst in dichloromethane at reflux for 8 hours furnished the sensitive aldehyde (**4.46**) in 70% yield, along with 8% of the racemic azepine [(±)-**4.47**] and self-metathesis product (**4.48**) in 3% after purification (**Table 4.2**, entry 1). The ^{1}H NMR spectrum of aldehyde (**4.46**) showed a doublet at 9.50 ppm (1H, *J* = 7.8 Hz), for the characteristic peak for the aldehyde functionality and a doublet of triplet at 6.80 ppm (1H, *J* = 15.6, 6.8 Hz) and a doublet of doublet of triplet at 6.10 ppm (1H, *J* = 15.6, 7.7 & 1.4 Hz) with the *trans* coupling constant (~15 Hz) indicative of the *trans* alkene protons. The cyclised by product azepine [(±)-**4.47**] was clearly identifiable by the ^{1}H NMR spectrum which showed the absence of alkene protons and the presence of apparent quartet at 3.32 ppm (1H, *J* = 7.85 Hz) for the pyrrolic proton. The formation of dimer (**4.48**) was confirmed by the HRMS analysis.



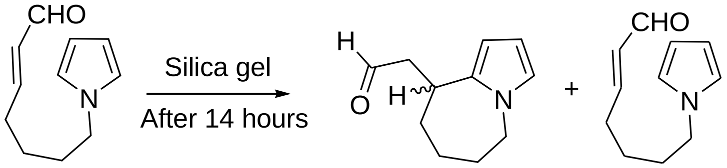
4.45 **4.46** (±) **4.47** **4.48**

Scheme 4.12. Cross-metathesis

Table 4.2.

Entry	Conditions	**4.46** yield/%	(±)-**4.47** yield/%	**4.48** yield/%	Comment
1	Crotonaldehyde (2 eq), Grubbs II (5 mol%), dichloromethane, 40 °C, 8 h.	70	8	3	chromatography on silicagel
2	Distilled crotonaldehyde (2 eq), Grubbs II (5 mol%), dichloromethane, 40 °C, 8 h.	72	6	2	chromatography on silica gel
3	Crotonaldehyde (2 eq), Grubbs II (5 mol%), dichloromethane, 40 °C, 8 h.	84	0	1	chromatography on basified silica gel
4	Crotonaldehyde (5 eq), Grubbs II (0.5 mol%), dichloromethane, 40 °C, 45 h.	86	0	1	chromatography on basified silica gel
5	Crotonaldehyde (3 eq), Grubbs II (0.5 mol%), toluene, 110 °C, 36 h.	83	0	4	chromatography on basified silica gel
6	Crotonaldehyde (3 eq), Grubbs II (0.5 mol%), dichloromethane, 40 °C, 56 h.	86	0	2	chromatography on basified silica gel

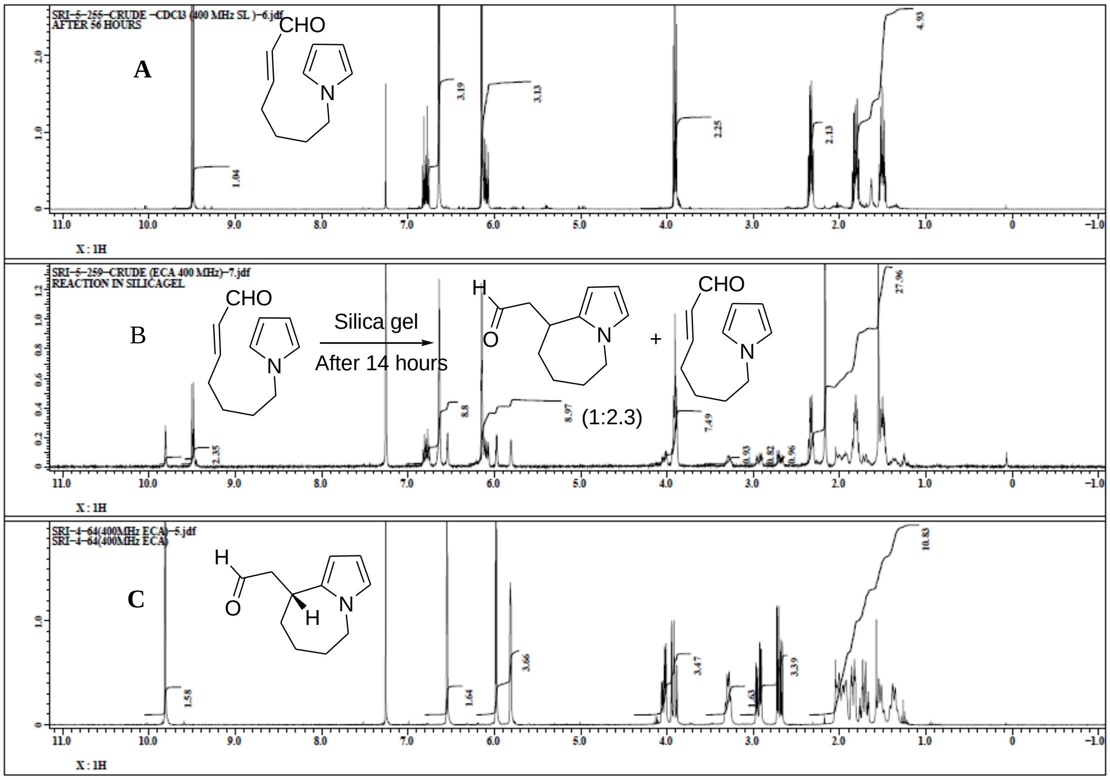
Initially, we postulated that the cyclisation could be catalysed by a small amount of crotonic acid which may have come from aerial oxidation of the crotonaldehyde. However, the cyclised product (**4.47**) was also observed when the reaction was carried out with pure crotonaldehyde (distilled from K_2CO_3) (entry 2). On the other hand, no cyclised product was observed in the crude ^{1}H NMR spectrum obtained prior to purification. From the results we concluded that the cyclisation could happen in the presence of silica gel during purification. To test our hypothesis a control experiment was carried out (**Scheme 4.13**). The aldehyde was absorbed onto silica gel and kept at room temperature under nitrogen. Interestingly, after 14 hours, the cyclised product (±**4.47**) and the unreacted aldehyde (**4.46**) in a ratio of 1:2.3 were observed in the ^{1}H NMR spectrum (**Figure 4.3**). After 48 hours, however the reaction mixture was decomposed. This result revealed the origin of the cyclisation product was silica gel catalysis. In order to prevent the premature cyclisation on silica gel, aldehyde (**4.46**) was carefully purified by chromatography on basified silica gel (triethylamine). As a result the yield was successfully increased to 84%, with 1% of the self-metathesis product (entry 3).



(1:2.3)

4.46 (±) **4.47** **4.46**

Scheme 4.13. Cyclisation in silica gel



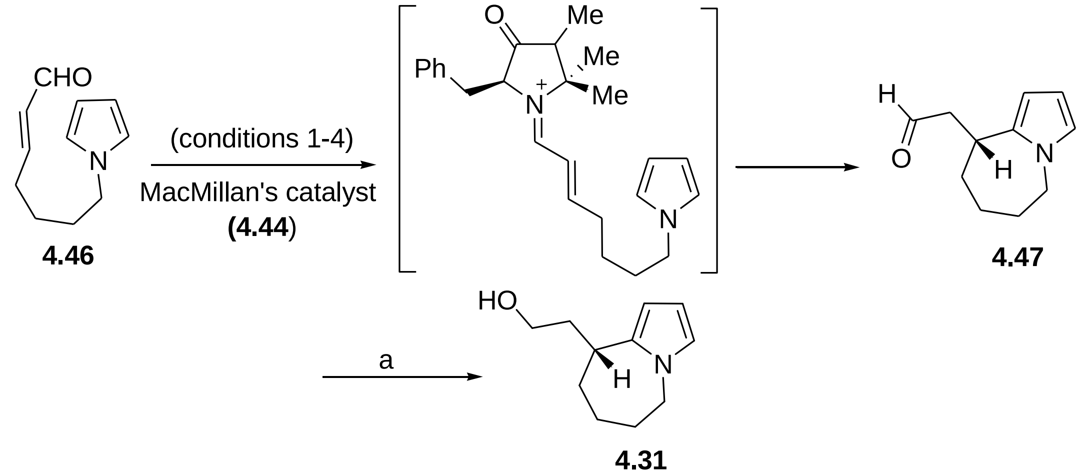
A: Starting material (**4.46**); **B**: Starting material after expose to silica gel; **C**: Pure azepine aldehyde (**4.47**).

Figure 4.3. Cyclisation in silica gel

Although the cross-metathesis was achieved in good yield, we decided to reduce the amount of the Grubbs 2nd generation catalyst. A series of conditions were examined including varying the amount of catalyst with different concentrations and different solvents such as toluene and dichloromethane (entries 3 and 4). Finally, the optimum condition for this reaction was found to be the use of 0.5 mol% of catalyst and 3 equivalents of crotonaldehyde in dichloromethane at 40 °C for 56 hours, giving the aldehyde (**4.46**) in a yield of 86% , with a trace amount of self-metathesis product (**4.48**) (2%) (entry 5).

4.4.4. Synthesis of azepine alcohol (4.31)

With the chemically pure aldehyde (**4.46**) in hand, cyclization with MacMillan's catalyst was then investigated (**Scheme 4.14**). This cyclisation was highly dependent on the amount of catalyst and concentration. Higher concentrations and low loading of the catalyst resulted in a low yield of the azepine aldehyde, together with a complex mixture of unidentifiable compounds (**Table 4.3**, entries 1-3). The optimum conditions for the cyclization of aldehyde (**4.46**) were found to be use of 20 mol% of MacMillan's catalyst in THF at 0.28 M concentration (substrate), which provided the azepine aldehyde (**4.47**)[88] in a yield of 68% (entry 4). Subsequent reduction with $NaBH_4$ in ethanol furnished the alcohol (**4.31**) in a yield of 93% without purification. The formation of the alcohol (**4.31**) was recognized by the disappearance of the aldehyde band and the presence of a broad OH band at 3361 cm^{-1} in the IR spectrum. The ^1H NMR spectrum showed a broad singlet for the oxygen attached methylene protons at 3.77 ppm, which confirmed the product formation. The *ee* of the alcohol (**4.31**) was determined by chiral HPLC and was found to be 95% (appendix page 277).



Scheme 4.14.

Reagent and conditions: a) $NaBH_4$, ethanol, 0 °C to RT, 2 h, 90%.

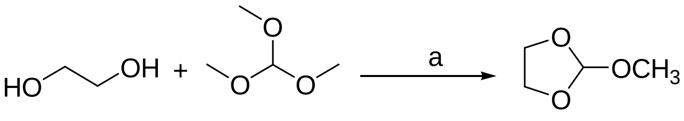
Table 4.3.

Entry	Conditions[a]	Time/h	Yield/%
1	MacMillan's catalyst (10 mol%), THF (0.56M).	14	40
2	MacMillan's catalyst (10 mol%), THF (0.28M).	30	50
3	MacMillan's catalyst (20 mol%), THF (0.56M).	16	60
4	MacMillan's catalyst (20 mol%), THF (0.28M).	20	68

[a] All reactions were carried out at -20 °C and 6 eq of water was added.

4.4.5. Synthesis of dioxolane-pyrrole (4.52)

With the aldehyde (**4.47**) in hand, protection as its 1,3-dioxolane was then carried out (**Scheme 4.16**). The reaction with ethylene glycol in the presence of *p*-TsOH in toluene using a Dean-Stark apparatus, furnished the dioxolane-pyrrole (**4.52**) in 8% yield along with complex mixtures (**Table 4.4**, entry 1). The product formation was confirmed by the disappearance of aldehyde peak and the presence of acetal proton at 5.0 ppm as a broad singlet in the ^{1}H NMR spectrum. We attribute the low yield in the protection to the formation of pyrrole oligomers, which would occur under the harsh conditions of high temperature and strong acid. In order to improve the yield a mild acid and low temperature was investigated under Paquette's conditions.[98]

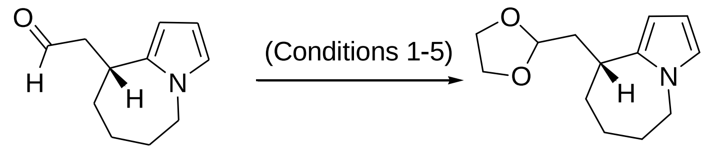


4.49 **4.50** **4.51**

Scheme 4.15.

Reagent and conditions: a) Amberlyst-15, neat, 50%.

The required 2-methoxy-1,3-dioxolane (**4.51**)[99] was prepared from ethylene glycol (**Scheme 4.15**).[100]Unfortunately, attempts using 2-methoxy-1,3-dioxolane (**4.51**) under mild conditions (PS-PPTS, RT or 0 °C) proved fruitless (entries 2-4) giving very low yields with the majority of the material decomposing. On the other hand, under basic reaction conditions,[101]the starting material merely degraded: treatment of aldehyde (**4.47**) with 2-bromoethanol in the presence of DBU, resulted in decomposition (entry 5).



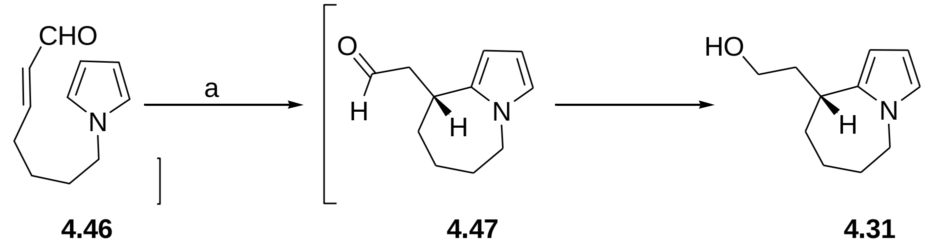
4.47 **4.52**

Scheme 4.16.

Table 4.4.

Entry	Conditions	Yield/%
1	Ethylene glycol, *p*-PTSA, toluene, 110 °C, 2 h.	8
2	2-Methoxy-1,3-dioxolane, PS-PPTS, toluene, RT, 20 h.	0
3	2-Methoxy-1,3-dioxolane, PS-PPTS, CH_2Cl_2, RT, 20 h.	10
4	2-Methoxy-1,3-dioxolane, PS-PPTS, neat, 0 °C, 24 h.	10
5	2-Bromoethanol, DBU, THF, RT.	0

Disappointed with the protection of the aldehyde (**4.47**), we decided to continue our synthesis with the alcohol (**4.31**). To our pleasant surprise, the alcohol (**4.31**) was isolated in good yield (75%) during one-pot synthesis from aldehyde (**4.46**) and without change in the *ee* (95%) (**Scheme 4.17**). In the two step sequence the alcohol (**4.31**) was obtained in 61% (two steps overall yield) (**Scheme 4.14**).

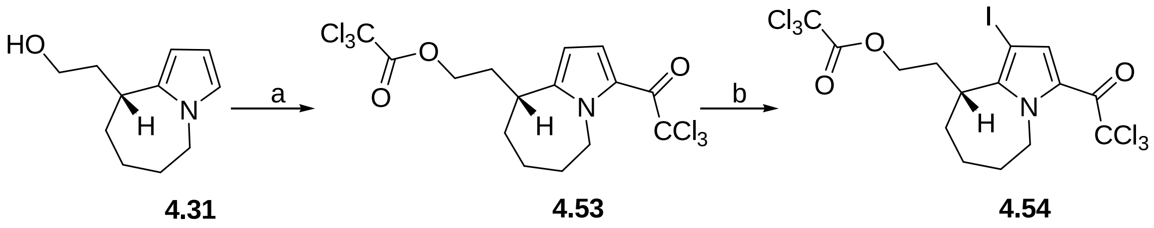


Scheme 4.17. One-pot synthesis of alcohol

Reagent and conditions: i) MacMillan's catalyst (20 mol%), THF, H_2O, -20 °C, 20 h; ii) $NaBH_4$, EtOH, RT, 2 h, (75% two steps yield) .

4.4.6. Synthesis of Sonogashira precursor (4.54)

In order to chemically access the *β*-carbon (iodination), an electron withdrawing group at the *α'*-position was required (**Scheme4.18**).[89] During Friedel-Crafts reaction of alcohol (**4.31**) with trichloroacetyl chloride in diethyl ether, the *α'*-carbon and the free alcohol was acylated, which provided the trichloro ester (**4.53**) in a yield of 95%. The formation of trichloro ester (**4.53**) was confirmed from the IR spectrum with the absence of broad band at 3361 cm^{-1} for the hydroxy group and the presence of bands at 1764 cm^{-1} and 1661 cm^{-1} for the ester functionality and acetyl ketone respectively. The ^1H NMR spectrum of trichloro ester (**4.53**) showed an extensive line broadening for the signal of the nitrogen attached methylene protons at room temperature. Variable temperature (VT) NMR studies were carried out and the signals were clearly resolved at -50 °C (**Figure 4.4**). At -50 °C, the methylene protons attached to the nitrogen atom showed two separate clear peaks. One of the methylene proton shows up as a doublet of doublet at 5.59 ppm (*J* = 14.2, 5.0 Hz) and the other proton appeared as an apparent triplet at 3.71 ppm (*J* = 12.8 Hz).



Scheme 4.18.

Reagent and condition: a) $ClCOCCl_3$, diethyl ether, RT, 95%; b) ICl, CH_2Cl_2, RT, 90%.

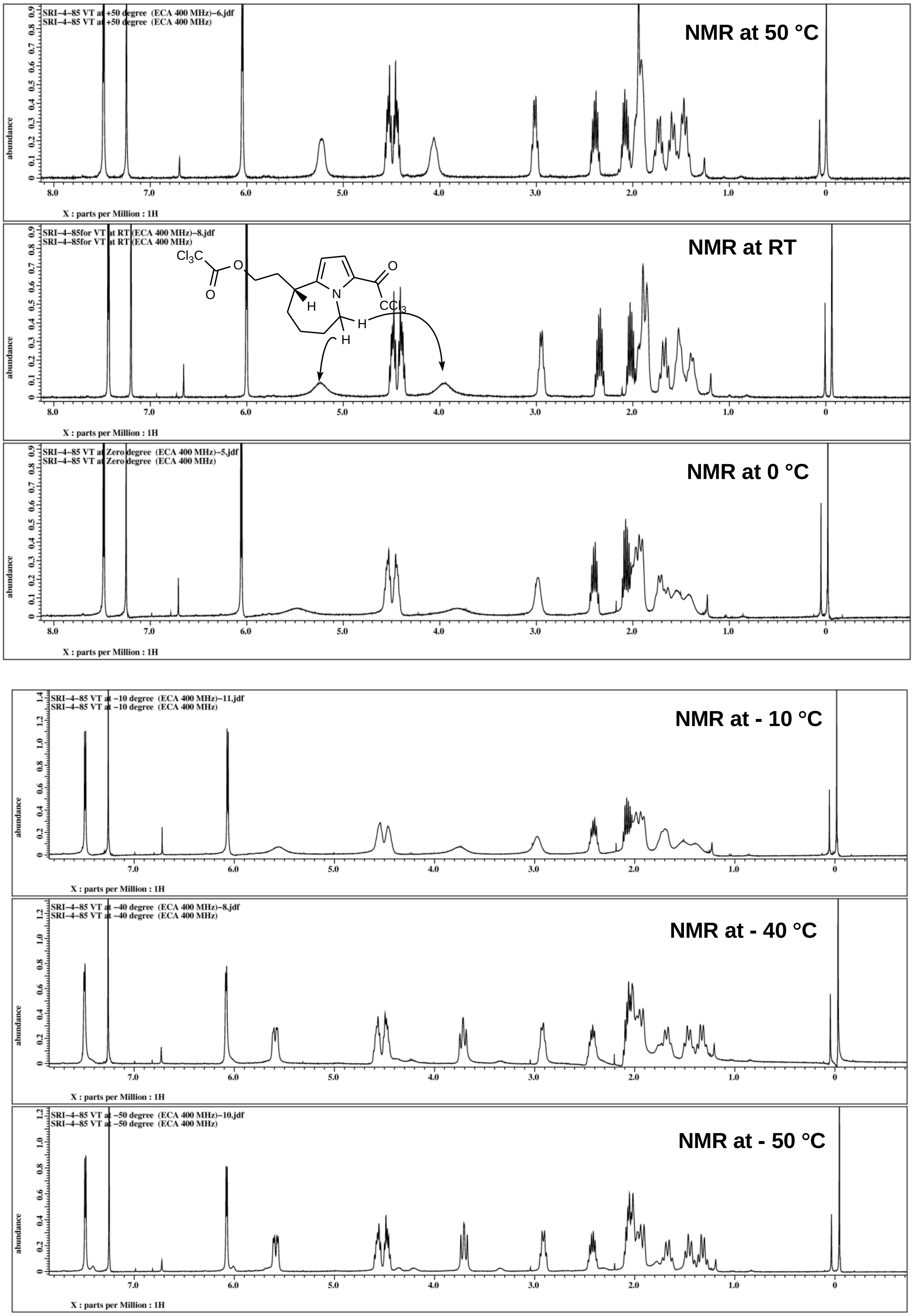
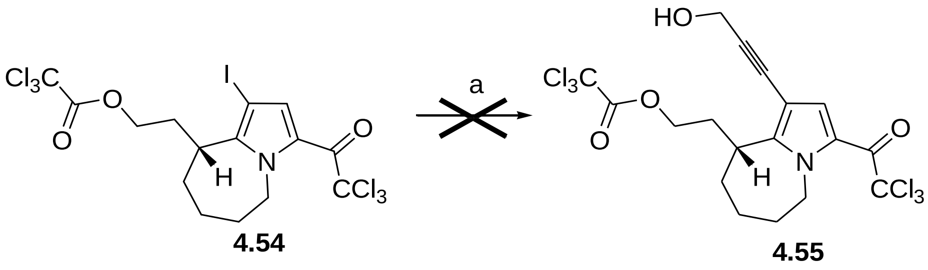


Figure 4.4. ^{1}H NMR (400 MHz, $CDCl_3$) of trichloro ester (**4.53**) at different temperatures

The next step in the synthesis is the β-iodination of trichloro ester (**4.53**). The reaction between trichloro ester (**4.53**) and iodine monochloride in dichloromethane provided the iodo-ester (**4.54**) after 14 hours in a yield of 90% without purification (**Scheme 4.18**). As there was no difference in R_f between the starting material and the product, the reaction mixture was allowed to stir for a prolonged time. After 14 hours the reaction was monitored by the ^1H NMR analysis. The desired iodo-ester (**4.54**) was identifiable from the disappearance of peak at 6.08 ppm in the ^1H NMR spectrum which indicates the β-iodination in the pyrrole ring. Furthermore, this was confirmed by the appearance of peak at 67.1 ppm for the iodine attached quaternary carbon in the ^{13}C NMR spectrum.

4.4.7. Sonogashira coupling with TBS methyl ester (4.30)

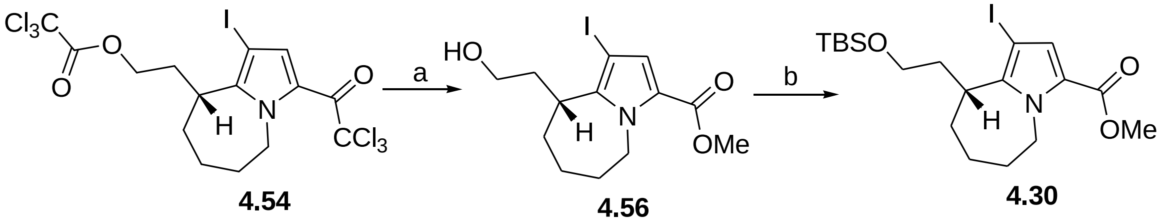
With the iodo trichloro ester (**4.54**) in hand, the well known Sonogashira coupling reaction was then carried out (**Scheme 4.19**).[102,103]Unfortunately, attempts to couple iodo-ester (**4.54**) with propargyl alcohol under the usual homogeneous conditions resulted in complete decomposition.[104] We believe that the decomposition of the starting material is due to the competitive attack of palladium on the carbon-chlorine bond. As a result we decided to cleave the trichloro acetyl group into the methyl ester derivative (**4.56**) by Belanger's procedure.[89]



Scheme 4.19.

Reagent and conditions: a)Propargyl alcohol, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, THF, RT, 6 h.

Treatment of iodo trichloro ester (**4.54**) with sodium methoxide in methanol furnished the clean hydroxy methyl ester (**4.56**) in a yield of 90% without purification (**Scheme 4.20**). During this process, the trichloroacetate was concomitantly cleaved. The appearance of broad band at 3367 cm^{-1} for the characteristic OH functionality in the IR spectrum and the presence of distinguished singlet for the methoxy group at 3.76 ppm in the ^1H NMR spectrum confirmed the product formation.

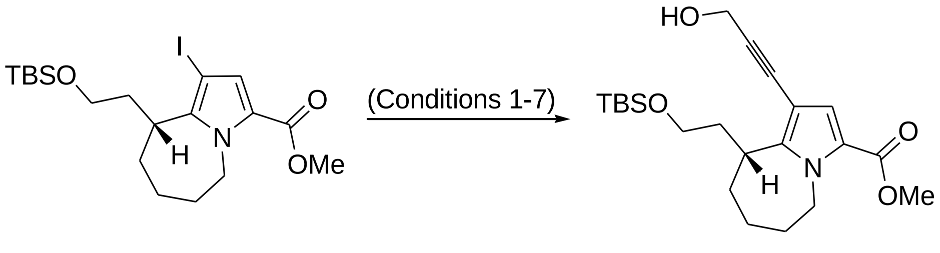


Scheme 4.20.

Reagent and conditions: a)NaOMe, MeOH, 8 h, 90%; b) TBSCl, imidazole, CH_2Cl_2, 8 h, 80%.

Before proceeding to the Sonogashira coupling, we needed to protect the alcohol (**Scheme 4.20**). There are many protection groups available, as shown in the literature. The TBS group is the one of the best protecting groups, which can be easily introduced and removed under mild conditions. The reaction of methyl ester (**4.56**) with TBSCl in the presence of imidazole furnished the TBS methyl ester (**4.30**) in a yield of 80% after purification. The disappearance of OH functionality in the IR spectrum and the appearance of singlets at 0.88, 0.04 and 0.03 ppm for the TBS group in the ^{1}H NMR spectrum confirmed the product formation.

Sonogashira coupling with TBS methyl ester (**4.30**) was more challenging in our synthesis due to the electron rich pyrrole (**Scheme 4.21**). Under standard conditions, treatment of TBS methyl ester (**4.30**) with propargyl alcohol in the presence of $(Ph_3P)_2PdCl_2$ and CuI in triethylamine at 40 °C, resulted in decomposition of the starting material (**Table 4.5**, entry 1).[105] However, when the solvent was replaced with THF with the addition of triethylamine as a base additive (3 eq.), the coupling reaction proceeded slowly and furnished the alkyne alcohol (**4.29**) in a yield of 14% along with 70% of the starting material (entry 2). The IR spectrum showed a characteristic alkyne peak at 2230 cm^{-1} and a broad band at 3430 cm^{-1} for the OH functionality.The ^{1}H NMR spectrum displayed a singlet for theoxygen attached methylene proton at 4.42 ppm, which confirmed the product formation. Only a modest yield improvement was observed in THF or ethyl acetate at a substantially higher temperature (entries 3 and 4). An acceptable yield of 60% was obtained in DMSO at 50 °C (entry 5). On the other hand, when the temperature was increased to 100 °C, the yield was decreased to 30% and only 5% of the starting material could be recovered (entry 6).



4.30 **4.29**

Scheme 4.21.

Table 4.5.

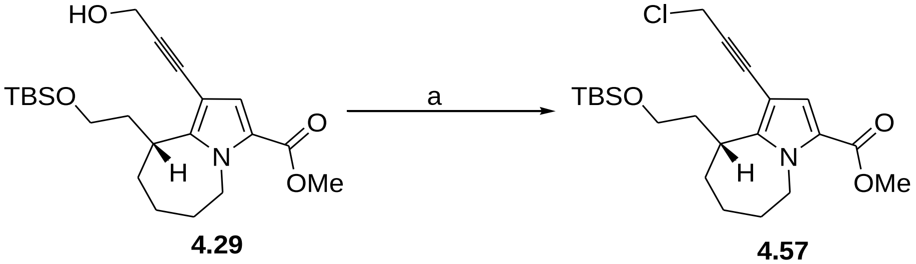
Entry	Conditions[a]	Time / h	T/ °C	Yield /%	Comment
1	Et_3N, $(Ph_3P)_2PdCl_2$	6	40	0	Decomposed
2	THF, $(Ph_3P)_2PdCl_2$	18	RT	14	70% of starting material recovered
3	THF, $(Ph_3P)_2PdCl_2$	18	65	44	30% of starting material recovered
4	EtOAc, $(Ph_3P)_2PdCl_2$	18	75	48	20% of starting material recovered
5	DMSO, $(Ph_3P)_2PdCl_2$	28	50	60	30% of starting material recovered
6	DMSO, $(Ph_3P)_2PdCl_2$	28	100	30	5% of starting material recovered
7	CH_3CN, $(CH_3CN)_2PdCl_2$	10	75	0	40% of starting material recovered

a: CuI was used as a co-catalyst and 3 eq. of Et_3N was added as a base additive.

In contrast, on replacement of $(Ph_3P)_2PdCl_2$ with $PdCl_2(CH_3CN)_2$, no reaction was observed and 40% of the starting material recovered (entry 7), which shows the need for the phosphine ligands to stabilize Pd intermediates. In order to get a higher yield in the Sonogashira coupling, oxygen free conditions were required to prevent homo coupled acetylenes. The coupling reaction of the terminal alkynes in the presence of oxygen and copper salt is known as Glaser coupling.[106] In the catalytic cycles the role of oxygen is to reoxidize the copper(I) species into active copper(II) species.[107] However, the exact mechanism of the Glaser coupling is not fully understood.

4.4.8. Attempted synthesis of bromo-methylester (4.58)

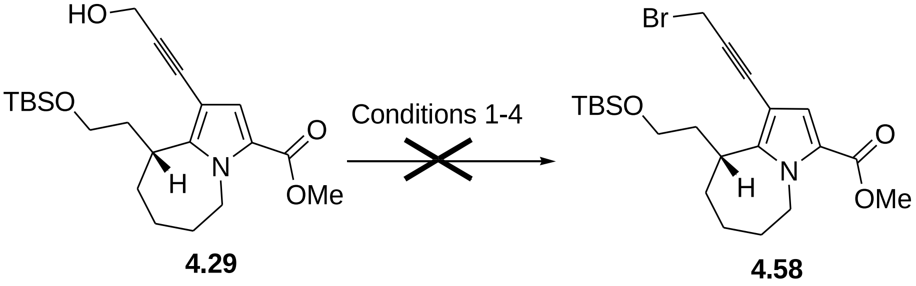
With the alkyne alcohol (**4.29**) in hand, we intended to convert the alcohol into the bromide *via* the mesylate, a method which we successfully employed in our previous synthesis of mintlactone (**2.1**) and (±)-stemoamide (**3.1**). However in this pyrrole system, attempts to synthesize the mesylate failed and we were only able to isolate the corresponding chloride (**4.57**) in a yield of 10% (**Scheme 4.22**). Furthermore, when the reaction was carried out at -10 °C, the alkyne alcohol (**4.57**) decomposed. Unfortunately, attempts to obtain the *O*-tosyl derivative also failed. The formation of chloride (**4.57**) was confirmed from the absence of the OH band in the IR spectrum and the presence of a singlet at 4.36 ppm for the chloro attached methylene protons. It was further confirmed from the HRMS analysis (calculated for $C_{22}H_{35}{}^{35}ClNO_3Si$ (M^++H) 424.2075 found 424.2065).



Scheme 4.22.

Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1h, 10%.

Disappointed with the mesylation step, we decided to convert the alcohol into the bromide in one step under Appel's conditions (**Scheme 4.23**).[108] Unfortunately, all attempts resulted in decomposition of the alkyne alcohol (**4.29**). Under Appel conditions, alkyne alcohol (**4.29**) was treated with CBr_4 in the presence of Ph_3P at 0 °C in dichloromethane or acetonitrile, but failed to give the bromo-ester (**4.58**). Only decomposition of the staring material was observed (**Table 4.6**, entry 1). Similarly, further lowering the reaction temperature to -20 °C resulted in decomposition of the starting material (entry 2).



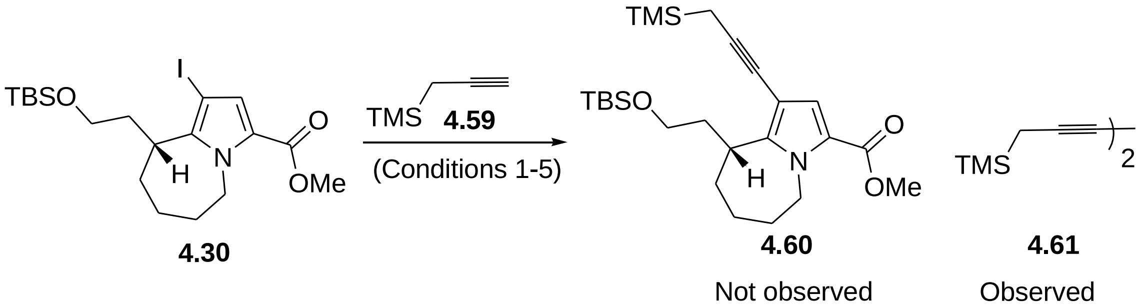
Scheme 4.23.

Table 4.6.

Entry	Conditions	Time/ h	Temp	Comment
1	CBr_4, PPh_3, CH_2Cl_2/CH_3CN	1	0	Decomposed
2	CBr_4, PPh_3, CH_2Cl_2	3	-20 °C	Decomposed
3	NBS, Dimethyl sulphide, CH_2Cl_2	1	0 °C	Decomposed
4	NBS, PPh_3, THF	5	0 °C to RT	Decomposed

Employing Corey's neutral conditions[109,] and Bose conditions[110] also resulted in decomposition of the starting material (entries 3 and 4). With these results we believe that propargyl bromide functionality may not be stable in the pyrrole system. The alternative scenario would be theinstallation of the more stable propargyltrimethylsilane (**4.59**) in the pyrrole system (**Scheme 4.24**).

The propargyltrimethylsilane (**4.59**) was prepared from the propargyl bromide according to the method of Cox.[111]With the coupling partners in hand, a series of Sonogashira reactions and Negishi couplings were explored between propargyl trimethylsilane and TBS methyl ester (**4.30**) (**Scheme 4.24**). Unfortunately, we were unable to obtain the trimethyl-pyrrole (**4.60**) using several conditions with different Pd sources. The Sonogashira reaction with propargyl trimethylsilane (**4.59**) and TBS methyl ester (**4.30**) under our optimum conditions to prepare the pyrrole-propargyl alcohol (**4.29**), failed and resulted in recovery of starting material (**Table 4.7**, entry 1). Furthermore, when the reaction was carried out in a sealed tube [due to the low boiling point of propargyl trimethylsilane (91-93 °C)] at 100 °C, decomposition of the starting material occurred (entry 2). On the other hand, no product was observed under Cosford's heterogeneous conditions using palladium on carbon (entry 3).[112]



Scheme 4.24.

Table 4.7.

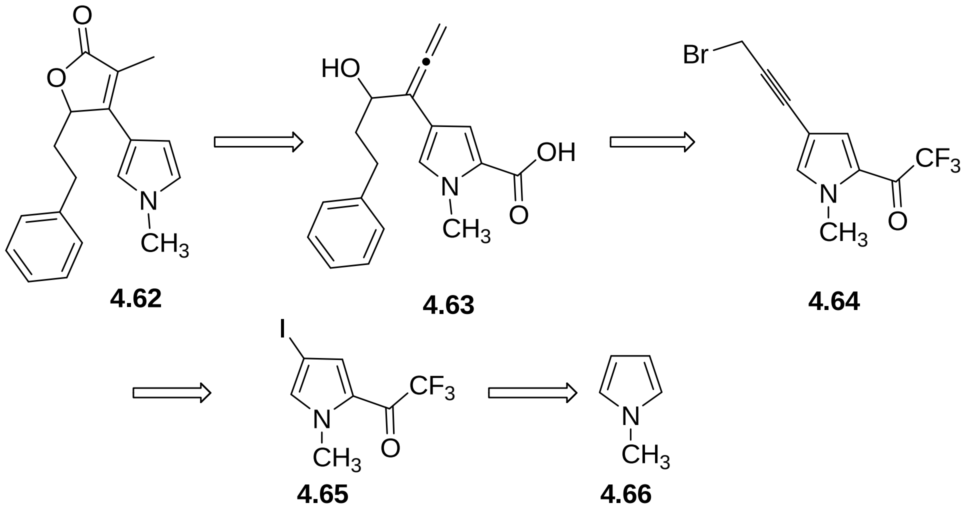
Entry	Conditions	Comment
1	$(Ph_3P)_2PdCl_2$,CuI, Et_3N, 50 °C, DMSO/ THF, 14 h.	40% of starting material recovered.[a]
2	$(Ph_3P)_2PdCl_2$, CuI, Et_3N, 100 °C, DMSO, 8 h (sealed tube).	Starting material decomposed.[a]
3	10% Pd on carbon, CuI, K_2CO_3, 70 °C, 1,2-dimethoxyethane, 14 h.	50% of starting material recovered.[a]
4	$Pd(PPh_3)_4$, $ZnCl_2$, *n*-BuLi, THF, -78 °C to RT, 12 h.	80% of starting material recovered.
5	$(Ph_3P)_2PdCl_2$, $ZnBr_2$, *i*-PrMgBr, THF, -78 °C to RT, 16h.	60% of starting material recovered.

a: 10-20% of homo couple product (**4.61**) was isolated.

Even though all the reactions were carried out under oxygen free conditions, a self coupled product (**4.61**)[113] was isolated in 10-20 % yield (entries 1-3).[114] The formation of self coupled product (**4.61**) was observed by the absence of terminal alkyne proton and the presence of a singlet at 1.56 ppm for the silicon attached methylene protons in the ^1H NMR spectrum. The ^{13}C NMR spectrum confirmed the product formation by the appearance of characteristic internal alkyne peaks at 74.4 ppm and 64.5 ppm. Frustratingly, Negishi coupling in the presence of $ZnBr_2$ or $ZnCl_2$ also failed and starting material was recovered unchanged (entries 4 and 5).[115,116] The difficulty of this transformation may be due to the steric obstacle between the OTBS group and trimethylsilylin the transmetalationstep.

4.5. New strategy in the pyrrole system

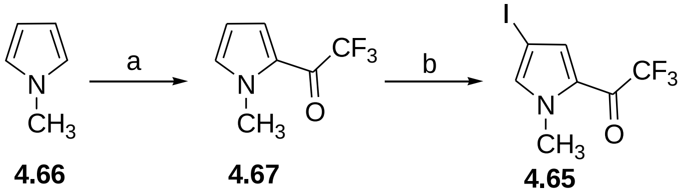
Disappointed with our inability to access the bromide (**4.58**) or the silane (**4.60**), a new strategy was investigated with the use of trifluoromethyl ketone functionality, which would act as a stronger electron withdrawing group in the pyrrole system. We hoped that changing the electron withdrawing group from methyl ester to trifluoromethyl ketone group would improve the yield in the Sonogashira coupling and increase the stability of the electron rich pyrrole. It is known that Sonogashira coupling is faster with more electron poor aryl systems.[117]This hypothesis could be tested by synthesizing the pyrrole butenolide (**4.62**) in eight steps from simple *N*-methyl pyrrole (**4.66**). Based on our original retrosynthesis analysis, pyrrole butenolide (**4.62**) would be constructed by the carbonylation and decarboxylation sequence of the allenic acid (**4.63**)(**Scheme 4.25**). An intermolecular Barbier reaction would lead to the allenol (**4.63**). The Barbier precursor (**4.64**) could arise from the Sonogashira coupling. The Sonogashira precursor (**4.65**) could be prepared from *N*-methyl pyrrole (**4.66**).



Scheme 4.25.

4.5.1. Synthesis of Sonogashira precursor (4.65)

Our model study commenced with the Friedel-Crafts acylation of *N*-methyl pyrrole (**4.66**) (**Scheme 4.26**). Using Cooper's procedure,[118] *N*-methyl pyrrole (**4.66**) was treated with trifluoroacetic anhydride in diethyl ether, which provided the desired trifluoro-pyrrole (**4.67**) in a yield of 74%.The formation of product was clearly shown by the presence of strong band at 1665 cm^{-1} for the ketone group in the IR spectrum. The ^{1}H NMR spectrum displayed a singlet for the nitrogen attached methyl group at 3.98 ppm. Furthermore, the ^{13}C NMR analysis showed a quartet at 117.1 ppm with a coupling constant of 288.8 Hz for the characteristic CF_3 functionality and the ketone group appeared as a quartet at 169.8 ppm with a coupling constant of 34.6 Hz.



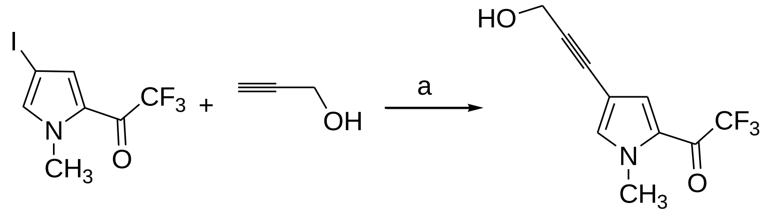
Scheme 4.26.

Reagents and conditions: a) $(CF_3CO)_2O$, diethyl ether, RT, 2 h, 74%; b) ICl, CH_2Cl_2, 12 h, RT, 80%.

Clean β-iodination was then achieved by treatment of trifluoro-pyrrole (**4.67**) with iodine monochloride in dichloromethane (**Scheme 4.26**). Since the product of this reaction has the same $R_f$as the starting material, the reaction was allowed to stir for an extended time (12 h). A yield of 80% of iodo trifluoro-pyrrole (**4.65**) was obtained after purification. The desired iodo trifluoro-pyrrole (**4.65**) was identified from the disappearance of the β-hydrogen proton peak at 6.26 ppm in the ^{1}H NMR spectrum,which clearly indicates the *β*-iodination in the pyrrole ring. The ^{13}C NMR spectrum displayed a peak at 60.9 ppm for the iodine attached carbon, which confirmed the product formation.

4.5.2. Sonogashira coupling with trifluoro-alkyne (4.65)

With the iodo trifluoro-pyrrole (**4.65**) in hand, our anticipated Sonogashira reaction was then investigated (**Scheme 4.27**). As we expected, Sonogashira coupling preceded smoothly under mild homogeneous conditions. Treatment of iodo trifluoro-pyrrole (**4.65**) with propargyl alcohol and Et_3N in the presence of $(Ph_3P)_2PdCl_2$ and CuI in THF at RT, provided trifluoro-alkyne (**4.68**) in an excellent yield of 90% yield after purification. In contrast, under the same conditions TBS methyl ester (**4.30**) provided alkyne alcohol (**4.29**) in 14% yield (**Scheme 4.21**). The formation of trifluoro-alkyne (**4.68**) was identified form the IR spectrum, which showed a broad band at 3523 cm^{-1} for the OH functionality and a characteristic alkyne peak at 2234 cm^{-1}.



4.65

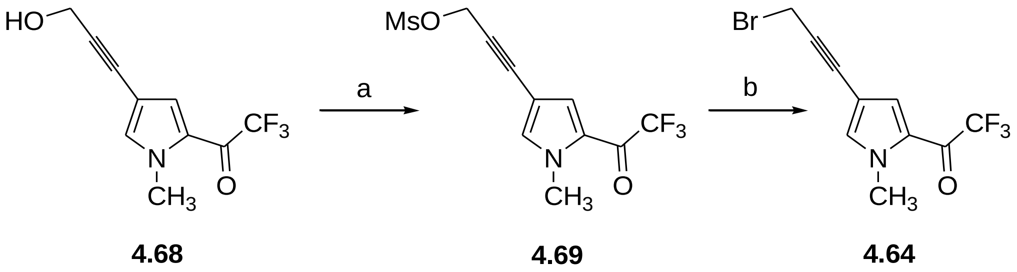
4.68

Scheme 4.27.

Reagents and conditions: a) $(Ph_3P)_2PdCl_2$,CuI, Et_3N, THF, 0 °C to RT, 90%, 14 h.

4.5.3. Synthesis of pyrrole-bromide (4.64)

Encouraged by the Sonogashira coupling under mild conditions, we then focused on the synthesis of trifluoro-bromo pyrrole (**4.64**) *via* the mesylate (**Scheme 4.28**). The pyrrole-methanesulfonate (**4.69**) was obtained in quantitative yield from the treatment of trifluoro-alkyne (**4.68**) with methanesulfonyl chloride in the presence of triethylamine in dry dichloromethane at 0 °C. The formation of pyrrole-mesylate (**4.69**) was identified from the IR spectrum with the absence of the broad absorption band at 3523 cm^{-1} for the hydroxyl group and the presence of the sulfonyl characteristic absorption bands at 1351 cm^{-1} and 1172 cm^{-1}.

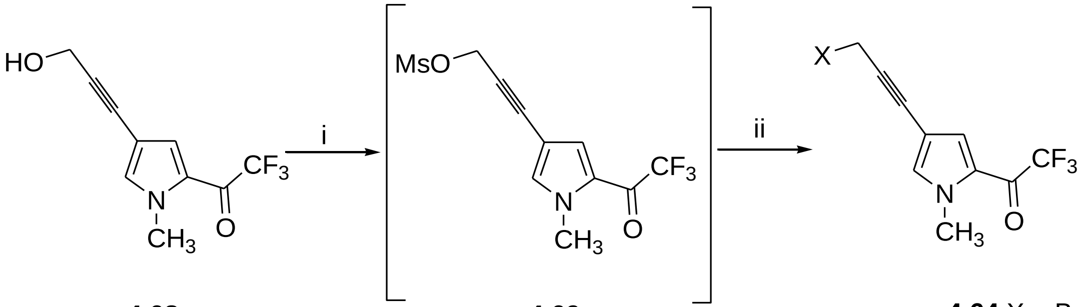


Scheme 4.28.

Reagents and conditions: a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 99%; b) LiBr, THF, RT, 4 h, 80%.

However, the pyrrole-mesylate (**4.69**) was not stable at room temperature for long periods. As a result, the pyrrole-mesylate (**4.69**) was subjected to the next step without delay. The reaction of pyrrole-mesylate (**4.69**) with lithium bromide in THF provided pyrrole-bromide (**4.64**) in a yield of 80% after purification (**Scheme 4.28**). The formation of the pyrrole-bromide (**4.64**) was identified by the absence of the characteristic absorption bandsfor the sulfonyl group at 1351 cm^{-1} and 1172 cm^{-1} in the IR spectrum.The ^{1}H NMR spectrum displayed the absence of the methyl sulfonyl peak at

3.13 ppm and the presence of a singlet at 4.12 ppm was indicative of the bromo attached methylene protons, which confirmed the product. Due to the low stability of pyrrole-mesylate (**4.69**), we then focused on the one-pot synthesis of trifluoro-bromo (**4.64**) from trifluoro-alkyne (**4.68**) without isolating the pyrrole-mesylate (**4.69**) (**Scheme 4.29**). Unfortunately, during one-pot synthesis an inseparable mixture of pyrrole-bromide (**4.64**) and pyrrole-chloride (**4.70**) was isolated in a ratio of 1:1. The trifluoro-chloro compound (**4.70**) was clearly identified from the HRMS analysis (calculated for $C_{10}H_8{}^{35}ClF_3NO$ (M^++H) 250.0247 found 250.0247).

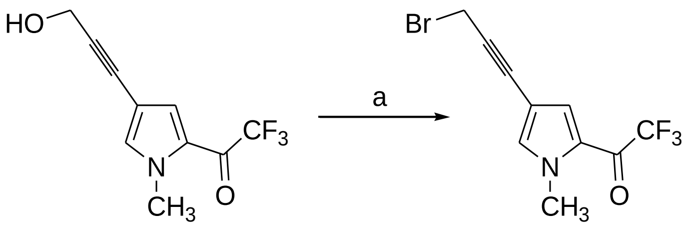


4.68 **4.69** **4.64** X = Br
4.70 X = Cl

Scheme 4.29.

Reagents and conditions: i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h; ii) LiBr, THF, RT, 3 h.

The Appel reaction was also examined as an alternative (**Scheme 4.30**).[108]Trifluoro-alkyne (**4.68**) was treated with PPh_3 and CBr_4 in dichloromethane giving the pyrrole-bromide (**4.64**) in 60% yield. To our delight, addition of 4Å molecular sieves to the reaction mixture resulted in excellent yield of 90% after purification. The molecular sieves were used to trap the water present in the commercially available CBr_4 (6% of H_2O).



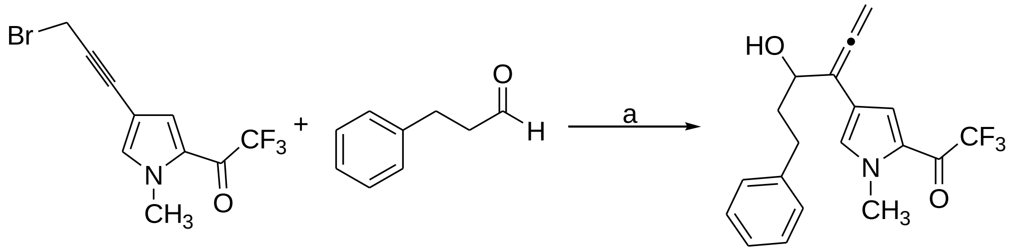
4.68 **4.64**

Scheme 4.30.

Reagents and conditions: a) CBr_4, PPh_3, 4Å molecular sieves, CH_2Cl_2, 0 °C, 1 h, 90%.

4.5.4. Synthesis of allenol (4.63)

With the pyrrole-bromide (**4.64**) in hand, the intermolecular Barbier reaction was then carried out (**Scheme 4.31**). Treatment of pyrrole-bromide (**4.64**) with 3-phenylpropanal (**4.71**) in the presence of indium and acetic acid in THF, furnished the allenol (**4.63**) in a low yield of 10%. On the other hand, under Mukaiyama's conditions the reaction resulted in an excellent yield.[10]The reaction between pyrrole-bromide (**4.64**) and 3-phenylpropanal (**4.71**) in the presence of stannous chloride and sodium iodide in DMF at room temperature yielded the allenol (**4.63**)in 94% yield (**Scheme 24**). The formation of allenol (**4.63**)was clearly confirmed by the IR spectrum,which displayed the OH functionality as a broad band at 3424 $cm^{-1}$and characteristic band for the allene at 1944 cm^{-1}. This was further supported by the appearance of characteristic peak for the central allene carbon at 205.9 ppm in the ^{13}C NMR spectrum.



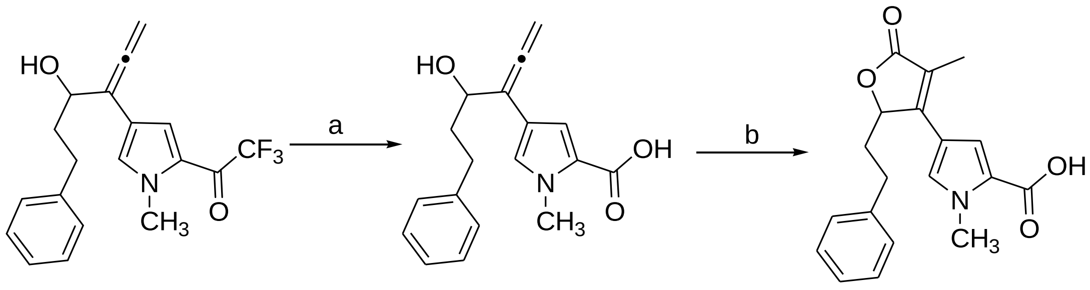
4.64 **4.71** **4.63**

Scheme 4.31

Reagents and conditions: a) $SnCl_2$, NaI, DMF, H_2O, RT, 12 h, 94%.

4.5.5. Synthesis of pyrrole butenolide (4.62)

With the allenol (**4.63**)in hand, hydrolysis was then carried out. The hydrolysis of the ketone to a carboxylic acid may be regarded as a hemihaloform reaction.[119] Under Moody's conditions, allenol (**4.63**) was treated with lithium hydroxide in DMF at 70 °C, which furnished the allenic acid (**4.72**) in 52% yield (**Scheme 4.32**).[120] The formation of allenic acid (**4.72**) was clearly identified in the ^{13}C NMR spectrum, which showed the absence of characteristic quartet peak for the CF_3 functionality at 116.9 ppm and the presence of acid carbonyl group at 165.6 ppm. Without optimization of this step, carbonylation was then carried out.

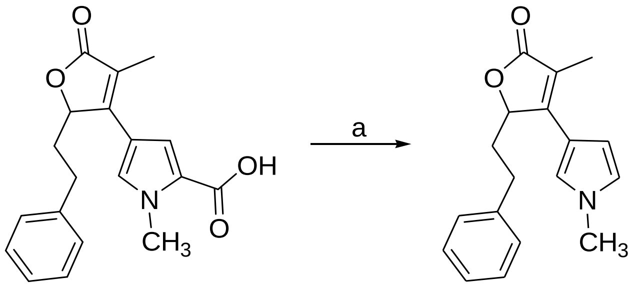


Scheme 4.32.

Reagents and conditions: a) LiOH, H_2O, DMF, 70 °C, 12 h, 52%; b) $Ru_3(CO)_{12}$, Et_3N, CO (100 psi), dioxane, 100 °C, 14 h, 53%.

Treatment of allenic acid (**4.72**)with triruthenium dodecacarbonyl in the presence of triethylamine under a pressure of 100 psi of CO, afforded the pyrrole acid (**4.73**) in a yield of 53% after purification.3 In the IR spectrum, the absence of the characteristic allene absorption band and the presence of band at 1737 cm^{-1} indicative of the *α,β*-unsaturated carbonyl peak, confirmed the product formation. This assignment was further supported by the ^{13}C NMR spectrum, which showed a peak at 174.2 ppm for the newly formed lactone functionality.

The model study was completed by the decarboxylation of pyrrole acid (**4.73**) (**Scheme 4.33**). Electron rich pyrrole carboxylic acids are readily decarboxylated under solvent free thermal conditions or acidic conditions.[121,122] Employing Boger's procedure, the pyrrole acid (**4.73**) treated with trifluoroacetic acid in dichloromethane at reflux, to afford the pyrrole butenolide (**4.62**) in 90% yield.[123] The formation of pyrrole butenolide (**4.62**) was identified from the absence of carboxylic acid functionality in the IR spectrum, while the ^{1}H NMR displayed a triplet for the nitrogen attached *α* proton at 6.66 ppm (*J* = 2.4 Hz).



4.73 **4.62**

Scheme 4.33.

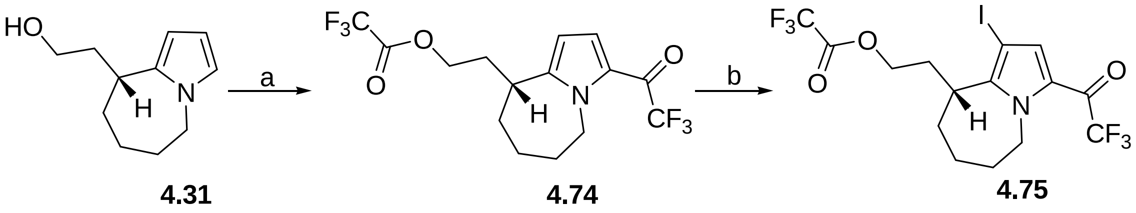
Reagents and conditions: a) Trifluoroacetic acid, CH_2Cl_2, 40 °C, 2 h, 90%.

From this model study, we have successfully identified the trifluoromethyl ketone as a suitable electron withdrawing group in our pyrrole system, which resulted in higher yield in the Sonogashira coupling at room temperature and also increased the stability of the pyrrole. In addition, the trifluoroacetyl substituent could be easily removed. Subsequent investigation will be in our real system.

4.6. Alternative approach to stenine ring system

4.6.1. One-pot synthesis of Sonogashira precursor (4.75)

Encouraged by the success of this model study, we decided to install the trifluoromethyl ketone as an electron withdrawing group in the pyrrole system. Under our optimum conditions, the Friedel-Crafts reaction of alcohol (**4.31**) was then carried out with the trifluoroacetic anhydride in diethyl ether (**Scheme 4.34**). A good yield of 83% of trifluoroacetyl-pyrrole (**4.74**) was isolated after purification. During this process the free alcohol was also acylated. The formation of the product was confirmed by the absence of the broad band at 3361 cm^{-1} for the hydroxyl functionality and the appearance of bands at 1785 cm^{-1} and 1657 cm^{-1} for the ester ketone and acetyl ketone respectively. The ^{1}H NMR spectrum of trifluoro-pyrrole (**4.74**) showed extensive line broadening signal for the nitrogen attached methylene protons at room temperature, which we previously observed in the trichloro ester (**4.53**) (**Scheme 4.18**, **Figure 4.4**). The disappearance of the triplet peak at 5.88 ppm for the *α*-carbon proton and the appearance of multiplet between 4.55-4.38 ppm indicative for the oxygen attached methylene protons confirmed the product formation.

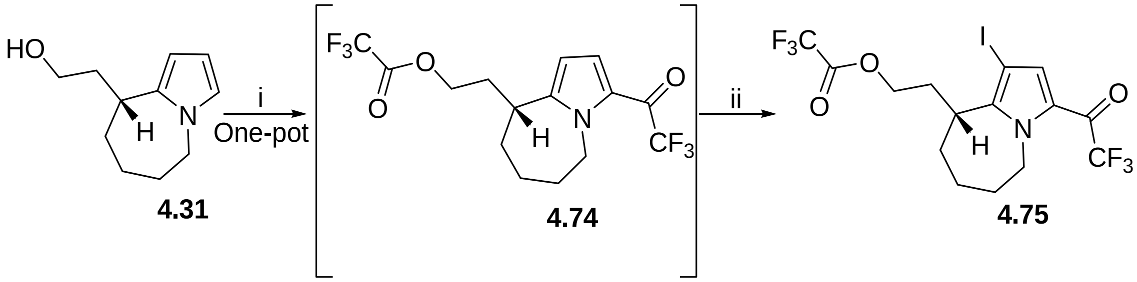


Scheme 4.34

Reagents and conditions: a) $(CF_3CO)_2O$, diethyl ether, RT, 2 h, 83%; b) ICl, CH_2Cl_2, 2 h, 0 °C to RT, 88%.

Clean *β*-iodination was then achieved by treatment with iodine monochloride in dichloromethane, providing the iodo-trifluoro ketone (**4.75**) in 88% yield after purification (**Scheme 4.34**). As before, the R_f of the product and the starting material were the same and the reaction progress was monitored by the ^{1}H NMR analysis. The formation of iodo-trifluoro ketone (**4.75**) was clearly identifiable from the disappearance of peak at 6.08 ppm in the ^{1}H NMR spectrum, which indicates the *β*-iodination in the pyrrole ring. This was further confirmed by the appearance of the quaternary carbon attached to iodine at 68.0 ppm in the^{13}C NMR spectrum.

As the acylation and iodination reactions are very clean, we then examined a novel one-pot synthesis of iodo-trifluoro ketone (**4.75**) from the alcohol (**4.31**) (**Scheme 4.35**). In addition, the by-products for both substitution reactions are acids (CF_3COOH and HCl). The rate of acylation is the same in dichloromethane and diethyl ether (**Table 4.8**, entries 1 and 2). However, the rate of iodination is highly solvent dependent: at RT, iodination of trifluoro-pyrrole (**4.74**) in dichloromethane is complete within two hours in a good yield of 70% (two steps yield, entry 1). In diethyl ether, a period of 48 hours was required to complete the reaction and a lower yield of 45% was obtained (two steps yield, entry 2). We reasoned that this is due to the formation of a less reactive solvent-pseudohalogen complex with ether (**Figure 4.5**).[124] Interestingly, after several experiments we found that switching the solvent between the two reactions resulted in an excellent yield of 81% (two steps) (entry 3). After the completion of the Friedel-Crafts reaction in diethyl ether, the solvent was removed under vacuum and then dichloromethane was added to the reaction mixture for the iodination.



Scheme 4.35. One-pot synthesis of Sonogashira precursor

Reagents and conditions: i) $(CF_3CO)_2O$, diethyl ether, RT, 2 h; ii) ICl, CH_2Cl_2, 2 h, 0 °C to RT, 2 h, 81%.

Table 4.8.

Entry	Conditions	FC reaction time/ h	Iodination time /h	Yield
1	CH_2Cl_2, RT	2	2	70%
2	Diethyl ether	2	48	45%
3	Diethyl ether, CH_2Cl_2, RT	2	2	81%

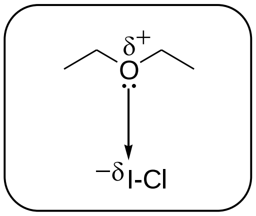
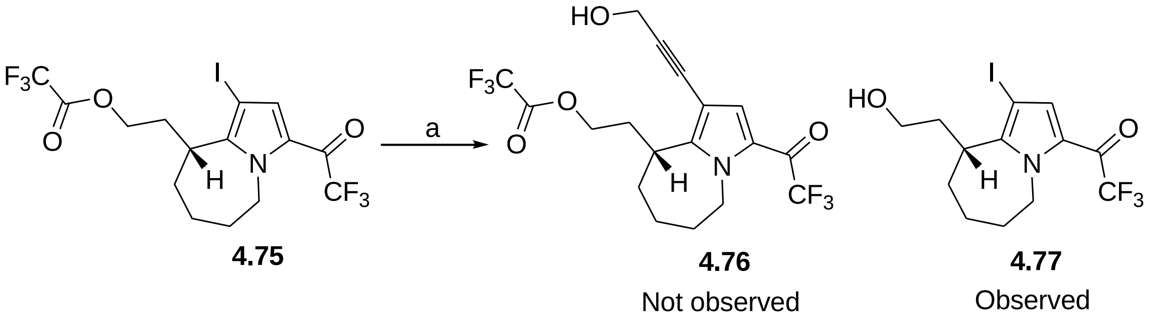


Figure 4.5. Pseudohalogen complex of diethyl ether with ICl

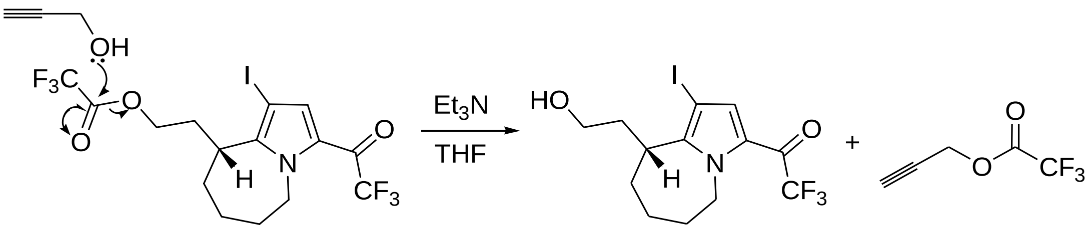
4.6.2. Sonogashira coupling with iodo-trifluoro ketone (4.75)

With the iodo-trifluoro ketone (**4.75**) in hand, the Sonogashira coupling was then attempted. Unfortunately, under the optimum conditions used to prepare the trifluoro-alkyne (**4.68**) (**Scheme 4.27**), the reaction failed and hydroxy-trifluoro ketone (**4.77**) was isolated in 80% yield (**Scheme 4.36**). The formation of the hydroxy-trifluoro ketone (**4.77**) presumably is due to transesterification of the trifluoroacetate group (**Scheme 4.37**). The formation of deacylation product (**4.77**) was identified from the absence of band at 1786 cm^{-1} for the ester ketone and the presence of a broad band at 3351 cm^{-1} for the OH functionality. While the ^1H NMR spectrum displayed a triplet at 3.62 ppm (J = 4.9 Hz) indicative for the oxygen attached methylene protons. The by-product trifluoroacetate-alkyne (**4.78**) was not isolated (**Scheme 4.37**). On the other hand, the coupling reaction with the THP ether of propargylic alcohol (**2.41**) under the same conditions, failed due to decomposition of the starting material. Disappointing with this result and without further exploration, we decided to investigate the Sonogashira coupling with the TBS trifluoroketone (**4.79**), which is similar to our previous synthesis of alkyne alcohol (**4.29**) (**Scheme 4.21**).



Scheme 4.36.

Reagents and conditions: a) propargyl alcohol, $(Ph_3P)_2PdCl_2$,CuI, Et_3N, THF, 0 °C to RT, 14 h.

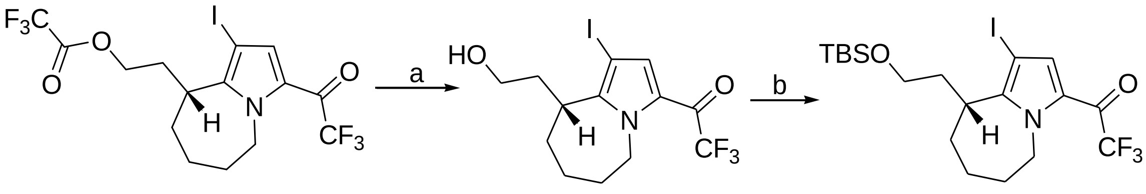


4.75 **4.77** **4.78**

Scheme 4.37. Possible mechanism for transesterification

4.6.3. Synthesis of TBS trifluoroketone (4.79)

The trifluoroacetate group of (**4.75**) was cleaved by treatment with triethylamine in methanol, yielding the hydroxy-trifluoro ketone (**4.77**) in 95% yield. In order to simplify the workup procedure, the use of solid supported resins was investigated. Interestingly, employing poly(4-vinyl pyridine) as a base catalyst resulted in a quantitative yield without purification (**Scheme 4.38**). On the other hand, under acidic conditions with the use of Amberlyst-15 in methanol, furnished the hydroxy-trifluoro ketone (**4.77**) in 80% yield, and along with 10% of starting material.



4.75 **4.77** **4.79**

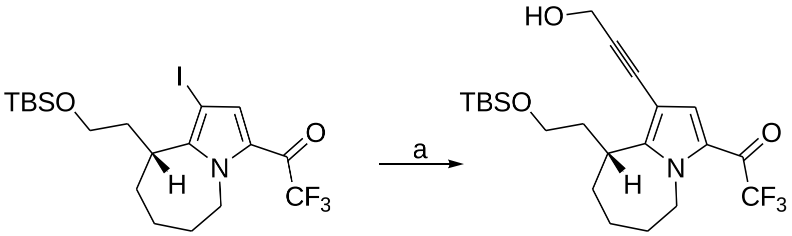
Scheme 4.38.

Reagents and conditions: a) MeOH, poly(4-vinyl pyridine), RT, 22 h, 99%; b) TBSCl, imidazole, CH_2Cl_2, 3 h, 99%.

The free alcohol of hydroxy-trifluoro ketone (**4.77**) was protected as its TBS ether under standard conditions, to give TBS trifluoro-ketone (**4.79**) in quantitative yield (**Scheme 4.38**). The disappearance of broad band at 3351 cm^{-1} for the OH group in the IR spectrum and the presence of singlets at 0.88, 0.04 and 0.03 ppm in the ^{1}H NMR spectrum were indicative of the TBS functionality and confirmed the product formation.

4.6.4. Sonogashira coupling with TBS trifluoroketone (4.79)

The Sonogashira coupling of TBS-trifluoroketone (**4.79**) with propargyl alcohol under the optimum homogeneous conditions used to prepare trifluoro-alkyne (**4.68**) furnished the TBS-alkyne (**4.80**) in 70% yield. To our delight, under Cosford conditions,[112] using palladium on carbon, an excellent yield of 87% was obtained after purification (**Scheme 4.39**). The IR spectrum showed a broad band at 3412 cm^{-1} indicative of the hydroxy group and a characteristic band for the alkyne at 2233 cm^{-1}. The ^{1}H NMR spectrum displayed a doublet at 4.42 ppm (J = 5.3 Hz) for the oxygen attached methylene protons, which confirmed the product formation. The advantage of Cosford's heterogeneous conditions is the simple purification method. The palladium can be removed by simple filtration, whereas in the homogeneous conditions careful purification was required in order to separate the TBS-alkyne (**4.80**) from the palladium residue during column chromatography.



4.79 **4.80**

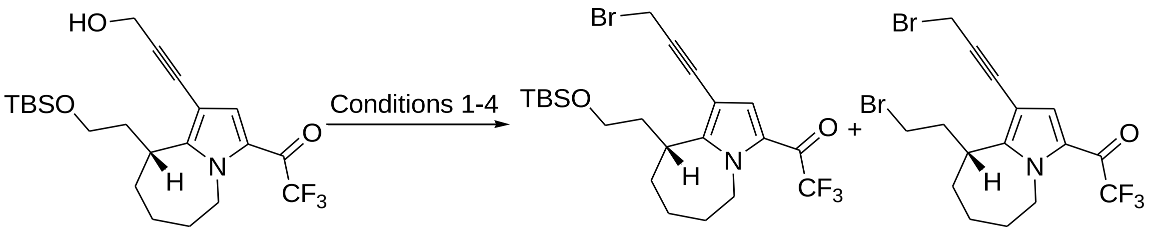
Scheme 4.39.

Reagents and conditions: a) Propargyl alcohol, 10% Pd/C, PPh_3, CuI, K_2CO_3, 85 °C, 1,2-dimethoxyethane, 14 h, 87% [three steps yield from iodo-trifluoro ketone (**4.75**)].

4.6.5. Synthesis of bromo-trifluoroketone (4.81)

With the Sonogashira coupled product (**4.80**) in hand, the crucial step in our synthetic route, the preparation of bromo-trifluoroketone (**4.81**), was then carried out under modified Appel conditions (**Scheme 4.40**). The TBS-trifluoroketone (**4.80**) was treated with CBr_4 and PPh_3 in the presence of 4 Å molecular sieves in anhydrous dichloromethane under our optimum conditions used to prepare pyrrole-bromide (**4.64**) (**Scheme 4.30**). A moderate yield of 41% of bromo-trifluoroketone (**4.81**) was obtained accompanied by a small amount of the dibromide (**4.82**) (**Table 4.9**, entry 1).[125] The formation of the desired bromo-trifluoroketone (**4.81**) was confirmed from the absence of the OH band in the IR spectrum and the presence of a singlet at 4.14 ppm for the bromo attached methylene protons in the ^1H NMR spectrum. The structure and stereochemistry of the pyrrole-bromide (**4.81**) was confirmed by X-ray crystallography[42] (**Figure 4.6**). The formation of dibromide (**4.82**) was identified from the ^1H NMR spectrum, which showed the disappearance of the TBS group and the presence of a multiplet between 3.51-3.32 ppm for the bromo attached methylene protons. This was further supported by the HRMS analysis (calculated for $C_{16}H_{17}F_3{}^{79}Br_2NO$ (M^++H) 453.9629 found 453.9630). The isolation of this by-product (**4.82**) indicated to us the formation of HBr from adventitious moisture. A possible mechanism for the formation of HBr is shown in **Scheme 4.41**. This noteworthy observation also revealed the reason for the decomposition of alkyne alcohol (**4.27**) in our previous attempts to synthesis the bromo-ester (**4.58**) under Appel conditions (**Scheme 4.23**).

In order to avoid the by-product (**4.82**), a series of conditions were screened with different bases. Addition of calcium carbonate resulted in an increased yield of the desired bromide (**4.81**) and a reduced yield of the dibromide (**4.82**) (entry 2). To our delight, use of a weak homogeneous base with low nucleophilicity, collidine, resulted in the formation of the desired bromide in a good yield of 83% (entry 4). On the other hand, use of Pyne's conditions, by addition of Et_3N, resulted in no isolable bromide and decomposition of the starting material was observed (entry 3).[126]This is likely to be due to the nucleophilicity of Et_3N.



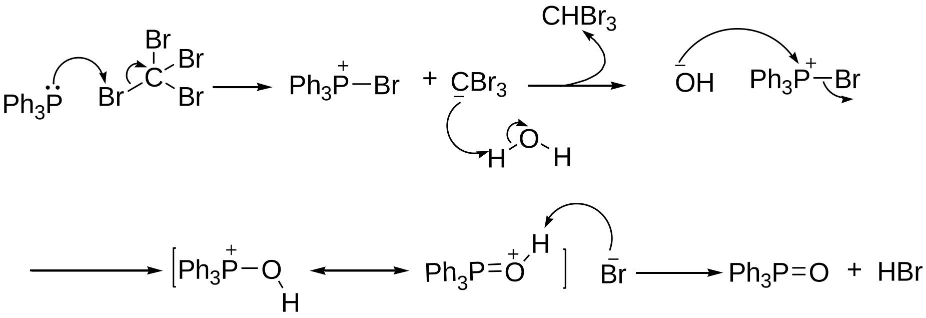
4.80 **4.81** **4.82**

Scheme 4.40.

Table 4.9.

Entry	Conditions[a]	Yield of **4.81**/%	Yield of **4.82**/%
1	CBr_4, PPh_3	41	10
2	CBr_4, PPh_3, $CaCO_3$	60	5
3	CBr_4, PPh_3, Et_3N	0	0
4	CBr_4, PPh_3, Collidine	83	0

[a] All reactions were carried out in anhydrous CH_2Cl_2 for 1 hour at 0 °C in the presence of 4Å molecular sieves.



Scheme 4.41. Mechanism of HBr formation

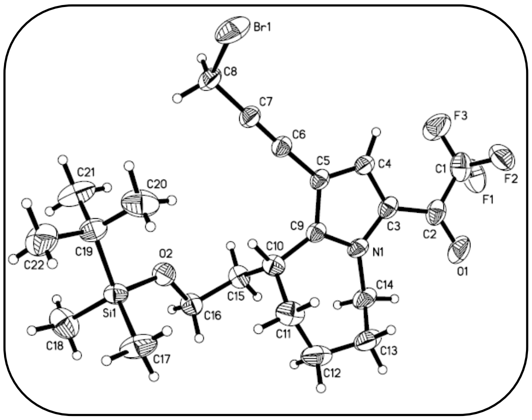
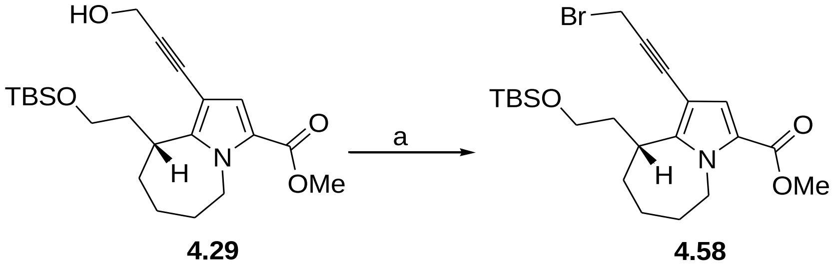


Figure 4.6. X-ray structure of bromo-ester (4.81)

4.6.6. Synthesis of bromo-ester (4.58)

Subsequently, the synthesis of bromo-ester (**4.58**) was re-examined under our modified optimal Appel conditions (**Scheme 4.42**). The alkyne alcohol (**4.29**) was reacted with CBr_4 and PPh_3 in the presence of molecular sieves and collidine, to furnish the bromo-ester (**4.58**) in a moderate yield of 57%. We reasoned that the difference in yields between the two reactions (**Scheme4.40** and **4.42**) were due to the presence of the more electron withdrawing trifluoroacetyl group over the methoxycarbonyl group.

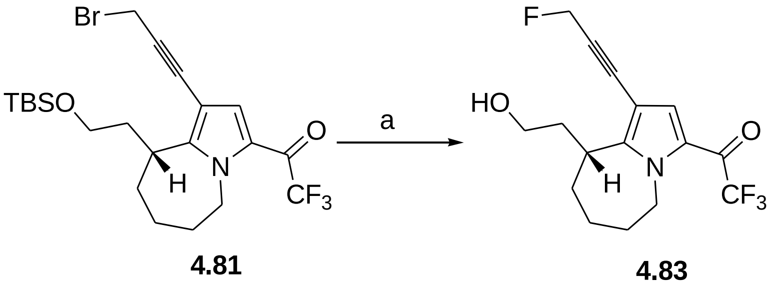


Scheme 4.42.

Reagents and conditions: a) CBr_4, PPh_3, Collidine, 4Å molecular sieves, CH_2Cl_2, 0 °C, 57%.

4.6.7. Deprotection of TBS group

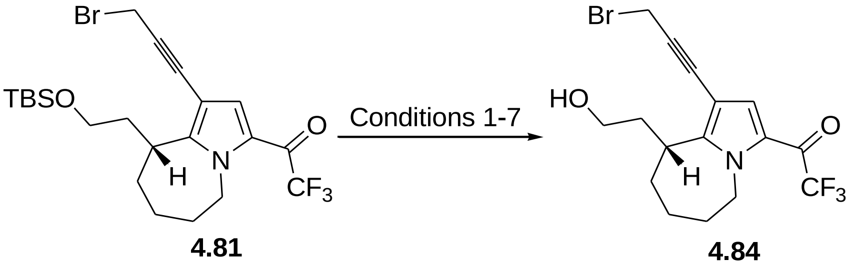
The removal of silyl protection group was another troublesome transformation in our synthesis, again due to the electron rich nature of the pyrrole. Deprotection of bromo-trifluoroketone (**4.81**)under usual conditions with the use of TBAF, resulted in the formation of the propargylic fluoride (**4.83**) in 48% yield (**Scheme 4.43**). The IR spectrum showed a broad band at 3418 cm^{-1}indicative for the alcohol functionality. The ^{1}H NMR spectrum displayed a doublet at 5.16 ppm with a characteristic coupling F-H constant of 48.5 Hz for the fluoro attached methylene protons, which confirmed the product formation.



Scheme 4.43.

Reagents and conditions: a) TBAF, THF, RT, 14 h, 48%.

On the other hand, deprotection of pyrrole-bromide (**4.81**) under acidic conditions with the use of Amberlyst-15 in methanol, failed due to decomposition of the starting material (**Scheme 4.44**) (**Table 4.10**, entry 1).[127]Similarly, mildly acidic conditions,use of PS-PPTS, also resulted in decomposition (entry 2). Fortunately, a trace amount of the pyrrole-alcohol (**4.84**) was isolated with a limited reaction time along with 20% of recovered starting material (entry 3). We hypothesized that the decomposition and reduced yield was through a S_N1 (carbocation) pathway (**Scheme 4.45**). In general, the S_N1 pathway is less favored in a less polar solvent. Hence, we reduced the polarity of the medium by, first, diluting the methanol with dichloromethane, which resulted in an increased yield of pyrrole-alcohol (**4.84**) to 60% (entry 4).



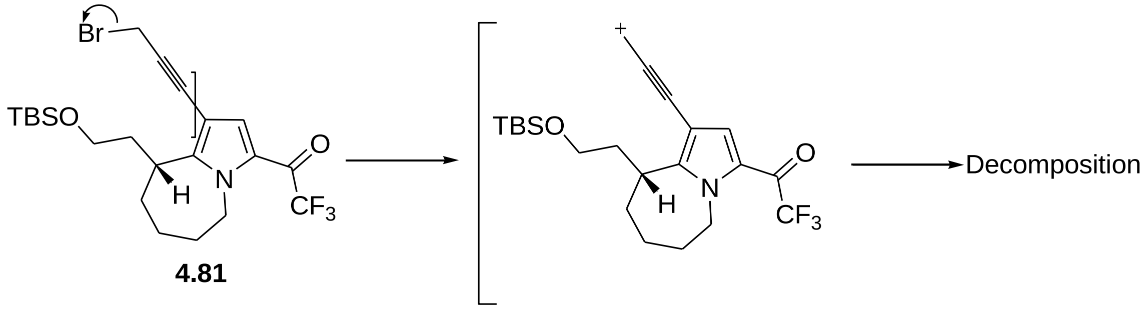
Scheme 4.44.

Table 4.10.

Entry	Conditions	Time/ h	Temp/°C	Yield/%
1	Methanol, Amberlyst-15	14	RT	Decomposed
2	Methanol, PPTS	10	RT	Decomposed
3	Methanol, Amberlyst-15	2	RT	10[a]
4	CH_2Cl_2, Methanol (10:1)	24	RT	60
5	*i*-PrOH, Amberlyst-15[b]	48	RT	70
6	IPA, DOWEX-50WX2[b]	24	RT	70
7	*i*-PrOH, Amberlyst-15	12	60	60
8	*i*-PrOH, Amberlyst-15[c]	24	RT	90

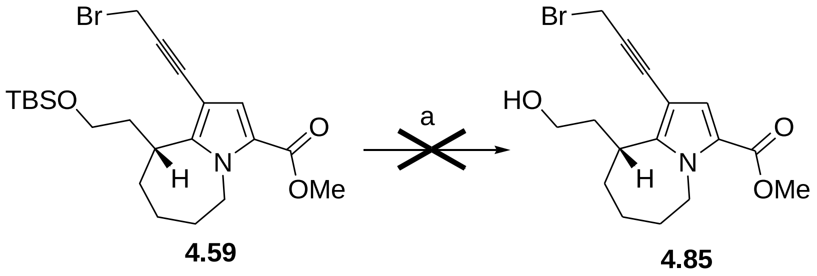
[a] 20% of starting material recovered. [b] technical grade; [c] anhydrous.

Furthermore, when the deprotection was carried out in *iso*-propanol, an acceptable yield of 70% was obtained after 48 hours (entry 5). A similar result was observed under the same conditions using DOWEX-50WX2 (entry 6). At an elevated temperature (60 °C), pyrrole-alcohol (**4.84**) was isolated in a moderate yield only (entry 7). In the end, the best result, a 90% yield of pyrrole-alcohol (**4.84**) was obtained using anhydrous *iso*-propanol (entry 8). The desired pyrrole-alcohol (**4.84**) was identified from the presence of broad band at 3467 cm^{-1} for the alcohol group. The ^{1}H NMR spectrum showed the absence of TBS group and displayed a multiplet between 3.74-3.54 ppm indicative of the oxygen attached methylene protons,which confirmed our desired product.



Scheme 4.45. Possible mechanism for the decomposition of pyrrole-bromide (**4.81**)

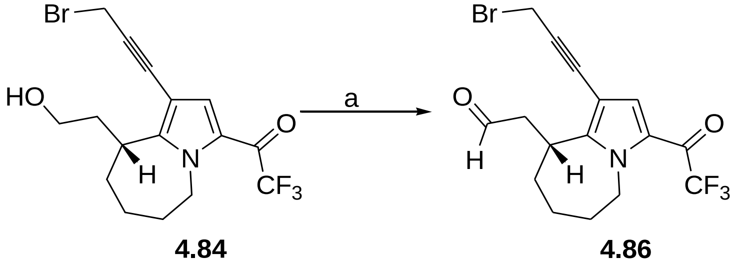
In contrast, even under these conditions, attempted deprotection of the bromo-ester (**4.59**) resulted in decomposition (**Scheme 4.46**). As a consequence we could not carry any of the methyl ester substituted materials further in the synthesis. This result confirmed the unique capability of the trifluoroacetyl functionality in the pyrrole system.



Scheme 4.46.

Reagents and conditions: a) *i*-PrOH, Amberlyst-15, RT.

With the pyrrole-alcohol (**4.84**) in hand, oxidation was then carried out using the Dess-Martin periodinane. A yield of 84% of pyrrole-aldehyde (**4.86**) was isolated after purification (**Scheme 4.47**). On the other hand, employing IBX in DMSO resulted in a low yield of 20% with decomposition of the remaining material. The formation of pyrrole-aldehyde was observed from the absence of OH band and the presence of an aldehyde band at 1723 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum also displayed the characteristic aldehyde peak at 9.83 ppm, which confirmed our desired product.

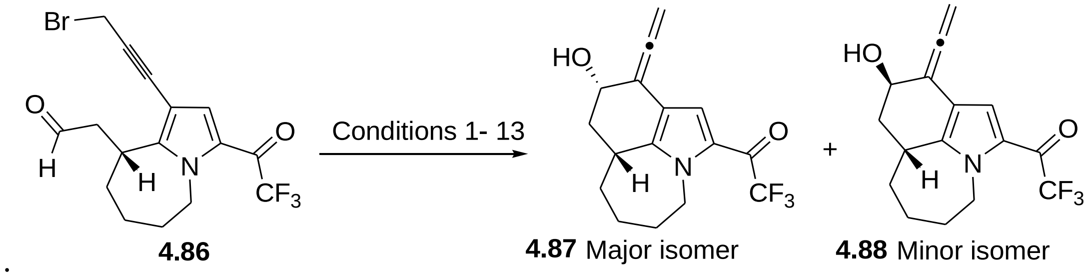


Scheme 4.47.

Reagents and conditions: a)DMP, CH_2Cl_2, 0 °C to RT, 3 h, 84%.

4.6.8. Synthesis of allenol (4.87)

With the pyrrole-aldehyde (**4.86**) in hand, the key intramolecular Barbier reaction for the formation of the six membered ring of allenol (**4.87**) was surveyed (**Scheme 4.48**).In our previous synthesis we successfully employed stannous chloride, zinc and indium in such transformations. Using zinc in the presence of NH_4Cl or acetic acid, a mixture of allenol (**4.87**) and its epimer (**4.88**) was observed in a ratio of 50:50 (**Table 4.11**, entries 1 and 2). On the other hand, a slight improvement in *dr* with good yield was found under Mukaiyama'sconditions[10] employing stannous chloride at a reduced temperature (entries 3 and 4). Given these poor results, we therefore, turned our attention to indium.The first attempts with indium in DMF gave no cyclisation product and only recovery of starting material (entry 5). However, the allenic alcohol (**4.87**) was obtained employing indium in mixture of acetic acid with organic solvents (DMF, DMSO, THF and toluene) in moderate diastereoselectivity. The highest diastereoselectivity and yield was obtained using indium in acetic acid-DMF mixture at -40 °C (entry 13). Replacing DMF with THF gave, under the same conditions, the same diastereoselectivity, but in a lower yield of 40% (entry 12). The presence of acetic acid is essential to obtaining high reactivity at this low temperature. The major isomer was isolated in pure form in 52% yield by column chromatography



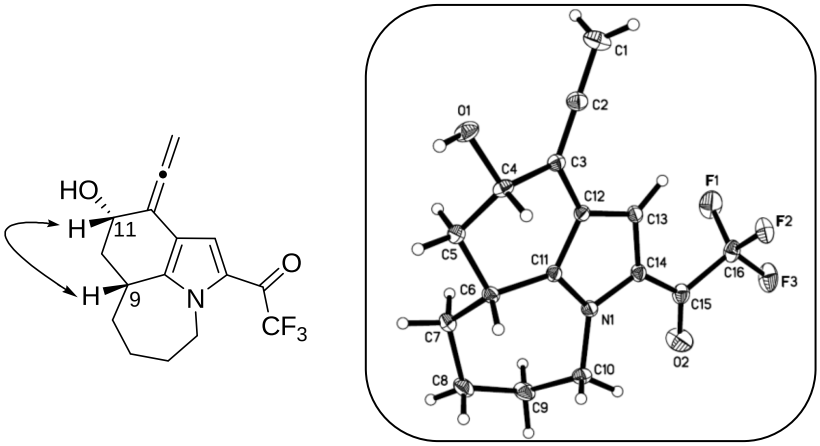
Scheme 4.48.

Table 4.11.

Entry	Conditions	T/ h	T/ °C	Yield/%[a]	*dr* ratio
1	Zn, NH_4Cl, THF (1:4)	5	RT	40	50:50
2	Zn, AcOH , DMF (1:1)	4	RT	15	50:50
3	$SnCl_2$, NaI, DMF, H_2O (10:1)	2	RT	80	57:43
4	$SnCl_2$, NaI, DMF, H_2O (10:1)	12	-10	70	67:33
5	In, DMF	12	RT	0[b]	-
6	In, AcOH	2	RT	70	74:26
7	In, AcOH (10 eq.), THF	4	RT	60	74:26
8	In, AcOH (10 eq.), Toluene	18	RT	50	67:33
9	In, AcOH (10 eq.), DMSO, H_2O (10:1)	2	RT	73	67:33
10	In, AcOH (10 eq.), DMF, H_2O (10:1)	4	RT	75	67:33
11	In, AcOH, DMF (1:1)	2	RT	78	74:26
12	In, AcOH (10 eq.), THF	20	-40	40	78:22
13	In, AcOH, DMF (1:1)	20	-40	70	78:22

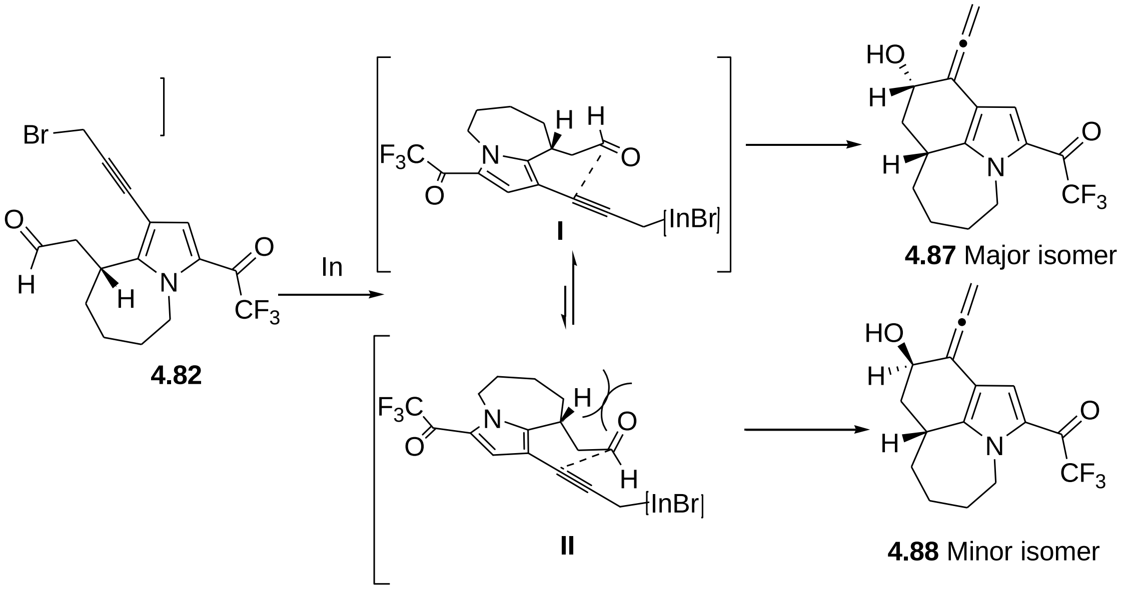
[a] Combined yield of the two diastereoisomers; [b] starting material was recovered.

The ^1H NMR and ^{13}C NMR spectrum of allenol (**4.87**) are given in appendix (page 282). The formation of our desired allenol (**4.87**) was confirmed by the presence of characteristic allene band at 1948 cm^{-1} and a broad band at 3265 cm^{-1} for the OH group. This was further supported by the ^{13}C NMR spectrum, which showed a distinctive allene central carbon peak at 202.1 ppm. Based on the NOESY spectrum, the major isomer (**4.87**) was identified as the *cis*-isomer from the NOE correlation between H-9 and H-11 (**Figure 4.7**). Subsequently this was confirmed by X-ray crystallography[42] (**Figure 4.7**).



NOE correlation X-ray structure

Figure 4.7. NOE correlation and X-ray crystallography of allenol (**4.87**)

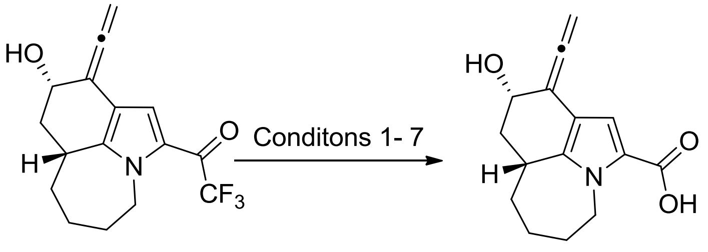


Scheme 4.49. Rationale for *trans* selectivity in cyclisation

A possible mechanism for the formation of the six membered *cis* and *trans* allenol isomer is shown in **Scheme 4.49**. We speculate that the stereoselectivity is controlled by the 1-3 interaction between the carbonyl oxygen and pyrrolic hydrogen. In the reaction, two transition states **I** and **II**are possible. In transition state **I** there is less steric interaction between the carbonyl oxygen and pyrrolic hydrogen, would give *cis* allenol (**4.87**) as the major product. In the other transition state **II**, a 1-3 steric interaction would be encounter between the carbonyl oxygen and pyrrolic hydrogen, which may provide *trans* allenol (**4.88**) as a minor product.

4.6.9. Serendipitous discovery in the synthesis of allenic-acid (4.89 a)

To synthesize the butenolide-acid (**4.91**), two different sequences were subsequently investigated. The first route involved hydrolysis of the trifluoroacetyl ketone of allenol (**4.87**) followed by cyclocarbonylation. The alternative route was the cyclocarbonylation of allenol (**4.87**) followed by hydrolysis. The most challenging step in our synthesis was the hydrolysis of the allenol (**4.87**) (**Scheme 4.50**). A number of conditions with different solvents and different temperatures were investigated (**Table 4.12).** Unfortunately, treatment of allenol (**4.87**) with lithium hydroxide in DMF at 70 °C failed due to decomposition (**Table 4.12**, entry 1). These same conditions were used to prepare allenic acid (**4.73**) in our model studies (**Scheme 4.32**). Replacing DMF with ethanol also resulted in starting material decomposition. Furthermore, no reaction was observed in CH_3CN in the presence of lithium hydroxide at 50 °C (entry 3). Fortunately, after several attempts with different conditions, hydrolysis was successfully achieved in DMSO with the use of lithium hydroxide at 50 °C. However, unexpectedly the allenic acid (**4.89 b**) was isolated in 80% but as a mixture of diastereoisomers (entry 4). A possible mechanism for epimerization of allenol (**4.87**) is shown in **Scheme 4.51**. We speculate that epimerization occurs at the pyrrolic position as the corresponding carbanion is conjugated through the pyrrole ring with the ketone group.Similarly, when the reaction was reaction carried out for a prolonged time at roomtemperature, it also resulted in epimerization (4.4:1) (entry 5). The ^{1}H NMR data of epimerized allenic acid (**4.89 b**) is shown in **Figure 4.8**.The formation of allenic acid (**4.89 b**) was clearly identified in the ^{13}C NMR spectrum, which showed the absence of characteristic quartet peak for the CF_3 functionality and the presence of acid carbonyl group at 162.1 ppm.



4.87

4.89 a

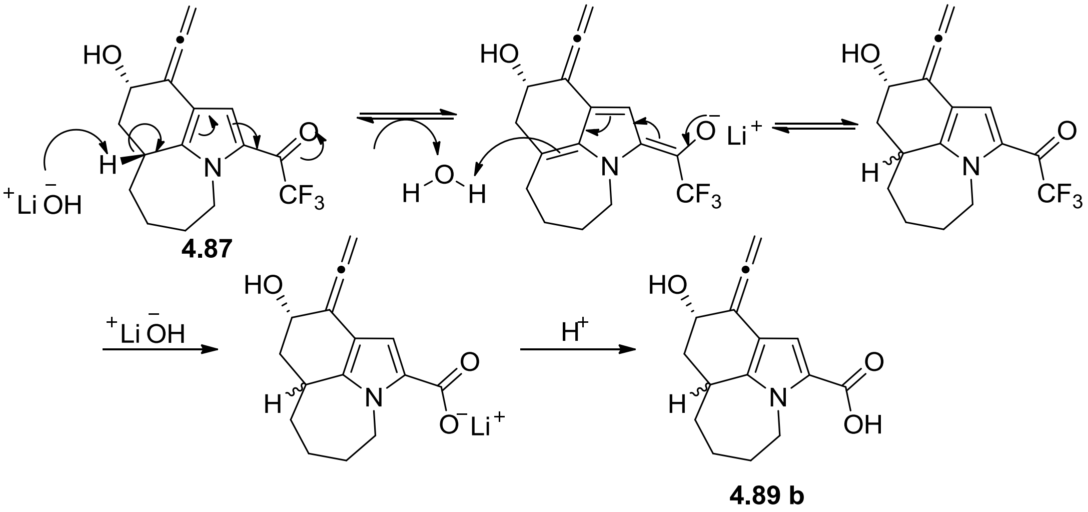
Scheme 4.50

Table 4.12.

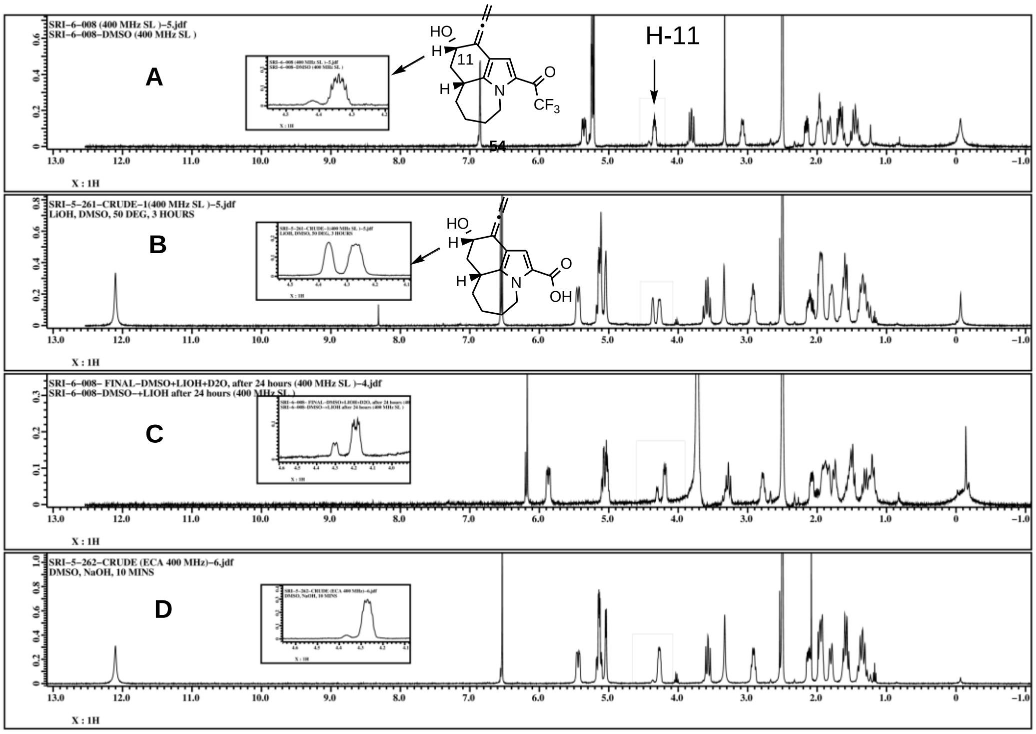
Entry	Conditions	Time/ h	Temp/ °C	Yield/%	Comment
1	LiOH, DMF, H_2O	14	70	0	Decomposed
2	LiOH, EtOH, H_2O	14	50	0	Decomposed
3	LiOH, CH_3CN, H_2O	12	50	0	No reaction[a]
4	LiOH, DMSO, H_2O	3	50	80	Epimerization[b] (1:1)
5	LiOH, DMSO, H_2O	24	RT	80	Epimerization[b] (4.4:1)
6	NaOH, DMSO, H_2O	0.25	RT	90	No epimerization
7	CsOH, DMSO, H_2O	1	RT	80	No epimerization

[a] starting material recovered; [b] see scheme 4.51.

To our pleasant surprise, the hydrolysis of ketone (**4.87**) was found to proceed rapidly upon treatment with sodium hydroxide in wet DMSO, giving the allenic acid (**4.89 a**) in excellent yield of 90% and without epimerization (entry 6). Similarly, under same conditions, employing cesium hydroxide also resulted in good yield, without epimerization (entry 7). We postulate that lithium hydroxide remains ion-paired and hence less reactive in DMSO. A longer reaction time is therefore needed. Whereas, in DMSO, for sodium and cesium, the hydroxide anions are naked which would resultinmorenucleophilicspecies.[128,129]



Scheme 4.51. Possible mechanism for the epimerization of allenol (**4.87**)

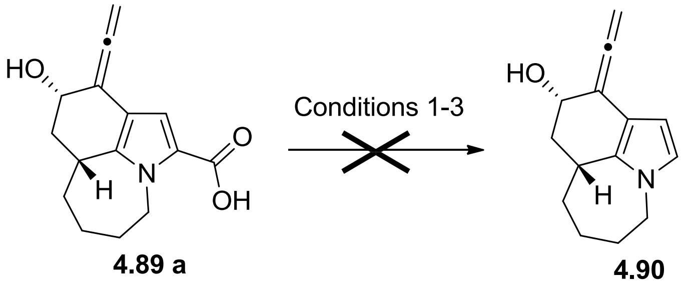


A: Pure allenol (**4.87**); **B**: Allenic acid (**4.89 b**), LiOH, DMSO, H_2O, 50 °C, 3 h; **C**: Allenic acid (**4.89 b**), LiOH, DMSO, H_2O, RT, 24 h; **D**: Allenic acid (**4.89 a**), NaOH, DMSO, H_2O, 15 minutes.

Figure 4.8. ^{1}H NMR (400 MHz, DMSO-d_6) ofallenol (**4.87**), allenic acid (**4.89 b**)and allenic acid (**4.89 a**)

4.6.10. Attempted synthesis of pyrrole-allene (4.90)

Decarboxylation of allenol (**4.89 a**) was then attempted (**Scheme 4.52**). Decomposition of starting material was observed when allenol (**4.89 a**) was treated with TFA in dichloromethane (entry 1). Similarly, heating neat or in the presence of acetic acid (entries 1 and 2) caused decomposition of starting material. We believe that the sensitive allenic alcohol functionality may not be stable to heat or strongly acidic conditions. As a result, we decided to decarboxylate at a later stage, after cyclocarbonylation of allenol (**4.91 a**).



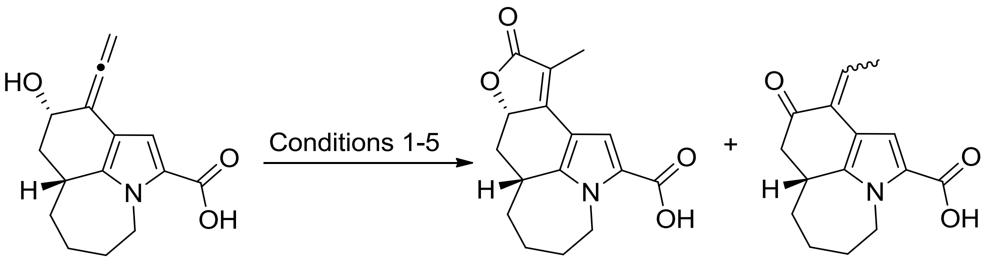
Scheme 4.52.

Table 4.13.

Entry	Conditions	Time/ hr	T/ °C	Comment
1	CH_2Cl_2, TFA	-	RT	Decomposition
2	CH_2Cl_2, acetic acid	3	40	Decomposition
3	Neat, heating	3	140	Decomposition

4.6.11. Synthesis of pyrrole-carboxylic (4.91a)

We next examined the cyclocarbonylation of allenic acid (**4.89 a**) with the $Ru_3(CO)_{12}$ catalyst, which we successfully employed in our previous synthesis of (-)-mintlactone and (±)-stemoamide. However in this case, cyclocarbonylation of the carboxylic acid (**4.89 a**) under Takahashi's conditions3 proceeded to give the butenolide-acid (**4.91 a**) in just 40% yield with concurrent formation of by-product enone (**4.92**) in 30% yield (**Scheme 4.53**) (Table 4.14, entry 1). Both Takahashi3[c] (**Scheme 2.17**,Page no. 61) and Hong[59h] (**Scheme 3.14**,Page no 83) have proposed mechanisms for the cyclocarbonylation that involve formation of a carbon ruthenium single bond at the central carbon of the allene. Formation of enone (**4.92**) could involve C-H bond formation by reductive elimination from such intermediates. The formation of our desired butenolide (**4.91 a**) was observed from the absence of the allene group and the presence of an *α,β*-unsaturated carbonyl band at 1747 cm^{-1} in the IR spectrum. The ^{13}C NMR spectrum displayed a peak at 175.5 ppm for the *α,β*-carbonyl functionality, which confirmed the product formation. The ^1H NMR and ^{13}C NMR spectrum of the enone (**4.92**) are shown in **Figure 4.9.** The by-product enone (**4.92**) was identified from the ^1H NMR spectrum, which showed a quartet peak for the alkene proton at 6.25 ppm with a coupling constant of 7.6 Hz and a doublet for the allylic methyl at 2.12 ppm with the same coupling constant of 7.6 Hz. This was further confirmed by the appearance of alkene carbons peak at 141.1 and 129.4 ppm and the *α,β*-unsaturated carbonyl peak at 200.0 ppm.The NMR assignments were based on COSY and HMQC experiments. Unfortunately, from the NOESY studies we were unable to resolve the structure of *E* and *Z* isomers of enone (**4.92**).



4.89 **4.91 a** **4.92**

Scheme 4.53.

Table 4.14

Entry	Conditions[a]	Yield of **4.91 a**/%	Yield of **4.92**/%
1	Dioxane, Et_3N (6 eq), $Ru_3(CO)_{12}$ (4 mol%)	40%	30%[b]
2	Dioxane, Et_3N, $Ru_3(CO)_{12}$ (10 mol%)	42%	30%[b]
3	Et_3N, $Ru_3(CO)_{12}$ (4 mol%)	20%	40%[c]
4	2,4,6-Collidine, $Ru_3(CO)_{12}$ (4 mol%)	50%	5%[d]
5	Dioxane, 2,4,6-Collidine (6 eq), $Ru_3(CO)_{12}$ (4 mol%)	68%	14%[d]

[a]All reaction were carried out at 100 °C, under 100 psi for 8-14 hours. [b] 2:1 of *E/Z* isomer; [c] 10:1 of *E/Z* isomer. [d]one isomer.

No marked difference in the yield was found with increasing the amount of catalyst loading up to 10 mol% (entry 2). The reaction in collidine under Tsubuki's conditions[33n]gave the enone (**4.92**) in 5% yield and our desired product (**4.91 a**) was isolated in 50% yield.Finally, the best result was achieved when collidine was employed as a base additive, under a pressure of 100 psi of CO (entry 5). The yield of our desired product was increased to 68% and the enone (**4.92**) was obtained in just 14% yield (entry 5). In contrast, the reaction in triethylamine as a solvent resulted in a reduced yield (20%) of the butenolide-acid (**4.91 a**) and an increased yield (40%) of enone (**4.92**) (entry 4).

The ratio of *E* and *Z* isomers of enone (**4.92**) varies with the different conditions (**Table 4.14**). The role of base in this carbonylation is not clear.

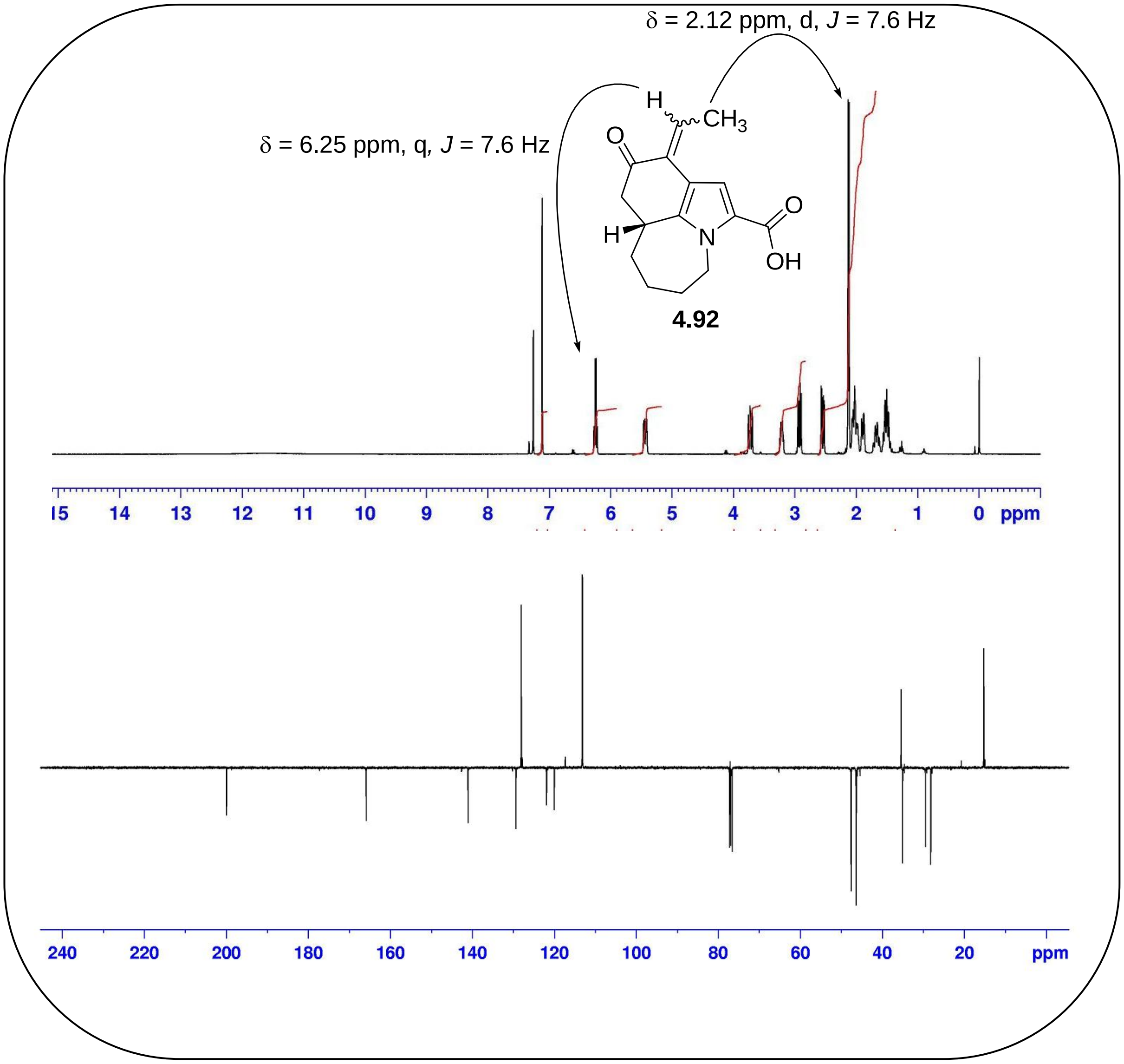
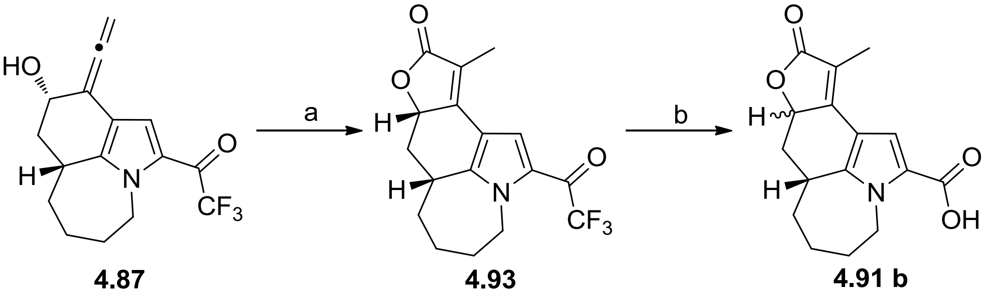


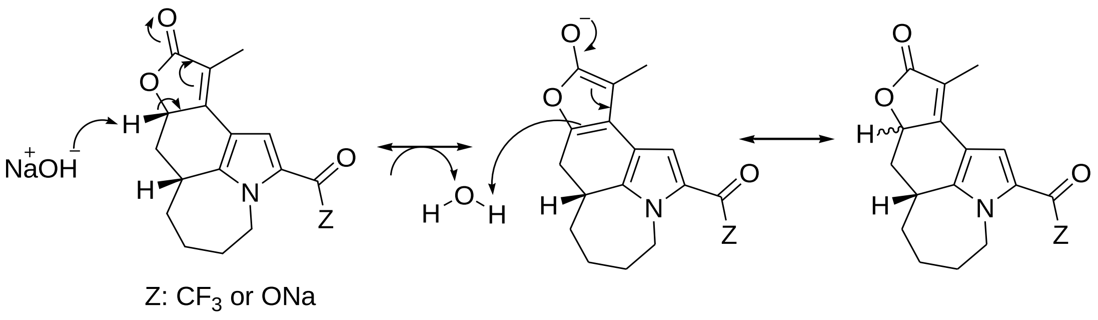
Figure 4.9. ^{1}H NMR (400 MHz, CDCl$_3$) and ^{13}C NMR (100 MHz, PENDANT, CDCl$_3$) of enone (**4.92**)

The alternative sequence, cyclocarbonylation followed by hydrolysis was also investigated for the synthesis of butenolide-acid (**4.91 a**) (**Scheme 4.54**). The cyclocarbonylation of allenol (**4.87**) proceeded smoothly, furnishing the trifluoro-butenolide (**4.93**) in excellent yield of 87% and none of the corresponding enone. The formation of trifluoro-butenolide (**4.93**) was identified from the absence of the allene band and the presence of a band due to an *α,β*-unsaturatedcarbonyl at 1747 cm^{-1} in the IR spectrum. Disappointingly, when hydrolysis of trifluoro-butenolide (**4.93**) was carried out under our optimized conditions (NaOH, DMSO, **Table 4.12**, entry 6) epimerized butenolide-acid **(4.91 b**) was isolated in quantitative yield. A possible mechanism for epimerization of trifluoro-butenolide (**4.93**)is shown in **Scheme 4.55**. We speculate that the epimerization could occur at oxygen attached methine carbon proton, which is adjacent to the conjugated *α,β*-unsaturatedcarbonyl system.[130]



Scheme 4.54.

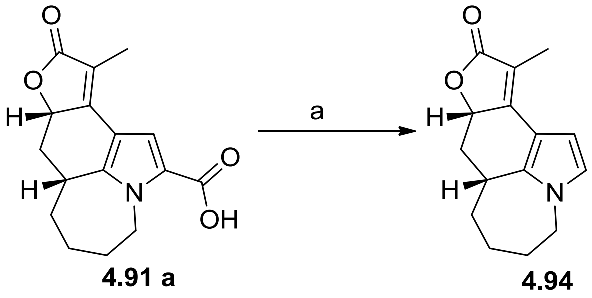
Reagent and conditions: a) $Ru_3(CO)_{12}$, Et_3N, CO (100 psi), dioxane, 100 °C, 14 h, 87%; b) NaOH, DMSO, RT, 30 minutes, 99%.



Scheme4.55. Possible mechanism for epimerization of trifluoro-butenolide (**4.93**)

4.6.12. Synthesis of tetra cyclic pyrrole (4.1)

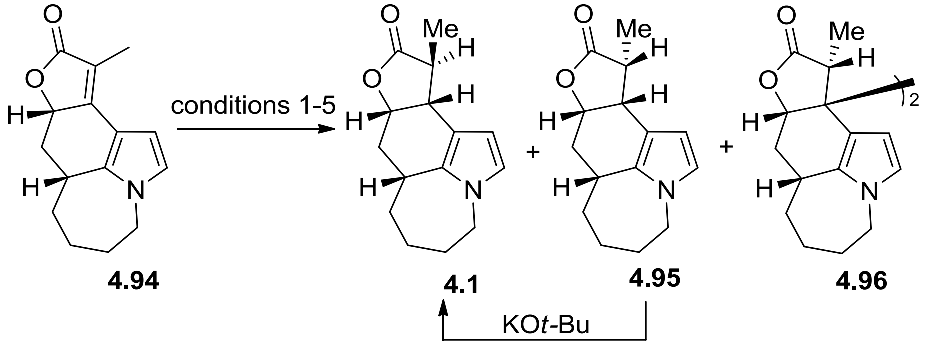
The next step in our synthesis is the decarboxylation of butenolide-acid (**4.91 a**) (**Scheme 4.56**). Heating the butenolide-acid (**4.91a**) at 160 °C resulted in decarboxylation and gave pyrrole (**4.94**) in 80% yield. Alternatively, treatment of the butenolide-acid (**4.91 a**) with trifluoroacetic acid in dichlormethane at reflux, furnished the pyrrole (**4.94**) in a slightly higher yield of 90%. The pyrrole survives the acidic condition because of conjugation to an*α,β*-unsaturatedcarbonyl lactone. The IR spectrum showed the absence of the carboxylic acid functionality. This was further confirmed by the appearance of doublet at 6.61 ppm with a coupling constant of 2.9 Hz for the nitrogen attached aromatic *α*-carbon proton.



Scheme 4.56.

Reagent and conditions: a) Neat 160 °C, 2 h, 80% or TFA, CH_2Cl_2, 40 °C, 4 h, 90%.

For the end game, we attempted to reduce the alkene of the butenolide (**4.94**) under Jacobi's conditions,[63] which we successfully employed in the (±)-stemoamide synthesis. Treatment of pyrrole (**4.94**) with $NaBH_4$ in the presence of $NiCl_2$, failed to give our desired product and only starting material was recovered (**Scheme 4.57**) (**Table 4.14**, entry 1).Similarly, even under forcing conditions of refluxing methanol or ethanol also resulted in starting material being recovered (entry 2). We believe that the failure of this reaction may be due to the conjugation of the butenolide double bond with the pyrrole ring.



Scheme 4.57.

Table 4.14.

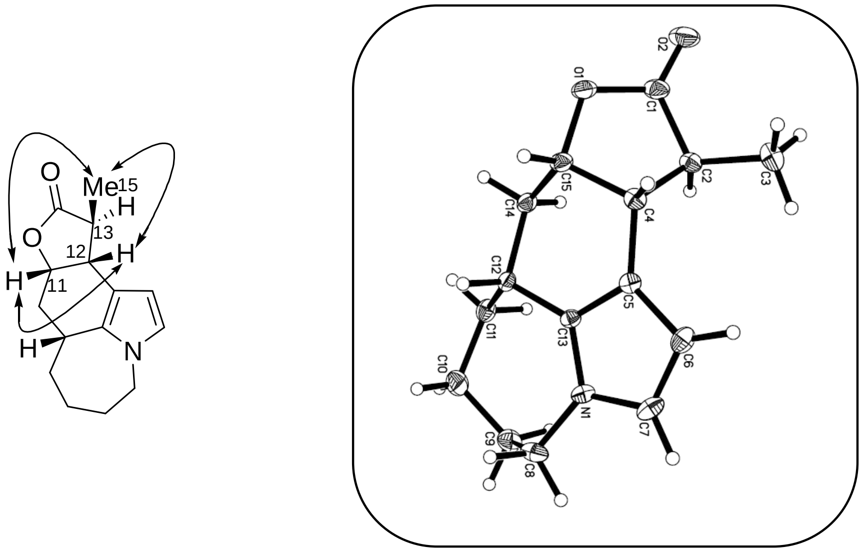
Entry	Conditions	Yield of **4.1**/%	Yield of **4.95**/%	Yield of **4/96**/%
1	$NaBH_4$, $NiCl_2$, MeOH, -30 °C, 20 h	0[a]	-	-
2	$NaBH_4$, $NiCl_2$, MeOH or EtOH, reflux, 10 h.	0[a]	-	-
3	Mg, $HgCl_2$ (10 mol%) MeOH, RT, 3 h.	35	12	15
4	Mg, $HgCl_2$ (10 mol%) MeOH, THF (3:1), -40 °C, 24 h.	20	10	10
5	Mg, MeOH, RT, 24 h.	45	-	22

[a] Starting material was recovered in 60-80%.

Delightfully, reduction was successfully achieved under Pak's conditions (**Scheme 4.57**).[131] The butenolide (**4.94**) was treated with magnesium in the presence of mercuric chloride, resulting in a mixture of products. Upon careful purification by column chromatography, we were able to yield isolate our desired product (**4.1**) in 35% yield along with its epimer (**4.95**) in 12% yield and dimer (**4.96**) in 15% yield. The epimer (**4.95**) could be converted into our desired tetracyclic pyrrole (**4.1**), by treatment with potassium *tert*-butoxide in a mixture of THF and methanol in quantitative yield

(**Scheme 47**). Lowering the reaction temperature for the reductionto -40 °C caused a low yield of lactone (**4.1**) of 20% (entry 4). On the other hand, employing magnesium powder, which eliminates the need for the mercuric chloride and for a prolonged reaction time, led to a stereoselective reduction giving lactone (**4.1**) in 45% yield and accompanied by dimer (**4.96**) in 22% yield (entry 5).

The ^{1}H NMR and ^{13}C NMR spectrum of tetra cyclic pyrrole (**4.1**) are given in appendix (page 283). The ^{13}C NMR spectrum of tetra cyclic pyrrole (**4.1**) showed the absence of alkene carbons and the presence of a carbonyl group at 179.7 ppm. The ^{1}H NMR spectrum displayed a doublet at 1.4 ppm with a coupling constant of 7.1 Hz indicative for the methyl protons which is α to the carbonyl group. The pyrrolic proton was observed as a doublet of doublet at 3.13 ppm with coupling constants of 10.8 and 7.7 Hz. The NMR assignments are based on COSY and HMBC experiments. The major isomer was determined to have the structure shown by the analysis of NOE interactions in the NOESY spectrum (**Figure 4.10**). The NOESY spectrum (Appendix page 284) showed a correlation between H-11 and H-12, which indicates that these two protons are *cis* to each other. On the other hand, the absence of a NOE correlation between H-12 and H-13 and the presence of a definite NOE correlation between H-12 and CH_3-15 and H-11 suggested that CH_3-15 to be β oriented. These assignments were later confirmed by X-ray crystallography[42] (**Figure 4.10**).



NOE correlations

X-ray structure

Figure 4.10. NOE correlations and X-ray crysatallography of tetra cyclic pyrrole (**4.1**).

The ^{1}H NMR spectrum of minor isomer (**4.95**) showed an apparent triplet at 3.61 ppm with a coupling constant of 7.0 Hz indicative of the pyrrolic proton. As in tetra cyclic pyrrole (**4.1**), the same NOE correlation was observed between H-11 and H-12 (**Figure 4.11**) in the NOESY spectrum of minor isomer (**4.95**) (Appendix page 284.). However, the absence of correlation between H-12 and CH_3-15 and the presence of NOE correlations between H-11 and H-13 and H-15, indicated that H-13 should be on same side as H-11. These correlations revealed that the minor isomer (**4.95**) was epimeric at the position *α* to the lactone carbonyl (**Figure 4.11**).

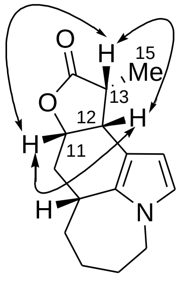
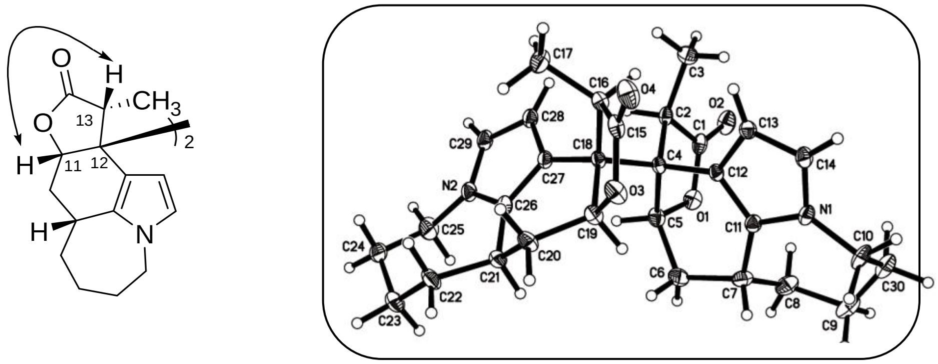


Figure 4.11. NOE correlations of minor isomer (**4.95**)

The dimer (**4.96**) was identified by the absence of pyrrolic carbon proton (C-12) in the ^{1}H NMR spectrum and presence of quaternary carbon peak at 54.0 ppm in the ^{13}C NMR spectrum. This was supported by HRMS analysis (calculated for $C_{30}H_{37}N_2O_4$ (M$^+$+H) 489.2753 found 489.2751). In the NOESY spectrum (Appendix page 285), a definite correlation was observed between H-11 and H-13, which suggested that H-13 is β orientated. Subsequently, the structure and stereochemistry of dimer (**4.96**) was confirmed from X-ray crystallography[42] (**Figure 4.12**).

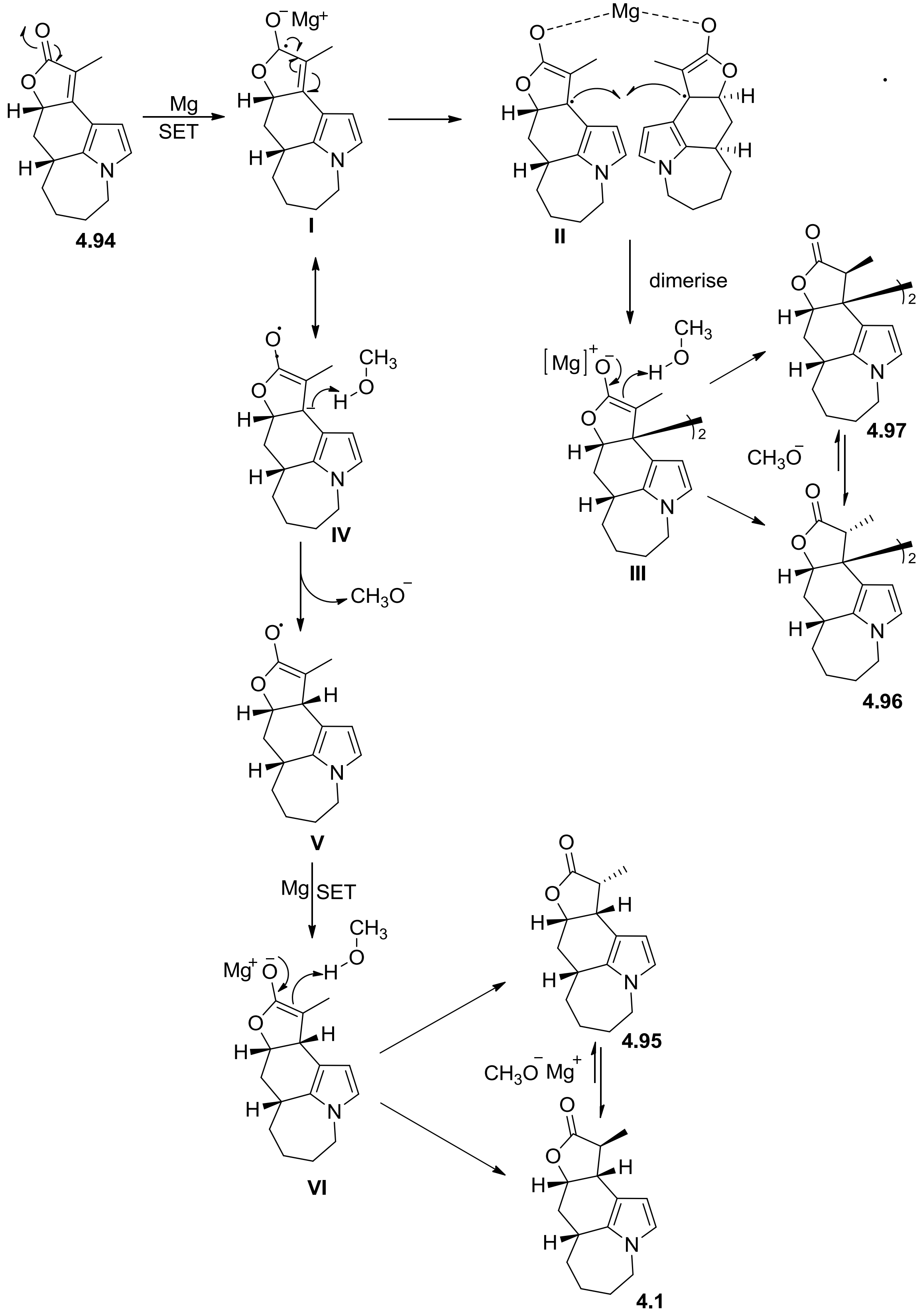


NOE correlation

X-ray structure

Figure 4.12. NOE correlation and X-ray crystallography of dimer (**4.96**)

A possible mechanism for the formation of the tetracyclic pyrrole (**4.1**) and dimer **4.96**) is shown in **Scheme 4.58**. The first step is similar to the pinacol reaction[132] and acyloin reaction,[133] which is the single electron transfer from magnesium to the carbonyl to provide ketyl anion radical intermediate (**I**). Subsequently,leading the formation of radical anioncomplex (**II**) and *O*-radical anion intermediate (**IV**). The self coupling of radical anion intermediate (**II**) from the less hindered convex face would give the dimeric enol (**III**). Protonation occurs from the less hindered *β*-face to give the thermodynamically stable dimer (**4.96**) which could be in equilibrium with kinetically stable dimer (**4.97**). The *O*-radical anion intermediate (**IV**) accepts a proton on the top face (*β*-face) and then accepts a second electron from the metal to give an enolate intermediate (**VI**). Then, protonation from the less hindered *β*-face gives a kinetically stable epimer (**4.95**) which is equilibrium with the thermodynamically more stable tetracyclic pyrrole (**4.1**).


4.94
Mg
SET
I
II
dimerise
III
4.97
CH_3O^-
4.96
IV
CH_3O^-
V
Mg
SET
VI
4.95
CH_3O^- Mg^+
4.1

Scheme 4.58.

4.7. Conclusion

In summary, the synthesis of tetracyclic compound (**4.1**) demonstrates the versatility of pyrrole of a starting material for the alkaloids by bond formation at multiple sites around the heteroaromatic nucleus. The high density electron density of the pyrrole ring can cause complications in many otherwise straight forward reactions, but can be controlled by using the trifluoroacetyl group. This group is more effective than methoxycarbonyl group in modulating the electron density of the pyrrole nucleus. In this synthetic study, we have discovered mild and efficient conditions for the hydrolysis of trifluoroacetyl functionality. The utility of the intramolecular propargylic Barbier reaction has been again demonstrated stereoselectively to construct the complex butenolide ring system.

Chapter 5 Experimental

5.1. General experimental details

All reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using oven-dried glassware (120 °C), which was cooled under vacuum. Anhydrous tetrahydrofuran and diethyl ether were distilled from sodium metal and benzophenone under nitrogen. Anhydrous dichloromethane was dried by distillation from CaH_2 immediately prior to use under nitrogen. Anhydrous methanol and isopropyl alcohol was distilled from activated magnesium under nitrogen. All other solvents and reagents were used as received. Analytical TLC was carried out on precoated plates (silica gel 60, F254). Column chromatography was performed with silica gel 60 (230–400 mesh).

^{1}H NMR spectra were recorded on a Bruker Advance DPX at 300, 400, 500 MHz or Jeol ECA/SL 400 MHz . ^{13}C NMR spectra were recorded on 75, 100 or 125 MHz. Chemical shifts are recorded in ppm and coupling constants *J*are recorded in Hz. Multiplicities are recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), apparent (app.), broad (br.), multiplet (m).

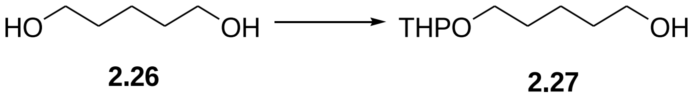
Mass spectra were recorded on a Finnigan LCQ DECA XP MAX Ultra instrument or Finnigan Polaris Q, GCMS XP mass spectrometer.High resolution mass spectra were recorded on a Waters Q-Tof premier instrument or Finnigan MAT95XP instrument. Infrared spectra were recorded ona Shimadzu IR Prestige-21 FTIR or a Bruker Alpha-E FTIR.

Melting points were determined on an OptiMelt MPA 100 and were uncorrected. Optical rotationswere recorded on a Jasco P-1030 polarimeter and are given with units of 10^{-1}degcm^{2}g^{-1}. The angles of rotations were measured at wavelength of 589 nm.

Enantiomeric excess was determined by chiral HPLC analysis, performed on a Shimadzu HPLC and Daicel Chemical Industries Chiralcel OD-H column, eluting with IPA/hexane.

5.2. Experimental section for chapter2

5-(tetrahydro-2*H*-pyran-2-yloxy)pentan-1-ol (2.27)[36]



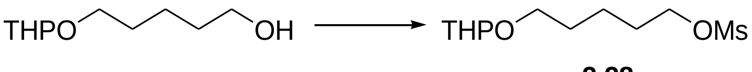
PPTS (1.50 g, 5.94 mmol) was added to a solution of pentane-1,5-diol (**2.26**) (18.7 mL, 179 mmol) and 3,4-dihydro-2*H*-pyran (5.40 mL, 59.5 mmol) in dichloromethane (200 mL) at room temperature. After stirring at room temperature for 12 hours, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL). The mixture was extracted with ethyl acetate (2x300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 50% EtOAc/hexane) to give THP-alcohol(**2.27**) (6.70 g, 60%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 3431, 908.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (1H, t, *J* = 3.5 Hz), 3.91-3.70 (2H, m), 3.64 (2H, app. q, *J* = 6.1 Hz), 3.54-3.33 (2H, m), 1.88-1.40 (12H, m).

^{13}C NMR (100 MHz, $CDCl_3$):δ 98.8, 67.4, 62.5, 62.3, 32.4, 30.6, 29.3, 25.4, 22.4, 19.5.

-(tetrahydro-2*H*-pyran-2-yloxy)pentyl methanesulfonate (2.28)[134]



2.27 **2.28**

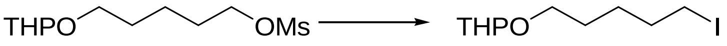
Triethylamine (7.40 mL, 53.2 mmol) and methanesulfonylchloride (4.10 mL, 53.2 mmol) were added to an ice cold solution of THP-alcohol (**2.27**)(5.0 g, 26.5 mmol) in dichloromethane (100 mL) and the mixture was stirred at the same temperature for 2 hours. Saturated aqueous NH_4Cl solution (100 mL) was added and the mixture was extracted with ethylacetate (2×200 ml). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give mesylate (**2.28**) (7.00 g, 99%) as yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 2943, 1465, 1354, 1175, 910.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.55 (1H, t, *J* = 3.6 Hz), 4.22 (2H, m), 3.91-3.64 (2H, m), 3.58-3.31 (2H, m), 2.99 (3H, s), 1.86-1.44 (12H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 98.9, 69.9, 67.0, 62.4, 37.3, 30.7, 29.1, 28.9, 25.4, 22.3, 19.6.

2-(5-iodopentyloxy)-tetrahydro-2*H*-pyran (2.29)[135]



2.28 **2.29**

Sodium iodide (118 mg, 1.03 mmol) followed by sodium bicarbonate (63.0 mg, 0.75 mmol)were added to a stirred solution of THP-mesylate (**2.28**) (1.00 g, 3.75 mmol) in acetone (15 mL) at room temperature. The reaction mixture was refluxed for 14 hours. Water (30 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give THP-iodide (**2.29**) (1.00 g, 90%) as a yellow oil, which was used without purification.

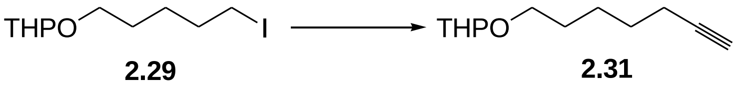
FTIR (neat, cm^{-1}): ν_{max} 2938, 1452.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.56 (1H, t, *J* = 3.5 Hz), 3.89-3.65 (2H, m), 3.53-3.31 (2H, m), 3.23-3.12 (2H, m), 1.92-1.38 (12H, m).

^{13}C NMR (100 MHz, $CDCl_3$):δ 98.8, 67.1, 62.3, 33.3, 30.7, 29.6, 27.2, 25.4, 19.6, 6.8.

HRMS calculated for $C_{10}H_{20}IO_2$(M^++H) 299.0508 found 299.0510.

2-(hept-6-ynyloxy)-tetrahydro-2*H*-pyran (2.31)[136]



To a stirred suspension of lithium acetylenide-ethylenediamine complex (**2.30**)(2.30 g, 25.2 mmol) in dry DMSO (20 mL), a solution of THP-iodide (**2.29**)(5.00 g, 16.7 mmol) in dry DMSO (20 mL) was added slowly under nitrogen at 15 °C. After stirring at room temperature for 4 hours, the reaction mixture was poured into ice cold water (100 mL). The mixture was extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (100 g, 5% EtOAc/hexane) to give THP-alkyne (**2.31**)(2.63 g, 80%) as a yellow oil.

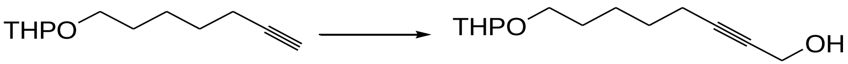
FTIR (neat, cm^{-1}): ν_{max}3296, 2939, 2116, 1136.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.57 (1H, t, *J* = 3.5 Hz), 3.91-3.68 (2H, m), 3.54-3.31(2H, m), 2.21-2.14 (2H, m), 1.93 (1H, t, *J* = 2.7 Hz), 1.88.1.41 (12H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 98.8, 84.5, 68.2, 67.3, 62.3, 30.7, 29.2, 28.3, 25.5, 25.4, 19.6, 18.3.

HRMS calculated for $C_{12}H_{21}O_2$(M^++H) 197.1542 found 197.1546.

8-(tetrahydro-2*H*-pyran-2-yloxy)oct-2-yn-1-ol (2.32)



2.31 **2.32**

n-BuLi (43.1 mL of a 1.60 M solution in hexane, 68.9 mmol) was slowly added to a solution of THP-alkyne (**2.31**) (10.4 g, 53.1 mmol) in THF (200 mL) under nitrogen at -78 °C. The mixture was stirred at the same temperature for one hour. Paraformaldehyde (7.95 g, 265 mmol) was added, and the mixture was allowed to warm to room temperature. After stirring at room temperature for 1 hour, a saturated aqueous NH_4Cl solution (200 mL) was added, and the mixture was extracted with ethyl acetate (2×200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (300 g, 20% EtOAc/hexane) to give THP-propargyl alcohol (**2.32**) (9.00 g, 75%) as a colourless oil.

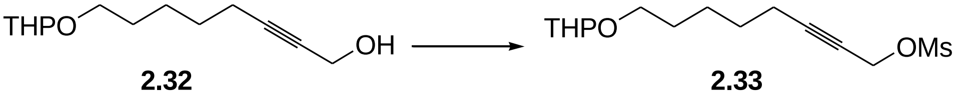
FTIR (neat, cm^{-1}): ν_{max} 3383, 2224, 1354.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.57 (1H, t, *J* = 3.5 Hz), 4.24 (2H, br. s), 4.08-3.69 (2H, m), 3.54-3.33 (2H, m), 2.28-2.21 (2H, m), 2.08-1.38 (12H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 98.9, 86.3, 78.5, 67.4, 62.4, 51.3, 30.7, 29.2, 28.3, 25.5, 25.4, 19.6, 18.6.

HRMS calculated for $C_{13}H_{22}O_3Na$ (M^++Na) 249.1467 found 249.1477.

8-(tetrahydro-2*H*-pyran-2-yloxy)oct-2-ynyl methanesulfonate(2.33)

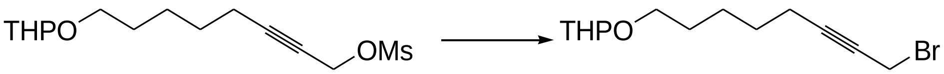


Triethylamine (8.60 mL, 61.9 mmol) followed by methanesulfonylchloride (4.80 mL, 61.9 mmol) were added to an ice cold solution of THP-propargyl alcohol (**2.32**) (7.00 g, 31.0 mmol) in dichloromethane (50 mL). The mixture was stirred at the same temperature for 2 hours. A saturated aqueous solution of NH_4Cl (50 mL) was added and the mixture was extracted with Et_2O (2×400 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give mesylate (**2.33**) (9.34 g, 99%) as yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 2223, 1468, 1367, 1175, 910.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.83 (2H, t, *J* = 2.1Hz), 4.57 (1H, t, *J* = 3.6 Hz), 3.88-3.65 (2H, m), 3.52-3.31 (2H, m), 3.10 (3H, s), 2.31-2.21 (2H, m), 1.88-1.22 (12H, m).

2-(8-bromooct-6-ynyloxy)-tetrahydro-2*H*-pyran(2.34)



2.33 **2.34**

Lithium bromide (7.76 g, 89.4 mmol) was added to an ice cold solution of mesylate (**2.33**) (9.10 g, 29.7 mmol) in THF (100 mL). The mixture was stirred at room temperature for 8 hours. Water (150 mL) was added and the mixture was extracted with Et_2O (3×150 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (200 g, 10% EtOAc/hexane) to give bromide (**2.34**) (6.80 g, 80%) as a colourless oil.

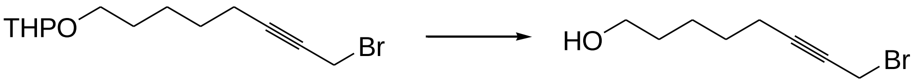
FTIR (neat, cm^{-1}): v_{max} 2251, 1209.

^{1}H NMR (400 MHz, CDCl$_3$): δ4.57 (1H, t, *J* = 3.5 Hz), 3.92 (2H, t, *J* = 2.3 Hz), 3.90-3.74 (2H, m), 3.56-3.31 (2H, m), 2.39-2.22 (2H, m), 1.91-1.41 (12H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 98.8, 88.0, 75.0, 67.3, 62.3, 31.2, 30.7, 29.2, 28.1, 25.4, 19.6, 18.7, 15.6.

HRMS calculated for $C_{13}H_{22}{}^{79}BrO_2$ (M^++H) 289.803 found 289.0817.

8-bromooct-6-yn-1-ol (2.35)



2.34 **2.35**

Amberlyst-15 (3.00 g) was added to a solution of THP-bromide (**2.34**) (6.00 g, 20.8 mmol) in methanol (100 mL) and the mixture was stirred at room temperature. After 20 hours, the reaction mixture was filtered through celite and washed with dichloromethane. The solvent was removed under reduced pressure, to give alcohol (**2.35**) (3.80 g, 90%) as a yellow oil, which was used without purification.

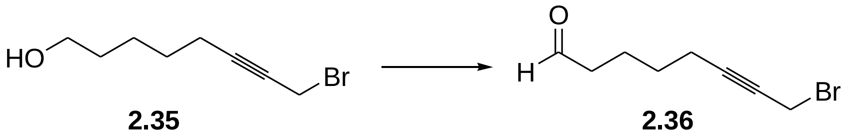
FTIR (neat, cm^{-1}): ν_{max} 3431, 2253, 1211.

^{1}H NMR (400 MHz, CDCl$_3$): δ 3.91 (2H, t, *J* = 2.4 Hz), 3.64 (2H, t, *J* = 6.6 Hz), 2.29-2.21 (3H, m), 1.64-1.35 (6H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 87.9, 75.5, 62.7, 32.0, 28.0, 24.9, 18.9, 15.7.

HRMS calculated for $C_8H_{14}{}^{79}BrO$ (M^++H) 205.0228 found 205.0223.

8-bromooct-6-ynal(2.36)



Dess-Martin periodinane (8.71 g, 20.5 mmol) was added to an ice cold solution of alcohol (**2.35**) (3.82 g, 18.6 mmol) in dry dichloromethane (50 mL) under nitrogen. After stirring at room temperature for 3 hours, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (150 g, 10% EtOAc/hexane) to give bromo-aldehyde (**2.36**) (3.00 g, 80%) as a colourless oil.

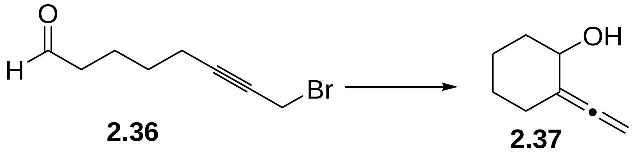
FTIR (neat, cm^{-1}): ν_{max} 2231, 1722, 1217.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.77 (1H, t, *J* = 1.5 Hz), 3.91 (2H, t, *J* = 2.3 Hz), 2.46 (2H, td, *J* = 7.3 & 1.5 Hz), 2.33-2.21 (2H, m), 1.79-1.65 (2H, m), 1.60-1.48 (2H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 202.1, 87.2, 75.8, 43.3, 27.6, 21.1, 18.7, 15.5.

HRMS calculated for $C_8H_{12}{}^{79}BrO_2(M^+ + H)$ 203.0072 found 203.0073.

2-vinylidenecyclohexanol(2.37)



SnCl$_2$ (280 mg, 1.47 mmol) followed by NaI (221 mg, 1.47 mmol) were added to a solution of bromoaldehyde (**2.36**) (149 mg, 0.73 mmol) in dry DMF (5 mL) under nitrogen at room temperature. After stirring at same temperature for 12 hours, 10 mL of water and 30 mL of Et$_2$O were added. The mixture was stirred at room temperature for 30 minutes, then filtered through celite, washed with Et$_2$O. The organic layer was separated and washed with water, brine and dried (MgSO$_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g, 15% EtOAc/hexane) to give allenic alcohol (**2.37**) (45.5 mg, 50%) as a colourless oil.

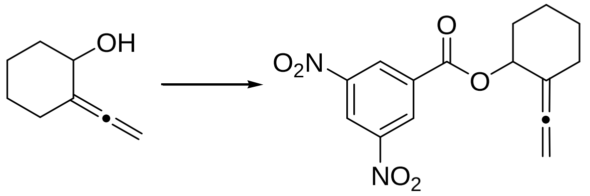
FTIR (neat, cm^{-1}): ν_{max}3391, 1960, 1443.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.94-4.81 (2H, m), 4.03 (1H, br. s), 2.44-2.36 (1H, m), 2.18-1.33 (7H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 200.5, 106.6, 78.6, 68.6, 35.6, 29.3, 26.3, 23.5.

HRMS calculated for $C_8H_{12}ONa(M^++Na)$ 147.0786 found 147.0782.

2-vinylidenecyclohexyl 3,5-dinitrobenzoate(2.39)



2.37 **2.39**

3,5-dinitrobenzoyl chloride (**2.38**) (362mg, 1.57 mmol) followed by 4-(dimethylamino)pyridine (26.0 mg, 0.21 mmol) were added to an ice cold solution of allenic alcohol (**2.37**) (130 mg, 1.05 mmol), and Et_3N (0.29 mL, 2.09 mmol) in dichloromethane (3 mL). The mixture was stirred at room temperature for 3 hours. Saturated sodium bicarbonate (15 mL) was added and the mixture was extracted with ethyl acetate (2×50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g, 15% EtOAc/hexane) to give nitro benzoate allene (**2.39**) (267 mg, 80%) as a yellow solid.

Melting point: 96-98 °C.

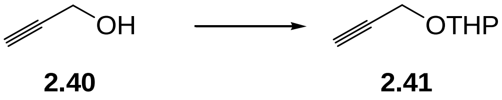
FTIR (neat, cm^{-1}): ν_{max} 1962, 1730, 1628, 1545, 1344.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.22 (1H, t, *J* = 2.1Hz), 9.17 (2H, d, *J* = 2.1 Hz), 5.59-5.50 (1H, m), 4.88-4.70 (2H, m), 2.48-2.40 (1H, m), 2.21-1.40 (7H, m).

^{13}C NMR (100 MHz, $CDCl_3$):δ 202.9, 161.5, 148.6 (2C), 134.4 (2C), 129.4, 122.2, 100.7, 89.6, 74.0, 31.9, 28.8, 25.9, 22.8.

HRMS calculated for $C_{15}H_{15}N_2O_6$ 319.0930 (M^++H) found 319.0937.

2-(prop-2-ynyloxy)-tetrahydro-2*H*-pyran(2.41)[137]



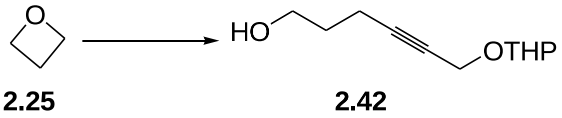
Amberlyst-15 (2 g) was added to a solution of propargyl alcohol (**2.40**) (26.3 mL, 444 mmol) and 3,4-dihydro-2*H*-pyran (52.0 mL, 579 mmol) in dry dichloromethane (500 mL) at 0 °C. After stirring at room temperature for 20 hours the reaction mixture was filtered through celite and washed with dichloromethane. The solvent was removed under reduced pressure. The residue was distilled under reduced pressure (3 psi) at 50 °C, to give THP-alkyne (**2.41**) (50.9 g, 82%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 3289, 2118, 1442.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.81 (1H, t, *J* = 3.3 Hz), 4.29 (1H, dd, *J* = 15.7, 2.4 Hz), 4.22 (1H, dd, *J* = 15.7, 2.4 Hz), 3.87-3.78 (1H, m), 3.58-3.48 (1H, m), 2.40 (1H, t, *J* = 2.4 Hz), 1.88-1.48 (6H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 96.5, 82.2, 73.9, 61.7, 53.8, 29.9, 25.1, 18.7.

6-(Tetrahydro-2*H*-pyran-2-yloxy)hex-4-yn-1-ol (2.42)



n-BuLi (77.4 mL of a 1.60 M solution in hexane, 124 mmol) was slowly added to a solution of the THP ether of propargyl alcohol (**2.41**) (17.3 g, 124 mmol) in THF (200 mL) at -78 °C. The mixture was stirred at the same temperature for one hour. $BF_3{\cdot}Et_2O$(15.5 mL, 123.9 mmol) was added, followed by oxetane (**2.25**) (6.70 mL, 103 mmol) and the mixture was stirred at -78°C for one hour. Saturated sodium bicarbonate (150 mL) was added. The mixture was allowed to warm to room temperature. The mixture was extracted with ethyl acetate (3×300 mL) and the combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (200 g, 20% EtOAc/hexane) to give alkynol (**2.42**) (15.4 g, 75%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max}3402, 2943, 2870, 2226, 1115, 1022.

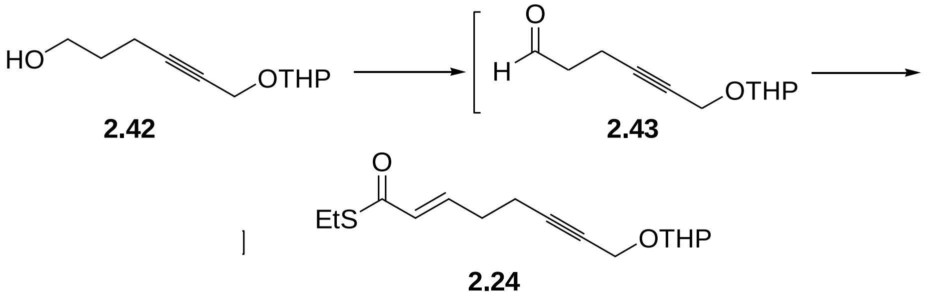
^{1}H NMR (300 MHz, CDCl$_3$): δ 4.78 (1H, t, *J*=3.1 Hz), 4.27 (1H, dt, *J*=15.2, 2.1 Hz), 4.17 (1 H, dt, *J*= 15.2, 2.1 Hz), 3.89-3.79 (1 H, m), 3.73 (2 H, t, *J*=5.9 Hz), 3.55-3.46 (1 H, m), 2.34 (2 H, dt, *J*=6.9, 2.1 Hz), 1.88-1.45 (8 H, m).

^{13}C NMR (75.4 MHz, CDCl$_3$):δ96.6, 85.8, 76.4, 62.0, 61.7, 54.6, 31.2, 30.3, 25.4, 19.0, 15.4.

MS (ESI+):*m/z* (%) 221 (M$^+$+Na, 100).

HRMS calculated for$C_{11}H_{18}O_3Na$ 221.1154 (M$^+$+Na) found 221.1148.

(*E*)-(*S*)-Ethyl 8-(tetrahydro-2*H*-pyran-2-yloxy)oct-2-en-6-ynethioate (2.24)



Dess-Martin periodinane (23.5 g, 55.5 mmol) was added to a mixture of compound (**2.42**) (10 g, 50.5 mmol) and $NaHCO_3$ (12.7 g, 151 mmol) in dichloromethane (100 mL) at 0 °C. The mixture was allowed to warm to room temperature. The reaction was monitored by TLC to ensure the complete oxidation. After 3 hours the reaction mixture was cooled to 0 °C, $Ph_3PCHCOSEt$ (23.8 g, 65.6 mmol) was added. The mixture was stirred at room temperature for 14 hours. Water (100 mL) and Et_2O (300 mL) were added. The mixture was stirred at room temperature for 10 minutes, and filtered through celite, washed with Et_2O. The organic layer was separated and washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (200 g, 5% EtOAc/hexane) to give thioester (**2.24**) (10.1g, 71%) as a yellow oil.

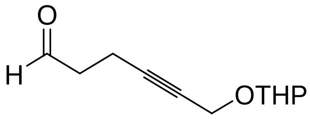
FTIR (neat, cm^{-1}): ν_{max} 2939, 2235, 1672, 1633, 1024.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92-6.81 (1 H, m), 6.14 (1H, d, *J*=15.4 Hz), 4.77 (1H, t, *J*=3.1 Hz), 4.27 (1H, d, *J*=15.3 Hz), 4.18 (1H, d, *J*=15.3 Hz), 3.88-3.76 (1H, m), 3.55-3.46 (1H, m), 2.93 (2H, q, *J*=7.4 Hz), 2.45-2.32 (4H, br. s), 1.89-1.48 (6H, m), 1.26 (3H, t, *J*=7.4 Hz).

^{13}C NMR (75.4 MHz, CDCl$_3$): δ 189.9, 142.6, 129.4, 96.4, 84.5, 76.6, 62.0, 54.4, 31.1, 30.2, 25.3, 23.1, 19.1, 17.8, 14.6.

HRMS calculatedfor $C_{15}H_{22}O_3SNa$ 305.1187 (M$^+$+Na) found 305.1183.

6-(tetrahydro-2*H*-pyran-2-yloxy)hex-4-ynal (2.43)



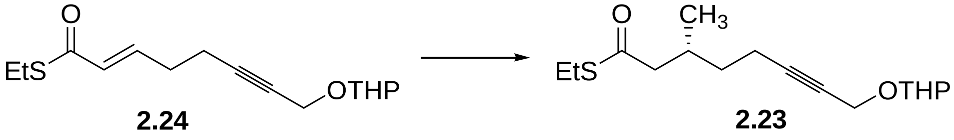
FTIR (neat, cm^{-1}): v_{max} 2235, 1730.

^{1}H NMR (400 MHz, CDCl$_3$): δ 9.77 (1H, s), 4.75 (1H, br. s), 4.25 (1H, d, *J* = 15.3 Hz), 4.15 (1H, d,*J* = 15.3 Hz), 3.85-3.75(1H, m), 3.53-3.46 (1H, m), 2.66 (2H, t, *J* = 7.0 Hz), 2.53 (2H, t, *J* = 6.7 Hz), 1.86-1.44 (6H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 200.3, 96.7, 84.2, 76.9, 61.9, 54.4, 42.4, 30.2, 25.3, 19.0, 12.0.

HRMS calculated for $C_{11}H_{16}O_3Na$ (M$^+$+Na) 219.0997 found 219.1003.

(3*R)*-(*S*)-Ethyl 3-methyl-8-(tetrahydro-2*H*-pyran-2-yloxy)oct-6-ynethioate(2.23)



A solution of *R*-Tol-BINAP (269 mg, 0.40 mmol) and CuI (54.0 mg, 0.28 mmol) in dry dichloromethane (20 mL) was stirred under nitrogen at room temperature for 2 hours. *t*-

BuOMe (150 mL) was added and the clear solution was cooled to -70 °C. MeMgBr (37.5 mL, of a 3.00M solution in ether, 113 mmol) was added slowly. After stirring for 5 minutes, a solution of unsaturated thioester (**2.24**) (8.00 g, 28.3 mmol) in *t*-BuOMe (20 mL) was added slowly. After stirring at -70°C for 14 hours, MeOH (50 mL) and saturated aqueous NH_4Cl (50 mL) were sequentially added, and the mixture was allowed to warm to room temperature. The aqueous layer was extracted with Et_2O (2×200 mL) and the combined organic layers were washed with water, brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (200 g, 4% EtOAc/hexane) to give thioester (**2.23**) (7.10 g, 84%) as a yellow oil.

FTIR (neat, cm^{-1}): ν_{max}2934, 2870, 2222, 1687, 1022.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.79 (1H, t, *J*=3.1 Hz), 4.27 (1H, dt, *J*=15.2, 2.1 Hz), 4.17 (1H, dt,*J*=15.2, 2.1 Hz), 3.89-3.78 (1H, m), 3.58-3.48 (1H, m), 2.86 (2H, q, *J*=7.4 Hz), 2.54 (1H, dd, *J*=14.5,5.9 Hz), 2.35 (1H, dd, *J*=14.5, 8.0 Hz), 2.28-2.11 (3H, m), 1.86-1.32 (8H, m), 1.23 (3H, t, *J*=7.4 Hz),0.93 (3H, d, *J*=6.6 Hz).

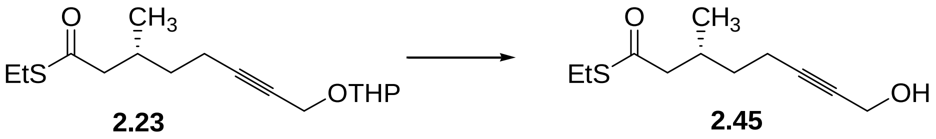
^{13}C NMR (75.4 MHz, $CDCl_3$): δ198.8, 96.7, 85.9, 76.2, 62.0, 54.6, 50.8, 35.2, 30.3 (2C), 25.4, 23.3,19.1, 19.0, 16.5, 14.8.

MS (ESI+):*m/z* (%) 321 (M^++Na, 100).

HRMS calculated for $C_{16}H_{26}O_3SNa$ (M^++Na) 321.1500found 321.1499.

$[\alpha]_D^{21.9}$ = +4.8 (*c* =2, $CHCl_3$).

(***R***)-(***S***)-Ethyl 8-hydroxy-3-methyloct-6-ynethioate (2.45)



Amberlyst-15 (2.00 g) was added to a solution of compound (**2.23**) (7.00 g, 23.4 mmol) in methanol (150 mL) and the mixture was stirred at room temperature. After 20 hours, the reaction mixture was filtered through celite and washed with dichloromethane. The solvent was removed under reduced pressure, to afford alcohol (**2.45**) (4.95 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 3417, 2960, 2931, 2231, 1681, 1672, 1453, 1019.

^{1}H NMR (300 MHz, CDCl$_3$): δ4.25-4.20 (2H, m), 2.87 (2H, q, *J*=7.4 Hz), 2.55 (1H, dd, *J*=14.5, 5.9Hz), 2.37 (1H, dd, *J*=14.5, 8.0 Hz), 2.35-2.10 (3H, m), 1.71 (1H, *J*=5.7 Hz), 1.64-1.32 (2H, m), 1.24(3H, t, *J*=7.4 Hz), 0.95 (3H, d, *J*=6.6 Hz).

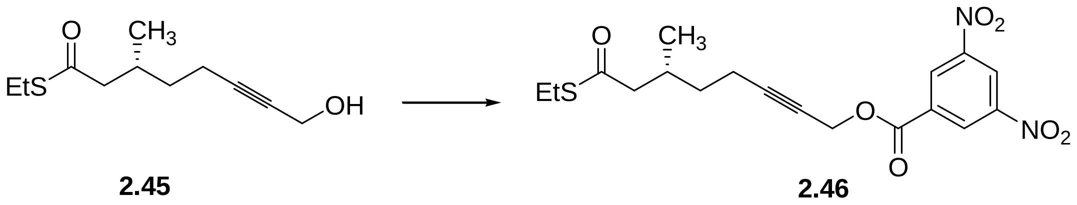
^{13}C NMR (75.4 MHz, CDCl$_3$): δ199.0, 85.8, 78.8, 51.4, 50.8, 35.0, 30.4, 23.4, 18.9, 16.4, 14.5.

MS (ESI+):*m/z* (%) 237 (M$^+$+Na, 20), 139 (100).

HRMS calculated for $C_{11}H_{18}O_2SNa$ (M$^+$+Na) 237.0925 found 237.0941.

$[\alpha]_D^{23.5}$ = +2.9 (*c* =1, CHCl$_3$).

(*R*)-8-(ethylthio)-6-methyl-8-oxooct-2-ynyl 3,5-dinitrobenzoate (2.46)



3,5-dinitrobenzoyl chloride (129 mg, 0.56 mmol) was added to an ice cold mixture of compound (**2.45**) (100 mg, 0.47 mmol), and Et_3N (0.13 mL, 0.93 mmol) in dry dichloromethane(5 mL), followed by 4-(dimethylamino)pyridine (11.0 mg, 0.09). The mixture was stirred at room temperature for 2 hours. Saturated sodium bicarbonate (15 mL) was added. The mixture was extracted with ethyl acetate (2×50 mL) and the combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g, 10% EtOAc/hexane) to give nitro benzoate (**2.46**) (155 mg, 81%) as a yellow oil.The *ee* was found to be 94% (appendix page 276).

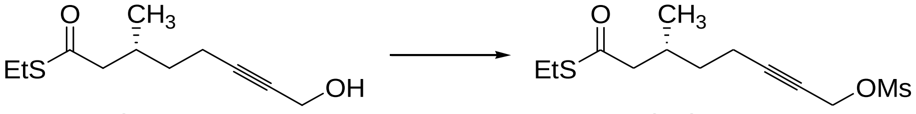
FTIR (neat, cm^{-1}): ν_{max} 1733, 1681, 1629, 1546, 1334, 1273, 1159.

^{1}H NMR (300 MHz, CDCl$_3$): δ9.24 (1H, t, *J*=2.1 Hz), 9.20 (2H, d, *J*=2.1 Hz), 5.02 (2H, t, *J*=2.1 Hz), 2.85 (2H, q,*J*=7.4 Hz), 2.54 (1H, dd, *J*=14.5, 6.0 Hz), 2.37 (1H, dd, *J*=14.5, 8.0 Hz), 2.34-2.10 (3H,m), 1.68-1.52 (1H, m), 1.49-1.31 (1H, m), 1.23 (3H, t, *J*=7.4 Hz), 0.95 (3H, d, *J*=6.6 Hz).

^{13}C NMR (75.4 MHz, CDCl$_3$): δ198.7, 162.0, 148.7, 133.5 (2C), 130.6 (2C), 122.9, 88.6, 73.2, 55.1,50.7, 34.7, 30.1, 23.4, 19.3, 16.5, 14.5.

$[\alpha]_D^{24.9}$= +1.7 (*c* =1, $CHCl_3$).

(*R*)-(*S*)-Ethyl 3-methyl-8-(methylsulfonyloxy)oct-6-ynethioate (2.48)



2.44 **2.48**

Triethylamine (6.40 mL, 45.8 mmol) and methanesulfonylchloride (4.50 mL, 45.8 mmol) were added to an ice cold solution of compound (**2.44**) (4.90 g, 22.8 mmol) in dry dichloromethane (50 mL) and the mixture was stirred at the same temperature for 2 hours. Saturated aqueous NH_4Cl solution was added and the mixture was extracted with Et_2O (2×200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give mesylate (**2.48**) (6.6 g, 99%) as yellow oil, which was used without purification.

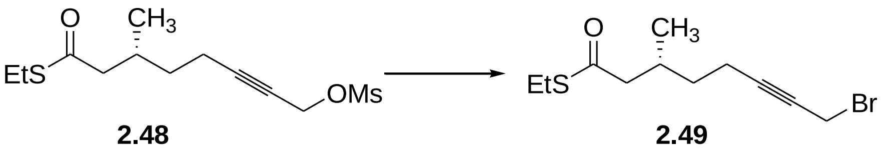
FTIR (neat, cm^{-1}): ν_{max} 2962, 2931, 2235, 1681, 1454, 1359, 1174, 937.

^{1}H NMR (300 MHz, CDCl$_3$): δ4.83 (2H, t, *J*=2.1 Hz), 3.10 (3H, s), 2.86 (2H, q, *J*=7.4 Hz), 2.53(1H, dd, *J*=14.6, 6.2 Hz), 2.38 (1H, dd, *J*=14.6, 7.7 Hz), 2.35-2.03 (3H, m), 1.68-1.52 (1H, m), 1.49-1.31(1H, m), 1.24 (3H, t, *J*=7.4 Hz), 0.94 (3H, d, *J*=6.6 Hz).

^{13}C NMR (75.4 MHz, CDCl$_3$): δ 198.6, 90.2, 72.6, 58.5, 50.7, 38.9, 34.6, 30.2, 23.3, 19.0, 16.4, 14.8.

$[\alpha]_D^{23.8}$= +3.1 (*c* =1.4, $CHCl_3$).

(*R*)-(*S*)-Ethyl 8-bromo-3-methyloct-6-ynethioate(2.49)



LiBr (3.90 g, 44.5 mmol) was added to an ice cold solution of compound (**2.48**) (6.50 g, 22.6 mmol) in THF (60 mL). The mixture was stirred at room temperature for 10 hours. Water (50 mL) was added and the mixture was extracted with Et_2O (3×150 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (150 g, 5% EtOAc/hexane) to give bromide (**2.49**) (5.41 g, 86%) as a colourless oil.

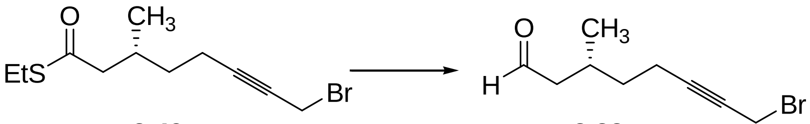
FTIR (neat, cm^{-1}): ν_{max} 2960, 2929, 2231, 1681, 1454.

^{1}H NMR (300 MHz, CDCl$_3$): δ3.91 (2H, t, *J*=2.3 Hz), 2.87 (2H, q, *J*=7.4 Hz),), 2.53 (1H, dd,*J*=14.5, 6.0 Hz), 2.37 (1H, dd, *J*=14.5, 7.9 Hz), 2.35-2.10 (3H, m), 1.65-1.52 (1H, m), 1.47-1.32 (1H,m), 1.24 (3H, t, *J*=7.4 Hz), 0.94 (3H, d, *J*=6.6 Hz).

^{13}C NMR (75.4 MHz, CDCl$_3$):δ198.8, 87.4, 75.7, 50.8, 34.9, 29.9, 23.4, 18.8, 16.7, 15.6, 14.4.

$[\alpha]_D^{23.8}$= +3.9 (c=1.6, $CHCl_3$).

(*R*)-8-Bromo-3-methyloct-6-ynal (2.22)



2.49 **2.22**

DIBAL-H (24.8 mL, of a 1M solution in hexane, 24.8 mmol) was added slowly to a solution of compound (**2.49**) (5.31 g, 19.1 mmol) in dry dichloromethane (60 mL) under nitrogen at -78°C. After stirring at the same temperature for 10 minutes, MeOH (30 mL) and water (4 mL) were sequentially added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 30 minutes, Na_2SO_4 (~5 g) was added and the mixture was stirred at room temperature for 30 minutes. When a crystalline precipitate had fully formed, the mixture was filtered through celite, washed with dichloromethane. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (150 g, 5% EtOAc/hexane) to give aldehyde (**2.22**) (3.82 g, 92%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 2956, 2931, 2231, 1722, 1217.

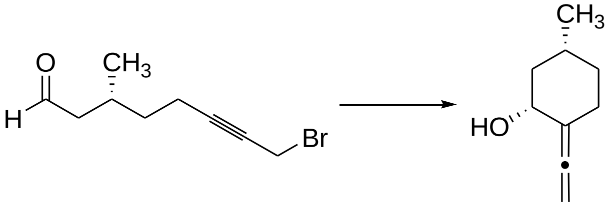
^{1}H NMR (300 MHz, $CDCl_3$): δ 9.76 (1H, t, *J*=2.0 Hz), 3.91 (2H, t, *J*=2.3 Hz), 2.51-2.15 (5H, m), 1.68-1.40 (2H, m), 0.98 (3H, d, *J*=6.5 Hz).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ202.4, 87.3, 75.8, 50.5, 35.1, 27.3, 19.5, 16.6, 15.5.

HRMS calculated for $C_9H_{13}{}^{79}BrO$ (M^++H) 217.0228 found 217.0227

$[\alpha]_D^{24.8}$= +16.1 (*c* =1.4, $CHCl_3$).

(1*R*, 5*R*)-5-Methyl-2-vinylidenecyclohexanol (2.21)



2.22 **2.21**

To a solution of compound (**2.22**) (780 mg, 3.60 mmol) in DMF (16 mL) and water (2 mL) under nitrogen, was added $SnCl_2$ (1.02 g, 5.40 mmol) followed by NaI (808 mg, 5.40 mmol) at -10 °C. After stirring at -10°C for 56 hours, 20 mL of water and 50 mL of Et_2O were added. The mixture was stirred at room temperature for 30 minutes, then filtered through celite, washed with Et_2O. The organic layer was separated and washed with water, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (30.0 g, 10% EtOAc/hexane) to give allenic alcohol (**2.21**) (372 mg, 75%) as a colourless solid.

Melting point: 54-56°C.

FTIR (KBr, cm^{-1}): ν_{max} 3325, 2951, 2924, 1956, 1458, 1666.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.99-4.85 (2H, m), 4.05-3.91 (1H, m), 2.39 (1H, ddd, *J*=13.7, 3.7, 2.6 Hz), 2.16-1.92 (3H, m), 1.79-1.45 (2H, m), 1.08-0.97 (2H, m), 0.94 (3H, *J*=6.6 Hz).

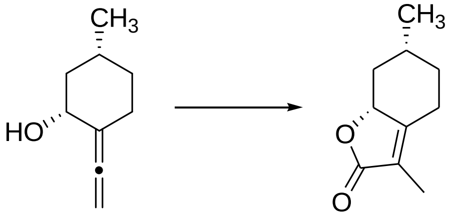
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 199.6, 107.1, 79.7, 67.9, 44.5, 34.7, 31.3, 29.5, 22.2.

MS (ESI+):*m/z* (%) 139 (M^++1, 100).

HRMS calculated for $C_9H_{15}O(M^++H)$ 139.1123 found 139.1117.

$[\alpha]_D^{23.6}$= +15.1 (*c*=1, $CHCl_3$).

(-)-mintlactone (2.1)



2.21 **2.1**

Triruthenium dodecacarbonyl (4.61 mg, 0.01 mmol) was added to a mixture of compound (**2.21**) (50.0 mg, 0.36 mmol) and Et_3N (0.20 mL, 1.45 mmol) in dioxane (2 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 hours. The reaction mixture was cooled to 0°C for 10 min., then the carbon monoxide was released, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10 g, 15% EtOAc/hexane) to give of (–)-mintlactone (**2.1**) (50.1 mg, 83%) as a pale yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 2953, 2927, 1747, 1730, 1687.

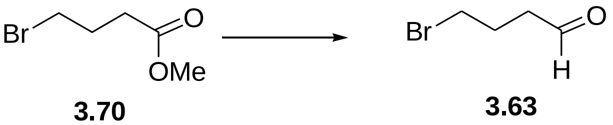
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.60 (1H,dd, *J*=11.0, 6.0 Hz), 2.77 (1H, ddd, *J*=14.2, 4.3, 1.8 Hz),2.43-2.35 (1H, m), 2.17 (1H, td, *J* = 3.7, 5.4 Hz), 1.95-1.85(1H, m), 1.78 (3H, t, *J*= 1.4 Hz), 1.76-1.62 (1H, m), 1.09-0.86(2H, m), 0.98 (3H, d, *J* = 6.6 Hz).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ174.9, 162.4, 119.6, 80.0, 42.0, 34.6, 29.8, 25.5, 21.2, 8.2.

$[\alpha]_D^{24.1}$= -59.2 (*c* =2.4, $CHCl_3$).

5.3. Experimental section for chapter 3

4-bromobutanal (3.63)[138]



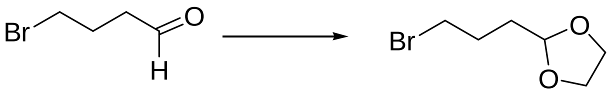
DIBAL-H (36 mL, of a 1M solution in hexane, 35.9 mmol) was added slowly to a solution of methyl-4-bromobutanoate(**3.70**) (5.00 g, 27.6 mmol) in dry dichloromethane (100 mL) under nitrogen at -78 °C. After stirring at the same temperature for 10 minutes, MeOH (25 mL) and water (5 mL) were sequentially added, and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 30 minutes, Na_2SO_4 was added. The mixture was diluted with dichloromethane and stirring was continued for 3 hours. When a crystalline precipitate had fully formed, the mixture was filtered through celite, washed with dichloromethane. The solvent was removed under reduced pressure, to give an aldehyde(**3.63**) (3.51 g, 84%) as a colourless liquid.

FTIR (neat, cm^{-1}): ν_{max} 2960, 1726, 1251.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (1H, t, *J* = 0.8 Hz), 3.46 (2H, t, *J* = 6.4 Hz), 2.68 (2H, td, *J* = 7.0, 0.8 Hz), 2.18 (2H, quintet, *J* = 6.7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.0, 42.1, 26.7, 24.9.

2-(3-bromopropyl)-1, 3-dioxolane(3.71)[138]


3.63 **3.71**

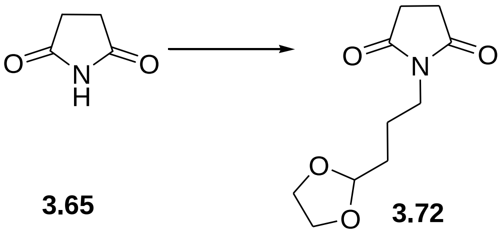
p-Toluenesulfonic acid (440 mg, 2.31 mmol) was added to a stirred mixture of bromo-aldehyde(**3.63**) (3.50 g, 23.1 mmol) and ethylene glycol (3.92 mL, 69.5 mmol) in toluene (40 mL). The mixture was heated at reflux for 1.5 hours using a Dean-Stark trap. The mixture was cooled to room temperature. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (150 g, 4% EtOAc/hexane) to give bromo-dioxolane(**3.71**) (3.31 g, 73%) as a colourless liquid.

FTIR (neat, cm^{-1}): ν_{max} 2883, 1252.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.9 (1H, t, *J* = 4.5 Hz), 3.98-3.93 (2H, m), 3.88-3.81 (2H, m), 3.45 (2H, t, *J* = 6.8 Hz), 2.0 (2H, quin, *J*=7.1 Hz), 1.85-1.78 (2H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ103.7, 64.9 (2C), 33.6, 32.3, 27.1.

1-(3-(1,3-dioxolan-2-yl)propyl)pyrrolidine-2,5-dione(3.72)


3.65 **3.72**

Sodium hydride (60%, 262 mg, 6.56 mmol) was added to a stirred solution of amide(**3.65**) (500 mg, 5.05 mmol) in dry DMF (5 mL) under nitrogen at 0 °C. After one hour, a solution of bromodioxolane(**3.71**) (1.03 g, 5.30 mmol) in dry DMF (2 mL) was added and the mixture was stirred at room temperature for 16 hours. The reaction mixture was quenched with water (50 mL) and extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with water, brine and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give imide(**3.72**) (840 mg, 78%) as a yellow oil, which was used without purification.

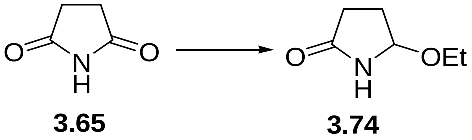
FTIR (neat, cm^{-1}): ν_{max} 2926, 1701, 910.

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.79 (1H, t, *J* = 4.0 Hz), 3.91-3.68 (4H, m), 3.47 (2H, t, *J* = 8.0 Hz), 2.62 (4H, s), 1.68-1.51 (2H, m), 0.85-0.71 (2H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1 (2C), 103.6, 64.7 (2C), 38.4, 30.8, 29.5, 28.0, 21.8.

MS (ESI+): *m/z* (%) 214 (M^++1), 196 (46), 162 (38).

5-ethoxypyrrolidin-2-one(3.74)[66]



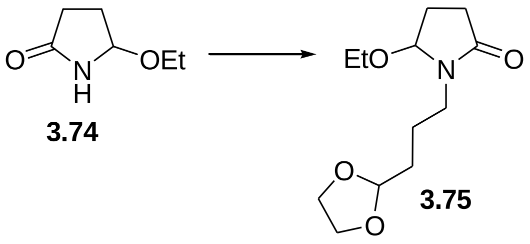
Sodium borohydride (5.72 g, 152 mmol) was added to a stirred solution of succinimide(**3.65**) (10.0 g, 101 mmol) in ethanol (300 mL) at -5 °C. At regular intervals of 15 minutes, 5 drops of2N HCl were added. After 5 hours stirring at same temperature, the reaction mixture was acidified to pH ~ 2 with 2N HCl and stirring was continued for two hours. The reaction mixture was neutralized with 2M NaOH and then solvent was removed under reduced pressure. The residue was saturated with sodium chloride and extracted with $CHCl_3$ (5 ×300 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure to afford the amide(**3.74**) (8.00 g, 61%) as a colourless solid.

FTIR (neat, cm^{-1}): ν_{max} 3221, 2249, 1697.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (1H, br. s), 4.96 (1H, dt, *J* = 6.1, 1.2 Hz), 3.58-3.34 (2H, m), 2.62-1.98 (4H, m), 1.21 (3H, t, *J* = 7.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 85.7, 62.6, 28.5, 28.3, 14.9.

1-(3-(1,3-dioxolan-2-yl)propyl)-5-ethoxypyrrolidin-2-one(3.75)



n-BuLi (36.8 mL of a 1.6 M solution in hexane, 59.0 mmol) was slowly added to a solution of the amide(**3.74**) (7.60 g, 59.0 mmol) in dry THF (80 mL) at -78 °C. The mixture was stirred at the same temperature for one hour. A solution of bromo-dioxolane (**3.71**) (8.85 g, 45.3 mmol) in dry DMSO (60 mL) was added slowly and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 18 hours, water (250 mL) was added. The mixture was extracted with ethyl acetate (3×500 mL) and the combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give lactam(**3.74**) (10.1 g, 92%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}):ν_{max} 2972, 2932, 2882, 1693, 1454, 1420, 1283, 1140, 1074.

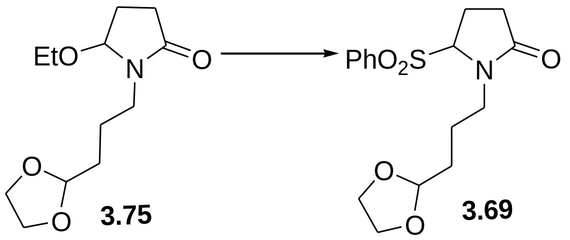
^{1}H NMR (500 MHz, $CDCl_3$):δ 4.98 (1H, d, *J* = 6.3 Hz), 4.87 (1H, t, *J* = 4.2 Hz), 3.98-3.92 (2H, m), 3.87-3.81 (2H, m), 3.58-3.51 (1H, m), 3.46 (2H, q, *J* = 7 Hz), 3.18-3.08 (1H, m), 2.57-2.48 (1H, m), 2.34-2.26 (1H, m), 2.18-2.08 (1H, m), 2.02-1.94 (1H, m), 1.76-1.61 (4H, m), 1.21 (3H, t, *J*=7 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.9, 103.8, 88.9, 64.9, 64.8, 61.3, 40.1, 31.1, 29.0, 24.8, 21.9, 15.2.

ESI (*m/z*): 244 (M^++1, 100), 229 (18), 198 (34).

HRMS *m/z*calculated for $C_{12}H_{21}NO_4Na$(M^++Na) 266.1368 found 266.1371.

1-(3-(1,3-dioxolan-2-yl)propyl)-5-(phenylsulfonyl)pyrrolidin-2-one(3.69)



Trifluoroacetic acid (4.37 mL, 56.7 mmol) was added to a stirred mixture of sodium benzenesulfonate (10.7 g, 65.4 mmol) and magnesium sulphate (10.5 g, 87.2 mmol) in dry dichloromethane (250 mL), under nitrogen and the mixture was stirred at room temperature for 30 minutes. A solution of lactam (**3.75**) (10.6 g, 43.6 mmol) in dry dichloromethane (50 mL) was added to the reaction mixture and stirring was continued for 3.5 hours. The reaction mixture was filtered and washed with dichloromethane. The filtrate was washed with a saturated solution of $NaHCO_3$, water, brine and then dried ($MgSO_4$). The solvent was removed under reduced pressure to give sulfone(**3.69**) (14.6 g, 99%) as a yellow oil, which was used without purification.

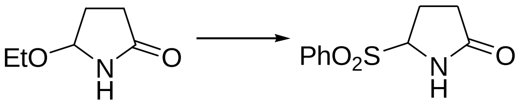
FTIR (neat, cm^{-1}):ν_{max} 2951, 1697, 1404, 1303, 1131.

^{1}H NMR (MHz, $CDCl_3$):δ 7.89-7.55 (5H, m), 4.83 (1H, t,*J* = 4.2 Hz), 4.75 (1H, dd, *J* = 7.6, 1.0 Hz), 4.0-3.76 (4H, m), 3.38-3.22 (2H, m), 2.53-1.51 (8H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 135.3, 134.8, 129.7 (2C), 129.4 (2C) 103.7, 78.0, 65.0, 64.9, 41.7, 30.6, 28.1, 21.3, 21.0.

MS (ESI+): *m/z* (%) 362 (M^++Na, 14), 250 (28), 230 (100).

5-(phenylsulfonyl)pyrrolidin-2-one (3.78)[73]



3.41 **3.78**

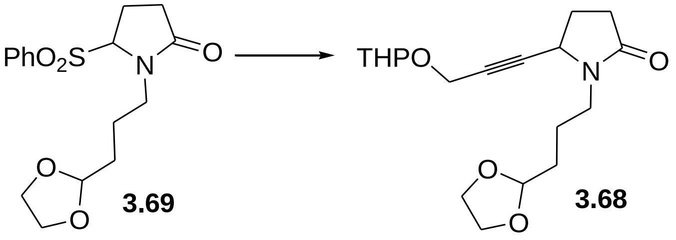
A mixture of amide (**3.41**) (500 mg, 3.87 mmol), benzenesulfonic acid (1.65 g, 11.6 mmol) and $CaCl_2$ (1.31 g, 11.6 mmol) in dry dichloromethane (10 mL) were sstirred at room temperature for 16 hours. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (30 mL)and extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed with water, brine and died ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (30 g, 2% MeOH/$CHCl_3$) to give sulfonamide (**3.78**) (476 mg, 55%) as a colourless solid.

FTIR (neat, cm^{-1}): ν_{max} 3373, 1707, 1265, 908.

^{1}H NMR (MHz, $CDCl_3$): δ 7.98-7.90 (2H, m), 7.78-7.70 (1H, m), 7.68-7.58 (2H, m), 6.60 (1H, br. s), 4.68 (1H, dt, *J* = 8, 1.5 Hz), 2.64-1.94 (4H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 135.7 (2C), 129.7 (2C), 129.6 (2C), 74.5, 27.9, 21.8.

1-(3-(1,3-dioxolan-2-yl)propyl)-5-(3-(tetrahydro-2H-pyran-2-yloxy)prop-1-ynyl)pyrrolidin-2-one(3.68)



Iso-Propylmagnesium chloride (2M, 29.8 mL, 59.7 mmol) was added to a stirred solution of alkyne(**3.69**) (8.41 g, 59.7 mmol) in dry THF (150 mL) under nitrogen at 0 °C. After one hour zinc bromide (1M, 59.7 mL in THF) was added and stirred for 30 minutes. A solution of sulfone (**3.69**) (13.5 g, 39.8 mmol) in dry THF (50 mL) was added and stirred at room temperature for 4 hours. The reaction mixture was quenched with water (200 mL) the mixture was extracted with ethyl acetate (3x 300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (300 g, 0.8% MeOH/$CHCl_3$) to give propargyl-amide(**3.68**) (9.71 g, 72%) as a colourless oil.

FTIR (neat, cm^{-1})^{139}**:**ν_{max} 2943, 1683.1021.

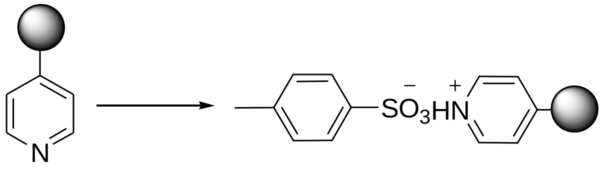
^{1}H NMR (400 MHz, $CDCl_3$):δ 4.84 (1H, t,*J* = 4.2 Hz), 4.73 (1H, br. s), 4.39-4.31 (1H, m), 4.28 (1H, dd,*J* = 15.7, 1.6 Hz), 4.20 (1H, dd,*J* = 15.7, 1.6 Hz), 3.94-3.73 (4H, m), 3.69-3.41 (2H, m), 3.14-3.01 (1H, m), 2.48-1.45 (15H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 103.9, 96.9, 83.4, 81.2, 64.9 (2C), 62.0, 54.1, 49.1, 40.6, 31.0, 30.2, 29.9, 26.3, 25.3, 21.5, 18.9.

MS (ESI+): *m/z* (%) 337 (M^++1, 100), 254 (20).

HRMS calculated for $C_{18}H_{28}NO_5$ (M^++H) 338.1967 found 338.1967.

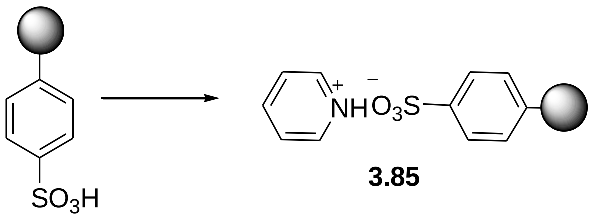
PS-PPTS-A(**3.84**)



3.84

Poly-4-vinyl pyridine (1.00 g) was added to a stirred solution of *p*-TsOH (5.00 g) in dichloromethane, and stirring was continued slowly for 24 hours. Resin was filtered and washed with dichloromethane then dried to afford PS-PPTS-**A** (**3.84**) as a colourless resin.

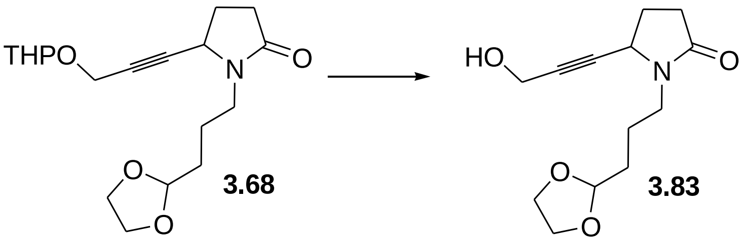
PS-PPTS-B **(3.85)**



3.85

Amberlyst-15 resin (1.00 g) was added to a stirred solution of pyridine (5.00 mL) in dichloromethane and stirring was continued slowly for 24 hours. Resin was filtered and washed with dichloromethane then dried to afford PS-PPTS (**3.85**) as a purple colour resin.

1-(3-(1,3-dioxolan-2-yl)propyl)-5-(3-hydroxyprop-1-ynyl)pyrrolidin-2-one(3.83)



3.68 **3.83**

PS-PPTS- A (**3.84**) resin (3.00 g) was added to a stirred solution of propargyl-amide (**3.68**) (6.51 g, 19.3 mmol) in dry methanol (230 mL) under nitrogen at room temperature. After 8 hours, the reaction mixture was filtered through celite and washed with ethyl acetate. The solvent was removed under reduced pressure, to give alcohol(**3.83**) (4.85 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 3398, 1665, 1027.

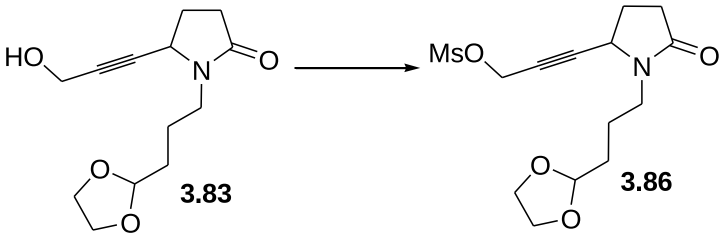
^{1}H NMR (500 MHz, CDCl$_3$):δ 4.83 (1H, t, *J* = 4.0 Hz), 4.32 (1H, t, *J* = 4.2 Hz), 4.20 (2H, br. s), 3.95-3.73 (4H, m), 3.55-3.36 (2H, m), 3.24-3.13 (1H, m), 2.51-1.93 (4H, m), 1.75-1.43 (4H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ 174.4, 103.9, 84.0, 82.7, 64.9 (2C), 50.5, 49.4, 40.9, 30.9, 29.9, 26.3, 21.5.

MS (ESI+): *m/z* (%) 254 (M^{+}+1, 100), 214 (33).

HRMS calculated for $C_{13}H_{20}NO_4$ (M^{+}+H) 254.1392 found 254.1390.

3-(1-(3-(1,3-dioxolan-2-yl)propyl)-5-oxopyrrolidin-2-yl)prop-2-ynyl methanesulfonate (3.86)



Triethylamine (5.3 mL, 38.1 mmol) followed by methanesulfonyl chloride (2.93 mL, 38.1 mmol) were added to an ice cold solution of propargyl alcohol(**3.83**)(4.81 g, 19.0 mmol) in dry dichloromethane (50 mL) and the mixture was stirred for 1 hour. Saturated aqueous NH_4Cl solution (50 mL) was added and the mixture was extracted with ethyl acetate (2 x200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give methanesulfonate(**3.86**)(6.27 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}):ν_{max} 2937, 1680, 1349, 1169.

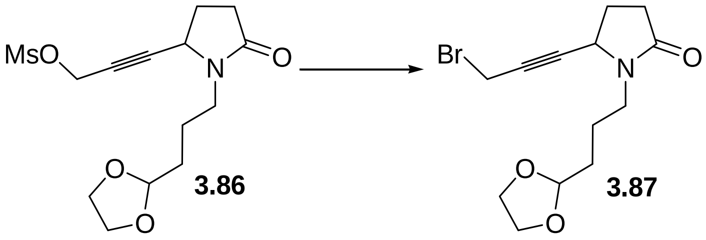
^{1}H NMR (500 MHz, CDCl$_3$):δ 4.82 (3H, br. s), 4.37 (1H, br. s), 3.98-3.70 (4H, m), 3.64-3.52 (1H, m), 3.08-3.02 (1H, m), 3.0 (3H, s), 2.54-2.22 (3H, m), 2.14-1.98 (1H, m), 1.74-1.52 (4H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ 173.8, 103.5, 87.0, 76.5, 64.6 (2C), 52.9, 48.7, 40.5, 38.4, 30.6, 29.5, 25.7, 21.2.

MS (ESI+): *m/z* (%) 332 (M^++1, 100), 282 (15), 213 (18).

HRMS calculated for $C_{14}H_{22}NO_6S$ (M^++H) 332.1168 found 332.1162.

1-(3-(1,3-dioxolan-2-yl)propyl)-5-(3-bromoprop-1-ynyl)pyrrolidin-2-one (3.87)



3.86 **3.87**

Lithium bromide (2.98 g, 34.4 mmol) was added to an ice cold solution of methanesulfonate(**3.86**) (5.70 g, 17.22 mmol in dry THF (60 mL). The mixture was stirred at room temperature for 4 hours. Water (50 mL) was added and the mixture was extracted with EtOAC (3×150 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give bromide(**3.87**)(5.30 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}):ν_{max}2951, 1680, 1352.

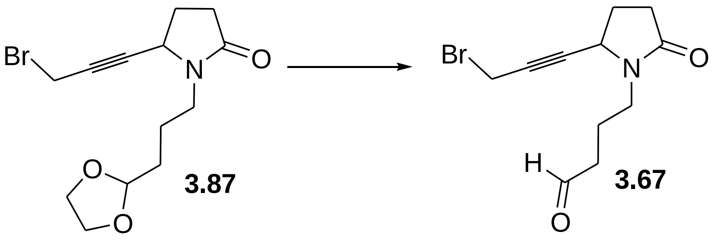
^{1}H NMR (500 MHz, CDCl$_3$): δ 4.88 (1H, t, *J* = 4.2 Hz), 4.46-4.35 (1H, m), 3.98-3.80 (4H, m), 3.90 (2H, d, *J* = 1.9 Hz), 3.71-3.54 (1H, m), 3.18-3.05 (1H, m), 2.55-2.24 (3H, m), 2.14-2.02 (1H, m), 1.78-1.55 (4H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ 174.1, 103.9, 84.4, 80.3, 64.9 (2C), 49.1, 40.8, 31.0, 29.9, 26.1, 21.5, 13.8.

MS (ESI+): *m/z* (%) 316 (M^++1, ^{79}Br, 100), 318 (M^++1, ^{81}Br, 99), 254 (20).

HRMS calculated for $C_{13}H_{19}{}^{79}BrNO_3$ (M^++H) 316.0548 found 316.0543.

4-(2-(3-bromoprop-1-ynyl)-5-oxopyrrolidin-1-yl)butanal (3.67)



p-Toluenesuphonic acid (603 mg, 3.21 mmol) was added to a stirred mixture of bromide(**3.87**) (5.00 g, 15.9 mmol) in acetone-water (30-30 mL). After 16 hours, the reaction mixture was quenched with a saturated solution of NaHCO$_3$ (20 mL). The mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water and brine, then dried (MgSO$_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (150 g, 0.8% MeOH/CHCl$_3$) to give bromo-aldehyde(**3.67**) (2.03 g, 47%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 2954, 1717, 1673, 1413.

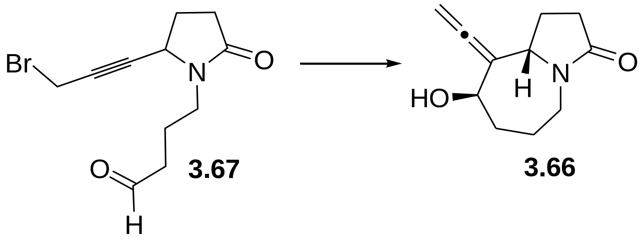
^{1}H NMR (400 MHz, CDCl$_3$): δ 9.76 (1H, s), 4.40 (1H, br. s), 3.90 (2H, s), 3.61-3.48 (1H, m), 3.24-3.12 (1H, m), 2.61-1.76 (8H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ 201.7, 174.4, 84.3, 80.5, 49.4, 41.3, 40.6, 29.8, 26.1, 19.8, 13.7.

MS (ESI+): *m/z* (%) 272 (M$^+$+1, ^{79}Br,100), 274 (M$^+$+1, ^{81}Br, 85), 248 (15).

HRMS calculated for $C_{11}H_{15}{}^{79}BrNO_2$ (M$^+$+H) 272.0286 found 272.0288.

8-hydroxy-9-vinylidene-octahydropyrrolo[1,2-a]azepin-3-one (3.66)



Indium (118 mg, 1.03 mmol) followed by acetic acidwere added (117 µL, 2.06 mmol) to a stirred solution of bromo-aldehyde(**3.67**) (140 mg, 0.51 mmol) in THF (2 mL) and water (0.25 mL) under nitrogen, at -20 °C. After stirring at the same temperature for 24 hours, the reaction mixture was diluted with chloroform (100 mL). The mixture was stirred at room temperature for 10 minutes, and filtered through celite, washed with chloroform. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10.0 g, 1.5 % MeOH/CHCl$_3$) to give allenic alcohol(**3.66**) (81.1 mg, 82 %) as a colourless solid.

Melting point: 98-100 °C.

FTIR (neat, cm^{-1}): ν_{max} 3377, 2933, 1954, 1651, 1416.

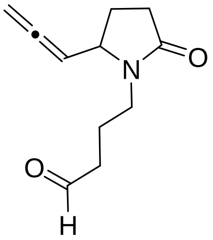
^{1}H NMR (500 MHz, CDCl$_3$): δ 5.11 (2H, t, *J* = 1.7 Hz), 4.35 (1H, t, *J* = 7.7 Hz), 4.18 (1H, br. s), 3.99-3.94 (1H, m), 2.78-2.72 (1H, m), 2.48-2.34 (2H, m), 2.31-2.23 (1H, m), 2.16-2.08 (1H, m), 1.98-1.86 (1H, m), 1.84-1.73 (2H, m), 1.68-1.53 (2H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ 203.7, 174.3, 110.6, 81.6, 67.8, 58.6, 41.7, 38.8, 30.7, 25.9, 24.7.

MS(ESI): 194 (M$^+$+1, 100).

HRMS calculated for $C_{11}H_{16}NO_2$ (M$^+$+H)194.1181found 194.1181.

4-(2-oxo-5-(propa-1,2-dienyl)pyrrolidin-1-yl)butanal (3.88)



FTIR (neat, cm^{-1}):ν_{max} 2937, 1956, 1714, 1651.

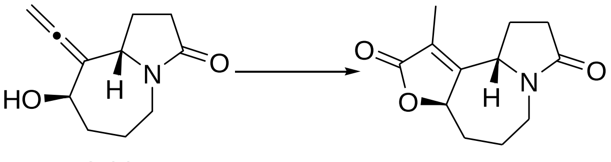
^{1}H NMR (400 MHz, CDCl$_3$):δ 9.76 (1H, s), 5.0 (1H, app. q, *J* = 6.6 Hz), 4.93-4.80 (2H, m), 4.11 (1H, app. q, *J* = 7.7 Hz), 3.61-3.48 (1H, m), 3.09-2.98 (1H, m), 2.47 (2H, t, *J* = 7.1 Hz), 2.45-2.28 (3H, m), 1.95-1.71 (3H, m).

^{13}C NMR (100 MHz, CDCl$_3$): δ 209.0, 201.5, 175.0, 91.1, 77.3, 58.0, 41.3, 40.0, 29.9, 25.9, 19.8.

MS (ESI+): *m/z* (%) 194 (M$^+$+1, 100), 166 (8).

HRMS calculated for $C_{11}H_{16}NO_2$ (M$^+$+H) 194.1181 found 194.1183.

Butenolide (3.52)[59f]



3.66 **3.52**

Triruthenium dodecacarbonyl (4.51 mg, 0.01 mmol) was added to a mixture of allenic alcohol(**3.66**) (68.0 mg, 0.35 mmol) and triethylamine (196 µL, 1.41 mmol) in dioxane (2 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 hours. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10 g, 1% MeOH/$CHCl_3$) to give butenolide(**3.52**) (63.0 mg, 81%) as a yellow solid.

FTIR (neat, cm^{-1}): ν_{max} 2928, 1745, 1681.

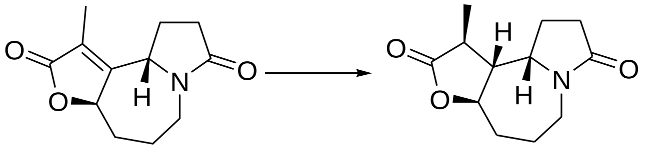
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.86 (1H, ddq, *J* = 11.6, 1.7 & 1.7 Hz), 4.72 (1H, t, *J* = 7.7 Hz), 4.25 (1H, br. d), 2.56-2.40 (5H, m), 1.98-1.60 (6H, m), 1.38-1.20 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$): δ 174.1, 173.2, 164.8, 123.7, 81.3, 57.5, 43.4, 34.7, 30.0, 25.65, 25.57, 8.9.

MS (ESI+): *m/z* (%) 222 (M^++1, 100), 196.2 (15).

HRMS calculated for $C_{12}H_{16}NO_3$ (M^++H) 222.1130 found 222.1132.

(±)-Stemoamide (3.1)



Sodium borohydride (34.1 mg, 0.90 mmol) was added to a stirred solution of butenolide(**3.52**) (50.0 mg, 0.22 mmol) and nickel chloride (7.10 mg, 0.005 mmol) in methanol (2 mL) at -30°C. After 2.5 hours,the reaction mixture was diluted with dichloromethane (50 mL). The organic layer was washed with 2.0M HCl, followed by a saturated solution of $NaHCO_3$, water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was recrystalised from ethyl acetate to give stemoamide(**3.1**) (28.2 mg, 55%) as a colourless solid.

Melting point: 180-182 °C (lit 184-185 °C).[59b]

FTIR (neat, cm^{-1}): ν_{max} 2935, 1763, 1672, 1170.

^{1}H NMR (500 MHz, CDCl$_3$): δ4.19 (1H, dt, *J* = 10.5, 2.7 Hz), 4.18-4.09 (1H, m), 3.99 (1H, dt, *J* = 10.5, 6.4 Hz), 2.72-2.62 (1H, m), 2.61-2.54 (1H, m), 2.43-2.34 (4H, m), 2.08-1.98 (1H, m), 1.88-1.82 (1H, m),1.72 (1H, quin, *J* = 10.7 Hz), 1.58-1.43 (2H, m), 1.27 (3H, d, *J* = 6.9 Hz).

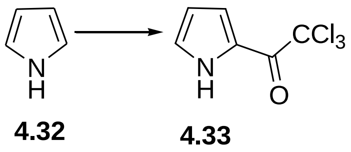
^{13}C NMR (125 MHz, CDCl$_3$): δ 177.4, 174.0, 77.6, 55.8, 52.7, 40.2, 37.3, 34.8, 30.6, 25.6, 22.6, 14.1.

MS (ESI+): *m/z* (%) 224 (M^++1, 100), 213 (90).

HRMS calculated for $C_{12}H_{18}NO_3$ (M^++H) 224.1287 found 224.1281.

5.4. Experimental section for chapter 4

2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone) (4.33)[89]



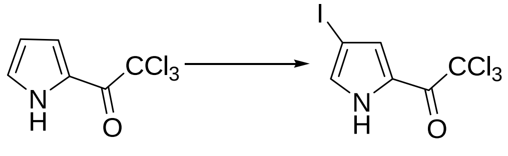
A solution of trichloroacetyl chloride (9.17 mL, 82.0 mmol) in dry diethyl ether (50 mL) was added slowly to a stirred solution of pyrrole (**4.32**) (4.63 g, 25.9 mmol) in dry diethyl ether (80 mL) at 0 °C. After stirring at room temperature for 3 hours, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL). The mixture was extracted with diethyl ether (2x200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (100 g, 5% EtOAc/hexane) to give trichloroacetyl-pyrrole (**4.33**) (14.6 g, 93%) as a colourless solid.

FTIR (neat, cm^{-1}): ν_{max} 3342, 1651, 1537.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (1H, br. s), 7.43-7.37 (1H, m), 7.21-7.16 (1H, m), 6.43-6.35 (1H, m).

^{13}C NMR (125 MHz, $CDCl_3$):δ 173.2, 127.7, 122.9, 121.3, 111.8, 94.9.

2,2,2-trichloro-1-(4-iodo-1H-pyrrol-2-yl)ethanone (4.34)[89]



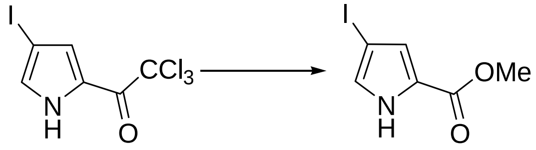
4.33 **4.34**

A solution of iodine monochloride (9.35 g, 51.4 mmol) in dry dichloromethane (80 mL) was added slowly to a solution of trichloroacetyl-pyrrole (**4.33**) (10.6 g, 51.4 mmol) in dry dichloromethane (140 mL) at 0 °C. After stirring at room temperature for 16 hours, a solution of sodium thiosulphate (2.0 M, 100 mL) was added and the mixture was stirred at room temperature. After 10 minutes, a saturated aqueous solution of sodium bicarbonate (100 mL) was added and stirring was continued for 10 minutes. The reaction mixture was filtered through a plug of celite and washed with dichloromethane. The organic layer was separated, washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give iodo-pyrrole (**4.34**) (13.7 g, 90%) as a purple solid, which was used without purification.

^{1}H NMR (MHz, $CDCl_3$): δ 9.60 (1H, br. s), 7.48-7.45 (1H, m), 7.28-7.20 (1H, m).

^{13}C NMR (MHz, $CDCl_3$):δ172.4, 131.6, 127.1, 124.5, 94.0, 63.5.

Methyl 4-iodo-1H-pyrrole-2-carboxylate (4.35)[140]



4.34 **4.35**

Sodium methoxide (2.54 g, 47.0 mmol) was added to a solution ofiodo-pyrrole (**4.34**) (22.7 g, 67.1 mmol) in methanol (150 mL) at room temperature. After stirring for 5 hours, the reaction mixture was quenched with water (150 mL). The mixture was extracted with diethyl ether (3x400 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, to give iodo methyl ester (**4.35**) as a purple solid, which was recrstallised from hexane-CH_2Cl_2 (6:1) to give pure iodo methyl ester (**4.35**) (11.8 g, 70%) as a colourless solid.

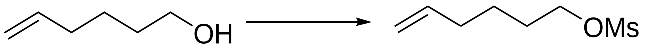
FTIR (neat, cm^{-1}): ν_{max} 3283, 1693, 1384.

^{1}H NMR (MHz, $CDCl_3$): δ 9.55 (1H, br. s), 7.04-6.96 (2H, m), 3.86 (3H, s).

^{13}C NMR (MHz, $CDCl_3$):δ 160.6, 127.8, 124.3, 121.8, 61.6, 51.8.

HRMS calculated for $C_6H_7INO_2$ (M^++H) 251.9522 found 251.9530.

Hex-5-enyl methanesulfonate (4.37)[141]



4.36 **4.37**

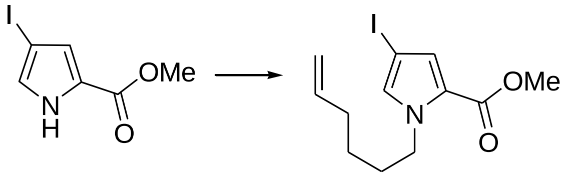
Triethylamine (41.7 mL, 300 mmol) and methanesulfonyl chloride (23.1 mL, 300 mmol) were added to an ice-cold solution of hex-5-en-1-ol(**4.36**) (20.0 g, 200 mmol) in dry dichloromethane (200 mL) and the mixture was stirred at the same temperature for 1 hour. A saturated aqueous NH_4Cl solution (200 mL) was added and the mixture was extracted with Et_2O (2x300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give mesylate (**4.37**) 35.2 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 2939, 1639, 1354, 1175.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.71 (1H, m), 5.08-4.95 (2H, m), 4.23 (2H, t, *J* = 6.4 Hz), 3.0 (3H, s), 2.10 (2H, app. q, *J* = 7.1 Hz), 1.76 (2H, quin, *J* = 6.8 Hz), 1.51 (2H, quin, *J* = 7.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 115.0, 69.9, 37.0, 32.8, 28.2, 24.4.

methyl 1-(hex-5-enyl)-4-iodo-1H-pyrrole-2-carboxylate (4.39)



4.35 **4.39**

Sodium hydride (60%dispersion in mineral oil, 239 mg, 5.97 mmol) was added to a solution of iodo methyl ester (**4.35**) (1.00 g, 3.98 mmol) in dry THF (10 mL) under nitrogen at 0 °C and stirred at room temperature. After stirring for 10 minutes, hexene-mesylate (**4.37**) (921 mg, 5.2 mmol) was added at room temperature and heated at 65 °C for 28 hours. The reaction mixture was cooled to room temperature and poured into ice water (100 mL) and extracted with Et_2O (3x100 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (30 g, 4% EtOAc/hexane) to give methoxy-pyrrole (**4.39**) (1.1 g, 80%) as a yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 1708, 1408.

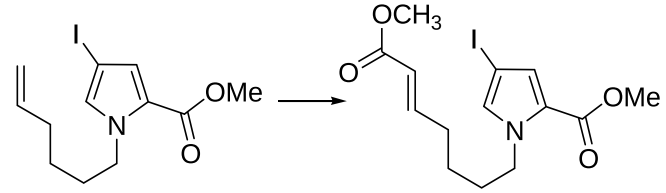
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.01 (1H, d, *J* = 1.8 Hz), 6.86 (1H, d, , *J* = 1.8 Hz), 5.85-5.68 (1H, m), 5.06 (1H, d, *J* = 17.0 Hz), 4.96 (1H, d, *J* = 9.2 Hz), 4.29 (2H, t, *J* = 7.2 Hz), 3.80 (3H, s), 2.06 (2H, t, *J* = 7.1 Hz), 1.75 (2H, t, *J* = 7.5 Hz), 1.36 (2H, t, *J* = 7.8 Hz).

^{13}C NMR (125 MHz, CDCl$_3$):δ 160.3, 138.3, 133.1, 124.7, 123.5, 115.0, 58.9, 51.3, 49.2, 33.3, 31.0, 25.8.

MS (ECI): *m/z* (%) 334 (M$^+$+1, 100).

HRMS calculated for $C_{12}H_{17}INO_2$ (M$^+$+H) 334.0304 found 334.0308.

(*E*)-methyl4-iodo-1-(7-methoxy-7-oxohept-5-enyl)-1*H*-pyrrole-2-carboxylate (4.40)



4.39 **4.40**

To a solution of methoxy-pyrrole (**4.39**) (634 mg, 1.93 mmol) in dry dichloromethane (10 mL) was added methyl acrylate (689 µL, 7.61 mmol), followed by Grubbs II catalyst (81.2 mg, 0.12 mmol) under an inert atmosphere. The reaction mixture was heated at reflux for 14 hours. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (30.0 g, 4% EtOAc/hexane) to give methoxy-alkene (**4.40**) (593 mg, 80%) as a colourless solid.

Melting point: 58-60 °C

FTIR (neat, cm^{-1}): ν_{max} 2947, 1704, 1655.

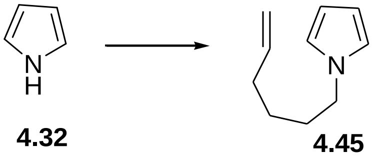
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.02 (1H, d, *J* = 1.8 Hz) , 6.92 (1H, dt, *J* = 15.9, 7.0 Hz), 6.86 (1H, d, *J* = 1.8Hz), 5.81 (1H, dt, *J* = 15.6, 1.5 Hz), 4.30 (2H, t, *J* = 7.2 Hz), 3.80 (3H, s), 3.72 (3H, s), 2.27-2.16 (2H, m), 1.77 (2H, quin, *J* = 7.4 Hz), 1.46 (2H, quin, *J* = 7.7 Hz).

^{13}C NMR (100 MHz, CDCl$_3$):δ166.9, 160.3, 148.5, 132.8, 124.7, 123.5, 121.4, 59.1, 51.4 (2C), 48.9, 31.7, 31.0, 25.0.

MS (ECI): *m/z* (%) 392 (M$^+$+1, 100).

HRMS calculated for $C_{14}H_{19}INO_4$ (M$^+$+H) 392.0359 found 392.0359.

1-(hex-5-enyl)-1*H*-pyrrole (4.45)



Pyrrole(**4.32**) (13.8 mL, 200 mmol) was added to a suspension of sodium hydroxide (16 g, 400 mmol) in dry DMSO (130 mL) under nitrogen at room temperature. After stirring for 30 minutes at room temperature, hex-5-enyl methanesulfonate (**4.37**) (35.6 g, 200 mmol) was added slowly at 0 °C. The mixture was allowed to warm to room temperature gradually (ice bath was not removed, but allowed to melt). After stirring for 14 hours at room temperature, the reaction mixture was poured into ice water (300 mL) and the mixture was extracted with Et_2O (3x400 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (300 g, 2% EtOAc/hexane) to give pyrrole-hexene(**4.45**) (25.9 g, 87%) as a yellow oil.

FTIR (neat, cm^{-1}): v_{max} 2930, 1640.

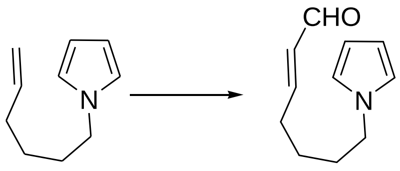
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (2H, br. s), 6.14 (2H, br. s), 5.85-5.72 (1H, m), 5.0 (1H, br. d, *J* = 19 Hz), 4.97 (1H, br. d, *J* = 11.4 Hz), 3.88 (2H, t, *J* = 7.1 Hz), 2.08 (2H, q, *J* = 7.1 Hz), 1.79 (2H, quin, *J* = 7.3Hz), 1.4 (2H, quin, *J* = 7.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 120.2 (2C), 114.8, 107.7 (2C), 49.4, 33.2, 30.9, 25.9.

MS (ESI+):*m/z* (%) 150 (M+1, 100).

HRMS calculated for $C_{10}H_{16}N$ (M^++H) 150.1283 found 150.1281.

(*E*)-7-(1*H*-pyrrol-1-yl)hept-2-enal (4.46)



4.45 **4.46**

To a solution of pyrrole-hexene(**4.45**) (20.0 g, 134 mmol) in dry dichloromethane (200 mL) was added crotonaldehyde (55.3 mL, 671 mmol), followed by Grubbs II catalyst (569 mg, 0.67 mmol) under an inert atmosphere. The reaction mixture was heated at reflux for 56 hours. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography on basified silica gel (300 g, 15.0 mL of Et_3N) eluting with 5% EtOAc/hexane to give pyrrole aldehyde (**4.46**) (20.3 g, 86%) as a yellow oil.

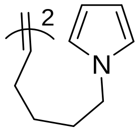
FTIR (neat, cm^{-1}): ν_{max} 2933, 1683, 1637, 1500.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.50 (1H, d, *J* = 7.8 Hz), 6.80 (1H, dt, *J* = 15.6, 6.8 Hz), 6.65 (2H, d, *J* = 2.0 Hz), 6.15 (2H, d, *J* = 2.0 Hz), 6.10 (1H, ddt, *J* = 15.6, 7.8 & 1.4 Hz), 3.91 (2H, t, *J* = 6.9 Hz), 2.4-2.28 (2H, m), 1.82 (2H, quin, *J* = 7.0 Hz), 1.52 (2H, quin, *J* = 7.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$):δ 193.7, 157.5, 133.0, 120.2 (2C), 107.9 (2C), 49.0, 31.9, 30.8, 24.8.

HRMS calculated for $C_{11}H_{16}NO$ (M^++H) 178.1232 found 178.1232.

Dimer (**4.48**)

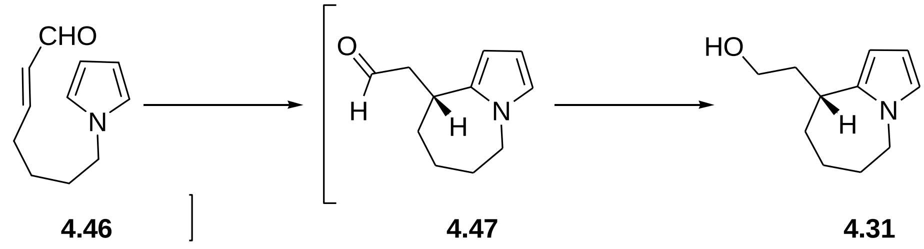


^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (4H, d, *J* = 1.8 Hz), 6.15 (4H, d, *J* = 1.8 Hz),5.39-5.33(2H, m), 3.88(4H, t, *J* = 7.3 Hz),2.08-1.96 (4H, m), 1.76 (4H, quin, *J* = 7.3 Hz), 1.35 (4H, quin, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$):δ 130.2 (2C), 120.4(4C), 107.7 (4C), 49.4 (2C), 32.0 (2C), 31.0 (2C), 26.6 (2C).

HRMS calculated for $C_{18}H_{27}N_2$ (M^++H) 271.2174 found 271.2177.

(*R*)-2-(6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethanol (4.31)



To a solution of pyrrole-aldehyde(**4.46**) (10.0 g, 56.5 mmol) in THF (200 mL) was added (*S*)-MacMillan's catalyst (3.76 g, 11.2 mmol), followed by 6.0 mL of water at -20 °C. The reaction was monitored by TLC to ensure complete cyclisation. After stirring 20 hours, the reaction mixture was diluted with 100 mL of ethanol and warmed to 0 °C. Sodium borohydride (2.13 g, 56.5 mmol) was added portion wise to the reaction mixture. After stirring for 2 hours at room temperature, the reaction mixture was poured slowly into a saturated aqueous solution of NH_4Cl (300 mL) and the mixture was extracted with ethyl acetate (3x400 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (300 g, 15% EtOAc/hexane) to give prrrole-alcohol (**4.31**) (7.60 g, 75%) as a colourless oil.The *ee* of the alcohol (**4.31**) was found to be 95% (appendix page 277).

FTIR (neat, cm^{-1}): ν_{max} 3361, 2922, 1486, 1078.

^{1}H NMR (500 MHz, CDCl$_3$): δ 6.51 (1H, t, *J* = 2.1 Hz), 5.98 (1H, t, *J* = 3.0 Hz), 5.88 (1H, t, *J* = 2.3 Hz), 4.12-3.86 (2H, m), 3.77 (2H, br. s), 2.89 (1H, br. s), 2.18-2.10 (1H, m), 2.02-1.62 (8H, m).

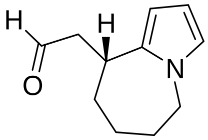
^{13}C NMR (125 MHz, CDCl$_3$):δ 137.7 (br.), 121.6, 105.6, 105.0 (br.), 61.4, 50.0, 36.3 (br.), 34.8, 34.1(br.), 29.6, 28.7 (br.).

MS (ESI+): *m/z* (%) 180 (M^++1, 100).

HRMS calculated for $C_{11}H_{18}NO$ (M^++H) 180.1388 found 180.1389.

$[\alpha]_D^{22.4}$ =0.75 (*c* =1.75, $CHCl_3$).

(*R*)-2-(6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)acetaldehyde (4.47)[88]



Nature: Colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 2923, 1719, 1294.

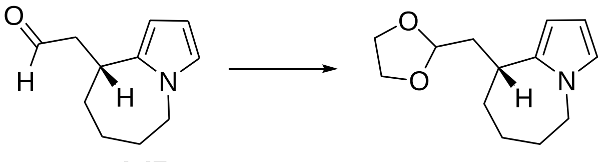
^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (1H, s), 6.57 (1H, br. s), 6.0 (1H, t, *J* = 3.0 Hz), 5.83 (1H, br. s), 4.06 (1H, dd, *J* = 14.3, 5.7 Hz), 3.94 (1H, dd, *J* = 14.0, 11.1 Hz), 3.32 (1H, app. q, *J* = 7.85 Hz), 2.95 (1H, dd, *J* = 16.7, 6.4 Hz), 2.74-2.65 (1H, m), 2.1-1.12 (6H, m).

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.9, 136.3, 121.8, 105.5, 104.9, 49.8, 47.6, 34.4, 32.8, 29.5 (br.), 29.3.

MS (ESI+): *m/z*(%) 178 (M^++1, 100).

HRMS calculated for $C_{11}H_{16}NO$ (M^++H) 178.1232 found 178.1233.

(*R*)-9-((1,3-dioxolan-2-yl)methyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (4.52)


4.47 **4.52**

Methoxy-dioxolane (**4.51**)(117 mg, 1.13 mmol) followed by PS-PPTS (**3.84**)(10.0 mg) were added to a stirred solution of aldehyde (**4.47**) (100 mg, 0.56 mmol) in dry dichloromethane under nitrogen at room temperature. After stirring at the same temperature for 20 hours, the reaction mixture was diluted with dichloromethane (10 mL) and filtered through celite, washed with dichloromethane. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10.0 g, 4% EtOAc/hexane) to give dioxolane-pyrrole(**4.52**)(12.1 mg, 10%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 2924, 1487, 1138.

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.51(1H, t, *J* = 2.3 Hz), 5.98 (1H, t, *J* = 2.8 Hz), 5.92-5.86 (1H, m), 5.0 (1H, br. s), 4.06-3.73 (6H, m), 2.93 (1H, br. s), 2.34-2.17 (1H, m), 2.05-1.30 (7H, m).

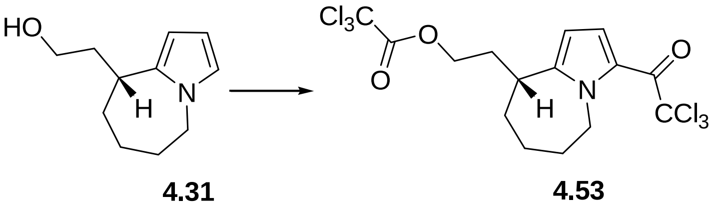
^{13}C NMR (100 MHz, CDCl$_3$):δ 137.5, 121.4, 105.4, 104.9, 103.5, 64.9, 64.6, 49.8, 37.8, 34.4 (2C), 29.5, 29.1.

MS (ECI): *m/z* (%) 222 (M$^+$+1, 100), 192 (14).

HRMS calculated for $C_{13}H_{20}NO_2$ (M$^+$+H) 222.1494 found 222.1502.

$[\alpha]_D^{20.8}$ =- 11.8 (*c* = 1.4, CHCl$_3$).

(R)-2-(3-(2,2,2-trichloroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trichloroacetate (4.53)



A solution of trichloroacetyl chloride (11.8 mL, 64.7 mmol) in dry diethyl ether (50 mL) was added slowly to a solution of hydroxypyrrole (**4.31**) (4.63 g, 25.8 mmol) in dry diethyl ether (100 mL) at 0 °C. After stirring at room temperature for 4 hours, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (100 mL). The mixture was extracted with diethyl ether (2x300 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give trichloroacetate (**4.53**)(11.5 g, 95%) as a grey solid, which was used without purification.

Melting point: 78-80 °C.

FTIR (neat, cm^{-1}): ν_{max} 2931, 1764, 1661, 1235.

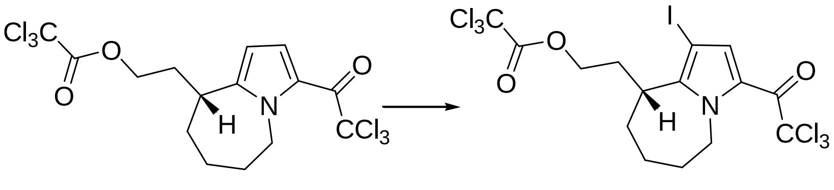
^{1}H NMR (400 MHz, $CDCl_3$, - 50 ˚C):δ 7.5 (1H, d, *J* = 4.6 Hz), 6.08 (1H, d, *J* = 4.1 Hz), 5.59 (1H, dd, *J* = 14.2, 5.0 Hz), 4.72-4.38 (2H, m), 3.71 (1H, app. t, *J* = 12.8 Hz), 2.92 (1H, app. q, *J* = 7.3 Hz), 2.51-2.38 (1H, m), 2.21-1.22 (7H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 161.9, 150.0, 124.1, 121.5, 106.7, 96.8, 89.7, 67.2, 46.2, 34.7, 32.5, 31.6, 28.8, 27.6.

HRMS calculated for $C_{15}H_{16}Cl_6NO_3$ (M^++H) 467.9261 found 467.9262.

$[\alpha]_D^{20.9}$=- 62.6 (*c* = 1.5, $CHCl_3$).

(*R*)-2-(1-iodo-3-(2,2,2-trichloroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trichloroacetate (4.54)



4.53 **4.54**

A solution of iodine monochloride (5.42 g, 33.2 mmol) in dry dichloromethane (30 mL) was added slowly to a solution of trichloroacetate (**4.53**)(12.0 g, 25.5 mmol) in dry dichloromethane (100 mL) at 0 °C. After stirring at room temperature for 14 hours, a solution of sodium thiosulphate (2.00M, 100 mL) was added and the mixture was stirred at room temperature. After 10 minutes, a saturated aqueous solution of sodium bicarbonate (100 mL) was added and stirring was continued for 15 minutes. The reaction mixture was filtered through a plug of celite and washed with dichloromethane. The organic layer was separated, washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give iodo trichloroacetate (**4.54**)(13.7 g, 90%) as a purple foam, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 2929, 1763, 1665, 1240.

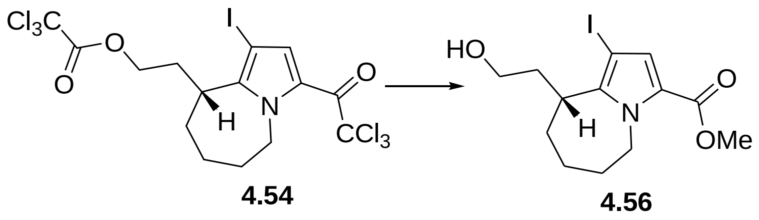
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, s), 5.56 (1H, dd, *J* = 14.9, 3.9 Hz), 4.51-4.32 (2H, m), 3.84 (1H, app. t, *J* = 13.5 Hz), 3.62-3.51 (1H, m), 2.37-1.31 (8H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 161.9, 148.4, 130.5, 123.7, 96.2, 89.6, 67.4, 67.1, 47.0, 35.4, 29.9, 29.4, 28.2, 24.1.

HRMS calculated for $C_{15}H_{15}Cl_6INO_3$ (M^++H) 593.8228 found 593.8226.

$[\alpha]_D^{21.7}$ = -58.6 (*c* = 1, $CHCl_3$).

(*R*)-methyl 9-(2-hydroxyethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (4.56)



Sodium methoxide (2.04 g, 37.8 mmol) was added to a solution of iodo trichloroacetate (**4.54**)(15.0 g, 25.2 mmol) in methanol (150 mL) at room temperature. After stirring for 8 hours, the reaction mixture was quenched with water (100 mL). The mixture was extracted with ethyl acetate (2x500 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, to give hydroxy methyl ester pyrrole (**4.56**)(8.30 g, 90%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 3367, 1698, 1512, 1149.

^{1}H NMR (400 MHz, $CDCl_3$): 6.96 (1H, s), 5.66 (1H, dd, *J* = 14.7, 4.1 Hz), 3.76 (3H, s), 3.79-3.72 (1H, m), 3.59 (2H, t, *J* = 5.9 Hz), 3.85-3.40 (1H, m), 2.12-1.18 (9H, m).

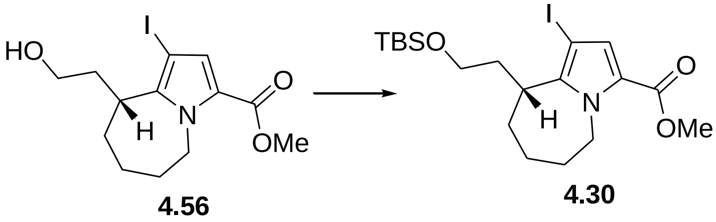
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 144.9, 124.5, 123.5, 65.0, 60.8, 51.2, 46.1, 34.6, 33.9, 30.8, 28.9, 24.6.

MS(ESI+): *m/z* (%) 364 (M^++1, 100), 279 (20), 210 (54).

HRMS calculated for $C_{13}H_{19}INO_3$ (M^++H) 364.0410 found 364.0409.

$[\alpha]_D^{20.8}$ = -33.8 (*c* = 1.1, $CHCl_3$).

(*R*)-methyl-9-(2-(tert-butyldimethylsilyloxy)ethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (4.30)



Imidazole (2.36 g, 34.7 mmol) and *tert*-butyl dimethyl silyl chloride (5.23 g, 34.7 mmol) were added to an ice cold solution of hydroxy methyl ester pyrrole (**4.56**)(8.40 g, 23.1 mmol) in dry dichloromethane (80 mL). After stirring at room temperature for five hours, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (100 mL) and the mixture was extracted with dichloromethane (2x200 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (150 g, 10% EtOAc/hexane) to give pyrrole TBS ether (**4.30**)(8.83 g, 80%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max}2927, 1702, 1094.

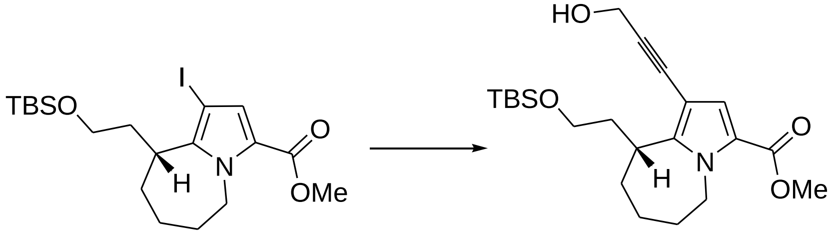
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (1H, s), 5.65 (1H, dd, *J* = 11.6, 4.0 Hz), 3.77 (3H, s), 3.82-3.36 (4H, m), 2.12-1.36 (8H, m), 0.88 (9H, s), 0.04 (3H, s), 0.03 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ 161.1, 145.7, 124.6, 123.2, 64.7, 61.3, 51.1, 46.1, 34.7, 34.0, 30.1, 29.0, 26.0 (3C), 24.6, 18.3, - 5.2, - 5.3.

HRMS calculated for $C_{19}H_{33}INO_3Si$ (M^++H) 478.1274 found 478.1274.

$[\alpha]_D^{21.7}$ = -37.4 (*c* = 2.5, $CHCl_3$).

(*R*)-methyl 9-(2-(tert-butyldimethylsilyloxy)ethyl)-1-(3-hydroxyprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (4.29)



4.30

4.29

To a stirred solution of pyrrole TBS ether (**4.30**)(3.00g, 6.29 mmol) and propargyl alcohol (1.11 mL, 18.9 mmol) in DMSO (20 mL), copper(I) iodide (119 mg, 0.62 mmol), triethylamine (2.62 mL, 18.9 mmol), $PdCl_2(PPh_3)_2$ (221 mg, 0.31 mmol) were added at room temperature. After degassing with nitrogen gas for 30 minutes, the reaction mixture was heated to 50 °C and stirred for 28 hours under nitrogen. The mixture was allowed to cool to RT, diluted with ethyl acetate (100mL) and filtered through celite, washed with ethyl acetate. The filtrate was washed with water (3x200 mL) and brine then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (200 g, 20% EtOAc/hexane) to give pyrrole propargyl alcohol (**4.29**)(1.53 g, 60%) as a pale yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 3430, 2928, 2230, 1703, 1156.

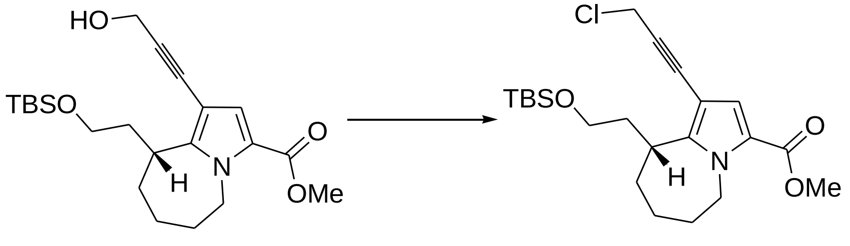
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (1H, s), 5.3 (1H, br. s), 4.42 (2H, s), 4.0 (1H, br. s), 3.76 (3H, s), 3.75-3.38 (3H, m), 2.16-1.45 (9H, m), 0.87 (9H, s), 0.02 (6H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 148.4, 120.6, 120.4, 102.5, 88.0, 80.5, 61.5, 51.8, 51.1, 45.9, 34.2, 33.2, 30.8, 28.6, 25.9 (3C), 25.4, 18.3, - 5.3, - 5.4.

HRMS calculated for $C_{22}H_{36}NO_4Si$ (M^++H) 406.2414 found 406.2417.

$[\alpha]_D^{21.0}$= -25.4 (*c* = 0.9, $CHCl_3$).

(*R*)-methyl9-(2-(tert-butyldimethylsilyloxy)ethyl)-1-(3-chloroprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (4.57)



4.29 **4.57**

Triethylamine (185 µL, 1.33 mmol) followed by methanesulfonyl chloride (770 µL, 1.01 mmol) were added to an ice cold solution of pyrrole propargyl alcohol(**4.29**)(270 mg, 0.66 mmol) in dry dichloromethane (3 mL) and the mixture was stirred for 1 hour. A saturated aqueous NH_4Cl solution (20 mL) was added and the mixture was extracted with ethyl acetate (2x20 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (15.0 g, 10% EtOAc/hexane) to give chloro pyrrole (**4.57**)(28.3 mg, 10%) as a pale yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 2928, 2229, 1703, 1157.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91 (1H, s), 5.38 (1H, br. s), 4.36 (2H, s), 3.94 (1H, br. s), 3.76 (3H, s), 3.74-3.39 (3H, m), 2.12-1.41 (8H, m), 0.87 (9H, s), 0.02 (3H, s), 0.017 (3H, s).

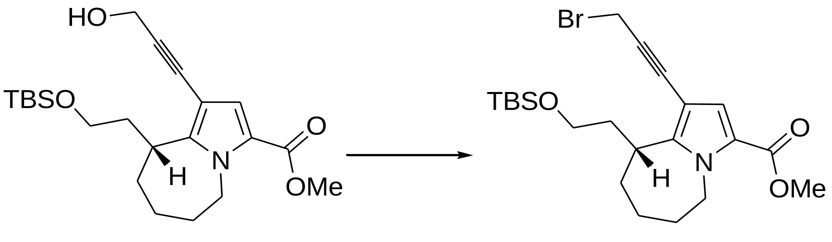
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 148.9, 120.7, 120.5, 102.2, 84.6, 81.6, 61.4, 51.1, 46.0, 34.1, 33.2, 31.9, 30.6, 28.6, 25.9 (3C), 25.2, 18.2, - 5.38, - 5.4.

MS (GC):*m/z* (%) 423 (M^+, 10), 387 (30), 330 (40), 278 (72), 256 (100).

HRMS calculated for $C_{22}H_{35}Cl^{35}NO_3Si$ (M^++H) 424.2075 found 424.2065.

$[\alpha]_D^{21.5}$ = - 14.0 (*c* = 3.0, $CHCl_3$).

(*R*)-methyl 1-(3-bromoprop-1-ynyl)-9-(2-(tert-butyldimethylsilyloxy)ethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate (4.58)



4.29 **4.58**

To a stirred solution of pyrrole propargyl alcohol (**4.29**)(500 mg, 1.23 mmol) and 2,4,6-collidine (244 µL, 1.85 mmol) in dry dichloromethane (5 mL), 5 Å molecular sieves (1.04 g) were added under an inert atmosphere. After stirring for 15 minutes at room temperature, the reaction mixture was cooled to 0 °C. A stirred solution of carbon tetrabromide [90% (6% water), 546 mg, 1.48 mmol] in dry dichloromethane (3 mL) predried over 5 Å molecular sieves (2.04 g) was added slowly to the reaction mixture at 0 °C, followed by a solution of triphenyl phosphine (388 mg, 1.48 mmol) in dry dichloromethane (3 mL). After stirring at 0 °C for one hour, the reaction mixture was filtered through celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (20.0 g, 5% EtOAc/hexane) to give pyrrole propargyl bromide (**4.58**)(329 mg, 57%) as a pale yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 2950, 2225, 1707, 1475, 1158.

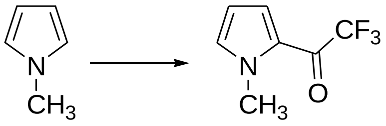
^{1}H NMR (500 MHz, CDCl$_3$): δ 6.90 (1H, s), 5.38 (1H, br. s), 4.16 (2H, s), 3.94 (1H, br. s), 3.76 (3H, s), 3.72-3.41 (3H, m), 2.12-1.48 (8H, m), 0.87 (9H, s), 0.02 (6H, s).

^{13}C NMR (125 MHz, CDCl$_3$): δ 161.4, 149.0, 120.8, 120.5, 102.3, 85.0, 82.3, 61.5, 51.1, 46.0, 34.1, 33.2, 30.6, 28.6, 25.9 (3C), 25.3, 18.2, 16.5, - 5.3, -5.4.

HRMS calculated for $C_{22}H_{35}{}^{79}BrNO_3Si$ (M^++H) 468.1570 found 468.1581.

$[\alpha]_D^{21.0}$ = - 11.2 (c = 5.0, CHCl$_3$).

2,2,2-trifluoro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (4.67)



4.66 **4.67**

Trifluoroacetic anhydride (3.80 mL, 27.1 mmol) was added to an ice cold solution of *N*-methyl pyrrole (**4.66**)(2.00 g, 24.7 mmol) in dry diethyl ether (20 mL). After stirring at room temperature for 2 hours, the reaction mixture was quenched with a saturated aqueous solution of NaHCO$_3$ (50 mL). The mixture was extracted with diethyl ether (2x50 mL). The combined organic layers were washed with water and brine, then dried (MgSO$_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (40.0 g, 5% EtOAc/hexane) to give trifluoro-pyrrole (**4.67**)(3.21 g, 74 %) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 1665, 1408, 1135.

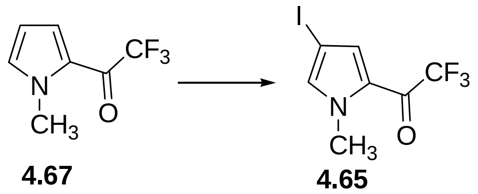
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.24-7.18 (1H, m), 7.03 (1H, br. s), 6.26 (1H, dd, *J* = 4.4, 2.4 Hz), 3.98 (3H, s).

^{13}C NMR (100 MHz, CDCl$_3$):δ 169.8 (q, *J* = 34.6 Hz), 134.8, 124.6, 123.7 (q, *J* = 3.9 Hz), 117.1 (q, *J* = 288.8 Hz), 110.0, 37.6.

MS (GC): *m/z* (%) 177 (M$^+$, 62), 108 (100).

HRMS calculated for $C_7H_6F_3NONa$ (M$^+$+Na) 200.0299 found 200.0301.

2,2,2-trifluoro-1-(4-iodo-1-methyl-1*H*-pyrrol-2-yl)ethanone (4.65)



A solution of iodine monochloride (2.12 g, 13.0 mmol) in dry dichloromethane (15 mL) was added slowly to a stirred solution of trifluoro-pyrrole (**4.67**)(2.10 g, 11.8 mmol) in dry dichloromethane (25 mL) at 0 °C. After stirring at room temperature for 12 hours, a solution of sodium thiosulphate (2.00 M, 50 mL) was added and the mixture was stirred at room temperature. After 10 minutes, a saturated aqueous solution of sodium bicarbonate (50 mL) was added and stirring was continued for 10 minutes. The reaction mixture was filtered through a plug of celite and washed with dichloromethane. The organic layer was separated, washed with water and brine, then dried (MgSO$_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (50.0 g, 5% EtOAc/hexane) to give iodo trifluoro-pyrrole(**4.65**)(2.82 g, 80 %) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 1672, 1276, 1149.

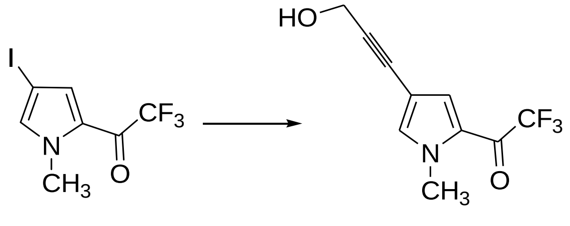
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28 (1H, q, *J* = 1.6 Hz), 7.06 (1H, s), 3.97 (3H, s).

^{13}C NMR (125 MHz, CDCl$_3$):δ 169.3 (q, *J* = 35.6 Hz), 138.7, 129.7 (q, *J* = 4.2 Hz), 126.3, 116.5 (q, *J* = 288.7 Hz), 60.9, 37.9.

MS (GC): *m/z* (%) 303 (M$^+$, 100), 234 (90).

HRMS calculated for $C_7H_6F_3INO$ (M$^+$+H) 303.9446 found 303.9409.

2,2,2-trifluoro-1-(4-(3-hydroxyprop-1-ynyl)-1-methyl-1*H*-pyrrol-2-yl)ethanone (4.68)



4.65 **4.68**

To a stirred solution of iodo trifluoro-pyrrole(**4.65**)(9.00 g, 29.7 mmol) and propargyl alcohol (5.00 mL, 89.1 mmol) in THF (150 mL), copper(I) iodide (1.14 g, 6.01 mmol), triethylamine (12.4 mL, 89.1mmol), $PdCl_2(PPh_3)_2$ (1.02 g, 1.48 mmol) were added at 0 °C. After stirring at room temperature for 14 hours, the reaction mixture was filtered through celite and washed with ethyl acetate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (200 g, 20% EtOAc/hexane) to give trifluoro-alkyne (**4.68**)(6.22 g, 90%) as a pale yellow solid.

Melting point: 78-80 °C.

FTIR (neat, cm^{-1}): ν_{max} 3523, 2234, 1671, 1145.

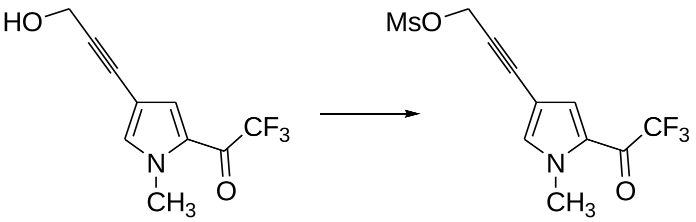
^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28-7.23 (1H, m), 7.14 (1H, s), 4.45 (2H, d, *J* = 6.1 Hz), 3.96 (3H, s), 1.68 (1H, t, *J* = 5.8 Hz).

^{13}C NMR (125 MHz, CDCl$_3$):δ 170.2 (q, *J* = 35.8 Hz), 137.0, 126.0 (q, *J* = 3.8 Hz), 124.2, 116.6 (q, *J* = 288.7 Hz), 105.7, 87.5, 78.0, 51.4, 38.1.

MS (GC): *m/z* (%) 231(M$^+$, 100), 162 (62), 134 (72).

HRMS calculated for $C_{10}H_9F_3NO_2$ (M$^+$+H) 232.0585 found 232.0594.

3-(1-methyl-5-(2,2,2-trifluoroacetyl)-1*H*-pyrrol-3-yl)prop-2-ynyl methanesulfonate (4.69)



4.68 **4.69**

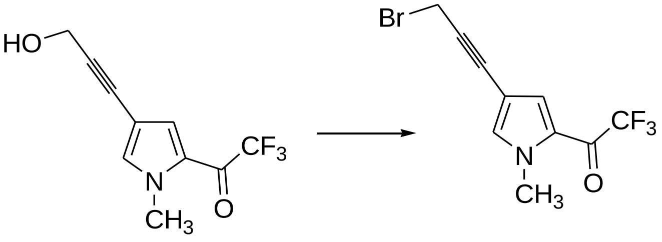
Triethylamine (240 μL, 1.74 mmol) and methanesulfonyl chloride (100 μL, 1.29 mmol) were added to an ice cold solution of trifluoro-alkyne (**4.68**)(200 mg, 0.85 mmol) in dry dichloromethane (5 mL) under nitrogen. The reaction mixture was stirred at the same temperature for 1 hour. A saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with Et_2O (2x20mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, to give pyrrole-mesylate (**4.69**) (265 mg, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): v_{max} 2242, 1736, 1351, 1172.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28 (1H, q, *J* = 1.8 Hz), 7.21 (1H, s), 5.04 (2H, s), 3.98 (3H, s), 3.13 (3H, s).

^{13}C NMR (125 MHz, CDCl$_3$):δ 170.3 (q, *J* = 36.5 Hz), 137.4, 126.2 (q, *J* = 4.0 Hz), 124.4, 116.5 (q, *J* = 288.8 Hz), 104.2, 82.2, 81.3, 58.3, 38.9, 38.2.

1-(4-(3-bromoprop-1-ynyl)-1-methyl-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethanone (4.64)



4.68 **4.64**

To a stirred solution of trifluoro-alkyne (**4.68**)(4.00 g, 17.3 mmol), 5 Å molecular sieves (5.04 g) were added under an inert atmosphere. After stirring for 10 minutes at room temperature, the reaction mixture was cooled to 0 °C. A stirred solution of carbon tetrabromide [90% (6% water), 7.63 g, 20.7 mmol] in dry dichloromethane (50 mL), was added slowly to the reaction mixture at 0 °C, followed by a solution of triphenyl phosphine (5.45 g, 20.7 mmol) in dry dichloromethane (50 mL). After stirring at 0 °C for one hour, the reaction mixture was filtered through celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (100 g, 5% EtOAc/hexane) to give pyrrole-bromide (**4.64**) (4.61 g, 90%) as a pale colourless solid.

Melting point: 80-82 °C.

FTIR (neat, cm^{-1}): ν_{max} 2233, 1674, 1134.

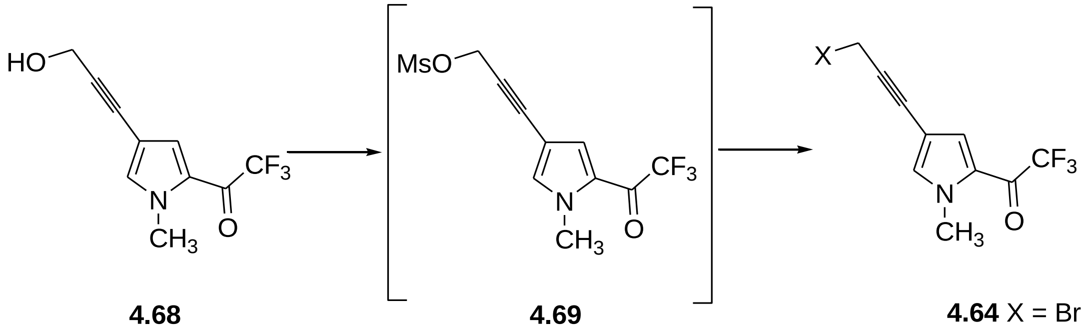
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28-7.25 (1H, m), 7.17 (1H, q, *J* = 1.4 Hz), 4.12 (2H, s), 3.96 (3H, s).

^{13}C NMR (100 MHz, CDCl$_3$):δ 170.1(q, *J* = 35.3Hz), 137.2, 126.0, 124.2, 116.6 (q, *J* = 289.1Hz), 105.1, 84.5, 79.3, 38.1, 15.3.

MS (GC): *m/z* (%) 214(M$^+$-Br, 100), 117 (40).

HRMS calculated for $C_{10}H_8{}^{79}BrF_3NO$ (M$^+$+H) 293.9741 found 293.9745.

1-(4-(3-chloroprop-1-ynyl)-1-methyl-1*H*-pyrrol-2-yl)-2,2,2-trifluoroethanone (4.70)



4.68 **4.69** **4.64** X = Br
4.70 X = Cl

To an ice cold solution of trifluoro-alkyne **(4.68)** (500 mg, 2.16 mmol) in dry dichloromethane (5 mL) triethylamine (602 µL, 4.23 mmol) and methanesulfonyl chloride (251 µL, 3.24 mmol) were added under nitrogen. The reaction was monitored by TLC to ensure the complete mesylation. After 1 hour,thereaction mixture was diluted with THF (5 mL). Lithium bromide was added and stirring was continued for 3 hours at room temperature. A saturated aqueous NH_4Cl solution (10 mL) was added and the mixture was extracted with Et_2O (2x30mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (10.0 g, 5% EtOAc/hexane) to give an inseparable mixture of pyrrole-bromide (**4.64**) and pyrrole-chloride (**4.70**)in a ratio of 1:1.

Pyrrole-chloride (4.70)

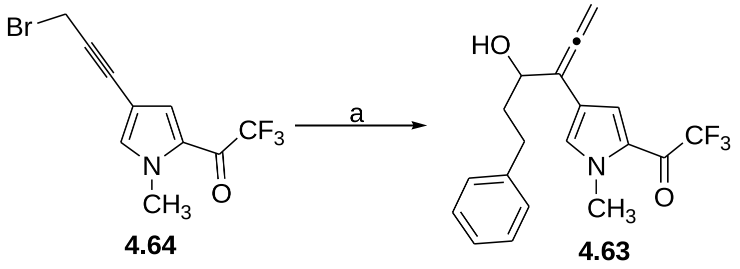
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.23 (1H, m), 7.17 (1H, s), 4.33 (2H, s), 3.96 (3H, s).

^{13}C NMR (125 MHz, $CDCl_3$):δ 170.0 (q, *J* = 35.6 Hz) 137.2, 126.0, 124.2, 116.5 (q, *J* = 288.7 Hz), 105.0, 84.0, 78.9, 31.1, 15.2.

MS (GC): *m/z* (%) 249 (M^+, 24), 214 (100). 117 (38).

HRMS calculated for $C_{10}H_8{}^{35}ClF_3NO$ (M^++H) 250.0247 found 250.0247.

2,2,2-trifluoro-1-(4-(4-hydroxy-6-phenylhexa-1,2-dien-3-yl)-1-methyl-1*H*-pyrrol-2-yl)ethanone (4.63)



To a stirred solution of pyrrole-bromide(**4.64**) (3.60 g, 12.2 mmol) and 3-phenylpropanal (3.24 mL, 24.5 mmol) in DMF (35 mL) and water (3.5 mL) under nitrogen, was added $SnCl_2$ (4.62 g, 24.5 mmol) followed by NaI (3.63 g, 24.5 mmol) at room temperature. After stirring at room temperature for 12 hours, 200 mL of water and 250 mL of EtOAc were added. The mixture was stirred at room temperature for 30 minutes, then filtered through celite, washing with EtOAc. The organic layer was separated and washed with water, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (100 g, 20% EtOAc/hexane) to give allenic alcohol (**4.63**) (4 g, 94%) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 3424, 1944, 1661, 1137.

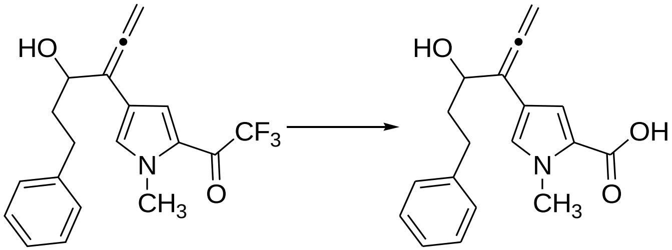
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.33-7.02 (7H, m), 5.21 (2H, d, *J* = 1.8 Hz), 4.41 (1H, br. s), 3.92 (3H, s), 2.88-2.65 (2H, m), 2.14-1.85 (3H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 205.9, 170.3 (q, *J* = 35.3 Hz), 141.5, 132.8, 128.5 (2C), 128.4 (2C), 125.9, 124.8, 121.1 (q, *J* = 3.9 Hz), 119.2, 116.9 (q, *J* = 388.8 Hz), 102.6, 80.5, 70.2, 37.9, 37.6, 32.0.

MS (GC): *m/z* (%) 349 (M$^+$, 42), 258 (32), 216 (70), 105 (68), 91 (100).

HRMS calculated for $C_{19}H_{19}F_3NO_2$ (M$^+$+H) 350.1368 found 350.1359.

4-(4-hydroxy-6-phenylhexa-1,2-dien-3-yl)-1-methyl-1*H*-pyrrole-2-carboxylic acid (4.72)



4.63 **4.72**

LiOH (300 mg, 7.16 mmol) was added to a stirred solution of allenol (**4.63**) (250 mg, 0.7 mmol) in DMF-H_2O (10:1, 3 mL) mixture at room temperature. The reaction mixture was heated to 70 °C and stirred for 12 hours. The mixture was poured into ice water (10 mL) and acidified with 2 M citric acid. The resulting precipitate was filtered, washed with water and then dried to afford the carboxylic acid (**4.72**)as a pale yellow solid (110 mg, 52%).

Melting point: 160-162 °C.

FTIR (neat, cm^{-1}): ν_{max} 3441, 1943, 1667.

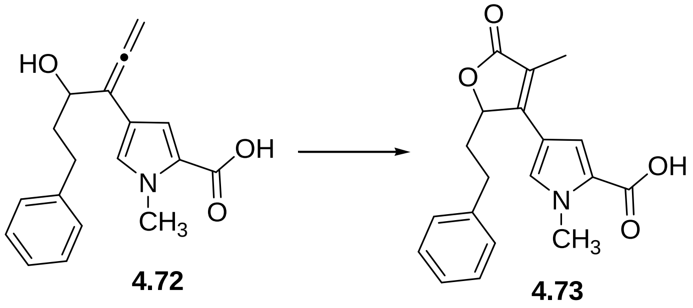
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34-7.14 (5H, m), 7.05 (1H, d, *J* = 1.7 Hz), 6.82 (1H, d, *J* = 1.7 Hz), 5.17 (2H, d, *J* = 1.7 Hz), 4.48-4.40 (1H, m), 3.87 (3H, s), 2.94-2.62 (2H, m), 2.11-1.90 (2H, m).

^{13}C NMR (75 MHz, CDCl$_3$):δ 205.8, 165.6, 141.8, 128.5 (2C), 128.3 (3C), 125.8, 122.0, 117.7, 117.2, 103.4, 80.3, 70.1, 37.6, 37.1, 32.0.

MS (GC): *m/z* (%) 253 (M^+- CO_2, 30), 120 (100).

HRMS calculated for $C_{18}H_{20}NO_3$ 298.1443 (M^++H) found 298.1448.

1-methyl-4-(4-methyl-5-oxo-2-phenethyl-2,5-dihydrofuran-3-yl)-1*H*-pyrrole-2-carboxylic acid (4.73)



Triruthenium dodecacarbonyl (28.1 mg, 0.04 mmol) was added to a solution of allenic acid(**4.72**)(259 mg, 0.87 mmol) and Et_3N (0.62 mL, 4.34 mmol) in dioxane (5 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 hours. The reaction mixture was cooled to 0 °C for 10 minutes, and then the carbon monoxide was released. The reaction mixture was acidified with 0.5 M of HCl and diluted with 20 mL of water. The mixture was extracted with ethyl acetate (3x30 mL).The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (10.0 g, 75% EtOAc/hexane) to give of pyrrole acid (**4.73**)(150 mg, 53 %) as a pale yellow solid.

Melting point: 190-192 °C.

FTIR (KBr, cm^{-1}): ν_{max} 3491, 1737, 1678, 1547, 1298.

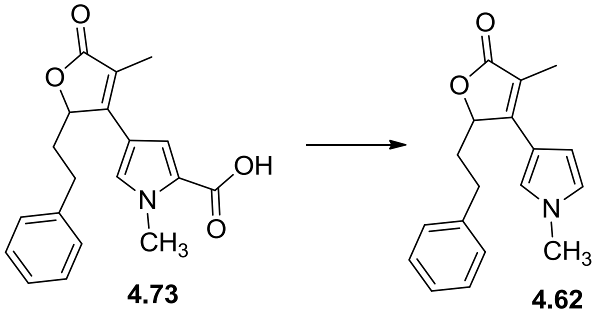
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.67 (1H, br. s), 7.59 (1H, s), 7.31-7.02 (6H, m), 5.39 (1H, d, *J* = 6.6 Hz), 3.92 (3H, s), 2.74-2.51 (2H, m), 2.32-2.18 (1H, m), 1.95 (3H, s), 1.83-1.71 (1H, m).

^{13}C NMR (100 MHz, DMSO-d$_6$):δ 174.2, 161.6, 153.8, 141.0, 130.6, 128.3(2C), 128.2 (2C), 125.9, 124.2, 116.8, 116.0, 113.3, 79.7, 36.9, 35.6, 30.1, 9.8.

MS (GC): *m/z* (%) 281 (M^+-CO_2, 34), 177 (100), 149 (98).

HRMS calculated for $C_{19}H_{20}NO_4$ (M^++H) 326.1392 found 326.1393.

3-methyl-4-(1-methyl-1*H*-pyrrol-3-yl)-5-phenethylfuran-2(5*H*)-one (4.62)



Trifluoroacetic acid (680μL, 0.92 mmol) was added to a stirred solution of acid (**4.73**) (100 mg, 0.31mmol) in dry dichloromethane (3 mL) under nitrogen at room temperature. The reaction mixture was heated to 40 °C. After 2 hours heating, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (5.00 g, 10% EtOAc/hexane) to give pyrrole(**4.62**)(732 mg, 90%) as a pale yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 1732, 1644, 1332.

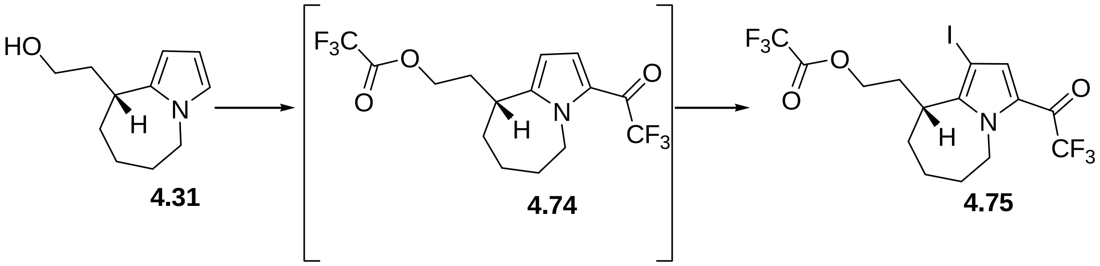
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.14 (5H, m), 6.77 (1H, t, *J* = 1.7 Hz), 6.66 (1H, t, *J* = 2.4 Hz), 6.22 (1H, dd, *J* = 2.7, 1.8 Hz), 5.10 (1H, d, *J* = 7.7 Hz), 3.70 (3H, s), 2.84-2.70 (2H, m), 2.38-2.25 (1H, m), 2.02 (3H, d, *J* = 1.3 Hz), 1.89-1.78 (1H, m).

^{13}C NMR (125 MHz, CDCl$_3$): δ 175.6, 154.9, 141.1, 128.6 (2C), 128.4 (2C), 126.0, 123.4, 122.7, 116.7, 115.5, 108.3, 79.9, 36.6, 36.5, 31.0, 10.2.

MS (GC): *m/z* (%) 281 (M$^+$, 32), 177 (96), 149 (100).

HRMS calculated for $C_{18}H_{20}NO_2$ (M$^+$+H) 282.1494 found 282.1495.

(*R*)-2-(1-iodo-3-(2,2,2-trifluoroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trifluoroacetate (4.75)



4.31 **4.74** **4.75**

Trifluoroacetic anhydride (18.8 mL, 135 mmol) was added to an ice cold solution of alcohol (**4.31**)(9.68 g, 54.5 mmol) in dry diethyl ether (100 mL). After stirring for 2 hours at room temperature, the solvent was removed under reduced pressure without external heating. The crude reaction mixture was dissolved in dry dichloromethane (100 mL). A solution of iodine monochloride (13.2 g, 81.1 mmol) in dry dichloromethane (50 mL) was added to the reaction mixture at 0 °C. After stirring for two hours at room temperature, a solution of sodium thiosulphate (2M, 100 mL) was added and the mixture was stirred at room temperature. After 15 minutes, a saturated aqueous solution of sodium bicarbonate (100 mL) was added and stirring was continued for 15 minutes. The reaction mixture was filtered through a plug of celite and washed with dichloromethane.

The organic layer was separated, washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 5% EtOAc/hexane) to give iodopyrrole (**4.75**)(21.9 g, 81 %) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 2938, 1786, 1666, 1143.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.24 (1H, q, *J* = 2.2 Hz), 5.73 (1H, dd, *J* = 14.7, 4.4 Hz), 4.40-4.26 (2H, m), 3.82 (1H, dd, *J* = 14.1, 12.5 Hz), 3.61-3.49 (1H, m), 2.35-2.21 (1H, m), 2.2-2.17 (6H, m), 1.6-1.5 (1H, m).

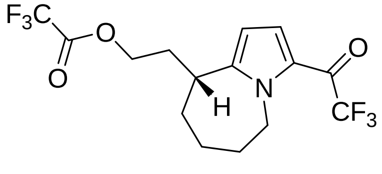
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.4 (q, *J* = 35.1Hz), 157.3 (q, *J* = 42 Hz), 149.5, 130.7 (q, *J* = 4.4 Hz), 126.2, 118.0 (q, *J* = 289.4 Hz), 114.3 (q, *J* = 284 Hz), 68.0, 65.9, 46.9, 35.2, 29.8, 29.1, 28.2, 24.2.

MS(GC):*m/z* (%) 497 (M$^+$, 40), 355 (100).

HRMS calculated for $C_{15}H_{15}F_6INO_3$ (M$^+$+H) 498.0001 found 498.0001.

$[\alpha]_D^{21.4}$ = - 70.0 (*c* = 5, $CHCl_3$).

R)-2-(3-(2,2,2-trifluoroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethyl 2,2,2-trifluoroacetate (4.74)



FTIR (neat, cm^{-1}): ν_{max} 2936, 1785, 1657, 1134.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.19-7.13 (1H, m), 6.08 (1H, d, *J* = 4.4 Hz), 5.37 (1H, br. s), 4.55-4.38 (2H, m), 4.11(1H, br. s), 2.95 (1H, app. q, *J* = 7.8 Hz), 2.43-2.32 (1H, m), 2.14-1.21 (7H, m).

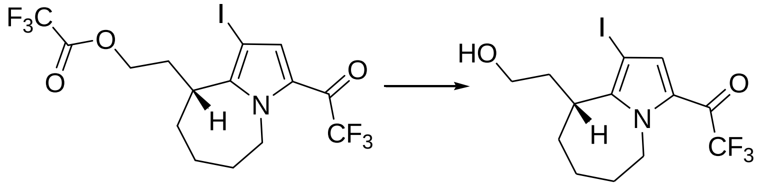
^{13}C NMR (100 MHz, CDCl$_3$): δ 169.5 (q, *J* = 34.4 Hz), 157.3(q, *J* = 42.0 Hz), 151.0, 124.2 (2C), 117.2 (q, *J* = 278 Hz), 114.3 (q, *J* = 286 Hz), 108.0, 66.0, 46.0, 34.8, 32.4, 31.4, 28.6, 27.6.

MS (GC): *m/z*(%) 371 (M$^+$, 82), 302 (50), 230 (100).

HRMS calculated for $C_{15}H_{16}F_6NO_3$ (M$^+$+H) 372.1034 found 372.1037.

$[\alpha]_D^{21.6}$ = - 79.6(*c* = 2, CHCl$_3$).

(*R*)-2,2,2-trifluoro-1-(9-(2-hydroxyethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)ethanone (4.77)



4.75 **4.77**

Poly(4-vinyl pyridine) resin (11.3 g) was added to a solution of trifluoroacetate (**4.75**) (22.6 g, 45.5 mmol) in methanol (230 mL) and the mixture was stirred at room temperature. After 22 hours, the reaction mixture was filtered through celite and washed with ethyl acetate. The solvent was removed under reduced pressure, to give alcohol (**4.77**)(18.2 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 3351, 2931, 1661, 1479, 1140.

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.23 (1H, q, *J* = 1.4 Hz), 5.68 (1H, dd, *J* = 14.6, 4.5 Hz), 3.84 (1H, app. t, *J* = 13.3 Hz), 3.62 (2H, t, *J* = 4.9 Hz), 3.58-3.50 (1H, m), 2.2-1.48 (9H, m).

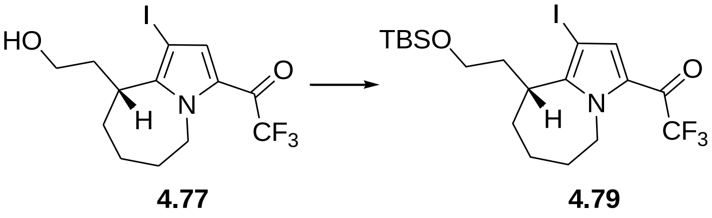
^{13}C NMR (125 MHz, CDCl$_3$): δ 169.0 (q, *J* = 34.4 Hz), 151.3, 130.7 (q, *J* = 4.3 Hz), 125.9, 116.9 (q, *J* = 289 Hz), 67.9, 60.5, 46.9, 34.8, 33.3, 29.9, 28.3, 24.2.

MS (GC):*m/z* (%) 401 (M$^+$, 60), 355 (100), 230 (92).

HRMS calculated for $C_{13}H_{16}F_3INO_2$ (M$^+$+H) 402.0178 found 402.0178.

$[\alpha]_D^{21.2}$ =- 58.3 (*c* = 3, CHCl$_3$).

(*R*)-1-(9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-iodo-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (4.79)



Imidazole (4.63 g, 68.1 mmol) and *tert*-butyl dimethyl silyl chloride (10.2 g, 68.1 mmol) were added to an ice cold solution of alcohol (**4.77**)(18.2 g, 45.4 mmol) in dry dichloromethane (200 mL). After stirring at room temperature for three hours, the reaction mixture was quenched with a saturated aqueous NH$_4$Cl solution (200 mL) and the mixture was extracted with dichloromethane (2x300 mL). The combined organic layers were washed with water and brine, then dried (MgSO$_4$). The solvent was removed under reduced pressure, to give trifluoroethanone (**4.79**)(23.3 g, 99%) as a yellow oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 2930, 1665, 1242, 1141.

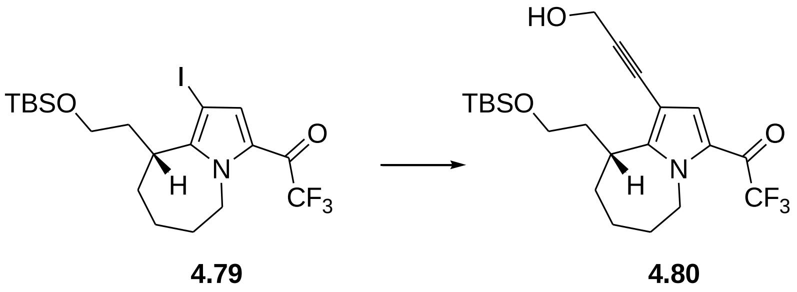
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.23 (1H, q, *J* = 2.3 Hz), 5.67 (1H, dd, *J* = 14.0, 4.8 Hz), 3.87 (1H, dd, *J* = 13.7, 12.3 Hz), 3.72-3.65 (1H, m), 3.62-3.47 (2H, m), 2.08-1.75 (6H, m), 1.7-1.43 (2H, m), 0.88 (9H, s), 0.04(3H, s), 0.03 (3H, s).

^{13}C NMR (100 MHz, CDCl$_3$): δ 168.9 (q, *J* = 35.4 Hz), 152.1, 130.8, 125.7, 117.0 (q, *J* = 293.2 Hz), 67.7, 60.8, 46.7, 35.1, 33.3, 29.2, 28.3, 25.9 (3C), 24.2, 18.2, -5.4, -5.5.

HRMS calculated for $C_{19}H_{30}F_3INO_2Si$ (M^++H) 516.1043 found 516.1040.

$[\alpha]_D^{21.3}$ =-67.4(*c* = 5, CHCl$_3$).

(*R*)-1-(9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-1-(3-hydroxyprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone(**4.80**)



To a stirred solution of iodopyrrole (**4.79**)(17.7 g, 34.4 mmol) and propargyl alcohol (8.21 mL, 137mmol) in DME (200 mL), copper(I) iodide (1.32 g, 6.87 mmol), potassium carbonate (18.9 g, 137 mmol), palladium on carbon (10%, 910 mg, 0.85 mmol) and triphenyl phosphine (901mg, 3.41 mmol) were added at room temperature. After degassing with nitrogen gas for 30 minutes, the reaction mixture was heated to 85 °C and stirred for 16 hours under nitrogen. The mixture was allowed to cool to RT and filtered through celite, washed with ethyl acetate. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 10% EtOAc/hexane) to give propargyl alcohol (**4.80**)(13.2 g, 87%) as a pale yellow oil.

FTIR (neat, cm^{-1}): ν_{max} 3412, 2930, 2233, 1665, 1142.

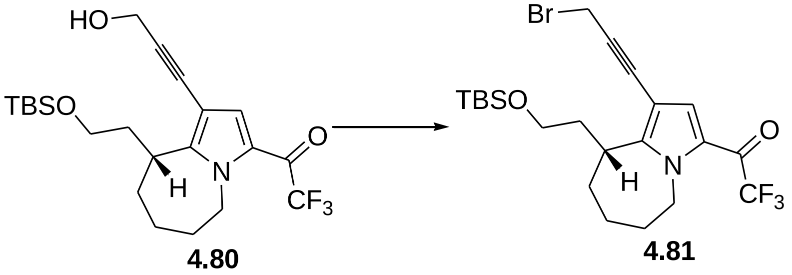
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.18 (1H, q, *J* = 1.9 Hz), 5.34 (1H, br. s), 4.42 (2H, d, *J* = 5.3 Hz), 4.08 (1H, s), 3.74-3.48 (3H, m), 2.37 (1H, t, *J* = 5.7 Hz), 2.16-1.48 (8H, m), 0.85 (9H, s), 0.06 (3H, s), 0.013 (3H, s).

^{13}C NMR (100 MHz, CDCl$_3$): δ 169.4 (q, *J* = 35 Hz), 154.2, 126.8 (q, *J* = 4 Hz), 122.8, 117.0 (q, *J* = 289 Hz), 105.8, 89.4, 78.8, 61.2, 51.5, 46.6, 33.7, 33.5, 29.9, 28.0, 25.8 (3C), 25.0, 18.2, - 5.4, - 5.5.

HRMS calculated for $C_{22}H_{33}F_3NO_3Si$ (M^++H) 444.2182 found 444.2184.

$[\alpha]_D^{20.6}$ = - 69.5(*c* = 3, CHCl$_3$).

(*R*)-1-(1-(3-bromoprop-1-ynyl)-9-(2-(*tert*-butyldimethylsilyloxy)ethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (4.81)



To a stirred solution of propargyl alcohol (**4.80**)(12.9 g, 29.1 mmol) and 2,4,6-collidine (5.8 mL, 43.7 mmol) in dry dichloromethane (130 mL), 5 Å molecular sieves (13.0 g) were added under an inert atmosphere. After stirring for 15 minutes at room temperature, the reaction mixture was cooled to 0 °C. A stirred solution of carbon tetrabromide [90% (6% water), 16.1 g, 43.7 mmol] in dry dichloromethane (100 mL), predried over 5 Å molecular sieves (16.5 g) was added slowly to the reaction mixture at 0 °C, followed by a solution of triphenyl phosphine (9.16 g, 34.9 mmol) in dry dichloromethane (50 mL). After stirring at 0 °C for one hour, the reaction mixture was filtered through celite and washed with dichloromethane. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 5% EtOAc/hexane) to give propargyl bromide (**4.81**)(12.2 g, 83%) as a pale yellow solid.

Melting point: 45-47 °C.

FTIR (neat, cm^{-1}): ν_{max} 2929, 2232, 1668, 1147, 1145.

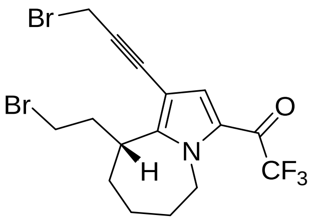
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.2 (1H, q, *J* = 1.8 Hz), 5.42 (1H, br. d, *J* = 7.8 Hz), 4.14 (2H, s), 4.04 (1H, app. t, *J* = 13.3 Hz), 3.74-3.50 (4H, m), 2.14-2.05 (1H, m), 1.95-1.48 (6H, m), 0.86 (s, 9H), 0.025 (3H), 0.02 (3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 169.5 (q, *J* = 34.3 Hz), 154.6, 126.8 (q, *J* = 3.8 Hz), 122.9, 116.9 (q, *J* = 289.5 Hz), 105.4, 86.2, 80.3, 61.1, 46.7, 33.6 (2C), 29.8, 28.0, 25.8 (3C), 24.9, 18.2, 15.6, - 5.4, - 5.5.

HRMS calculated for $C_{22}H_{32}{}^{79}BrF_3NO_2Si$ (M^++H) 506.1338 found 506.1378.

$[\alpha]_D^{20.5}$ =- 61.9 (*c* = 3, CHCl$_3$).

(*R*)-1-(9-(2-bromoethyl)-1-(3-bromoprop-1-ynyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (4.82)



Nature: Colourlessoil.

FTIR (neat, cm^{-1}): ν_{max} 2932, 2232, 1669, 1143.

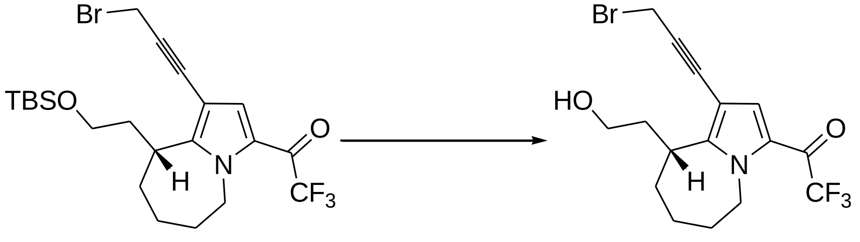
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (1H, q, *J* = 2.0 Hz), 5.38 (1H, br. d, *J* = 10.6 Hz), 4.16 (2H, s), 4.06 (1H, app. t, *J* = 12.3 Hz), 3.65-3.58 (1H, m), 3.51-3.32 (2H, m), 2.58-2.41 (1H, m), 2.26-2.10 (1H, m), 2.0-1.4 (6H, m).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8 (q, *J* = 35.0 Hz), 152.5, 126.6 (q, *J* = 4.2 Hz), 123.3, 120.7 (q, *J* = 289 Hz), 105.9, 86.8, 79.9, 46.8, 35.7, 34.4, 30.9, 30.3, 27.9, 25.1, 15.5.

HRMS calculated for $C_{16}H_{17}F_3{}^{79}Br_2NO$ (M^++H) 453.9629 found 453.9630.

$[\alpha]_D^{20.7}$ =- 97.3 (*c* = 1.25, $CHCl_3$).

(*R*)-1-(1-(3-bromoprop-1-ynyl)-9-(2-hydroxyethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)-2,2,2-trifluoroethanone (4.84)



4.81 **4.84**

Amberlyst-15 (8.50 g) was added to a stirred mixture of propargyl bromide (**4.81**)(8.50 g, 16.8 mmol) and 5 Å molecular sieves (16.4 g) in freshly distilled isopropyl alcohol (250 mL) under an inert atmosphere. After 24 hours, the reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was concentrated under reduced pressure, to give alcohol (**4.84**)(5.91 g, 90%) as a purple oil, which was used without purification.

FTIR (neat, cm^{-1}): ν_{max} 3467, 2930, 2232, 1665.

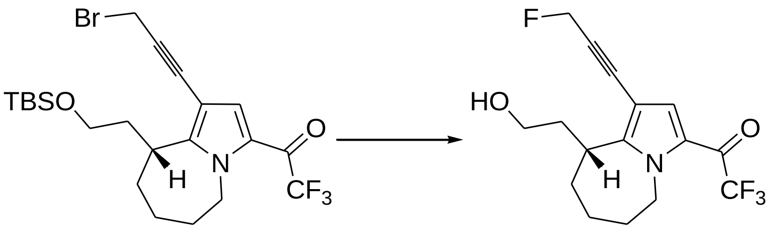
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.21 (1H, q, *J* = 1.8 Hz), 5.51 (1H, br. d, *J* = 10.1Hz), 4.16 (2H, s), 3.94 (1H, app. t, *J* = 12.1 Hz), 3.74-3.54 (3H, m), 2.2-1.45 (9H, m).

^{13}C NMR (100 MHz, CDCl$_3$):δ 169.3 (q, *J* = 35.4 Hz), 154.0, 126.3, 123.0, 117 (q, *J* = 292.1 Hz), 105.5, 86.5, 80.1, 60.3, 46.8, 33.4, 33.0, 30.2, 27.8, 24.7, 15.5.

HRMS calculated for $C_{16}H_{18}{}^{79}BrF_3NO_2$ (M^++H) 392.0473 found 392.0478.

$[\alpha]_D^{21.1}$ =- 79.9 (*c* = 3, CHCl$_3$).

(*R*)-2,2,2-trifluoro-1-(1-(3-fluoroprop-1-ynyl)-9-(2-hydroxyethyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-3-yl)ethanone (4.83)



4.81 **4.83**

Tetra-*n*-butylammonium fluoride (37.0 mg, 0.12 mmol) was added to a solution of propargyl bromide (**4.81**) (50.0 mg, 0.10 mmol) in THF (1 mL) at room temperature. After stirring 14 hours, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (5 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (5.00 g, 20% EtOAc/hexane) to give propargylic fluoride(**4.83**)(15.2 mg, 48%) as a purple oil.

FTIR (neat, cm^{-1}): ν_{max} 3418, 2932, 2235, 1656, 1263.

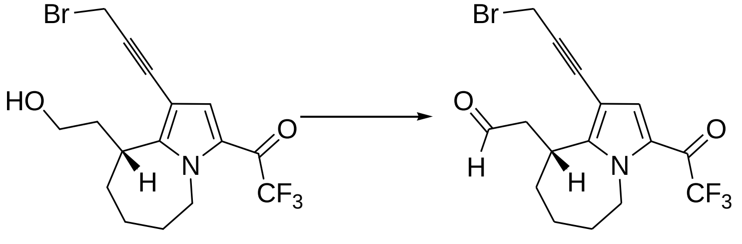
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (1H, q, *J* = 1.8 Hz), 5.53 (1H, br. d, *J* = 9.2 Hz), 5.16 (2H, d, *J* = 48.5 Hz), 3.94 (1H, t, *J* = 12.3 Hz), 3.75-3.48 (3H, m), 2.17-1.48 (9H, m).

^{13}C NMR (100 MHz, $CDCl_3$): δ169.8 (q, *J* = 34.3 Hz), 153.9, 126.7, 123.3, 116.9 (q, *J* = 290 Hz), 105.3, 85.2 (d, *J* = 21.0 Hz), 83.1 (d, *J* = 11.4 Hz), 71.1 (d, *J* = 164.1 Hz), 60.6, 47.0, 33.6, 33.1, 30.5, 28.0, 24.9.

HRMS calculated for $C_{16}H_{18}F_4NO_2$ (M^++H) 332.1274 found 332.1276.

$[\alpha]_D^{21}$ =- 88.5 (*c* = 1, $CHCl_3$).

(*R*)-2-(1-(3-bromoprop-1-ynyl)-3-(2,2,2-trifluoroacetyl)-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)acetaldehyde(4.86)



4.84 **4.86**

Dess-Martin periodinane (8.60 g, 20.3 mmol) was added to an ice cold solution of bromoalcohol (**4.84**)(6.11 g, 15.6 mmol) in dry dichloromethane (60 mL) under nitrogen. After stirring at room temperature for 3 hours, the solvent was removed under reduced pressure without external heating. The residue was taken up in diethyl ether (150 mL) and stirred for 15 minutes. The mixture was filtered through a short pad of celite and silica gel, and washed with diethyl ether. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (300 g, 15% EtOAc/hexane) to give bromoaldehyde (**4.86**)(5.09 g, 84 %) as a colourless oil.

FTIR (neat, cm^{-1}): ν_{max} 2934, 2232, 1723, 1664, 1538, 1131.

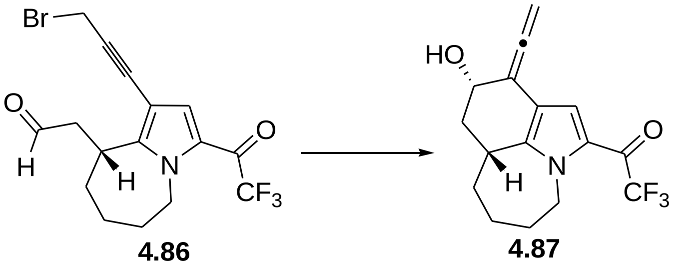
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.83 (1H, s), 7.20 (1H, q, *J* = 2.3 Hz), 5.1-4.4 (2H, m), 4.15 (2H, s), 3.9 (1H, br. s), 3.28-3.12 (1H, m), 2.9 (1H, dd, *J* = 17.6, 7.6 Hz), 1.90-1.68 (6H, m).

^{13}C NMR (100 MHz, CDCl$_3$): δ 199.4, 169.7 (q, *J* = 34.3 Hz), 151.8, 127.1, 123.0, 116.7 (q, *J* = 290 Hz), 104.1, 86.9, 80.1, 46.4, 45.2, 31.5, 30.7, 27.4, 26.1, 15.4.

HRMS calculated for $C_{16}H_{16}{}^{79}BrF_3NO_2$ (M^++H) 390.0316 found 390.0314.

$[\alpha]_D^{21}$ =- 53.4 (*c* =10, CHCl$_3$).

2,2,2-trifluoro-1-((9*S*,10a*R*)-9-hydroxy-8-vinylidene-1,2,3,4,8,9,10,10*a*-octahydroazepino[3,2,1-*hi*]indol-6-yl)ethanone (4.87)



Acetic acid (70 mL) was added to a solution of bromo-aldehyde (**4.86**)(7.10 g, 18.2 mmol) in DMF (70 mL) at -40°C under nitrogen, followed by indium (8.38 g, 73.0 mmol). After stirring at the same temperature for 20 hours, the reaction mixture was warmed to room temperature. Approximately two-thirds of the solvent was removed by distillation at 30 °C under reduced pressure (0.8 torr). The residue was poured into ice-water (200 mL). The resulting precipitate was filtered, washed with water and then dried. The crude compound was purified by flash column chromatography on silica gel (300 g, 80% CH_2Cl_2/hexane) to give allenic alcohol (**4.87**) (2.95 g, 52 %) as a colourless solid.

Melting point: 160-162 °C.

FTIR (KBr, cm^{-1}): ν_{max} 3265, 1948, 1670, 1500, 1456, 1265.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.05 (1H, q, *J* = 2.1 Hz), 5.59 (1H, dd, *J* = 14.3, 6.0 Hz), 5.38 (1H, dd, *J* = 11.3, 3.5 Hz), 5.31 (1H, dd, *J* = 11.3, 3.6 Hz), 4.52-4.42 (1H, m), 3.66 (1H, dd, *J* = 13.9, 3.6 Hz), 2.95 (1H, dd, *J* = 16.4, 8.3 Hz), 2.4-2.31(1H, m), 2.14-2.0 (1H, m), 1.95 (1H, d, *J* = 4.1 Hz), 1.93-1.91 (1H, m), 1.84-1.50 (5H, m).

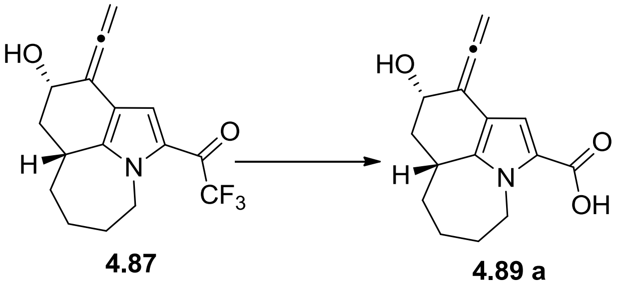
^{13}C NMR (100 MHz, CDCl$_3$): δ 202.1, 169.7 (q, *J* = 34.5 Hz), 147.3, 124.7, 120.0 (q, *J* = 4.0 Hz), 117.1 (q, *J* = 289 Hz), 115.7, 102.1, 83.1, 66.8, 47.8, 39.3, 35.0, 34.2, 30.1, 27.8.

MS (GC): *m/z* (%) 311 (M^+, 100), 242 (34), 214 (92), 186 (34), 172 (32).

HRMS calculated for $C_{16}H_{17}F_3NO_2$ (M^++H) 312.1211 found 312.1213.

$[\alpha]_D^{21}$ = 7.7 (*c* = 1, CHCl$_3$).

(9*S*,10a*R*)-9-hydroxy-8-vinylidene-1,2,3,4,8,9,10,10a-octahydroazepino[3,2,1-*hi*]indole-6-carboxylic acid (4.89 a)



NaOH (2.0 M, 13.3 mL, 26.5 mmol) was added slowly to a solution of allenic alcohol (**4.87**)(2.75 g, 8.84 mmol) in DMSO (30 mL) at 15°C. After stirring at room temperature for 15 minutes, the reaction mixture was poured into ice-water (300 mL) and acidified with 2.0M citric acid. The resulting precipitate was filtered, washed with water and then dried to afford the carboxylic acid (**4.89 a**)as a pale yellow solid (2.06 g, 90%).

Melting point: 152-154 °C.

FTIR (KBr, cm^{-1}): ν_{max} 3283, 2353, 1946, 1684, 1491.

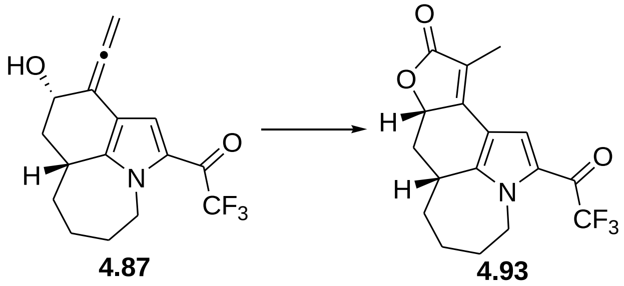
^{1}H NMR (400 MHz, DMSO-d$_6$): δ 12.1(1H, br. s), 6.54 (1H, s), 5.44 (1H, br. d, *J* = 10.4 Hz), 5.16 (1H, dd, *J* = 10.9, 3.5 Hz), 5.12 (1H, dd, *J* = 10.9, 3.5 Hz), 5.03 (1H, d, *J* = 5.0 Hz), 4.27 (1H, br. s), 3.57 (1H, app. t, *J* = 12.1 Hz), 2.92 (1H, dd, *J* = 16.0, 8.8 Hz), 2.2-1.75 (4H, m), 1.59 (2H, app. q, *J* =10 Hz), 1.35 (2H, app. quin, *J* = 12.4 Hz).

^{13}C NMR (100 MHz, DMSO-d$_6$): δ 203.5, 162.1, 140.9, 122.2, 112.9, 112.7, 103.0, 80.4, 66.1, 46.0, 40.4, 35.4, 33.6, 29.6, 28.0.

HRMS calculated for $C_{15}H_{18}NO_3$ (M^++H) 260.1287 found 260.1290.

[α]$_D^{21.5}$ =55.1 (*c* = 0.5, CH_3OH).

Butenolide (4.93)



Triruthenium dodecacarbonyl (9.00 mg, 0.01mmol) was added to a mixture of allenic alcohol (**4.87**)(90.0 mg, 0.29 mmol) and triethylamine (120 µL, 0.87 mmol) in dioxane (2 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 hours. The reaction mixture was cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (10.0 g, 20% EtOAc/hexane) to give lactone (**4.93**)(85.0 mg, 87%) as a yellow solid.

Melting point: 114-116 °C.

FTIR (neat, cm^{-1}): ν_{max} 2930, 1747, 1666, 1531, 1265.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.32 (1H, q, *J* = 1.8 Hz), 5.60 (1H, dd, *J* = 14.4, 5.7 Hz), 4.86-4.75 (1H, m), 3.74 (1H, dd, *J* = 14.0, 11.2 Hz), 3.14-3.05 (1H, m), 2.79-2.67 (1H, m), 2.21-1.8 (3H, m), 2.04 (3H, d, *J* = 1.8 Hz), 1.85-1.42 (4H, m).

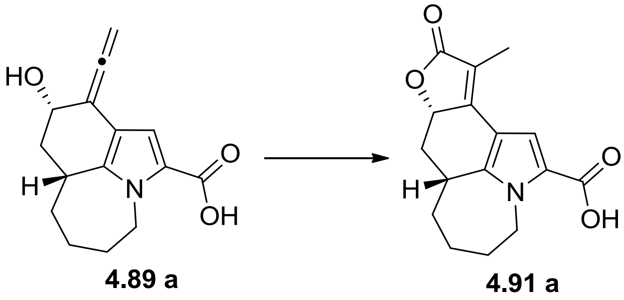
^{13}C NMR (100 MHz, CDCl$_3$):δ174.8, 170.3 (q, *J* = 34.5 Hz), 151.7, 149.7, 125.9, 119.6 (q, *J* = 3.8 Hz), 116.8 (q, *J* = 292.2 Hz), 116.2, 114.3, 71.1, 48.6, 36.7, 35.2, 34.3, 29.3, 27.0, 9.1.

MS (ESI+): *m/z* (%) 340 (M$^+$+1, 100), 287 (16), 190 (27).

HRMS calculated for $C_{17}H_{17}F_3NO_3$ (M$^+$+H) 340.1161 found 340.1160.

$[\alpha]_D^{21.1}$ =- 96.8(*c* = 1.5, CHCl$_3$).

Lactone (4.91 a)



Triruthenium dodecacarbonyl (50.0 mg, 0.08 mmol) was added to a mixture of allenic acid (**4.89 a**) (500 mg, 1.93 mmol) and 2,4,6-collidine (1.53 mL, 11.6 mmol) in dioxane (20 mL) at room temperature in a Fisher-Porter tube. The tube was flushed with carbon monoxide and pressurized to 100 psi, then stirred at 100 °C for 14 hours. The reaction mixture was cooled to 0 °C and acidified with 0.5M of HCl. The reaction mixture was diluted with 50 mL of water and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (30 g, 40% EtOAc/hexane, 50.0μL of acetic acid) to give lactone (**4.91 a**)(376 mg, 68%) as a purple foam.

FTIR (KBr, cm^{-1}): ν_{max} 3470, 2924, 1747, 1664, 1161.

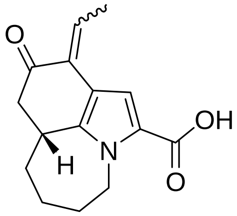
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28 (1H, s), 5.59 (1H, dd, *J* = 14.0, 5.2 Hz), 4.88-4.70 (1H, m), 3.67 (1H, dd, *J* = 13.8, 11.0 Hz), 3.12-3.0 (1H, m), 2.76-2.66 (1H, m), 2.2-1.93 (3H, m), 2.04 (3H, d, *J* = 5.6 Hz), 1.79-1.38 (4H, m).

^{13}C NMR (100 MHz, CDCl$_3$): δ 175.5, 165.4, 153.3, 145.7, 123.5, 116.0, 114.6, 112.7, 77.4, 47.9, 37.1, 35.7, 34.5, 29.6, 27.6, 8.9.

HRMS calculated for $C_{16}H_{18}NO_4$ (M^++H) 288.1236 found 288.1239.

$[\alpha]_D^{21.1}$ =- 81.0 (*c* = 1.1, $CHCl_3$).

(*R*)-8-ethylidene-9-oxo-1,2,3,4,8,9,10,10a-octahydroazepino[3,2,1-*hi*]indole-6-carboxylic acid (4.92)



Nature: Purple color solid.

Melting point: 176-178 °C.

FTIR (KBr, cm^{-1}): ν_{max} 3150, 1689, 1602, 1469.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (1H, s), 6.25 (1H, q, *J* = 7.6 Hz), 5.44 (1H, dd, *J* = 14.2, 5.4 Hz), 3.73 (1H, dd, *J* = 14.4, 11.2 Hz), 3.27- 3.16 (1H, m), 2.92 (1H, dd, *J* = 14.8, 7.2 Hz), 2.55 (1H, dd, *J* = 15.0, 6.2 Hz), 2.12 (3H, d, *J* = 7.6 Hz), 2.08-1.41 (6H, m).

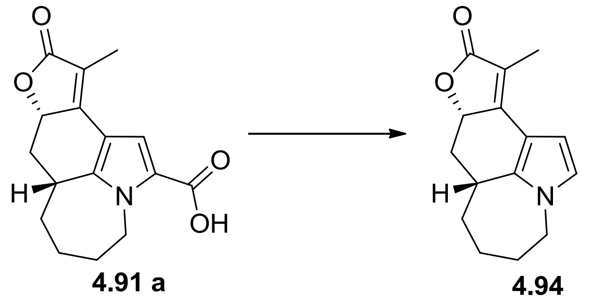
^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 166.0, 141.1, 129.4, 128.1, 121.9, 120.1, 113.2, 47.7, 46.2, 35.1, 34.7, 29.5, 28.2, 15.3.

MS (ESI+): *m/z* (%) 260 (M^++1, 100), 216 (92), 181 (42).

HRMS calculated for $C_{15}H_{18}NO_3$ (M^++H) 260.1287 found 260.1283.

$[\alpha]_D^{21.3}$ =- 35.7 (*c* = 1.4, $CHCl_3$).

Pyrrole (4.94)



Trifluoroacetic acid (340 μL, 8.71 mmol) was added to a solution of acid (**4.91 a**)(500 mg, 1.74 mmol) in dry dichloromethane (8 mL) under nitrogen at room temperature. The reaction mixture was heated to 40 °C. After 4 hours heating, the reaction mixture was cooled to room temperature and quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (15.0 g, 15% EtOAc/hexane) to give pyrrole(**4.94**)(381 mg, 90%) as a pale yellow solid.

Melting point: 170-172 °C.

FTIR (KBr, cm^{-1}): ν_{max} 2930, 1744, 1664, 1294.

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.61 (1H, d, *J* = 2.9 Hz), 6.29 (1H, d, *J* = 2.9 Hz), 4.87-4.73 (1H, m), 4.15-4.05 (1H, m), 3.88-3.77 (1H, m), 3.03-2.92 (1H, m), 2.68-2.59 (1H, m), 2.18-2.02 (2H, m), 2.0 (3H, d, *J* = 1.2 Hz), 1.98-1.87 (1H, m), 1.72-1.32 (4H, m).

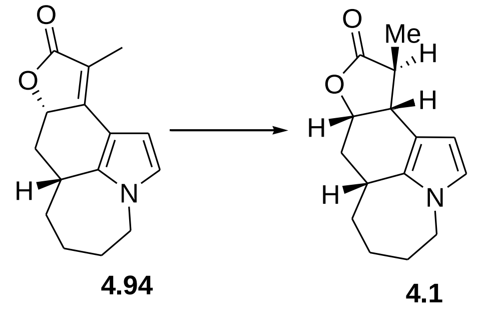
^{13}C NMR (100 MHz, CDCl$_3$): δ 175.9, 155.2, 137.6, 124.9, 113.2, 111.7, 103.8, 77.8, 51.7, 37.8, 36.4, 34.7, 29.6, 28.7, 8.8.

MS (ESI+): *m/z* (%) 244 (M^++1, 100).

HRMS calculated for $C_{15}H_{18}NO_2$ (M^++H) 244.1338 found 244.1338.

$[\alpha]_D^{20.6}$ =-152.9 (c = 1.0, $CHCl_3$).

Lactone (4.1)



Magnesium powder (30.0 mg, 1.23 mmol) was added to a stirred solution of pyrrole (**4.94**)(30.0 mg, 0.12 mmol) in dry methanol (2 mL) under nitrogen at room temperature. After stirring for 24 hours, the reaction mixture was quenched with 1.0 M of HCl (5 mL). The mixture was diluted with water (20 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (5.0 g, 15% EtOAc/hexane) to give lactone (**4.1**)(13.5 mg, 45%) as a colourless solid.

Melting point: 122-124 °C.

FTIR (neat, cm^{-1}): ν_{max} 2928, 1768, 1004.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (1H, d, J = 2.7 Hz), 5.94 (1H, d, J = 2.7 Hz), 4.72 (1H, ddd, J = 11.8, 7.3 & 4.6 Hz), 4.05 (1H, dd, J = 13.8, 5.2 Hz), 3.77 (1H, dd, J = 13.7, 11.4 Hz), 3.13 (1H, dd, J = 10.8, 7.7 Hz), 2.82-2.72 (1H, m), 2.58-2.48 (1H, m), 2.29

(1H, ddd, *J* = 13.0, 10.0 & 5.0 Hz), 2.18-1.85 (3H, m), 1.73-1.52 (3H, m), 1.4 (3H, d, *J* = 7.1 Hz), 1.38-1.21 (1H, m).

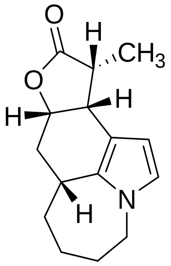
^{13}C NMR (100 MHz, CDCl$_3$): δ 179.7, 131.9, 122.5, 116.5, 104.9, 76.8, 51.4, 42.1, 41.7, 36.5, 35.2, 33.4, 30.1, 29.5. 14.0.

MS (ESI+): *m/z* (%) 246 (M+1, 100), 197 (48).

HRMS calculated for $C_{15}H_{20}NO_2$ (M^++H) 246.1494 found 246.1490.

$[\alpha]_D^{21.1}$ = -1.11(*c* = 0.7, CHCl$_3$).

Minor isomer (4.95)



Nature: Colourlessoil.

FTIR (neat, cm^{-1}): ν_{max} 2931, 1767, 1175.

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.48 (1H, d, *J* = 2.7 Hz), 5.87 (1H, d, *J* = 2.7 Hz), 4.79 (1H, ddd, *J* = 9.5, 6.1 & 3.4 Hz), 3.97 (1H, dd, *J* = 13.9, 5.2 Hz), 3.80 (1H, app. t, *J* = 12.5 Hz), 3.61 (1H, app. t, *J* = 7.0 Hz), 3.10-2.91(1H, m),2.82-2.72 (1H, m), 2.28-2.13 (1H, m), 2.11-2.01 (2H, m), 1.98-1.82 (2H, m), 1.59-1.35 (3H, m), 1.31 (3H, d, *J* = 7.5 Hz).

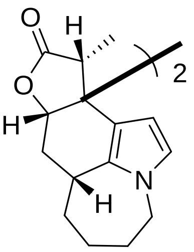
^{13}C NMR (100 MHz, CDCl$_3$): δ 179.8, 132.8, 120.9, 111.0, 104.9, 77.9, 50.0, 40.8, 38.4, 36.7, 34.2, 32.0, 30.8, 29.4, 12.6.

MS(ESI+): *m/z* (%) 246 (M^++1, 100).

HRMS calculated for $C_{15}H_{20}NO_2$ (M^++H) 246.1494 found 246.1495.

$[\alpha]_D^{21.6}$ = 22.1 (*c* = 0.7, $CHCl_3$).

Dimer (4.96)



Nature: Colourless solid.

Mp: 242-244 °C.

FTIR (neat, cm^{-1}): ν_{max} 2932, 1772.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (1H, d, *J* = 2.8 Hz), 5.96 (1H, d, *J* = 2.8 Hz), 4.35 (1H, dd, *J* = 8.0, 3.5 Hz), 4.0 (1H, dd, *J* = 14.2, 5.2 Hz), 3.86 (1H, app. t, *J* = 11.6 Hz), 3.40 (1H, q, *J* = 7.5 Hz), 2.78-2.62 (1H, m), 2.44-1.38 (8H, m), 1.33 (3H, t, *J* = 7.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 133.9, 121.7, 113.2, 107.7, 80.8, 54.0, 50.2, 43.5, 36.5, 36.3, 31.5, 29.5, 28.8, 16.1.

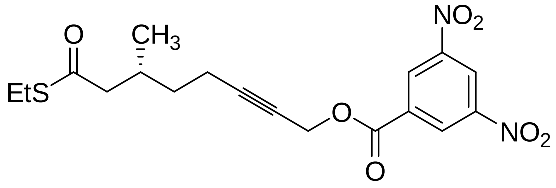
MS(ESI+): *m/z* (%) 489 (M^++1, 100).

HRMS calculated for $C_{30}H_{37}N_2O_4$ (M^++H) 489.2753 found 489.2751.

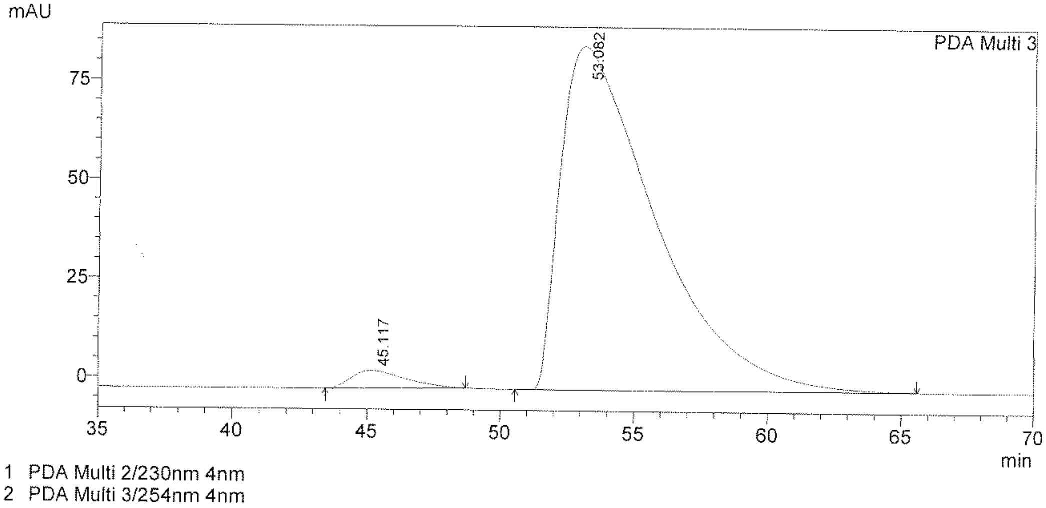
$[\alpha]_D^{21.1}$ =137.65 (*c* = 0.4, $CHCl_3$).

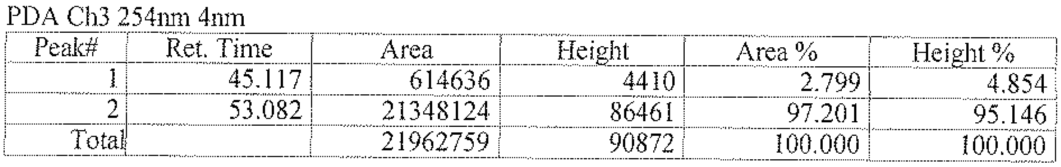
Appendix

dinitrobenzoate (2.46)



The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel ODH column (Hexane:*i*-propanol 90:10, 1 mL/min): t_1 = 45.1 min (minor) , t_2 = 53.1 min (major).

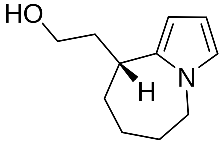




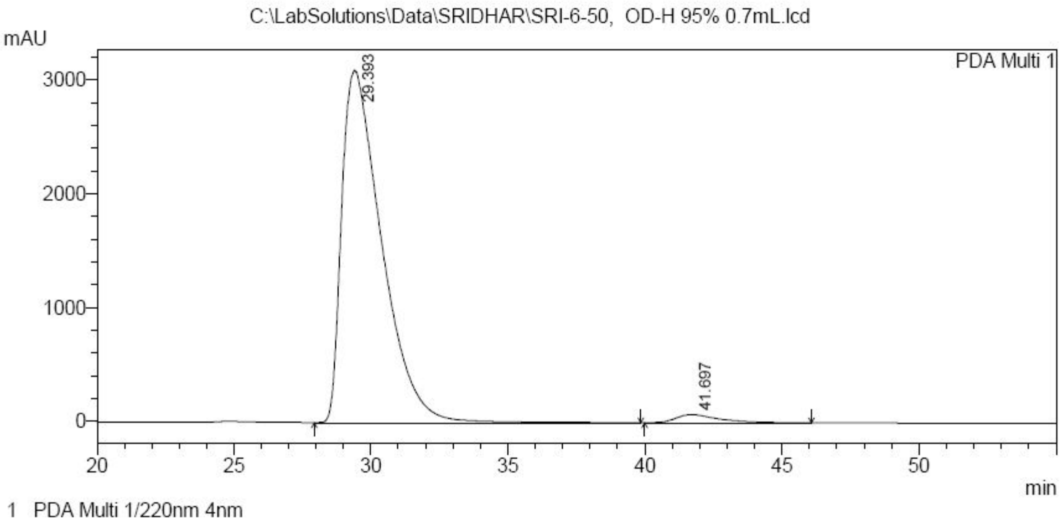
PDA Ch3 254nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	45.117	614636	4410	2.799	4.854
2	53.082	21348124	86461	97.201	95.146
Total		21962759	90872	100.000	100.000

Chiral HPLC analysis for (*R*)-2-(6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepin-9-yl)ethanol(**4.31**)



The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel ODH column (Hexane:*i*-propanol 95:5, 0.7 mL/min), t_1 = 29.4 min (major), t_2 = 41.7 min (minor).

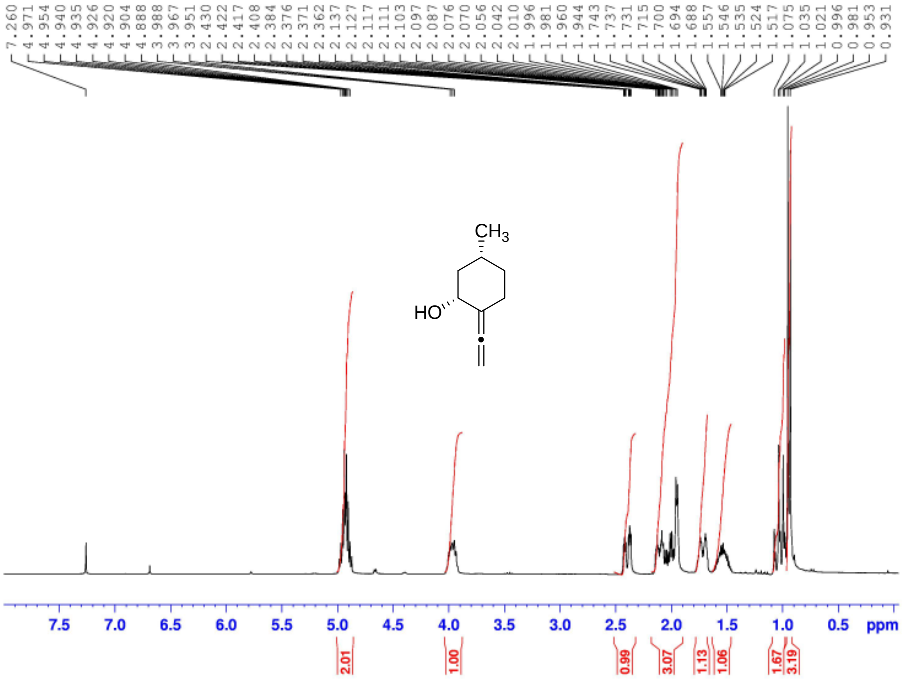


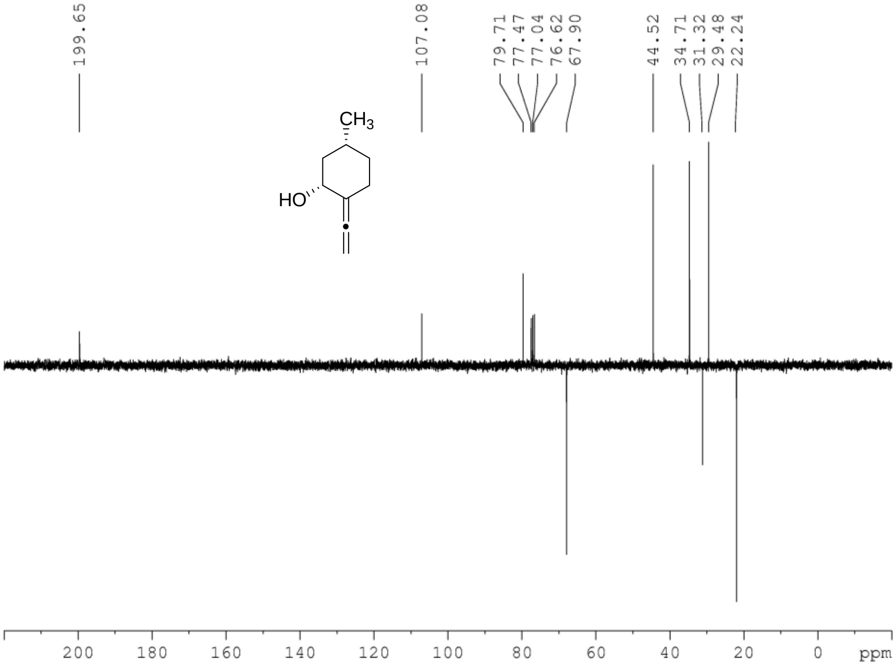
PeakTable

PDA Ch1 220nm 4nm

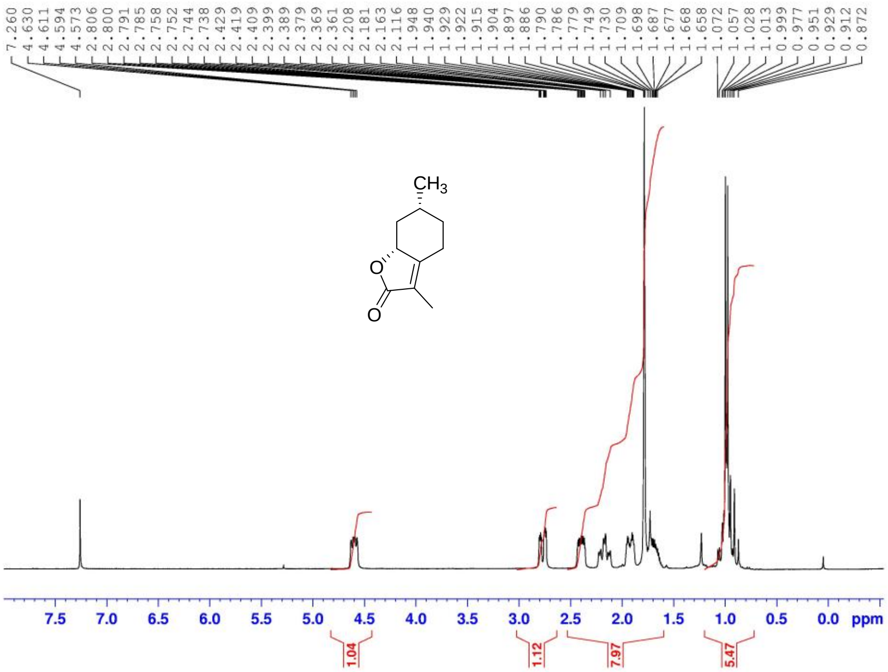
Peak#	Ret. Time	Area	Height	Area %	Height %
1	29.393	313464721	3094544	97.534	97.707
2	41.697	7924670	72616	2.466	2.293
Total		321389391	3167160	100.000	100.000

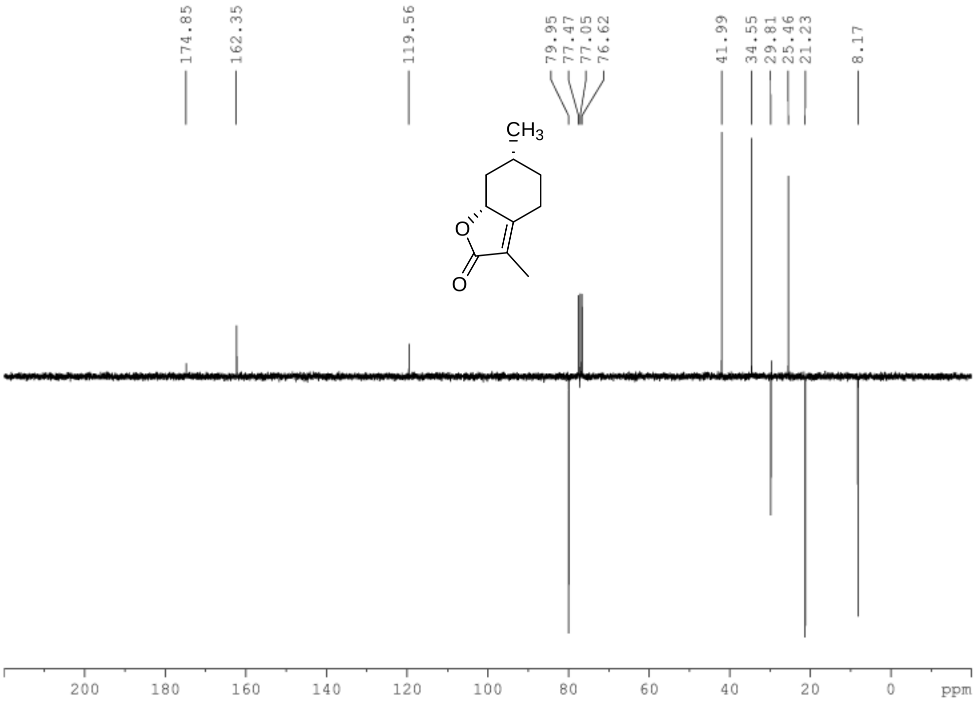
^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75.4 MHz, CDCl$_3$, PENDANT) spectrum of (1*R*, 5*R*)-5-Methyl-2-vinylidenecyclohexanol(**2.21**)



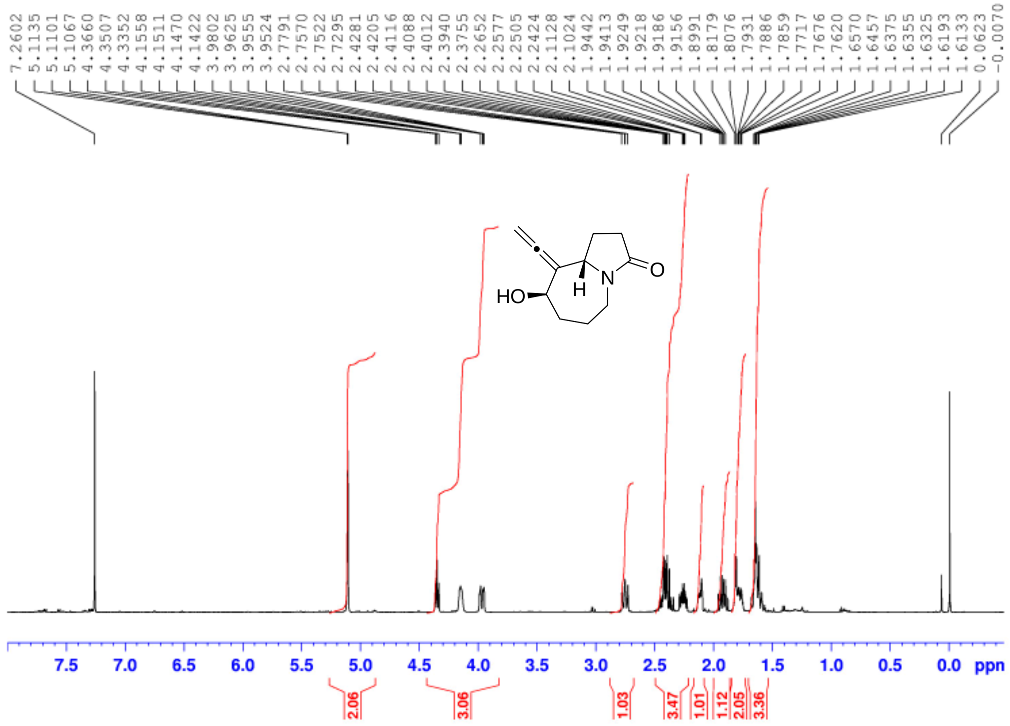


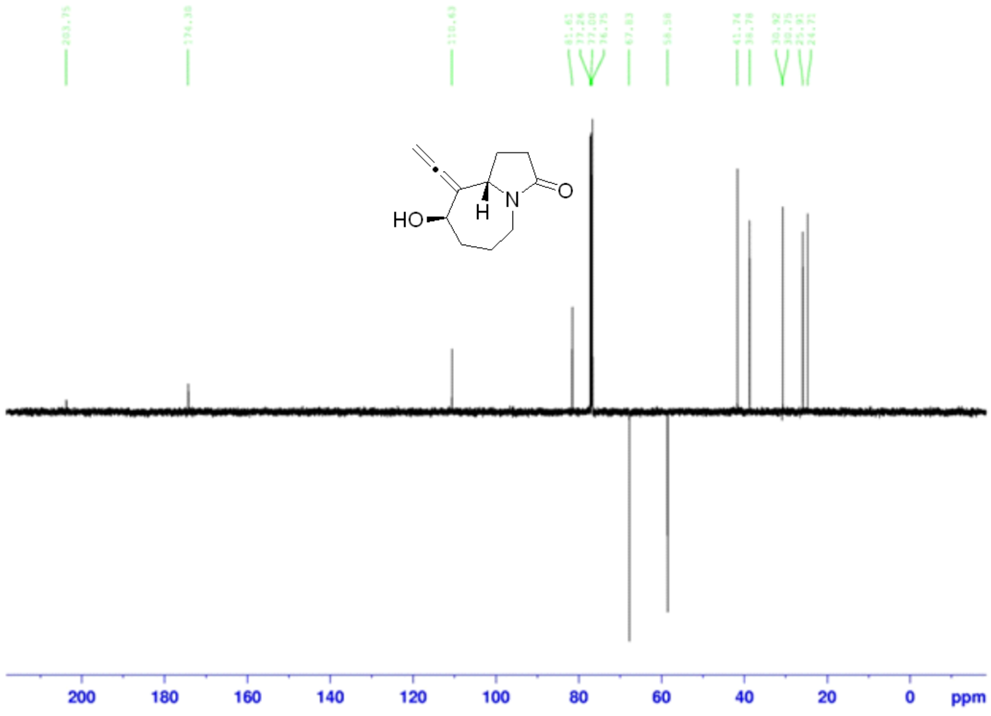
^{1}H NMR (300 MHz, CDCl$_3$) and ^{13}C NMR (75.5 MHz, CDCl$_3$, PENDANT) spectrum of (-)-mintlactone (**2.1**)



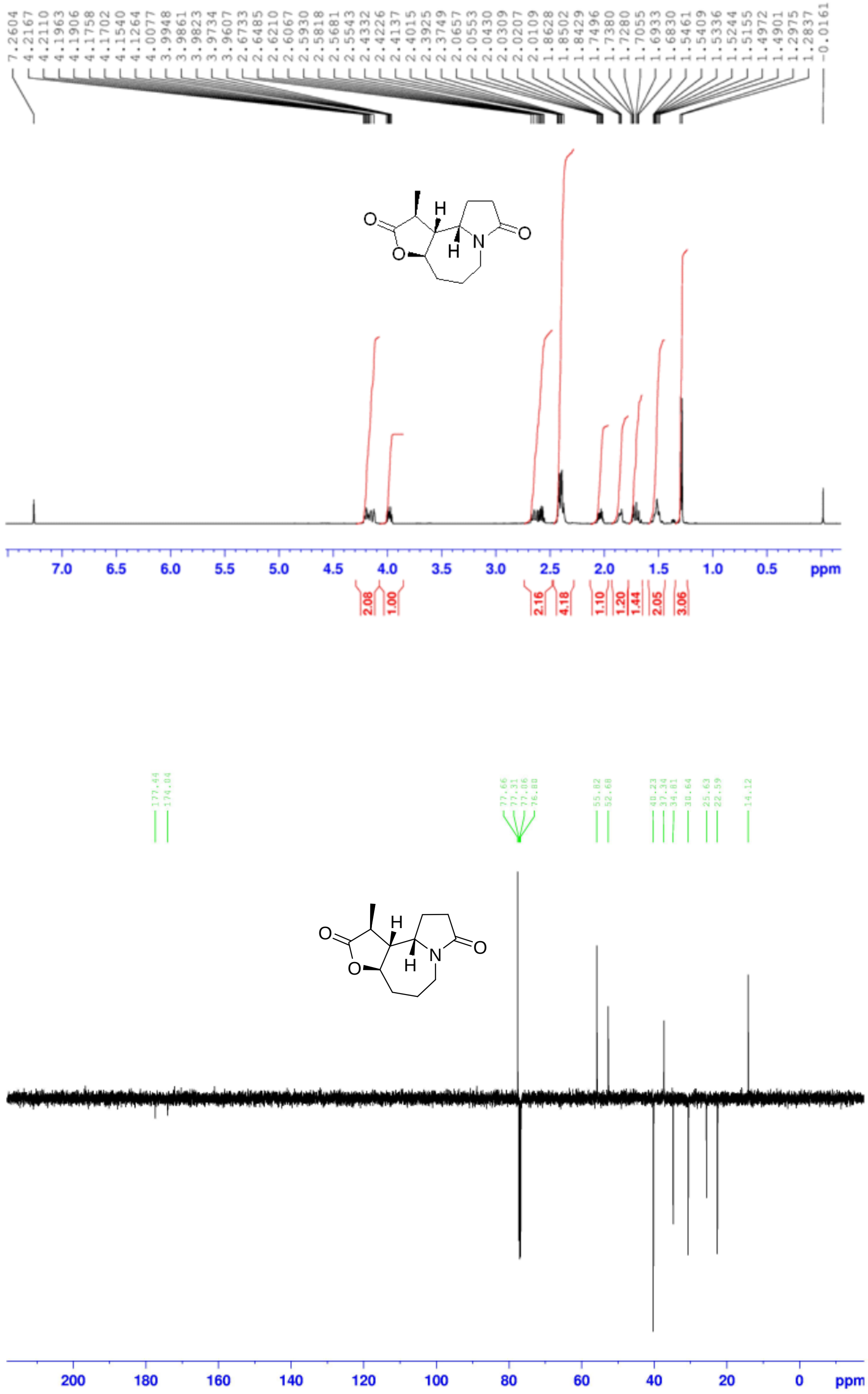


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$, PENDANT) spectrum of allenol(**3.66**)

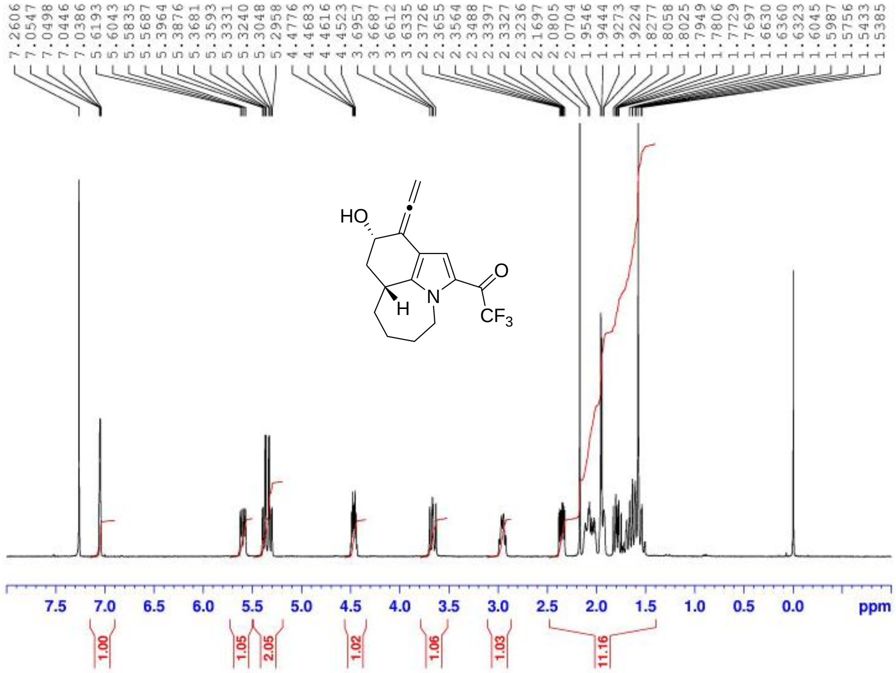


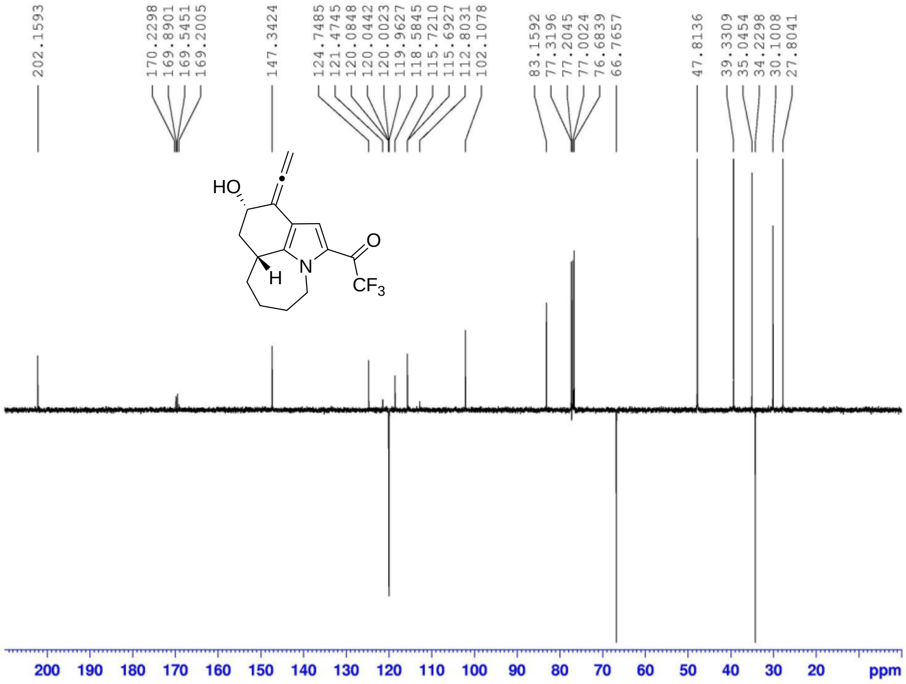


^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$, PENDANT) spectrum of (±)-stemoamide (**3.1**)

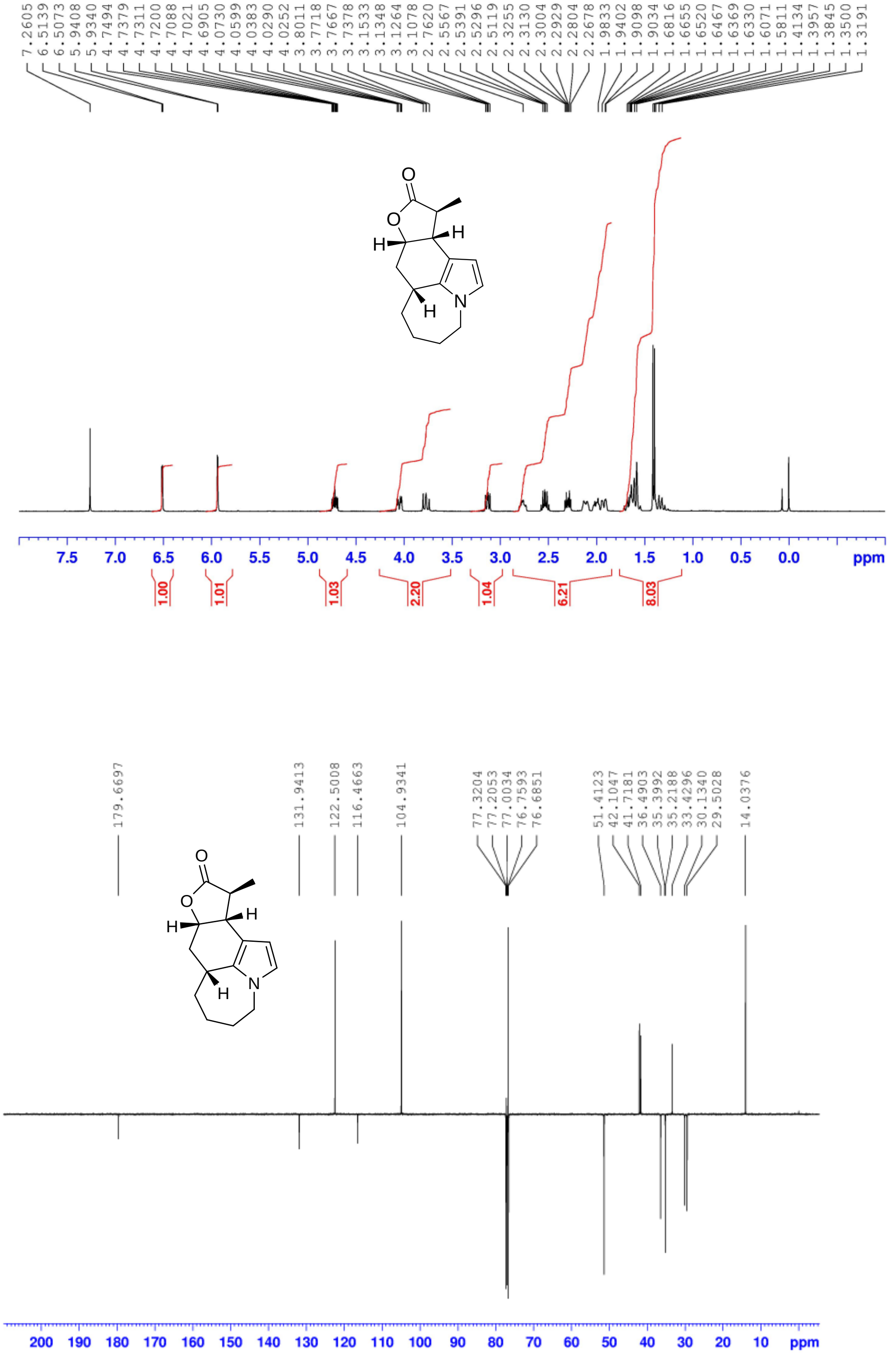


^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$, PENDANT) spectrum of allenol (**4.87**)

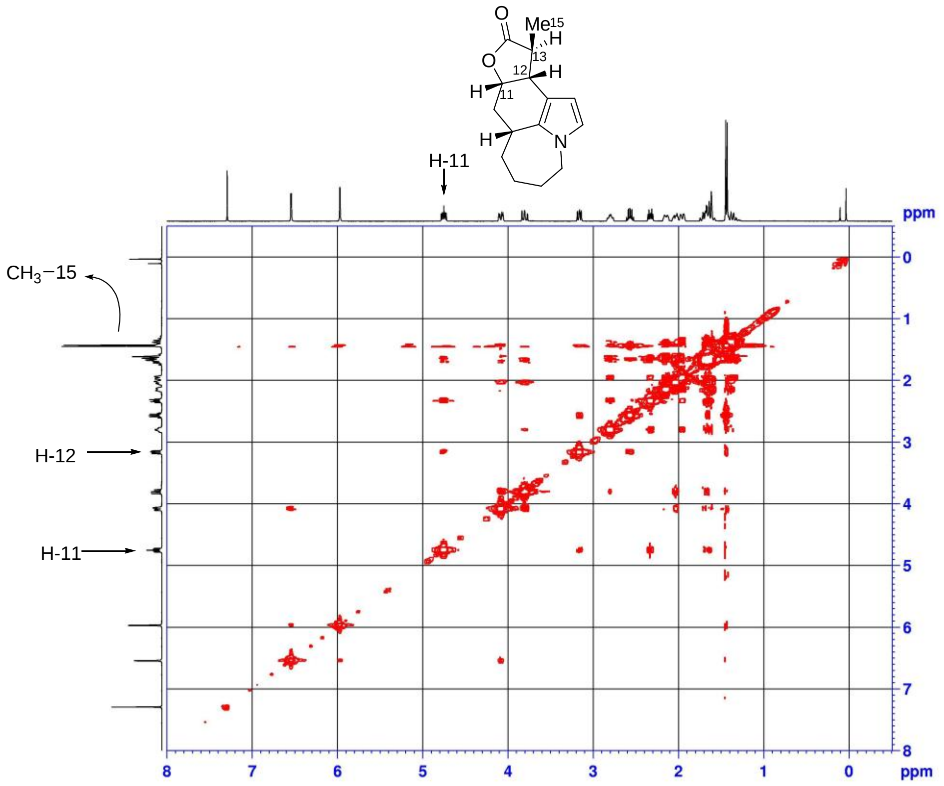




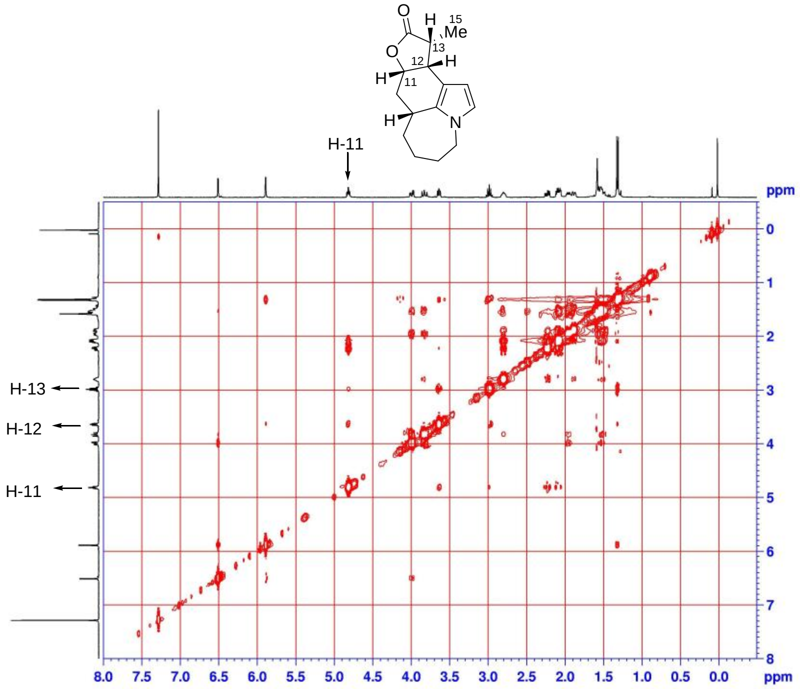
^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$, PENDANT) spectrum of tetracyclic pyrrole (**4.1**)



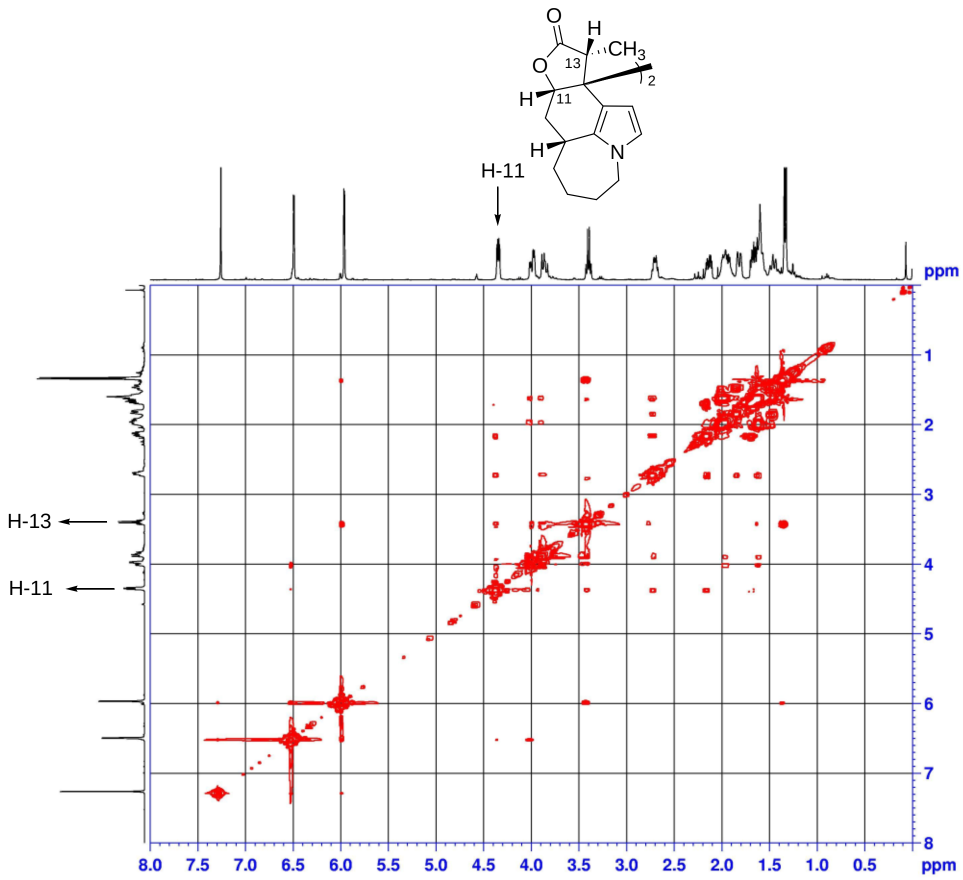
NOESY spectrum of tetracyclic pyrrole (**4.1**)



NOESY spectrum of minor isomer (**4.95**)



NOESY spectrum of dimer (**4.96**)



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