UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE AND MATHEMATICS

School of Chemistry

Stereoselective Synthesis of (–)-Galanthamine and Lupin-Type Alkaloids

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ABSTRACT

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STEREOSELECTIVE SYNTHESIS OF (–)-GALANTHAMINE AND LUPIN-TYPE ALKALOIDS

by Iain Robert Miller

A new asymmetric synthetic route to (–)-galanthamine **(1.01)**, a potent *Amaryllidaceae* alkaloid used in the symptomatic treatment of early on-set Alzheimer's Disease (AD), was successfully developed with complete stereocontrol. Key to achieving high chemo- and stereo-selectivity in this approach was the use of transition metal (TM) mediated reactions, in the form of: an enyne RCM; a Heck coupling and a titanium based asymmetric allylation.

Additionally, application of an asymmetric imino-aldol reaction resulted in the short total synthesis of two Lupin-type alkaloids, tashiromine **(3.01)** and epilupinine **(3.02)**. These syntheses were undertaken to confirm the diastereomeric outcome of our modified imino-aldol reaction. Extensive modification to literature reaction conditions in a model system **3.42** was required to successfully reinstate the same sense of diastereoselectivity after, curiously, we obtained a different diastereomeric product to the one reported. Subsequently, to expand this area of interest, we applied our findings towards the synthesis of (+)-leontine **(3.03)**, a more complex, naturally occurring, tetracyclic alkaloid. Significant progress was made up to a quinolizidinone intermediate **(–)-6.12** which incorporated the desired relative stereochemistry at C5 and C6 and most of the carbon framework for transformation to the natural product.

Contents

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Abbreviations

AIBN	2,2′-Azobis(2-methylpropionitrile)
Ac	Acetate
acac	Acetylacetonate
BBN	borabicyclo[3.3.1]nonane
Boc	*tert*-Butyl carbonate
bp	Boiling point
Bu	Butyl
Bz	Benzoate
CI	Chemical Ionisation (mass spectrometry)
Cp	Cyclopentadienyl ring
Cp*	Pentamethyl cyclopentadienyl ring
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIAD	Di*iso*propyl azodicarboxylate
DIBAL-H	Di*iso*butyl aluminium hydride
DIP	Di*iso*pinocampheylborane
DIPEA	Di*iso*propyl ethyl amine
DMAP	Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMF	Dimethyl formamide
dmgH	Dimethylglyoxime monoanion
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DPPA	Diphenyl phosphoryl azide
dppp	Diphenylphosphinopropane
dr	Diastereomeric ratio
ds	Diastereoselectivity
EDC	*N*-Ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EI	Electron Impact (mass spectroscopy)
eq.	Equivalent

er	Enantiomeric ratio
ES	Electrospray positive ion (mass spectroscopy)
Et	Ethyl
g	Grams
h	Hour
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxy-1*H*-benzotriaole
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
i	Iso
IPA	*iso*-Propyl alcohol
IR	Infrared spectroscopy
IPTT	*iso*-Propyl-1,3-thiazolidine-2-one
LDA	Lithium di*iso*propylamide
Me	Methyl
min	Minutes
mL	Millilitre
MP	Melting point
MS	Molecular sieves
Ms	Methyl sulfonyl
Mw	Molecular weight
NaHMDS	Sodium hexamethyldisilazide
NBS	*N*-Bromosuccinimide
NMO	*N*-Methyl morpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
nbd	Norbornadiene
o/n	Overnight
p	Para
Ph	Phenyl
PIFA	Phenyliodine(III)-bis(trifluoroacetate)
PMB	*para*-Methoxy benzyl
PPTS	Pyridinium *para*-toluene sulfonate
Pr	Propyl
pyr.	Pyridine

rt	Room Temperature
t	Tert
TADDOL	Tartaric Acid Derived Diol
TBS	*tert*-Butyl dimethyl silyl
TBSA	*tert*-Butanesulfinyl amine
TEMPO	2,2,6,6-Tetramethyl-piperidin-1-oxyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TIPS	Tri*iso*propylsilyl
TMEDA	Trimethylethyldiamine
TMS	Trimethylsilyl
Troc	Trichloroethoxycarbonyl chloride
Ts	*para*-Toluenesulfonyl
Tf	Trifluoromethanesulfonate

Chapter 1 (–)-Galanthamine

1.1 Background

(–)-Galanthamine **(1.01)** is a naturally occurring alkaloid and is the parent member of the *Amaryllidaceae* alkaloids (Figure 1.01). Galanthamine **(1.01)** may be isolated from the Caucasian snowdrop (*Galanthus woronowii*) and the bulbs of daffodils (*Narcissus Pseudonarcissus L.*), although procedures are relatively low yielding (0.1-2% dry weight).[1]

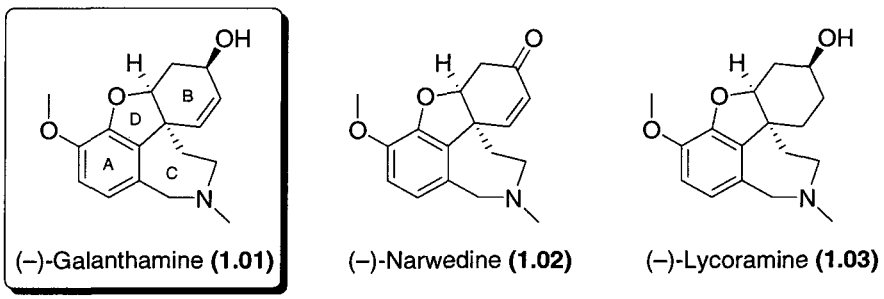


Figure 1.01. Members of the *Amaryllidaceae* family of alkaloids.

Recent biological interest in (–)-galanthamine **(1.01)** is largely due to its activity as a selective, reversible and competitive acetylcholinesterase (AChE) inhibitor in addition to being an allosteric modulator to the nicotinic receptor for acetylcholine.[2] It has been established that the acetylcholine neurotransmission pathway plays a crucial role in learning and memory in humans, and therefore has potential medicinal significance.[3]

Alzheimer's Disease (AD) is characterized by profound memory loss, emotional disturbance and personality changes and is linked to a cholinergic insufficiency in the brain.[4] Consequently, galanthamine **(1.01)** has become a focus for the treatment of mild to moderate AD as it acts to restore nominal levels of acetylcholine in the central nervous system.[3,4]

Cholinesterase inhibitors are the only class of drug approved for the treatment of mild to moderate AD and as a result (–)-galanthamine has become one of the top drugs for the symptomatic treatment of early on-set AD.[5] It is sold under the names: galanthamine hydrobromide or Razadyne®.[4,5] Alternatively there are two other AChE inhibitors on the market: Donepezil® **(1.04)** and Rivastigmine® **(1.05)** (Figure 1.02).[4]

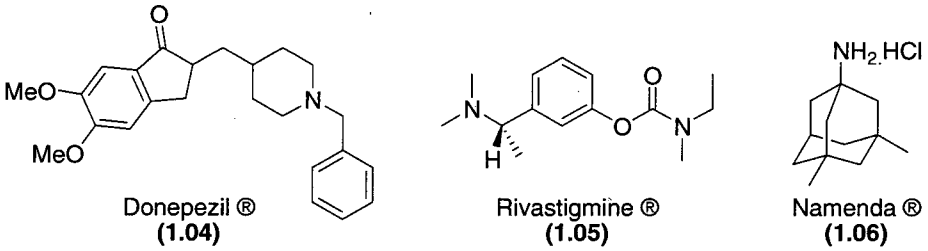


Figure 1.02. Alternative current therapeutic drugs used to treat AD.

For moderate to severe AD there is memantine hydrochloride **1.06** (Figure 1.02), a *N*-methyl-D-aspartate (NMDA) receptor antagonist in the *in vivo* glutamate neurotransmitter pathway.[6] It is sold under the trade names: Namenda®, Ebixa®, Axura® and Akatinol® in the USA and Europe.[7] (–)-Galanthamine **(1.01)** has also been tested for the treatment of human ailments varying from: facial paralysis to schizophrenia.[5,8]

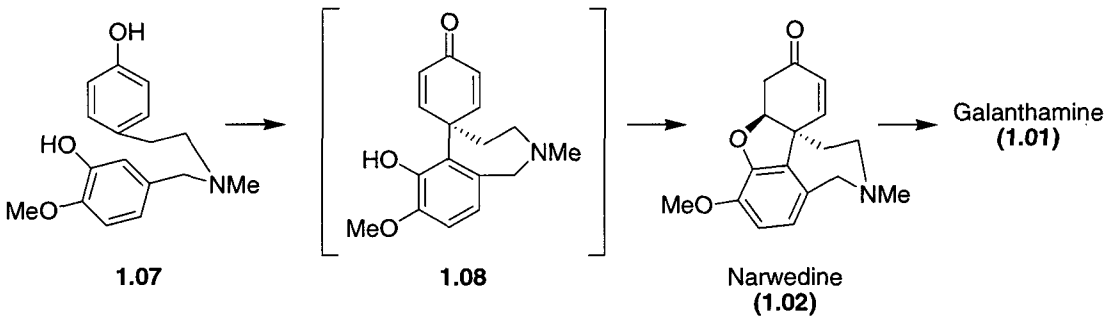
1.2 Previous syntheses

Isolation of galanthamine from natural sources for clinical use is expensive (~$50,000/kg)[9] due to the modest extraction yield. Therefore, significant research has been devoted towards the total synthesis of (–)-galanthamine **(1.01)**.[9-11] The complex nature of the molecule, containing multiple fused rings and a quaternary centre bearing stereochemical information bridging the BCD rings, provides an interesting challenge for synthetic chemists. For a comprehensive overview on the pharmacology and synthetic strategies to (–)-galanthamine **(1.01)** the readers attention is directed to the excellent recent review by Marco-Contelles *et al.* published in 2006[1] and the thesis by McLean.[12] A brief overview of some of this synthetic work will be detailed herein, focusing on key and recent achievements.

To date, there are several racemic syntheses of **1.01**[1,13-15] and the structurally related alkaloid, lycoramine **(1.03)**[16-20] but few groups have disclosed asymmetric syntheses. A robust and selective asymmetric synthesis is of academic interest and potential medicinal benefit if analogues can be accessed. Here, as in the Marco-Contelles review, strategies to yield galanthamine **(1.01)** are categorised under two general groupings: biomimetic processes and a non-biomimetic processes.

1.2.1 Biomimetic syntheses

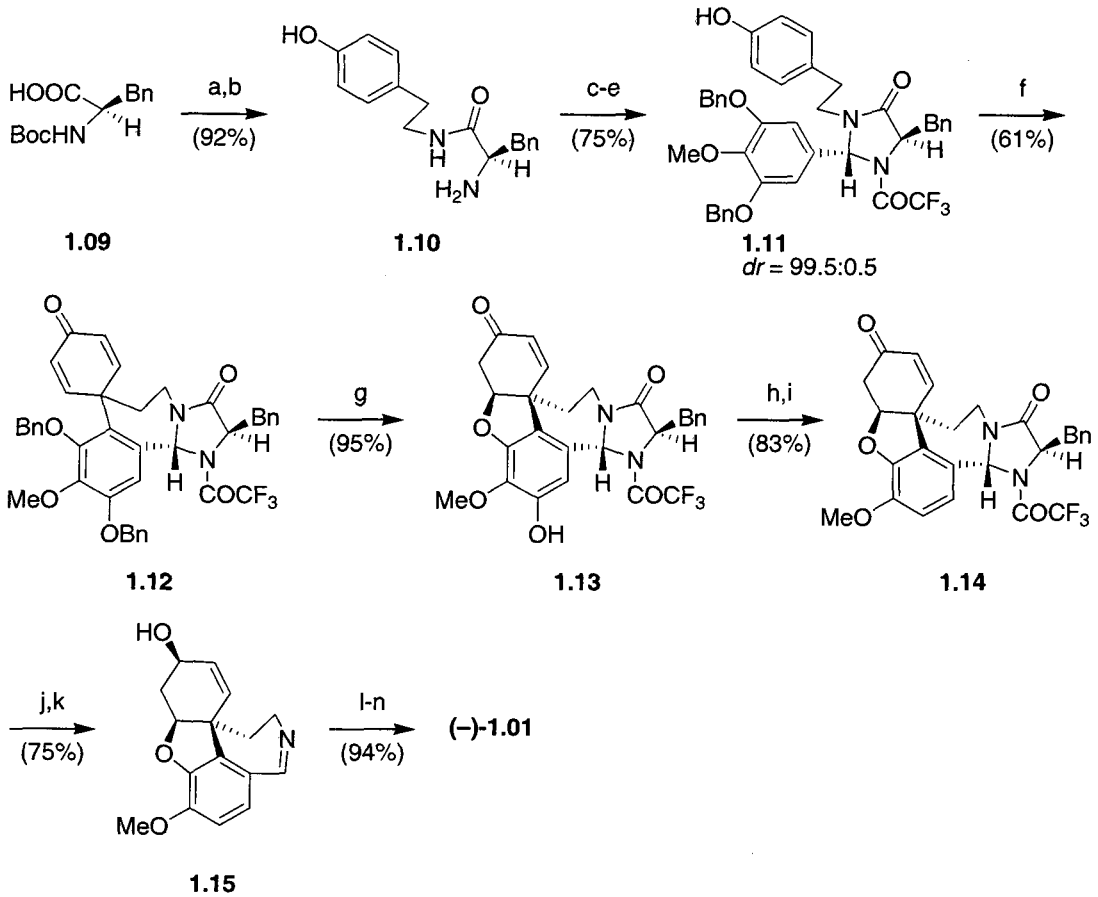
There has been substantial interest in the synthesis of galanthamine for over four decades. The first, and landmark, synthesis was Barton's biomimetic synthesis from the alkaloid *O*-methylnorbelladine **(1.07)** (Scheme 1.01).[21] In 1962, Barton and co-workers devised a phenolic oxidative coupling method to form azepine ring C, which led to the Michael addition of the phenolic oxygen to the dienone system affording narwedine **(1.02)**.



Scheme 1.01. Biomimetic synthesis of (±)-galanthamine.

The synthetic oxidative phenolic coupling employed by Barton and Kirby is facilitated by the presence of metal oxidants; such as potassium ferricyanide ($K_3Fe(CN)_6$) although initially racemic narwedine **(1.02)** was only obtained in 1.4% yield.[21] Optimisation of this approach led to considerably higher yields for the oxidative phenolic coupling (40-54%)[22] in addition, other oxidants have been utilised, for example, $Mn(acac)_3$ (49%)[23] and phenyliodine(III)-bis(trifluoroacetate) (PIFA) (61-85%).[10,24] This oxidative coupling strategy combined with a spontaneous total resolution of enantiomers of racemic narwedine **(1.02)** forms the basis of an efficient industrial process to produce (–)-galanthamine.[9,22]

In 2004, Node and co-workers published an asymmetric synthesis of (–)-galanthamine **(1.01)**, based on the biomimetic approach, in 14 steps and 23% overall yield from (*R*)-*N*-Boc-D-phenylalanine **(1.09)** (Scheme 1.02).[25] Interestingly, asymmetric induction for the oxidative phenolic coupling was controlled remotely by a chiral imidazolidinone auxiliary.



Scheme 1.02. *Reagents and conditions*: a) tyramine, EDC.HCl, HOBt, THF, rt; b) MsOH, MeOH, 40 °C; c) 3,5-dibenzyloxy-4-methoxybenzaldehyde, dioxane, rt; d) 4 M HCl/dioxane; e) $(CF_3CO)_2O$, pyr., 0 °C; f) PIFA, CF_3CH_2OH, –40 °C; g) BCl_3, CH_2Cl_2, –78 °C; h) Tf_2O, pyr., 0 °C; i) $Pd(OAc)_2$, PPh_3, NEt_3, HCOOH, DMF, 60 °C; j) L-selectride, THF, –78 °C; k) KOH, Bu_4NBr, EtOH, 80 °C; l) $NaBH_4$, MeOH; m) HCOOEt, MeOH, 60 °C; n) $LiAlH_4$, THF.

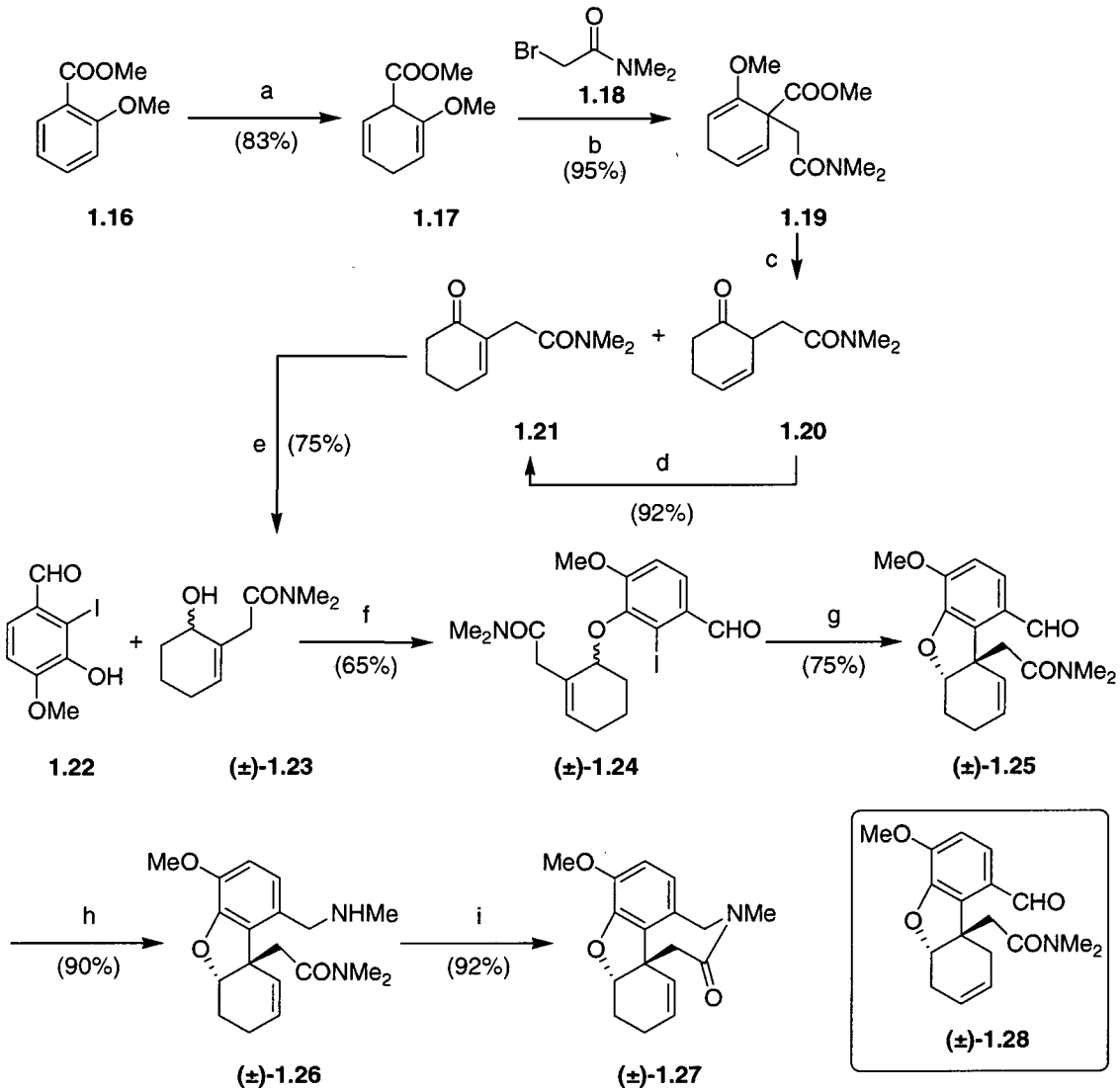
The key phenolic oxidative coupling of imidazolidinone **1.11** (single diastereomer) to yield spirodienone **1.12** was achieved in good yield (61%) using the hyper-valent iodine species, PIFA. Previous syntheses of racemic galanthamine **(1.01)** from the same group reported PIFA to be a superior coupling reagent to other metal oxidants.[10,24] An *O*-debenzylation with BCl_3 allowed the chemoselective addition of the phenol to the α,β-unsaturated ketone, furnishing pentacyclic intermediate **1.13** as a single diastereomer in excellent yield (95%). Activation of the remaining phenol functionality as the triflate followed by a palladium catalysed reduction formed intermediate **1.14**. Finally, a selective reduction of enone **1.14** to allylic alcohol **1.15**, reductive cleavage of the chiral auxiliary and *N*-methylation completed the total synthesis of (–)-galanthamine **(1.01)**.

1.2.2 Non-biomimetic syntheses

Non-biomimetic approaches do not utilise an oxidative phenolic coupling but employ alternative synthetic strategies to construct the stereogenic quaternary carbon centre. Most notable is an intramolecular Heck reaction initially disclosed in separate publications by Fels and Parsons.[26,27] This key step has been exploited by other groups, including Trost and Brown in their total syntheses of galanthamine (**1.01**).[11,28] Alternatively, more recently semipinacol[13] and Claisen rearrangements[29] were shown to be effective methods at generating the quaternary centre in galanthamine (**1.01**).

Individually, and almost simultaneously, Fels[26] and Parsons[27] reported conceptually similar approaches to the same tetracyclic intermediate **1.27** (Scheme 1.03, Parsons' synthesis). In 2000, Fels *et al.* disclosed their synthesis of **1.27** utilising a Mitsunobu coupling and an intramolecular Heck reaction. Parsons *et al.* published their route to **1.27**, also featuring a Mitsunobu coupling and intramolecular Heck reaction. Curiously, neither group disclosed final transformations of **1.27** to galanthamine. Parsons *et al.* described a problematic allylic oxidation of cyclohexene **1.27** for their omission to report a total synthesis of (±)-galanthamine (**1.01**).

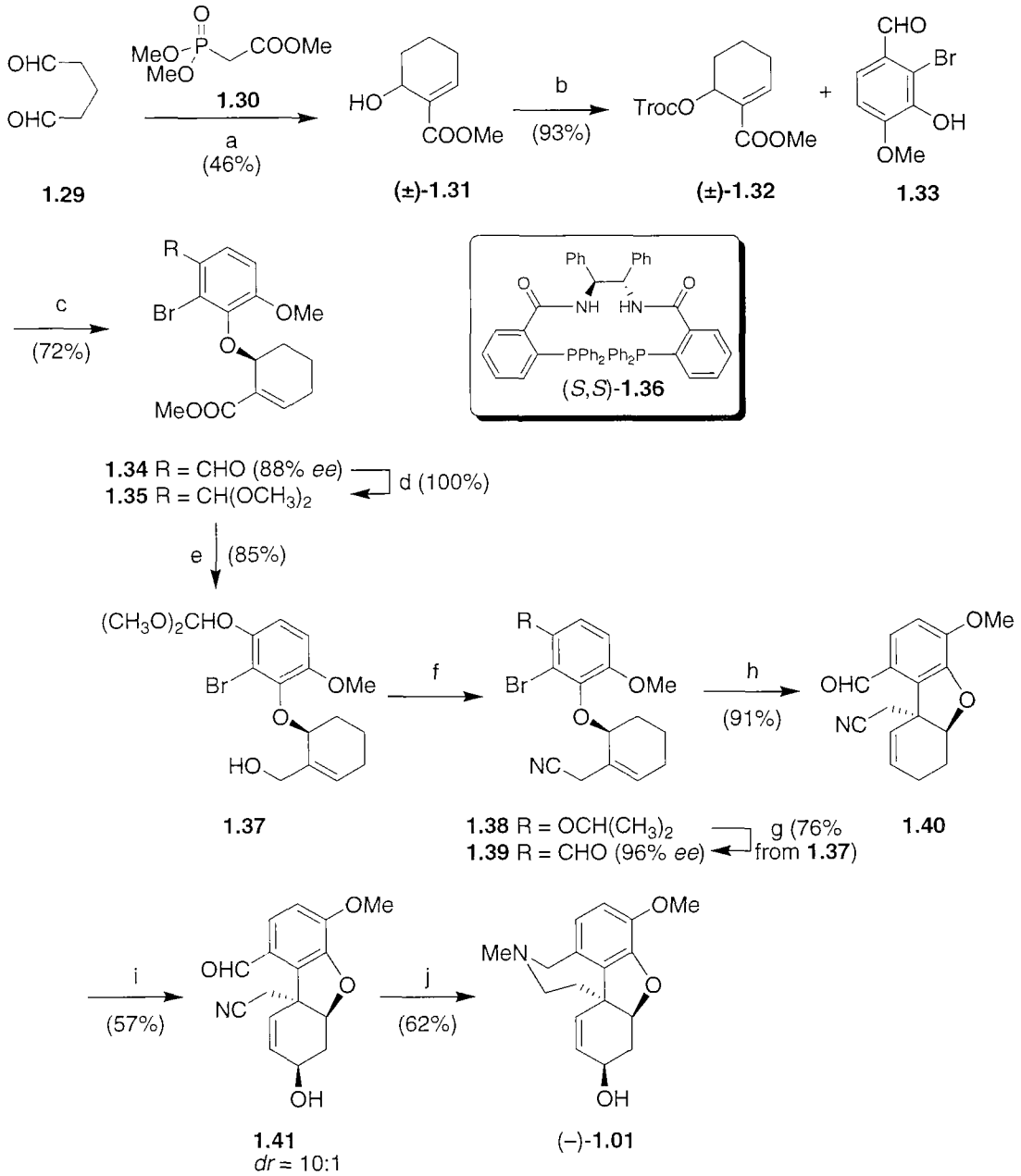
The first key step, the Mitsunobu coupling of phenol **1.22** and C2-substituted cyclohexenol **1.23**, gave the desired aryl ether **1.24** in good yield. Synthesis of cyclohexenol **1.23** was a 5 step process from methyl 2-methoxy-benzoate (**1.16**). The Birch reduction of **1.16** gave cyclohexadiene **1.17** which was subsequently alkylated with bromoacetamide (**1.18**). Saponification then hydrolysis of **1.19** gave an intermediate β-keto acid which underwent spontaneous decarboxylation to yield cyclohexene isomers **1.20** and **1.21**. Treatment of the isomeric mixture with dilute acid gave exclusively the conjugated isomer **1.21**. Reduction with $NaBH_4$ yielded cyclohexenol **1.23** with no 1,4 reduction observed. The intramolecular Heck coupling of iodoaryl ether **1.24** exclusively formed **1.25** in high yield incorporating the quaternary centre. Reaction conditions described by Overman *et al.*[30] were utilised (Ag_2CO_3 as base) to prevent the double bond isomerisation to alkene **1.28**, observed when standard conditions were used (K_2CO_3 as base). Next, condensation of aldehyde **1.25** with methylamine followed by reduction of the resulting imine gave secondary amine **1.26**. Finally, the galanthamine skeleton was completed by heating the hydrochloride salt of **1.26** under vacuum to furnish **1.27** in excellent yield (92%).



Scheme 1.03. *Reagents and conditions*: a) K, NH_3 (l), THF, *t*-BuOH, NH_4Cl; b) LDA, THF; c) NaOH, H_2O then conc. HCl; d) 1 M HCl, THF; e) $NaBH_4$, MeOH; f) azodicarboxylic dimorpholide, Bu_3P, THF; g) $Pd(OAc)_2$, Ag_2CO_3, dppe, DMF, Δ; h) $MeNH_2$, EtOH, then $NaBH_4$, MeOH; i) HCl, MeOH, vacuum, 120 °C.

Trost and co-workers in 2000,[31] with further elaborations in 2002[32] and 2005,[11] were the first group to report an asymmetric total synthesis of (–)-galanthamine **(1.01)** based on the approach described above (Scheme 1.04). A palladium catalysed asymmetric allylic alkylation (AAA) of substrates **1.32** and **1.33** was used to yield the enantiomerically enriched aryl ether **1.34**.

In 2005, an improved third generation synthesis was published. This shorter, 10 step process from commercially available glutaraldehyde **(1.29)** furnished (–)-galanthamine **(1.01)** in higher overall yield (8%) and with higher *ee* (96% *ee*) after a single recrystallisation (Scheme 1.04).[11]

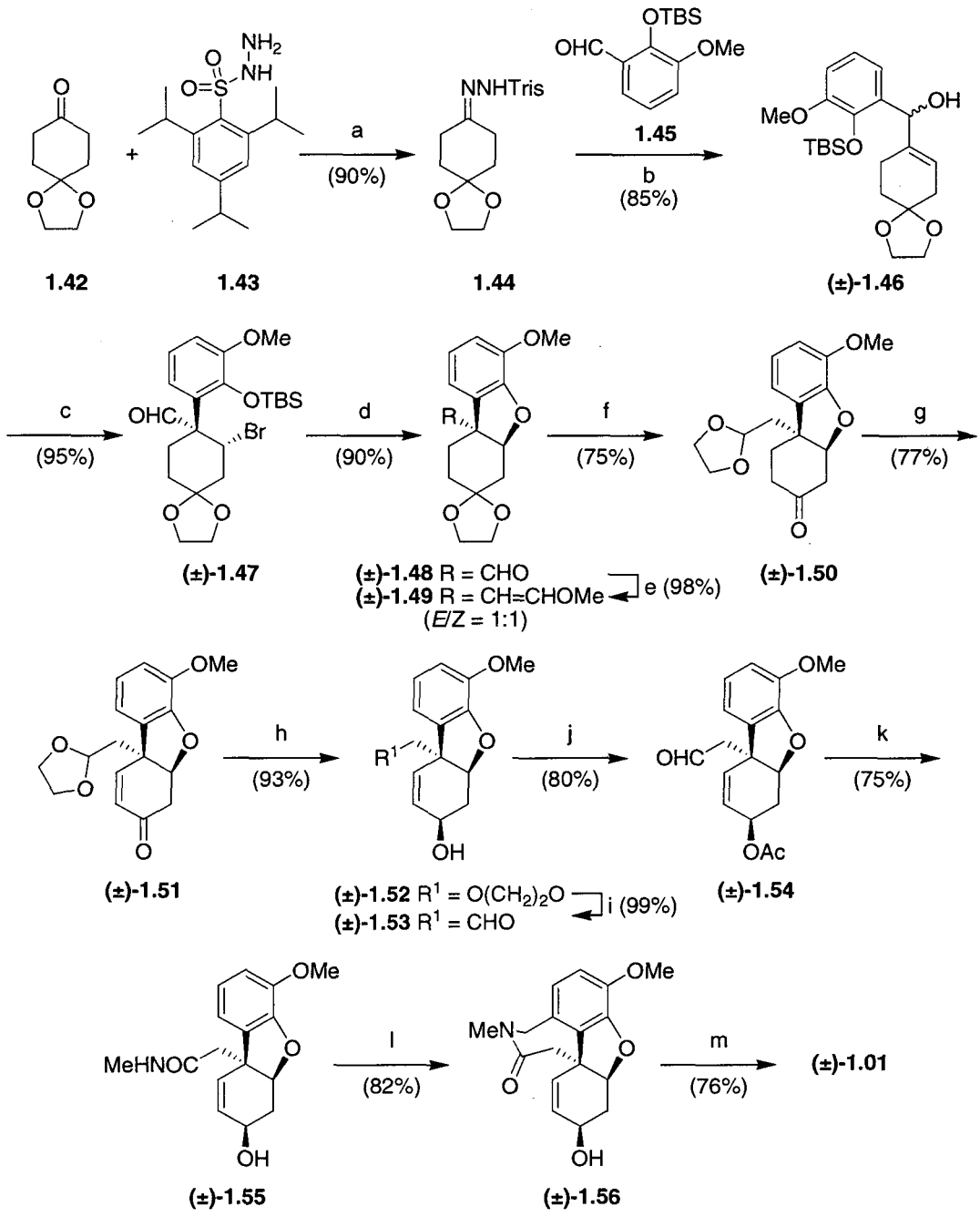


Scheme 1.04. *Reagents and conditions*: a) K_2CO_3, H_2O, 2 days; b) Troc-Cl, DMAP, pyr., CH_2Cl_2; c) $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (2.2 mol%), **1.36** (3.0 mol%), NEt_3, CH_2Cl_2; d) TsOH (1.5 mol%), $CH(OMe)_3$, MeOH; e) DIBAL-H, toluene; f) acetone cyanohydrin, PPh_3, DIAD, Et_2O; g) TsOH (2.2 mol%), THF/H_2O; h) $Pd(OAc)_2$ (15 mol%), dppp (15 mol%), Ag_2CO_3, toluene; i) SeO_2, NaH_2PO_4, dioxane, 150 °C; j) i) $MeNH_2$, MeOH, ii) DIBAL-H, iii) $NaCNBH_3$.

The Horner-Wadsworth-Emmons reaction of glutaraldehyde (**1.29**) and trimethyl phosphonoacetate (**1.30**) in aqueous K_2CO_3 yielded cyclohexenol **1.31** in modest yield. Conversion to trichloroformate **1.32** was achieved by reaction with the corresponding chloroformate (Troc-Cl). The AAA coupling of the highly sterically congested *ortho*

di-substituted phenol **1.33** and C2-substituted cyclohexene **1.32** proceeded with good enantioselectivity (88% *ee*). The deracemisation of a chiral racemic mixture of cyclohexene **1.32** was achieved by the formation of a π-allyl palladium complex with chiral ligand (*S*,*S*)-**1.36**. The result was the regio- and enantioselective alkylation of phenol **1.33** to afford aryl ether **1.34**. Previous generations of this synthesis highlighted the incompatibility of the electron withdrawing nature of the ester functionality with achieving high yields in the Heck coupling step. Therefore ester **1.34** was converted to cyanomethyl **1.38** prior to the coupling. Aromatic aldehyde **1.34** was protected as the acetal prior to converting α,β-unsaturated ester to allylic alcohol **1.37** then nitrile **1.38**, through a subsequent one carbon homologation. The intramolecular Heck coupling of nitrile **1.39** proceeded smoothly and in excellent yield (91%). The authors found that the oxidation of cyclohexene **1.40** directly to allylic alcohol **1.41** could be achieved using SeO_2.[32] The desired diastereoisomer was isolated with a ratio of 10:1 (*dr*). Interestingly, the Se electrophile reacts at the more hindered face of the double bond through an ene mechanism to give the desired diastereomer.[11] Finally, a one-pot procedure to form the azepine ring by an amine condensation, reduction and cyclisation completed the synthesis of (–)-galanthamine **(1.01)**. The late-stage incorporation of the amine allowed analogues of (–)-galanthamine **(1.01)** at this position to be synthesised.

In 2006, Tu and co-workers reported their total synthesis of racemic galanthamine.[13] The selective bromonium ion promoted semipinacol rearrangement, desilylation and cyclisation of intermediate **1.46** was originally designed by Tu *et al.* in their total synthesis of racemic lycoramine **(1.03)**.[16] With the addition of a modified Saegusa-Ito oxidation this approach has found use in the synthesis of galanthamine **(1.01)** (Scheme 1.05).



Scheme 1.05. *Reagents and conditions*: a) 1 N HCl, MeOH; b) *n*-BuLi (2.2 eq), TMEDA/hexane (1:9), –78 °C to 0 °C then **1.45**; c) NBS, CH_2Cl_2, 0 °C; d) DBU, DMSO, 95 °C; e) $MeOCH{=}PPh_3$, THF, *t*-BuOK; f) PPTS (10 mol%), glycol, acetone; g) LDA, TMSCl, –78 °C then $Pd(OAc)_2$, Na_2CO_3, MeCN; h) L-selectride, THF, –78 °C; i) 1 N HCl, THF, 40 °C; j) Ac_2O, pyr., DMAP, CH_2Cl_2; k) NBS, AIBN (cat.), CCl_4, 95 °C then $MeNH_{2(g)}$; l) $(CH_2O)_n$, TFA, 1,2-dichloroethane; m) $LiAlH_4$, DME.

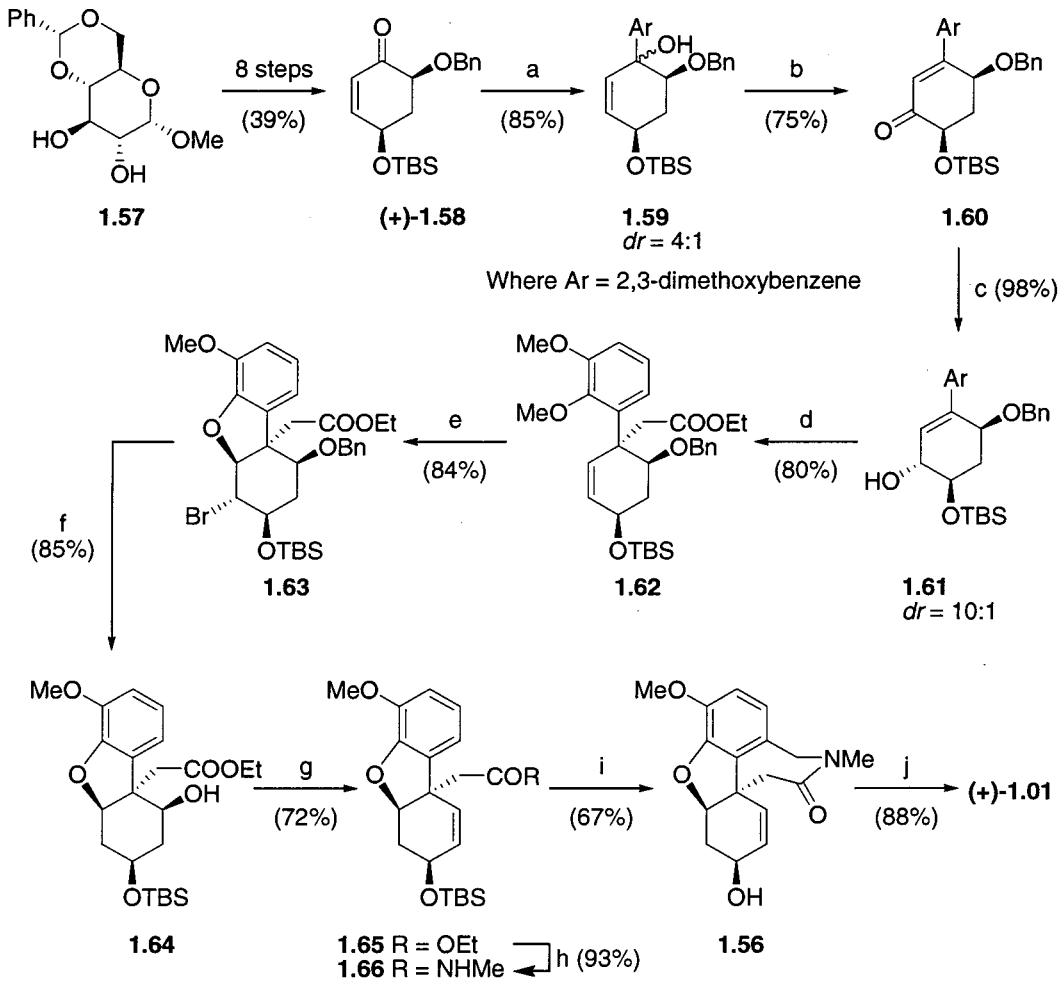
The Shapiro reaction of hydrazone **1.44** and aryl aldehyde **1.45** afforded intermediate **1.46** in 85% yield. Treatment with NBS in CH_2Cl_2 at 0 °C induced the semipinacol rearrangement to aldehyde **1.47** in excellent yield (95%) which generated the quaternary

centre. Desilylation and displacement of the bromide in a S_N2 reaction afforded benzofuran **1.48** also in excellent yield (90%). Next, the carbonyl homologation of **1.48** was readily achieved through a Wittig reaction to secure vinyl ether **1.49** (*E*/*Z* 1:1). Treatment of **1.49** with catalytic acid in the presence glycol resulted in an exchange of glycol protecting group and unmasked ketone **1.50**. Enone formation via the elegant use of a modified Saegusa-Ito oxidation installed the desired double bond efficiently (77%) and the selective reduction with L-selectride yielded allylic alcohol **1.52**. Radical formation of the corresponding acid bromide of aldehyde **1.53** followed by treatment with gaseous methylamine led to the formation of primary amide **1.55**. Prior *O*-Ac protection was required but fortunately the protecting group was labile under reaction conditions. Finally, azepine ring formation via a Pictet-Spengler reaction with *p*-formaldehyde and reduction of the resulting amide **1.56** yielded (±)-galanthamine in 13 steps (from commercially available **1.42** and **1.43**) in 12% overall yield.

In 2007 a new total synthesis of the unnatural enantiomer of galanthamine was described by Chida *et al.*[29] in 19 steps and 5% overall yield starting from commercially available protected D-glucose **(1.57)** (Scheme 1.06). This new non-biomimetic approach differs from previous asymmetric syntheses in that the crucial stereogenic quaternary carbon is installed using a Claisen rearrangement.

The total synthesis began with the 8 step conversion of protected D-glucose **(1.57)** to cyclohexenone **1.58** (B ring), a known intermediate in the total synthesis of the *Amaryllidaceae* alkaloid (+)-haemanthamine, according to the procedure described by Chida.[33] The 1,2-addition of a Grignard reagent to α,β-unsaturated ketone **1.58** introduced the aromatic portion of the molecule and subsequent oxidation then rearrangement mediated by PCC afforded substituted cyclohexenone **1.60**. A Luche reduction then afforded cyclohexenol **1.61** with good selectivity (*dr* = 10:1). The key quaternary carbon centre was constructed in a stereospecific manner through the chirality transfer from cyclohexenol **1.61** in a Claisen rearrangement. Next, formation of benzofuran **1.63**, via the one-pot sequential chemoselective dealkylation and etherification was facilitated through the bromonium ion and proceeded in good yield (84%). The superfluous alcohol functionality was removed by dehydration using (thiocarbonyl)diimidazole to afford ester **1.65**. Subsequent saponification and conversion under conditions described by Shioiri and co-workers[34] gave primary amide **1.66**. With the same approach as Hu *et al.*, the azepine ring was constructed via a Pictet-Spengler reaction with *p*-formaldehyde in the presence of TFA to form the bridge

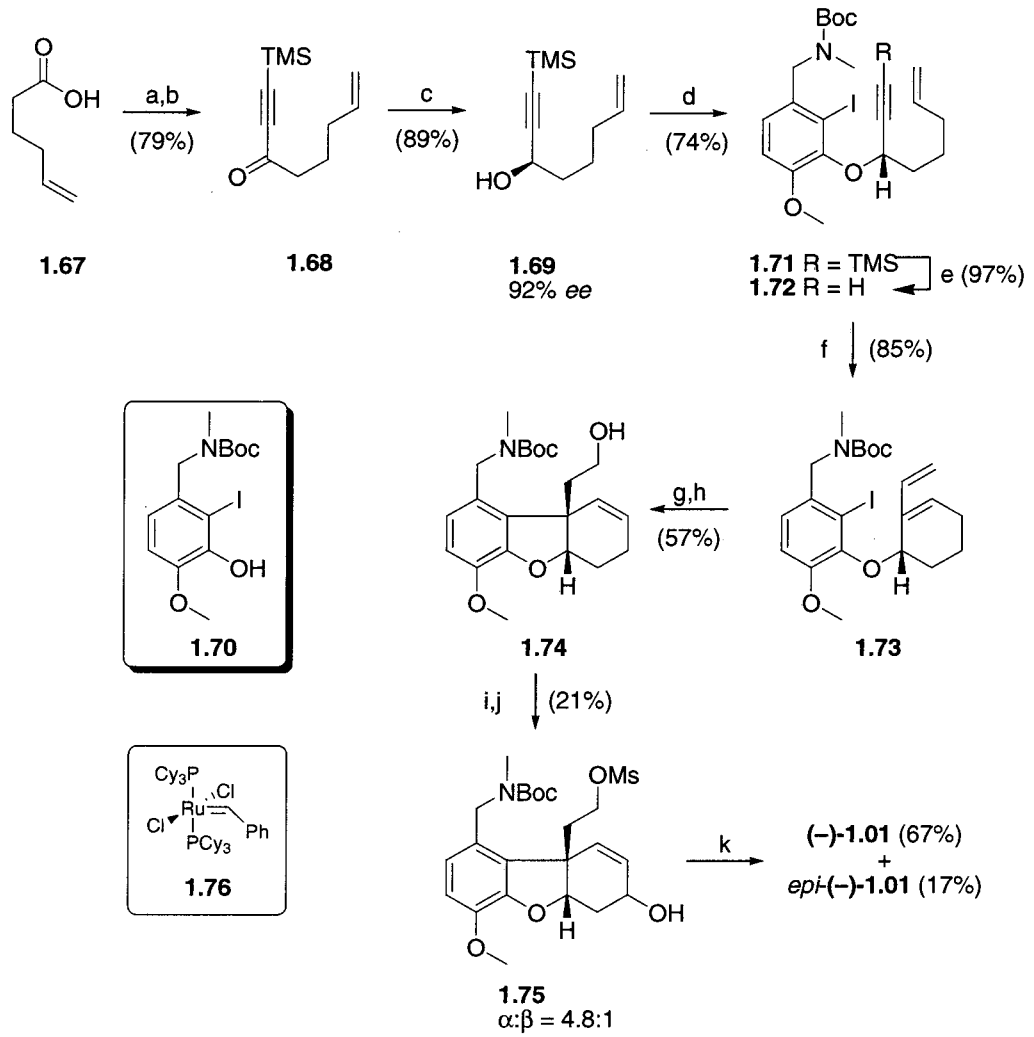
between the C1 carbon and the amide nitrogen. In addition, reaction conditions facilitated *O*-TBS deprotection to give the known tetracyclic intermediate **1.56**. Finally, the documented reduction of the resulting amide with $LiAlH_4$ gave enantiomerically pure (+)-galanthamine (**1.01**).



Scheme 1.06. *Reagents and conditions*: a) 2,3-dimethoxyphenylmagnesium bromide, THF; b) PCC, NaOAc, CH_2Cl_2; c) $NaBH_4/CeCl_3$, –78 °C, MeOH/ CH_2Cl_2; d) 2-nitrophenol, $CH_3C(OEt)_3$; e) NBS, DMF, 0 °C; f) H_2, 10% Pd/C then K_2CO_3, EtOH; g) (thiocarbonyl)diimidazole, DMAP, 1,2-dichlorobenzene, Δ; h) i) LiOH, $MeOH/H_2O$ ii) $MeNH_2.HCl$, NEt_3, $(EtO)_2P(O)CN$, THF; i) $(CH_2O)_n$, TFA, CH_2Cl_2; j) $LiAlH_4$, THF.

The Brown group[28] approached the construction of the fused ring system of galanthamine through the use of enyne ring-closing metathesis (RCM), to yield ring B, and application of the intramolecular Heck reaction developed by Parsons and Fels. Work commenced with Kemp[35] and Satcharoen[36] on the synthesis of (±)-deoxygalanthamine and more recently McLean completed an asymmetric synthesis of (–)-galanthamine (**1.01**) building upon the same synthetic strategy.[12] The 11 step

synthesis by McLean constitutes the first generation asymmetric synthesis within our group (Scheme 1.07).[12]



Scheme 1.07. *Reagents and conditions*: a) NHMeOMe.HCl, EDCI; b) *n*-BuLi, TMS acetylene, THF, –40 °C; c) *R*-Alpineborane, 0 °C, THF; d) DIAD, PPh_3, **1.70**, THF; e) K_2CO_3, MeOH; f) **1.76** (3 mol%), CH_2Cl_2, rt; g) 9-BBN, THF; h) $Pd(OAc)_2$ (15 mol%), dppp (15 mol%), Ag_2CO_3 (3.0 eq.), toluene; i) NaH_2PO_4, quartz sand, SeO_2, dioxane; j) MsCl, NEt_3, CH_2Cl_2; k) TFA, CH_2Cl_2 then $NaHCO_3$ (aq.).

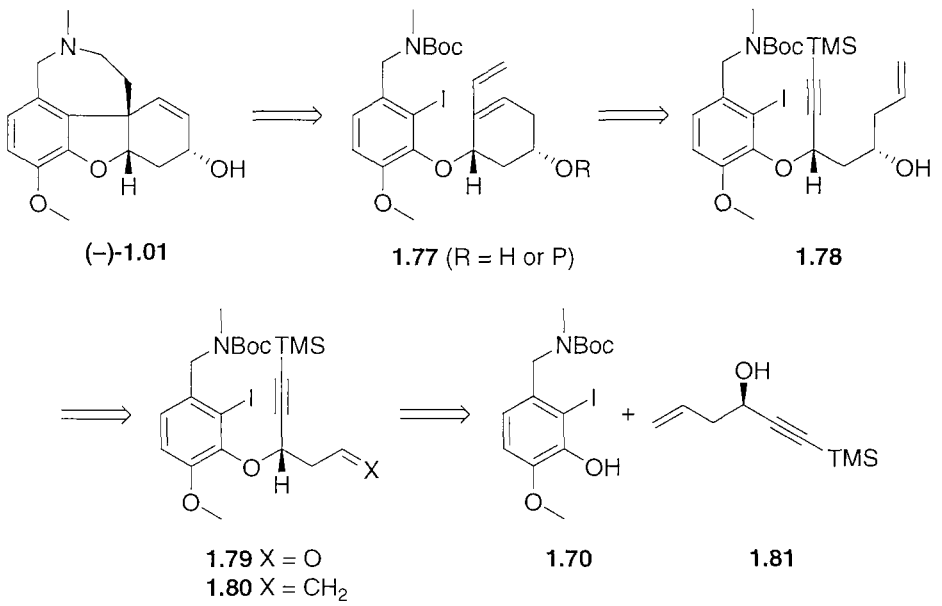
The stereocontrolled reduction of ketone **1.68** afforded enantiomerically enriched propargylic alcohol **1.69** in excellent yield and high *ee* (92% *ee*). Subsequent Mitsunobu coupling with aromatic fragment **1.70** gave aryl ether **1.71** in good yield (74%). The straight-forward deprotection of alkyne **1.71** proceeded smoothly and gave the desired enyne **1.72** with high *ee* (92% by HPLC analysis). Next, the key intramolecular RCM step to yield diene **1.73** proceeded in excellent yield using Grubbs' I catalyst (**1.76**) producing the requisite functionality for the formation of the remaining

C and D rings. The decrease of metathesis catalyst loading from 10 mol% in refluxing CH_2Cl_2, in the synthesis described by Satcharoen, to 3 mol% at rt brought about a much more efficient transformation to **1.73**. As observed by Satcharoen in the synthesis of (±)-deoxygalanthamine,[36] it was necessary to remove the terminal double bond prior to performing the Heck coupling on intermediate **1.73**. This strategy avoids formation of the unwanted Heck coupling product whereby the aromatic palladium species adds to the less hindered end of the diene system. Regiocontrol in the Heck reaction was ultimately controlled by first hydroborating the mono substituted alkene in diene **1.73**. With the ABD ring system in place, application of Trost's conditions for the allylic oxidation[32] of cyclohexene **1.74** afforded the desired alcohol **1.75** in a disappointing diastereomeric excess (4.8:1 *cf* 10:1) yet comparable yield reported by Trost. In addition, mesylation of the 1° alcohol in the inseparable mixture of diastereomers **1.75** proved to be a much lower yielding process than expected, with bis-mesylation being the major by-product. Finally, sequential treatment of mesylate **1.76** with TFA and aqueous $NaHCO_3$ gave (–)-galanthamine **(1.01)** and *epi*-galanthamine **(1.01)** (67% and 17% respectively) after column chromatography.

In summary, a new 11 linear step, asymmetric synthesis of (–)-galanthamine **(1.01)** was developed (overall yield 4%), which relied on an asymmetric ketone reduction and enyne RCM as key steps. The low overall yield can be accounted for by an inefficient mono-mesylation step. It should be noted that no attempt was made to optimise this step.

1.3 Proposed second generation asymmetric synthesis

Modification to our current retrosynthetic analysis to circumvent the notoriously problematic allylic oxidation step was expected to provide access to (–)-galanthamine with a greater degree of stereocontrol while still incorporating the use of enyne RCM. The major amendment is the proposed installation of the allylic stereocentre at an earlier stage in the synthesis (Scheme 1.08).



Scheme 1.08. New retrosynthetic analysis of (–)-galanthamine.

Our main objective was to overcome the moderate diastereoselectivity issues associated with McLean's synthesis resulting from the application of Trost's SeO_2 oxidation protocol (*vide supra*). Replacement of this protocol with an asymmetric allylation of aldehyde **1.79** by various reagents is to be explored.

Enantiomerically enriched propargylic alcohol **1.81** will be coupled to the same aromatic fragment **1.70** as previously described. Oxidative cleavage of terminal olefin **1.80** will secure aldehyde **1.79**, which may serve as a substrate for a diastereoselective allylation to install the desired allylic alcohol stereocentre present in (–)-galanthamine (**1.01**). Our synthesis of diol **1.81** would rely on recent developments in the construction of 1,3-*syn* diols with minimal protecting group manipulations.[37-40]

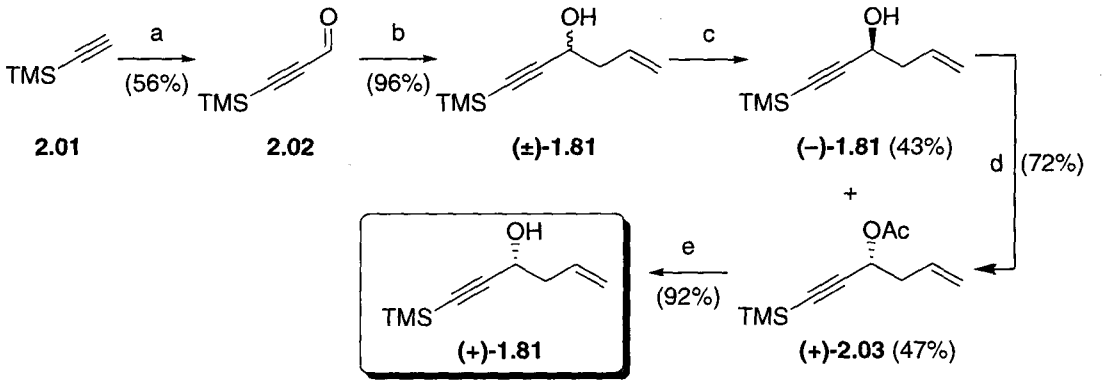
Following on a similar path to Satcharoen and McLean, the successive enyne RCM, regioselective hydroboration, Heck coupling then azepine ring formation of intermediate **1.78** would close the BCD rings and complete an improved synthesis of (–)-galanthamine (**1.01**).

Chapter 2 Total synthesis of (–)-galanthamine

Execution of our proposed synthetic strategy successfully produced (–)-galanthamine (**1.01**). Key modifications for our second generation synthesis are: the synthesis of an acyclic precursor containing the 1,3-diol motif and conversion of this intermediate to the natural product.

2.1 Synthesis of enantiomerically enriched propargylic alcohol (+)-1.81

The first important objective was to produce enantiomerically enriched alcohol (+)-**1.81**. A number of routes were examined. The most efficient route proved to be the enzymatic resolution of racemic alcohol (±)-**1.81** (Scheme 2.01). The enzymatic resolution of alcohol (±)-**1.81** described by Burova *et al.*,[41] was employed with the inclusion of the Mitsunobu step to recycle the undesired enantiomer (–)-**1.81** to (+)-**2.03**.



Scheme 2.01. *Reagents and conditions*: a) i) *n*-BuLi, Et_2O, ii) DMF; b) AllylMgBr, THF; c) Amano® AK20 lipase, vinyl acetate, hexane; d) DEAD, PPh_3, AcOH, pyr., THF; e) DIBAL-H, CH_2Cl_2, –78 °C.

Commercially available TMS acetylene (**2.01**) was formylated using conditions described by Journet *et al.* to give propargylic aldehyde **2.02** in moderate yield (56%).[42] The low b.p. of the compound accounted for the reduced yield. Removal of the reaction solvent (Et_2O) was achieved by careful distillation at atmospheric pressure and purification by Kugelrohr distillation afforded the desired aldehyde **2.02**. Next, treatment with freshly prepared allylmagnesium bromide (allylMgBr) gave racemic propargylic alcohol **1.81** in quantitative yield (96%). The enzymatic resolution with

lipase Amano® AK20 acylated the desired enantiomer **(+)-2.03** in excellent yield (47%, 94% theoretical maximum yield). The undesired enantiomer **(–)-1.81** was inverted to acetate **(+)-2.03** through a Mitsunobu reaction with acetic acid and DEAD as the azodicarboxylic coupling agent in good yield (72%), as described by Weinreb *et al.* Deprotection with DIBAL-H selectively cleaved the *O*-Ac protecting group, in favour of the *C*-TMS protection, to afford alcohol **(+)-1.81** in excellent yield (92%).

Through this modified route enantiopure propargylic alcohol **(+)-1.81** (Experimental: +41.0 (*c* 0.60, $CHCl_3$), lit: +34.0 (*c* 0.94, rt, $CHCl_3$)[41] was synthesised easily and in good yield (72%) from the racemate, although the enantiomeric excess could not be determined at this point.

Initially, two different routes were studied to install the stereocentre in alcohol **1.81** (Figure 2.01). An asymmetric hydrogen transfer route would utilise a stereoselective hydrogenation of propargylic ketone **2.04**, and an asymmetric allylation route would involve the allylation of propargylic aldehyde **2.02**.

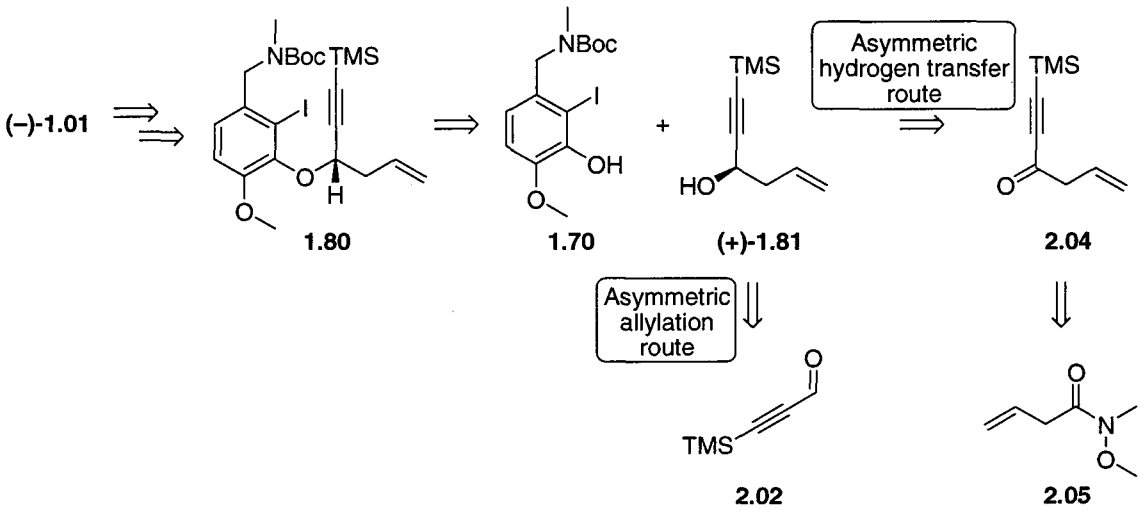
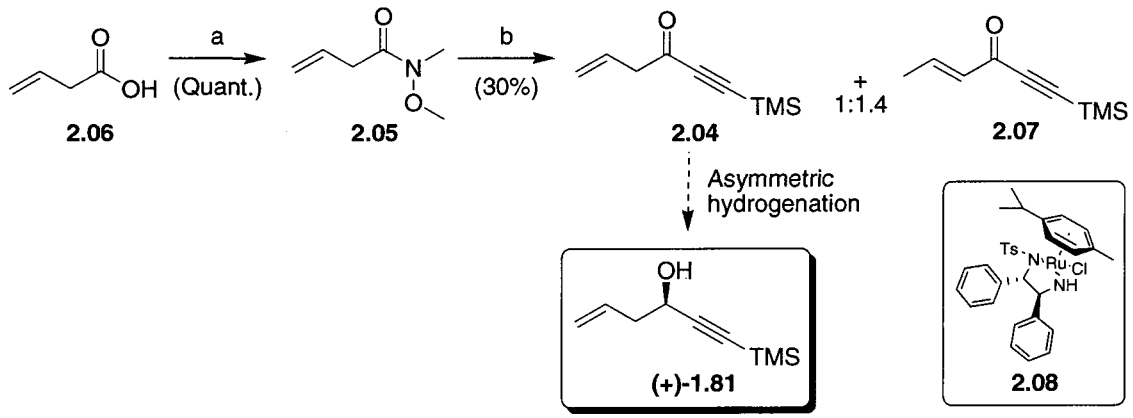


Figure 2.01. Allylic disconnection of alcohol **1.81**.

To begin with, the asymmetric hydrogen transfer route was investigated. This route draws parallels to the first generation asymmetric synthesis of galanthamine completed within our laboratory by McLean.[28]

2.1.1 Route 1: Asymmetric hydrogen transfer approach

It was envisaged that an enantioselective hydrogenation of propargylic ketone **2.04** would yield alcohol **(+)-1.81** (Scheme 2.02) using the well documented Noyori hydrogen transfer catalyst **2.08**,[43] known to give excellent *ee* (94 to >99% *ee*) for propargylic systems.[44] However, the synthesis of the pivotal ketone proved problematic. Ketone **2.04** and precursor **2.05** were susceptible to isomerisation to the undesired fully conjugated isomer **2.07**, both under the reaction conditions and on purification (silica gel).



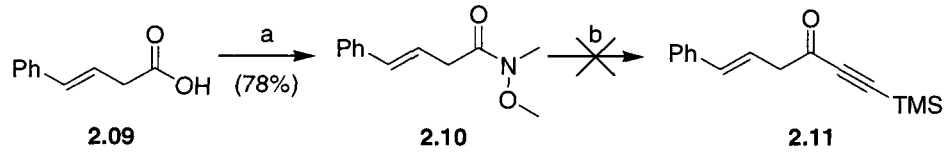
Scheme 2.02. *Reagents and conditions*: a) NHMeOMe, PPh_3, CBr_4, CH_2Cl_2; b) *n*-BuLi, TMS acetylene, THF, –78 °C.

To begin with, the formation of Weinreb amide **2.05** from the corresponding acid chloride was investigated but failed to yield the desired product in a higher yield than 15%. Eventually, milder conditions described by Einhorn *et al.*[45] gave the desired Weinreb amide **2.05** from the coupling of butenoic acid **(2.06)** and Weinreb amine (NHMe(OMe)) mediated by CBr_4/PPh_3. Volatility issues hampered complete separation of amide **2.05** from the by-product ($CHBr_3$).

The conditions of the lithium TMS acetylide anion addition to **2.05** led to a mixture of isomers **2.04** and **2.07** that proceeded to isomerise further upon purification (observed by TLC analysis). Ketone **2.04** was synthesised from Weinreb amide **2.05** as a mixture of regioisomers (1:1.4, determined by ^1H NMR analysis) favouring the unwanted, fully conjugated system **2.07** in poor overall yield.

Unfortunately, preliminary reduction studies using the *in situ* generated Noyori catalyst **2.08** to this inseparable mixture of regioisomers of ketone **2.04** failed to yield any desired product, **(+)-1.81**.

A modification to this route was investigated; *trans*-styrylacetic acid **(2.09)** was used in place of vinyl acetic acid **(2.06)** to avoid the issue of volatility and inhibit the propensity of the substrate to isomerise to the α,β-unsaturated carbonyl (Scheme 2.03). Removal of the superfluous phenyl group would be trivial as this double bond will be cleaved at a later stage in our total synthesis of (–)-galanthamine.



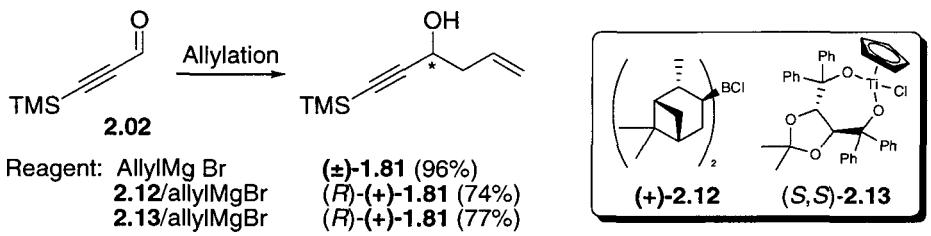
2.09 **2.10** **2.11**

Scheme 2.03. *Reagents and conditions*: a) NHMeOMe, PPh_3, CBr_4, CH_2Cl_2; b) *n*-BuLi, TMS acetylene, THF, –78 °C.

It was believed that Weinreb amide **2.10** would be less susceptible to isomerisation in comparison to the terminal double bond analogue **2.05**. However, ketone **2.11** isomerised to the fully conjugated system upon addition of the lithium TMS acetylide anion under the reaction conditions, probably due to the greater acidity of **2.10**. Due to the facile isomerisation of the alkene in both substrates, these routes were not investigated further.

2.1.2 Route 2: Asymmetric allylation approach

The asymmetric allylation of aldehyde **2.02** to alcohol **(+)-1.81** was accomplished in good yield (74-77%) with varying enantioselectivity (~75% *ee* to >99% *ee*) using two different chiral allylating reagents, **(+)-2.12** and (*S*,*S*)-**2.13** (Scheme 2.04).

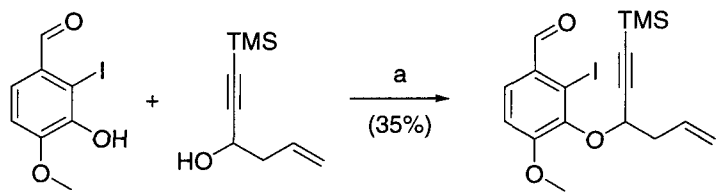


Scheme 2.04. Investigations into the asymmetric allylation of aldehyde **2.02**.

The asymmetric allylation of aldehydes has received much attention, notably from work performed by H. C. Brown and co-workers through use of boron based reagents.[46-48] Following much precedent in the literature, the α-pinene derived boron reagent, (+)-DIP-chloride **(2.12)** was chosen to induce enantioselectivie allylation. The only

reported asymmetric allylation of propargylic aldehyde **2.02** was achieved with the corresponding reagent, (+)-DIP-OMe/allylMgBr, in modest *ee* (72% *ee*).[49] Additionally, Smith *et al.* reported the related asymmetric allylation of propyne with (–)-DIP-OMe/allylMgBr in moderate yield (57%) but good selectivity (90% *ee*).[50]

Treatment of commercially available (+)-DIP-chloride **(2.12)** with freshly prepared allylMgBr afforded the active allyl transfer reagent which, when reacted with aldehyde **2.02**, yielded the desired alcohol **1.81** in good yield (74%) but in a disappointingly low selectivity (~3:1). Enantiomeric ratio (*er*) was determined by chiral HPLC following derivatisation of alcohol **1.81** as phenolic ether **1.22** in an unoptimised yield (35%) (Scheme 2.05). As noted by McLean, more efficient separation of enantiomers of aldehyde **2.14**, by chiral HPLC, was observed in comparison to the *N*-Boc protected amine analogue **1.80**.



1.22 **1.81** **2.14**

Scheme 2.05. *Reagents and conditions*: a) DIAD, PPh_3, THF, Δ.

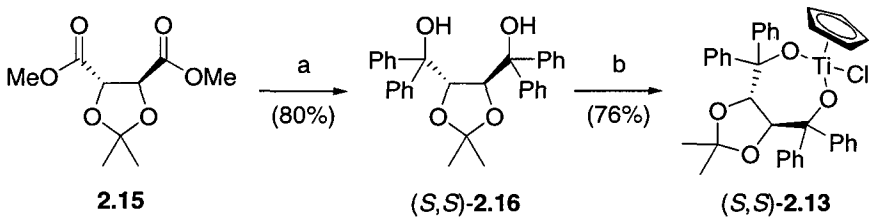
Chiral HPLC analysis (OD-H column) of phenolic ether **2.14** revealed a mixture of two enantiomers in a ratio of ~3:1. Baseline separation of enantiomers was not achieved therefore an approximate ratio is quoted.

Despite extensive investigations, the enantioselectivity of this allylation reaction was not improved upon. It is unclear whether this is due to the low steric bulk of aldehyde **2.02** or, more likely, the quality of the reagent. Other groups have also reported the capricious nature of (+)-DIP-chloride reagent.[51]

Contemporaneously, the cyclopentadienyldialkoxychlorotitanium complex **2.13**, derived from the TADDOL diol **2.16**, was examined as an asymmetric allyl transfer reagent. Titanium complex **2.13** treated with allylMgBr is a highly selective allylating agent developed in 1992 by Hafner and co-workers,[52] known to give high yields and very high enantiomeric excess (>98% *ee*) when used with propargylic aldehyde systems.[53] The reagent has been used to great effect in the synthesis of a variety of natural products, most notably by Cossy and co-workers. The allyltitanation of an intermediate in the

synthesis of marinomycin A proceeded with good selectivity (*dr* 95:5)[54] and in the synthesis of the C1-C14 polyol fragment of amphotericin B (70%, *dr* 97:3).[55]

Synthesis of reagent (*S*,*S*)-**2.13** was straight-forward and high yielding (Scheme 2.06). The Grignard addition of four phenyl groups to diester **2.15** afforded TADDOL (*S*,*S*)-**2.16** in high yield (80%). Complexation with $TiCpCl_3$ under anhydrous, basic conditions described by Hafner and co-workers[52] gave the desired titanium TADDOLate **2.13** in good yield (76%).



2.15 (*S*,*S*)-**2.16** (*S*,*S*)-**2.13**

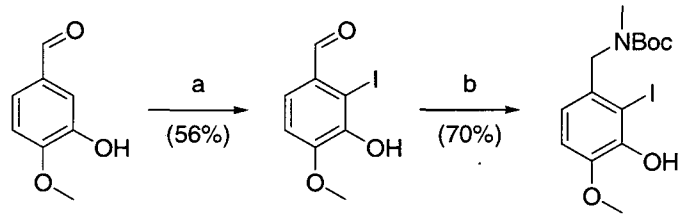
Scheme 2.06. *Reagents and conditions*: a) PhMgBr, Et_2O; b)$TiCpCl_3$, NEt_3, Et_2O.

Pleasingly, allylation of aldehyde **2.02** with reagent (*S*,*S*)-**2.13** (pre-treated with allylMgBr) proceeded in good yield (77%) and, far more gratifyingly, a single enantiomer of **(+)-1.81** was obtained in high optical purity ($[\alpha]_D^{27}$ = +36.6 *cf* lit. $[\alpha]_D^{25}$= +34.0)[41] (Scheme 2.04, *vide supra*). Enantiopurity was determined by HPLC analysis (OD-H column) following derivatisation as described above. Unfortunately, even though reagent **2.13**/allylMgBr gave excellent results the limited quantity to hand and high Mw of **2.13** (628 $gmol^{-1}$) compared to aldehyde **2.02** (126 $gmol^{-1}$) deemed this approach inefficient for larger scale work. Thus, the equally highly selective enzymatic resolution process was incorporated into our total synthesis in place of this allyl titanation in order to produce the requisite quantities of enantiomerically pure alcohol **1.81**.

2.2. Synthesis of aromatic fragment 1.70

The aromatic fragment **1.70** was synthesised according to the route developed previously within our laboratory (Scheme 2.07).[12] Thus, commercially available *iso*-vanillin (**2.17**) was treated with ICl to effect regioselective iodination of the aromatic ring according to the procedure described by Markovich *et al.*[56] The reaction is extremely slow, requiring 5 days at rt and moderately yielding. Isolation after a single recystallisation afforded iodide **1.22** in 56% yield. Next, the aldehyde was converted to

N-Boc protected amine **1.70** via a 3 step condensation, reduction and *N*-Boc protection process used by McLean.[12] No isolation of intermediate compounds was attempted and the crude mixtures were carried forward to afford **1.70** in a respectable yield of 70% over 3 steps.



2.17 **1.22** **1.70**

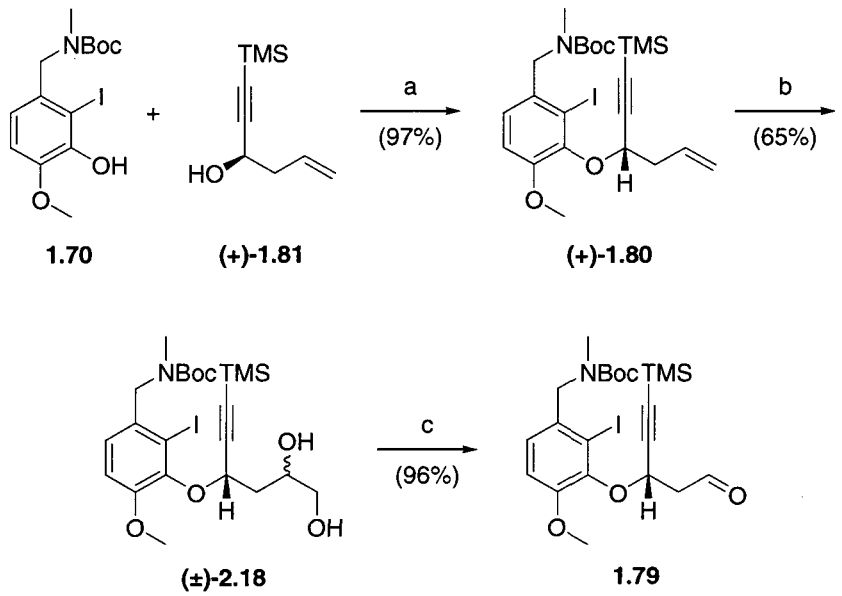
Scheme 2.07. *Reagents and conditions*: a) ICl, pyr., dioxane, 5 days; b) i) $MeNH_2$, MeOH, ii) $NaBH_4$, MeOH, iii) Boc_2O, dioxane/NaOH.

2.3 Synthesis of aldehyde 1.79

With the key alcohol **(+)-1.81** in hand the remaining elements of the total synthesis could be explored (Scheme 2.08). The Mitsunobu coupling of phenol **1.70** and alcohol **(+)-1.81** using the coupling reagent DIAD afforded olefin **(+)-1.80** as a single enantiomer, determined by chiral HPLC analysis (OD-H). Satcharoen[36] detailed the more effective use of DBAD for a similar coupling (56% yield) in the synthesis of deoxygalanthamine but, McLean[12] described the more successful use of DIAD (74%). Using modified conditions, the yield of this DIAD mediated coupling vastly increased to 97%. Initially envisaged as a one-step process, the direct conversion of the terminal alkene **1.80** to the corresponding aldehyde **1.79** proved unfruitful. Both, ozonolysis and the Lemieux oxidative cleavage process (cat. $OsO_4/NaIO_4$, NMO)[57] failed to yield any product. In both cases the major by-product recovered was aromatic fragment **1.70**, suggesting the propargylic aromatic ether bond is quite labile under a variety of reaction conditions.

A separate, two-step dihydroxylation/oxidative cleavage was employed. Successful dihydroxylation conditions reported by Dupau *et al.* (OsO_4/NMO, citric acid)[58] gave diol **(±)-2.18**. Recent research has shown that the dihydroxylation process is more efficient when the pH of the reaction is slightly acidic. Under these modified conditions the competitive phenolic cleavage reaction pathway occurred to a lesser extent. This usually very high yielding transformation eventually afforded diol **(±)-2.18** in an acceptable yield (65%) after considerable investment of time into the optimisation of

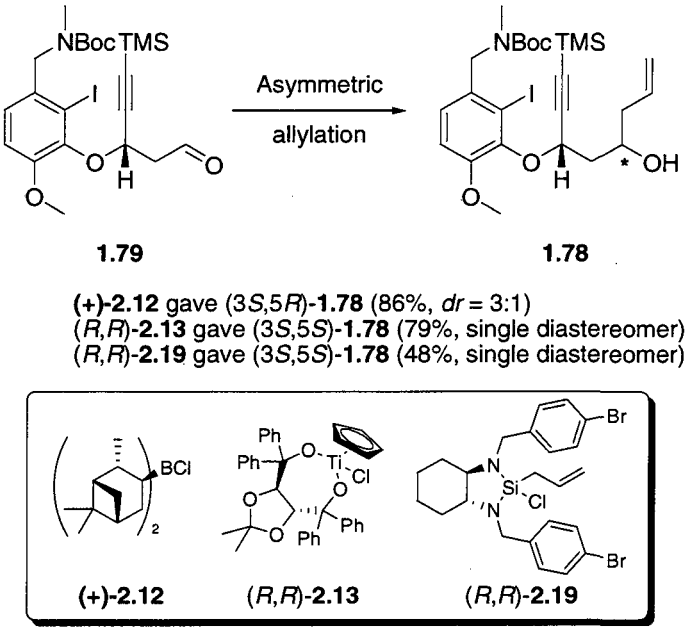
reaction conditions. Various other dihydroxylation methods were also explored: a flash dihydroxylation method with $RuCl_3$ and $NaIO_4$ reported by Shing *et al.*[59] and a $KMnO_4$ dihydroxylation reported by Alphonse *et al.*[60] Both yielded diol **(±)-2.18** in considerably lower yield. Gratifyingly, $NaIO_4$ mediated oxidative cleavage of diol **(±)-2.18** gave the desired aldehyde **1.79** in quantitative yield (96%).



Scheme 2.08. *Reagents and conditions*: a) DIAD, PPh_3, THF; b) cat. OsO_4, NMO, citric acid, *t*-BuOH/H_2O; c) $NaIO_4$, acetone/H_2O.

2.4 Investigations into the asymmetric allylation of aldehyde 1.79

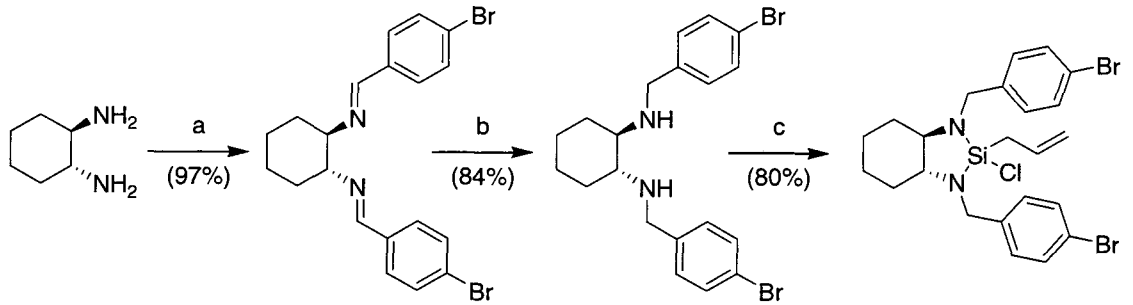
With aldehyde **1.79** successfully in hand, the important second asymmetric allylation of **1.79** to **1.78** could be explored using three different enantioselective allylating agents (Scheme 2.09). To begin with (+)-DIP-chloride **(2.12)** was used to test the efficacy of this type of reagent in this transformation (as it was known to give the undesired diastereomer of **1.78**).



Scheme 2.09. Asymmetric allylation of aldehyde **1.79**.

The active allylating reagent ((+)-DIP-allyl) afforded alcohol (3*S*,5*R*)-(–)-**1.78** in excellent yield (86%) for this class of reaction but as a mixture of diastereomers (*dr* 3:1) (determined by ^{13}C NMR and $[\alpha]_D$ comparison: –1.5° *cf* +5.5 for the epimer). At this point in time, the starting aldehyde **1.78** was derived from the enantiomeric mixture of alcohols **1.81** synthesised using (+)-DIP-chloride. The low diastereoselectivity observed in alcohol (3*S*,5*R*)-**1.78** may be attributed to this or, it is was a further reflection of the low selectivity of (+)-DIP-chloride (*viz.* the prior use of **2.12** (Scheme 2.04)). The ambiguity associated with this reagent resulted in an alternative allylation protocol being sought after.

Leighton and co-workers have developed alternative reagents for the enantioselective allylation of aldehydes.[61,62] This reagent (*R*,*R*)-**2.19** (Scheme 2.10), based on silicon constrained within a 5-membered ring, has sufficient Lewis acidity to effect the uncatalysed allylation of aliphatic aldehydes in excellent selectivity (typically 96-98% *ee*) and chiral aldehydes in excellent diastereoselectivity (*dr* 98:2).[62] The reagent has also been used in natural product synthesis with great success, for instance, in the synthesis of anamarine (95%, >99% *ee* and *de*).[63] The synthesis of silyl reagent **2.19** is a three step process with one purification necessary (Scheme 2.10).



2.20 **(–)-2.21** **(–)-2.22** **(*R*,*R*)-2.19**

Scheme 2.10. *Reagents and conditions*: a) 4-bromobenzaldehyde, K_2CO_3, EtOH/H_2O; b) $NaBH_4$, MeOH; c) allyltrichlorosilane, DBU, CH_2Cl_2.

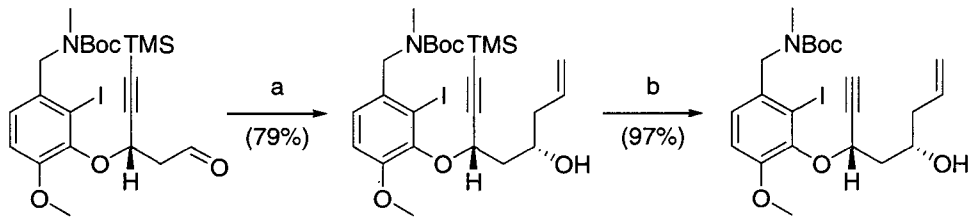
Diamine **2.22** was prepared from the condensation of commercially available (1*R*,2*R*)-(+)-1,2-diaminocyclohexane L-tartrate **(2.20)** and 4-bromobenzaldehyde followed by the reduction of the resulting bis-imine **2.21** with $NaBH_4$. Complexation with allyltrichlorosilane gave reagent (*R*,*R*)-**2.19** as a white solid (80%) following the general procedure described by Leighton[62] with advice received from Jeffrey Johnson.[64]

The allylation of aldehyde **2.02** proceeded with much improved selectivity (one diastereomer observed by ^{13}C NMR) but in a disappointing and reproducibly low yield (48%). Unfortunately the 2° alcohol **1.78** was found to be inseparable from the major by-product, phenol **1.70**. The nature of the reaction produces one equivalent of HCl. The acid sensitive propargylic ether bond in **1.78** proved to be labile under the allylation reaction conditions as the major by-product observed was phenol **1.70**. Addition of base (2,6-di-*tert*-butyl-methyl pyridine, 1.0 eq.) to the reaction mixture did not abate the cleavage of the aromatic aryl ether bond. Generation of the *in situ* molar equivalent of HCl is an integral part of this allylation mechanism as protonation of the free amine significantly increases the Lewis acidity of the silane.[61] Hence, attempts to limit the formation of HCl did not seem a reasonable course of action to follow. With this information in hand, the application of this reagent was abandoned in favour of TADDOL reagent (*R*,*R*)-**2.13**. TADDOL reagent (*S*,*S*)-**2.13** formerly gave excellent selectivity in the synthesis of propargylic alcohol **(+)-1.81**. Again, use of this reagent for the enantioselective allylation proved to be superior. Homoallylic alcohol **(+)-1.78** was synthesised in good yield (79%) with excellent diastereoselectivty (one diastereomer by ^{13}C NMR analysis) from the (*R*,*R*)-TADDOL complex **2.13**. Commercial (4*R*,5*R*)-5-[hydroxy(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-

yl(diphenyl)methanol (**2.16**) was complexed with $TiCpCl_3$ to give the (*R*,*R*) reagent **2.13** in an identical yield (75%) to that obtained for the synthesis of the (*S*,*S*) complex.

2.5 Closure of B, C and D rings

With an efficient second allylation protocol in place the next transformation was to unmask enyne (**–**)-**2.23** and perform RCM to construct the cyclohexene ring present in galanthamine. The alkyne protecting group was removed in excellent yield (97%) giving enyne **2.23** which required no purification (Scheme 2.11).



Scheme 2.11. *Reagents and conditions*: a) (*R*,*R*)-**2.13**, allylMgBr, Et_2O, –78 °C; b) K_2CO_3, MeOH, rt.

Protection of the free hydroxyl functionality present was necessary as attempts to perform the RCM on the free alcohol **2.23** failed using Grubbs' I catalyst (**1.76**) and only yielded starting material (Scheme 2.12). It would appear that the Grubbs' catalyst mediated enyne RCM is incompatible with our substrate **2.23** incorporating free hydroxyl functionality. There are many examples of free hydroxyl group in substrates under going metathesis transformations[65-67] but conversely, it has been established that Lewis-basic oxygen is capable of chelation to the ruthenium alkylidene intermediates. This may limit or shut down the catalytic process,[68] as observed in our system, **2.24** and **2.25** (Figure 2.02).

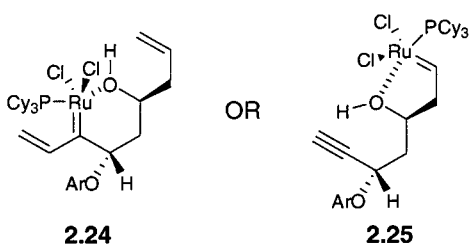
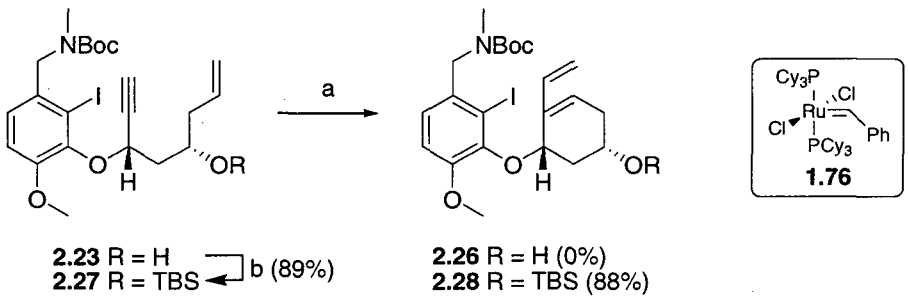


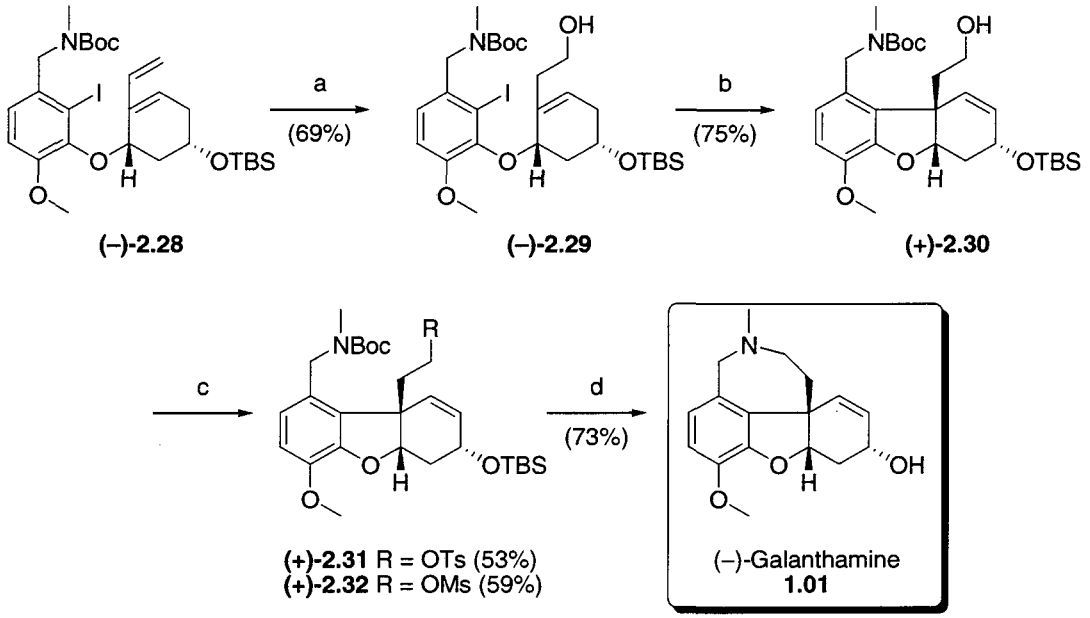
Figure 2.02. Possible stabilised metal-carbene intermediates for our system.

Conversion of alcohol **2.23** to *O*-silyl ether **2.27**, which proceeded in high yield (89%), removed this problem and allowed the RCM to proceed smoothly. It should be noted that protection of the allylic alcohol at this stage in the synthesis would also remove the need for a selective mono-mesylation of a diol, required in the first asymmetric synthesis. The RCM was accomplished on enyne **(–)-2.27** to yield diene **2.28** in excellent yield (88%) with low catalyst loading (Scheme 2.12). Two separate additions of Grubbs' I catalyst **(1.76)** were required to complete the metathesis; initially 4.4 mol% was used but after 4 h at rt the reaction mixture had turned brown/black signifying the active alkylidene intermediate had degraded. A further addition of 1.4 mol% of **1.76** and continued stirring for 14 h yielded the desired diene. Diene **2.28** encompasses all the functionality required for the last elaborations towards (–)-galanthamine **(1.01)**.



Scheme 2.12. *Reagents and conditions*: a) Grubbs' I **(1.76)** (5.8 mol%), CH_2Cl_2, rt; b) TBSOTf, CH_2Cl_2, –78 °C.

The selective hydroboration of the terminal double bond **2.28** was carried out using 9-BBN in good yield (69%) (Scheme 2.13). The reaction produced a complex mixture of products that, with careful column chromatography, yielded the desired alcohol **2.29**. The removal of this double bond eliminates selectivity issues in the intramolecular Heck coupling. The conditions developed by Fels and Parsons[26,27] were employed and yielded tricyclic intermediate **2.30** in excellent yield (75%) along with unreacted starting material (5%). Pleasingly, this yield was an improvement over the first generation synthesis (63%). The stereochemistry at the quaternary centre was controlled in the Heck coupling by the adjacent stereocentre with only diastereomer **2.30** being produced. Gratifyingly, the potential side reactions via elimination through a palladium π-allyl type mechanism were not observed. The penultimate stage of the total synthesis was to activate the primary alcohol in **2.30**. Afterwards, a simultaneous double deprotection of the *O*-TBS and *N*-Boc groups would effect the cyclisation to (–)-galanthamine **(1.01)**.



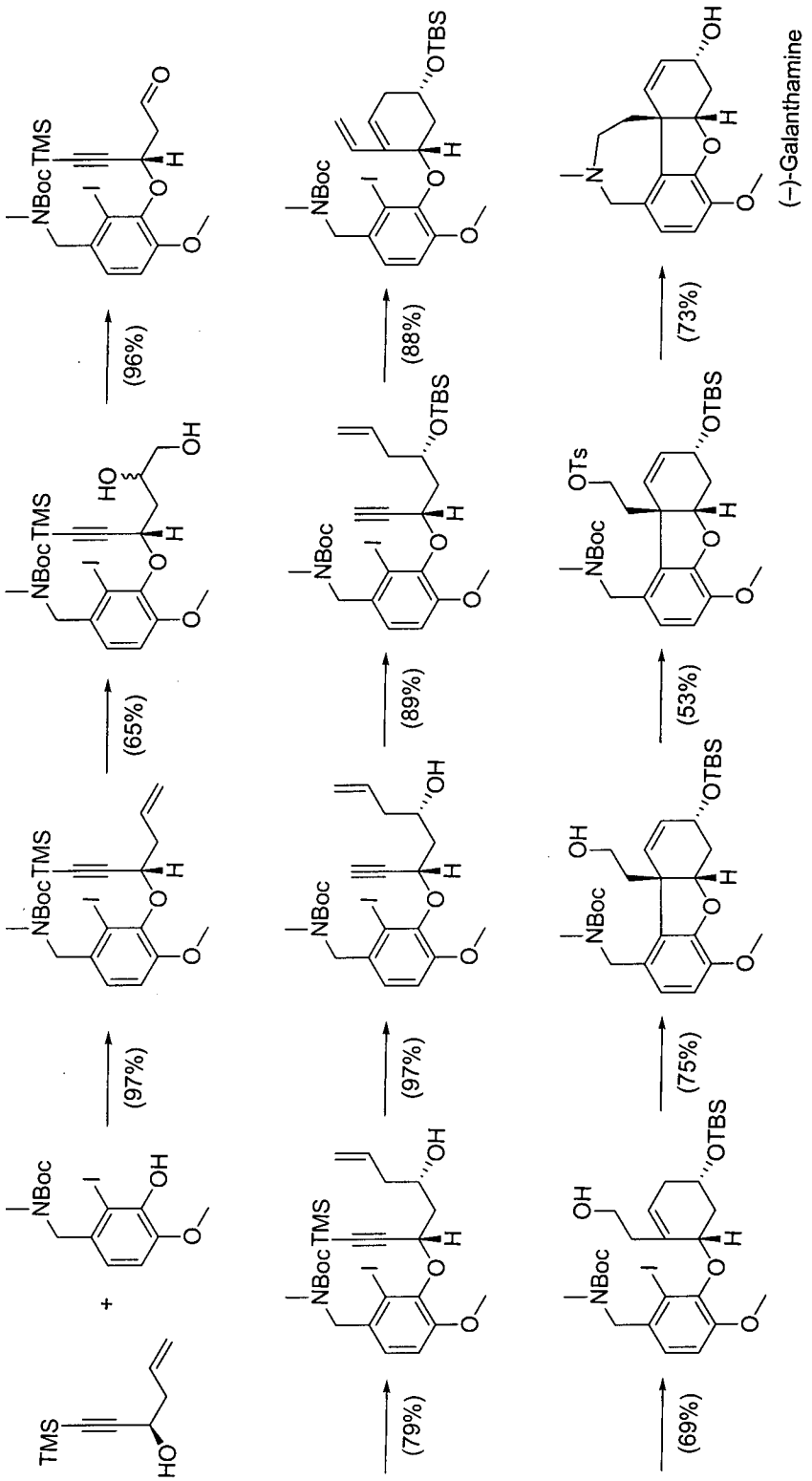
Scheme 2.13. *Reagents and conditions*: a) 9-BBN, THF then $NaOH/H_2O_2$; b) $Pd(OAc)_2$ (13 mol%), dppp (15 mol%), Ag_2CO_3, toluene; c) TsCl, pyr. or MsCl, NEt_3, CH_2Cl_2; d) AcCl/MeOH then $NaHCO_3$ (aq.).

After the issues associated with the mesyl activation in McLean's synthesis, tosyl and mesyl activating groups were explored concurrently. Disappointingly, both sulfonate esters (**2.31** and **2.32**) were formed with lower than expected yields (53% and 59% respectively). In the case of the tosylation **2.31**, the reaction was very sluggish requiring >40 h reaction time with a considerable portion of starting material **2.30** being recovered (27%). The *in situ* formation of pyridinium *p*-toluene sulfonate (PPTS) may have led to cleavage of the *N*-Boc protection in a portion of the material over the long reaction times resulting in the 80% mass recovery. The free amine would be extracted in the aqueous phase upon work-up resulting in the mass recovery difference. The low mesylation yield may simply be attributed to errors associated in performing small scale reactions (*ca.* 15 mg). Treatment of tosylate **2.31** with an acidic MeOH solution (10% AcCl in MeOH) removed the *N*-Boc protecting group within 2 h. Continued stirring for 20 h in total was necessary to remove the less labile *O*-TBS protection. The reaction mixture was then basified with $NaHCO_3$ (aq.) to facilitate the S_N2 displacement of the activated alcohol by the free secondary amine and resulted in azepine ring formation. After careful purification (silica gel, 19:1 to 9:1 CH_2Cl_2/MeOH), (–)-galanthamine (**1.01**) was isolated in good yield (73%) and very high optical purity ($[\alpha]_D$ = –92.3, lit. (natural galanthamine) $[\alpha]_D$ = –91.0; (synthetic galanthamine, 99% *ee*): –93.4, *c* 1.00,

$CHCl_3$).[9] Optical rotation of synthetic (–)-galanthamine **(1.01)** was also higher than previously observed in the first generation synthesis (*cf* $[\alpha]_D = -81.3$).[28] Additionally, spectroscopic data correlates exactly to data published in the literature.[9] (For ^1H and ^{13}C NMR spectra of (–)-galanthamine, see Appendix).

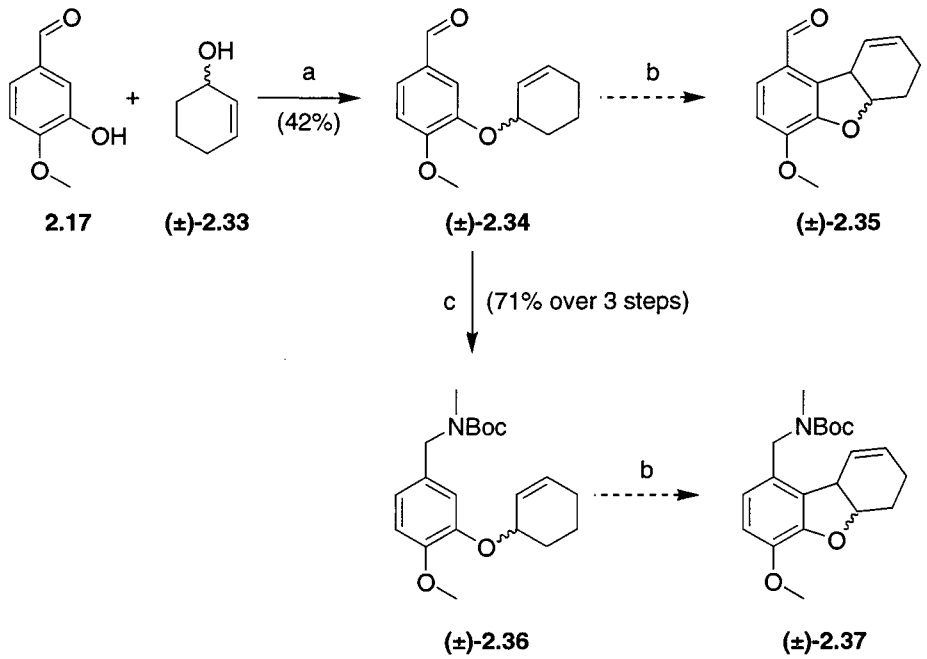
This constitutes an improved second asymmetric synthesis of (–)-galanthamine in 11 linear steps and 7.3% overall yield from alcohol **1.81** and phenol **1.70** (15 linear steps and 4% overall yield from TMS acetylene **2.01**) within our group.

Total synthesis of (–)-galanthamine:



2.6 Investigations into a direct oxidative Heck route

The Heck reaction is an important C-C bond forming process in modern synthetic chemistry. The necessity to have a halogenated precursor frequently involves an extra step in a synthesis for the halogenation (e.g. the incorporation of the iodide in our total synthesis of galanthamine). A potentially more appealing process would be an intramolecular Fujiwara-Moritani arylation, where by an oxidative coupling of an un-substituted aryl occurs directly with an un-functionalised alkene.[69] This would be desirable as it removes the requisite halogenation step in a total synthesis, potentially increasing the overall yield. To investigate the validity of this route in our synthesis of galanthamine a model system was constructed (Scheme 2.14).



Scheme 2.14. *Reagents and conditions*: a) DEAD, PPh_3, THF; b) $Pd(OAc)_2$ (10 mol%), ethyl nicotinate (20 mol%), NaOAc (0.1 eq.), benzoquinone (0.5 eq.), *t*-AmOH/AcOH; c) i) $MeNH_2$, MeOH, ii) $NaBH_4$, iii) Boc_2O, dioxane/NaOH.

Commercially available *iso*-vanillin (**2.17**) was coupled with cyclohexenol (**2.33**) under Mitsunobu conditions to afford aryl ether **2.34** in an unoptimised yield (42%). Substrate **2.34** was subjected to standard oxidative Heck coupling conditions reported[69] but disappointingly failed to yield any desired dihydrobenzofuran **2.35**. Only unreacted starting material was present.

Aldehyde **2.34** was converted to *N*-Boc protected amine **2.36** (*cf.* our synthesis of galanthamine) in good overall yield (71%, 3 steps) using identical reaction conditions

stated previously. Similarly, the attempted oxidative Heck coupling of aryl ether **2.36** failed to yield dihydrobenzofuran **2.37**.

This preliminary model study was carried out to determine if the aromatic ring would be activated enough to undergo the desired insertion under reported conditions. Current oxidative Heck methodology is limited to electron-rich aromatics where the C-H bond involved in the oxidative insertion of palladium is activated by the presence of an electron-donating group in the *para* position.[69] Our model system does not incorporate these features, therefore no reaction occurred.

2.7 Conclusions

To date there are relatively few asymmetric syntheses of (–)-galanthamine **(1.01)**. We have accomplished a new 11 step synthesis of (–)-galanthamine **(1.01)** that pleasingly, was completed in good overall yield (7.3%) from the known aromatic fragment **1.70** and enantiomerically enriched alcohol **1.81**.

Our novel method brings together the use of enyne RCM, an asymmetric allylation and an intramolecular Heck reaction to construct (–)-galanthamine. These transition metal mediated reactions were pivotal in achieving the high chemo- and stereo-control. In particular, the reagent derived stereocontrol from the titanium TADDOL reagent was key to achieving complete diastereocontrol. The main objective to circumvent the rather inefficient allylic oxidation has been realised. Interestingly, selection of appropriate reagents lends our strategy to the synthesis other diastereomers of galanthamine, potentially useful for pharmacological studies.

2.8 Future work

Our second generation asymmetric synthesis of (–)-galanthamine addressed all stereochemical selectivity issues with the former synthesis. Continuation of this work can be separated into 3 areas: the use of our route to synthesise analogues of galanthamine; the more in-depth investigation into the use of an oxidative Heck coupling and the use of a catalytic route to synthesise enantiomerically enriched aldehyde **(+)-1.79**, hence replacing the enzymatic resolution. A large amount of time was devoted to the synthesis of alcohol **(+)-1.81**. Through a different retrosynthetic disconnection intermediate **2.39** could be constructed (Figure 2.03).

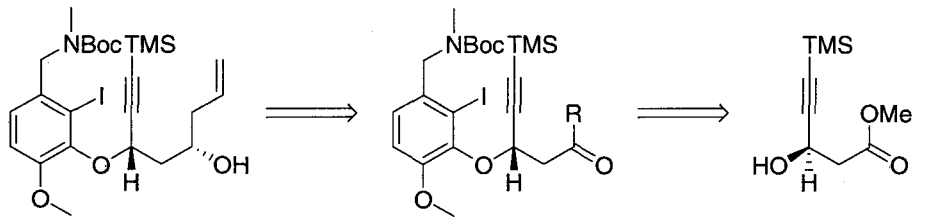
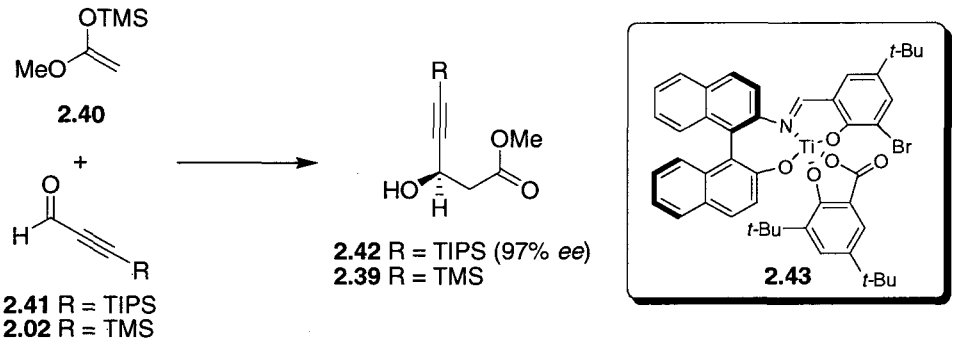


Figure 2.03. Modified retrosynthetic analysis to construct homoallylic alcohol **1.78**.

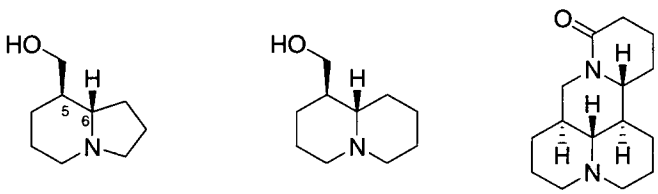
Carreira and co-workers have developed a highly enantioselective Ti(IV) catalyst **2.43** for use in an acetate Mukaiyama-aldol addition (Scheme 2.15).[70, 71] Catalyst loading as low as 2 mol% can facilitate the addition of a silyl-ketene acetal **2.40** with a propargylic aldehyde in high enantioselectivities (84-97% *ee*). The TIPS analogue of ester **2.39** was synthesised by Carreira *et al.* with excellent selectivity (97% *ee*).[70] This approach would remove the need for the enzymatic resolution step and, more desirably, reduce the number of linear steps in our synthesis.



Scheme 2.15. Catalytic enantioselective Mukaiyama-aldol reaction.

Chapter 3 The imino-aldol reaction in β-amino acid synthesis.

The indolizidine and quinolizidine cores are commonly encountered in naturally occurring alkaloids.[72] Examples range from the simplest, tashiromine **(3.01)** and epilupinine **(3.02)** up to more complex and more biologically active compounds, for instance, leontine **(3.03)** (Figure 3.01).[73] The relative stereochemistry of the C5 and C6 stereogenic centres make these three natural products ideal candidates for total synthesis incorporating a β-amino acid intermediate that could be accessed via an asymmetric imino-aldol reaction. Before commencing discussion of our efforts to synthesise these alkaloids, the imino-aldol reaction will be reviewed.



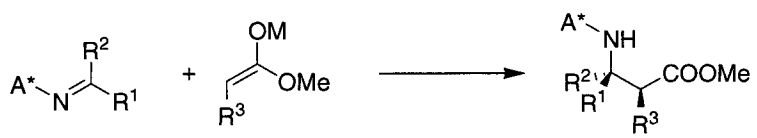
(–)-Tashiromine **(3.01)** (–)-Epilupinine **(3.02)** (+)-Leontine **(3.03)**

Figure 3.01. Structures of related *lupin*-type alkaloids.

3.1 Imino-aldol reaction

3.1.1 Background

The well documented addition of metal enolate nucleophiles **3.05** to imines **3.04** in an imino-aldol[74] (or Mannich) type reaction provides access to β-amino acid derivatives with the general structure **3.06** (Scheme 3.01).[75]



3.04 **3.05** **3.06**

Scheme 3.01. General imino-aldol type reaction, where A* is a chiral auxiliary.

The presence of a chiral auxiliary (A*) can provide a high degree of stereocontrol in a nucleophilic addition to the imine for the synthesis of β-amino acids **3.06**, essential for asymmetric natural product synthesis. The auxiliary is also of importance to inhibit imine oligomerisation and to impart stability to the imine for handling and storage

purposes.[76] Use of an auxiliary might not appear as appealing compared to modern chiral or a biological catalytic methods but their use has remained routed in many reliable synthetic strategies.[77] Furthermore, attachment of the chiral auxiliary usually allows easy separation of diastereomers and simply, in many cases, there exists no asymmetric catalytic equivalent.[77]

In recent years, two groups have demonstrated the effectiveness of the chiral sulfinyl imine moiety as a powerful stereodirecting group.[78,79] Pioneering work by Davis and co-workers developed the *p*-tolyl sulfinyl auxiliary (*R*)-**3.09** (named Davis auxiliary) derived from Andersen's menthyl ester **(3.07)** or **3.08** (Figure 3.02).[80]

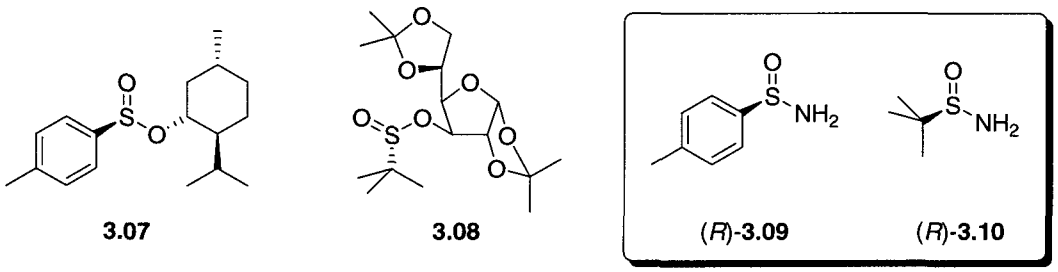
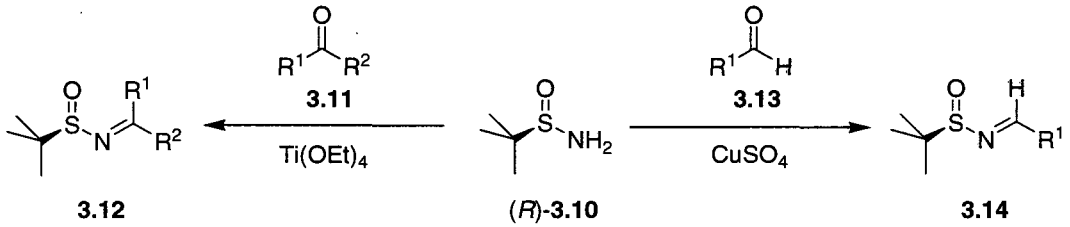


Figure 3.02. Commonly used sulfoxides and sulfinamide chiral auxiliaries.

Implementation of the Davis sulfinyl auxiliary **3.09** as a chiral imine building block in the asymmetric synthesis of chiral amines, α- and β- amino acids and aziridine carboxylic acids proved to be very successful. Many biologically active nitrogen containing compounds have been synthesised through this approach, such as, (*R*)-(–)-dysidazirine, a cytotoxic antitumour antibiotic.[80,81] The aromatic *p*-tolyl substituent provided good diastereofacial selectivity in addition to stabilising and activating the imine towards nucleophilic attack.

Ellman and co-workers later developed a similar auxiliary based on *tert*-butyl moiety, (*R*)-**3.10** for the synthesis of chiral amines.[82] In direct comparison with the Davis auxiliary **(3.09)** the new Ellman auxiliary **(3.10)** was more sterically hindered providing better regio- and stereo-control for nucleophilic additions.[79] The greater electron donating effect of the *tert*-butyl group also facilitates direct condensation with a variety of aldehydes **3.11** and ketones **3.13**, not observed with the Davis auxiliary (Scheme 3.02).[83]

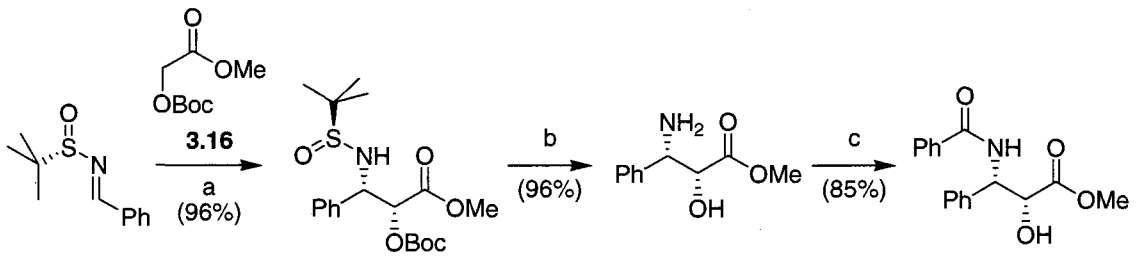


Scheme 3.02. Synthesis of sulfinyl-imines (**3.12**) and sulfinyl-ketimines (**3.14**).

Chemistry of sulfinyl imines **3.12** and **3.14** is dominated by nucleophilic additions of enolates or carbanions. Uniquely, the nature of nucleophile allows highly substituted β-amino acids and chiral α-branched amines to be synthesised efficiently. In addition, the versatility of the *tert*-butyl sulfinyl imine moiety allows α,α-disubstituted amines, α-amino acids, α or β- aminophosphoric acids, aziridines or aziridine-2-carboxylates to be synthesised.[83] We focused our interest on the synthesis of highly functionalised α,β-disubstituted β-amino acids with this approach. Interestingly, employing sulfinyl imines in this way has not been well documented.

3.1.2 Synthesis of β-amino acids

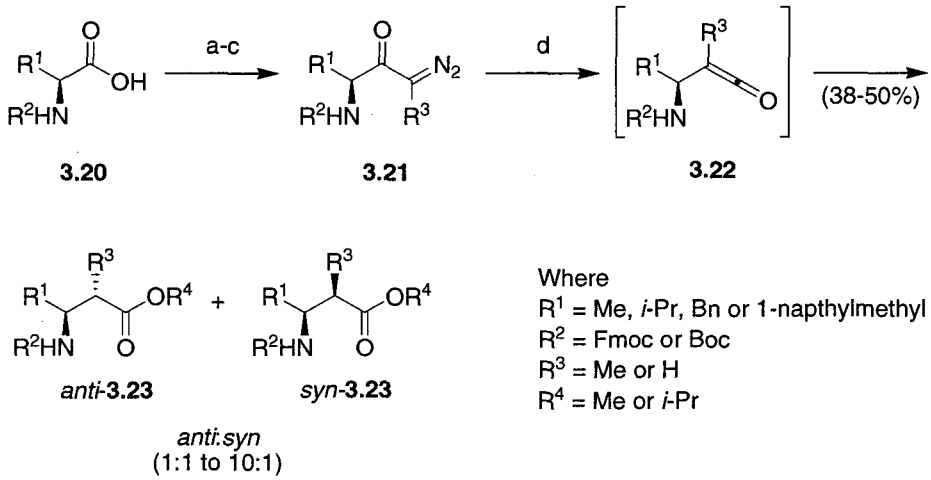
In nature β-amino acids are considerably less common than α-amino acids,[84] in particular, α,β- *syn*-dialkyl β-amino acids are relatively rare.[85] Recently, β-amino acids have become important pharmaceutical drug targets due to increased stability of peptides incorporating β-amino acids to enzymatic hydrolysis in comparison with α-amino acids.[86] They are also important building blocks for natural products that exhibit cytotoxic properties, including: antifungal; antibiotic[87-89] and antitumor activities. For example, the taxol side chain, necessary for the high degree of cytotoxicity is an α-hydroxy β-amino acid, phenyl*iso*serine (**3.19**).[90,91] Recently, the synthesis of this side chain has incorporated Ellman sulfinyl imine methodology and resulted in a highly selective approach (78%, >99% *de*) (Scheme 3.03).[92]



Scheme 3.03. *Reagents and conditions*: a) LiHMDS, –78 °C, THF; b) 6 N HCl/MeOH; c) PhCOCl, $NaHCO_3$ (aq.), THF.

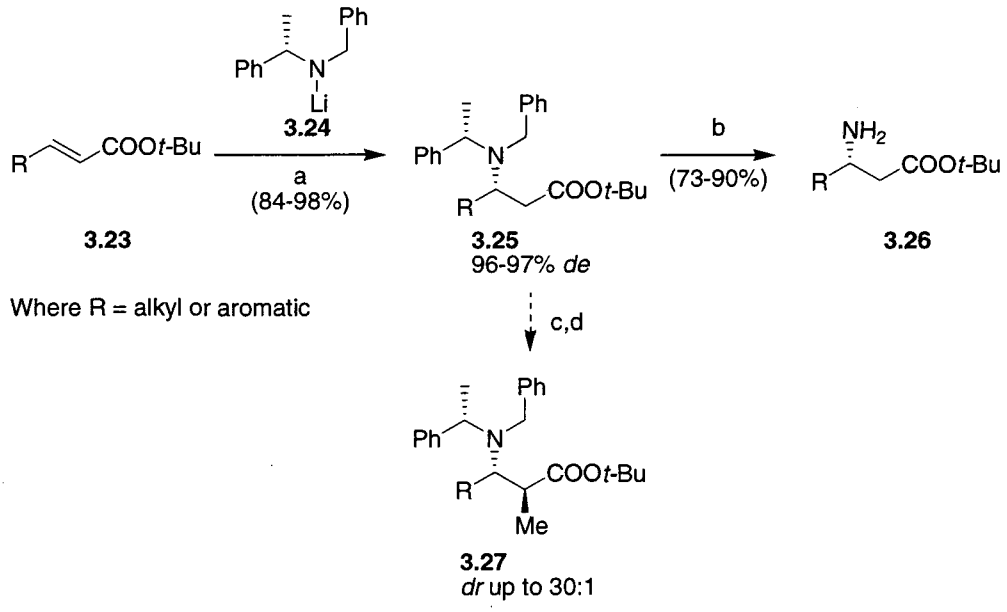
There are a wide variety of alternative methods for the construction of β-amino acid esters. For a complete overview of β-amino acid synthesis see the excellent review by Liu and Sibi.[93] We will focus on the classical approaches: the Arndt-Eistert homologation of α-amino acids; amine Michael addition to acrylates or hydrogenation of 3-amino acrylates.[84] In particular, these methods can be limited due to an inherent inability to provide access to highly substituted substrates.

The Arndt-Eistert homologation route has been successfully applied in the synthesis of di-substituted β-amino acids with varying degree of stereocontrol (Scheme 3.04).[94] The photo-induced or silver nitrate mediated Wolff rearrangement of α-diazoketone **3.21** leads to the formation of β-amino acid **3.23** as a mixture of *syn/anti* diastereomers. However, this strategy is unable to produce α,α,-disubstituted β-aminoacids.



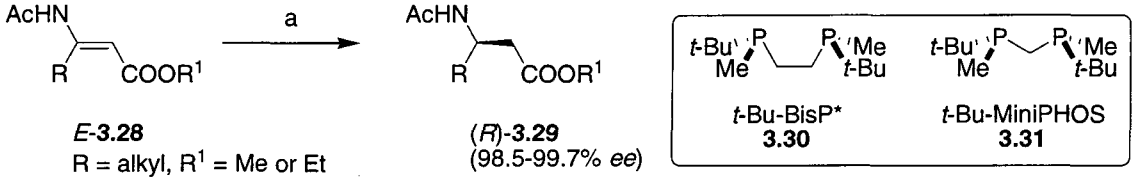
Scheme 3.04. *Reagents and conditions*: a) *i*-BuOCOCl/NEt_3, THF, –10 °C; b) CH_2N_2; c) KHMDS, THF, HMPA, R^3X, –78 °C; d) hν, CH_2Cl_2, R^4OH.

Stereocontrol in a Michael addition relies upon either: the conjugate addition of a chiral amine (**3.24**) which can be highly selective (96-97% *ee*) (Scheme 3.05);[95] a chiral catalyst or a chiral auxiliary incorporated in the enolate.[84] There are few syntheses of β,β substituted β-amino acids and no direct syntheses of α,β-substituted β-amino acids syntheses disclosed in the literature.[75,85] Davies *et al.* have disclosed the asymmetric alkylation of intermediates with the general structure **3.25** in high diastereoselectivity (*dr* = 30:1, *anti*/ *syn*) affording α,β-substituted β-amino acids **3.27**.[96]



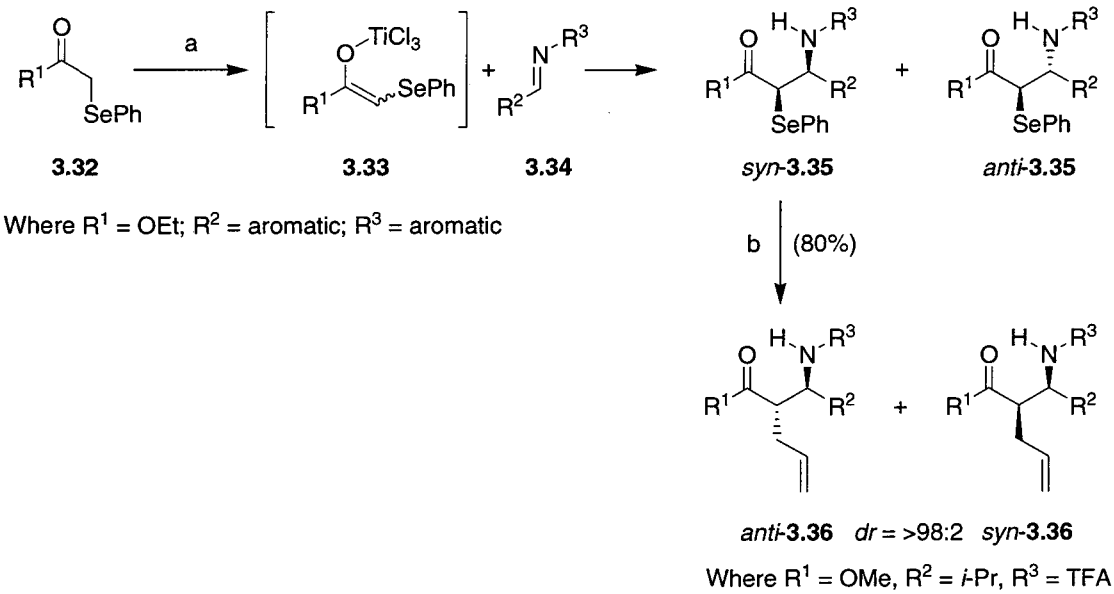
Scheme 3.05. *Reagents and conditions*: a) THF, –78 °C, 2 h; b) H_2 (1 atm.), $Pd(OH)_2/C$, MeOH, H_2O, AcOH, rt, 15 h; c) LDA, THF; d) MeX.

An asymmetric hydrogenation is one of the simplest and most straight-forward routes to access β-amino acids. Imamoto *et al.* used the electron rich diphosphine ligands *t*-Bu-BisP* **3.30** and *t*-Bu-MiniPHOS **3.31** in a Rh complex to achieve excellent selectivity (98.5-99.7% *ee*) in the asymmetric hydrogenation of (*E*)-β-(acylamino)acrylates (**3.28**) to (*R*)-β-acylamino acids (**3.29**) (Scheme 3.06).[97] Again, this approach cannot yield β-disubstituted β-amino acids and low selectivity is observed for α-substituted β-amino acids (72% *ee*).[98]



Scheme 3.06. *Reagents and conditions*: a) $Rh(L^*)(nbd)BF_4$, H_2 (3 atm), THF, 2 h.

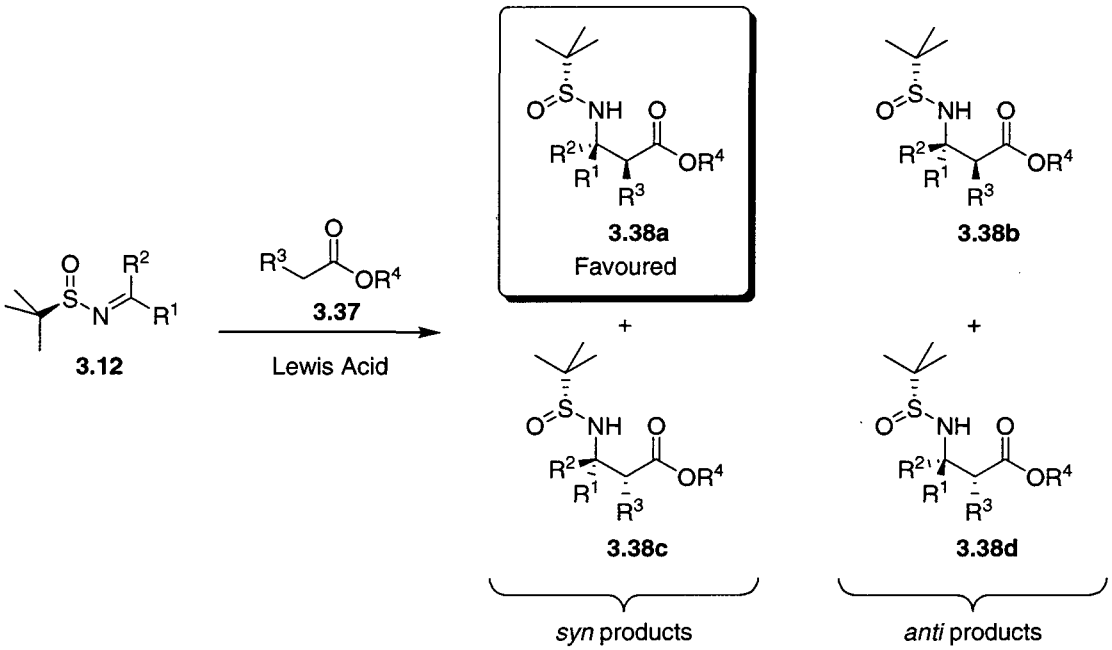
The Mannich reaction of an ester enolate to an imine is, in theory, able to provide an excellent, general and diverse route to all substitution patterns of β-amino acids. Ellman and co-workers used a chiral sulfinyl imine whereas Silveira *et al.* based their approach on aromatic aldimines (**3.34**). The Mannich-type reaction of α-seleno chlorotitanium enolates **3.33** and aromatic aldimines **3.34** to yield modified β-amino acid ester precursors **3.35** was described by Silveira *et al.*[99] The *syn* diastereomeric products are preferentially formed in reasonable to good *dr* (66:34 to 90:10). Hanessian and co-workers have elaborated such intermediates to yield α,β-substituted β-amino acids **3.36** in excellent diastereoselectivity (*dr* = >98:2) and yield (80%) through a *C*-allylation of the α-acyl radical accessed from α-selenophenyls with the general structure **3.35** (scheme 3.07).[100]



Scheme 3.07. *Reagents and conditions*: a) DIPEA, $TiCl_4$, CH_2Cl_2, –78 °C; b) allyltributylstannane, AIBN, *hv*, toluene, –40 °C.

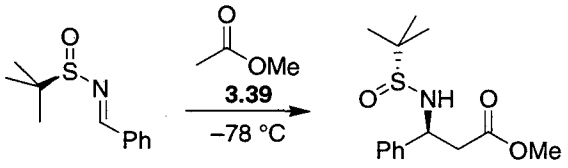
3.1.3 The Ellman group approach

Ellman *et al.* demonstrated the application of the addition of simple enolates to chiral sulfinyl imines, based on the chiral auxiliary **(+)-3.10**, for the synthesis of *syn* β-amino esters.[75] The addition of enolate **3.37** to a chiral imine **3.12** can result in four possible diastereomers, **3.38a-d** (Scheme 3.08). The chiral auxiliary (*R* configuration) and the Lewis acid used in the reaction directs a preference for the *syn* diastereomer **3.38a**.



Scheme 3.08. All possible diastereomeric products from the imino-aldol reaction.

Ellman and co-workers showed that varying the Lewis acid (LA) had a profound effect on the selectivity of the reaction and demonstrated that extremely high levels of selectivity (99:1) could be realised (Scheme 3.09).[75] A dramatic increase in yield (76 to 90%) and facial selectivity (83:17 to 99:1) is observed when the Lewis acid becomes more covalent in character, Li to Na to TiCl(O*i*-Pr)$_3$ (Entry 1 to 5). Complementary to this, increasing the stoichiometry of TiCl(O*i*-Pr)$_3$ from 1.0 to 4.0 eq. (with respect to the base used to generate the enolate) increased selectivity from 87:13 to 99:1 (Entry 5 to 8). This is in accordance with prior observations by Siegel and Thornton regarding the use of LDA as a base and TiCl(O*i*-Pr)$_3$ as the Lewis acid in aldol-type reactions.[101] A noteworthy observation by Fujisawa *et al.* indicated that the choice of Lewis acid, solvent and additive (e.g. HMPA) could reverse the sense of diastereoselectivity for an enolate addition to a *p*-tolylsulfinyl imine.[102]

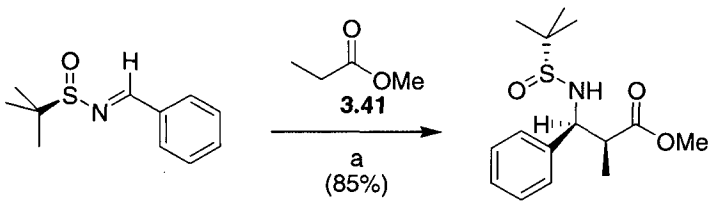


(−)-3.15 **3.40**

Entry	Base/Lewis acid	Solvent	Yield (%)	*dr*
1	LDA	THF	76	83:17
2	LDA	Et_2O	91	67:33
3	NaHMDS	THF	89	75:25
4	NaHMDS	Et_2O	78	96: 4
5	LDA/1 eq. of $TiCl(O\textit{i}\text{-}Pr)_3$	THF	90	87:13
6	**LDA/2 eq. of $TiCl(O\textit{i}\text{-}Pr)_3$**	**THF**	**90**	**98:2**
7	**LDA/3 eq. of $TiCl(O\textit{i}\text{-}Pr)_3$**	**THF**	**90**	**99: 1**
8	**LDA/4 eq. of $TiCl(O\textit{i}\text{-}Pr)_3$**	**THF**	**90**	**99:1**

Scheme 3.09. Effect the Lewis acid has on the diastereomeric outcome in the imino-aldol reaction.[75]

The highest diastereoselectivity achieved for an α-substituted enolate by Ellman and co-workers was the addition of the titanium enolate of methyl propionate **(3.41)** to aromatic sulfinyl imine **3.15** (Scheme 3.10).[75] Sulfinyl amine **3.42** was produced in very high *dr* (96:4:0:0) and in high yield (85%).

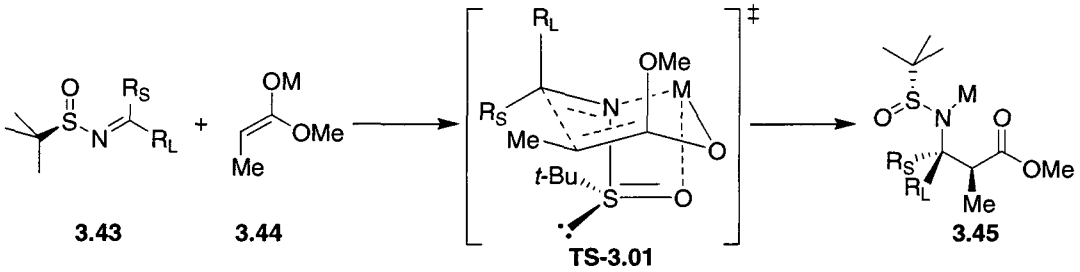


3.15 **3.42**
dr = 96:4:0:0

Scheme 3.10. *Reagents and conditions*: a) $TiCl(O\textit{i}\text{-}Pr)_3$ (2.0 eq.), LDA, THF, −78 °C.

3.1.3.1 Origin of diastereoselectivity

In accordance with observed diastereoselective results, Ellman *et al.*[75] proposed that the stereoselective addition of metal enolates **3.44** to chiral sulfinyl imines **3.43** proceeded through a Zimmerman-Traxler type closed six-membered transition state (TS) **TS-3.01** (Scheme 3.11).[103]



Scheme 3.11. Proposed Zimmerman-Traxler type transition state **TS-3.01**.

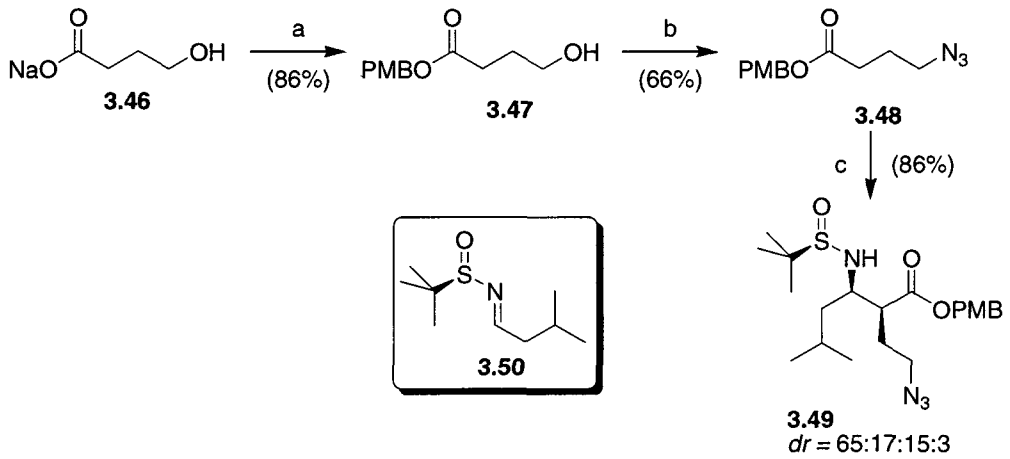
A notable key feature of **TS-3.01** is the unexpected axial orientation of the sterically dominant substituent (R_L) in place of the subordinate substituent (R_S) present in sulfinyl imine **3.43**. This orientation is dictated by the exclusive *trans* geometry present in sulfinyl imine **3.43** and coordination of the sulfinyl oxygen to the Lewis acid. Therefore, the imine is locked in this orientation in the TS. The facial selectively is derived from the bulky *tert*-butyl group shielding the *Re*-face of the imine from attack by the enolate nucleophile **3.44**. Finally, the sterically less demanding lone pair protrudes into the centre of the six-membered transition state resulting in a configuration that minimises the non-bonding interactions. It is proposed that this chelation controlled model directs a preference for formation of the sulfinyl amine **3.45** diastereomer with *syn* geometry across the newly formed C2-C3 bond.

In addition, geometry of the enolate is an important factor in the stereochemical outcome of the reaction. For enolate formation from methyl propionate **(3.41)** Heathcock *et al.* stated that the *trans* enolate (kinetic product) is favoured from deprotonation by LDA and leads to the *syn*-aldol product. At –78 °C, the *trans*:*cis* enolate ratio for methyl propionate was reported to be 95:5.[104,105]

3.1.3.2 Synthesis of α,β substituted long-chain β-amino acids

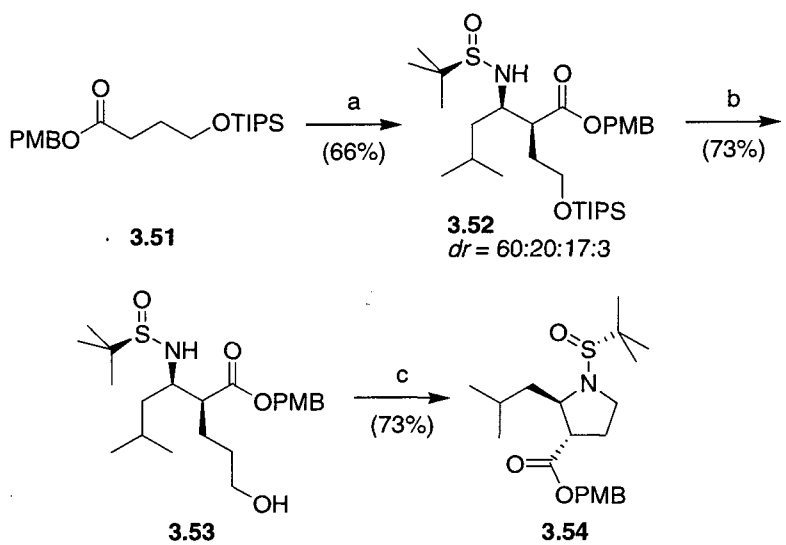
Despite the plethora of examples demonstrating very high diastereoselectivities for acetate enolate additions to sulfinyl imines,[75,78,106] there are only two examples in the literature where a long chain α-substituted enolate is exploited, giving only moderate selectivity (Scheme 3.12).[75] In an effort to construct water soluble β-peptides, Ellman *et al.* investigated the use of azide **3.48** in the imino-aldol reaction. The asymmetric alkylation of aliphatic sulfinyl imine **3.50** by the enolate of azide **3.48**, generated *in situ* from the reaction with NaHMDS, gave modest stereocontrol (65:17:15:3).

Interestingly, the standard Lewis acid, $TiCl(O\textit{i}\text{-}Pr)_3$, proved to be incompatible with the azide functionality and only decomposition of the starting material was observed.



Scheme 3.12. *Reagents and conditions*: a) PMB-Cl, Bu_4NI, acetone; b) DPPA, DIAD, PPh_3, THF; c) i) NaHMDS, ii) sulfinyl imine **3.50**, Et_2O, –78 °C.

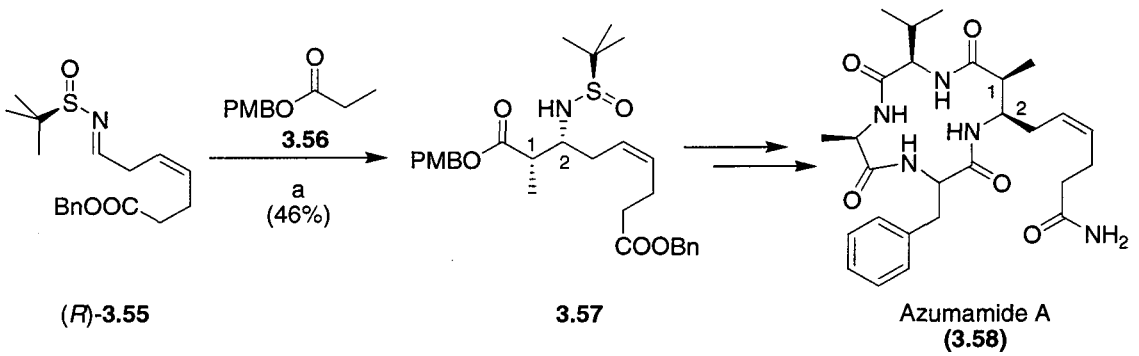
The authors modified the procedure, replacing azide **3.48** with the PMB ester of γ-tri*iso*propylbutanoic acid **(3.51)** (Scheme 3.13). Addition of the bulky TIPS protected alcohol **3.51** at the terminus had a negligible effect on the diastereoselectivity observed in the imino-aldol reaction (60:20:17:3 *cf* 65:17:15:3). Removal of the *O*-TIPS protecting group to yield alcohol **3.53**, followed by an intramolecular Mitsunobu cyclisation constituted a short asymmetric synthesis of 2,3-distubstituted pyrrolidine **3.54**.



Scheme 3.13. *Reagents and conditions*: a) i) LDA, ii) $TiCl(O\textit{i}\text{-}Pr)_3$ (2.0 eq.), iii) sulfinyl imine **3.50**, THF; b) HF/pyr., THF; c) DEAD, PPh_3, THF.

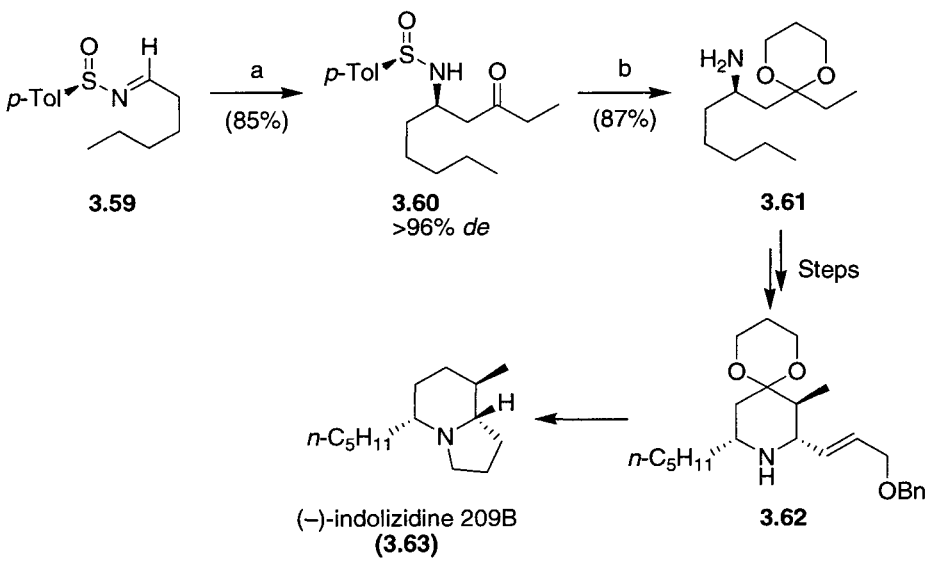
3.1.3.3 Applications in natural product synthesis

The imino-aldol reaction with simple α-substituted, short chain enolates has already been exploited by many groups in natural product synthesis. Ganesan and co-workers used the titanium enolate of PMB propionic acid ester **(3.56)** to alkylate functionalised sulfinyl imine **3.55** in modest yield (46%) and high diastereoselectivity in their synthesis of azumamide A **(3.58)** (Scheme 3.14).[107]



Scheme 3.14. *Reagents and conditions*: a) LDA, $TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$ (10:1, 8.0 eq.), THF, –78 °C.

Similarly, Davis and co-workers synthesised β-aminoketone **3.60** through the addition of the potassium enolate of methyl ethyl ketone to sulfinyl imine **3.59** in good yield (85%) and excellent diastereoselectivity (>96% *de*) towards the synthesis of (–)-indolizidine 209B **(3.63)** (Scheme 3.15).[108]



Scheme 3.15. *Reagents and conditions*: a) $C_2H_5C(O)CH_2K$, –78 °C; b) TsOH, $HO(CH_2)_3OH$, 78 °C then 2.6 N KOH.

3.1.4 Conclusions

Use of TBSA sulfinyl imines as a chiral auxiliary in asymmetric synthesis is a versatile approach which has been used effectively in natural product synthesis. We believed this methodology could be extended to more functionalised systems and provide concise routes to the alkaloid natural products: tashiromine; epilupinine and leontine, which contain indolizidine and quinolizidine ring systems.

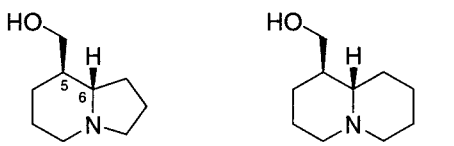
Chapter 4 Synthetic studies of tashiromine, epilupinine and leontine

4.1 Tashiromine and epilupinine

4.1.1 Background

Tashiromine **(3.01)** is an indolizidine alkaloid isolated from the stems of the leguminous deciduous shrub *Maackia Tashiroi* distributed across subtropical Asia.[109] The optical rotation of natural **3.01** remains unknown due to shortages of isolated material although the exact configuration of enantiomers is known by elucidation from previous asymmetric syntheses.

Epilupinine **(3.02)** is a naturally occurring alkaloid, related to tashiromine in reference to the relative stereochemistry across the C5-C6 bond and isolation from the same leguminous plants as **3.01**. Epilupinine has the simplest quinolizidine core common to a majority of *lupin*-type alkaloids.[110] (+)-Epilupinine has been shown to exhibit *in vitro* inhibitory activity against: Leukaemia P-388 (LD_{50} = 28 μg/mL) and lymphocytic Leukaemia L1210 (LD_{50} = 28 μg/mL) cells; and has shown cytotoxic behaviour towards cancer cell lines.[110, 111]



(–)-Tashiromine **(3.01)** (–)-Epilupinine **(3.02)**

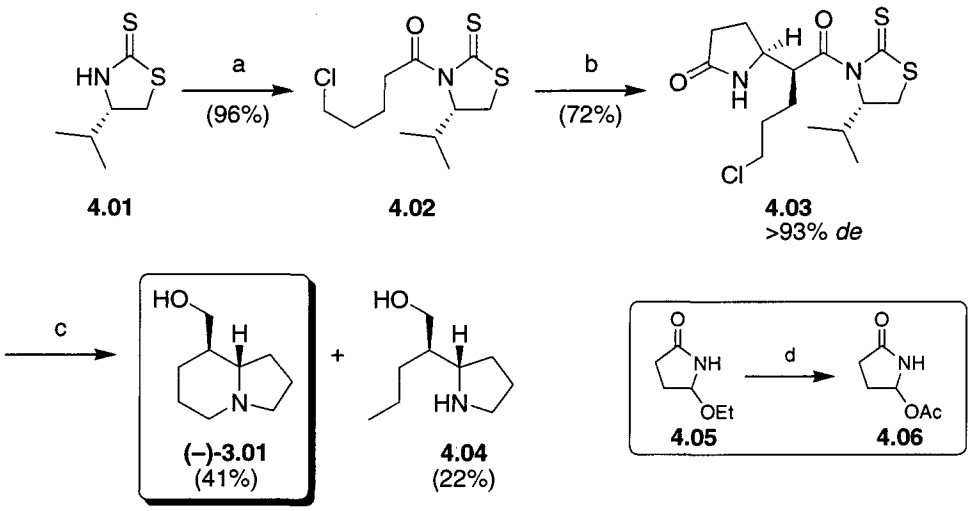
Figure 4.01. Structure of (–)-tashiromine and (–)-epilupinine.

4.1.2 Previous syntheses

Synthesis of both alkaloids has frequently been undertaken, either to: determine the absolute stereochemistryof the natural products; demonstrate the application of newly developed methodology or confirm the diastereoselective outcome in a reaction by comparison with known material. Strategies are based on either a selective reduction of an aromatic precursor or an annulation of an acyclic precursor with the more elegant syntheses typically featuring 4-6 steps. There are over 10 total syntheses of tashiromine **(3.01)**[112-123] and more than 25 total syntheses of epilupinine **(3.02)**[111,120,124-146] reported in the literature. An overview of some of this synthetic work will be detailed, focusing on key and recent achievements.

4.1.2.1 Tashiromine

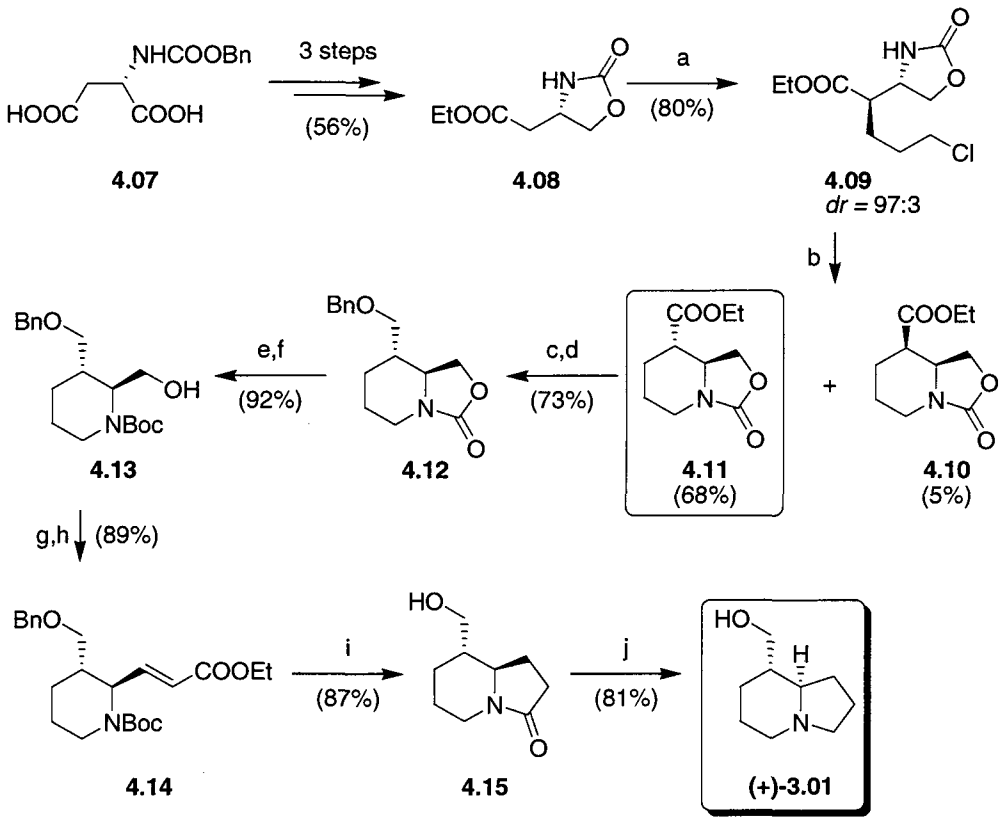
There has been interest in the synthesis of tashiromine **(3.01)** for nearly 20 years with several total syntheses reported. The first asymmetric synthesis of (–)-tashiromine **(3.01)** was published by Nagao and co-workers in 1990. The addition of a chiral tin (II) enolate to a cyclic acyl iminium ion of **4.06** formed the basis of this highly selective approach (Scheme 4.01).[147]



Scheme 4.01. *Reagents and conditions*: a) NaH, 5-chlorovaleryl chloride, THF; b) $Sn(OSO_2CF_3)$, *N*-ethylpiperidine, THF then **4.06**; c) $LiAlH_4$ (4.0 eq.), THF; d) AcOH.

The key step in this total synthesis is the formation of the Sn(II) enolate of **4.02** then the subsequent alkylation of the *in situ* generated acyl iminium ion of 5-acetoxy-2-pyrrolidinone **(4.06)**. Substituted pyrrolidinone **4.03** is synthesised in good yield (72%) and in a very highly diastereoselective manner (>93% *de*) with stereoselectivity being controlled by the 4-(*S*)-isopropyl-1,3-thiazolidine-2-thione (4-(*S*)-IPTT) chiral auxiliary **(4.01)**. Reductive annulation by $LiAlH_4$ produced **(–)-3.01** in addition to the acyclic over reduced by-product **4.04** and completed this extremely short, 4 step asymmetric synthesis. It should be noted that both enantiomers of epilupinine **(3.02)** were also synthesised according to this approach.

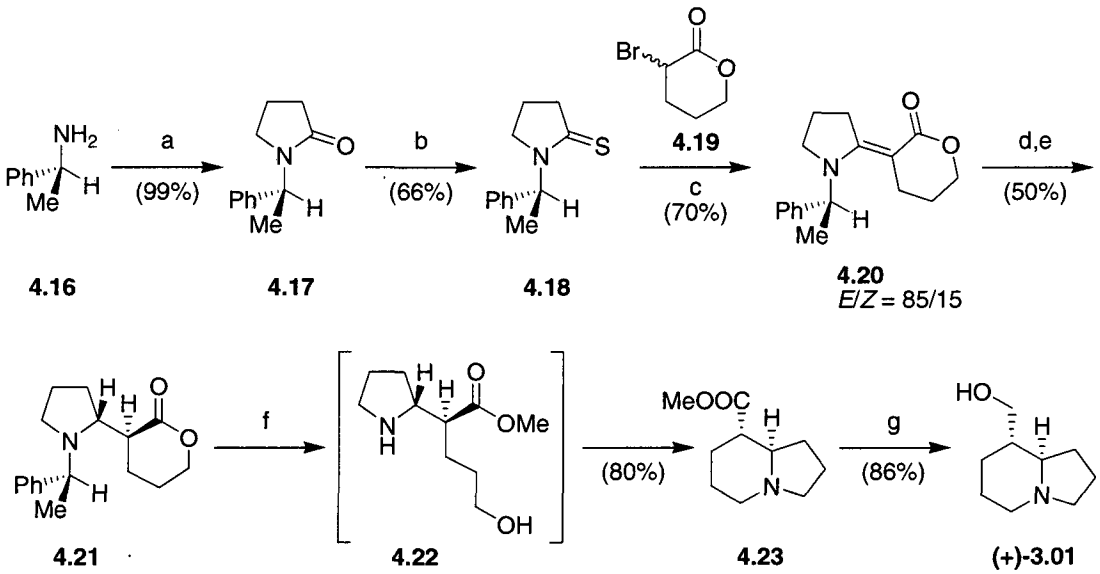
Ha and co-workers reported the first asymmetric synthesis of (+)-tashiromine in 1998 based on the highly diastereoselective alkylation of chiral oxazolidinone **4.08** (*dr* = 97:3) derived from aspartic acid **(4.07)** (Scheme 4.02).[118]



Scheme 4.02. *Reagents and conditions*: a) 1-chloro-3-iodopropane, NaHMDS, THF, 0 °C ; b) K_2CO_3, *n*-Bu_4NI, THF, Δ; c) $LiAlH_4$, THF, 0 °C; d) NaH, BnBr, cat. *n*-Bu_4NBr, THF; e) NaOH, EtOH; f) Boc_2O; g) ClCOCOCl, DMSO, NEt_3; h) Ph_3P=CHCOOEt; i) H_2, Pd-C, EtOH then Dowex 50-W, 1-BuOH, Δ; j) $LiAlH_4$, THF.

Cyclisation of **4.09** with K_2CO_3 in THF led to the formation of oxazolidinone **4.11** in good yield. Next, functional group manipulations to allow a 2 carbon homologation resulted in a high yielding route to indolizidinone **4.15**. Finally, reduction of the amide gave **(+)-3.01** in good overall yield (18%). The ^1H and ^{19}F NMR of the Mosher ester derivative of **3.01** showed a single enantiomer was obtained.

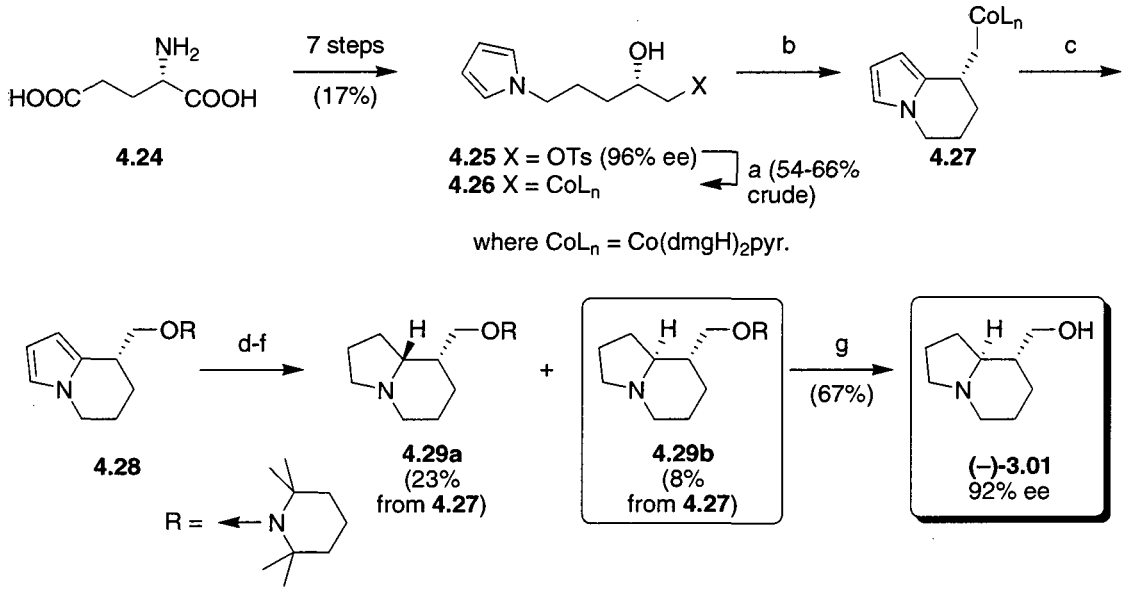
The synthesis of (+)-tashiromine described by David *et al.* in 2001,[148] utilised an alkylation-sulphur contraction reaction of chiral thiolactam **4.18** and α-bromolactone **4.19** followed by a reduction to simultaneously generate the two chiral centres with stereocontrol ultimately derived from (*S*)-1-phenyl ethylamine **(4.16)** (Scheme 4.03).



Scheme 4.03. *Reagents and conditions*: a) 5-chlorovaleryl chloride, pyr., CH_2Cl_2, 0 °C; b) P_4S_{10}, benzene, Δ; c) α-bromovalerolactone, neat, 75 °C, then PPh_3, NEt_3, CH_2Cl_2; d) H_2, 5% Pt/C, EtOAc, rt; e) Picric acid (1.1 eq.), MeOH/Et_2O, recrystallisation (EtOH) then K_2CO_3; f) H_2, 10% Pt/C, MeOH then CBr_4, PPh_3, CH_2Cl_2; g) $LiAlH_4$, THF, rt.

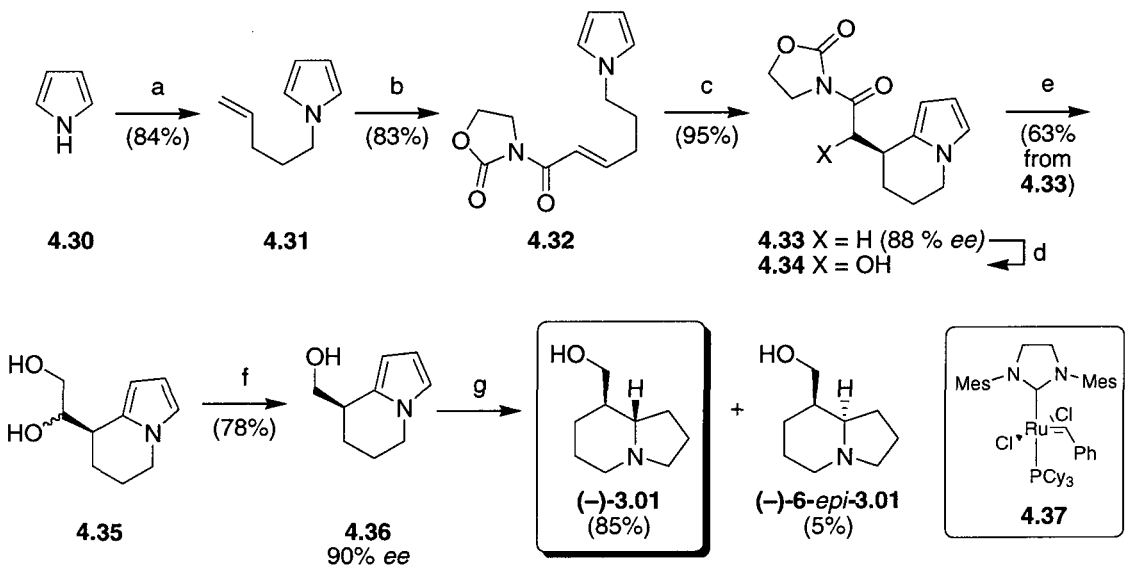
Enamine lactone **4.20** was obtained in good yield as a mixture of *E*/*Z* (85:15) isomers. Reduction led to a mixture of diastereomeric products (*dr* = 2.6:1) which were readily separated via a picratation/recrystallisation/depicratation protocol to yield enantiomerically pure **4.21**. Hydrogenolysis of the chiral auxiliary also led to the concomitant lactone ring opening. Without isolation amino-alcohol **4.22** was treated with PPh_3/CBr_4 to afford indolizidine **4.23** in good yield. Finally, reduction with $LiAlH_4$ yielded **(+)-3.01** in 6 steps, 16% overall yield and in high optical purity (+44.8 *cf* +43.4).[118]

Gage *et al.* in 1997 devised a synthetic strategy to **(–)-3.01** from L-glutamic acid **(4.24)** through the highly enantioselective, intramolecular electrophilic aromatic substitution of a cobaloxime π-cation to a pyrrole ring in intermediate **4.26** (Scheme 4.04).[117] The 6-*exo*-cyclisation afforded cobaloxime **4.27** where the C-Co bond was oxygenatively cleaved by the photolysis with visible light in the presence of TEMPO to yield **4.28**. With the carbon skeleton of tashiromine in place, hydrogenation of **4.28** yielded indolizidines **4.29a** and **4.29b**. Separation as the corresponding borane adducts (to avoid *N*-oxide formation) then cleavage of the N-O bond afforded (–)-tashiromine **(3.01)** in 92% *ee* (^{19}F of Mosher ester derivative) in 14 steps and low overall yield (0.6%).



Scheme 4.04. *Reagents and conditions*: a) Na[Co(dmgH)$_2$pyr.], MeOH; b) PPTS, CH_3Cl; c) TEMPO, MeOH, hν; d) H_2, Rh/Al_2O_3; e) BH_3.THF, THF; f) EtOH, Δ; g) Zn, $AcOH/H_2O$.

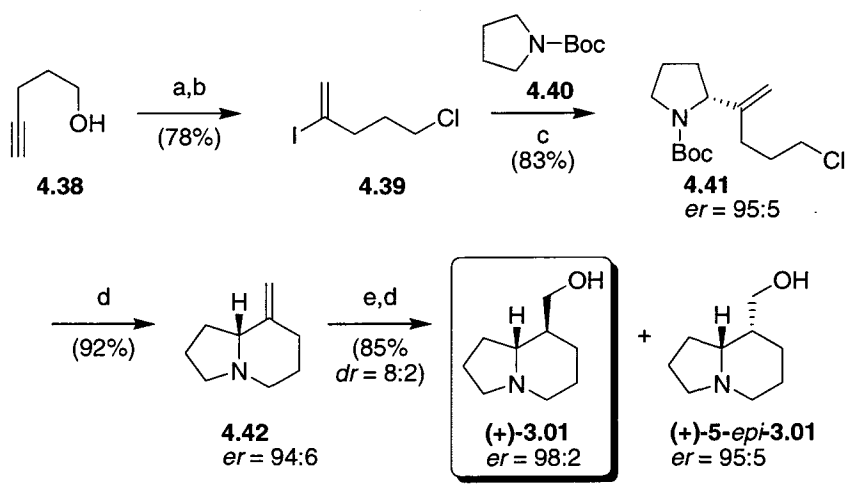
In 2004, Banwell *et al.* undertook a study into the ability of *N*-tethered acrylates to undergo diastereo- and enantio-selective intramolecular Michael additions. As a consequence, the synthesis of tashiromine **(3.01)** was completed to determine the diastereoselective outcome of the asymmetric addition step (Scheme 4.05, step c).[112]



Scheme 4.05. *Reagents and conditions*: a) KH, THF; b) Grubbs' II **(4.37)**, *N*-acryloyl oxazolidinone, CH_2Cl_2; c) Cu[(*R*,*R*)-Ph-box)]$(SbF_6)_2$, THF; d) Davis oxaziridine, NaHMDS, THF; e) $LiBH_4$, THF, –78 °C; f) $NaIO_4$, THF then $NaBH_4$, EtOH; g) H_2, 5% Rh/Al_2O_3, $(CF_3)_2CHOH$.

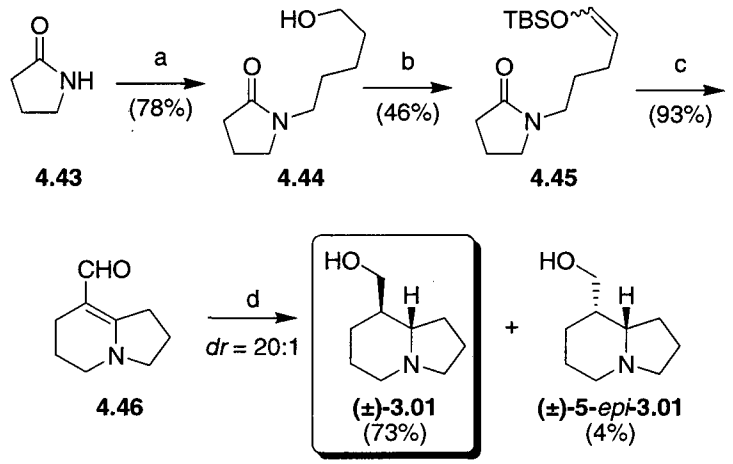
The application of a chiral Cu-box ligand (Cu[(*R*,*R*)-Ph-box)](SbF$_6$)$_2$) to substrate **4.32** afforded the desired oxazolidinone **4.33** in excellent yield and good stereoselectivity (88% *ee*). Treatment of the enolate of oxazolidone **4.33** with Davis oxaziridine gave the α-hydroxylated substrate **4.34** (*dr* 1:1). Reduction with $LiBH_4$ gave *vic*-diol **4.35** that was cleaved by $NaIO_4$. The resulting aldehyde was reduced immediately with $NaBH_4$ to give alcohol **4.36** in good yield (78% over two steps) and good *ee* (90% *ee* determined by HPLC analysis). Finally, hydrogenation of the tetrahydroindolizine **4.36** over Rh on alumina gave (–)-tashiromine **(3.01)** (85%) and 6-*epi*-tashiromine (5%) completing the total synthesis.

Dieter and Watson in 2002,[116] with elaboration in 2005 to disclose an asymmetric synthesis,[149] described the construction of indolizidine cores via the vinylation of a *N*-Boc-2-pyrrolidinylcuprate. The asymmetric deprotonation of *N*-Boc pyrrolidine **(4.40)** and treatment with CuCN.2LiCl afforded the desired cuprate that was exposed to vinyl iodide **4.39** to secure **4.41** in high *er* (95:5) (Scheme 4.06). A cyclisation and hydroboration yielded **(+)-3.01** and **(+)-5-*epi*-3.01** in good yield and enantioselectivity.



Scheme 4.06. *Reagents and conditions*: a) $SOCl_2$, pyr. (cat.); b) TMSCl, NaI, MeCN, H_2O (0.5 eq.); c) i) *s*-BuLi, (–)-sparteine, Et_2O, –78 °C, ii) CuCN.2LiCl, THF, –78 °C, iii) **4.40**; d) TMSCl, MeOH, 12 h, rt; e) i) BH_3.THF, THF, ii) 9-BBN, 60 °C, iii) 10 M NaOH, H_2O_2, 0 °C to rt.

In 2006, Bélanger and co-workers chose to construct the indolizidine core of tashiromine **(3.01)** by a Vilsmeier-Haack type cyclisation.[114] Trapping the *in situ* generated iminium ion by a tethered, internal nucleophile transpired to provide efficient synthesis of (±)-tashiromine **(3.01)** (Scheme 4.07).

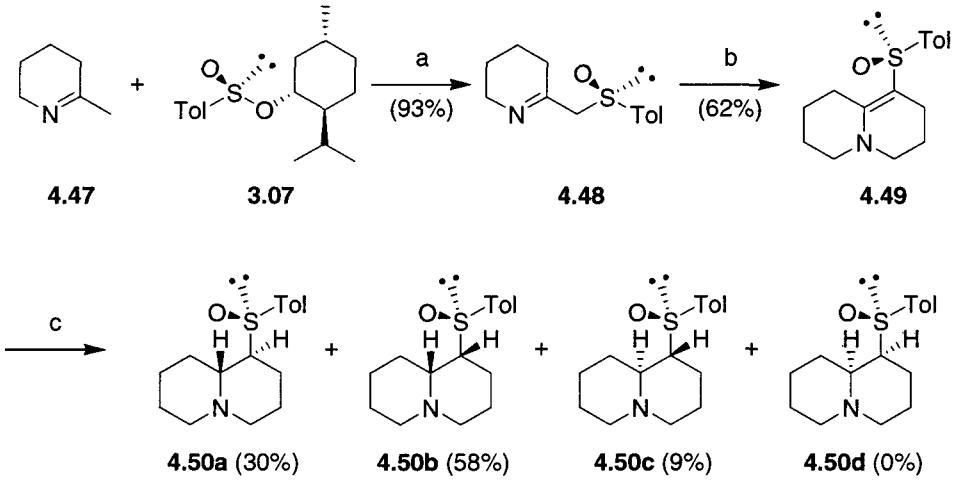


Scheme 4.07. *Reagents and conditions*: a) KH, $I(CH_2)_5OBz$ then KOH, MeOH; b) Swern oxidation then TBSOTf, NEt_3;[150] c) 2,6-di-*tert*-butyl-4-methylpyridine, Tf_2O, CH_2Cl_2, 0 °C; d) H_2 (1000 psi), Pd/C, Na_2CO_3, EtOH.

Conventional Vilsmeier-Haack reaction conditions (*cf* $POCl_3$) to generate the iminium ion did not tolerate the sensitive TBS enol ether moiety present in lactam **4.45**. Tf_2O and base in CH_2Cl_2 were found to facilitate the cyclisation extremely efficiently (95%) at 0 °C in 15 min. The 6-*endo*-cyclisation of silyl enol **4.45** forms the fused indolizidine core of tashiromine (**3.01**). A *syn* hydrogenation of enaminal **4.46** would lead solely to **(±)-5-*epi*-3.01**. It was believed that after reduction of the alkene, epimerisation of the intermediate aldehyde in the presence of Na_2CO_3, to the thermodynamic product, was a faster process than hydrogenation of the aldehyde and hence **(±)-3.01** was formed as the major product. This completed the racemic synthesis of tashiromine in 6 steps (overall yield 26%).

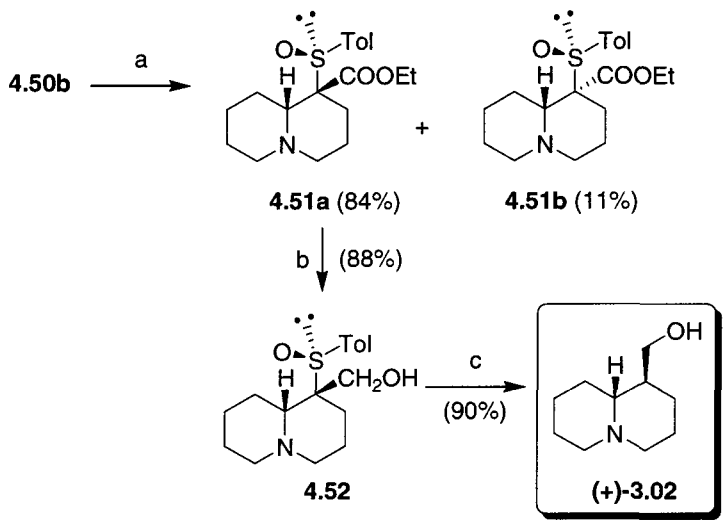
4.1.2.2 Epilupinine

A number of groups have reported the total synthesis of epilupinine (**3.02**). After the disclosure of the first asymmetric synthesis by Nagao *et al.* in 1990,[147] Hua and co-workers published a 6 step, asymmetric synthesis of (+)-epilupinine (**3.02**) in 1991 (Schemes 4.08 and 4.09). Interestingly, it demonstrated the effectiveness of the α-sulfinyl-ketimine anion intermediate in the synthesis of fused bicyclic cores.[111]



Scheme 4.08. *Reagents and conditions*: a) LDA, THF; b) LDA then 1,3-diiodopropane; c) $NaBH_4$, $CeCl_3$, MeOH.

The first key step was the stereocontrolled reduction of enamine **4.49** to quinolizidine **4.50**, accomplished with $CeCl_3/NaBH_4$. Observed was a preference of 10:1 (β:α face) producing *syn* diastereomers **4.50a** and **4.50b** (*er* 1:2). Quinolizidine **4.50b** was carried forward in the synthesis of (+)-epilupinine **(3.02)** after separation by column chromatography (Scheme 4.09).

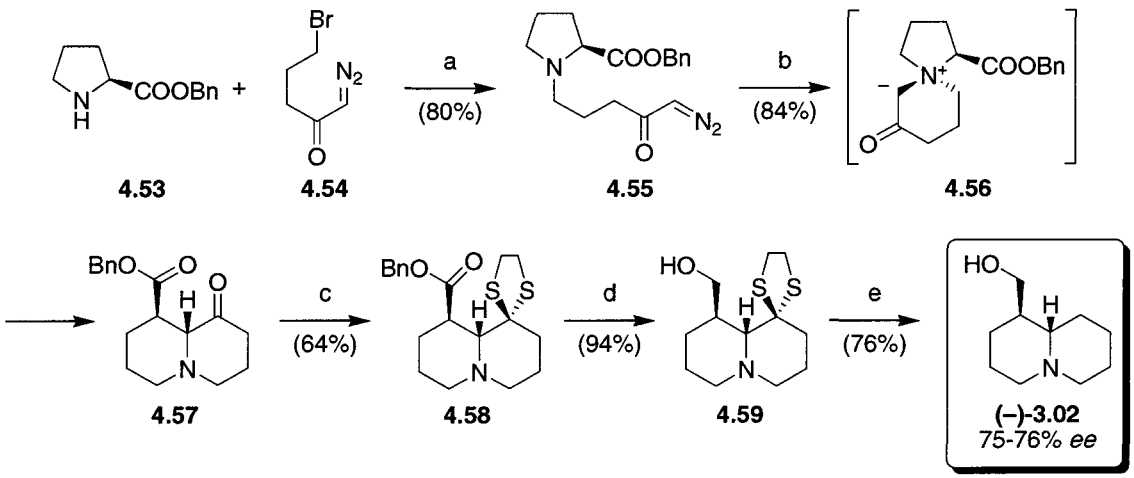


Scheme 4.09. *Reagents and conditions*: a) LDA, ethyl cyanoformate, THF; b) $LiAlH_4$, THF; c) Raney-Ni, EtOH.

Deprotonation α to the sulfinyl auxiliary then treatment with ethyl cyanoformate gave **4.51a** and **4.51b** as a separable mixture of diastereomers (*dr* 8:1). Authors cite preference for ethoxy-cabonylation to occur at the less hindered β-face to account for the observed diastereoselectivity. Finally, reduction of ester **4.51a** to alcohol **4.52** then

desulfurisation over Raney-Ni proceeded smoothly and gave **(+)-3.02** as single diastereomer ($[\alpha]_D$ = +32.0, lit. $[\alpha]_D$ = +31.2) and completed the synthesis in good overall yield (22%). It should be noted that subjecting quinolizidine **4.50a** (Scheme 4.08) to the same procedure led to the synthesis of the epimer of **3.02**, (–)-lupinine.

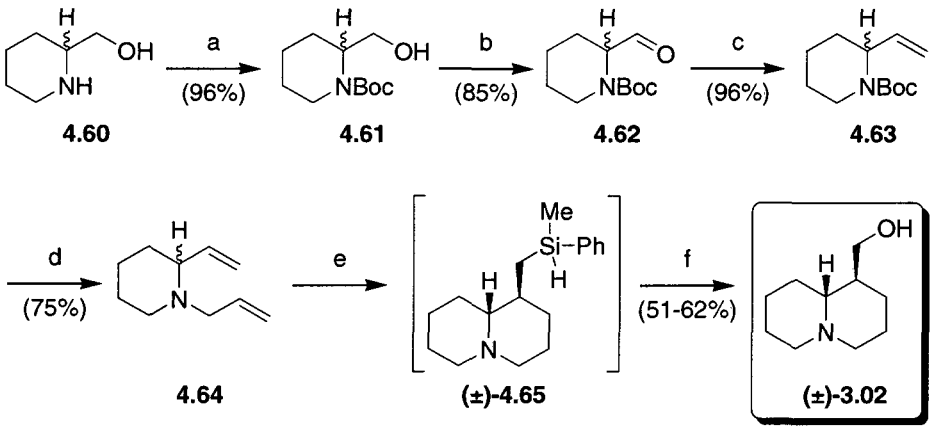
West and co-workers in 1994 developed a ring expansion approach for the synthesis of quinolizidine cores by the migration of a chiral group via a Stevens ammonium ylide [1,2]-shift of **4.56** with predominant retention of configuration.[146,151] L-Proline **(4.53)** was chosen as the chiral building block (Scheme 4.10).



Scheme 4.10. *Reagents and conditions*: a) NEt_3, EtOAc, Δ; b) Cu(acac) (15 mol%), toluene, Δ; c) $HSCH_2CH_2SH$, $BF_3.OEt_2$; d) $LiAlH_4$, THF, rt; e) Na, N_2H_4, ethylene glycol, 190 °C.

The key carbene insertion step was found to proceed with greater yield and diastereoselectivity (*dr* 19:1) when Cu(acac) was used in place of $Rh_2(OAc)_2$ for the generation of the benzyl ester **4.55** carbene. The key carbenoid/ylide/[1,2]-shift in bicyclic intermediate **4.56** then gave quinolizidine **4.57** in good yield (84%), high diastereoselectivty and moderate enantioselectivity (65-75% *ee*) (*cf* yield 76%, 40-55% *ee* mediated by Rh). Protection of the ketone as dithiane **4.58**, reduction of the benzyl ester to 1° alcohol **4.59** followed by desulfurisation completed the 5 step synthesis of (–)-epilupinine **(3.02)** in a superior overall yield (30%).

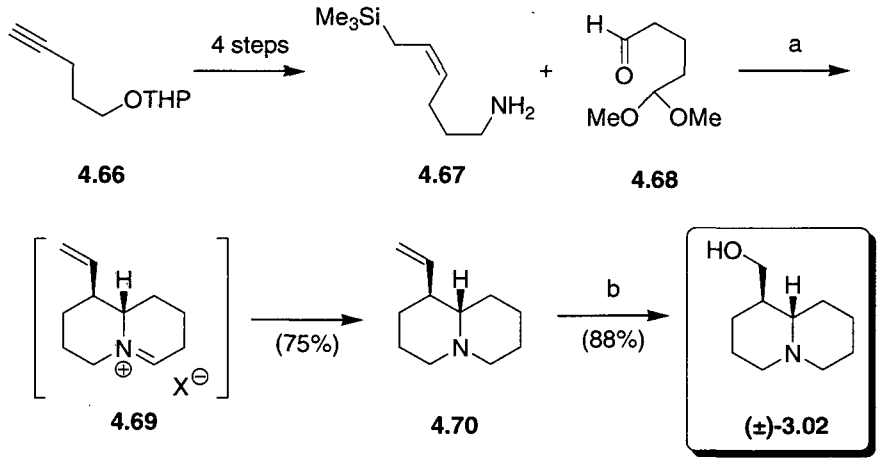
Molander *et al.*, in 1997, were interested in the construction of the quinolizidine core of epilupinine **(3.02)** through a selective organoyttrium-catalysed cyclisation/silylation of a heterocyclic diene **4.64** (Scheme 4.11).[110]



Scheme 4.11. *Reagents and conditions*: a) Boc_2O, NEt_3; b) pyr.SO_3, NEt_3; c) *t*-BuOK, Ph_3PMeBr; d) i) TFA, CH_2Cl_2, ii) allyl bromide, K_2CO_3; e) 5% $Cp^*_2YCH_3$.THF, $MePhSiH_2$, cyclohexane; f) *t*-BuOOH, KH, DMF, CsF.

As a potential pathway to pharmacologically active alkaloids the synthesis of diene **4.64** was undertaken to probe the tolerance of the highly Lewis acidic metal hydride catalyst, 'Cp^*_2YH', in the presence of Lewis basic nitrogen. The catalyst, formed *in situ* from $Cp^*_2YCH_3$.THF, preferentially attacked the less hindered double bond present in diene **4.64**. The high diastereoselectivity is due to the large steric bulk of the two Cp* rings. Oxidation of silane **4.65** proved challenging after acidic oxidative techniques resulted in complete decomposition of material. Fortunately, non-acidic conditions developed by Woerpel and Smitrovich (*t*-BuOOH, KH, DMF)[152] afforded **(±)-3.02** selectively in varying yield (51-62%) with no evidence of the epimer, lupine.

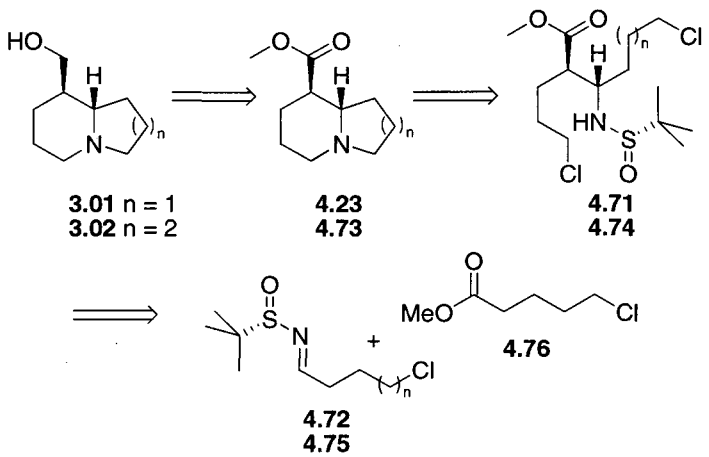
In 2005, Amorde *et al.* developed an extremely concise and novel cascade reaction to form the quinolizidine core of racemic epilupinine (**3.02**) from simple acyclic precursors **4.67** and **4.68** (Scheme 4.12).[124] Condensation of amine **4.67** and mono-protected aldehyde **4.68** led to formation of bicyclic imine **4.69**. Without isolation, **4.69** was treated with Et_3SiH resulting in the reduction of the imine to give the known intermediate **4.70**[153] as a single diastereomer. The reader's attention is directed towards the exclusive *trans* relationship of hydrogen atoms across the newly formed C5-C6 bond in **4.69** produced with this approach. Ozonolysis of the terminal bond incorporating a reductive work-up gave racemic epilupinine (**3.02**) in 6 steps.



Scheme 4.12. *Reagents and conditions*: a) i) MeCN, 4 Å MS then TFA, ii) Et_3SiH; b) TFA, Et_2O, O_3 then $LiAlH_4$.

4.1.3 The Brown group approach to tashiromine and epilupinine

Our retrosynthetic analysis is applicable to both the synthesis of tashiromine and epilupinine. The key step in our proposed concise asymmetric synthesis is the use of an imino-aldol reaction to concomitantly install both stereogenic centres in the β- amino acid intermediates **4.23** and **4.73** (Scheme 4.13).



Scheme 4.13. Our retrosynthetic analysis of (–)-tashiromine (n = 1) and (–)-epilupinine (n = 2).

Our approach is based on the diastereoselective alkylation of chiral sulfinyl imines **4.72** and **4.75** (derived from the Ellman auxiliary (**3.10**)) by an achiral Ti (IV) enolate of ester **4.76**. Stereocontrol will be derived from the chiral auxiliary. A double annulation

of deprotected β-amino acids **4.71** and **4.74** will give indolizidine **4.23** and quinolizidine **4.73** followed by a reduction step will complete our proposed syntheses.

4.2 (+)-Leontine

4.2.1 Background

(+)-Leontine (**3.03**) is a member in a family of naturally occurring alkaloids based on the same tetracyclic-quinolidizine core with matrine (**4.77**) as the parent member (Figure 4.02). There are over 10 *matrine*-type alkaloids that are related by virtue of possessing different relative stereochemistry at ring junctions (**4.77**); possessing additional double bonds (**4.78**) and/or additional hydroxyl groups (**4.79**).[154]

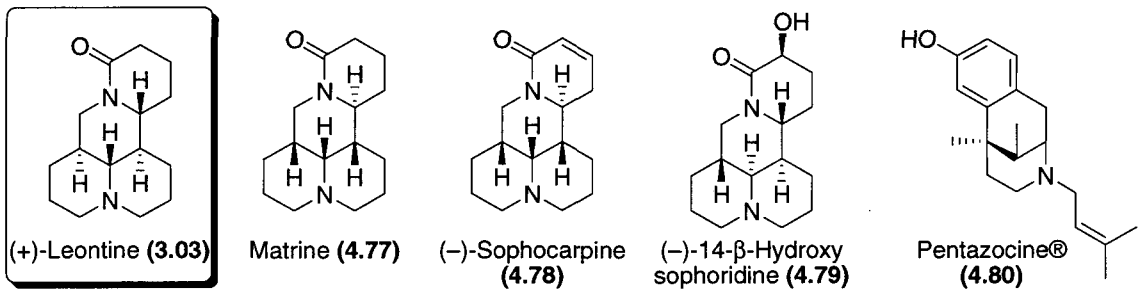


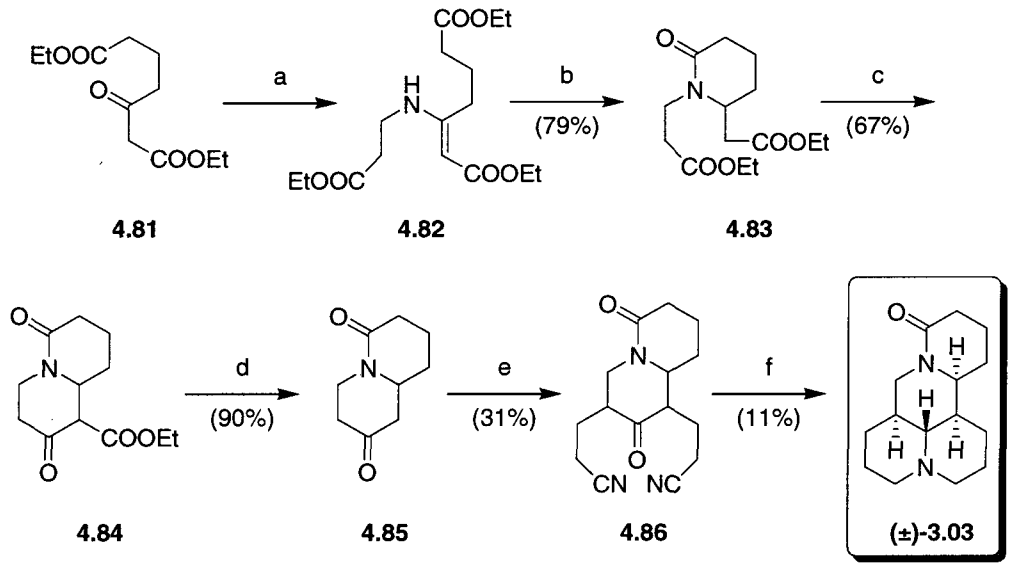
Figure 4.02. Members of the *Matrine* family of alkaloids and the opiod analgesic, Pentazocine ®.

Leontine is isolable from the roots of the plant *Leontice eversmanni Bge.*,[155] of the genus *Sophora*.[156] Plants of this genus are core components of traditional Chinese medicines, such as 'Ku-shen' and 'Shan-dou-gen'.[157] The main applications are in the treatment of cancers, viral hepatitis, cardiac diseases, and skin diseases (such as eczema and dermatitis).[157,154,73]

Leontine selectively produces an inhibitory effect on the κ-opioid receptors in the body giving rise to an antinociceptive effect.[158] κ-Opioid receptors mediate the potent analgesic and addictive actions of κ-opioid drugs and also regulate responses to pain and stress.[159] Matrine (**4.77**) exhibits the highest efficacy of any member, identical to that of the marketed opioid analgesic, Pentazocine® (**4.80**), and produces an inhibitory effect through the κ- and δ-opiod receptors.[154] This class of alkaloids is also of biological interest because the tetracyclic structure is significantly different from the pharmacophore of conventional κ-opioid receptor agonists and might serve as a more selective drug, not producing undesirable, morphine-like side effects.[158]

4.2.2 Previous synthesis of (±)-leontine

Owing to the complex structural nature of all matrine-type alkaloids, there are a limited number of total syntheses for two of the alkaloids in the family, all racemic. The only published synthesis of leontine **(3.03)** was described by Mandell *et al.* in 1965.[155] This early synthesis, although concise, was indiscriminate in producing the stereochemical centres present in the molecule (Scheme 4.14).



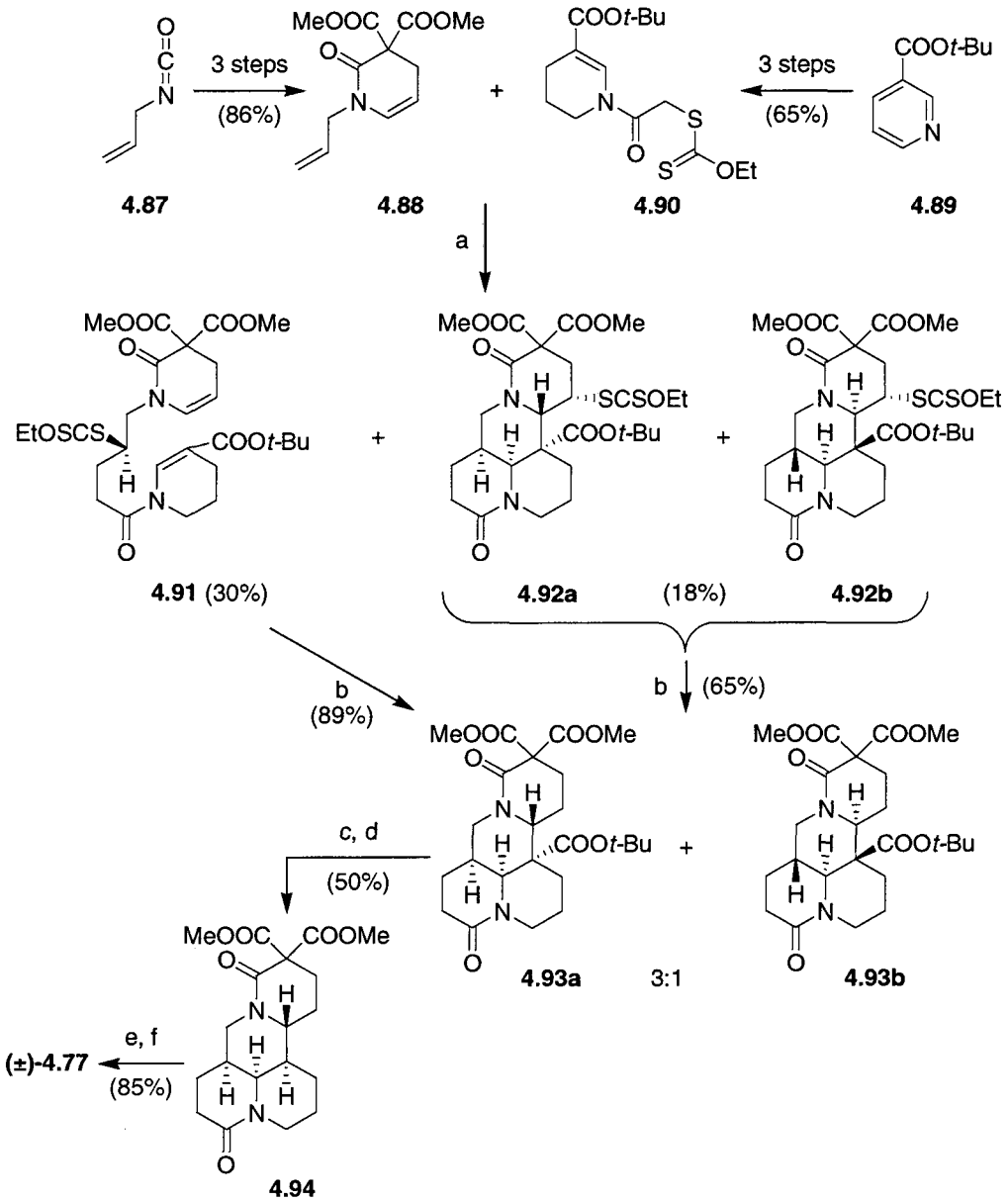
Scheme 4.14. *Reagents and conditions*: a) Ethyl β-alaninate; b) Pt-H_2, Δ; c) NaH, benzene, Δ; d) glacial acetic acid; e) Acrylonitrile, Δ; f) 10% Pd/C.

Diethoxy-3-oxopimelate **(4.81)** was condensed with ethyl β-alaninate to give enamine **4.82** which was subjected to a hydrogenation over Adam's catalyst affording piperidinone **4.83**. Dieckmann cyclisation of **4.83** gave substituted quinolizidinone **4.84** followed by hydrolysis and decarboxylation afforded oxo-quinolizidinone **4.85** in good yield (60% over 3 steps). Next, a bis-α,α'-alkylation with acrylnitrile via a Stork enamine procedure and hydrogenation gave racemic leontine **(3.03)** in a poor conversion (3%). Structural identification of the final compound was only established by comparison of IR and melting point data with authentic material.

4.2.3 Related synthesis of (±)-matrine

Matrine **(4.77)** is the principle alkaloid found in *Sophora flavenscens* Ait. and is claimed to posses antiulcerogenic and anticancer activity, but data is scarce.[160] The challenge to synthesise matrine has only been achieved four times previously in racemic form.[155,160-

[162] The most recent strategy, reported in 1998, involved the radical cascade cyclisation of xanthate **4.90** to install the tetracyclic core (Scheme 4.15).



Scheme 4.15. *Reagents and conditions*: a) lauroyl peroxide, benzene; b) lauroyl peroxide, IPA, Δ; c) TFA, CH_2Cl_2; d) $(COCl)_2$, CH_2Cl_2, *N*-hydroxy-4-methylthiazolinethione, NEt_3, *tert*-dodecanethiol, cyclohexane, cat. AIBN; e) $BH_3.Me_2S$, THF; f) 2 M HCl, Δ.

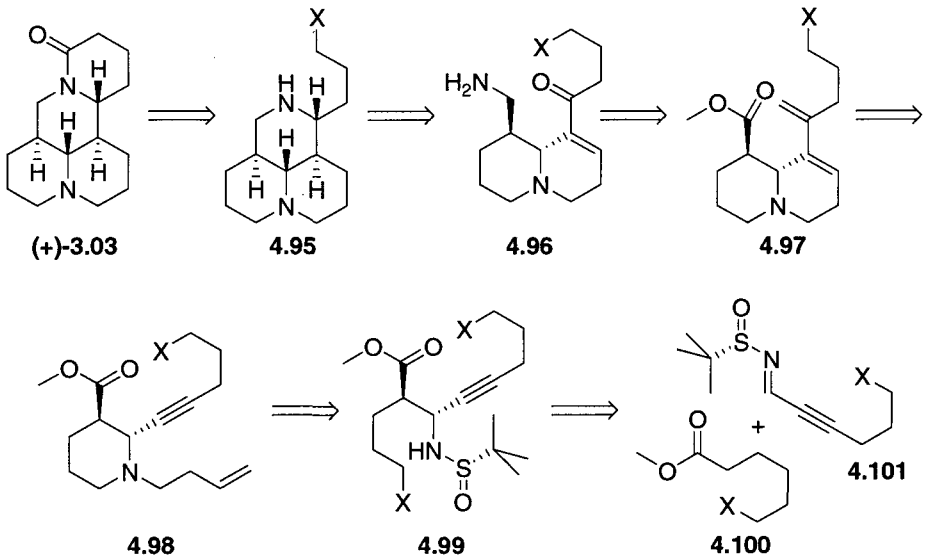
The peroxide initiated radical cyclisation of precursors **4.88** and **4.90** gave a mixture of 3 products, acyclic **4.91** (30%) and tetracyclic structures **4.92a** and **4.92b** in low yield (18%). Reductive cleavage of the xanthate moiety, via a radical pathway, in all three components lead to a separable mixture of two tetracyclic compounds **4.93a** and **4.93b**

in a ratio of 3:1. Compound **4.93a** possesses the relative stereochemistry found in matrine and, interestingly, **4.93b** has the same relative stereochemistry found in leontine. Next, chemo-selective cleavage of the *tert*-butyl ester present in **4.93a** to the free acid in the presence of the geminal methoxy esters was accomplished with TFA in CH_2Cl_2 in high yield (90%). Subsequently, the reductive cleavage of the free acid gave **4.94**. The final two step process selectively reduced the quinolidinic lactam with borane, in the presence of the lactam flanked by the geminal methoxy esters. Hydrolysis and decarboxylation of these geminal diesters in dilute HCl finalised the racemic synthesis in 9 steps and good overall yield (8%). This radical approach forms 4 C-C bonds and 5 contiguous stereocentres in one step, but, unfortunately is restricted due to the low yield coupled with the modest selectivity exhibited. Use of a chiral amine intermediate gives this route the potential to yield matrine **(4.77)** in an asymmetric fashion.

4.2.4 The Brown group approach to leontine

Our proposed retrosynthetic analysis is built around the application of an asymmetric imino-aldol reaction; enyne RCM and a stereoselective reduction to produce the first asymmetric synthesis of a *matrine*-type alkaloid (Scheme 4.16).

The main synthetic challenge in the synthesis of all *matrine*-type alkaloids lies with the stereospecific assembly of the four contiguous stereocentres. We envisaged the use of an imino-aldol type reaction to give β-amino acid ester **4.99** and subsequently lead to piperidine **4.98** with the desired stereochemical configuration across the C5-C6 bond. Enyne RCM will establish the quinolizidine core unit **4.97** incorporating a diene moiety requisite for elaborations to secure the final two heterocyclic rings. The intramolecular cyclisation of 1,5-ketoamine **4.96**, via amine condensation then selective reduction of the resulting enamine, will introduce the remaining two stereocentres. A one carbon homologation of the aliphatic chain in tricyclic intermediate **4.95** accompanied by a hydrolysis and intramolecular amide coupling will complete our proposed synthesis of leontine **(3.03)**.

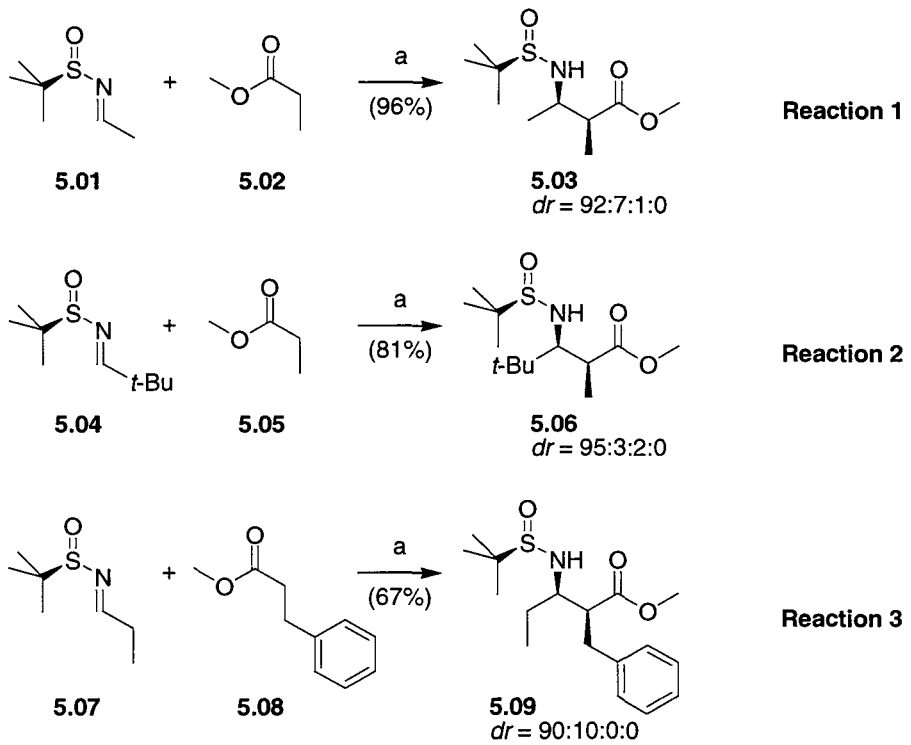


Scheme 4.16. Our retrosynthetic analysis of (+)-leontine, where X = leaving group.

Chapter 5 Investigatory work into the imino-aldol reaction

5.1 Background

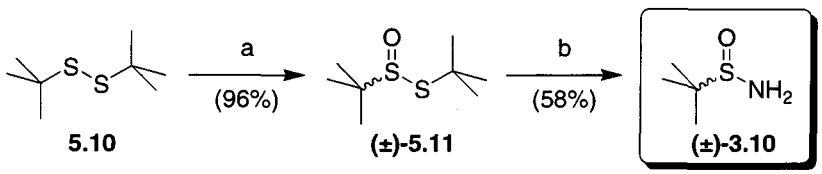
Ahead of commencing our syntheses of tashiromine (**3.01**), epilupinine (**3.02**) and leontine (**3.03**) we studied the pivotal imino-aldol reaction with a model reaction reported by Ellman *et al.*, which gave excellent diastereoselectivity (*dr* = 96:4:0:0).[75] Ellman and co-workers were first to report successful conditions to produce α.β substituted β-amino acids with high diastereoselective control by the imino-aldol reaction (using the TBSA chiral auxiliary) (scheme 5.01). To determine the absolute stereochemistry of the diastereomeric products Ellman *et al.* compared the optical rotation of the *N*-Benzoyl methyl ester derivative of **5.03** and the *N*-Boc methyl ester derivative of **5.06** with literature values and obtained a crystal structure of the major diastereomer of **5.09**. The configuration of all other derivatives obtained from the imino-aldol reaction was assigned by analogy. Initially we assigned the diastereoselective outcome of our imino-aldol adducts with Ellman's studies as precendent. However, this assumption may not hold true for all examples after we obtained conflicting results, which are detailed over the following two chapters.



Scheme 5.01. *Reagents and conditions:* a) $TiCl(O\textit{i}\text{-}Pr)_3$ (4.0 eq.), LDA, THF, –78 °C.[75]

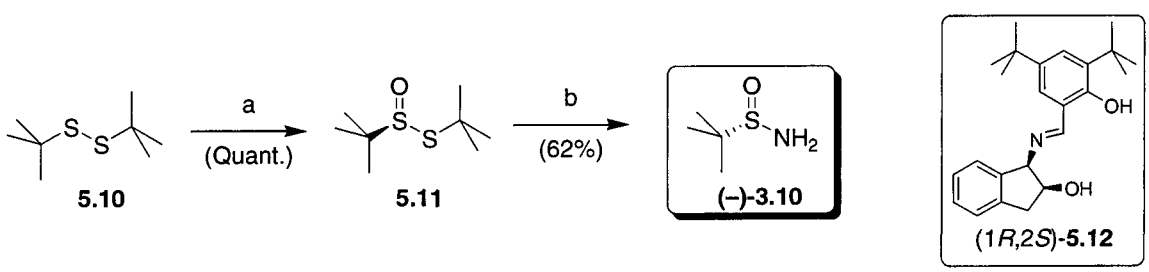
5.2 Synthesis of the *tert*-butyl sulfinyl amine chiral auxiliary

Our investigations into the imino-aldol reaction initially focussed on the use of racemic sulfinyl imines due to the ease of synthesis of racemic TBSA (**3.10**) (Scheme 5.02). The oxidation of di-*tert*-butyl sulphide (**5.10**) to thiosulfinate (±)-**5.11** with H_2O_2[163] and subsequent treatment of the crude mixture with $LiNH_2/NH_3$ afforded the desired sulfinyl amine (±)-**3.10** in 2 steps and good overall yield (56%).



Scheme 5.02. *Reagents and conditions*: a) H_2O_2, AcOH, 0 °C; b) $LiNH_2/NH_3$, THF, –78 °C.

During the course of our studies an elegant asymmetric version of this strategy was published by Weix *et al.*[164] Accordingly, the stereoselective oxidation was achieved by the slow addition of H_2O_2 (20 h) to a cooled solution of $VO(acac)_2$, chiral ligand (1*R*,2*S*)-**5.12** and commercially available di-*tert*-butyl disulphide (**5.10**). Thiosulfinate **5.11** was isolated as a crude mixture and treated with $LiNH_2/NH_3$ to produce enantiomerically pure (S_S)-TBSA (**3.10**) in good yield (62%) after a single recrystallisation (hexanes) on a multi-gram scale (Scheme 5.03).

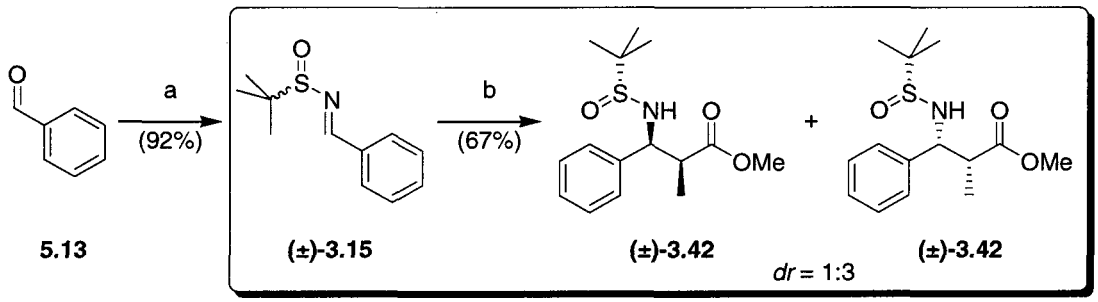


Scheme 5.03. *Reagents and conditions*: a) $VO(acac)_2$ (5.0 mol%), **5.12** (5.1 mol%), acetone, H_2O_2 over 20 h, 0 °C; b) i) $LiNH_2/NH_3$, THF, –78 °C, ii) recrystallisation.

5.3 Determining the diastereoselective outcome of the imino-aldol reaction.

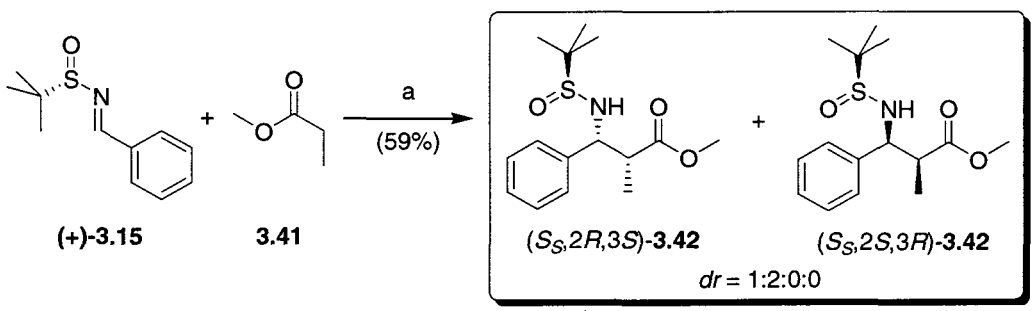
Our preliminary imino-aldol studies met with some unexpected results. Inexplicably, the high level of selectivity was not reproduced in our hands under the conditions reported by Ellman *et al.* (Scheme 5.04). The reportedly highly stereoselective alkylation of sulfinyl imine (±)-**3.42** with the titanium enolate of methyl propionate (4.0

eq.)[†] gave, reproducibly a 1:3 mixture of diastereomeric products (determined by ^{1}H NMR analysis of crude mixture). The reason for lack of selectivity was not understood, and furthermore when the Lewis acid was obtained from commercial supplier (Sigma-Aldrich) or prepared by us,[165] the results were the same.



Scheme 5.04. *Reagents and conditions*: a) (±)-TBSA, $CuSO_4$, CH_2Cl_2, Δ; b) TiCl(O*i*-Pr)$_3$ (4.0 eq.), LDA, methyl propionate, THF, –78 °C.

We then examined the same alkylation with enantiomerically pure sulfinyl imine **(+)-3.15** (Scheme 5.05). Reassuringly, this gave a similar diastereoselective result in comparison to our racemic series, again in contradiction with the literature data. Sulfinyl amine **3.42** was synthesised in good yield (59%) but with low diastereoselectivity (1:2:0:0, determined from isolated yields).



Scheme 5.05. *Reagents and conditions*: a) TiCl(O*i*-Pr)$_3$ (4.0 eq.), LDA, THF, –78 °C.

Surprisingly it was determined that the major diastereomeric product obtained in our reaction did not correspond to the one obtained by Ellman. The minor diastereomer synthesised in our hands gave spectroscopic data which corresponded to that for the major diastereomeric product reported by Ellman *et al.*[75] Cited key resonances in the

[†] It is noteworthy to add that, Ellman and co-workers[75] state the use of 2.0 eq. of Lewis acid in their discussions but report the use of 4.0 eq. of Lewis acid in the experimental section. We chose to use 4.0 eq. of Lewis acid in our study. We later observe that the stoichiometry of Lewis acid is important.

^{13}C NMR spectrum at 46.1 (**C**$OOCH_3$), 55.8 (**C**HN) and 59.8 (**C**$(CH_3)_3$) ppm for their major diastereomer more closely corresponded to our minor diastereomer (46.4, 56.2 and 60.2 ppm) compared to our major diastereomer (46.4, 56.8 and 62.1 ppm). This assignment was supported by ^1H NMR data: the literature diastereomeric product, (R_S,2*S*,3*R*)-**3.42**, exhibited a resonance at 4.47 (1H, d, J = 3.5 Hz, N**H**) ppm for the sulfinyl amine proton. This data more closely correlated to our isolated minor diastereomer (4.41-4.40 (1H, m, N**H**) ppm) not our isolated major diastereomer (3.78 (1H, br d, J = 7.5 Hz, N**H**) ppm). Both the chemical shift and coupling constants for our major diastereomer are significantly different from the published *syn* diastereomer.[75] Removal of the chiral auxiliary from our major and minor diastereomers gave enantiomeric compounds revealing that our imino-aldol products were *syn* diastereomers (determined by ^1H NMR data analysis). We therefore assigned the stereochemistry of our major imino-aldol adduct as (S_S,2*S*,3*R*)-**3.42** and the minor as (S_S,2*R*,3*S*)-**3.42**, based on this body of evidence (Figure 5.01). Our major *syn* diastereomer, (S_S,2*S*,3*R*)-**3.42**, opposite to the *syn* diastereomer predicted by the model put forward by Ellman *et al.* would be favoured through a non-chelation controlled six-coordinate closed transition state **TS-5.02** (Figure 5.01).

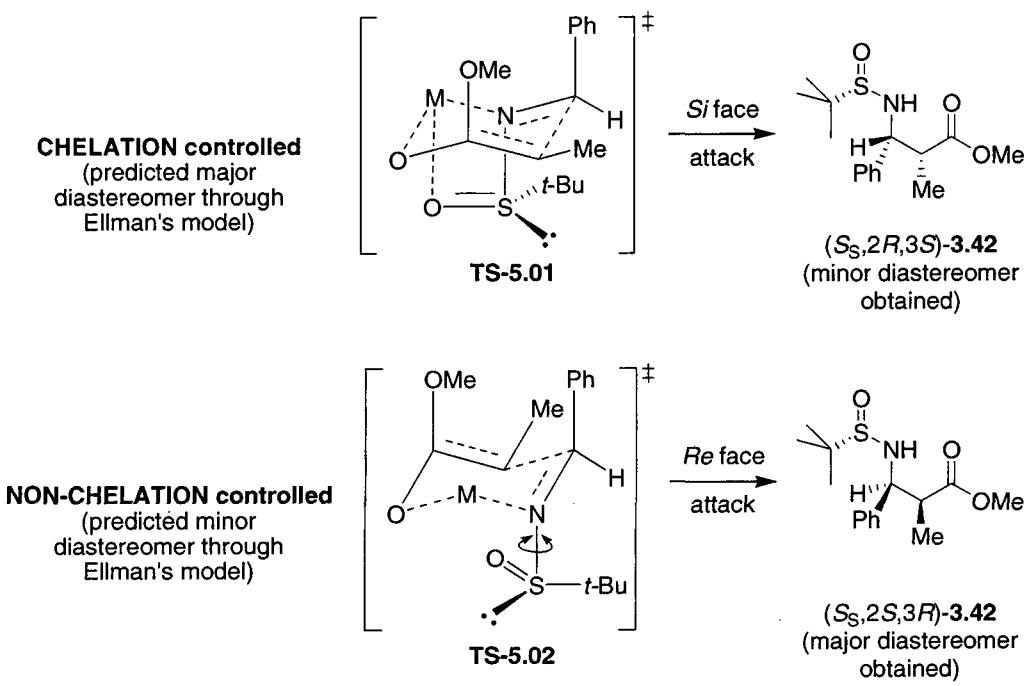
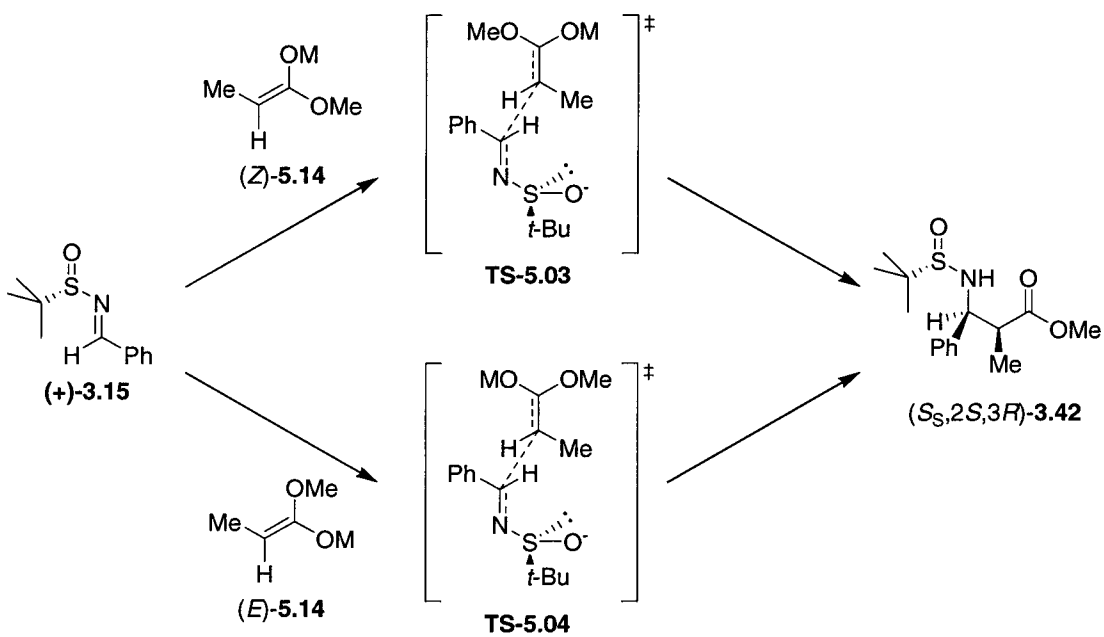


Figure 5.01. Possible chelation controlled and non-chelation controlled TS.

Lack of coordination of the sulfinyl oxygen to the metal centre in the transition state would allow limited rotation around the N-S bond and could promote the opposite facial selectivity by addition to the *Re*-face of the imine.

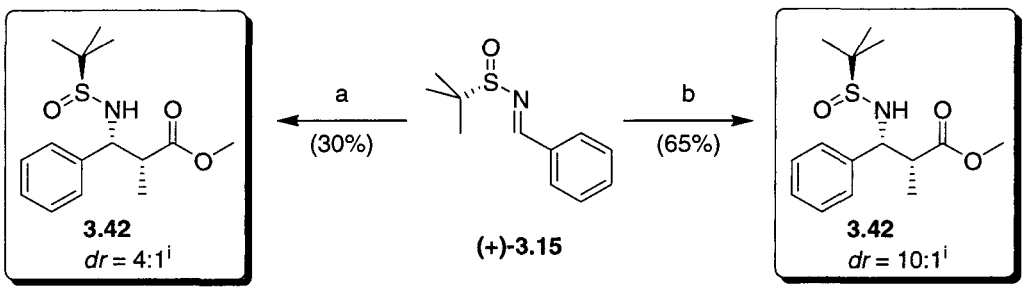
An acyclic transition state could also lead to the formation of our major *syn* diastereomer, (S_S,2*S*,3*R*)-**3.42** from either the *cis* (*Z*) or *trans* (*E*) enolate of methyl propionate **(3.41)** (Scheme 5.06). Facial selectivity would be controlled by the bulky *t*-Bu group of the chiral auxiliary blocking the *Si*-face to attack. However, acyclic transition state **TS-5.03** is less probable transition state as formation of *cis* enolate (Z)-**5.14** would be unlikely as the amide deprotonation (LDA) of ester **3.41** is well documented[104,105] and is reported to exhibit a strong preference for the *trans* (*E*) enolate (95:5, *E*/*Z*). Therefore, acyclic transition state **TS-5.04** would appear a more reasonable pathway to lead to the formation of diastereomeric product (S_S,2*S*,3*R*)-**3.42**. At this point, a full explanation for the lack of agreement with published results could not be elucidated.



Scheme 5.06. Possible acyclic transition states for the reaction of sulfinyl imine **3.15** and ester **3.41**.

Speculatively, we hypothesised these anomalies were due to the composition of the Lewis acid ($TiCl(O\textit{i}\text{-}Pr)_3$). Reportedly stable as a stock solution under inert conditions for long periods of time,[165] the decomposition of this hydroscopic, air and moisture sensitive metal complex was not thought to be an issue. We wanted to observe the diastereoselective outcome of the imino-aldol reaction when the composition of Lewis

acid was modified from what we assumed to be TiCl(O-*i*Pr)$_3$. We chose to dope the Lewis acid separately with either 0.1 eq. of $TiCl_4$ or Ti(O*i*-Pr)$_4$ (with respect to the stoichiometry of TiCl(O*i*-Pr)$_3$). TiCl(O*i*-Pr)$_3$ can be prepared from the disproportionation reaction of Ti(O*i*-Pr)$_4$ and $TiCl_4$ hence, these appeared reasonable additives to commence investigations (Scheme 5.07).



Scheme 5.07. *Reagents and conditions*: a) TiCl(O*i*-Pr)$_3$/Ti(O*i*-Pr)$_4$ (10:1, 4.0 eq.), methyl propionate, LDA, THF, –78 °C; b) TiCl(O*i*-Pr)$_3$/$TiCl_4$ (10:1, 4.0 eq.), methyl propionate, LDA, THF, –78 °C.

Gratifying, pre-treatment of the Lewis acid with either additive prior to the addition in the imino-aldol reaction resulted in a dramatic effect on the outcome of the reaction. The same sense of diastereoselectivty as reported by Ellman *et al.*[75] was produced to varying degree dependent on the additive (determined by ^{1}H NMR and ^{13}C NMR data analysis of the isolated diastereomers). The highest selectivity for the transformation to sulfinyl amine **3.42** was recorded (10:1, based on isolated yield) in good yield (65%) when the Lewis acid was pre-doped with $TiCl_4$. The addition of Ti(O*i*-Pr)$_4$ also had the desired effect, although to a lesser degree (4:1, based on isolated yield) with the yield for the conversion also lower (30%). Again, the stereochemistry of both diastereomeric products was determined from direct extrapolation of NMR data (^{1}H and ^{13}C) published by Ellman *et al.*[75] With regard to the diastereomeric imino-aldol products obtained by the addition of $TiCl_4$, key resonances in the ^{1}H NMR spectrum for our major diastereomer (*S*$_S$,2*R*,3*S*)-**3.42** closely correlated with reported literature data. Observed: 4.69 (1H, appt. t, C**H**NH) *cf* 4.69 (1H, m, C**H**NH); 4.45 (1H, br d, *J* = 3.7 Hz, N**H**) *cf* 4.47 (1H, d, *J* = 3.5 Hz, N**H**) and 1.18 (3H, d, *J* = 7.0 Hz, C**H**$_3$) *cf* 1.16 (3H, d, *J* = 7.2 Hz, C**H**$_3$) ppm. Our minor diastereomer exhibited poor correlation to the reported

[i] The diastereomeric ratio is of both *syn* diastereomers. The samples of the minor diastereomeric *syn* product were also observed to contain trace amounts of what we thought to be other diastereomeric products.

major diastereomeric product in both chemical shift and coupling constants in these selected peaks: 4.75 (1H, dd, J = 7.9, 6.1 Hz, **CH**NH); 3.99 (1H, d, J = 7.9 Hz, N**H**) and 1.19 (3H, d, J = 2.9 Hz, **CH$_3$**) ppm. This study has shown that composition of the Lewis acid is vital to the diastereoselective outcome of the reaction. Our Lewis acid must differ significantly from the stated literature Lewis acid (TiCl(O-*i*Pr)$_3$), yet puzzlingly, these modifications were essential to restore the same sense of diastereoselectivity reported by Ellman *et al.*[75] for this example imino-aldol reaction. The stereochemistry of all more complex diastereomeric products obtained from all subsequent imino-aldol reactions was tentatively assigned on the basis of our results from this study of a model system.

5.4 Application of acetylenic sulfinyl imines in the imino-aldol reaction

As outlined in our retrosynthetic analysis of (+)-leontine we required the use of an acetylenic sulfinyl imine in the imino-aldol reaction. The focus of the following study was to find an acetylenic sulfinyl imine and ester enolate to couple together in a synthetically useful diastereoselectivty to give an intermediate in our asymmetric synthesis of leontine. Utilising acetylenic sulfinyl imines in this way has not been documented in the literature and, as a consequence, a range of imines were synthesised with differing substituents attached to the alkyne in order to study the effect on the diastereoselectivity in the imino-aldol reaction (Figure 5.02).

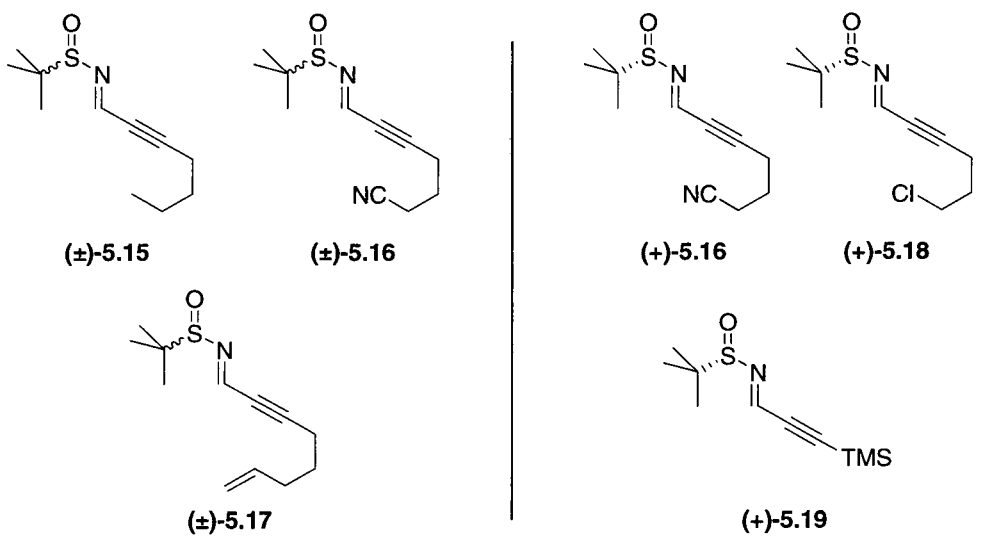
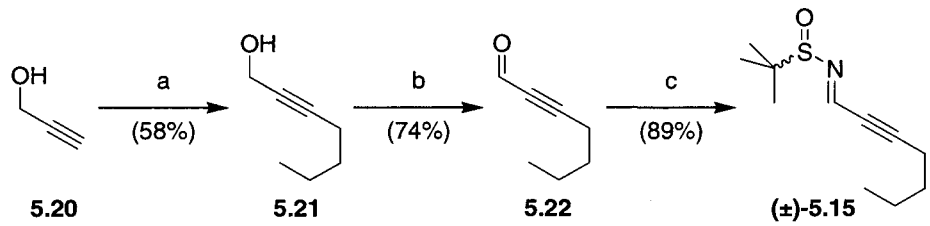


Figure 5.02. Sulfinyl imines under investigation in the imino-aldol reaction.

5.4.1 Synthesis of sulfinyl imines

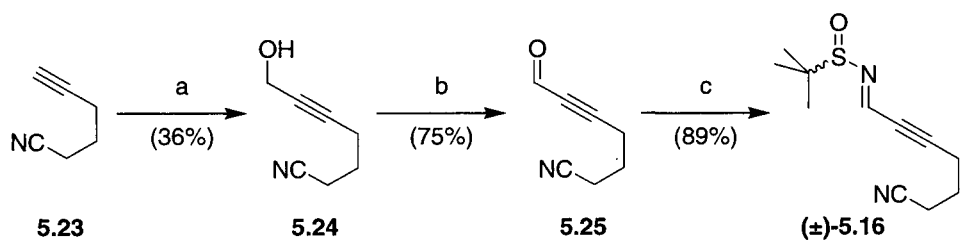
Sulfinyl imine **(±)-5.15** was synthesised in 3 steps (Scheme 5.08). The mono-alkylation of commercially available propargyl alcohol **(5.20)** with 1-bromobutane yielded propargylic alcohol **5.20**. Oxidation of alcohol **5.21** to propargylic aldehyde **5.22** was achieved with $BaMnO_4$ in good yield (74%). Next, the $CuSO_4$ mediated condensation of aldehyde **5.22** with (±)-TBSA yielded the desired sulfinyl imine **(±)-5.15** in excellent yield (89%).



5.20 **5.21** **5.22** **(±)-5.15**

Scheme 5.08. *Reagents and conditions*: a) *n*-BuLi then DMPU, 1-bromobutane; b) $BaMnO_4$, CH_2Cl_2; c) (±)-TBSA, $CuSO_4$, CH_2Cl_2, Δ.

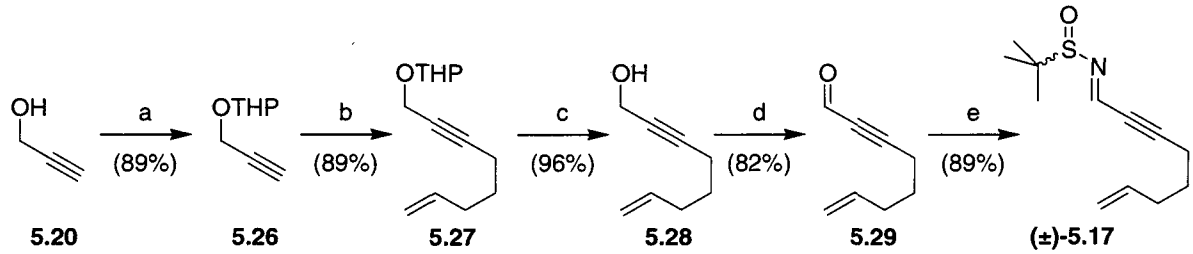
Synthesis of sulfinyl imine **(±)-5.16** commenced with the alkylation of commercially available 5-cyanohex-1-yne **(5.23)** to afford alcohol **5.24**, followed by a MnO_2 oxidation to propargylic aldehyde **5.25**. Finally, condensation of aldehyde **5.25** with racemic TBSA gave the desired sulfinyl imine **(±)-5.16** in overall yield of 24% over 3 steps (Scheme 5.09).



5.23 **5.24** **5.25** **(±)-5.16**

Scheme 5.09. *Reagents and conditions*: a) *n*-BuLi, THF, $(CH_2O)_n$, –78 °C; b) MnO_2, CH_2Cl_2; c) (±)-TBSA, $CuSO_4$, CH_2Cl_2, Δ.

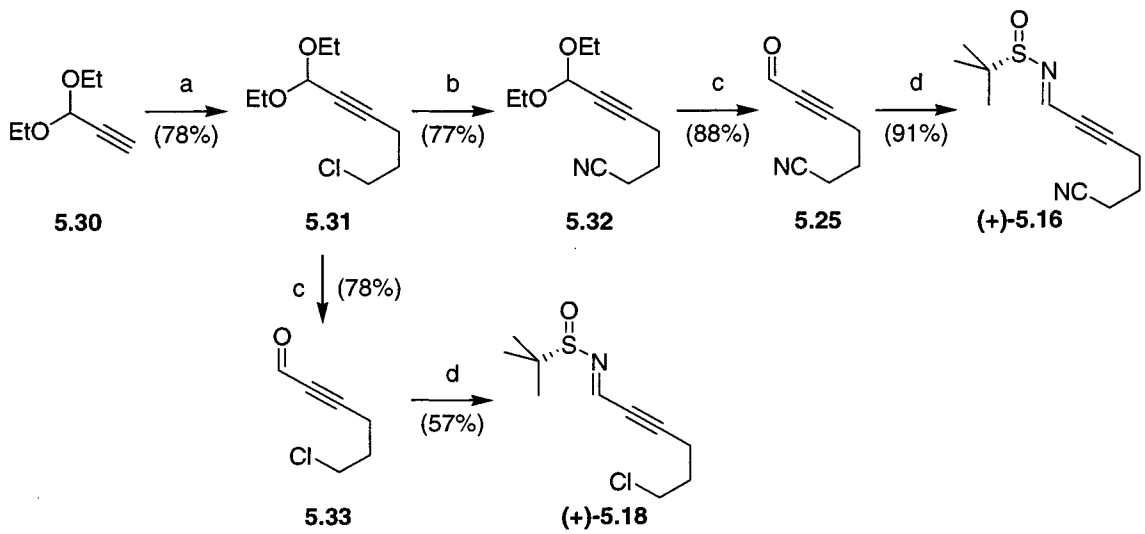
A five step process was required for the synthesis of sulfinyl imine **(±)-5.17** (Scheme 5.10). Thus, commercially available propargylic alcohol **(5.20)** was protected as the THP ether **5.26** before alkylation with 5-bromo-pent-1-ene could proceed. Acid deprotection to alcohol **5.28** then oxidation with Dess-Martin periodinane reagent yielded aldehyde **5.29**. Finally, condensation with (±)-TBSA gave the desired sulfinyl imine **(±)-5.17** in good overall yield (55%).



5.20 **5.26** **5.27** **5.28** **5.29** **(±)-5.17**

Scheme 5.10. *Reagents and conditions*: a) DHP, sulfamic acid; b) *n*-BuLi, THF, HMPA, 5-bromo-pent-1-ene; c) *p*-TsOH, $MeOH/H_2O$; d) Dess-Martin periodinane, Et_2O; e) (±)-TBSA, $CuSO_4$, CH_2Cl_2, Δ.

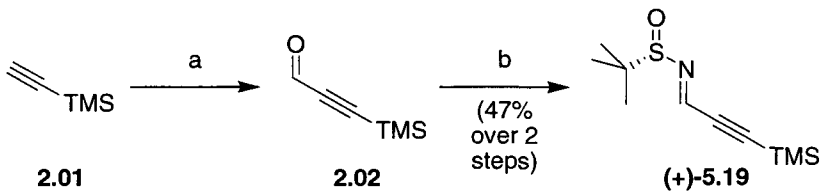
To avoid the low yielding and problematic alkylation of 5-cyanohex-1-yne (**5.23**) in the racemic synthesis of sulfinyl imine **5.16** (Scheme 5.09) we chose an alternative route for the synthesis of optically pure **5.16** (Scheme 5.11). Alkylation of diethoxy propyne (**5.30**) gave substituted alkyne **5.31** that was obtained in good yield. Next, treatment with NaCN displaced the chloride and gave nitrile **5.32**. Acid deprotection unmasked aldehyde **5.25** and subsequent condensation with (S_S)-TBSA yielded sulfinyl imine **(+)-5.16** and completed this new route in 1 additional step but twice the previous overall yield (4 steps, overall yield 49%). Serendipitously, this route also provided access to the chloro-substituted sulfinyl imine **(+)-5.18**. Acetal deprotection of intermediate chloride **5.31** and condensation with (S_S)-TBSA yielded the chloro analogue, sulfinyl imine **(+)-5.18**, in a modest yield of 35% over 3 steps.



5.30 **5.31** **5.32** **5.25** **(+)-5.16** **5.33** **(+)-5.18**

Scheme 5.11. *Reagents and conditions*: a) *n*-BuLi, HMPA, 1-bromo-3-chloropropane; b) NaCN, DMF, Δ; c) Amberlyst 15, acetone/H_2O; d) (S_s)-TBSA, $CuSO_4$, Δ.

Synthesis of sulfinyl imine **(+)-5.19** was a 2 step procedure; formylation of TMS acetylene **(2.01)** afforded aldehyde **2.02** that was partially separated from the reaction solvent due to the volatility of the product (described previously in chapter 2). Subsequent condensation of the crude mixture with (S_S)-TBSA **(3.10)** afforded sulfinyl imine **(+)-5.19** in 47% overall yield (Scheme 5.12).



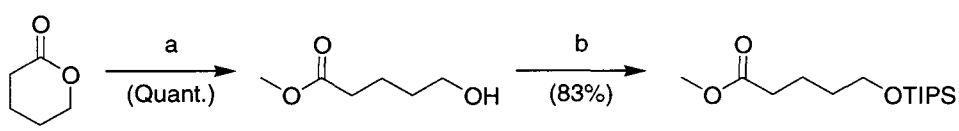
2.01 **2.02** **(+)-5.19**

Scheme 5.12. *Reagents and conditions*: a) i) *n*-BuLi, ii) DMF then NaH_2PO_4; b) (S_S)-TBSA, $CuSO_4$, CH_2Cl_2, Δ.

Synthesis of the unprotected, terminal alkyne analogue of sulfinyl imine **5.19** was initially envisaged. However, the Jones oxidation of propargylic alcohol did not yield propyne as described by Veliev *et al.*[166] We believed the volatility of the extremely low boiling three carbon fragment, propyne, and complicated isolation from the reaction mixture. By virtue of incorporating the TMS protecting group, sulfinyl imine **(+)-5.19** was successfully synthesised.

5.4.2 Synthesis of esters

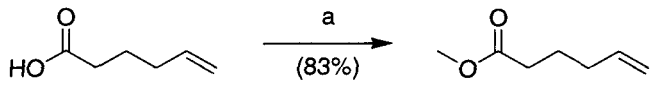
Synthesis of the substituted esters, **5.36, 5.38** and **4.76**, utilised in our imino-aldol reaction study was also required. Synthesis of TIPS protected 5-oxypentanoic acid methyl ester **(5.36)** was achieved by the acidic methanolysis of δ-valerolactone to methyl ester **5.35** and a TIPS protection of the free alcohol furnished the desired ester **5.36** in good yield (83% over 2 steps) (Scheme 5.13).



5.34 **5.35** **5.36**

Scheme 5.13. *Reagents and conditions*: a) H_2SO_4, MeOH, Δ; b) TIPSCl, imidazole, THF.

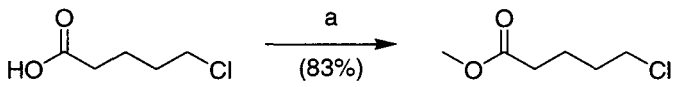
Synthesis of methyl ester **5.38** required the acidic methanolysis of commercially available hex-5-enoic acid **(5.37)**, which proceeded in good yield (83%) and required no further purification (Scheme 5.14).



5.37 **5.38**

Scheme 5.14. *Reagents and conditions*: a) AcCl, MeOH, Δ.

Similarly, the chloro-substituted methyl ester **4.76** was synthesised by the acidic methanolysis of commercially available 5-chloropentanoic acid **(5.39)** under dry conditions (Scheme 5.15). No further purification was needed.



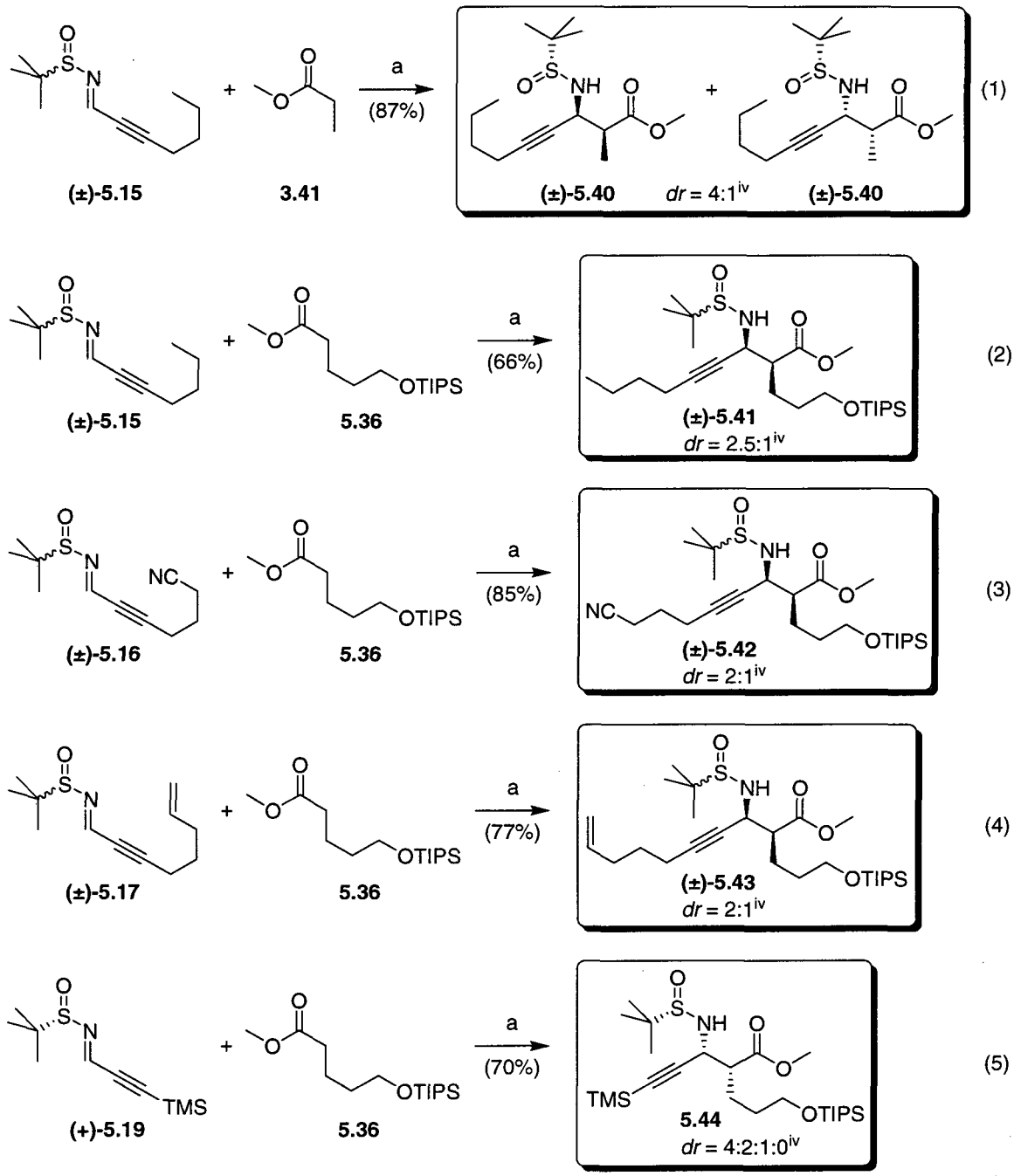
5.39 **4.76**

Scheme 5.15. *Reagents and conditions*: a) AcCl, MeOH, Δ.

5.4.3 Acetylenic sulfinyl imines in the imino-aldol reaction

The acetylenic sulfinyl imines discussed above were coupled with a variety of α-substituted esters in the imino-aldol reaction (Schemes 5.16 and 5.17). The yields for the conversion to the imino-aldol adduct are generally high (66-88%) and, more importantly, we were able to control the diastereoselective outcome of the reaction by modifying the reaction conditions.

The attention of the reader is also drawn to the fact that the first set of reactions (Scheme 5.16, Entries 1-5) were performed under the reported conditions by Ellman *et al.*, ($TiCl(O\textit{i}\text{-}Pr)_3$, 4.0 eq.)[75] before our discovery in our model study regarding the doping of the Lewis acid with $TiCl_4$ prior to the addition to the reaction. The second set of reactions (Scheme 5.17, Entries 6-9) were performed using the modified Lewis acid ($TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$) with increased equivalents of Lewis acid (8.0 eq.). Additionally, imino-aldol adduct **5.48** (Scheme 5.17, entry 9) will be discussed as part of our on going efforts to synthesis (+)-leontine in the succeeding chapter.



Scheme 5.16. *Reagents and conditions*: a) $TiCl(O\textit{i}\text{-}Pr)_3$ (4.0 eq.), LDA, THF, –78 °C.[i, ii, iii]

[i] The relative and absolute stereochemistry of products was tentatively assigned on the basis of the stereochemical assignment of imino-aldol adduct **3.42** obtained by Ellman *et al.*[75]

[ii] Trace amounts of other diastereomer may be present.

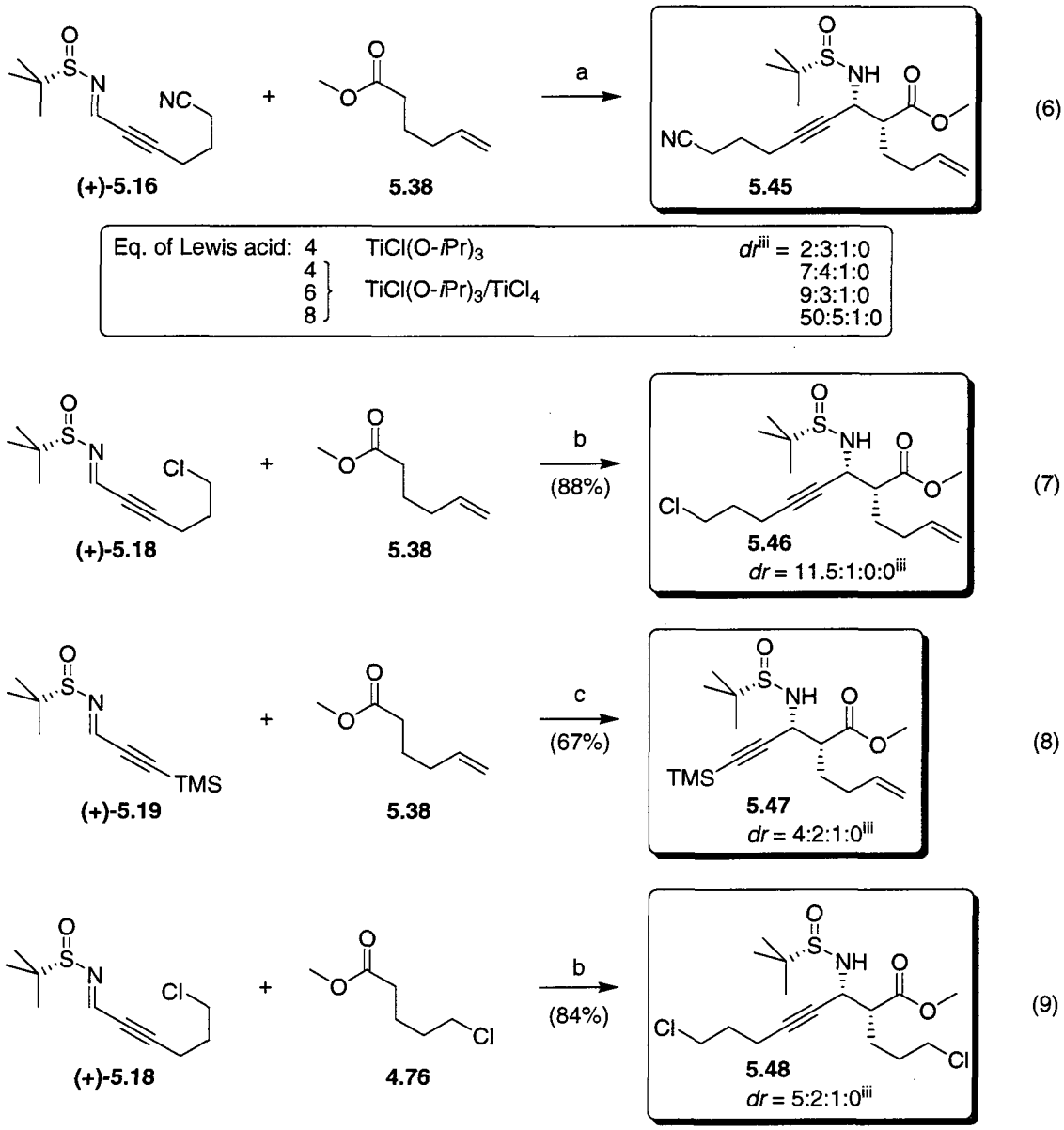
[iii] Predicted major diastereomer shown.

[iv] Diastereomeric ratio assigned as *syn*:*syn* or *syn*:*syn*:*anti*:*anti*.

Previously, acetylenic sulfinyl imines had only been employed in aziridine synthesis.[167] To determine the effect the acetylenic moiety had on the diastereoselectivty of the imino-aldol reaction, the hexyne portion was incorporated into sulfinyl imine **(±)-5.15**. This chain length would represent that required in our proposed synthetic route to leontine while not incorporating any further polar functionality that could influence the diastereoselectivity. Pleasingly, the reaction of sulfinyl imine **(±)-5.15** with two different titanium enolates gave the desired products demonstrating that acetylenic sulfinyl imines could be used successfully in the imino-aldol reaction. Formation of imino-aldol adduct **5.40** was investigated solely as a model because the addition of the titanium enolate of methyl propionate to a sulfinyl imine is known to give high diastereoselectivity in the imino-aldol reaction.[75] TIPS protected 5-oxypentanoic acid methyl ester **(5.36)** contained requisite functionality for the further elaboration towards leontine. Both imino-aldol adducts **5.40** and **5.41** were synthesised in good yield but in a disappointingly low diastereomeric ratio. The reaction with methyl propionate gave higher selectivity in comparison to the longer chain analogue **5.41** (4:1 *cf.* 2.5:1), a trait reflected in literature examples.[75] Unfortunately, the diastereomers of sulfinyl amine **5.40** were inseparable by column chromatography and diastereomers of **5.41** were only partially separable. The effect of incorporating the bulky O-TIPS protecting group appeared to lower the diastereoselectivity in the reaction.

The synthesis of imino-aldol adducts **5.42**, **5.43** and **5.44** served to determine the effect a functionalised substituent attached to the alkyne exhibited on the imino-aldol diastereoselectivty. Functional groups were chosen that would allow easy elaboration in our synthesis of (+)-leontine. Interestingly, the formation of these three imino-aldol adducts demonstrated a similar level of diastereoselectivity previously observed for the formation of adducts **(±)-5.40** and **(±)-5.41**. The synthesis of imino-aldol adduct **(±)-5.42** was completed in good yield (85%) but again in a disappointingly low diastereomeric ratio of products (2:1, determined by ^{1}H NMR of the crude reaction mixture) that were separable by column chromatography. Next, to probe the effect a non-coordinating substituent at the chain terminus produced on the diastereoselective outcome of the imino-aldol reaction, sulfinyl imine **(±)-5.17** was coupled with the enolate of ester **5.36** to yield **5.43**. Once more, a low diastereomeric ratio of products was recorded (*dr* = 2:1, determined by ^{1}H NMR analysis of the crude reaction mixture), with diastereomers partially separable by column chromatography, in a similar high yield (77%). Finally, we wanted to probe the effect of different chain lengths in the

imine substrate upon diastereoselectivity of the imino-aldol reaction. As a result imino-aldol adduct **5.44** was constructed. Again, a low diastereomeric ratio of products was obtained (4:2:1:0, determined from ^{1}H NMR of crude material) under the reported original imino-aldol reaction conditions.[75] We tentatively assigned the major adducts as the *syn* diastereomers and the ratio of these diastereomers was the same as the preceeding examples, 2:1. The reduced chain length would appear not to be beneficial to the diastereoselective outcome of the reaction as no previous system had produced three distinct diastereomers (separable by column chromatography). As a side note, the required alkylation of the terminal alkyne at a later stage in our synthesis of leontine would be problematic. Standard anionic couplings require harsh reaction conditions and standard Sonogashira Pd couplings are generally incompatible with the sp^3 centre on the alkyl halide component. However, conditions described recently by Fu *et al.*[168] could allow the late stage elaboration of the terminal alkyne.



Scheme 5.17. *Reagents and conditions*: a) Lewis acid, LDA, THF, –78 °C; b) TiCl(O*i*-Pr)$_3$/TiCl$_4$ (10:1, 8.0 eq.), LDA, THF, –78 °C; c) TiCl(O*i*-Pr)$_3$/TiCl$_4$ (10:1, 4.0 eq.), LDA, THF, –78 °C.[i, ii]

A series of imino-aldol adducts were synthesised derived from the enolate of hex-5-enoic acid methyl ester **(5.38)** (Scheme 5.17). Use of this enolate was favoured over the TIPS protected 5-oxypentanoic acid methyl ester analogue **(5.36)** as we envisaged a

[i] Relative and absolute stereochemistry was assigned based on the evidence that our modified Lewis acid reagent and stoichiometry restored the same sense of diastereoselectivity observed in the model study with aromatic sulfinyl amine **3.42**, section 5.3.

[ii] Predicted major diastereomer shown.

[iii] Diastereomeric ratio assigned *syn*:*syn*:*anti*:*anti*.

higher diastereoselectivity may be achieved due to the non-coordinating nature and lower steric bulk of the alkene compared to the TIPS protecting group. Additionally, the modification to the Lewis acid ($TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$) discovered to control the sense of diastereoselectivity in our model imino-aldol reaction (Section 5.3), was applied to the reaction. Pleasingly, this resulted in a marked improvement to the diastereoselective outcome. To begin with, imino-aldol adduct **5.45** was constructed. The imino-aldol reaction proceeded to yield a low diastereoselective ratio of products both with the reported reaction conditions (2:3:1:0) and our modified conditions (7:4:1:0). In addition, separation of diastereomers by column chromatography proved to be impossible due to the high polarity of the nitrile group. A further major breakthrough into improving the diastereomeric ratio of products in the imino-aldol reaction came when the stoichiometry of Lewis acid ($TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$) was increased. Augmentation to 6.0 and 8.0 eq. significantly increased diastereoselectivity in the imino-aldol reaction of **(+)-5.16** and **5.38** (9:3:1:0 to 50:5:1:0 determined by ^1H NMR of the crude reaction mixture). We tentatively assigned the two major imino-aldol adducts as *syn* diastereomers and the minor adduct was assigned as the *anti* diastereomer.[†] Increasing the stoichiometry of Lewis acid increased the *syn:anti* selectivity from 11:1 to 12:1 then 55:1 (4.0, 6.0 and 8.0 eq. of Lewis acid respectively). Pleasingly, the enantiomeric ratio of *syn* products also increased (syn_{maj}:syn_{min}) from 1.8:1 to 3:1 and finally, 10:1 (4.0, 6.0 and 8.0 eq. respectively). As a result, these conditions ($TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$ (10:1), 8.0 eq.) were then applied to all subsequent imino-aldol reactions carried out in our laboratory.

This trend is in accordance with observations by Siegel and Thornton that stated an excess of Lewis acid is necessary for improved diastereoselectivity in titanium-mediated aldol-type reactions.[101] The first equivalent of Lewis acid forms a $Li^+Cl_2Ti^-(O\textit{i}\text{-}Pr)_3$ 'ate' complex with the LiCl present, effecting its removal from the reaction. Lithium salts are known to favour the non-chelation controlled product, in effect lowering diastereoselectivity in the reaction.[102] The remaining equivalents of $TiCl(O\textit{i}\text{-}Pr)_3$ are believed to shift the equilibrium to favour the formation of the titanium enolate complex required for high selectivities.[75] Contrary to all other examples explored, greater diastereoselectivity was observed for the formation of imino-aldol adduct **5.46** (11.5:1:0:0, determined from isolated yield and ^1H NMR spectrum) using our modified

[†] Based on the diastereoselective outcome of imino-aldol reactions reported by Ellman and the formation of both *syn* diastereomers in our model system (Section 5.3).

Lewis acid composition and stoichiometry conditions ($TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$ (10:1), 8.0 eq.). This result was highly encouraging as it demonstrated that two complex substrates could be brought together in the imino-aldol reaction and exhibit a high degree of diastereoselectivity. It would appear that our modification to reported conditions[75] was successful at producing an enhanced ratio of diastereomeric products from an acetylenic sulfinyl imine in high yield (88%). The replacement of the nitrile moiety with the chloride removed the difficulties associated with separation of the resulting diastereomeric imino-aldol adducts. Diastereomers of **5.46** were separable by column chromatography and, again, were tentatively assigned as the *syn* imino-aldol adducts.[†] It would appear that the application of our modified conditions ($TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$), only using 4.0 eq. of Lewis acid, had a negliable effect of the diastereoselectivity in formation of imino-aldol adduct **5.47**. The yield for the conversion was similar to the other adducts with 3 diastereomers being produced (separable by column chromatography). The reaction was not repeated with increased equivalents of Lewis acid as we concluded previously that an imino-aldol adduct with this general structure was not synthetically useful for our synthesis of leontine. No further time was invested to optimise the diastereoselectivity of this conversion.

5.5 Conclusions

Our attempts to repeat a literature example imino-aldol reaction produced different diastereomeric products to those reported. However, we successfully managed to control the diastereoselective outcome of this reaction and achieve a reasonable diastereomeric ratio of products for the reaction by modifying the Lewis acid used. In addition, our study of acetylenic sulfinyl imines in the imino-aldol reaction repeatedly gave low levels of diastereoselectivity until we applied our modification to the Lewis acid and changed the stoichiometry of the reaction. This served to highlight that the diastereoselective outcome of this reaction is highly substrate and Lewis acid dependent. We overcame these issues to control the diastereoselective outcome with diastereoselectivities around 10:1 favouring the major *syn* diastereomer. However, due to the discrepancies noted for the diastereomeric outcome of certain imino-aldol

[†] Relative and absolute stereochemistry was assigned based on the evidence that our modified Lewis acid reagent and stoichiometry restored the same sense of diastereoselectivity for the model study with aromatic sulfinyl amine **3.42**, section 5.3.

reactions, it would be premature to speculate on the nature of the transition state. The significant improvement in diastereoselectivity associated with increasing the stoichiometry of Lewis acid raises doubt whether the closed 6-membered Zimmerman-Traxler type transition state models reported by Ellman *et al.* are likely. Alternative open transition state arrangements may well play a larger role in the diastereoselective outcome of the imino-aldol reaction than initially considered.

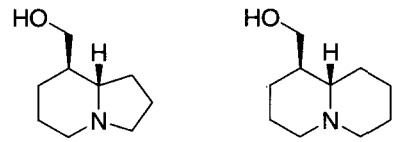
Finally, a key aim was to elucidate a suitable intermediate for our synthetic route towards the alkaloid, (+)-leontine **(3.03)**. Over the course of this study we successfully managed to determine a suitable imino-aldol adduct **(5.48)** that was elaborated further towards our synthesis of (+)-leontine (see Chapter 6).

Chapter 6 Total synthesis of tashiromine, epilupinine and towards the synthesis of leontine

6.1 Total synthesis of tashiromine and epilupinine

6.1.1 Background

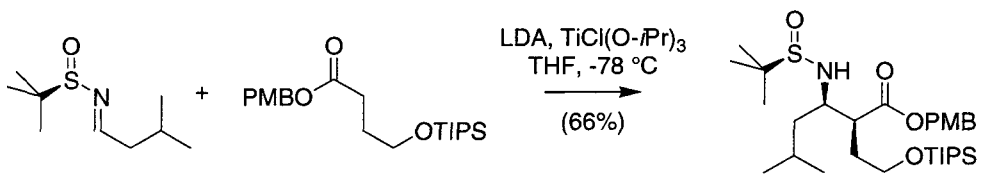
Following the unexpected diastereoselectivities observed for our model imino-aldol studies it was deemed necessary to obtain more concrete structural determination in more complex imino-aldol systems with our modified reaction conditions. One way to approach this would be to synthesise a known compound for which the relative and absolute stereochemistry was unambiguous. The synthesis of tashiromine **(3.01)** and epilupinine **(3.02)** would serve this purpose.



Tashiromine **(3.01)** Epilupinine **(3.02)**

Figure 6.01. Structure of (−)-tashiromine and (−)-epilupinine.

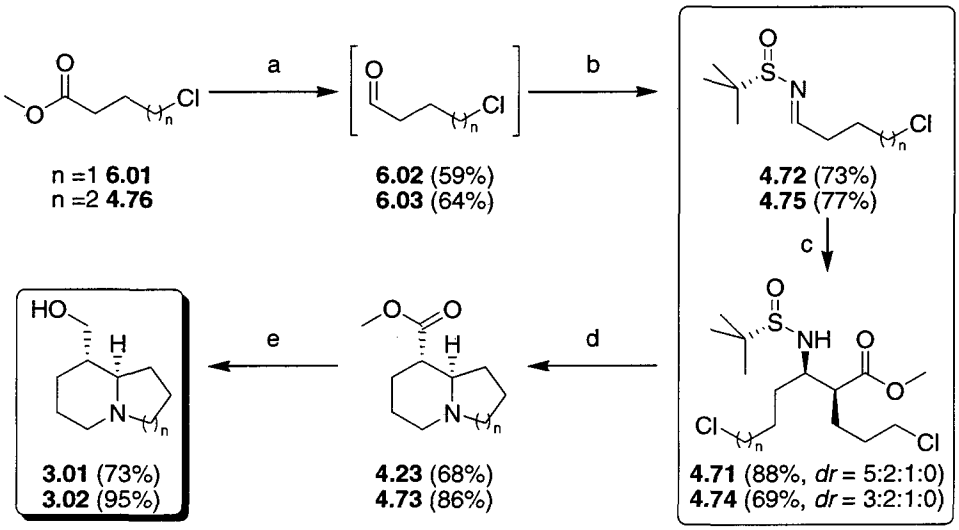
Implementation of our proposed synthetic strategy furnished both natural products in good yield through the same approach (Scheme 6.02). Application of our modified conditions did not give high levels of selectivity. However, our observed diastereoselectivities appeared to be consistent with literature precedent. Previously, Ellman *et al.* observed that the reaction of alkyl sulfinyl imines and complex enolates showed lower selectivity (60:20:17:3) (Scheme 6.02) compared to aromatic sulfinyl imine counterparts.[75]



3.50 **3.51** **3.52**
dr = 60:20:17:3

Scheme 6.01. Synthesis of α,β- substituted β-amino acid **3.52** via an imino-aldol reaction.[75]

6.1.2 Results and discussion



Scheme 6.02. *Reagents and conditions*: a) DIBAL-H, CH_2Cl_2; b) (S_s)-TBSA, $CuSO_4$, CH_2Cl_2; c) $TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$ (10:1, 8.0 eq.), LDA/5-chloropentanoic acid methyl ester (**4.76**), THF, –78 °C; d) 4 N HCl/dioxane, MeOH then K_2CO_3, NaI, MeCN, Δ; e) $LiAlH_4$, THF.

Alkyl sulfinyl imines **4.72** and **4.75** were synthesised via a DIBAL-H reduction from the corresponding ester followed by condensation with (*S*)-(–)-*tert*-butyl sulfinyl amine ((S_S)-TBSA) (**3.10**). Next, the sulfinyl imines were coupled with the enolate of ester **4.76** in the imino-aldol reaction which produced the desired sulfinyl amines **4.71** and **4.74** in good yield (88 and 69% respectively) with modest selectivity (labeled a, b and c correspondingly). Separation of the minor diastereomeric component (c) of sulfinyl amines **4.71** and **4.74** from the corresponding major diastereomers (a, b) was accomplished by column chromatography. Unfortunately, separation of the two major diastereomers proved to be impossible by column chromatography and the mixture was carried forward in our synthesis. The relative and absolute configuration of these diastereomers was not known at this point. For sulfinyl amine **4.71**, the ratio of separable major:minor adducts (**[4.71a+b]**:**4.71c**) was 7:1 (determined from isolated yield) and the ratio of the two inseparable major imino-aldol adducts (**4.71a**:**4.71b**) was 3:1 (determined by ^{1}H NMR of the mixture) hence, an approximate *dr* = 5:2:1:0. For sulfinyl amine **4.74**, the ratio of separable major:minor adducts (**[4.74a+b]**:**4.74c**) was 4.6:1 (determined from isolated yield) and the ratio of the two inseparable major imino-aldol adducts (**4.74a**:**4.74b**) was 1.6:1 (determined by ^{1}H NMR analysis of the mixture) hence, an approximate diastereomeric ratio of 3:2:1.

The next stage in our synthetic approach was the acid deprotection of the mixture of diastereomers of sulfinyl amines **4.71a,b** and **4.74a,b** followed by treatment with carbonate to induce an efficient cyclisation to the corresponding indolizidine **4.23** and quinolizidine **4.73** systems. Following this removal of the chiral auxillary and double annulation, the ^{1}H and ^{13}C NMR spectra for both the indolizidine and quinolizidine systems (**4.23** and **4.73** respectively) showed one set of resonances indicating that the inseparable major imino-aldol products of sulfinyl amine **4.71** and **4.74** were in fact both *syn* diastereomers. Consequently, the minor imino-aldol product of **4.71** and **4.74** was elucidated to be an *anti* adduct.

Comparison of ^{13}C NMR data of indolizidine **4.23**, synthesised from the enantiomeric mixture of *syn* diastereomers of sulfinyl amine **4.71**, closely correlated to data for the known indolizidine with established stereochemistry.[125] This confirmed that indolizidine **4.23** had *trans* relative stereochemistry across the C5-C6 bond (Table 6.01). Analysis of ^{1}H NMR data for indolizidine **(+)-4.23** supported this observation with the resonance at 2.27 ppm (1H, ddd, J = 12.1. 9.5 and 3.8 Hz, $CHCOOCH_3$) exhibiting two axial-axial and one axial-equatorial coupling. This coupling pattern would only be observed from the annulation of the *syn* diastereomers produced in the imino-aldol reaction provided no epimerisation took place under the annulation conditions. The positive optical rotation indicated that our major *syn* diastereomer produced in the imino-aldol reaction had the opposite stereochemistry to that predicted from work performed by Ellman *et al.*[75] The reduced optical rotation value (+27.4 *cf* +69.0)[122] is due to indolizidine **4.23** being a chiral non-racemic mixture of enantiomers.

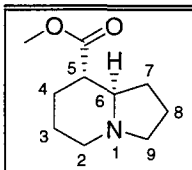
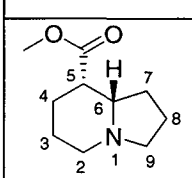
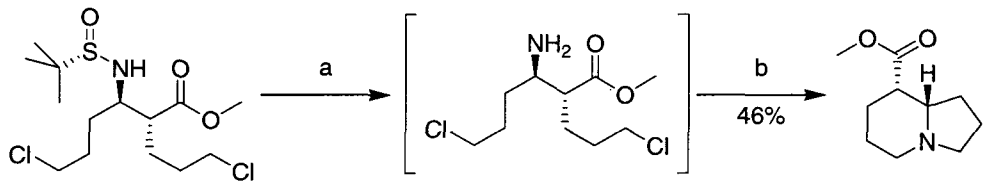
		C6	C9	C2	C5	C4	C7	C3/8	C3/8	$[\alpha]_D$
 **(+)-4.23**	**Obs.**	65.1	54.0	52.2	48.0	29.2	28.2	24.8	20.5	+27.4
	Lit.[125]	65.3	54.1	52.3	47.8	29.2	28.2	24.7	20.5	+69.0[122]
 *anti*-**(+)-4.23**	**Obs.**	64.5	54.8	53.5	41.9	26.8	26.3	22.4	20.6	+18.6

Table 6.01. Observed and literature ^{13}C NMR data for indolizidine **4.23** recorded at 100 and 75 MHz respectively (note: for residual $CHCl_3$ is referenced to 77.00 ppm).

Separately, the minor sulfinyl amine adduct diastereomer **4.71c** was subjected to the same annulation conditions and yielded indolizidine *anti*-(+)-**4.23** (Scheme 6.03). The ^{13}C NMR data for *anti*-(+)-**4.23** did not correspond to those for the known *trans* indolizidine (+)-**4.23** (Table 6.01). This indicated that indolizidine *anti*-(+)-**4.23** had *cis* relative stereochemistry across the C5-C6 bond, although the absolute stereochemistry could not be determined. Also, this served to demonstrate that no epimerisation to the thermodynamic product, indolizidine **4.23**, had occured under annulation reaction conditions. This confirmed that the enantiomeric mixture of (+)-**4.23** was a true representation of the syn_{maj}:syn_{min} ratio of sulfinyl amine **4.71** diastereomers obtained from the imino-aldol reaction.



Scheme 6.03. *Reagents and conditions*: a) 4 N HCl/dioxane, MeOH; b) K_2CO_3, MeCN, NaI, Δ.

The synthesis of quinolizidine (+)-**4.73** proceeded similarly to give a compound that exhibited a single set of resonances in its ^1H and ^{13}C NMR spectra. The comparison of ^{13}C NMR data with known material showed excellent correlation (Table 6.02). Correspondingly, we concluded the inseparable mixture of major diastereomeric products of sulfinyl amine **4.74** were both *syn* adducts, which gave rise to an inseparable mixture of enantiomers of (+)-**4.73**.

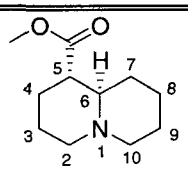
		C6	C10	C2	C5	C7	C4	C9	C3/8	C3/8	$[\alpha]_D$
 (+)-4.73	Obs.	63.5	56.6	56.0	49.4	30.9	28.6	25.7	24.5	24.3	+8.5
	Lit.	63.6	56.7	56.1	49.5	31.1	28.8	25.8	24.7	24.4	-

Table 6.02. Observed and literature ^{13}C NMR data for quinolizidine **4.73** recorded at 100 and 75 MHz respectively (note: residual $CHCl_3$ is referenced to 77.00 ppm).

Evidence to support the *trans* relative stereochemistry assignment in quinolizidine (+)-**4.73** is observed in the ^1H NMR data in the resonances at 2.28 (1H, ddd, J = 12.3, 10.0,

3.7 Hz, $CHCOOCH_3$) and 1.99 (1H, td, J = 10.0, 2.3 Hz, CHN) ppm which each exhibited two axial-axial and one axial-equatorial coupling. The positive optical rotation value of synthetic quinolizidine **4.73** confirmed unambiguously the absolute configuration (by comparison with known material) (Figure 6.02). This also allowed us to determine that the major *syn* diastereomer from the imino-aldol reaction was (S_S,2*S*,3*R*)-**4.74**. This is the opposite *syn* diastereomer to that predicted by the model proposed by Ellman *et al.*[75] and our studies of a model system.

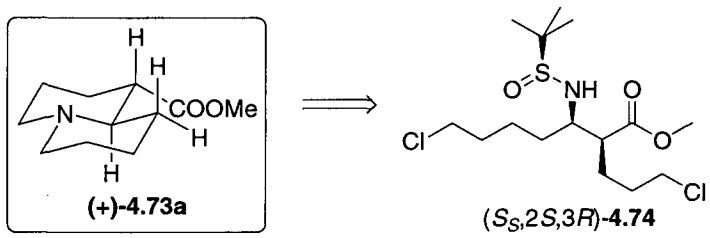


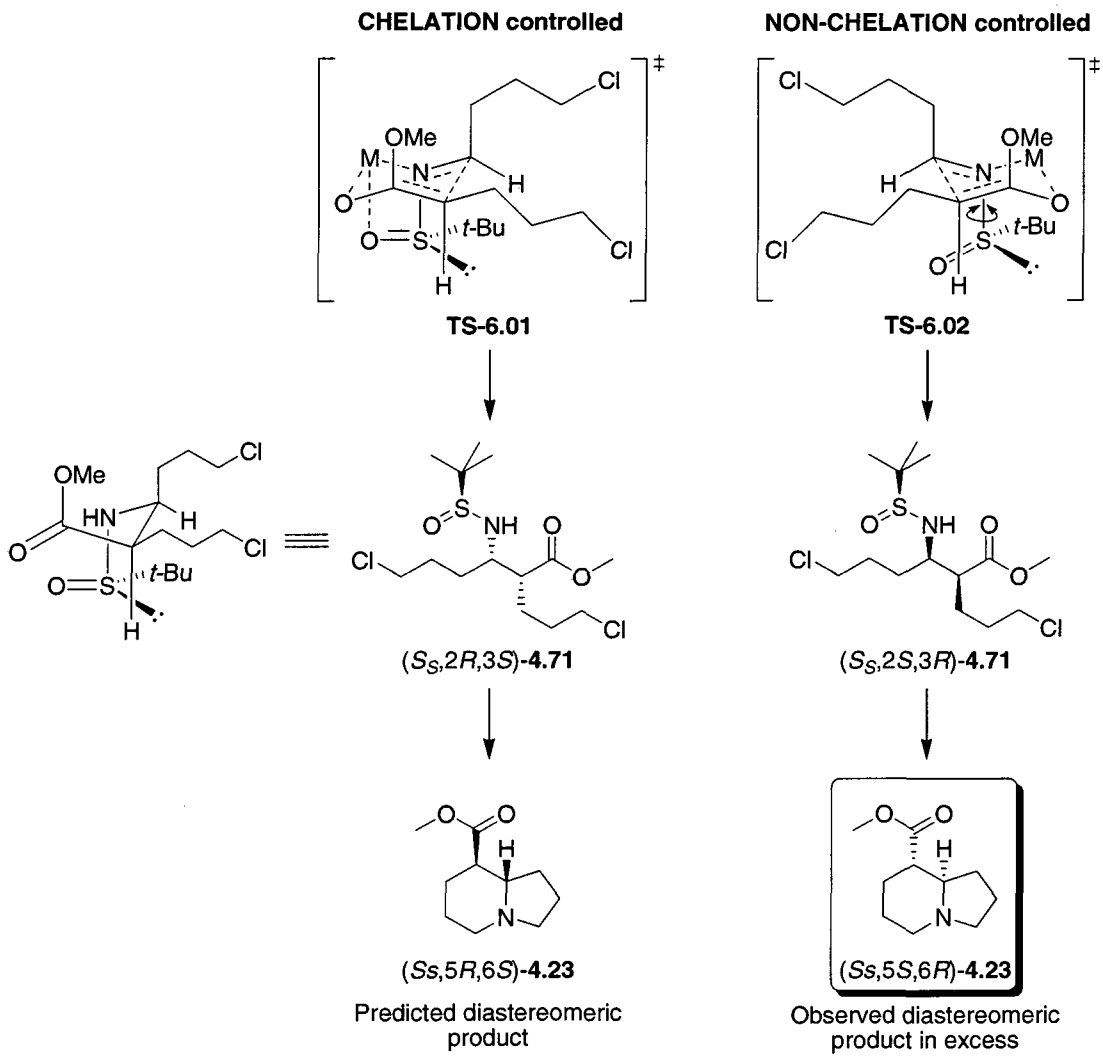
Figure 6.02. Configuration of quinolizidine **4.73** and the major *syn* imino-aldol adduct **4.74**.

Finally, the reduction of esters **4.23** and **4.73** using conditions described by Beckwith *et al.*[125] proceeded smoothly to yield enantiomerically enriched tashiromine **(3.01)** and epilupinine **(3.02)** in good to excellent yield (73 and 95% respectively). An aqueous work-up procedure was avoided as the natural products are sparingly soluble in water. No further purification of the final compounds was necessary and epimerization of the substrates was not observed under these reaction conditions.[148] Both synthetic natural products exhibit ^1H and ^{13}C NMR spectra that are identical to published data (see Appendix).

Our synthetic plan, based on direct extrapolation of results published by Ellman *et al.*[75] and supported by our results from our model study, predicted that both natural products **3.01** and **3.02** should have been formed as the (–) enantiomer using the *S* enantiomer of the chiral auxiliary (TBSA) (Aldrich: observed $[\alpha]_D$ = –5.5, lit. $[\alpha]_D$ = –5.1). Synthetic tashiromine **(3.01)** was isolated with an optical rotation of $[\alpha]_D$ = +28.6 (lit. $[\alpha]_D$ ((+)-tashiromine): = +43.4)[118] and synthetic epilupinine **(3.02)** was isolated with $[\alpha]_D$ = +5.7 (lit. $[\alpha]_D$ ((+)-epilupinine) = +31.0).[147] It appears that the modified imino-aldol reaction conditions used directed a preference for the opposite enantiomer of sulfinyl amines **4.71** and **4.73** to that predicted.

The major *syn* diastereomer, (S_S,2*S*,3*R*)-**4.71**, isolated from the imino-aldol reaction in our synthesis of tashiromine **(3.01)** could be accounted for by either a non-chelation

controlled closed six-membered transition state or an acyclic transition state. Lack of chelation to the metal centre by the sulfinyl oxygen in the non-chelation controlled model could allow partial rotation of the N-S bond and favour attack of the enolate from the *Re*-face of the imine (Scheme 6.04). The predicted diastereomeric product, (S_S,2*R*,3*S*)-**4.71**, synthesised in the imino-aldol reaction was obtained as the minor *syn* component, suggesting that a small portion of material followed the predicted chelation controlled closed transition state reaction pathway.

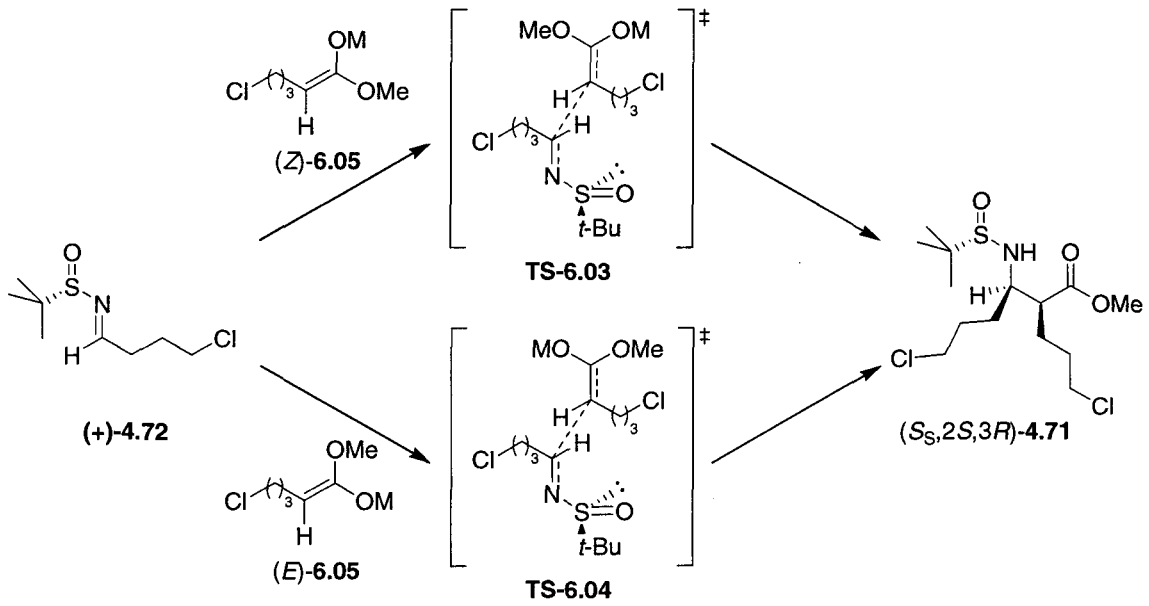


Scheme 6.04. Proposed chelation controlled and non-chelation controlled six-membered transition state in the imino-aldol reaction.

A noteworthy point is the observation by Thornton and co-workers regarding reduced selectivity in an aldol reaction. They reported, for their study into the addition of chiral oxazolidinone titanium enolates to aldehydes, that chelation of a solvent molecule (THF) in the transition state adversely effected diastereoselectivity by favouring a non-

chelated model.[169] The detrimental effect of coordination of a THF molecule to the closed transitions states **TS-6.01** or **6.02** would appear unlikely as THF was shown by Ellman *et al.*[75] to give the highest selectivity of the solvents screened in the imino-aldol reaction. This does highlight the potential that other substrates could coordinate in the transition state and reduce the diastereoselectivity of products in the imino-aldol reaction.

Alternatively, again an acyclic transition state would lead to the formation of the major diastereomeric product we obtained (S_S,2*R*,3*S*)-**4.71** from either the *cis* or the *trans* ester enolate **6.05** (Scheme 6.05). With the large excess of Lewis acid used (8.0 eq.) this acyclic mechanistic pathway would aldo appear to be reasonable.



Scheme 6.05. Possible acyclic transition state in the imino-aldol reaction.

6.1.3 Conclusions

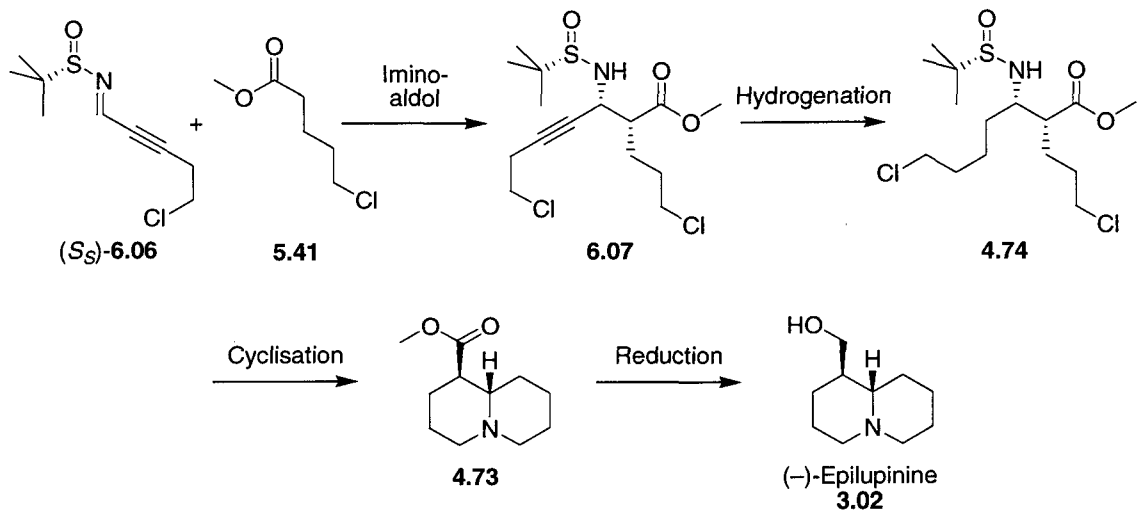
Tashiromine and epilupinine were successfully synthesised in 5 steps and high overall yield (19% and 28% respectively). The aim of synthesising these two natural products was to determine the diastereoselective outcome of the imino-aldol reaction when more complex sulfinyl imines were used with our modified conditions. The diastereoselectivity produced in the imino-aldol reaction is similar to other observed results (see proceeding chapter) but, more interestingly, we observed a reversal in selectivity of *syn* imino-aldol adducts produced compared to the our studies into a model imino-aldol reaction. Our proposed synthetic strategy should have led to the synthesis of (–)-tashiromine and (–)-epilupinine, based on work performed by Ellman *et*

al. This, coupled with our findings from the previous chapter, led to the conclusion that the diastereoselective outcome of this reaction appears to be highly dependent on multiple factors, such as the substrates (sulfinyl imine and enolate) and the Lewis acid, both the stoichiometry and composition.

6.1.4 Future work

To better understand the observed reversal in preference of imino-aldol adduct produced when alkyl sulfinyl imines are used, we could compare the outcome of the imino-aldol reaction with the acetylenic analogue of sulfinyl imine **4.72** or **4.75**. This will assist us in establishing whether this reversal is a factor when other complex sulfinyl imines are used (under our modified conditions).

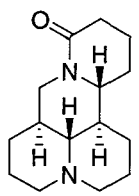
Modification to our synthesis of epilupinine, incorporating acetylenic sulfinyl imine **6.06** will yield acetylenic sulfinyl amine **6.07** and, through a hydrogenation, will give the common intermediate, sulfinyl amine **4.74** (Scheme 6.06). The synthesis can then be completed in a similar manner to yield epilupinine (**3.02**). Comparing the optical rotation data of epilupinine from this modified route, to that already collected will allow us to determine the preference of *syn* diastereomeric adduct **6.07** obtained when the corresponding acetylenic sulfinyl imine is used. Additionally, to place us on a firmer footing we also need to confirm the geometry of the major enolate produced by deprotonation of ester **5.41** with LDA in THF.



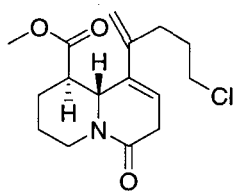
Scheme 6.06. Incorporation of an acetylenic sulfinyl imine (S_S)-**6.06** into our synthesis of (–)-epilupinine.

6.2 Towards the synthesis of (+)-leontine

Following on from our study of acetylenic sulfinyl imines in the imino-aldol reaction and modification to reaction conditions (described in the previous chapter), we were in a position to control the relative stereochemistry produced in the reaction and tentatively assign the absolute stereochemistry of the major products.† Eager to apply our findings to our proposed synthesis of leontine **(3.03)** we made significant progress to the natural product with the construction of the lower bicyclic core, quinolizidinone **(–)-6.12**, (Figure 6.03).



(+)-Leontine **(3.03)**



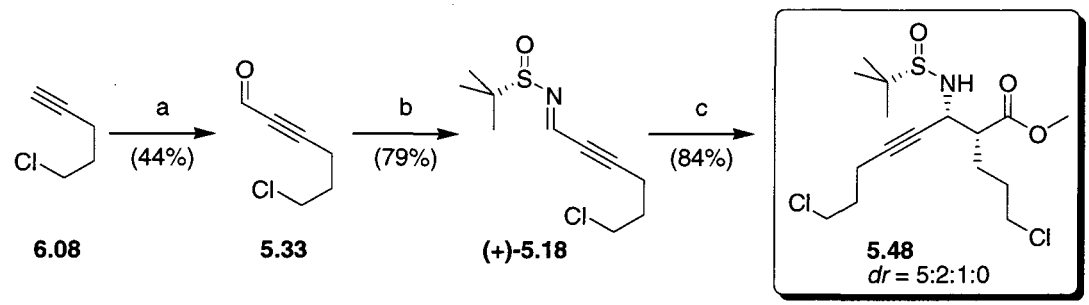
(–)-6.12

Figure 6.03. Structure of (+)-leontine and the lower bicyclic core synthesised.

6.2.1 Synthesis of quinolizidinone (–)-6.12

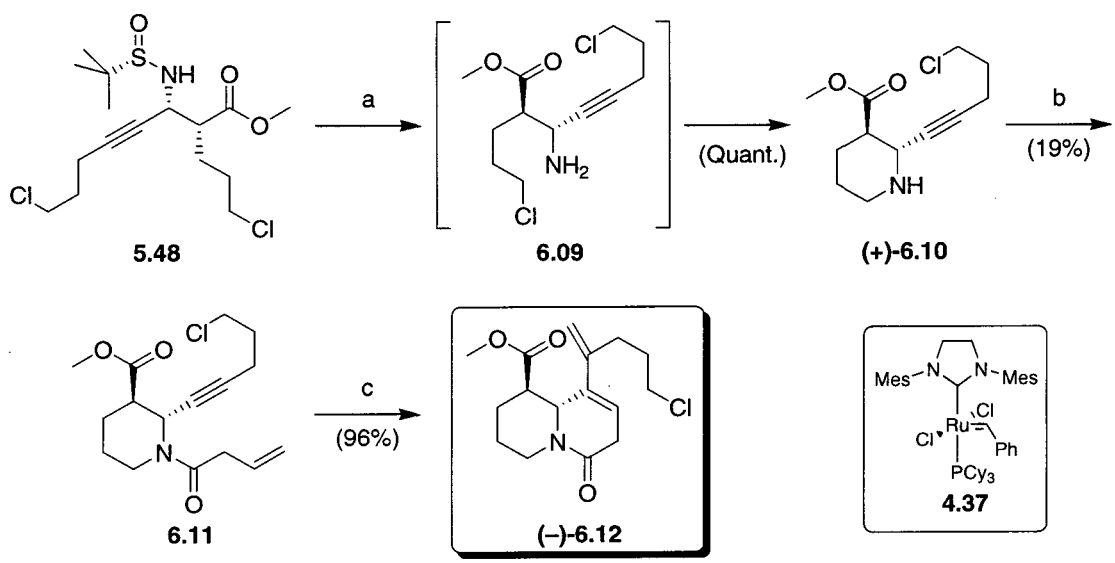
Synthesis of quinolizidinone **(–)-6.12** was accomplished with control of the relative and absolute stereochemistry in 6 linear steps.† Imino-aldol adduct **5.49** was chosen as it could undergo direct annulation to the corresponding piperidine. Formylation of commercially available 5-chlorohexyne **(6.08)** gave aldehyde **5.33** in low yield (44%) due in part to the volatility of the aldehyde. This was followed by condensation with (S_S)-TBSA which afforded sulfinyl imine **(+)-5.18**. The application of our modified imino-aldol reaction conditions ($TiCl(O\text{-}iPr)_3/TiCl_4$ (10:1), 8.0 eq.) gave sulfinyl amine **5.49** in a reasonable diastereomeric ratio (5:2:1:0) and excellent yield (84%). Increasing the stoichiometry of the titanium enolate from 2.0 to 4.0 eq. (with respect to the imine) was also found to be necessary for complete conversion to sulfinyl amine **5.48**. Separation of the minor and major diastereomeric products was achieved by careful column chromatography and only the major diastereomer of imino-aldol adduct **5.48** was carried forward in our total synthesis. The stereochemistry of this major adduct was tentatively assigned as the predicted *syn* diastereomer.†

† Relative and absolute stereochemistry was assigned based on the evidence that our modified Lewis acid reagent and stoichiometry restored the same sense of diastereoselectivity for the model study with aromatic sulfinyl amine **3.42**, section 5.3 and before our synthesis of tashiromine and epilupinine.



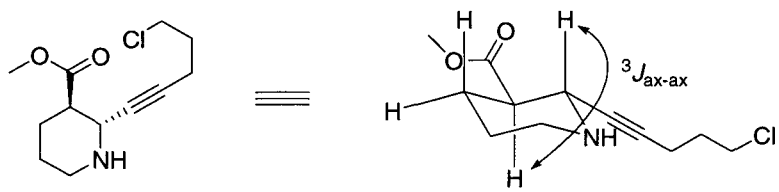
Scheme 6.07. *Reagents and conditions*: a) *n*-BuLi, THF, –78 °C then DMF; b) (S_s)-TBSA, $CuSO_4$, CH_2Cl_2, Δ; c) $TiCl(Oi\text{-}Pr)_3/TiCl_4$ (10:1, 8.0 eq.), 5-chloropentanoic acid methyl ester (**4.76**), LDA, THF, –78 °C

Next, brief treatment of imino-aldol adduct **5.48** with stoichiometric HCl in a protic solvent removed the sulfinyl group and acylation yielded two products, piperidine **(+)-6.10** and **6.11** (59% and 19% respectively) (Scheme 6.08). Unknown to us at the time, prior to acylation complete cyclisation of primary amine **6.09** to piperidine **(+)-6.10** occurred. The HCl salt of piperidine **6.10** was therefore utilised in the acylation reaction, not primary amine **6.09**, and reaction conditions were not modified accordingly resulting in the low acylation yield (19%). Gratifyingly RCM of enyne **6.11** proceeded in excellent yield (96%) in under 2 h employing Grubbs' II catalyst **(4.37)** and completed the synthesis of quinolizidinone **(–)-6.12**.



Scheme 6.08. *Reagents and conditions*: a) i) 4 N HCl/dioxane, MeOH, ii) Standing at rt; b) but-1-enoic acid chloride, NEt_3, CH_2Cl_2; c) Grubbs' II (**4.37**) (19 mol%), CH_2Cl_2, Δ.

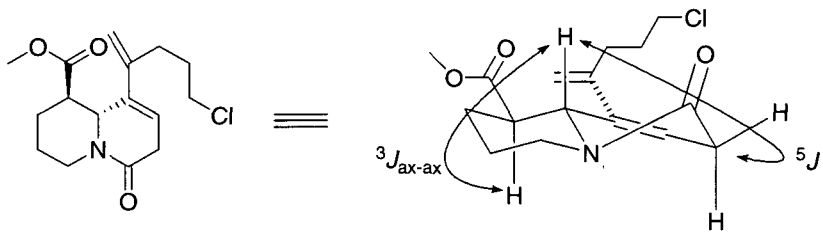
The relative stereochemistry in piperidine **(+)-6.10** and quinolizidinone **(–)-6.12** was confirmed by analysis of ^{1}H NMR spectroscopic data (Figures 6.04 and 6.05). Consequently, this substantiated our assignment of the relative stereochemistry (*syn*) in the major diastereomeric product of sulfinyl amine **5.48** obtained from the imino-aldol reaction. However, the absolute stereochemistry was only tentatively assigned. For piperidine **(+)-6.10** the resonance at 3.79 (1H, d, J = 8.5 Hz) ppm, corresponding to the CHN proton, exhibited a ^3J = 8.5 Hz coupling, implying an axial-axial interaction to the adjacent proton (Figure 6.04).



(+)-6.10

Figure 6.04. Stereochemistry of 2,3- disubstituted piperidine **(+)-6.10**.

Analysis of spectroscopic data (^{1}H NMR) for quinolizidinone **(–)-6.12** indicated the RCM step produced the desired product with the desired relative stereochemistry (Figure 6.05). The resonance at 4.26 (1H, dt, J = 10.3, 2.3 Hz) ppm, corresponding to CHN proton, exhibited a coupling constant of ^3J = 10.3 Hz, hence an axial-axial coupling to the unresolved α-ester proton. A long range coupling (^5J = 2.3 Hz) to the CH_2 group adjacent to the amide was also observed.



(–)-6.12

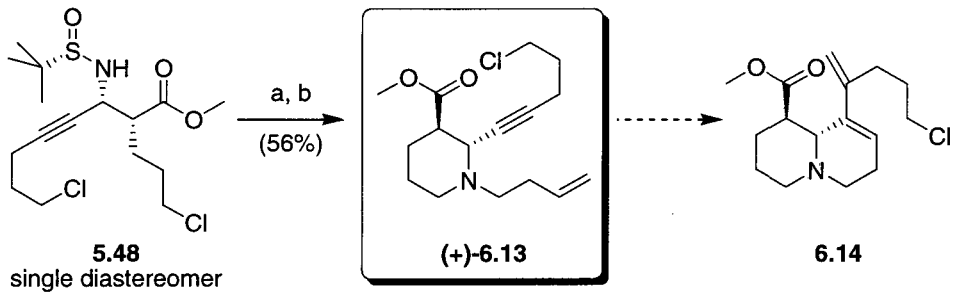
Figure 6.05. Stereochemistry of quinolizidinone **(–)-6.12**.

6.2.2 Alternative synthetic pathways explored

6.2.2.1 Quinolizidine synthesis via RCM of a tertiary amine

Initially, RCM of enyne **(+)-6.13** was to be considered as a means to access the lower bicyclic core, quinolizidine **6.14** (Scheme 6.09). In contrast to the high yielding enyne

RCM of amide **6.12** all attempts to effect RCM of the corresponding amine analogue **(+)-6.13** failed. Altering the temperature, solvent, pressure, catalyst loading and catalyst stoichiometry of the reaction did not yield the desired product **6.14**.



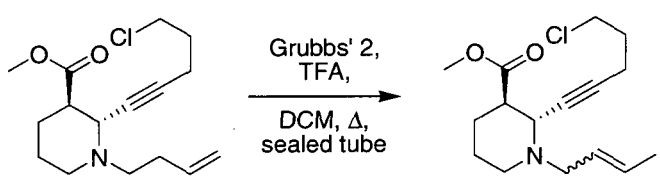
5.48
single diastereomer

(+)-6.13

6.14

Scheme 6.09. *Reagents and conditions*: a) i) 4 N HCl/dioxane, MeOH ii) K_2CO_3, DMF, Δ; b) 4-bromo-but-1-ene, 18-crown-6, MeCN, Δ.

Free amines are often incompatible with RCM reactions[170] as Lewis basic nitrogen chelates to the active metal alkylidene species causing inhibition of the catalyst. Incorporation of nitrogen as an amide, carbamate or by the *in situ* protonation of the free amine has been shown to circumvent this issue.[170,171] The first successful RCM reaction of an amine hydrochloride salt was performed by Grubbs *et al.*[172] Complementary to this, work performed within our laboratory by Salim *et al.* made use of TFA as the proton source.[173] The addition of TFA to the current system **(+)-6.13** did not afford the desired metathesis product, quinolizidine **6.14**. The addition of >1.0 eq. of TFA only facilitated the isomerisation of the terminal double bond to the more highly substituted internal double bond **6.15** under reaction conditions (Scheme 6.10).



(+)-6.13

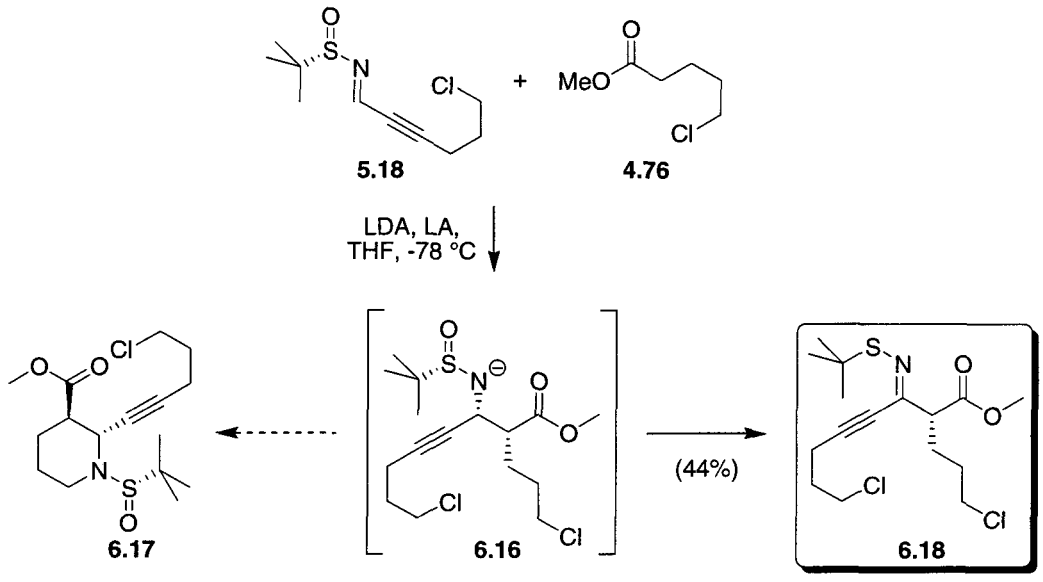
6.15

Scheme 6.10. Isomerisation of enyne **6.13** under RCM conditions.

6.2.2.2 One-pot piperidine ring formation via an imino-aldol reaction

As an alternative approach to the synthesis of piperidine **6.10** (via the protected *tert*-butyl sulfinyl analogue **6.17**), a one-pot imino-aldol reaction of sulfinyl imine **(+)-5.18** and ester **4.76** and spontaneous cyclisation of the intermediate species upon warming

was investigated (Scheme 6.11). A similar approach was used by Ruano *et al.* for the synthesis of optically pure 2-(1-hydroxybenzyl)-piperidines.[174]



Where LA = $TiCl(O\textit{i}\text{-}Pr)_3/TiCl_4$ (10:1, 8.0 eq.)

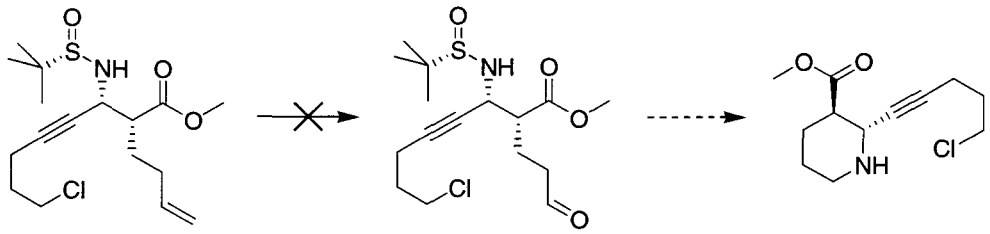
Scheme 6.11. Attempted one-pot piperidine ring formation via an imino-aldol reaction.

In place of quenching amide anion **6.16** at –78 °C, it was considered warming to rt could successfully induce annulation to afford piperidine **6.17**. In fact, only propargylic imine **6.18** was isolated. Intermediate **6.17** is believed to have undergone a Pummerer-type rearrangement upon warming. The dehydration of intermediate **6.16** was attributed to the presence of a large excess of the highly oxophilic Lewis acid ($TiCl(O\text{-}\textit{i}Pr)_3/TiCl_4$) which was not present in the strategy described by Ruano *et al.* Our strategy of quenching and isolating the intermediate sulfinyl amide **6.16** worked successfully therefore, no further time was invested in this one-pot approach.

6.2.2.3 Elaboration of alternative imino-aldol adduct

After formation of imino-aldol adduct **5.46** showed a high degree of selectivity (*dr* = 92:8:0:0) in the imino-aldol reaction (described in the proceeding chapter) we wished to explore the use of this substrate in our synthesis of leontine (**3.03**). Oxidative cleavage of the alkene followed by reductive amination of the free amine would yield piperidine **6.10** (Scheme 6.12). Unfortunately, initial investigations into the oxidative cleavage (ozonolysis and $OsO_4/NaIO_4$) of the terminal double bond in sulfinyl amine **5.46** gave a

complex mixture of products of unknown configuration. As a result this route was not progressed further.



5.46 6.19 6.10

Scheme 6.12. Proposed transformation of sulfinyl amine **5.46** to piperidine **6.10**.

6.2.3 Conclusions

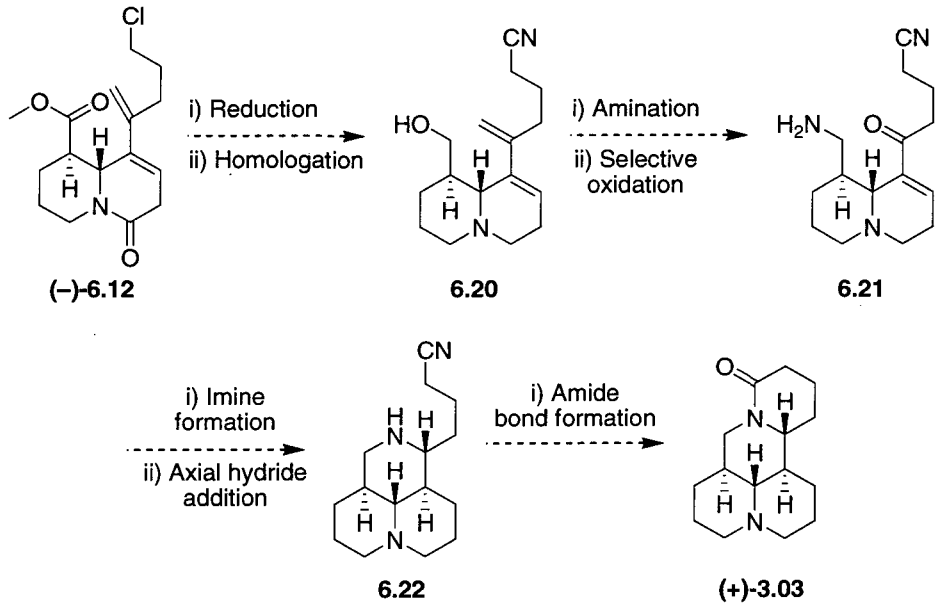
Significant progress has been made towards the stereoselective total synthesis of (+)-leontine. The asymmetric synthesis of the highly functionalised lower bicyclic portion, quinolizidinone **(–)-6.12**, represented a major achievement in the total synthesis. Control of the relative and absolute stereochemistry[†] at the C5 and C6 position was achieved through modified imino-aldol reaction conditions developed in our laboratory. The successful incorporation of a very high yielding enyne RCM step in the construction of the quinolizidine core was also realised. Gratifyingly, to date our retrosynthetic analysis of (+)-leontine **(3.03)** appears to offer a viable asymmetric route to the natural product.

6.2.4 Future work

The outlined latter stage synthetic conversions towards leontine can now be investigated (Scheme 6.13). The proposed ester and amide reduction of quinolizidinone **(–)-6.12** and homologation with NaCN will give substrate **6.20**. Subsequent amination then selective oxidative cleavage of the diene moiety should yield enone **6.21**. Fortunately, the synthesis of (+)-anatoxin-a by Brenneman and co-workers provides precedent for the selective oxidative cleavage of the less hindered alkene in a similar diene constrained

[†] Relative and absolute stereochemistry was assigned based on the evidence that our modified Lewis acid reagent and stoichiometry restored the same sense of diastereoselectivity for the model study with aromatic sulfinyl amine **3.42**, section 5.3.

within a bicyclic ring system.[175] Imine formation followed by a stereoselective hydride reduction will afford tricycle **6.22** with the desired stereochemistry. Finally amide formation will complete our proposed asymmetric synthesis of leontine **(3.03)**.



(–)-6.12 **6.20** **6.21**

6.22 **(+)-3.03**

Scheme 6.13. Outlined steps for conversion of quinolizidinone **(–)-6.12** to (+)-leontine **(3.03)**.

Chapter 7 Experimental

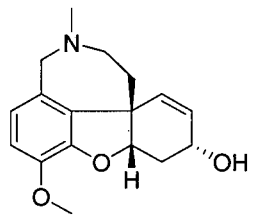
7.1 General experimental

Both ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AV-300 spectrometer at 300 MHz and 75 MHz respectively or a Bruker DPX-400 spectrometer at 400 MHz and 100 MHz respectively in $CDCl_3$ or d_4-MeOH at 300 K. Chemical shifts for proton and carbon spectra are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^{1}H and 77.36 ppm for ^{13}C; d_4-MeOH: 49.15 ppm for ^{13}C). Infrared data was collected on a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment using OMNIC software. The IR spectra are reported in wavenumbers (cm^{-1}). Absorption peaks are reported as either: weak (w), medium (m), strong (s) or broad (br). Optical rotations were collected on an Optical Activity PolAAr 2001 machine. Melting points were collected on a Gallenkamp Electrothermal® Melting point apparatus and are uncorrected. Column chromatography was carried out using Merck Kieselgel 60A (particle size 35-70 microns) or Merck Kieselgel 60 (particle size 40-60 microns) where specified. Thin layer chromatography was carried out on Merck silica gel 60 F_{254}, visualized under UV illumination (254 nm) and stained with potassium permanganate. Analytical HPLC was performed on a Hewlett Packard 1090 series HPLC with a Daicel Chemical Industries column (OD-H) eluting with IPA/hexane mixtures. All electrospray low resolution mass spectra were recorded on a Waters ZMD quadrupole spectrometer. EI and CI low resolution mass spectroscopic data were collected on a ThermoQuest TraceMS single quadrupole GC-MS. Dry solvents used were distilled before use; THF and Et_2O were distilled over sodium/benzophenone; CH_2Cl_2 over CaH_2; toluene and hexane over Na. Reactions were performed under an argon (Ar) atmosphere and all glassware used was oven dried prior to use unless otherwise stated.

7.2 Experimental detail

[4a*S*,-(4aα,6α,8a*R*)]-4a,5,9,10,11,12-Hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-ef][2]benzazepin-6-ol ((–)-1.01)

(–)-Galanthamine



$C_{17}H_{21}NO_3$
Mw = 287.35 $gmol^{-1}$
Off-white solid

Tosylate **2.31** (25.3 mg, 38 μmol) was dissolved in a mixture of MeOH (2 mL) and AcCl (0.1 eq.) then stirred at rt for 20 h. The mixture was basified with a sat. soln. of $NaHCO_3$ (6 mL) and stirred for 3 h at rt. The reaction mixture was then extracted with Et_2O (3x) and $CHCl_3$ (2x). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel 60, gradient elution 19:1 to 9:1 CH_2Cl_2/MeOH) yielded (–)-galanthamine as a white solid (8.0 mg, 73%). Spectroscopic data are consistent with those published in the literature.[9]

$[\alpha]_D^{29}$ –92.3 (*c* 0.39, $CHCl_3$) (lit: (natural galanthamine) –91.0, *c* 1.00, 25 °C, $CHCl_3$; (synthetic galanthamine, 99% *ee*) –93.4, *c* 1.00, $CHCl_3$).[9]

MP 118-121 °C (lit: 126-127 °C).[9]

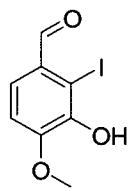
FT-IR ν_{max} (neat) 2918 (m), 1507 (m), 1437 (s), 1282 (m), 1046 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (1H, d, *J* = 8.2 Hz, C_{Ar}**H**), 6.63 (1H, d, *J* = 8.2 Hz, C_{Ar}**H**), 6.07 (1H, d, *J* = 10.2 Hz, CC**H**=CH), 6.01 (1H, dd, *J* = 10.2, 4.7 Hz, CCH=C**H**), 4.62 (1H, br s, **CH**OAr), 4.15 (1H, t, *J* = 4.3 Hz, **CH**OH), 4.10 (1H, d, *J* = 15.1 Hz, NC**H**H), 3.84 (3H, s, OC**H$_3$**), 3.69 (1H, d, *J* = 15.2 Hz, NCH**H**), 3.28 (1H, t, *J* = 13.3 Hz, NC**H**HCH$_2$), 3.06 (1H, br d, *J* = 14.4 Hz, NCH**H**CH$_2$), 2.69 (1H, d, *J* = 15.7 Hz, **CH**HCH(OH)), 2.41 (3H, s, NC**H$_3$**), 2.09 (1H, td, *J* = 13.3, 2.7 Hz, NCH$_2$C**H**H), 2.01 (1H, ddd, *J* = 15.7, 4.7, 2.2 Hz, CH**H**CH(OH)), 1.59 (1H, dd, *J* = 13.5, 1.8 Hz, NCH$_2$CH**H**), 1.26 (1H, s, O**H**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1 ($\mathbf{C}_{Ar}OCH_3$), 144.4 ($\mathbf{C}_{Ar}O$), 133.3 ($\mathbf{C}_{Ar}$), 129.5 ($\mathbf{C}_{Ar}CH_2$), 128.0 (**C**H=CH), 127.1 (CH=**C**HCH(OH)), 122.4 ($\mathbf{C}_{Ar}H$), 111.5 ($\mathbf{C}_{Ar}H$), 89.1 (**C**H(OAr)), 62.4 (**C**H(OH)), 60.9 ($\mathbf{C}_{Ar}CH_2N$), 56.2 ($O\mathbf{C}H_3$), 54.2 ($N\mathbf{C}H_2$), 48.5 (**C**CH=CH), 42.4 ($N\mathbf{C}H_3$), 34.1 ($\mathbf{C}H_2CH(OH)$), 30.3 ($C\mathbf{C}H_2$) ppm.

LRMS (ES+) *m/z* 288.0 (100%, $[M+H]^+$).

3-Hydroxy-2-iodo-4-methoxy benzaldehyde (1.22)



$C_8H_7IO_3$
Mw = 278.04 $gmol^{-1}$
Pale yellow crystals

Following the general procedure described by Markovich *et al.*,[56] isovanillin (12.8 g, 83.4 mmol) was dissolved in dry pyridine (48 mL) and cooled to 0 °C before a solution of ICl (14.1 g, 86.8 mmol) in dry dioxane (84 mL) was added. The cloudy yellow/brown solution turned clear and orange/brown over 1 h at 0 °C. The ice bath was removed and the reaction was stirred for 5 days at rt over which time the solution turned red in colour. The solvent was removed *in vacuo* before H_2O (200 mL) was added and the reaction mixture was acidified to pH 1 with 6 N HCl. The aqueous phase was extracted with EtOAc (3 x 150 mL, 1 x 50 mL). The combined organic layers were washed with 5% $Na_2S_2O_3$ (200 mL), 5% $NaHS_2O_3$ (60 mL), H_2O (2 x 200 mL), brine (200 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Recrystallisation (EtOAc) yielded the title compound as pale yellow crystals (13.0 g, 57%). Spectroscopic data are consistent with those published in the literature.[56]

MP 167-169 °C (EtOAc) (lit: 169-172 °C).[56]

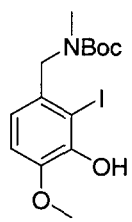
FT-IR ν_{max} (neat) 3184 (br, w), 2941 (w), 1665 (s), 1581 (s), 1556 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.04 (1H, s, **CHO**), 7.56 (1H, d, J = 8.5 Hz, C_{Ar}**H**), 6.93 (1H, d, J = 8.5 Hz, C_{Ar}**H**), 6.32 (1H, s, **OH**), 4.00 (3H, s, OCH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1 (**C**HO), 151.0 ($C_{Ar}OCH_3$), 146.1 (C_{Ar}OH), 129.1 (C_{Ar}CHO), 124.2 (C_{Ar}H), 110.3 (C_{Ar}H), 88.4 (C_{Ar}I), 56.9 (OCH_3) ppm.

LRMS (ES–) *m/z* 277.1 (100%, $[M-H]^-$).

***tert*-Butyl-3-hydroxy-2-iodo-4-methoxybenzylmethylcarbamate (1.70)**



$C_{14}H_{20}INO_4$
Mw = 393.22 $gmol^{-1}$
White powdery solid

Aldehyde **1.22** (1.99 g, 7.2 mmol, 1.0 eq.) was dissolved in MeOH (10 mL) and treated with $MeNH_2$ (7.2 mL of a 2.0 M soln. in MeOH, 14.3 mmol, 2.0 eq.). The pale yellow solution immediately turned bright yellow upon addition eventually turning orange upon complete addition then darkened to brown. The reaction mixture was stirred at rt for 18 h before the solvent was removed *in vacuo*. MeOH (70 mL) was added followed by 4 Å MS (~ 1 g). The reaction mixture was stirred for 15 min before $NaBH_4$ (0.30 g, 7.9 mmol, 1.1 eq.) was added cautiously portionwise over 15 min (CARE! - vigorous evolution of gas). The purple solution turned tan brown in colour upon complete addition. The reaction mixture was stirred for 4 h at rt before the solvent was removed *in vacuo*. The crude material was redissolved in dioxane (35 mL) and 1 N NaOH (20 mL) before Boc_2O (1.70 g, 7.9 mmol, 1.1 eq.) was added. The dark orange/brown solution was stirred for 16 h at rt. The aqueous layer was neutralised with 6 N HCl extracted with EtOAc (4x). The combined organic layers were washed with H_2O (4x), brine (1x) and dried ($MgSO_4$). Purification by column chromatography (silica gel 60A, 3:2 hexane/EtOAc) yielded the title compound as a white powdery solid (1.97 g, 70%). Spectroscopic data is consistent with those published in the literature.[28]

MP 108-111 °C (lit: 108-111 °C).[28]

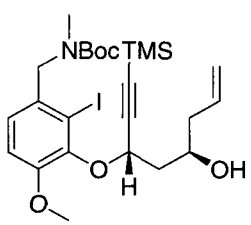
FT-IR ν_{max} (neat) 3270 (br, w), 2969 (w), 1665 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (1H, d, J = 7.9 Hz, C_{Ar}**H**), 6.69 (1H, br d, J = 7.9 Hz, C_{Ar}**H**), 6.20 (1H, s, ArO**H**), 4.44 (2H, br s, N**CH$_2$**), 3.91 (3H, s, O**CH$_3$**), 2.85 (3H, br s, N**CH$_3$**), 1.49-1.47 (9H, m, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3 (**C**O), 146.0 (**C**$_{Ar}$OCH$_3$), 145.3 (**C**$_{Ar}$OH), 132.8 (**C**$_{Ar}$CH$_2$), 118.7 (**C**$_{Ar}$H), 110.8 (**C**$_{Ar}$H), 80.1 (**C**(CH$_3$)$_3$), 57.4 (N**C**H$_2$), 56.7 (O**C**H$_3$), 34.5 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$) ppm. No **C**$_{Ar}$I peak observed.

LRMS (ES–) *m/z* 392.2 (100%, $[M-H]^-$).

(–)-*tert*-Butyl-3-((3*S*,5*R*)-5-hydroxy-1-(trimethylsilyl)oct-7-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((–)-1.78)



$C_{25}H_{38}INO_5Si$
Mw = 587.56 $gmol^{-1}$
Pale yellow oil
NMR spectra exhibited broadening of peaks due to restricted rotation

(+)-DIP-chloride™ (0.37 g, 1.16 mmol, 1.3 eq.) was weighed into a RB flask equipped with a Schlenk arm and vacuum refilled with Ar three times. The solid was then dissolved in Et_2O (10 mL) and cooled to –78 °C before freshly prepared allylMgBr (1.5 mL of a 0.74 M solution, 1.11 mmol, 1.25 eq.) was added dropwise. The resulting black solution was stirred for 5 min at –78 °C before being warmed to rt and stirred for a further 3 h. The black suspension was filtered through a pad of Celite® under Ar to remove the magnesium salts. The pale yellow solution was cooled to –100 °C before aldehyde **1.79** (0.49 g, 0.89 mmol, 1.0 eq.) was added as a solution in Et_2O (5 mL). The resulting solution was stirred at –100 °C for 1 h then quenched by the addition $NaBO_3.4H_2O$ (0.83 g, 5.40 mmol, 6.0 eq.). The suspension was stirred for 30 min. Next, H_2O (10 mL) was added and the layers were separated before the aqueous layer

was extracted with Et_2O (3x). The combined organic layers were washed sequentially with H_2O (1x), brine (1x) and dried ($MgSO_4$) before the solvent was removed *in vacuo*. Purification by column chromatography (silica gel 60A, 8:2 hexane/EtOAc) afforded the title compound as a pale yellow oil (0.45 g, 86%). Inseparable mixture of two diastereomers (3:1 by ^{13}C NMR).

$[\alpha]_D^{28}$ -1.5 (*c* 0.73, $CHCl_3$).

FT-IR ν_{max} (neat) 3459 (br, w), 2961 (m), 1695 (s), 1476 (s) cm^{-1}.

Major diastereomer:

^1H NMR (400 MHz, $CDCl_3$) δ 6.90-6.84 (2H, m, 2 x $C_{Ar}\mathbf{H}$), 5.92 (1H, dddd, *J* = 17.2, 14.1, 7.0, 3.0 Hz, $\mathbf{CH}{=}CH_2$), 5.40 (1H, br s, **CH**OAr), 5.20-5.12 (2H, m, $CH{=}C\mathbf{H_2}$), 4.46 (2H, appt. d, $NC\mathbf{H_2}$), 4.32-4.24 (1H, m, **CH**OH), 3.86 (3H, s, $OC\mathbf{H_3}$), 2.86-2.76 (3H, m, $NC\mathbf{H_3}$), 2.38-2.35 (2H, m, $C\mathbf{H_2}$), 2.20 (1H, ddd, *J* = 14.4, 8.0, 2.5 Hz, C**H**H), 2.06 (1H, ddd, *J* = 14.2, 9.7, 4.2 Hz, CH**H**), 1.48 (9H, appt. d, $C(C\mathbf{H_3})_3$), 0.06 (9H, s, $Si(C\mathbf{H_3})_3$) ppm.

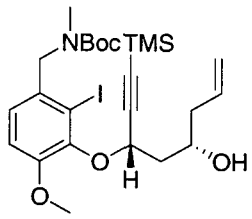
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (**C**O), 151.5 ($\mathbf{C}_{Ar}O$), 146.1 ($\mathbf{C}_{Ar}OCH_3$), 135.3 ($\mathbf{C}H{=}CH_2$), 133.2 ($\mathbf{C}_{Ar}CH_2$), 123.0 ($\mathbf{C}_{Ar}H$), 117.8 ($CH{=}\mathbf{C}H_2$), 112.4 ($\mathbf{C}_{Ar}H$), 103.4 ($SiC{\equiv}\mathbf{C}$), 93.6 ($Si\mathbf{C}{\equiv}C$), 80.1 ($\mathbf{C}(CH_3)_3$), 70.0 (**C**H(OH)), 67.8 (**C**H(OAr)), 57.4 ($N\mathbf{C}H_2$), 56.3 ($O\mathbf{C}H_3$), 42.7 ($\mathbf{C}H_2$), 41.7 ($\mathbf{C}H_2$), 34.5 ($N\mathbf{C}H_3$), 28.8 ($C(\mathbf{C}H_3)_3$), 0.0 ($Si(\mathbf{C}H_3)_3$) ppm. No $\mathbf{C}_{Ar}I$ peak observed.

Selected peaks tentatively assigned to minor diastereomer:

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8 ($\mathbf{C}_{Ar}O$), 135.0 ($\mathbf{C}H{=}CH_2$), 118.1 ($CH{=}\mathbf{C}H_2$), 94.0 ($Si\mathbf{C}{\equiv}C$), 71.1 (**C**H(OH)), 69.4 (**C**H(OAr)), 42.8 ($\mathbf{C}H_2$), 42.7 ($\mathbf{C}H_2$),

LRMS (ES+) *m/z* 610.2 (100%, $[M+Na]^+$).

(+)-*tert*-Butyl-3-((3*S*,5*S*)-5-hydroxy-1-(trimethylsilyl)oct-7-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((+)-1.78)



$C_{25}H_{38}INO_5Si$
Mw = 587.56 $gmol^{-1}$
Pale yellow oil
NMR spectra exhibited broadening of peaks due to restricted rotation

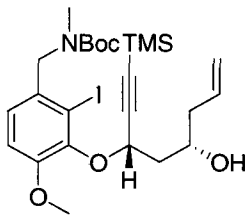
Following the general procedure described by Leighton *et al.*,[62] aldehyde **1.79** (30.8 mg, 57 μmol) was dissolved in dry CH_2Cl_2 (0.25 mL, 0.2 M) and cooled to –10 °C. Next, (*R*,*R*)-silyl complex **2.13** (33.0 mg, 59 μmol, 1.05 eq.) was added in one portion and the reaction mixture was stirred for 10 min before it was placed in a freezer for 17 h. 1 N HCl (1.5 mL) was added followed by EtOAc (2 mL) and stirring was continued for 15 min. The layers were separated between and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with brine (1x) and dried ($MgSO_4$). Purification was achieved by column chromatography (silica gel 60A, gradient elution 9:1 to 8:2 hexane/EtOAc) to yield the title compound as a pale yellow oil (16.2 mg, 48%) as single diastereomer inseparable from phenol **1.70**. ^{1}H NMR spectroscopic data of compound **1.78** is consistent with those previously acquired.

$[\alpha]_D^{27}$ + 3.0 (*c* 1.6, $CHCl_3$).

Selected peaks:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (1H, br d, *J* = 7.0 Hz, C_{Ar}**H**), 6.83 (1H, d, *J* = 8.3 Hz, C_{Ar}**H**), 5.92 (1H, ddt, *J* = 17.0, 9.8, 7.2 Hz, C**H**=CH_2), 5.40 (1H, br. s, C**H**OAr), 5.22-5.10 (2H, m, CH=C**H$_2$**), 4.24 (1H, ddt. *J* = 11.8, 6.2, 2.8 Hz, C**H**OH), 3.85 (3H, s, O**CH$_3$**), 2.37 (2H, t, *J* = 7.0 Hz, **CH$_2$**CH=CH_2), 2.26-2.08 (2H, m, **CH$_2$**CHOAr), 0.04 (9H, s, Si(**CH$_3$**)$_3$) ppm.

(+)-*tert*-Butyl-3-((3*S*,5*S*)-5-hydroxy-1-(trimethylsilyl)oct-7-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((+)-1.78)



$C_{25}H_{38}INO_5Si$
Mw = 587.56 $gmol^{-1}$
Pale yellow oil
NMR spectra exhibited broadening of peaks due to restricted rotation

TiCpCl((*R*,*R*)-TADDOL) complex **2.13** (0.38 g, 0.66 mmol, 1.2 eq.) was suspended in dry Et_2O (10 mL) and cooled to 0 °C. The yellow suspension was treated with freshly prepared allylMgBr (0.60 mL of a 0.83 M soln. in Et_2O, 0.61 mmol, 1.1 eq.) by slow dropwise addition. The brown reaction mixture was stirred for 1.5 h before it was cooled to –78 °C and aldehyde **1.79** (0.28 g, 0.50 mmol) was added dropwise in Et_2O (2 mL). The reaction was stirred for 2 h then quenched by the addition of H_2O (10 mL). The mixture was allowed to warm to rt and was stirred for 16 h. Next, filtration through Celite® and concentration *in vacuo* gave an orange/yellow solid. Purification by column chromatography (silica gel 60A, gradient elution 85:15 to 1:1 hexane/Et_2O) gave the desired product as a pale yellow oil (0.23 g, 79%).

$[\alpha]_D^{27}$ +5.5 (*c* 0.87, $CHCl_3$).

FT-IR ν_{max} (neat) 3459 (w), 2961 (m), 2928 (m), 2362 (w), 1697 (s), 1478 (s), 1250 (s), 1140 (s), 844 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89-6.84 (2H, m, 2 x C_{Ar}**H**), 5.92 (1H, ddt, *J* = 17.3, 10.3, 6.0 Hz, **CH**=CH_2), 5.40 (1H, br s, **CH**OAr), 5.20-5.14 (2H, m, CH=**CH$_2$**), 4.46 (2H, appt. d, N**CH$_2$**), 4.24 (1H, ddt, *J* = 8.5, 6.0, 3.5 Hz, **CH**OH), 3.86 (3H, s, O**CH$_3$**), 2.86-2.78 (4H, m, N**CH$_3$** and O**H**), 2.37 (2H, t, *J* = 6.0 Hz, **CH$_2$**CH=CH_2), 2.21-2.16 (2H, m, **CH$_2$**CHOAr), 1.51-1.44 (9H, m, C(**CH$_3$**)$_3$), 0.04 (9H, s, Si(**CH$_3$**)$_3$) ppm.

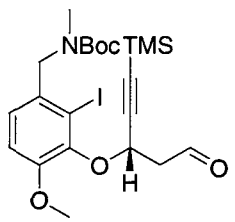
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (**C**O), 151.7 (**C**$_{Ar}$O), 146.0 (**C**$_{Ar}$OCH$_3$), 135.1 (**C**H=CH_2), 132.8 and 132.7 (**C**$_{Ar}$$CH_2$), 123.9 and 122.9 (**C**$_{Ar}$H), 118.2 (CH=**C**H_2), 112.3 (**C**$_{Ar}$H), 103.4 (SiC≡**C**), 93.9 (Si**C**≡C), 80.1 (**C**(CH$_3$)$_3$), 71.1 (**C**H(OH)), 69.4 (**C**H(OAr)), 58.0 and 56.9 (NCH_2),

56.4 (OCH_3), 42.7 (CH_2), 42.2 (CH_2), 34.5 (NCH_3), 28.9 ($C(CH_3)_3$), 0.0 ($Si(CH_3)_3$) ppm. No $C_{Ar}I$ peak observed.

LRMS (ES+) *m/z* 610.0 (100%, $[M+Na]^+$), 1198.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{25}H_{39}INO_5Si$, requires 588.1642 found 588.1635 Da.

***tert*-Butyl-3-((*S*)-1-formyl-4-(trimethylsilyl)but-3-yn-2-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate (1.79)**



$C_{22}H_{32}INO_5Si$
Mw = 545.48 $gmol^{-1}$
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Diol **(±)-2.18** (0.57 g, 0.98 mmol) was dissolved in acetone (4 mL) and H_2O (2 mL) before $NaIO_4$ (0.40 g, 1.87 mmol, 2.0 eq) was added in one portion. The mixture was stirred vigorously for 1.5 h over which time the solution became cloudy. The solvent was removed *in vacuo* before Et_2O and H_2O were added. The layers were separated and the aqueous layer was extracted with Et_2O (3x) before the combined organic layers were washed well with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica gel 60A, 7:3 hexane/EtOAc) to afford the title compound as a colourless oil (0.52 g, 96%).

FT-IR ν_{max} (neat) 2964 (m), 2361 (w), 1728 (s), 1694 (s), 1477 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.1 (1H, t, *J* = 1.9 Hz, **CHO**), 6.90-6.82 (2H, m, 2 x C_{Ar}**H**), 5.63 (1H, br s, **CH**(OAr)), 4.45 (2H, appt. br d, NCH_2), 3.85 (3H, s, OCH_3), 3.00 (2H, dd, *J* = 5.3, 1.9 Hz, CH_2), 2.85-2.81 (3H, m, NCH_3), 1.50-1.44 (9H, m, $C(CH_3)_3$), 0.05 (9H, s, $Si(CH_3)_3$) ppm.

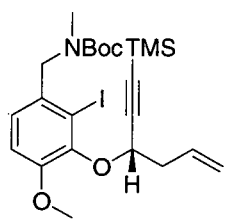
^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6 (**CHO**), 156.3 (**CO**), 151.7 ($C_{Ar}OCH_3$), 145.9 ($C_{Ar}O$), 132.9 ($C_{Ar}CH_2$), 123.6 ($C_{Ar}H$), 112.5 ($C_{Ar}H$), 101.7 (SiC≡**C**),

98.9 ($\mathbf{C}_{Ar}I$), 94.8 (Si**C**≡C), 80.3 (**C**$(CH_3)_3$), 67.3 (**C**H(OAr)), 57.4 (N**C**H_2), 56.3 (O**C**H_3), 49.0 (**C**H_2), 34.5 (N**C**H_3), 28.8 (C(**C**$H_3)_3$), –0.1 (Si(**C**$H_3)_3$) ppm.

LRMS (ES+) *m/z* 568.2 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{22}H_{32}INO_5SiNa$, requires 568.0992 found 568.0987 Da.

(+)-*tert*-Butyl-3-((*S*)-1-(trimethylsilyl)hex-5-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((+)-1.80)



$C_{23}H_{34}INOSi$
Mw = 543.51 $gmol^{-1}$
Pale yellow oil
NMR spectra exhibited broadening of peaks due to restricted rotation

To a solution of phenol **1.70** (75.0 mg, 0.19 mmol, 1.05 eq.) and PPh_3 (94.0 mg, 0.36 mmol, 2.0 eq.) in THF (1 mL) was added a solution of alcohol **(+)-1.81** (single enantiomer) (30.0 mg, 0.18 mmol, 1.0 eq.) in THF (2 mL). The resulting mixture was stirred for 5 min before DIAD (0.07 mL, 0.36 mmol, 2.0 eq.) was added dropwise giving a dark orange solution. The solution was heated at 55 °C for 3 h before being cooled to rt and concentrated *in vacuo*. Purification of the resulting brown oil by column chromatography (silica gel 60A, dry loaded, 9:1 hexane/EtOAc) gave the title product as a pale yellow oil (95.0 mg, 97%).

$[\alpha]_D^{31}$ +15.6 (*c* 0.95, $CHCl_3$).

FT-IR ν_{max} (neat) 2962 (m), 1695 (s), 1476 (s), 840 (s) cm^{-1}.

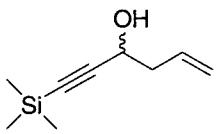
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96-6.74 (2H, m, 2 x C_{Ar}**H**), 6.04 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, C**H**=CH_2), 5.30-5.11 (3H, m, C**H**OAr and CH=C**H**$_2$), 4.57-4.36 (2H, appt d, NC**H**$_2$), 3.85 (3H, s, OC**H**$_3$), 2.92-2.70 (3H, br s, C**H**$_2$ and NC**H**$_3$), 1.47 (9H, appt d, C(C**H**$_3)_3$), 0.04 (9H, s, Si(C**H**$_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (**C**O), 151.8 ($\mathbf{C}_{Ar}OCH_3$), 146.5 ($\mathbf{C}_{Ar}O$), 133.9 (**C**H=CH_2), 132.8 ($\mathbf{C}_{Ar}CH_2$), 123.6 and 122.6 ($\mathbf{C}_{Ar}H$), 118.2 (CH=**C**H_2), 112.4 ($\mathbf{C}_{Ar}H$), 103.4 (SiC≡**C**), 100.6 and 97.6 ($\mathbf{C}_{Ar}I$), 93.1 (Si**C**≡C), 80.1 ($\mathbf{C}(CH_3)_3$), 71.8 (**C**H(OAr)), 58.0 and 56.9 (NCH_2), 56.3 (OCH_3), 40.8 ($\mathbf{C}H_2$), 34.5 (NCH_3), 28.8 ($C(\mathbf{C}H_3)_3$), 0.0 ($Si(\mathbf{C}H_3)_3$) ppm.

LRMS (ES+) *m/z* 566.2 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{23}H_{34}INO_4SiNa$, requires 566.1199 found 566.1194 Da.

1-Trimethylsilyl-hex-5-en-1-yn-3-ol ((±)-1.81)



$C_9H_{16}OSi$
Mw = 168.31 $gmol^{-1}$
Yellow oil

Aldehyde **2.02** (1.49 g, 11.8 mmol) in Et_2O (5 mL) was added dropwise to allylmagnesium bromide (13.1 mL of a 0.99 M soln. in Et_2O, 13.0 mmol) at –50 °C. The reaction was stirred for 1.5 h over which time the solution warmed to –10 °C. The reaction was quenched by pouring onto a sat. soln. of NH_4Cl (50 mL). The mixture was stirred rapidly for 10 min before it was separated and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (1x), brine (1x) then dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica gel 60A, 9:1 hexane/EtOAc) to yield the desired compound as a yellow oil (1.90 g, 96%). Spectroscopic data is consistent with that published in the literature.[176]

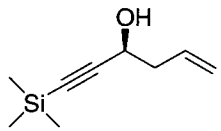
FT-IR ν_{max} (neat) 3334 (br w), 2960 (w), 2175 (w), 1250 (m), 837 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (1H, ddt, *J* = 17.8, 9.6, 7.1 Hz, **CH**=CH_2), 5.23-5.17 (2H, m, CH=**CH$_2$**), 4.41 (1H, q, *J* = 6.1 Hz, **CH**(OH)), 2.48 (2H, t, *J* = 6.1 Hz, **CH$_2$**), 1.93-1.91 (1H, m, **OH**), 0.18 (9H, s, $Si(\mathbf{CH_3})_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3 (**C**H=CH_2), 119.3 (CH=**C**H_2), 106.3 (SiC≡**C**), 90.2 (Si**C**≡C), 62.3 (**C**H(OH)), 42.5 (**C**H_2), 0.18 (Si(**C**H_3)$_3$) ppm.

LRMS (EI) 127 (90%, [M-$C_3H_5^+$]).

(*S*)-(–)-1-Trimethylsilyl-hex-5-en-1-yn-3-ol ((–)-1.81)

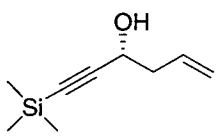


$C_9H_{16}OSi$
Mw = 168.31 gmol^{-1}
Yellow oil

Spectroscopic data for **(–)-1.81** is identical to those previously collected.

$[\alpha]_D^{29}$ –37.9 (*c* 0.98, $CHCl_3$) (lit: –29.0, *c* 0.85, rt, $CHCl_3$).[176]

(*R*)-(+)-1-Trimethylsilyl-hex-5-en-1-yn-3-ol ((+)-1.81)

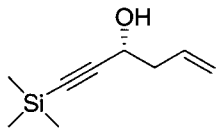


$C_9H_{16}OSi$
Mw = 168.31 gmol^{-1}
Pale yellow oil

Following the general procedure described by Burova *et al.*,[41] acetate **(+)-2.03** (0.66 g, 3.1 mmol) was dissolved in CH_2Cl_2 (6 mL) and cooled to –78 °C before DIBAL-H (5.30 mL of a 1.0 M soln. in hexanes, 5.3 mmol, 1.7 eq.) was added dropwise. The resulting pale yellow solution was stirred for 30 min before EtOAc (3 mL) was added. The reaction mixture was stirred for a further 20 min at –78 °C before it was poured on to a sat. aq. soln. of Rochelle's salt (50 mL) and stirred for 1 h. The layers were separated and the aqueous layer was extracted with Et_2O (2x) and EtOAc (1x). The combined organic layers were then dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica gel 60A, 85:15 hexane/EtOAc) to yield the desired alcohol as a pale yellow oil (0.48 g, 92%). Spectroscopic data are consistent with those previously collected.

$[\alpha]_D^{28}$ +41.0 (*c* 0.60, $CHCl_3$) (lit: +34.0, *c* 0.94, rt, $CHCl_3$).[41]

(*R*)-(+)-1-Trimethylsilyl-hex-5-en-1-yn-3-ol ((+)-1.81)

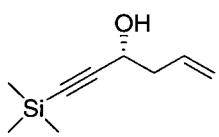


$C_9H_{16}OSi$
Mw = 168.31 $gmol^{-1}$
Yellow oil
~3:1 Ratio of enantiomers
determined by HPLC analysis

(+)-DIP-Chloride™ **(2.12)** (3.39 g, 10.6 mmol, 1.2 eq.) was weighed into a RB flask equipped with a Schlenk arm and vacuum refilled with Ar three times. The solid was then dissolved in Et_2O (10 mL) and cooled to –50 °C before freshly prepared allylMgBr (9.89 mL of a 0.97 M soln. in Et_2O, 9.6 mmol, 1.1 eq.) was added dropwise. The resulting black solution was stirred for 5 min at this temperature before it was allowed to warm to rt and stir for a further 2 h. The resulting suspension was filtered through a pad of Celite® under Ar to remove the magnesium salts. The pale yellow solution was cooled to –95 °C before aldehyde **2.02** (1.31 g, 8.6 mmol, 1.0 eq) was added dropwise as a solution in Et_2O (5 mL) over 5 min. The resulting solution was stirred between –95 and –89 °C for 1 h. The reaction was quenched by the addition of MeOH (1 mL) before being warmed to rt. Next, $NaBO_3.4H_2O$ (13.50 g, 88.0 mmol, 10 eq.) was added and the suspension was stirred for 16 h. H_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O (3x) before the combined organic layers were washed sequentially with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Purification by column chromatography (silica gel 60A, 9:1 hexane/EtOAc) afforded the title compound as a pale yellow oil (1.09 g, 74%). Spectroscopic data are consistent with those previously collected.

$[\alpha]_D^{27}$ +29.1 (*c* 0.99, $CHCl_3$) (lit: +34.0, *c* 0.94, rt, $CHCl_3$).[41]

(*R*)-(+)-1-Trimethylsilyl-hex-5-en-1-yn-3-ol ((+)-1.81)



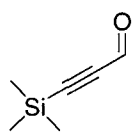
$C_9H_{16}OSi$
Mw = 168.31 $gmol^{-1}$
Yellow/brown oil

TiCpCl((*S,S*)-TADDOL) complex **2.13** (0.99 g, 1.56 mmol, 1.2 eq.) was suspended in dry Et_2O (10 mL) resulting in a pale yellow suspension. This was cooled to 0 °C and treated with freshly prepared allylMgBr (1.94 mL of a 0.74 M soln. in Et_2O, 1.44 mmol,

1.15 eq.) by slow dropwise addition over 10 min. The resulting dark orange/brown solution was stirred for 2 h at 0 °C before it was cooled to –78 °C. Next, aldehyde **2.02** (0.16 g, 1.25 mmol) was added slowly dropwise as a solution in Et_2O (5 mL). The reaction was allowed to stir for 1 h at –78 °C after which time H_2O (10 mL) was added. The mixture was allowed to warm to rt and was stirred for 48 h before being filtered through a pad of Celite®. The layers were separated and the aqueous layer was extracted with Et_2O (3x) before the combined organic layers were washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica gel 60A, 9:1 hexane/EtOAc) to yield the title compound as a yellow/brown oil (0.16 g, 77%). Spectroscopic data is consistent with that previously collected.

$[\alpha]_D^{27}$ +36.6 (*c* 0.99, $CHCl_3$) (lit: +34.0, *c* 0.94, rt, $CHCl_3$).[41]

3-(Trimethylsilyl)propioaldehyde (2.02)

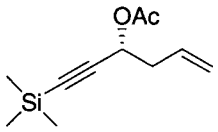


$C_6H_{10}OSi$
Mw = 126.23 $gmol^{-1}$
Yellow oil

Following the procedure described by Journet *et al.*,[42] TMS acetylene (8.0 mL, 56.6 mmol) was dissolved in dry Et_2O (100 mL) and cooled to –40 °C before *n*-BuLi (22.6 mL of a 2.5 M soln. in hexanes, 56.6 mmol) was added slowly. The reaction mixture was stirred for 5 min before anhydrous DMF (8.0 mL, 0.1 mol, 1.8 eq.) was added dropwise. The cold bath was removed and the reaction mixture was stirred vigorously for 30 min before it was quenched by pouring on to a rapidly stirred soln. of 10% NaH_2PO_4 (270 mL) and Et_2O (200 mL) at 5 °C. Stirring was continued for 10 min over which time the aqueous layer turned dark yellow. The layers were separated and the organic layer was washed with H_2O (1x) before the combined aqueous layers were extracted with Et_2O (2x). The combined organic layers were then dried ($MgSO_4$). The bulk of the solvent was removed by careful distillation (50 °C, atm. pres.) then the resulting oil was purified by Kugelrohr distillation (145-155 °C, 20 mbar) to yield a yellow free flowing oil (4.0 g, 56%). Spectroscopic data is consistent with that published in the literature.[177]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (1H, s, **CH**O), 0.28 (9H, s, Si(**CH$_3$**)$_3$) ppm.

(*R*)-(+)-1-(Trimethylsilyl)hex-5-en-1-yn-3-acetate ((+)-2.03)



$C_{11}H_{18}O_2Si$
Mw = 210.34 gmol^{-1}
Yellow oil

To a solution of alcohol **(±)-1.81** (1.19 g, 7.1 mmol) in hexanes (57 mL) over 4 Å MS (2.0 g) was added vinyl acetate (2.41 mL, 26.2 mmol, 3.7 eq.) and Amano® AK20 enzyme (1.3 g). The brown suspension was stirred at rt for 23 h before it was filtered through Celite® and washed thoroughly with Et_2O (2 x 50 mL). Purification by column chromatography (silica gel 60A, gradient elution 91:9 to 85:15 hexane/Et_2O) yielded the desired acetate **(+)-2.03** as a pale yellow oil (0.70 g, 47%) and alcohol **(–)-1.81** as a pale yellow oil (0.51 g, 43%). Spectroscopic data are consistent with those published in the literature.[41]

$[\alpha]_D^{30}$ +99.9 (*c* 0.97, $CHCl_3$) (lit: +85.0, *c* 0.97, rt, $CHCl_3$).[41]

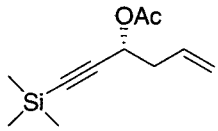
FT-IR ν_{max} (neat) 2960 (w), 2361 (w), 1745 (s), 1224 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 17.2, 10.2, 6.9 Hz, **CH**=CH_2), 5.43 (1H, t, *J* = 6.4 Hz, **CH**OAc), 5.49-5.12 (2H, m, CH=**CH$_2$**), 2.51 (2H, tt, *J* = 6.8, 1.3 Hz, **CH$_2$**), 2.08 (3H, s, **CH$_3$**), 0.17 (9H, s, Si(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (**C**O), 132.6 (**C**H=CH_2), 119.0 (CH=**C**H$_2$), 102.4 (SiC≡**C**), 91.2 (Si**C**≡C), 63.9 (**C**HOAc), 39.7 (**C**H$_2$), 21.3 (**C**H$_3$), 0.1 (Si(**C**H$_3$)$_3$) ppm.

LRMS (EI) 43 (100%, [$C_2H_3O^+$]), 169 (90%, [M-$C_3H_5^+$]).

(*R*)-(+)-1-(Trimethylsilyl)hex-5-en-1-yn-3-yl acetate ((+)-2.03)

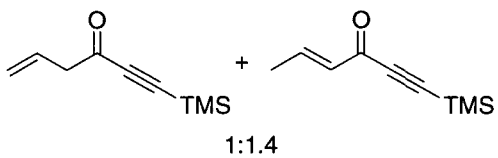


$C_{11}H_{18}O_2Si$
Mw = 210.34 $gmol^{-1}$
Colourless oil

Following the general procedure described by Weinreb *et al.*,[178] to a solution of alcohol **(–)-1.81** (0.50 g, 3.0 mmol), PPh_3 (3.00 g, 11.8 mmol, 4.0 eq.), pyridine (0.47 mL, 5.9 mmol, 2.0 eq.) and acetic acid (0.84 mL, 14.8 mmol, 5.0 eq.) in THF (30 mL) at –50 °C was added DEAD (1.86 mL, 11.8 mmol, 4.0 eq.). The resulting bright yellow solution was stirred for 10 min before being warmed to 0 °C and stirred for 18 h, allowing to warm to rt. The bright yellow solution faded to pale yellow over the first 15 min. The solvent was removed *in vacuo* before the crude oil was redissolved in Et_2O (100 mL) and washed with a sat. soln. of $NaHCO_3$ (1x), 5% HCl (1x) and brine (1x). Purification by column chromatography (silica gel 60A, dry loaded, gradient elution 19:1 to 9:1 hexane/Et_2O) yielded the desired acetate as a colourless oil (0.45 g, 72%). Spectroscopic data is consistent with that previously collected.

$[\alpha]_D^{30}$ +97.7 (*c* 0.99, $CHCl_3$) (lit: +85.0, *c* 0.97, rt, $CHCl_3$).[41]

1-(Trimethylsilyl)hex-5-en-1-yn-3-one (2.04)



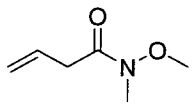
$C_9H_{14}OSi$
Mw = 166.29 $gmol^{-1}$
Orange oil

A solution of TMS acetylene (0.57 mL, 4.06 mmol) in THF (15 mL) was cooled to –78 °C before being treated with *n*-BuLi (1.73 mL of a 2.35 M soln., 4.06 mmol). The reaction was stirred for 5 min at this temperature before it was warmed to 0 °C and stirred for 40 min. The solution was cooled to –35 °C before a solution of Weinreb amide **2.05** (0.50 g, 0.39 mmol) in THF (5 mL) was added dropwise. The reaction mixture was allowed to stir for 1 h then warmed to –10 °C and stirred for 40 min. The reaction was quenched by the addition of a sat. soln. of NH_4Cl (10 mL). The layers were separated between Et_2O/H_2O and the aqueous layer was extracted with Et_2O (2x). The combined organic layers were washed with H_2O (20 mL), brine (30 mL) and dried

($MgSO_4$). The solvent was removed *in vacuo* to yield an orange oil that was purified by column chromatography (silica gel 60A, 39:1 hexane/Et_2O) to give the title compound as a mixture of isomers (0.19 g, 30%, 1:1.4 product:isomer). Spectroscopic data are consistent with that published in the literature.[177]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (1H, ddt, *J* = 17.1, 10.4, 7.0 Hz, C**H**=CH_2), 5.25-5.16 (2H, m, CH=C**H$_2$**), 3.33 (2H, dt, *J* = 7.0, 1.5 Hz, C**H$_2$**), 0.26 (9H, s, Si(C(**CH$_3$**)$_3$) ppm.

_N_-Methoxy-_N_-methylbut-3-enamide (2.05)



$C_6H_{11}NO_2$
Mw = 129.16 $gmol^{-1}$
Yellow oil

Following the procedure described by Eihorn *et al.*,[45] butenoic acid (8.0 g, 93.0 mmol), *N,O*-dimethylhydroxylamine hydrochloride (9.07 g, 93.0 mmol), NEt_3 (13.0 mL, 93.0 mmol) and carbon tetrabromide (30.8 g, 93.0 mmol) were dissolved in dry CH_2Cl_2 (200 mL) giving a yellow solution. To this was added PPh_3 (24.4 g, 93.0 mmol) portionwise over 10 min. The red/brown reaction mixture was stirred for 40 min before the solvent was removed *in vacuo*. The crude mixture was redissolved in EtOAc/hexane (1:1) and filtered to removed the insoluble by-products. The solvent was removed *in vacuo* and the oil was purified by distillation (Kugelrohr, 40 °C, 0.5 mbar) to give the title compound as a yellow oil (18.1 g, 150%). Contaminated with $CHBr_3$.

FT-IR ν_{max} (neat) 2972 (w), 1659 (s), 1414 (m) cm^{-1}.

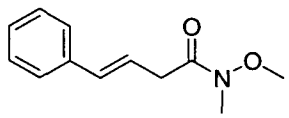
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (1H, ddt, *J* = 17.0, 9.7, 6.8 Hz, C**H**=CH_2), 5.19-5.13 (2H, m, CH=C**H$_2$**), 3.69 (3H, s, OC**H$_3$**), 3.22 (2H, d, *J* = 6.8 Hz, C**H$_2$**CH=CH_2), 3.18 (3H, s, NC**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5 (**C**ON), 131.5 (**C**H=CH_2), 118.4 (CH=**C**H_2), 61.6 (O**C**H_3), 37.5 (N**C**H_3), 32.6 (**C**H_2) ppm.

LRMS (ES+) *m/z* 130.1 (45%, $[M+H]^+$), 152.2 (25%, $[M+Na]^+$), 193.3 (100%, $[M+Na(MeCN)]^+$).

HRMS (EI) for $C_6H_{11}NO_2$, requires 129.0790 found 129.0787 Da.

(*E*)-*N*-Methoxy-*N*-methyl-4-phenylbut-3-enamide (2.10)



$C_{12}H_{15}NO_5$
Mw = 205.25 $gmol^{-1}$
Yellow oil

Following the procedure described (*vide supra*), the reaction of *trans*-styrylacetic acid (1.10 g, 6.78 mmol), *N,O*-dimethylhydroxylamine hydrochloride (0.66 g, 6.78 mmol), NEt_3 (0.94 mL, 6.78 mmol), carbon tetrabromide (2.25 g, 6.78 mmol) and PPh_3 (1.78 g, 6.78 mmol) in CH_2Cl_2 (15 mL) gave the title compound as a yellow oil (1.09 g, 78%) after purification by column chromatography (silica gel 60A, 1:1 hexane/EtOAc).

FT-IR ν_{max} (neat) 3026 (w), 2937 (w), 1660 (s), 1448 (m), 1415 (m), 1383 (m), 1174 (m), 965 (s), 734 (s), 692 (s) cm^{-1}.

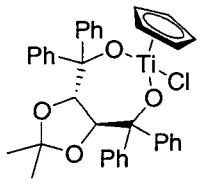
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.16 (5H, m, 5 x C_{Ar}**H**), 6.49 (1H, d, *J* = 15.9 Hz, PhC**H**=CH), 6.34 (1H, dt, *J* = 15.9, 6.4 Hz, PhCH=C**H**), 3.70 (3H, s, O**CH$_3$**), 3.36 (2H, d, *J* = 6.4 Hz, **CH$_2$**), 3.19 (3H, s, N**CH$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (**C**H=CH_2), 133.5 (**C**$_{Ar}$), 128.8 (**C**$_{Ar}$H), 127.7 (**C**$_{Ar}$H), 126.6 (**C**$_{Ar}$H), 123.1 (**C**$_{Ar}$H), 61.7 (O**C**H_3), 36.9 (N**C**H_3), 32.7 (**C**H_2) ppm. No **C**O peak observed.

LRMS (ES+) *m/z* 228.0 (95%, $[M+Na]^+$), 269.0 (100%, $[M+Na(MeCN)]^+$), 433.0 (35%, $[2M+Na]^+$).

HRMS (ES+) for $C_{12}H_{15}NO_5Na$, requires 228.0995 found 228.0998 Da.

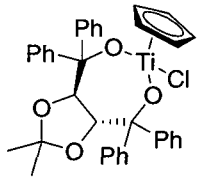
Cyclopentadienyl[(4S,*trans*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*'] titanium chloride ((*S*,*S*)-2.13)



$C_{37}H_{36}ClO_4Ti$
Mw = 628.00 $gmol^{-1}$
Pale yellow powdery solid

The title compound was prepared according to the literature procedure,[52] $TiCpCl_3$ (2.0 g, 9.12 mmol) was dissolved in Et_2O (72 mL) before diol **(+)-2.16** (4.3 g, 9.12 mmol) was added in one portion. The yellow solution was stirred for 2 min before NEt_3 (2.8 mL, 20.1 mmol) in Et_2O (23 mL) was added dropwise. The solution became opaque and was stirred at rt for 16 h. The solid was removed by filtration under Ar and washed well with Et_2O (3 x 10 mL). The filtrate was concentrated *in vacuo* to ~10 mL. Next, dry hexane (60 mL) was added and the resulting gum was triturated and the solid collected by filtration. The solid was dried under vacuum to yield a powdery pale yellow solid (4.4 g, 76%).

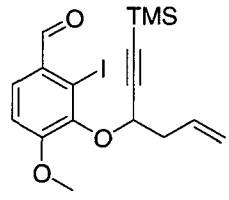
Cyclopentadienyl[(4*R*,*trans*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*'] titanium chloride ((*R*,*R*)-2.13)



$C_{37}H_{36}ClO_4Ti$
Mw = 628.00 $gmol^{-1}$
Pale yellow powdery solid

The title compound was prepared according to the procedure described (*vide supra*), as powdery pale yellow solid (3.1 g, 75%).

3-(1-(Trimethylsilyl)hex-5-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzaldehyde (2.14)



$C_{17}H_{21}IO_3Si$
Mw = 428.34 $gmol^{-1}$
Pale yellow oil

To a solution of aromatic aldehyde **1.22** (73.0 mg, 0.26 mmol) and PPh_3 (134.0 mg, 0.5 mmol) in THF (2 mL) was added a solution of alcohol **1.81** (42.5 mg, 0.25 mmol) in THF (1 mL). The resulting mixture was stirred for 5 min before DIAD (0.1 mL, 0.5 mmol) was added dropwise giving a golden yellow solution. The solution was heated at 45 °C for 16 h before being cooled to rt and concentrated *in vacuo*. Purification of the resulting brown oil by column chromatography (silica gel 60A, dry loaded, 9:1 hexane/EtOAc) gave the title product as a pale yellow oil (37.3 mg, 35%).

FT-IR ν_{max} (neat) 3079 (w), 2958 (w), 2845 (w), 1682 (s), 1574 (s), 1476 (s) cm^{-1}.

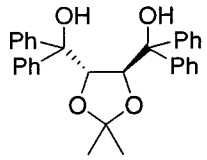
^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (1H, s, C**H**O), 7.71 (1H, d, J = 8.6 Hz, C_{Ar}**H**), 6.95 (1H, d, J = 8.6 Hz, C_{Ar}**H**), 6.04 (1H, ddt, J = 17.0, 10.1, 7.0 Hz, C**H**=CH_2), 5.29-5.16 (3H, m, CH=C**H$_2$** and C**H**(OAr)), 3.93 (3H, s, O**CH$_3$**), 2.82-2.77 (2H, m, C**H$_2$**), 0.00 (9H, s, Si(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (**C**HO), 158.0 (**C**$_{Ar}$OCH$_3$), 146.5 (**C**$_{Ar}$O), 133.6 (**C**H=CH_2), 129.4 (**C**$_{Ar}$CHO), 127.5 (**C**$_{Ar}$H), 118.4 (CH=**C**H$_2$), 111.8 (**C**$_{Ar}$H), 103.0 (SiC≡**C**), 102.6 (Si**C**≡C), 94.1 (**C**$_{Ar}$I), 72.1 (**C**H(OAr)), 56.5 (O**C**H$_3$), 40.7 (**C**H$_2$), –0.1 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ES+) *m/z* 451.1 (100%, [M+Na$^+$]).

HRMS (ES+) for $C_{17}H_{21}IO_3SiNa$, requires 451.0202 found 451.0196 Da.

(+)-(4*S*,5*S*)-5-[Hydroxy(diphenyl)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl(diphenyl)methanol ((+)-2.16)



$C_{31}H_{30}O_4$
Mw = 466.57 $gmol^{-1}$
White solid

To a flame-dried flask was added Mg turnings (0.89 g, 36.7 mmol, 8.0 eq) that were vigorously stirred under Ar for 16 h over which time the Mg turnings had turned black.

Next, THF (23 mL) was added followed by I_2 (2 crystals) in THF (1 mL). PhBr (3.87 mL, 36.7 mmol, 8.0 eq.) was added at such a rate as to maintain a steady reflux (initiated with a heat gun). Upon complete addition the reaction was heated at reflux for 15 min. before it was cooled to 0 °C. Addition of the (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid dimethyl ester **2.15** (1.00 g, 4.6 mmol) in THF (18 mL) in a slow, dropwise fashion turned the solution dark purple. The reaction mixture was heated to reflux for 3 h and then stirred for 18 h. The reaction mixture was cooled to 0 °C and quenched by the addition of a sat. soln. of NH_4Cl (30 mL). Et_2O and H_2O were added. The layers were separated and the aqueous layer was extracted with Et_2O (3x). The combined organic layers were washed with H_2O (2x), brine (1x) and dried ($MgSO_4$). Purification by column chromatography (silica gel 60A, gradient elution 19:1 to 17:3 hexane/EtOAc) afforded the title compound as a white solid (1.70 g, 79%). Spectroscopic data are consistent with those published in the literature.[179]

$[\alpha]_D^{24}$ +62.6 (*c* 1.00, $CHCl_3$) (lit: (*R*,*R*-enantiomer): –60.6, *c* 1.00, $CHCl_3$).[179]

MP 190-194 °C (CH_2Cl_2/hexane) (lit: 195-197 °C).[179]

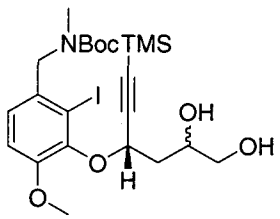
FT-IR ν_{max} (solid) 3440 (br, w), 3206 (br (w), 2890 (w), 1494 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51-7.48 (4H, m, 4 x C_{Ar}**H**), 7.34-7.20 (16H, m, 16 x C_{Ar}**H**), 4.58 (2H, s, 2 x C**H**), 3.82 (2H, s, 2 x O**H**), 1.00 (6H, s, 2 x **CH_3**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3 (**C_{Ar}**), 142.1 (**C_{Ar}**), 128.0 (**C_{Ar}**H), 127.5 (**C_{Ar}**H), 127.0 (**C_{Ar}**H), 126.9 (**C_{Ar}**H), 126.7 (**C_{Ar}**H), 126.6 (**C_{Ar}**H), 108.9 (**$C(CH_3)_2$**), 80.4 (2 x **C**OC), 77.5 (2 x **C**OH), 26.5 (2 x **CH_3**) ppm.

LRMS (ES–) *m/z* 465.4 (100%, $[M-H]^-$).

(±)-*tert*-Butyl-3-((*S*)-5,6-dihydroxy-1-(trimethylsilyl)hex-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((±)-2.18)



$C_{23}H_{36}INO_6Si$
Mw = 577.53 $gmol^{-1}$
Pale yellow oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Following the general procedure described by Fokin *et al.*,[58] alkene **(+)-1.80** (0.80 g, 1.46 mmol, 1.0 eq.) was dissolved in *t*-BuOH/H_2O (1:1, 1.5 mL, 1.0 M) treated with citric acid (0.56 g, 1.76 mmol, 1.2 eq.) and stirred for 5 min before OsO_4 (0.27 mL of 2.5 wt% soln. in *t*-BuOH, 22 μmol, 1.5 mol%) was added. Next, NMO (0.21 g, 1.76 mmol, 1.2 eq) was added in one portion giving a green/black solution. The reaction mixture was stirred for 20 h at rt then quenched by the addition of sodium dithionite (0.5 g) and stirred for 20 min. The mixture was separated between EtOAc/H_2O. The aqueous layer was extracted with EtOAc (3x) and CH_2Cl_2 (3x). The separate organic layers were washed H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a brown oil. Purification by column chromatography (silica gel 60A, gradient elution 85:15 to 3:7 hexanes/EtOAc) yielded the diol as a pale yellow oil (0.55 g, 65%).

FT-IR ν_{max} (neat) 3431 (m), 2961 (m), 1695 (s), 1476 (s), 1248 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89-6.85 (2H, m, 2 x C_{Ar}**H**), 5.42 (1H, br s, **CH**(OAr)), 4.50-4.31 (3H, m, N**CH$_2$** and O**H**), 3.87 (3H, appt. d, O**CH$_3$**), 3.79-3.71 (1H, m, **CH**HOH), 3.66-3.60 (1H, m, CH**H**OH), 3.35 (0.5H, s, **CH**OH), 3.09 (0.5H, s, **CH**OH), 2.86-2.80 (3H, appt. d, N**CH$_3$**), 2.31-2.07 (3H, m, **CH$_2$** and O**H**), 1.44-1.43 (9H, m, C(**CH$_3$**)$_3$), 0.05 (9H, appt. d, Si(**CH$_3$**)$_3$) ppm.

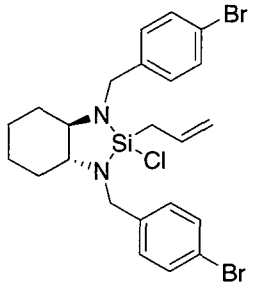
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (**C**O), 151.7 (**C**$_{Ar}$OCH$_3$), 146.0 (**C**$_{Ar}$O), 133.0 (**C**$_{Ar}$CH$_2$), 124.0 (**C**$_{Ar}$H), 112.4 (**C**$_{Ar}$H), 103.1 (SiC≡**C**), 94.1 (Si**C**≡C), 80.2 (**C**(CH$_3$)$_3$), 70.7 (**C**HOH), 70.0 (**C**HOH), 67.0 (**C**H$_2$OH), 57.4

(NCH_2), 56.3 (OCH_3), 39.7 (CH_2), 34.5 (NCH_3), 28.8 ($C(CH_3)_3$), –0.08 ($Si(CH_3)_3$) ppm. No $C_{Ar}I$ peak observed.

LRMS (ES+) *m/z* 600.2 (100%, $[M+Na]^+$), 1177.5 (50%, $[2M+Na]^+$).

HRMS (ES+) for $C_{23}H_{36}INO_6Si$, requires 600.1254 found 600.1249 Da.

2-Allyl-1,3-bis-(4-bromo-benzyl)-2-chloro-octahydro-benzo[1,3,2]diazasilole (2.19)



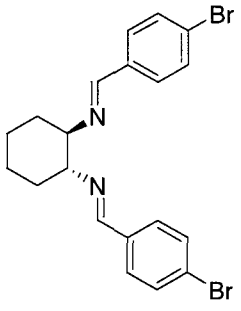
$C_{23}H_{27}Br_2ClN_2Si$
Mw = 554.82 $gmol^{-1}$
White solid

Great care was taken to exclude moisture and air from the reaction vessel at all stages. Following the procedure described by Leighton,[62] allyltrichlorosilane (1.13 mL, 7.9 mmol, 1.2 eq.) was dissolved in CH_2Cl_2 (20 mL) before freshly distilled DBU (2.36 mL, 15.8 mmol, 2.4 eq.) was added at 0 °C. Next, (*R,R*)-diamine **(–)-2.22** (2.99 g, 6.6 mmol) was added slowly dropwise over 25 min in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 16 h before the solvent was removed by vacuum transfer and then dried under high vacuum (0.4 mbar) for 30 min to give a yellow viscous oil. Next, dry pentane (2 x 5 mL) was added to afford a white precipitate. This suspension was stirred rapidly for 3 h before it was filtered through a filter stick under Ar and washed with pentane (3 x 5 mL). A solid formed instantly in the filtrate. Dry CH_2Cl_2 (2 mL) was added and the flask was placed in a freezer (–10 °C) for 16 h to induce slow crystallisation. The mother liquor was removed via a cannula and the resulting white solid dried under vacuum (2.88 g, 80%). No further purification was necessary. Spectroscopic data is consistent with that published in the literature.[62]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.36 (4H, m, $C_{Ar}\mathbf{H}$), 7.29 (2H, d, *J* = 8.4 Hz, $C_{Ar}\mathbf{H}$), 7.26 (2H, d, *J* = 8.4 Hz, $C_{Ar}\mathbf{H}$), 5.63 (1H, ddt, *J* = 18.5, 10.8, 8.0 Hz, $C\mathbf{H}=CH_2$), 4.94-4.89 (2H, m, $CH=C\mathbf{H_2}$), 4.15 (1H, d, *J* = 15.5 Hz,

CH_2Ar), 4.00 (1H, d, J = 15.5 Hz, CH_2Ar), 3.85 (2H, d, J = 15.5 Hz, CH_2Ar), 2.80 (1H, td, J = 9.2, 3.0 Hz, CHN), 2.72 (1H, td, J = 9.2, 3.0 Hz, CHN), 1.83-1.60 (6H, m, 3 x CH_2), 1.19-0.90 (4H, m, 2 x CH_2) ppm.

(–)-(1*R*,2*R*)-*N*,*N*'-Bis(4-bromobenzylidene)diiminocyclohexane ((–)-2.21)



$C_{20}H_{20}N_2Br_2$
Mw = 448.19 $gmol^{-1}$
White solid

(1*R*,2*R*)-(+)-1,2-Diaminocyclohexane L-tartrate (5.46 g, 20.4 mmol) was dissolved in EtOH (30 mL) and H_2O (30 mL) before it was treated with 4-bromobenzaldehyde (7.6 g, 40.8 mmol, 2.0 eq.) and K_2CO_3 (6.8 g, 40.8 mmol, 2.0 eq.). The reaction was heated to reflux temperature for 3 h where upon the solution turned yellow/orange in colour and a white precipitate formed. The reaction mixture was allowed to cool to rt and was separated between Et_2O and H_2O. The aqueous layer was extracted with Et_2O (3x) and the combined organic layers were washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a white powdery solid (8.8 g, 97%). No further purification was attempted. Spectroscopic data are consistent with those published in the literature.[180]

$[\alpha]_D^{29}$ –278.0 (*c* 0.68, $CHCl_3$) (lit: –266.0, *c* 1.20, 20 °C, $CHCl_3$).[181]

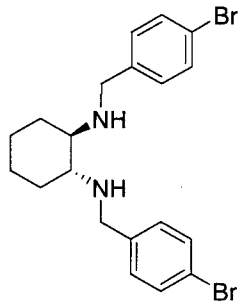
FT-IR ν_{max} (neat) 2928 (s), 2855 (s), 1643 (s), 1589 (s), 1485 (s), 1068 (s), 838 (m), 817 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, s, 2 x CHN), 7.45 (8H, s, 8 x $C_{Ar}H$), 3.46-3.30 (2H, m, 2 x CH_2CHN), 1.96-1.72 (6H, m, 3 x CH_2), 1.49 (2H, m, CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1 (**C**N), 135.5 ($\mathbf{C}_{Ar}$Br), 132.0 ($\mathbf{C}_{Ar}$H), 129.7 ($\mathbf{C}_{Ar}$H), 125.0 ($\mathbf{C}_{Ar}$), 74.1 (**C**HN), 33.2 ($\mathbf{C}H_2$), 24.8 ($\mathbf{C}H_2$) ppm.

LRMS (ES+) 449.0 (100%, $[M+H]^+$).

(–)-(*R,R*)-N,N'-bis-(4-Bromobenzyl)cyclohexane-1,2-diamine ((–)-2.22)



$C_{20}H_{24}N_2Br_2$
Mw = 452.23 $gmol^{-1}$
Yellow oil

To a suspension of (*R,R*)-imine **(–)-2.21** (8.60 g, 19.2 mmol) in MeOH (50 mL) cooled in an ice bath was added $NaBH_4$ (1.57 g, 42.2 mmol, 2.2 eq.) in 2 portions (CARE! – evolution of gas). The pale yellow opaque reaction mixture was stirred at rt for 16 h before it was quenched by the addition of H_2O (50 mL) and stirred for 20 min. Next, Et_2O (100 mL) was added and the layers were separated. The organic layer was acidified to pH 1 and the resulting suspension was filtered. The solid was redissolved in Et_2O (100 mL) and 3 N NaOH and the layers were separated. The organic layer was washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a yellow oil (7.28 g, 84%). No further purification was necessary. Spectroscopic data are consistent with those published in the literature.[182]

$[\alpha]_D^{29}$ –38.6 (*c* 0.97, $CHCl_3$) (lit: –39.6, *c* 1.12, $CHCl_3$).[182]

FT-IR ν_{max} (neat) 2925 (m), 2852 (m), 1485 (s), 1456 (m), 1114 (m), 1069 (s), 1010 (s), 795 (s) cm^{-1}.

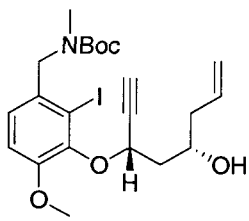
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (4H, d, *J* = 8.2 Hz, 4 x $\mathbf{C}_{Ar}$**H**), 7.18 (4H, d, *J* = 8.2 Hz, 4 x $\mathbf{C}_{Ar}$**H**), 3.84 (2H, d, *J* = 13.5 Hz, N**C**$\mathbf{H}_2$), 3.60 (2H, d, *J* = 13.5 Hz, N**C**$\mathbf{H}_2$), 2.25-2.19 (2H, m, **C**$\mathbf{H}_2$), 2.17-2.09 (2H, m, **C**$\mathbf{H}_2$), 1.80

(2H, br s, CH_2), 1.77-1.65 (2H, m, CH_2), 1.27-1.17 (2H, m, CH_2), 1.10-0.93 (2H, m, CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1 ($C_{Ar}Br$), 131.4 ($C_{Ar}H$), 129.7 ($C_{Ar}H$), 120.5 (C_{Ar}), 60.8 (CHNH), 50.2 (NCH_2), 31.5 (CH_2), 25.0 (CH_2) ppm.

LRMS (ES+) 453.0 (100%, $[M+H]^+$).

(–)-*tert*-Butyl-3-((3*S*,5*S*)-5-hydroxyoct-7-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((–)-2.23)



$C_{22}H_{30}INO_5$
Mw = 515.38 gmol^{-1}
Yellow oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Protected alkyne **1.78** (0.26 g, 0.44 mmol) was dissolved in MeOH (5 mL) giving a pale yellow solution. This was then treated with K_2CO_3 (0.11 g, 0.65 mmol, 1.5 eq). The heterogeneous mixture was stirred vigorously for 1.5 h. The solvent was removed *in vacuo* before the resulting oil was redissolved in Et_2O (15 mL). A sat. soln. of NH_4Cl (10 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3x). The combined organic layers were then washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* resulting in a yellow oil that required no further purification (0.22 g, 97%).

$[\alpha]_D^{27}$ –0.5 (*c* 0.38, $CHCl_3$).

FT-IR ν_{max} (neat) 3446 (br m), 3289 (m), 2973 (m), 2926 (m), 2360 (m), 2342 (m), 1689 (s), 1478 (s), 1392 (s), 1151 (s), 1029 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94-6.84 (2H, m, 2 x $C_{Ar}H$), 5.91 (1H, ddt, *J* = 17.1, 10.1, 7.3 Hz, $CH=CH_2$), 5.44 (1H, td, *J* = 8.0, 3.0 Hz, CHOAr), 5.20-5.15 (2H, m, $CH=CH_2$), 4.56-4.37 (2H, m, NCH_2), 4.18 (1H, ddt, *J*

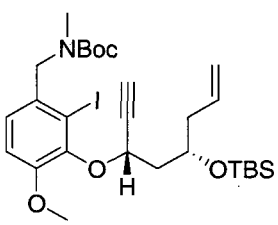
= 14.6, 6.3, 2.76 Hz, **CH**OH), 3.86 (3H, s, O**CH$_3$**), 2.86 (3H, br s, N**CH$_3$**), 2.55 (1H, d, *J* = 3.0 Hz, C≡**CH**), 2.41-2.14 (5H, m, 2 x **CH$_2$** and **OH**), 1.50-1.43 (9H, m, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (**C**O), 151.6 (**C**$_{Ar}$O), 145.8 (**C**$_{Ar}$OCH$_3$), 134.9 (**C**H=CH$_2$), 133.1 (**C**$_{Ar}$CH$_2$), 123.8 and 123.4 (**C**$_{Ar}$H), 118.4 (CH=**C**H$_2$), 112.6 (**C**$_{Ar}$H), 81.7 (**C**(CH$_3$)$_3$), 80.1 (HC≡**C**), 76.5 (H**C**≡C), 70.5 (**C**H(OH)), 69.2 (**C**H(OAr)), 57.9 (N**C**H$_2$), 56.4 (O**C**H$_3$), 42.8 (**C**H$_2$), 42.3 (**C**H$_2$), 34.6 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$) ppm. No **C**$_{Ar}$I peak observed.

LRMS (ES+) *m/z* 538.0 (100%, $[M+Na]^+$), 1053.0 (20%, $[2M+Na]^+$).

HRMS (ES+) for $C_{22}H_{30}INO_5Na$, requires 538.1066 found 538.1049 Da.

(+)-*tert*-Butyl-3-((3*S*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-7-en-1-yn-3-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((+)-2.27)



$C_{28}H_{44}INO_5Si$
Mw = 629.64 gmol^{-1}
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Alcohol **(–)-2.23** (0.19 g, 0.36 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with distilled 2,6-lutidine (85 μL, 0.73 mmol, 2.0 eq) and cooled to –78 °C before TBSOTf (87 μL, 0.38 mmol, 1.05 eq) was added dropwise over 2 min. The resulting solution was stirred for 5 min before it was warmed in an ice bath and stirred for 10 min. The reaction was quenched by the addition of a sat. soln. of NH_4Cl (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with a sat. soln. of $NaHCO_3$ (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica gel 60A, gradient elution 9:1 to 8:2 hexane/EtOAc) to afford the title compound as a colourless oil (0.20 g, 89%).

$[\alpha]_D^{28}$ +15.2 (*c* 0.71, $CHCl_3$).

FT-IR ν_{max} (neat) 3308 (w), 2955 (m), 2928 (m), 2856 (m), 2362 (w), 1693 (s), 1477 (s), 1390 (s), 1255 (s), 1139 (s), 836 (s) cm^{-1}.

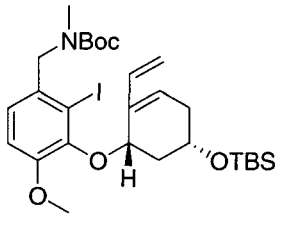
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89-6.87 (2H, m, 2 x C_{Ar}**H**), 5.88 (1H, ddt, *J* = 17.0, 10.3, 7.2 Hz, C**H**=CH_2), 5.36 (1H, br t, *J* = 6.6 Hz, C**H**OAr), 5.12-5.08 (2H, m, CH=C**H$_2$**), 4.58-4.35 (2H, m, NC**H$_2$**), 4.07 (1H, tt, *J* = 8.0, 4.0 Hz, C**H**OTBS), 3.83 (3H, s, OC**H$_3$**), 2.93-2.75 (3H, br m, NC**H$_3$**), 2.42-2.30 (3H, m, C**H$_2$** and C≡C**H**), 2.25 (1H, ddd, *J* = 12.0, 8.0, 4.0 Hz, C**H**H), 2.11 (1H, ddd, *J* = 12.0, 8.0, 4.0 Hz, CH**H**), 1.55-1.37 (9H, appt. d, C(C**H$_3$**)$_3$), 0.91 (9H, s, Si(C(C**H$_3$**)$_3$)), 0.09 (6H, s, Si(C**H$_3$**)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (**C**O), 151.6 (**C**$_{Ar}$O), 146.2 (**C**$_{Ar}$OCH$_3$), 134.8 (**C**H=CH_2), 133.0 (**C**$_{Ar}$), 123.4 and 122.9 (**C**$_{Ar}$H), 117.7 (CH=**C**H$_2$), 112.5 (**C**$_{Ar}$H), 82.2 (HC≡**C**), 80.1 (**C**(CH$_3$)$_3$), 76.2 (H**C**≡C), 70.1 (**C**H(OTBS)), 69.2 (**C**H(OAr)), 57.9 and 57.1 (N**C**H$_2$), 56.2 (O**C**H$_3$), 43.1 (**C**H$_2$), 42.6 (**C**H$_2$), 34.6 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$), 26.2 (SiC(**C**H$_3$)$_3$), 18.4 (Si**C**(CH$_3$)$_3$), –3.8 and –4.4 (Si(**C**H$_3$)$_2$) ppm. No **C**$_{Ar}$I peak observed.

LRMS (ES+) *m/z* 652.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{28}H_{44}INO_5SiNa$, requires 652.1931 found 652.1904 Da.

(–)-*tert*-Butyl-3-((1*S*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-ethenylcyclohex-2-en-1-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((–)-2.28)



$C_{28}H_{44}INO_5Si$
Mw = 629.64 $gmol^{-1}$
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Enyne **2.27** (0.19 g, 0.29 mmol) was dissolved in CH_2Cl_2 (10 mL) and was degassed for 5 min. Next, the pale yellow solution was treated with Grubbs' I catalyst (10.5 mg, 12.8 μmol, 4.4 mol%). The resulting purple solution was stirred at rt for 4 h over which time the solution had darkened to brown. An extra amount of Grubbs' I catalyst (3.3 mg, 4 μmol, 1.4 mol%) was added and the reaction mixture was stirred for a further 14 h. The solvent was removed *in vacuo* and the resulting oil was purified by column chromatography (silica gel 60A, gradient elution 9:1 to 85:15 hexane/EtOAc) giving the title compound as a colourless oil (0.16 g, 88%).

$[\alpha]_D^{27}$ –65.9 (*c* 0.75, $CHCl_3$).

FT-IR ν_{max} (neat) 2953 (m), 2928 (m), 2855 (m), 1698 (s), 1474 (s), 1389 (s), 1253 (s), 1138 (s), 836 (s) cm^{-1}.

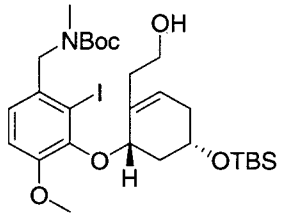
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 8.0 Hz, C_{Ar}**H**), 6.81 (1H, br s, C_{Ar}**H**), 6.48 (1H, dd, *J* = 17.6, 11.2 Hz, C**H**=CH_2), 5.87 (1H, br d, *J* = 5.3 Hz, C**H**OAr), 5.66-5.55 (2H, m, CH=C**H$_2$**), 5.07 (1H, d, *J* = 11.3 Hz, C=C**H**), 4.62-4.32 (2H, m, N**CH$_2$**), 3.86 (3H, s, O**CH$_3$**), 3.77 (1H, ddt, *J* = 15.8, 4.9, 4.5 Hz, C**H**OTBS), 2.92-2.73 (3H, br m, N**CH$_3$**), 2.41-2.17 (2H, m, **CH$_2$**), 2.05-1.89 (2H, m, **CH$_2$**), 1.55-1.35 (9H, m, C(**CH$_3$**)$_3$), 0.85 (9H, s, Si(C(**CH$_3$**)$_3$)), 0.02 (3H, s, Si(**CH$_3$**)$_2$), 0.01 (3H, s, Si(**CH$_3$**)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (**C**O), 151.3 (**C**$_{Ar}$O), 146.1 (**C**$_{Ar}$OCH$_3$), 138.0 (**C**=CH), 136.3 (**C**H=CH_2), 133.3 (**C**$_{Ar}$), 126.7 (C=**C**H), 122.6 and 121.9 (**C**$_{Ar}$H), 114.4 (CH=**C**H$_2$), 112.4 (**C**$_{Ar}$H), 80.1 (**C**(CH$_3$)$_3$), 76.4 (**C**H(OAr)), 67.6 (**C**H(OTBS)), 58.2 and 57.2 (N**C**H$_2$), 56.1 (O**C**H$_3$), 39.3 (CH(OAr)**C**H$_2$), 36.3 (**C**H$_2$CH(OTBS)), 34.6 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$), 26.2 (SiC(**C**H$_3$)$_3$), 18.5 (Si**C**(CH$_3$)$_3$), –4.2 and –4.3 (Si(**C**H$_3$)$_2$) ppm. No **C**$_{Ar}$I peak observed.

LRMS (ES+) *m/z* 652.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{28}H_{44}INO_5SiNa$, requires 629.1931 found 652.1906 Da.

(–)-*tert*-Butyl-3-((1*S*,5*S*)-5-[(*tert*-butyldimethylsilyl)oxy]-2-(2-hydroxyethyl) cyclohex-2-en-1-yloxy)-2-iodo-4-methoxybenzylmethylcarbamate ((–)-2.29)



$C_{28}H_{46}INO_6Si$
Mw = 647.66 $gmol^{-1}$
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Diene **2.28** (151 mg, 0.24 mmol) was dissolved in THF (2.5 mL) and treated with 9-BBN (0.72 mL of a 0.5 M soln. in THF, 0.36 mmol, 1.5 eq.). The yellow reaction mixture was stirred at rt for 17 h. 3 N NaOH (1.5 mL) was added followed cautiously by H_2O_2 (1.5 mL) over 15 min. The reaction mixture lightened in colour and turned opaque. Stirring was continued for 3 h before the layers were separated between Et_2O and H_2O. The aqueous layer was extracted with Et_2O (3x) and EtOAc (1x). The combined organic layers were washed with brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* and purification by column chromatography (silica gel 60A, gradient elution 85:15 to 3:7 hexane/EtOAc) yielded the desired product as a colourless oil (110 mg, 69%).

$[\alpha]_D^{27}$ –18.7 (*c* 0.67, $CHCl_3$).

FT-IR ν_{max} (neat) 3447 (br, w), 2952 (m), 2928 (m), 2855 (m), 1697 (s), 1475 (s), 1391 (s), 1139 (s), 836 (s) cm^{-1}.

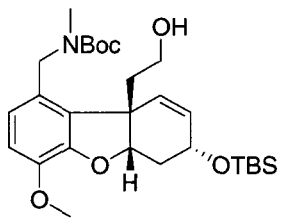
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 8.0 Hz, $C_{Ar}\mathbf{H}$), 6.83 (1H, br s, $C_{Ar}\mathbf{H}$), 5.57 (1H, br d, *J* = 5.3 Hz, **CH**OAr), 5.34 (1H, br. t, C=C**H**), 4.57-4.31 (2H, m, $NC\mathbf{H_2}$), 3.90-3.82 (5H, m, $OC\mathbf{H_3}$ and $C\mathbf{H_2}OH$), 3.82-3.72 (1H, m, **CH**OTBS), 2.94-2.80 (3H, br m, $NC\mathbf{H_3}$), 2.80-2.70 (1H, m, $C\mathbf{H}HCH_2$), 2.50 (1H, ddd, *J* = 14.0, 6.9, 6.7 Hz, $CH\mathbf{H}CH_2$), 2.35-2.23 (1H, m, CH(OAr)C**H**H), 2.19-2.06 (1H, m, CH(OAr)CH**H**), 1.91 (2H, dd, *J* = 9.1, 8.1 Hz, $=CHC\mathbf{H_2}$), 1.81 (1H, br s, O**H**), 1.55-1.37 (9H, m, $C(C\mathbf{H_3})_3$), 0.84 (9H, s, $Si(C(C\mathbf{H_3})_3)$), 0.02 (3H, s, $Si(C\mathbf{H_3})_2$), 0.00 (3H, s, $Si(C\mathbf{H_3})_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (**C**O), 151.3 (**C**$_{Ar}$O), 145.9 (**C**$_{Ar}$OCH$_3$), 136.4 (**C**=CH), 133.2 (**C**$_{Ar}$), 124.7 (C=**C**H), 122.7 and 122.4 (**C**$_{Ar}$H), 112.5 (**C**$_{Ar}$H), 98.9 (**C**$_{Ar}$I), 80.1 (**C**(CH$_3$)$_3$), 78.1 (**C**H(OAr)), 67.7 (**C**H(OTBS)), 62.2 (**C**H$_2$OH), 57.7 and 57.4 (N**C**H$_2$), 56.2 (O**C**H$_3$), 39.3 (**C**H$_2$CH$_2$OH), 36.5 (**C**H$_2$), 36.3 (**C**H$_2$), 34.7 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$), 26.2 (SiC(**C**H$_3$)$_3$), 18.5 (Si**C**(CH$_3$)$_3$), –4.2 and –4.3 (Si(**C**H$_3$)$_2$) ppm.

LRMS (ES+) *m/z* 670.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{28}H_{46}INO_6SiNa$, requires 670.2037 found 670.2029 Da

(+)-*tert*-Butyl-*N*-[((1a*S*,9a*S*,11a*R*)-11a-[(*tert*-butyldimethylsilyl)oxy]-1-(hydroxyethyl)-6-(methoxy)-1,9a,10,11a-tetrahydrodibenzo[b,d]furan-12-yl)-3-methyl]-*N*-methylcarbamate ((+)-2.30)



$C_{28}H_{45}NO_6Si$
Mw = 519.75 gmol^{-1}
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Iodide **2.29** (91.6 mg, 0.14 mmol) was dissolved in dry toluene (4.7 mL) and treated with Ag_2CO_3 (117.0 mg, 0.42 mmol, 3.0 eq.), dppp (8.8 mg, 21 μmol, 15 mol%) and $Pd(OAc)_2$ (4.2 mg, 19 μmol, 13 mol%). The dull green heterogeneous mixture was stirred at rt for 10 min then heated to 90 °C for 20 h over which time the solution turned black. The solvent was removed *in vacuo* and purification by column chromatography (silica gel 60, gradient elution 7:3 to 6:4 hexane/EtOAc) afforded the desired compound as a colourless oil (54.9 mg, 75%).

$[\alpha]_D^{29}$ +2.0 (*c* 1.34, $CHCl_3$).

FT-IR ν_{max} (neat) 3451 (br,w), 2953 (m), 2929 (m), 2856 (m), 2856 (m), 1681 (s), 1391 (s), 1252 (s), 1143 (s), 836 (s) cm^{-1}.

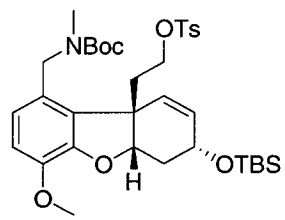
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, d, J = 8.3 Hz, C_{Ar}**H**), 6.60 (1H, d, J = 8.3 Hz, C_{Ar}**H**), 6.08 (1H, br s, C**H**=CHCH(OTBS)), 5.81 (1H, d, J = 10.3 Hz, CH=C**H**CH(OTBS)), 4.86 (1H, dd, J = 11.7, 4.9 Hz, C**H**OAr), 4.65 (1H, br s, NC**H**H), 4.38-4.17 (2H, m, C**H**OTBS and NCH**H**), 3.85 (3H, s, OC**H$_3$**), 3.58 (1H, dd, J = 11.8, 4.9 Hz, C**H**HOH), 3.50 (1H, dd, J = 11.6, 6.5 Hz, CH**H**OH), 2.80 (3H, br s, NC**H$_3$**), 2.36-2.17 (1H, m, CH**H**CH(OAr)), 1.96 (1H, ddd, J = 12.7, 7.8, 6.2 Hz, C**H**HCH$_2$), 1.88-1.65 (2H, m, CH**H**CH$_2$ and C**H**HCH(OAr)), 1.46 (9H, br s, C(C**H$_3$**)$_3$), 0.86 (9H, s, Si(C(C**H$_3$**)$_3$)), 0.07 (3H, s, Si(C**H$_3$**)$_2$), 0.06 (3H, s, Si(C**H$_3$**)$_2$) ppm. No O**H** peak observed.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (**C**O), 147.0 (**C**$_{Ar}$O), 144.9 (**C**$_{Ar}$OCH$_3$), 134.3 (**C**CH=CH), 130.5 (br, **C**$_{Ar}$), 128.4 (CCH=**C**H), 126.5 (**C**$_{Ar}$CH$_2$), 121.6 and 120.0 (**C**$_{Ar}$H), 111.8 (**C**$_{Ar}$H), 85.3 (**C**H(OAr)), 80.2 (**C**(CH$_3$)$_3$), 65.7 (**C**H(OTBS)), 59.8 (**C**H$_2$OH), 56.3 (O**C**H$_3$), 50.7 (**C**CH=CH), 49.3 (N**C**H$_2$), 42.3 (**C**H$_2$), 36.9 (**C**H$_2$CH$_2$), 34.3 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$), 26.1 (SiC(**C**H$_3$)$_3$), 18.4 (Si**C**(CH$_3$)$_3$), –4.3 and –4.4 (Si(**C**H$_3$)$_2$) ppm.

LRMS (ES+) *m/z* 542.0 (100%, $[M+Na]^+$), 1062.0 (28%, $[2M+Na]^+$).

HRMS (ES+) for $C_{28}H_{45}NO_6SiNa$, requires 542.2914 found 542.2906 Da.

(+)-*tert*-Butyl-*N*-[((1a*S*,9a*S*,11a*R*)-11a-[(*tert*-butyldimethylsilyl)oxy]-1-(ethyl(4-methyl benzenesulfonate))-6-(methoxy)-1,9a,10,11a-tetrahydrodibenzo[b,d]furan-12-yl)-3-methyl]-*N*-methylcarbamate ((+)-2.31)



$C_{35}H_{51}NO_8SSi$
Mw = 673.93 $gmol^{-1}$
Waxy gum
NMR spectra exhibited broadening of peaks due to restricted rotation

Alcohol **2.30** (54.0 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C before TsCl (30.8 mg, 0.16 mmol. 1.6 eq.) and pyridine (16 μL, 0.2 mmol, 2.0 eq.) were added. The reaction was stirred for 4 h before it was allowed to warm to rt and stir for

40 h. The solvent was removed *in vacuo* and purification (silica gel 60A, gradient elution 8:2 to 6:4 hexane/EtOAc) afforded the desired compound as a white waxy gum (36.0 mg, 53%) and the starting alcohol **2.30** (14.6 mg, 27%).

$[\alpha]_D^{27}$ +16.1 (*c* 1.14, $CHCl_3$).

FT-IR ν_{max} (neat) 2929 (m), 2856 (m), 1689 (s), 1363 (s), 1175 (s) 835 (s) cm^{-1}.

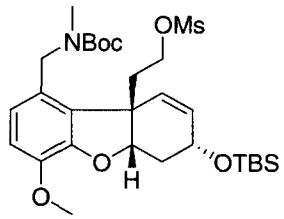
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.3 Hz, 2 x C_{Ar}**H**), 7.32 (2H, d, *J* = 8.0 Hz, 2 x C_{Ar}**H**), 6.72 (1H, d, *J* = 8.4 Hz, C_{Ar}**H**), 6.58 (1H, d, *J* = 8.4 Hz, C_{Ar}**H**), 6.03 (1H, br s, C**H**=CHCH(OTBS)), 5.82 (1H, d, *J* = 10.2 Hz, CH=C**H**CH(OTBS)), 4.71 (1H, dd, *J* = 11.8, 4.9 Hz, C**H**OAr), 4.67-4.42 (1H, br s, NC**H**H) 4.30-4.12 (2H, m, C**H**OTBS and NCH**H**), 4.09-3.97 (1H, m, C**H**HOTs), 3.90 (1H, dt, *J* = 10.2, 7.2 Hz, CH**H**OTs), 3.85 (3H, s, OC**H$_3$**), 2.75 (3H, br s, NC**H$_3$**), 2.44 (3H, s, C**H$_3$**), 2.24 (1H, dt, *J* = 11.8, 4.9 Hz, C**H**HCH(OAr)), 2.11 (1H, dt, *J* = 14.5, 7.2 Hz, C**H**HCH$_2$), 1.88 (1H, dt, *J* = 14.5, 6.0 Hz, CH**H**CH$_2$), 1.69 (1H, dt, *J* = 11.7, 10.8 Hz, CH**H**CH(OAr)), 1.46 (9H, br s, C(C**H$_3$**)$_3$), 0.87 (9H, s, Si(C(C**H$_3$**)$_3$)), 0.08 (3H, s, Si(C**H$_3$**)$_2$), 0.06 (3H, s, Si(C**H$_3$**)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (**C**O), 146.9 (**C**$_{Ar}$O), 145.1 (**C**$_{Ar}$OCH$_3$), 135.5 (C**C**H=CH), 133.3 (**C**$_{Ar}$), 128.2 (**C**$_{Ar}$H), 127.0 (**C**$_{Ar}$H), 126.3 (CCH=**C**H), 122.0 (**C**$_{Ar}$CH$_2$), 120.5 (**C**$_{Ar}$H), 112.0 (**C**$_{Ar}$H), 84.6 (**C**H(OAr)), 80.2 (**C**(CH$_3$)$_3$), 67.3 (**C**H$_2$OTs), 65.5 (**C**H(OTBS), 56.3 (O**C**H$_3$), 50.2 (**C**CH=CH), 49.0 (N**C**H$_2$), 37.9 (**C**H$_2$), 36.8 (**C**H$_2$), 34.1 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$), 26.1 (SiC(**C**H$_3$)$_3$), 22.0 (**C**H$_3$), 18.4 (Si**C**(CH$_3$)$_3$), –4.3 and –4.4 (Si(**C**H$_3$)$_2$) ppm. Two **C**$_{Ar}$ quaternary carbons were not observed.

LRMS (ES+) *m/z* 696.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{35}H_{51}NO_8SSiNa$, requires 696.3002 found 696.2981 Da.

(+)-*tert*-Butyl-*N*-[((1a*S*,9a*S*,11a*R*)-11a-[(*tert*-butyldimethylsilyl)oxy]-1-(ethyl(methanesulfonate))-6-(methoxy)-1,9a,10,11a-tetrahydrodibenzo[b,d]furan-12-yl)-3-methyl]-*N*-methylcarbamate ((+)-2.32)



$C_{29}H_{47}NO_8SSi$
Mw = 597.28 $gmol^{-1}$
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Alcohol **2.30** (15.0 mg, 29 μmol) was dissolved in CH_2Cl_2 (0.15 mL, 0.2 M) and treated with NEt_3 (8 μL, 57 μmol, 2.0 eq.) and MsCl (3 μL, 32 μmol, 1.1 eq.). The pale yellow solution was stirred for 3 h before MsCl (2 μL, 26 μmol) was added and stirred for 1 h. The solvent was removed *in vacuo* and purification by column chromatography (silica gel 60A, 7:3 hexane/EtOAc) afforded the desired compound as a colourless oil (10.3 mg, 59%).

$[\alpha]_D^{29}$ +23.5 (*c* 0.51, $CHCl_3$).

FT-IR ν_{max} (neat) 2955 (m), 2930 (m), 2857 (w), 1690 (s), 1506 (m), 1175 (s) cm^{-1}.

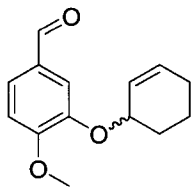
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, d, *J* = 8.4 Hz, C_{Ar}**H**), 6.63 (1H, d, *J* = 8.3 Hz, C_{Ar}**H**), 6.10 (1H, br s, C**H**=CHCH(OTBS)), 5.87 (1H, d, *J* = 10.2 Hz, CH=C**H**CH(OTBS)), 4.79 (1H, dd, *J* = 11.7, 5.0 Hz, C**H**OAr), 4.70 (1H, br s, NC**H**H), 4.37-4.30 (1H, m, C**H**OTBS), 4.24 (1H, br s, NCH**H**), 4.16 (1H, dt, *J* = 10.3, 6.8 Hz, C**H**HOMs), 4.05 (1H, dt, *J* = 10.3, 6.9 Hz, CH**H**OMs), 3.86 (3H, s, OC**H**$_3$), 2.94 (3H, s, C**H**$_3$), 2.80 (3H, br s, NC**H**$_3$), 2.29 (1H, ddt, *J* = 12.1, 4.9 Hz, C**H**HCH(OAr)), 2.19 (1H, dt, *J* = 14.3, 7.1 Hz, C**H**HCH$_2$OMs), 1.97 (1H, dt, *J* = 14.6, 6.5 Hz, CH**H**CH$_2$OMs), 1.73 (1H, td, *J* = 11.8, 10.7 Hz, CH**H**CH(OAr)), 1.48 (9H, br s, C(C**H**$_3$)$_3$), 0.87 (9H, s, Si(C(C**H**$_3$)$_3$)), 0.08 (3H, s, Si(C**H**$_3$)$_2$), 0.07 (3H, s, Si(C**H**$_3$)$_2$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (**C**O), 147.1 (**C**$_{Ar}$O), 145.1 (**C**$_{Ar}$OCH$_3$), 135.4 (C**C**H=CH), 127.2 (CCH=**C**H), 126.5 (**C**$_{Ar}$CH$_2$), 118.4 (**C**$_{Ar}$H), 112.1 (**C**$_{Ar}$H), 84.8 (**C**H(OAr)), 80.3 (**C**(CH$_3$)$_3$), 67.0 (**C**H$_2$OMs), 65.5 (**C**H$_2$(OTBS)), 56.3 (O**C**H$_3$), 50.3 (**C**CH=CH), 49.2 (N**C**H$_2$), 38.6 (**C**H$_2$), 37.6 (S(O)$_2$**C**H$_3$), 36.9 (**C**H$_2$), 34.2 (N**C**H$_3$), 28.8 (C(**C**H$_3$)$_3$), 26.1 (SiC(**C**H$_3$)$_3$), 18.5 (Si**C**(CH$_3$)$_3$), –4.3 and –4.4 (Si(**C**H$_3$)$_2$) ppm. **C**$_{Ar}$ peak not observed.

LRMS (ES+) *m/z* 620.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{29}H_{47}NO_8SSiNa$, requires 620.2689 found 620.2678 Da.

(±)-3-(Cyclohex-2-en-1yloxy)-4-methoxybenzaldehyde ((±)-2.34)



$C_{14}H_{16}O_3$
Mw = 232.28 gmol^{-1}
Pale yellow oil

To a solution of *iso*-vanillin (0.24 g, 1.60 mmol) and PPh_3 (0.59 g, 2.25 mmol) in THF (2 mL) was added 2-cyclohexen-1-ol (0.15 g, 1.5 mmol) in THF (2 mL) to give a peach coloured solution. Next, DEAD (0.35 mL, 2.25 mmol) was added dropwise to give a bright yellow solution. The reaction was stirred for 3 h at rt before the solvent was removed *in vacuo* resulting in a yellow oil (1.55 g). Purification by column chromatography (silica gel 60A, dry loaded, 7:3 hexane/EtOAc) yielded the title product as a pale yellow oil (0.15 g, 42%).

FT-IR ν_{max} (neat) 2934 (w), 2837 (w), 1682 (s), 1581 (s), 1505 (s), 1432 (s), 1258 (s), 1128 (s), 1018 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (1H, s, **C**HO), 7.54-7.40 (2H, m, 2 x C$_{Ar}$**H**), 6.99 (1H, d, *J* = 8.7 Hz, C$_{Ar}$**H**), 5.99 (1H, dtd, *J* = 10.1, 3.4, 0.9 Hz, CH=C**H**CH$_2$), 5.89 (1H, ddd, *J* = 10.2, 4.7, 2.0 Hz, C**H**=CHCH$_2$), 4.89

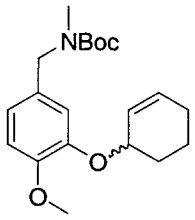
(1H, br s, **CH**OAr), 3.94 (3H, s, O**CH$_3$**), 2.25-1.80 (5H, m, **CH$_2$**), 1.77-1.54 (1H, m, **CH$_2$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2 (**C**HO), 156.2 (**C**$_{Ar}$OCH$_3$), 148.2 (**C**$_{Ar}$O), 132.9 (**C**$_{Ar}$H), 130.3 (**C**$_{Ar}$CH$_2$), 127.0 (**C**H=CH), 126.2 (CH=**C**H), 113.4 (**C**$_{Ar}$H), 111.3 (**C**$_{Ar}$H), 72.8 (**C**HOAr), 56.5 (O**C**H$_3$), 28.5 (**C**H$_2$), 25.4 (**C**H$_2$), 19.5 (**C**H$_2$) ppm.

LRMS (ES+) *m/z* 255.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{14}H_{17}O_3$, requires 233.1172 found 233.1170 Da.

(±)-*Tert*-butyl-3-(cyclohex-2-en-1yloxy)-4-methoxybenzylmethylcarbamate ((±)-2.36)



$C_{20}H_{29}NO_4$
Mw = 347.48 $gmol^{-1}$
Colourless oil
NMR spectra exhibited broadening of peaks due to restricted rotation

Aldehyde **(±)-2.34** (48.4 mg, 0.21 mmol) was dissolved in MeOH (3 mL) before $MeNH_2$ (0.21 mL of a 2.0 M soln. in MeOH, 0.42 mmol, 2.0 eq.) was added. The reaction was stirred at rt for 18 h before the solvent was removed *in vacuo*. The crude oil was redissolved in MeOH (2 mL) before 4 Å MS (crushed, 400 mg) and $NaBH_4$ (10.0 mg, 0.26 mmol, 1.3 eq.) were added. The reaction mixture was stirred for 2 h at rt before the solvent was removed *in vacuo*. The crude oil was redissolved in dioxane (2 mL) and 1 N NaOH (1 mL) and treated with Boc_2O (69.0 mg, 0.32 mmol, 1.5 eq.). The reaction was then stirred at rt for 16 h. The solution was extracted with EtOAc (4x). The combined organic layers were washed with H_2O (1x), brine (1x) and dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (silica gel 60A, 4:1 hexane/EtOAc) yielded the title product as a colourless oil (51.9 mg, 71% over 3 steps).

FT-IR ν_{max} (neat) 2932 (m), 1690 (s), 1509 (s), 1391 (s), 1256 (s), 1136 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71-6.94 (3H, m, 3 x C_{Ar}**H**), 5.94 (1H, dt, *J* = 10.1, 3.0 Hz, CH=C**H**CH_2), 5.89 (1H, dd, *J* = 10.1, 2.3 Hz, C**H**=$CHCH_2$), 4.75 (1H, br s, C**H**OAr), 4.33 (2H, br s, N$C\mathbf{H_2}$), 3.84 (3H, s, O$C\mathbf{H_3}$), 2.80 (3H, br s, N$C\mathbf{H_3}$), 2.19-2.08 (1H, m, CH**H**), 2.07-1.80 (4H, m, 2 x $C\mathbf{H_2}$), 1.69-1.53 (1H, m, C**H**H), 1.49 (9H, s, C($C\mathbf{H_3}$)$_3$) ppm.

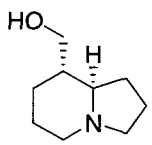
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (**C**O), 150.2 ($\mathbf{C}_{Ar}OCH_3$), 147.7 ($\mathbf{C}_{Ar}O$), 132.2 (**C**H=CH), 130.9 ($\mathbf{C}_{Ar}CH_2$), 127.0 (CH=**C**H), 121.2 and 120.8 ($\mathbf{C}_{Ar}H$), 116.3 and 116.0 ($\mathbf{C}_{Ar}H$), 112.3 ($\mathbf{C}_{Ar}H$), 79.9 ($\mathbf{C}(CH_3)_3$), 73.1 (**C**H(OAr)), 56.4 (OCH_3), 52.5 and 51.9 (NCH_2), 34.0 (NCH_3), 28.8 (C($\mathbf{C}H_3$)$_3$), 28.8 ($\mathbf{C}H_2$), 25.5 ($\mathbf{C}H_2$), 19.6 ($\mathbf{C}H_2$) ppm.

LRMS (ES+) *m/z* 370 (50%, $[M+Na]^+$), 718 (100%, $[2M+Na]^+$).

HRMS (ES+) for $C_{20}H_{29}NO_4Na$, requires 370.1994 found 370.1980 Da.

(+)-(8*S*,8a*R*)-octahydroindolizin-8-yl-methanol ((+)-3.01)

(+)-Tashiromine



$C_9H_{17}NO$
Mw = 155.24 $gmol^{-1}$
Colourless oil

Following the general procedure described by Beckwith *et al.*,[125] to a stirred suspension of $LiAlH_4$ (26.0 mg, 0.65 mmol, 3.7 eq.) in THF (2 mL) at 0 °C was added ester **4.71** (major diastereomers, 32.3 mg, 0.18 mmol) in THF (1 mL). The reaction was stirred for 10 min before it was allowed to warm to rt and stir for 16 h. The reaction was quenched by the addition of H_2O (30 μL), 20% NaOH (90 μL) and H_2O (30 μL). The mixture was allowed to stir for 20 min before it was filtered through Celite® and washed with CH_2Cl_2 (30 mL). The solvent was removed *in vacuo* to yield a colourless oil (20.0 mg, 73%). No further purification was attempted. Spectroscopic data are consistent with those published in the literature.[125]

$[\alpha]_D^{28}$ +28.6 (*c* 0.14, $CHCl_3$) (lit. ((+)-tashiromine): +43.4)[118]

FT-IR ν_{max} (neat) 3209 (br, w), 2927 (m), 2792 (m), 1444 (m), 1164 (m), 1038 (m) cm^{-1}.

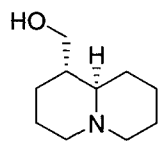
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (1H, dd, *J* = 10.8, 4.6 Hz, C**H**HOH), 3.46 (1H, dd, *J* = 10.7, 6.5 Hz, CH**H**OH), 3.14-2.99 (2H, m, 2 x NC**H**H), 2.05 (1H, q, *J* = 9.0 Hz, NC**H**), 2.00-1.83 (3H, m, C**H$_2$**), 1.83-1.39 (7H, m, 3 x C**H$_2$** and C**H**H), 1.33-1.14 (1H, br s, O**H**), 1.03 (1H, ddd, *J* = 12.7, 12.4, 4.6 Hz, C**H**H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 66.7 (**C**HN), 66.0 (**C**H_2OH), 54.5 (N**C**H_2), 53.0 (N**C**H_2), 45.0 (**C**HCH_2OH), 29.4 (**C**H_2), 28.0 (**C**H_2), 25.5 (**C**H_2), 21.1 (**C**H_2) ppm.

LRMS (ES+) *m/z* 156.0 (100%, $[M+H]^+$).

(+)-(1*S*,9a*R*)-octahydro-2*H*-quinolizin-1-yl methanol ((+)-3.02)

(+)-Epilupinine



$C_{10}H_{19}NO$
Mw = 169.26 $gmol^{-1}$
Colourless oil

To a stirred suspension of $LiAlH_4$ (38.0 mg, 1.04 mmol, 4.0 eq.) in THF (2 mL) at 0 °C was added ester **(+)-4.73** (major diastereomer, 52.1 mg, 0.26 mmol) in THF (1 mL). The reaction was stirred for 10 min before it was allowed to warm to rt and stir for 16 h. The reaction was quenched by the addition of H_2O (45 μL), 20% NaOH (130 μL) and H_2O (45 μL). The mixture was allowed to stir for 20 min before it was filtered through Celite® and washed well with CH_2Cl_2 (30 mL). The solvent was removed *in vacuo* to yield a colourless oil (40.4 mg, 95%). No further purification was attempted. Spectroscopic data are consistent with those published in the literature.[125]

$[\alpha]_D^{26}$ +5.7 (*c* 1.16, $CHCl_3$) (lit. ((+)-*epi*-lupinine): +32.0, *c* 0.86, 22 °C, EtOH).[111]

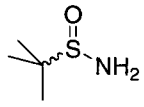
FT-IR ν_{max} (neat) 3281 (br, w), 2925 (s), 2856 (s), 2807 (m), 2759 (m), 1443 (m), 1111 (s), 1068 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (1H, dd, *J* = 10.8, 3.6 Hz, C**H**HOH), 3.53 (1H, dd, *J* = 10.8, 5.9 Hz, CH**H**OH), 2.87-2.70 (2H, m, 2 x NC**H**H), 2.40-2.08 (1H, br s, O**H**), 2.06-1.94 (2H, m, 2 x C**H**H) 1.93-1.52 (7H, m, 3 x **CH$_2$** and C**H**H), 1.45-1.10 (5H, m, 2 x **CH$_2$** and C**H**H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 64.8 (**C**H_2OH), 64.7 (**C**HN), 57.2 (N**C**H_2), 57.0 (N**C**H_2), 44.3 (**C**HCO), 30.1 (**C**H_2), 28.6 (**C**H_2), 25.9 (**C**H_2), 25.3 (**C**H_2), 24.9 (**C**H_2) ppm.

LRMS (ES+) *m/z* 170.0 (100%, $[M+H]^+$).

(±)-*tert*-Butyl sulfinamide ((±)-3.10)



$C_4H_{11}NOS$
Mw = 121.2 $gmol^{-1}$
White solid

Following the procedure described by Ellman *et al*,[82] a few crystals of $Fe(NO_3)_3.9H_2O$ were added to liquid ammonia (ca. 60 mL) at –78 °C. Next, lithium metal (1.4 g, 0.20 mol, 4.0 eq.) was added portion-wise with the cold bath removed. The cold bath was periodically raised to abate the ammonia refluxing too vigorously. Upon complete addition of lithium the mixture was stirred for 50 min at –78 °C (no grey suspension formed as described in the literature). Next, thiosulfinate **(±)-5.11** (10.0 g, 0.05 mol) was added as a solution in THF (50 mL) dropwise over 20 min then allowed to stir for 1 h. Solid NH_4Cl (13.8 g, 0.25 mol, 5.0 eq.) was added cautiously before the ammonia was allowed to evaporate. The resulting pale pink solid was placed under aspirator pressure for 20 min prior to the addition of H_2O (10 mL) followed by EtOAc (30 mL). The aqueous layer was extracted with EtOAc (40 mL) and the combined organic layers were washed with brine (40 mL) and dried (Na_2SO_4). Purification by column chromatography (silica gel 60A, gradient elution: EtOAc to 19:1 EtOAc/MeOH) yielded TBSA **((±)-3.10)** as a white solid (3.5 g, 58%). Spectroscopic data are consistent with those published in the literature.[82]

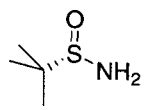
FT-IR ν_{max} (solid) 3225 (br, m), 2958 (m), 1029 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (2H, br s, NH_2), 1.22 (9H, s, $C(CH_3)_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7 ($C(CH_3)_3$), 22.5 ($C(CH_3)_3$) ppm.

LRMS (ES+) *m/z* 143.9 (30%, $[M+Na]^+$), 184.9 (100%, $M+Na(MeCN)]^+$).

(S_S)- (–)-*tert*-Butyl sulfinamide ((–)-3.10)



$C_4H_{11}NOS$
Mw = 121.20 $gmol^{-1}$
White powdery solid

Following the procedure described by Weix *et al.*,[164] the reaction of lithium (3.5 g, 0.50 mol) and $Fe(NO_3)_3.9H_2O$ (0.1 g, 0.25 mmol) in liquid ammonia (~ 150 mL) with thiosulfinate **5.11** (39.6 g, 0.20 mol) added in THF (60 mL) at –78 °C yielded sulfinyl amine **(–)-3.10** as an off white powdery solid (15.2 g, 62%) after recrystallisation from hexanes (82 mL, 5 mL/g). Spectroscopic data are consistent with those published in the literature.[164]

$[\alpha]_D^{24}$ –3.0 (*c* 0.76, $CHCl_3$) (lit: –5.1, *c* 1.00, rt, $CHCl_3$).[183]

MP 103-104 °C (lit: 101-102 °C).

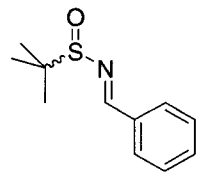
FT-IR ν_{max} (neat) 3319 (m), 3215 (m), 3112 (m), 2984 (w), 2950 (w), 1580 (w), 1024 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (2H, br s, NH_2), 1.22 (9H, s, $C(CH_3)_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 55.7 ($C(CH_3)_3$), 22.5 ($C(CH_3)_3$) ppm.

LRMS (ES+) *m/z* 144 (50%, $[M+Na]^+$), 185 (100%, $[M+Na(MeCN)]^+$).

(±)-*N*-(Benzylidene)-2-methyl propanesulfinamide ((±)-3.15)



$C_{11}H_{15}NOS$
Mw = 209.31 $gmol^{-1}$
Yellow oil

Following the general procedure described by Ellman *et al*,[83] racemic TBSA **(±)-3.10** (0.5 g, 4.0 mmol) was dissolved in dry CH_2Cl_2 (8.2 mL, 0.5 M) before anhydrous $CuSO_4$ (2.0 g, 12.4 mmol, 3.1 eq.) was added in one portion followed by benzaldehyde (0.46 mL, 4.4 mmol, 1.1 eq.). The reaction mixture was heated to 30 °C for 18 h then filtered through Celite® and washed with CH_2Cl_2. The solvent was removed *in vacuo* and the crude mixture purified by column chromatography (silica gel 60A, gradient elution: CH_2Cl_2 to 49:1 CH_2Cl_2/MeOH) to yield a yellow oil (0.77 g, 92%). Spectroscopic data are consistent with those published in the literature.[83]

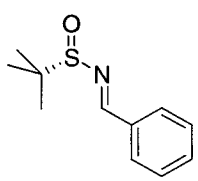
FT-IR ν_{max} (neat) 2958 (w), 1605 (s), 1572 (s), 1085 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ8.61 (1H, s, C**H**N), 7.87 (2H, dd, J = 7.9, 1.5 Hz, 2 x C_{Ar}**H**), 7.54-7.85 (3H, m, 3 x C_{Ar}**H**), 1.28 (9H, s, C(C**H**$_3$)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ163.1 (**C**H), 134.5 (**C**$_{ipso}$), 132.8 (**C**$_{para}$), 129.7 (**C**$_{ortho}$), 129.3 (**C**$_{meta}$), 58.1 (**C**(CH$_3$)$_3$), 23.0 (C(**C**H$_3$)$_3$) ppm.

LRMS (ES+) *m/z* 231.9 (100%, $[M+Na]^+$), 272.9 (90%, $[M+Na(MeCN)]^+$), 440.9 (25%, $[2M+Na]^+$).

(S_S)-(+)-*N*-(Benzylidene)-2-methylpropanesulfinamide ((+)-3.15)



$C_{11}H_{15}NOS$
Mw = 209.31 $gmol^{-1}$
Yellow oil

Using the procedure described (*vide supra*), (–)-TBSA **(–)-3.10** (0.20 g, 1.65 mmol), benzaldehyde (0.19 g, 1.82 mmol, 1.1 eq.) and anhydrous $CuSO_4$ (0.58 g, 3.60 mmol,

2.2 eq.) in CH_2Cl_2 (3.3 mL, 0.5 M) were heated at 40 °C for 18 h to yield the title compound as a yellow oil (0.26 g, 74%) after purification by column chromatography (silica gel 60A, CH_2Cl_2). Spectroscopic data is consistent with that published in the literature.[83]

$[\alpha]_D^{26}$ +117.5 (*c* 0.56, $CHCl_3$) (lit. ((R_s)-enantiomer): –122.0, *c* 1.00, 23 °C, $CHCl_3$).[83]

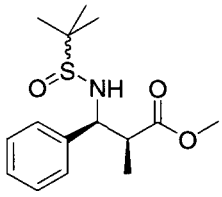
FT-IR ν_{max} (neat) 2960 (w), 1606 (s), 1573 (s), 1083 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, s, **CHN**), 7.87 (2H, dd, J = 7.5, 1.5 Hz, 2 x $C_{Ar}\mathbf{H}_{ortho\ to\ C(N)}$), 7.51-7.45 (3H, m, 3 x $C_{Ar}\mathbf{H}$), 1.28 (9H, s, $C(\mathbf{CH_3})_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (**C**HN), 133.5 ($\mathbf{C}_{ipso}$), 131.7 ($\mathbf{C}_{para}$H), 128.7 ($\mathbf{C}_{ortho}$H), 128.3 ($\mathbf{C}_{meta}$H), 57.1 ($\mathbf{C}(CH_3)_3$), 22.0 ($C(\mathbf{CH_3})_3$) ppm.

LRMS (ES+) *m/z* 232 (100%, $[M+Na]^+$), 273 (48%, $[M+Na(MeCN)]^+$).

(±)-2-Methyl-3-(2-methylpropane-2-sulfinylamino)-3-Phenylpropionic Acid Methyl Ester ((±)-3.42)



$C_{15}H_{23}NO_3S$
Mw = 297.41 $gmol^{-1}$
Pale yellow oil

Following the general procedure described by Ellman *et al*,[75] *i*-Pr_2NH (0.28 mL, 2.1 mmol, 2.2 eq.) was dissolved in THF (10.5 mL, 0.2 M) and cooled to 0 °C in flame dried glassware. Next, *n*-BuLi (0.9 mL, 2.0 mmol, 2.1 eq.) was added slowly dropwise. The solution was stirred for 30 min before being cooled to –78 °C. Methyl propionate (0.18 mL, 1.9 mmol, 2.0 eq.) was added in THF (1 mL, thoroughly degassed) and stirred for 30 min. This was followed by the slow addition of $TiCl(O\textit{i}\text{-}Pr)_3$ (3.8 mL of a 1.0 M soln. in THF, 3.8 mmol, 4.0 eq.) to form an orange solution. The reaction

mixture was stirred for 30 min before sulfinyl imine **(±)-3.15** (0.20 g, 0.96 mmol) was added slowly as a solution in THF (0.2 mL). The reaction was stirred for 3 h at –78 °C before a sat. soln. of NH_4Cl (0.51 g, 9.6 mmol, 10 eq.) was added. Next, H_2O (4 mL) was added and the suspension was stirred vigorously for 10 min. The organic layer was decanted and H_2O and EtOAc (3 mL each) were added and stirred vigorously for 15 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (40 mL) and dried ($MgSO_4$). Purification by column chromatography (silica gel 60A, gradient elution: 6:4 to 4:6 hexane/EtOAc) yielded two separable diastereomers of sulfinyl amine **(±)-3.42** as a pale yellow oil. Spectroscopic characteristics for the minor diastereomer are identical to those for the major diastereomer in the literature.[75]

Major diastereomer (0.15 g, 51%):

FT-IR ν_{max} (neat) 3496 (w), 2956 (w), 2926 (w), 1730 (s), 1036 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.27 (5H, m, 5 x C_{Ar}**H**), 4.75 (1H, dd, J = 7.9, 6.1 Hz, C**H**N), 3.84 (1H, br d, J = 7.7 Hz, N**H**), 3.60 (3H, s, OC**H$_3$**), 3.00 (1H, qd, J = 7.1, 6.0 Hz, C**H**COOCH$_3$), 1.22 (9H, s, C(C**H$_3$**)$_3$), 1.17 (3H, d, J = 7.1 Hz, C**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (**C**O), 140.6 (**C**$_{ipso}$), 128.9 (**C**$_{ortho}$H), 128.2 (**C**$_{meta}$H), 127.4 (**C**$_{para}$H), 62.1 (**C**HN), 56.9 (**C**(CH$_3$)$_3$), 52.1 (O**C**H$_3$), 46.4 (**C**HCOOCH$_3$), 23.0 (C(**C**H$_3$)$_3$), 12.8 (**C**H$_3$) ppm.

LRMS (ES+) *m/z* 320 (100%, $[M+Na]^+$), 617 (35%, $[2M+Na]^+$).

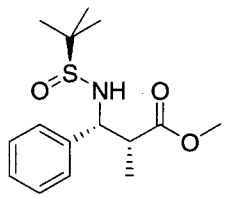
Minor diastereomer (0.05 g, 16%):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (5H, m, 5 x C_{Ar}**H**), 4.67 (1H, t, J = 4.3 C**H**N), 4.44 (1H, d, J = 3.4 Hz, N**H**), 3.63 (3H, s, OC**H$_3$**), 2.93 (1H, dq, J = 7.1, 5.1 Hz, C**H**COOCH$_3$), 1.23 (9H, s, C(C**H$_3$**)$_3$), 1.16 (3H, d, J = 6.9 Hz, C**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (**C**O), 139.4 ($\mathbf{C}_{ipso}$), 128.6 ($\mathbf{C}_{ortho}$H), 128.4 ($\mathbf{C}_{meta}$H), 127.4 ($\mathbf{C}_{para}$H), 60.2 (**C**HN), 56.1 (**C**$(CH_3)_3$), 52.4 (O**C**H_3), 46.4 (**C**HCOOCH_3), 23.0 (C(**C**$H_3)_3$), 12.6 (**C**H_3) ppm.

LRMS (ES+) *m/z* 320 (100%, $[M+Na]^+$).

(*S*$_S$,2*R*,3*S*)-2-Methyl-3-(2-methylpropane-2-sulfinylamino)-3-phenylpropionic acid methyl ester (3.42)



$C_{15}H_{23}NO_3S$
Mw = 297.41 gmol^{-1}
Yellow oil

Following the procedure described above, *i*-Pr_2NH (0.27 mL, 1.97 mmol, 2.2 eq.), *n*-BuLi (1.03 mL of a 1.82 M soln. in hexane, 2.1 eq.), methyl propionate (0.17 mL, 1.79 mmol, 2.0 eq.), TiCl(O*i*-Pr)$_3$ (3.57 mL of a 1.0 M soln. in THF, 3.57 mmol, 4.0 eq.) and sulfinyl imine **(+)-3.15** (0.19 g, 0.89 mmol, 1.0 eq.) in THF (9.8 mL, 0.2 M) stirred at –78 °C for 3 h afforded the title product as a separable mixture of two diastereomers. Purification was achieved by column chromatography (silica gel 60A, 19:1 to 1:1 hexane/EtOAc).

Major diastereomer (99.5 mg, 38%):

FT-IR ν_{max} (neat) 3217 (br, w), 2951 (w), 1735 (s), 1047 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (5H, m, 5 x C_{Ar}**H**), 4.69 (1H, dd, J = 7.7, 5.9 Hz, **CH**NH), 3.78 (1H, br d, J = 7.5 Hz, N**H**), 3.55 (3H, s, O**C**$\mathbf{H_3}$), 2.94 (1H, qd, J = 7.1, 6.0 Hz, **CH**COOCH_3), 1.16 (9H, s, C(**C**$\mathbf{H_3})_3$), 1.12 (3H, d, J = 7.0 Hz, **C**$\mathbf{H_3}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (**C**O), 140.6 ($\mathbf{C}_{ipso}$), 128.9 ($\mathbf{C}_{ortho}$H), 128.2 ($\mathbf{C}_{meta}$H), 127.4 ($\mathbf{C}_{para}$H), 62.1 (**C**HN), 56.8 (**C**$(CH_3)_3$), 52.1 (O**C**H_3), 46.4 (**C**HCOOCH_3), 22.9 (C(**C**$H_3)_3$), 12.8 (**C**H_3) ppm.

LRMS (ES+) *m/z* 319.9 (100%, $[M+Na]^+$), 361.0 (85%, $[M+Na(MeCN)]^+$), 617.2 (60%, $[2M+Na]^+$).

Minor diastereomer (54.4 mg, 21%) (shows evidence of other diastereomer present):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.23 (5H, m, 5 x C_{Ar}**H**), 4.65 (1H, t, *J* = 4.2 Hz, **CH**NH), 4.41 (1H, br. d, *J* = 3.1 Hz, N**H**), 3.61 (3H, s, O**CH$_3$**), 2.94 (1H, qd, *J* = 7.1, 6.0 Hz, **CH**COOCH$_3$), 1.20 (9H, s, C(**CH$_3$**)$_3$), 1.12 (3H, d, *J* = 7.0 Hz, **CH$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (**C**O), 139.5 (**C**$_{ipso}$), 128.9 (**C**$_{ortho}$H), 128.6 (**C**$_{meta}$H), 128.3 (**C**$_{para}$H), 60.2 (**C**HN), 56.2 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 46.5 (**C**HCOOCH$_3$), 23.0 (C(**C**H$_3$)$_3$), 12.7 (**C**H$_3$) ppm.

Procedure used for the doped Lewis acid reactions:

To a flame dried flask was added *i*-Pr$_2$NH (0.22 mL, 1.43 mmol, 2.2 eq.), THF (7.2 mL, 0.2 M) cooled to 0 °C before *n*-BuLi (0.6 mL of a 2.5 M soln. in hexanes, 1.5 mmol, 2.1 eq.) was added dropwise over 10 min giving a a pale yellow solution. The reaction was stirred for 30 min before it was cooled to –78 °C and methyl propionate (0.14 mL, 1.43 mmol, 2.0 eq.) was added. The reaction was stirred for 1 h. Separately, a solution of TiCl(O*i*-Pr)$_3$ (2.87 mL of 1.0 M soln. in THF, 2.87 mmol, 4.0 eq.) at 0 °C was added neat TiCl$_4$ or Ti(O*i*-Pr)$_4$ (0.1 eq. relative to TiCl(O*i*-Pr)$_3$). This was stirred for 30 min before it was added to the Li enolate solution. The resulting orange titanium enolate solution was allowed to stir for 1 h before sulfinyl imine **(+)-3.15** (0.15 g, 0.72 mmol) was added. The reaction was stirred for 3 h before being quenched by the addition of a sat. soln. of citric acid (10 eq.). The mixture was allowed to warm to rt before the layers were separated. The aqueous layer was extracted with EtOAc (4 x 20 mL) and the combined organic layers were washed with H_2O (50 mL) then brine (50 mL) and dried (Na_2SO_4). Purification was achieved by column chromatography (silica gel 60A, 6:4 hexane/EtOAc) to yield the title compound as a separable mixture of two diastereomers. Spectroscopic data is consistent with that previously collected.

Doped with $TiCl_4$

Major diastereomer (0.13 g, 59%):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.29 (5H, m, C_{Ar}**H**), 4.69 (1H, appt t, **CH**NH), 4.45 (1H, br d, *J* = 3.7 Hz, N**H**), 3.66 (3H, s, O**CH$_3$**), 2.94 (1H, qd, *J* = 7.0, 5.0 Hz, **CH**COOCH$_3$), 1.25 (9H, s, C(**CH$_3$**)$_3$), 1.18 (3H, d, *J* = 7.0 Hz, **CH$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (**C**O), 139.5 (**C$_{ipso}$**), 128.6 (**C$_{ortho}$**H), 128.3 (**C$_{meta}$**H), 128.2 (**C$_{para}$**H), 60.2 (**C**HN), 56.2 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 46.5 (**C**HCOOCH$_3$), 23.0 (C(**C**H$_3$)$_3$), 12.7 (**C**H$_3$) ppm.

Minor diastereomer (0.013 g, 6%), selected peaks:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, 5 x C_{Ar}**H**), 4.75 (1H, dd, *J* = 7.9, 6.1 Hz, **CH**NH), 3.99 (1H, br d, *J* = 7.9 Hz, N**H**), 3.60 (3H, s, O**CH$_3$**), 3.00 (1H, appt qn, *J* = 7.0 Hz, **CH**COOCH$_3$), 1.23 (9H, s, C(**CH$_3$**)$_3$), 1.19 (3H, d, *J* = 6.9 Hz, **CH$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (**C**O), 140.6 (**C$_{ipso}$**), 128.9 (**C$_{ortho}$**H), 128.2 (**C$_{meta}$**H), 127.5 (**C$_{para}$**H), 62.2 (**C**HN), 56.9 (**C**(CH$_3$)$_3$), 52.1 (O**C**H$_3$), 46.4 (**C**HCOOCH$_3$), 23.0 (C(**C**H$_3$)$_3$), 12.9 (**C**H$_3$) ppm.

Doped with Ti(O*i*-Pr)$_4$

Major diastereomer (0.051 g, 24%):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.21 (5H, m, 5 x C_{Ar}**H**), 4.69 (1H, appt. t, **CH**NH), 4.46 (1H, d, *J* = 3.4 Hz, N**H**), 3.65 (3H, s, O**CH$_3$**), 2.94 (1H, qd, *J* = 7.1, 5.0 Hz, **CH**COOCH$_3$), 1.24 (9H, s, C(**CH$_3$**)$_3$), 1.18 (3H, d, *J* = 7.1 Hz, **CH$_3$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (**C**O), 139.5 (**C$_{ipso}$**), 128.6 (**C$_{ortho}$**H), 128.3 (**C$_{meta}$**H), 128.2 (**C$_{para}$**H), 60.2 (**C**HN), 56.2 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 46.5 (**C**HCOOCH$_3$), 23.0 (C(**C**H$_3$)$_3$), 12.7 (**C**H$_3$) ppm.

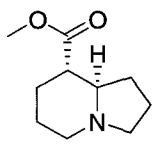
Minor diastereomer (0.013 g, 6%):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, 5 x C_{Ar}**H**), 4.74 (1H, dd, *J* = 7.9, 6.1 Hz, **CH**NH), 3.99 (1H, d, *J* = 7.9 Hz, N**H**), 3.60 (3H, s, O**CH$_3$**), 3.00 (1H, dq, *J* = 6.9, 6.7 Hz, **CH**COOCH$_3$), 1.23 (9H, s, C(**CH$_3$**)$_3$), 1.18 (3H, d, *J* = 7.0 Hz, **CH$_3$**) ppm.

Selected peaks:

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (**CO**), 140.6 (**C$_{ipso}$**), 62.3 (**CH**N), 57.0 (**C**(CH$_3$)$_3$), 52.1 (**C**(CH$_3$)$_3$), 46.4 (**CH**COOCH$_3$), 22.7 (C(**CH$_3$**)$_3$), 12.9 (**CH$_3$**) ppm.

(+)-Methyl-(8*S*,8a*R*)-octahydroindolizidine-8-carboxylate ((+)-4.23)



$C_{10}H_{17}NO_2$
Mw = 183.25 gmol^{-1}
Pale yellow oil

Sulfinyl amine **4.71** (mixture of 2 major diastereomers, 0.20 g, 0.56 mmol) was dissolved in MeOH (5 mL), treated with 4 N HCl/dioxane (0.6 mL) and stirred at rt for 3 h. The solvent was removed *in vacuo* before the crude oil was dissolved in MeCN (3 mL). Next, K_2CO_3 (0.65 g, 4.64 mmol, 8.0 eq.) and NaI (0.01 g, 67.0 μmol, 0.1 eq.) were added. The solution immediately turned orange and lightened to yellow over 2 h. The reaction was heated to 65 °C and stirred for 16 h before it was quenched by the addition of H_2O (10 mL). The mixture was separated between Et_2O/H_2O and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an orange oil (0.11 g). Purification by column chromatography (basic alumina, 3:1 hexane/EtOAc) yielded the title compound as a pale yellow oil (69.0 mg, 68%). Spectroscopic data are consistent with those published in the literature.[125]

$[\alpha]_D^{29}$ +27.4 (*c* 0.67, $CHCl_3$) (lit. (5*S*,6*R* diastereomer): +69.0, *c* 1.90, 20 °C, MeOH).[122]

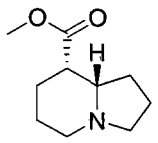
FT-IR ν_{max} (neat) 2937 (m), 2783 (m), 1732 (s), 1435 (m), 1313 (m), 1154 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (3H, s, OCH_3), 3.12-3.07 (1H, m, NCHH $_{6\ membered}$), 3.05 (1H, dt, J = 8.9, 2.1 Hz, NCHH $_{5\ membered}$), 2.27 (1H, ddd, J = 12.1, 9.5, 3.8 Hz, $CHCOOCH_3$), 2.13 (1H, q, J = 9.0 Hz, NCHH $_{5\ membered}$), 2.06-1.89 (4H, m, CHN; $CH(N)CH_2$ and NCHH $_{6\ membered}$), 1.85-1.70 (2H, m, 2 x NCH_2CHH), 1.70-1.56 (2H, m, 2 x NCH_2CHH), 1.53-1.38 (2H, m, CH_2CHCO) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2 (CO), 65.4 (CHN), 54.4 (NCH_2), 52.6 (NCH_2), 51.8 (OCH_3), 48.4 ($CHCOOCH_3$), 29.6 ($CH_2CHCOOCH_3$), 28.5 (CH_2CHN), 25.2 (CH_2), 20.8 (CH_2) ppm.

LRMS (ES+) *m/z* 184.0 (100%, $[M+H]^+$).

***anti*-(+)-Methyl octahydroindolizine-8-carboxylate (*anti*-(+)-4.23)**



$C_{10}H_{17}NO_2$
Mw = 183.25 $gmol^{-1}$
Pale yellow oil

Sulfinyl amine **(+)-4.71** (minor diastereomer, 45.0 mg, 0.12 mmol) was dissolved in MeOH (1.5 mL), treated with 4 N HCl/dioxane (0.5 mL) and stirred at rt for 2 h. The solvent was removed *in vacuo* before the crude oil was dissolved in MeCN (1.5 mL). Next, K_2CO_3 (140.0 mg, 1.00 mmol, 8.0 eq.) and NaI (5.0 mg, 33 μmol, 0.3 eq.) were added. The solution immediately turned orange and lightened to yellow over 2 h. The reaction was heated to 65 °C and stirred for 16 h before it was quenched by the addition of H_2O (10 mL). The mixture was separated between Et_2O/H_2O and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an orange oil (19.9 mg). Purification by column chromatography (basic alumina, gradient elution 7:3 to 1:1 hexane/EtOAc) yielded the title compound as a pale yellow oil (10.6 mg, 46%). Spectroscopic data are different from that previously collected.

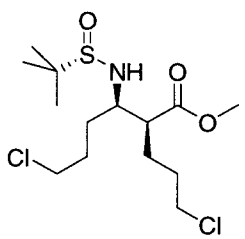
$[\alpha]_D^{29}$ +18.6 (*c* 0.22, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (3H, s, OCH_3), 3.15-3.00 (2H, m, 2 x NCHH), 2.81 (1H, td, *J* = 4.3, 4.0 Hz, CH), 2.21-2.13 (1H, m, CHH), 2.12-1.93 (4H, m, 2 x CH_2), 1.86-1.72 (4H, m, 2 x CH_2), 1.70-1.58 (2H, m, CH_2) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (CO), 64.9 (CHN), 55.2 (NCH_2), 53.4 (NCH_2), 51.5 (OCH_3), 42.2 ($CHCOOCH_3$), 27.2 (CH_2), 26.7 (CH_2), 22.8 (CH_2), 20.9 (CH_2) ppm.

LRMS (ES+) *m/z* 184.0 (100%, $[M+H]^+$).

(+)-Methyl-(S_S,2*S*,3*R*)-3-[(*tert*-butylsulfinyl)amino]-6-chloro-2-(3-chloropropyl)hexanoate ((+)-4.71)



$C_{14}H_{27}Cl_2NO_3S$
Mw = 360.34 $gmol^{-1}$
Partially separable mixture of diastereomers

To a flame dried RB flask was added *i*-Pr_2NH (1.40 mL, 10.0 mmol, 4.2 eq.) followed by THF (50 mL, 0.2 M) and cooled to 0 °C. Next, *n*-BuLi (4.63 mL of a 2.11 M soln. in hexanes, 9.8 mmol, 4.1 eq.) was added dropwise to give a pale yellow solution that was stirred for 30 min before it was cooled to –78 °C. Next, ester **4.76** (1.28 mL, 9.5 mmol, 4.0 eq.) was added dropwise. The reaction mixture was stirred for a further 30 min before a 10% $TiCl_4$ in $TiCl(Oi\text{-}Pr)_3$ solution (19.0 mL of a 1.0 M soln. in THF, 19.0 mmol, 8.0 eq.) was added slowly resulting in a deep orange colour. Sulfinyl imine **(+)-4.72** (0.5 g, 2.4 mmol) was added dropwise as a soln. in THF (5 mL). The reaction mixture was stirred for 1 h over which time the colour lightened marginally. The reaction was quenched by the addition of a sat. soln. of citric acid (10 eq.) and allowed to warm to rt. The layers were separated between EtOAc/H_2O and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with a sat

soln. of NH_4Cl (1x), H_2O (2x), brine (1x) and dried ($MgSO_4$). The crude yellow oil (2.05 g) was purified by column chromatography (silica gel 60, gradient elution 7:3 to 1:1 hexane/EtOAc) to yield the title compound as mixture of diastereomers.
Minor diastereomer (0.097 g, 11%).
Mixture of two diastereomers (0.66 g, 77%).

Minor diastereomer:

$[\alpha]_D^{29}$ +28.7 (*c* 0.87, $CHCl_3$).

FT-IR ν_{max} (neat) 3309 (w), 2955 (w), 2869 (w), 1720 (s), 1435 (s), 1196 (s), 1053 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48 (1H, d, *J* = 8.3 Hz, N**H**), 3.72 (3H, s, O**CH$_3$**), 3.63-3.50 (4H, m, 2 x **CH$_2$**Cl), 3.37 (1H, tt, *J* = 8.6, 4.2 Hz, **CH**N), 2.63 (1H, ddd, *J* = 8.3, 5.9, 3.9 Hz, **CH**COOCH$_3$), 1.99-1.56 (6H, m, 3 x **CH$_2$**), 1.70-1.49 (2H, m, **CH$_2$**), 1.24 (9H, s, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4 (**C**(O)), 57.7 (**C**HN), 56.7 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 49.0 (**C**HCOOCH$_3$), 44.8 (**C**H$_2$Cl), 44.6 (**C**H$_2$Cl), 33.4 (**C**H$_2$), 30.8 (**C**H$_2$), 29.6 (**C**H$_2$), 27.1 (**C**H$_2$), 23.2 (C(**C**H$_3$)$_3$) ppm.

LRMS (ES+) *m/z* 382.0 (100%, $[M+Na]^+$).

Inseparable mixture of diastereomers (referenced A and B):

$[\alpha]_D^{28}$ +45.4 (*c* 1.12, $CHCl_3$)

MP 71-73 °C.

FT-IR ν_{max} (neat) 3331 (w), 2958 (w), 1728 (s), 1433 (s), 1195 (s), 1051 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (1H$_A$, d, *J* = 8.9 Hz, N**H$_A$**), 3.74 (3H$_A$, s, OC(**H$_A$**)$_3$), 3.70 (3H$_B$, s, OC(**H$_B$**)$_3$), 3.62-3.45 (4H$_A$ + 4H$_B$, m, 2 x C(**H$_A$**)$_2$Cl and 2 x C(**H$_B$**)$_2$Cl), 3.42-3.29 (1H, m, C**H$_A$**N), 3.20 (1H$_B$, d, *J* = 7.9 Hz, N**H$_B$**), 2.95 (1H$_A$, ddd, *J* = 8.8, 4.8, 4.5 Hz, C**H$_A$**COOCH$_3$),

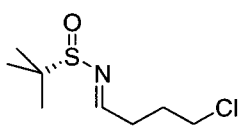
2.55 ($1H_B$, dt, J = 7.2, 6.3 Hz, CH_BCOOCH_3), 2.11-1.62 ($8H_A + 8H_B$, m, 4 x $C(H_A)_2$ and 4 x $C(H_B)_2$), 1.48 ($1H_A$, dt, J = 9.9, 4.3 Hz, CHH), 1.24 ($9H_A$, s, $C(C(H_A)_3)_3$), 1.22 ($9H_B$, s, $C(C(H_B)_3)_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2 (C_AO), 174.0 (C_BO), 58.5 (C_AHN), 58.4 (C_BHN), 56.7 ($C_B(CH_3)_3$), 56.6 ($C_A(CH_3)_3$), 52.3 (OC_AH_3), 52.1 (OC_BH_3), 51.1 ($C_BHCOOCH_3$), 50.2 ($C_AHCOOCH_3$), 44.9 (C_BH_2Cl), 44.9 (C_BH_2Cl), 44.8 (C_AH_2Cl), 31.5 (C_BH_2), 31.0 (C_AH_2), 30.8 (C_BH_2), 29.7 (C_AH_2), 29.6 (C_AH_2), 29.1 (C_BH_2), 26.4 ($C_AH)_2$), 25.5 (C_BH_2), 23.1 ($C(CH_3)_3$) ppm. Second C_AH_2Cl peak was not observed.

LRMS (ES+) *m/z* 382.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{14}H_{27}Cl_2NO_3SNa$, requires 382.0986 found 382.0974 Da.

(*S*$_S$)-(+)-*N*-[(*E*)-4-chlorobutylidene]-2-methylpropane-2-sulfinamide ((+)-4.72)



$C_8H_{16}ClNOS$
Mw = 209.74 $gmol^{-1}$
Pale yellow oil

According to the procedure described (*vide supra*), the reaction of TBSA **(–)-3.10** (1.05 g, 8.7 mmol), aldehyde **6.02** (0.92 g, 8.6 mmol) and $CuSO_4$ (3.03 g, 19.0 mmol) in CH_2Cl_2 (17 mL) heated to 40 °C for 16 h yielded the title product as a pale yellow free flowing oil (1.40 g, 73%) after column chromatography (silica gel 60A, 3:1 hexane/EtOAc).

$[\alpha]_D^{28}$ +215.7 (*c* 1.24, $CHCl_3$).

FT-IR ν_{max} (neat) 2960 (w), 2926 (w), 1622 (s), 1078 (s) cm^{-1}.

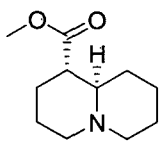
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (1H, t, J = 4.0 Hz, CHN), 3.64 (2H, td, J = 6.5, 0.9 Hz, CH_2Cl), 2.72 (2H, td, J = 6.8, 4.0 Hz, CH_2CHN), 2.15 (2H, qn, J = 6.6 Hz, CH_2CH_2Cl), 1.21 (9H, s, $C(CH_3)_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 (**C**HN), 57.0 (**C**$(CH_3)_3$), 44.3 (**C**H_2Cl), 33.5 (CH_2**C**HN), 28.4 (CH_2), 22.7 ($C(CH_3)_3$) ppm.

LRMS (ES+) *m/z* 210.3 (40%, $[M+H]^+$), 232.2 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_8H_{17}ClNOS$, requires 210.0719 found 210.0718 Da.

(+)-(1*S*,9a*R*)-Methyl octahydro-2*H*-quinolizine-1-carboxylate ((+)-4.73)



$C_{11}H_{19}NO_2$
Mw = 197.27 $gmol^{-1}$
Orange oil

Sulfinyl amine **4.74** (mixture of 2 major diastereomers, 0.24 g, 0.64 mmol) was dissolved in MeOH (4 mL), treated with 4 N HCl/dioxane (1.4 mL) and stirred at rt for 20 h. The solvent was removed *in vacuo* before the crude oil was dissolved in MeCN (5 mL). Next, K_2CO_3 (0.75 g, 5.43 mmol, 8.5 eq.) and NaI (10 mg, 67 μmol, 0.1 eq.) were added. The solution immediately turned orange and lightened to yellow over 2 h. The reaction was heated to 65 °C and stirred for 16 h before it was quenched by the addition of H_2O (10 mL). The mixture was separated between Et_2O/H_2O and the aqueous layer was washed with Et_2O (2x). The combined organic layers were washed with H_2O (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an orange oil. Purification by column chromatography (basic alumina, gradient elution 7:3 to 6:4 hexane/EtOAc) yielded the title compound as an orange oil (0.11 g, 86%). Spectroscopic data are consistent with those published in the literature.[125]

$[\alpha]_D^{29}$ +8.5 (*c* 0.99, $CHCl_3$).

FT-IR ν_{max} (neat) 2934 (m), 2856 (w), 2801 (w), 2754 (w), 1732 (s), 1435 (m), 1321 (m), 1145 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (3H, s, O**C**H_3), 2.86-2.74 (2H, m, 2 x NC**H**H), 2.28 (1H, ddd, *J* = 12.3, 10.0, 3.7 Hz, **C**HCOOCH$_3$), 2.12-2.02 (2H, m, 2 x NC**H**H), 1.99 (1H, td, *J* = 10.0, 2.3 Hz, **C**HN), 1.95-1.86 (1H, m,

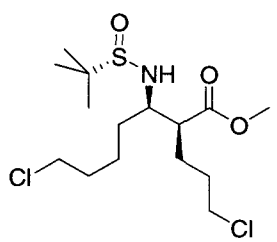
CHHCHCO), 1.75-1.46 (6H, m, 2 x $NCH_2\mathbf{CH_2}$, CHHCHCO and CH**H**), 1.30-1.17 (3H, m, $\mathbf{CH_2}$ and C**H**H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 (**C**O), 63.9 (**C**HN), 57.0 ($\mathbf{C}H_2N$), 56.4 ($\mathbf{C}H_2N$), 51.8 ($O\mathbf{C}H_3$), 49.7 ($\mathbf{C}HCOOCH_3$), 31.3 ($NCH_2\mathbf{C}H_2$), 29.0 ($\mathbf{C}H_2CHCO$), 26.0 ($NCH_2\mathbf{C}H_2$), 24.9 ($\mathbf{C}H_2$), 24.6 ($\mathbf{C}H_2$) ppm.

LRMS (ES+) *m/z* 198.0 (100%, $[M+H]^+$).

HRMS (ES+) for $C_{11}H_{20}NO_2$, requires 198.1494 found 198.1488 Da.

(+)-Methyl-(*S*$_S$,2*S*,3*R*)-3-[(*tert*-butylsulfinyl)amino]-6-chloro-2-(3-chloropropyl)-heptanoate ((+)-4.74)



$C_{15}H_{29}Cl_2NO_3S$
Mw = 374.37 $gmol^{-1}$
Partially separable mixture of diastereomers

To a flame dried RB flask was added *i*-Pr_2NH (1.26 mL, 8.99 mmol, 4.2 eq.) followed by THF (45 mL, 0.2 M) and cooled to 0 °C. Next *n*-BuLi (4.16 mL of a 2.11 M soln. in hexanes, 8.77 mmol, 4.1 eq.) was added dropwise to give a pale yellow solution that was stirred for 30 min before being cooled to –78 °C. Next, ester **4.76** (1.15 mL, 8.56 mmol, 4.0 eq.) was added dropwise. The reaction mixture was stirred for a further 30 min before a 10% $TiCl_4$ in $TiCl(O\textit{i}\text{-}Pr)_3$ solution (17.10 mL of a 1.0 M soln. in THF, 17.10 mmol, 8.0 eq.) was added slowly resulting in a deep orange colour. Next, sulfinyl imine **(+)-4.75** (0.50 g, 2.14 mmol) was added dropwise as a soln. in THF (5 mL). The reaction mixture was stirred for 1 h over which time the colour lightened marginally. The reaction was quenched by the addition of a sat. soln. of citric acid (10 eq.) and allowed to warm to rt. The layers were separated between EtOAc/H_2O and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with a sat. soln. of NH_4Cl (1x), H_2O (2x), brine (1x) and dried ($MgSO_4$). The crude yellow oil

(1.5 g) was purified by column chromatography (silica gel 60, gradient elution 7:3 to 1:1 hexane/EtOAc) to yield the title compound as mixture of three diastereomers.

Minor diastereomer (0.10 g, 12%).

Mixture of two diastereomers (0.46 g, 57%).

Minor diastereomer:

$[\alpha]_D^{29}$ +27.8 (*c* 0.96, $CHCl_3$).

FT-IR ν_{max} (neat) 3309 (w), 2954 (m), 2868 (w), 1720 (s), 1436 (br, m), 1196 (s), 1061 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, d, *J* = 8.2 Hz, N**H**), 3.72 (3H, s, O**CH$_3$**), 3.64-3.49 (4H, m, 2 x **CH$_2$**Cl), 3.41-3.30 (1H, m, **CH**N), 2.63 (1H, ddd, *J* = 8.3, 6.2, 3.8 Hz, **CH**COOCH$_3$), 1.98-1.67 (6H, m, 3 x **CH$_2$**), 1.67-1.54 (1H, m, **CH**H), 1.54-1.41 (3H, m, 3 x CH**H**), 1.24 (9H, s, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4 (**C**O), 58.1 (**C**HN), 56.8 (**C**(CH$_3$)$_3$), 52.2 (O**C**H$_3$), 48.9 (**C**HCOOCH$_3$), 45.0 (**C**H$_2$Cl), 44.7 (**C**H$_2$Cl), 35.4 (**C**H$_2$), 32.4 (**C**H$_2$), 30.8 (**C**H$_2$), 27.1 (**C**H$_2$), 23.8 (**C**H$_2$), 23.2 (C(**C**H$_3$)$_3$) ppm.

LRMS (ES+) *m/z* 396.0 (100%, $[M+Na]^+$), 771.0 (20%, $[2M+Na]^+$).

Inseparable mixture of diastereomers (referenced A and B):

$[\alpha]_D^{28}$ +36.7 (*c* 1.10, $CHCl_3$).

MP 29-30 °C.

FT-IR ν_{max} (neat) 2954 (w), 2868 (w), 1725 (s), 1433 (m), 1150 (s), 1051 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.15 (1H$_A$, d, *J* = 8.5 Hz, N**H$_A$**), 3.73 (3H$_A$, s, OC(**H$_A$**)$_3$), 3.69 (3H$_B$, s, OC(**H$_B$**)$_3$), 3.60-3.49 (4H$_A$ + 4H$_B$, m, 2 x C(**H$_A$**)$_2$Cl and 2 x C(**H$_B$**)$_2$Cl), 3.40-3.29 (1H$_B$, m, C**H$_B$**N), 3.16 (1H$_B$, d, *J* = 7.8 Hz, N**H$_B$**), 2.91 (1H$_A$, dt, *J* = 9.0, 4.6 Hz, C**H$_A$**COOCH$_3$), 2.54

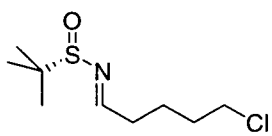
($1H_B$, q, J = 6.3 Hz, CH_BCOOCH_3), 1.96-1.59 ($8H_A$ + $8H_B$, m, 4 x $C(H_A)_2$ and 4 x $C(H_B)_2$), 1.56-1.32 ($2H_A$ + $2H_B$, m, $C(H_A)_2$ and $C(H_B)_2$), 1.24 ($9H_A$, s, $C(C(H_A)_3)_3$), 1.21 ($9H_B$, s, $C(C(H_B)_3)$) ppm. CH_AN peak masked by another peak.

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3 (C_AO), 174.2 (C_BO), 58.8 (C_BHN), 58.7 (C_AHN), 56.6 ($C_B(CH_3)_3$), 56.5 ($C_A(CH_3)_3$), 52.3 (OC_AH_3), 52.1 (OC_BH_3), 50.4 ($C_BHCOOCH_3$), 50.1 ($C_AHCOOCH_3$), 45.1 (C_AH_2Cl), 44.9 (C_BH_2Cl), 44.9 (C_BH_2Cl), 33.7 (CH_2), 32.4 (C_BH_2), 31.7 (C_AH_2), 31.0 (C_AH_2), 30.8 (C_BH_2), 26.3 (C_AH_2), 25.1 (C_BH_2), 24.0 (C_AH_2), 23.4 (C_BH_2), 23.1 (C ($C_AH_3)_3$), 23.0 ($C(C_BH_3)_3$) ppm. The second C_AH_2Cl and a CH_2 peak were not observed.

LRMS (ES+) *m/z* 396.0 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{15}H_{29}Cl_2NO_3SNa$, requires 396.1143 found 396.1134 Da.

(S_S)-(+)-*N*-[(*E*)-5-Chloropentylidene]-2-methylpropane-2-sulfamide ((+)-4.75)



$C_9H_{18}ClNOS$
Mw = 223.76 $gmol^{-1}$
Pale yellow oil

According to the procedure described (*vide supra*), the reaction of TBSA **(–)-3.10** (1.10 g, 9.05 mmol), aldehyde **6.03** (1.00 g, 8.62 mmol) and $CuSO_4$ (3.00 g, 19.0 mmol) in CH_2Cl_2 (17 mL) heated to 40 °C for 18 h yielded the title product as a pale yellow free flowing oil (1.50 g, 77%). Purification was achieved by column chromatography (silica gel 60A, 3:1 hexane/EtOAc).

$[\alpha]_D^{28}$ +221.7 (*c* 1.20, $CHCl_3$).

FT-IR ν_{max} (neat) 2958 (w), 2868 (w), 1622 (s), 1078 (s) cm^{-1}.

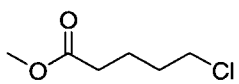
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (1H, t, *J* = 4.4 Hz, **CH**N), 3.56 (2H, t, *J* = 6.2 Hz, **CH$_2$**Cl), 2.57 (2H, td, *J* = 7.2, 4.6 Hz, **CH$_2$**CHN), 1.89-1.78 (4H, m, 2 x **CH$_2$**), 1.20 (9H, s, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0 (**C**HN), 56.9 (**C**(CH$_3$)$_3$), 44.8 (**CH$_2$**Cl), 35.5 (**CH$_2$**CHN), 32.3 (**CH$_2$**), 23.0 (**CH$_2$CH$_2$**Cl), 22.7 (C(**CH$_3$**)$_3$) ppm.

LRMS (ES+) *m/z* 224.3 (30%, $[M+H]^+$), 246.3 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_9H_{19}ClNOS$, requires 224.0876 found 224.0870 Da.

Methyl-5-chloropentanoate (4.76)

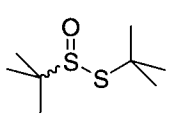


$C_6H_{11}ClO_2$
Mw = 150.60 gmol^{-1}
Colourless oil

MeOH (40 mL) was treated with AcCl (4 mL) (CARE! - exotherm) and the reaction mixture was stirred at rt for 5 min before 5-chlorovaleric acid (4.3 mL, 36.6 mmol) was added neat. The reaction mixture was then heated to reflux temperature for 3 h. Afterwards, the reaction was quenched by pouring on to H_2O (100 mL). The aqueous phase was extracted with Et_2O (3 x 30 mL) and the combined organic phases were washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a colourless oil (4.5 g, 82%). ^{1}H NMR Spectroscopic data is consistent with that published in the literature.[184]

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (3H, s, O**CH$_3$**), 3.56-3.52 (2H, m, **CH$_2$**Cl), 2.37-2.33 (2H, m, **CH$_2$**COOCH$_3$), 1.82-1.79 (4H, m, 2 x **CH$_2$**) ppm.

(±)-*tert*-Butyl thiosulfinate ((±)-5.11)



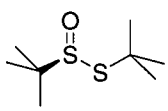
$C_8H_{18}OS_2$
Mw = 194.36 gmol^{-1}
Pale yellow oil

Following the procedure detailed by Netscher and Prinzbach,[163] hydrogen peroxide (1.28 mL of a 30% solution in water, 12.5 mmol) was added to a solution of *tert*-butyl disulphide (1.93 mL, 0.01 mol) and acetic acid (10 mL) cooled to 2 °C. The solution was stirred for 48 h at 2 °C. Consumption of starting material was monitored by ^{1}H NMR analysis of the reaction mixture. The reaction was quenched by pouring on to ice and extracting with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed sequentially with a sat. soln. of $NaHCO_3$, H_2O and brine (60 mL of each) before being dried (Na_2SO_4). The solvent was removed *in vacuo* to yield a pale yellow oil (1.86 g, 96%). No further purification was necessary. Spectroscopic data are consistent with those published in the literature.[163]

FT-IR ν_{max} (neat) 2959 (m), 1069 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (9H, s, *t*-Bu$_{thiosulfinate}$), 1.39 (9H, s, *t*-Bu$_{thiol}$) ppm.

(*S*$_S$)-(–)-*tert*-Butyl thiosulfinate ((–)-5.11)



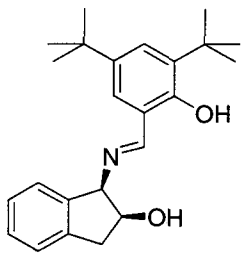
$C_8H_{18}OS_2$
Mw = 194.36 gmol^{-1}
Light brown oil

Following the procedure described by Weix *et al.*,[164] ligand **(+)-5.12** (0.38 g, 1.04 mmol) and $VO(acac)_2$ (0.27 g, 1.0 mmol) were dissolved in analar grade acetone (50 mL) and stirred vigorously for 30 min open to the air. Next, di-*tert*-butyl sulphide (38.6 mL, 0.20 mol) was added and the solution was cooled to 0 °C. To this vigorously stirred dark green solution was added H_2O_2 (22 mL of a 30% soln., 0.22 mol, 1.1 eq.) over 20 h via a syringe pump. The solution turned dark purple upon addition of the H_2O_2. Crude ^{1}H NMR analysis indicated the reaction had gone to completion (97% conversion, 3% starting material). Next, a sat. soln. of $Na_2S_2O_3$ (12 mL) was added over 30 min via a syringe pump. The dark brown solution was diluted with hexane (50 mL). The layers were separated and the aqueous layer was extracted with hexane (2 x 50 mL). The combined organic layers were washed with brine (4 x 10 mL) until the blue colour of the aqueous layer was no longer present, and then dried (Na_2SO_4). The solvent was removed *in vacuo* (water bath <30 °C, final traces of solvent removed on

high vacuum line) to yield a light brown oil (39.6 g, quantitative). No further purification was attempted. (Note: the thiosulfinate was stored at ~ –20 °C to prevent racemisation).

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (9H, s, *t*-$Bu_{thiosulfinate}$), 1.38 (9H, s, *t*-Bu_{thiol}) ppm.

(1*R*,2*S*)-(+)-1-[(2-Hydroxy-3,5-di-*tert*-butyl-benzylidene)-amino]-indan-2-ol ((+)-5.12)



$C_{24}H_{31}NO_2$
Mw = 365.51 $gmol^{-1}$
Bright yellow solid

3,5-Di-*tert*-butyl salicylaldehyde (0.63 g, 2.7 mmol) was dissolved in dry EtOH (20 mL) to give a pale yellow solution. Next, (1*R*,2*S*)-1-amino-2-indanol (0.42 g, 2.8 mmol, 1.04 eq.) was added in one portion and the solution turned bright yellow. The reaction mixture was stirred for 2 h at rt before the EtOH was removed *in vacuo*. The remaining oil was washed successively with CH_2Cl_2 (3 x 50 mL) and dried under vacuum for 16 h to yield a bright yellow powdery solid (0.92 g, 94%). Spectroscopic data is consistent with that published in the literature.[185]

$[\alpha]_D^{27}$ +27.6 (*c* 0.50, $CHCl_3$) (lit: +32.0, *c* 0.69, 25 °C, $CHCl_3$).[185]

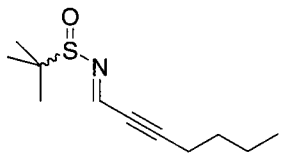
FT-IR ν_{max} (neat) 3396 (br, w), 2950 (s), 2903 (m), 2865 (m), 1621 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ8.64 (1H, s, **CH**N), 7.45 (1H, d, J = 2.4 Hz, $\mathbf{CH}_{ortho\ to\ C(N)}$), 7.35-7.19 (5H, m, $C_{Ar}\mathbf{H}$), 4.82 (1H, d, J = 5.3 Hz, **CH**N=CH), 4.70 (1H, q, J = 5.3 Hz, **CH**OH), 3.27 (1H, dd, J = 15.9, 5.9 Hz, CH**H**CHOH), 3.14 (1H, dd, J = 15.9, 5.0 Hz, C**H**HCHOH), 2.10 (1H, br s, O**H**), 1.44 (9H, s, $C(\mathbf{CH_3})_3$), 1.35 (9H, s, $C(\mathbf{CH_3})_3$) ppm. Second O**H** peak not observed.

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6 (**C**HN), 158.3 ($\mathbf{C}_{Ar}$OH), 141.3 ($\mathbf{C}_{Ar}$*t*-Bu), 141.2 ($\mathbf{C}_{Ar}$*t*-Bu), 140.8 ($\mathbf{C}_{Ar}$CHN), 137.3 ($\mathbf{C}_{Ar}CH_2$), 128.9 ($\mathbf{C}_{Ar}$H), 128.0 ($\mathbf{C}_{Ar}$H), 127.4 ($\mathbf{C}_{Ar}$H), 126.8 ($\mathbf{C}_{Ar}$H), 125.8 ($\mathbf{C}_{Ar}$H), 125.3 ($\mathbf{C}_{Ar}$H), 118.2 ($\mathbf{C}_{Ar}$CHN), 76.1 (**C**HOH), 75.6 (**C**HN), 40.1 ($\mathbf{C}H_2$), 35.4 ($\mathbf{C}(CH_3)_3$), 34.5 ($\mathbf{C}(CH_3)_3$), 31.8 ($C(\mathbf{C}H_3)_3$), 29.8 ($C(\mathbf{C}H_3)_3$) ppm.

LRMS (ES+) *m/z* 366.0 (100%, $[M+H]^+$).

(±)-*N*-2-[(*E*)-2-Heptynylidene]-2-methyl-2-propanesulfinamide ((±)-5.15)



$C_{11}H_{19}NOS$
Mw = 213.34 $gmol^{-1}$
Yellow oil

Using the procedure described (*vide supra*), racemic TBSA **(±)-3.10** (0.34 g, 2.8 mmol) was dissolved in CH_2Cl_2 (5.6 mL) before anhydrous $CuSO_4$ (1.34 g, 8.4 mmol) and aldehyde **5.22** (0.34 g, 3.0 mmol) were added and heated to 40 °C for 18 h. Purification was achieved by flash chromatography (silica gel 60A, 9:1 hexane/EtOAc) to yield imine **(±)-5.15** as a yellow free flowing oil (0.53 g, 89%).

FT-IR ν_{max} (neat) 2958 (m), 2216 (m), 1566 (m), 1080 (m) cm^{-1}.

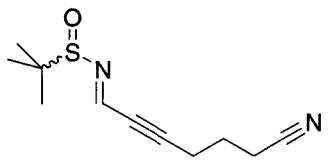
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, t, J = 1.7 Hz, C**H**N), 2.46 (2H, td, J = 6.9, 1.7 Hz, C≡CC**H**$_2$), 1.65-1.55 (2H, m, C**H**$_2$), 1.51-1.39 (2H, m, C**H**$_2$), 1.23 (9H, s, $C(\mathbf{C}H_3)_3$), 0.94 (3H, t, J = 7.2 Hz, C**H**$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9 (**C**HN), 104.0 (**C**≡CCHN), 78.1 (C≡**C**CHN), 58.3 ($\mathbf{C}(CH_3)_3$), 30.3 ($C{\equiv}CCH_2\mathbf{C}H_2$), 22.8 ($C(\mathbf{C}H_3)_3$), 22.3 ($\mathbf{C}H_2CH_3$), 19.8 ($C{\equiv}C\mathbf{C}H_2CH_2$), 13.8 ($\mathbf{C}H_3$) ppm.

LRMS (ES+) *m/z* 235.9 (100%, $[M+Na]^+$), 267.9 (65%, $[M+Na(MeOH)]^+$), 276.9 (58%, $[M+Na(MeCN)]^+$).

HRMS (ES+) for $C_{11}H_{20}NOS$, requires 214.1260 found 214.1261 Da.

(±)-*N*-2-[(*E*)-6-Cyano-2-hexynylidene]-2-methyl-2-propanesulfinamide ((±)-5.16)



$C_{11}H_{16}N_2OS$
Mw = 224.32 $gmol^{-1}$
Yellow oil

Following the general procedure (*vide supra*), the reaction of racemic TBSA **(±)-3.10** (0.55 g, 4.5 mmol, 1.0 eq.), anhydrous $CuSO_4$ (1.58 g, 9.9 mmol, 2.2 eq.) and aldehyde **5.25** (0.54 mL, 4.5 mmol) in dry CH_2Cl_2 (9.0 mL, 0.5 M) heated to 40 °C for 16 h afforded sulfinyl imine **(±)-5.16** as a yellow oil (0.90 g, 89%). Purification was achieved by column chromatography (silica gel 60A, gradient elution: 7:3 to 6:4 hexane/EtOAc).

FT-IR ν_{max} (neat) 2959 (br, w), 2926 (w), 2217 (m), 1564 (s), 1074 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, t, J = 1.7 Hz, C**H**N), 2.67 (2H, td, J = 6.9, 1.7 Hz, C≡CC**H$_2$**), 2.53 (2H, t, J = 6.9 Hz, C**H$_2$**CN), 1.99 (2H, qn, J = 6.9 Hz, C**H$_2$**), 1.23 (9H, s, C(C**H$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1 (**C**HN), 118.9 (**C**N), 99.6 (C≡**C**CH$_2$), 79.4 (**C**≡CCH$_2$), 58.6 (**C**(CH$_3$)$_3$), 24.2 (CH$_2$**C**H$_2$), 22.8 (C(**C**H$_3$)$_3$), 19.1 (C≡C**C**H$_2$), 16.7 (**C**H$_2$CN) ppm.

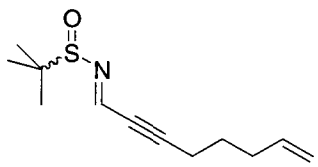
LRMS (ES+) *m/z* 191 (100%, [(M-*t*-Bu)+Na]$^+$), 247 (75%, [M+Na]$^+$).

HRMS (ES+) for $C_{11}H_{16}N_2OS$, requires 247.0876 found 247.0872 Da.

For **(+)-5.16**: Yellow oil (3.6 g, 91%). Spectroscopic data are consistent with those previously collected.

$[\alpha]_D^{29}$ +259.9 (*c* 0.73, $CHCl_3$).

(±)-*N*-2-[(*E*)-7-octen-2-ynylidene]-2-methyl-2-propanesulfinamide ((±)-5.17)



$C_{12}H_{19}NOS$
Mw = 225.35 $gmol^{-1}$
Yellow oil

Following the general procedure described (*vide supra*), the reaction of racemic TBSA **(±)-3.10** (0.20 g, 1.6 mmol, 1.0 eq.), anhydrous $CuSO_4$ (0.58 g, 3.6 mmol, 2.2 eq.) and aldehyde **5.29** (0.20 g, 1.6 mmol) in dry CH_2Cl_2 (3.3 mL, 0.5 M) heated to 40 °C for 16 h afforded sulfinyl imine **(±)-5.17** (0.30 g, 89%) as a yellow oil after purification by column chromatography (silica gel 60A, 9:1 hexane/EtOAc).

FT-IR ν_{max} (neat) 2930 (w), 2216 (m), 1641 (w), 1564 (s), 1455 (m), 1173 (m), 1084 (s) cm^{-1}.

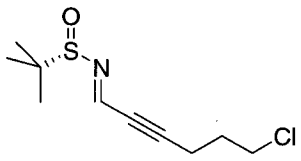
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, t, J = 1.7 Hz, C**H**N), 5.79 (1H, ddt, J = 17.0, 10.2, 6.6 Hz, C**H**=CH_2), 5.08-4.99 (2H, m, CH=C**H$_2$**), 2.48 (2H, td, J = 7.2, 1.7 Hz, C≡CC**H$_2$**), 2.23-2.16 (2H, m, C**H$_2$**CH=CH_2), 1.72 (2H, qn, J = 7.2 Hz, C**H$_2$**), 1.23 (9H, s, C(C**H$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8 (**C**HN), 137.6 (**C**H=CH_2), 116.0 (CH=**C**H$_2$) 103.5 (CH(N)C≡**C**), 78.3 (CH(N)**C**≡C), 58.3 (**C**(CH$_3$)$_3$), 33.1 (**C**H$_2$CH=CH_2), 27.4 (C≡CCH_2**C**H$_2$), 22.8 (C(**C**H$_3$)$_3$), 19.4 (C≡**C**H$_2$) ppm.

LRMS (ES+) *m/z* 248 (100%, $[M+Na]^+$), 473 (22%, $[2M+Na]^+$).

HRMS (ES+) for $C_{12}H_{19}N_1OSNa$, requires 248.10795 found 248.10786 Da.

(S_S)-(+)-*N*-[(*E*)-6-Chlorohex-2-yn-1-ylidene]-2-methylpropane-2-sulfinamide ((+)-5.18)



$C_{10}H_{16}ClNOS$
Mw = 233.76 $gmol^{-1}$
Orange oil

According to the procedure described (*vide supra*), the reaction of sulfinyl amine (–)-**3.10** (2.42 g, 19.9 mmol), aldehyde **5.33** (2.60 g, 19.9 mmol), $CuSO_4$ (6.99 g, 43.8 mmol, 2.2 eq.) in CH_2Cl_2 (40 mL) heated to 40 °C for 16 h yielded the title product as an orange oil (3.66 g, 79%) after purification by column chromatography (silica gel 60A, 3:1 *iso*-hexane/EtOAc).

$[\alpha]^{26}_D$ +259.2 (*c* 1.00, $CHCl_3$).

FT-IR ν_{max} (neat) 2961 (w), 2926 (w), 2218 (m), 1654 (s), 1082 (s) cm^{-1}.

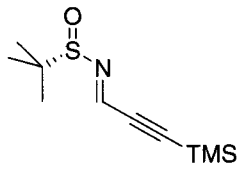
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, t, *J* = 1.7 Hz, **CH**N), 3.67 (2H, t, *J* = 6.2 Hz, **CH$_2$**Cl), 2.68 (2H, td, *J* = 6.9, 1.7 Hz, C≡C**CH$_2$**), 2.08 (2H, qn, *J* = 6.8 Hz, **CH$_2$**), 1.23 (9H, s, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5 (**C**HN), 101.3 (**C**≡CCHN), 78.7 (C≡**C**CHN), 58.5 (**C**(CH$_3$)$_3$), 43.7 (**CH$_2$**Cl), 31.0 (C≡C**CH$_2$**), 22.8 (C(**CH$_3$**)$_3$), 17.5 (**CH$_2$**) ppm.

LRMS (ES+) *m/z* 178.2 (100%, [M-*t*-Bu]), 234.2 (30%, $[M+H]^+$), 256.2 (20%, $[M+Na]^+$).

HRMS (ES+) for $C_{10}H_{17}ClNOS$, requires 233.0641 found 234.0714 Da.

(S_S)-(+)-*N*-2-[(*E*)-3-(1,1,1-Trimethylsilyl)-2-propynylidene]-2-methyl-2-propanesulfinamide ((+)-5.19)



$C_{10}H_{19}NOSSi$
Mw = 229.41 $gmol^{-1}$
Yellow oil

Using the procedure described (*vide supra*), (–)-TBSA **(–)-3.10** (0.62 g, 5.1 mmol, 1.1 eq.), aldehyde **2.01** (as a soln. in Et_2O) and anhydrous $CuSO_4$ (1.78 g, 11.2 mmol, 2.2 eq.) in CH_2Cl_2 (3.2 mL, 0.5 M) were heated at 40 °C for 24 h to yield the desired product as a yellow oil (0.61 g, 47% from TMS alkyne **2.01**). Purification was achieved by column chromatography (silica gel 60A, 9:1 hexane/EtOAc).

$[\alpha]_D^{25}$ +330.7 (*c* 0.67, $CHCl_3$).

FT-IR ν_{max} (neat) 2958 (w), 2897 (w), 1560 (s), 1095 (s) cm^{-1}.

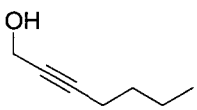
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, s, **CH**N), 1.24 (9H, s, C(**CH$_3$**)$_3$), 0.27 (9H, s, Si(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1 (**C**HN), 108.2 (**C**≡CSi), 100.0 (C≡**C**Si), 58.7 (**C**(CH$_3$)$_3$), 22.9 (C(**CH$_3$**)$_3$), –0.3 (Si(**CH$_3$**)$_3$) ppm.

LRMS (ES+) *m/z* 252 (100%, $[M+Na]^+$), 293 (70%, $[M+Na(MeCN)]^+$).

HRMS (ES+) for $C_{10}H_{20}ONSSi$, requires 230.1029 found 230.1026 Da.

Hept-2-yn-1-ol (5.21)



$C_7H_{12}O$
Mw = 112.17 $gmol^{-1}$
Pale yellow oil

Propargyl alcohol (1.0 mL, 17.8 mmol) was dissolved in dry THF (15 mL) and cooled to –78 °C before *n*-BuLi (15.8 mL of a 2.3 M soln. in hexanes, 36.5 mmol) and DMPU

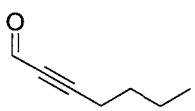
(6.45 mL, 53.4 mmol) were added dropwise. The solution was then warmed to –30 °C and stirred for 45 min before bromobutane (0.96 mL, 8.9 mmol) was added dropwise. After complete addition the solution was stirred at rt o/n where upon a white precipitate formed. 1 N HCl (30 mL) was added followed by Et_2O (50 mL). The aqueous layer was extracted with Et_2O (3 x 40 mL) and the combined organic layers were then washed with a sat. soln. of $NaHCO_3$, H_2O and brine (60 mL of each) before being dried ($MgSO_4$). Purification by column chromatography (silica gel 60A, 6:4 hexane/Et_2O) yielded alcohol **5.21** as a pale yellow oil (0.58 g, 58%). Spectroscopic data are consistent with that published in the literature.[186]

FT-IR ν_{max} (neat) 3341 (br, m), 2931 (m), 2223 (w), 1008 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ4.25 (2H, dt, J = 6.0, 2.2 Hz, C**H$_2$**OH), 2.22 (2H, tt, J = 7.0, 2.0 Hz, C≡CC**H$_2$**), 1.60 (1H, t, J = 6.0 Hz, CH$_2$O**H**), 1.55-1.34 (4H, m, 2 x C**H$_2$**), 0.91 (3H, t, J = 7.0 Hz, C**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 86.9 (C≡**C**CH$_2$OH), 78.6 (**C**≡CCH$_2$OH), 51.8 (**C**H$_2$OH), 31.0 (C≡CCH$_2$**C**H$_2$), 22.2 (**C**H$_2$CH$_3$), 18.7 (C≡**C**CH$_2$), 13.9 (**C**H$_3$) ppm.

Hept-2-yn-1-al (5.22)

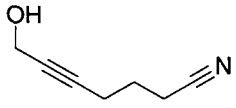


$C_7H_{10}O$
Mw = 110.15 $gmol^{-1}$
Yellow oil

$BaMnO_4$ (2.3 g, 9.0 mmol, 5.0 eq.) was added portion-wise to a stirred solution of alcohol **5.21** (0.2 g, 1.8 mmol) in dry CH_2Cl_2 (55 mL). The reaction mixture was stirred at rt for 4 h. The suspension was filtered through Celite® and washed with a minimum amount of CH_2Cl_2. The solvent was then removed *in vacuo* at 0 °C to yield the desired product as a yellow oil (0.15 g, 74%). No further purification was attempted. ^{1}H NMR spectroscopic data is consistent with that published in the literature.[186]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (1H, t, J = 0.8 Hz, **CHO**), 2.43 (2H, td, J = 7.0, 0.8 Hz, CC**H$_2$**), 1.66-1.38 (4H, m, 2 x C**H$_2$**), 0.95 (3H, t, J = 7.2 Hz, **CH$_3$**) ppm.

7-Hydroxyhept-5-ynenitrile (5.24)



C_7H_9NO
Mw = 123.15 gmol^{-1}
Yellow oil

To a stirred solution of 5-hexynenitrile (2.5 g, 26.8 mmol) in THF (8 mL) at –78 °C was added *n*-BuLi (15.8 mL of a 1.72 M soln. in hexane, 26.8 mmol, 1.0 eq.) slowly dropwise over 10 min. The solution was stirred for 1 h and transferred via a cannula into a suspension of paraformaldehyde (2.9 g, 97 mmol, 3.6 eq.) in THF (2 mL) at –78 °C. The suspension was allowed to warm to rt in the cold bath over 16 h. Next, H_2O (5 mL) was added and the aqueous layer was extracted with Et_2O (4 x 8 mL). The combined organics were washed with brine (1x) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude mixture was purified by column chromatography (silica gel 60A, 7:3 hexane/EtOAc) to yield the desired product as a yellow oil (1.2 g, 36%). Spectroscopic data are consistent with that published in the literature.[187]

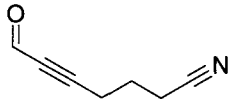
FT-IR ν_{max} (neat) 3406 (br, m), 2929 (m), 2869 (m), 2246 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (2H, dt, J = 5.9, 2.0 Hz, **CH$_2$**OH), 2.50 (2H, t, J = 6.9 Hz, **CH$_2$**CN), 2.41 (2H, tt, J = 6.9, 2.2 Hz, C≡CC**H$_2$**), 1.88 (2H, qn, J = 6.9 Hz, C**H$_2$**), 1.82 (1H, t, J = 5.8 Hz, CH$_2$O**H**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 119.4 (**C**N), 83.6 (**C**≡CCH$_2$OH), 80.8 (C≡**C**CH$_2$OH), 51.5 (**C**H$_2$OH), 24.7 (CH$_2$**C**H$_2$), 18.2 (C≡**C**CH$_2$), 16.5 (**C**H$_2$CN) ppm.

LRMS (ES+) *m/z* 146 (100%, [M+Na]$^+$).

7-Oxo-5-heptynenitrile (5.25)



C_7H_7NO
Mw = 121.14 $gmol^{-1}$
Orange oil

To a suspension of activated MnO_2 (azeotroped with toluene, 1.05 g, 12.0 mmol, 10 eq.) in CH_2Cl_2 (10 mL) was added a solution of alcohol **5.24** (148 mg, 1.2 mmol) in CH_2Cl_2 (5 mL). The suspension was stirred for 24 h at rt. The solid was removed by filtration through a pad of Celite® and washed well with CH_2Cl_2. The solvent was removed *in vacuo* to yield a dark orange oil (115 mg). Crude ^{1}H NMR spectrum showed 75% product and 25% un-reacted starting material. Due to the suspected volatility of the product no further purification was attempted.

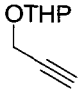
Alternative procedure:

Following the procedure described by Kel'in *et al.*,[188] acetal **5.32** (4.0 g, 20.0 mmol) was dissolved in acetone (100 mL) and H_2O (1.6 mL) whereupon the solution initially turned red before fading to yellow upon stirring. Next, Amberlyst 15 resin (0.95 g) was added in one portion. The reaction was stirred for 40 h before being filtered through Celite®. The solvent was removed *in vacuo* and purification was achieved by column chromatography (silica gel 60A, 3:1 hexane/EtOAc) to yield a yellow oil (2.1 g, 88%). Spectroscopic data is identical with that previously collected and consistent with that published in the literature.[188]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (1H, t, J = 0.8 Hz, **CHO**), 2.64 (2H, td, J = 6.8, 0.8 Hz, C≡CC**H$_2$**), 2.54 (2H, t, J = 6.8 Hz, C**H$_2$**CN), 1.99 (2H, qn, J = 6.8 Hz, C**H$_2$**CH_2CN) ppm.

LRMS (ES+) *m/z* 144 (100%, $[M+Na]^+$).

Tetrahydro-2-(2-propynloxy)-2*H*-pyran (5.26)



$C_8H_{12}O_2$
Mw = 140.18 $gmol^{-1}$
Colourless oil

Following the procedure described by Wang *et al*,[189] propargyl alcohol (3.11 mL, 53.5 mmol) and DHP (6.35 mL, 69.5 mmol, 1.3 eq.) were stirred neat at 0 °C before sulfamic acid (1.00 g, 10.7 mmol, 0.2 eq.) was added in one portion. The mixture was stirred at rt for 5 h. Upon completion, Et_2O (50 mL) was added to the yellow solution. The precipitate was removed by filtration and the filtrate was dried (Na_2SO_4) and concentrated *in vacuo* to yield a yellow oil. The crude mixture was purified by flash chromatography (silica gel 60A, 9:1 pet. ether/Et_2O) to yield THP ether **5.26** as a colourless oil (6.60 g, 89%). Spectroscopic data are consistent with those published in the literature.[190]

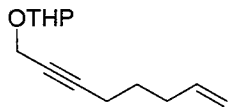
FT-IR ν_{max} (neat) 3288 (br, w), 2940 (m), 2869 (m), 1022 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (1H, t, J = 3.3 Hz, C**H**), 4.25 (2H, qd, J = 15.7, 2.4 Hz, C**H$_2$**C≡CH), 3.87-3.79 (1H, m, OC**H$_{ax}$**), 3.56-3.49 (1H, m, OC**H$_{eq}$**), 2.40 (1H, t, J = 2.4 Hz, C≡C**H**), 1.88-1.51 (6H, m, 3 x C**H$_2$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 97.2 (**C**H), 80.1 (CH$_2$**C**≡C), 74.3 (CH$_2$C≡**C**), 62.3 (O**C**H$_2$), 54.3 (OCH$_2$C≡C), 30.5 (CH**C**H$_2$), 25.7 (OCH$_2$**C**H$_2$), 19.3 (**C**H$_2$) ppm.

LRMS (EIMS) *m/z* 139.1 ($M^{+\cdot}$, 12%), 85.2 ([THP-H]$^+$), 56.2 ([M-THP]$^+$).

Tetrahydro-2-(oct-7-en-2-ynyloxy)-2*H*-pyran (5.27)



$C_{13}H_{20}O_2$
Mw = 208.30 $gmol^{-1}$
Pale yellow oil

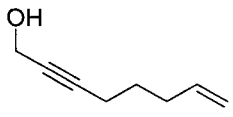
To a stirred solution of alkyne **5.26** (0.56 g, 4.0 mmol) in THF (10 mL) at –78 °C was added *n*-BuLi (1.9 mL of a 2.2 M soln. in hexane, 4.2 mmol, 1.05 eq.) slowly dropwise. The mixture was stirred for 20 min before HMPA (1.04 mL, 6.0 mmol, 1.5 eq.) and 5-bromopent-1-ene (0.52 mL, 4.4 mmol, 1.1 eq.) were added. The reaction was stirred for 10 min before it was warmed to rt and stirred for 16 h then quenched by the addition of

H_2O (5 mL). The crude mixture was separated between H_2O/EtOAc and the combined organic layers were washed with H_2O (3 x 15 mL), brine (20 mL) and dried (Na_2SO_4). The solid was removed by filtration and the solvent removed *in vacuo*. The crude mixture was purified by column chromatography (silica gel 60A, 19:1 hexane/EtOAc) to yield the desired product as a pale yellow oil (0.87 g, 89%). Spectroscopic data are consistent with those published in the literature.[191]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, J = 17.0, 10.2, 6.8 Hz, C**H**=CH_2), 5.07-4.96 (2H, m, CH=C**H$_2$**), 4.81 (1H, t, J = 3.1 Hz, C**H**), 4.24 (2H, qt, J = 15.2, 2.1 Hz, OC**H$_2$**C≡C), 3.84 (1H, td, J = 11.3, 3.2 Hz, OC**H$_{ax}$**), 3.54-3.50 (1H, m, OC**H$_{eq}$**), 2.24 (2H, tt, J = 7.2, 2.1 Hz, C≡CC**H$_2$**), 2.14 (2H, dt, J = 7.2, 6.8 Hz, C**H$_2$**CH=CH_2), 1.85-1.51 (8H, m, 1 x C**H**H and THP) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1 (**C**H=CH_2), 115.4 (CH=**C**H_2), 96.9 (**C**H), 86.6 (OCH_2C≡**C**), 76.4 (OCH_2**C**≡C), 62.3 (**C**H_2O), 54.9 (O**C**H_2C≡C), 33.1 (**C**H_2CH=CH_2), 30.6 (CH**C**H_2), 28.1 (C≡CCH_2**C**H_2), 25.7 (**C**H_2), 19.5 (**C**H_2), 18.5 (C≡**C**CH_2) ppm.

7- Octen-2-yn-1-ol (5.28)



$C_8H_{12}O$
Mw = 124.18 gmol^{-1}
Pale yellow oil

Protected alcohol **5.27** (0.87 g, 4.1 mmol) was dissolved in MeOH (15 mL) and H_2O (1 mL). Next, *p*-TsOH (0.08 g, 0.4 mmol, 0.1 eq.) was added in one portion. The reaction was stirred at rt for 16 h. The solvent was removed *in vacuo* before the residue was separated between Et_2O/H_2O (15 mL each). The organic layer was washed with H_2O (2 x 15 mL), brine (20 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude material was purified by column chromatography (silica gel 60A, gradient elution: 9:1 to 4:1 hexane/EtOAc) to yield the desired product as a colourless oil (0.49 g, 96%). Spectroscopic data are consistent with those published in the literature.[191]

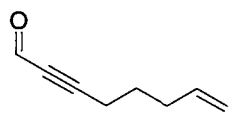
FT-IR ν_{max} (neat) 3305 (br, m), 3075 (w), 2931 (m), 2223 (w), 1640 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (1H, ddt, J = 17.0, 10.2, 6.8 Hz, C**H**=CH_2), 5.08-4.97 (2H, m, CH=C**H$_2$**), 4.26 (2H, t, J = 2.3 Hz, C**H$_2$**OH), 2.24 (2H, tt, J = 7.2, 2.3 Hz, C≡CC**H$_2$**), 2.20-2.12 (2H, m, C**H$_2$**CH=CH_2), 1.62 (2H, qn, J = 7.2 Hz, C≡CCH_2C**H$_2$**) ppm. No O**H** proton observed.

^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1 (**C**H=CH_2), 115.5 (CH=**C**H_2), 86.5 (CH_2(OH)C≡**C**CH_2), 78.9 (CH_2(OH)**C**≡CCH_2), 51.8 (**C**H_2OH), 33.1 (**C**H_2CH=CH_2), 28.1 (CH_2**C**H_2), 18.5 (C≡**C**CH_2) ppm.

LRMS (CIMS) *m/z* 125 (37%, M$^+$+H), 142 (86%, M$^+$+NH_4).

Oct-7-en-2-ynal (5.29)

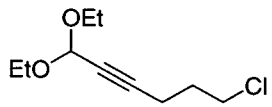


$C_8H_{10}O$
Mw = 122.16 $gmol^{-1}$
Pale yellow oil

Alcohol **5.28** (0.25 g, 2.0 mmol) was dissolved in CH_2Cl_2 (12 mL) and cooled to 0 °C before Dess-Martin periodinane reagent (1.0 g, 2.5 mmol, 1.2 eq.) was added in one portion. The reaction was allowed to stir for 10 min before being stirred at rt for 1 h. Next, pentane (10 mL) was added resulting in formation of a white precipitate. Filtration through a pad of silica gel 60A (2cm depth by 4 cm width, 19:1 pentane/Et_2O) yielded aldehyde **5.29** as a pale yellow oil (0.20 g, 82%, determined by ^{1}H NMR spectroscopy). No further purification was attempted due to the low b.p. of the product.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (1H, s, C**H**O), 5.78 (1H, ddt, J = 17.0, 10.2, 6.6 Hz, C**H**=CH_2), 5.11-5.01 (2H, m, CH=C**H$_2$**), 2.44 (2H, t, J = 7.2 Hz, C≡C**H$_2$**), 2.23-2.16 (2H, m, **CH$_2$**CH=CH_2), 1.71 (2H, qn, C≡CCH_2**CH$_2$**) ppm.

6-Chloro-1,1-di(ethyloxy)-2-hexyne (5.31)



$C_{10}H_{17}ClO_2$
Mw = 204.69 $gmol^{-1}$
Pale yellow oil

A solution of 3,3-diethoxy propyne (5.3 mL, 37.0 mmol) in THF (100 mL) at –78 °C was treated with *n*-BuLi (19.2 mL of a 2.03 M soln. in hexanes, 39.0 mmol, 1.05 eq) via dropwise addition over 20 min resulting in a yellow solution. The reaction mixture was stirred for 30 min before 1-bromo-3-chloropropane (4.4 mL, 44.0 mmol, 1.2 eq.) was added dropwise over 5 min. Next, HMPA (9.7 mL, 56.0 mmol, 1.5 eq.) was added over 5 min and the reaction was stirred for 10 min at –78 °C before being warmed to rt. The solution turned dark brown in colour. The reaction mixture was stirred at rt for 16 h before it was quenched by the addition of H_2O (100 mL) and EtOAc (100 mL). The layers were separated and the aqueous layer was washed with EtOAc (4 x 100 mL). The combined organic layers were washed with H_2O (4 x 100 mL), brine (200 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a crude brown oil (7.76 g). Purification was achieved by column chromatography (silica gel 60A, 19:1 hexane/EtOAc) to yield a pale yellow oil (5.93 g, 78%). Spectroscopic data are consistent with those published in the literature.[188]

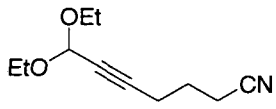
FT-IR ν_{max} (neat) 2976 (w), 2884 (w), 1048 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (1H, t, *J* = 1.6 Hz, C**H**), 3.78-3.49 (6H, m, 2 x O**CH$_2$**CH$_3$ and **CH$_2$**Cl), 2.45 (2H, td, *J* = 6.8, 1.6 Hz, C≡CC**H$_2$**), 1.99 (2H, qn, *J* = 6.8 Hz, C**H$_2$**), 1.24 (6H, t, *J* = 7.0 Hz, OCH$_2$C**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 91.7 (**C**H), 84.6 (CHC≡**C**), 77.2 (CH**C**≡C), 61.0 (O**C**H$_2$CH$_3$), 43.9 (**C**H$_2$Cl), 31.4 (**C**H$_2$CH$_2$Cl), 16.5 (C≡C**C**H$_2$), 15.4 (OCH$_2$**C**H$_3$) ppm.

LRMS (CI) *m/z* 159 (100%, [M-EtO˙]).

7,7-Di(ethyloxy)-5-heptynenitrile (5.32)



$C_{11}H_{17}NO_2$
Mw = 195.26 $gmol^{-1}$
Yellow oil

NaCN (1.40 g, 28.6 mmol) was dissolved in DMF (100 mL) before chloride **5.31** (5.84 g, 28.6 mmol) was added in DMF (50 mL). The reaction was heated to 60 °C for 16 h whereupon the solution turned orange and a white precipitate formed. The reaction mixture was allowed to cool to rt before it was separated between H_2O (250 mL) and EtOAc (250 mL). The aqueous layer was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with H_2O (5 x 100 mL), a sat. aq. soln. of $NaHCO_3$ (150 mL), H_2O (150 mL), brine (200 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an orange oil (5.60 g). Purification by column chromatography (silica gel 60A, gradient elution 9:1 to 7:3 hexane/EtOAc) yielded a yellow oil (4.3 g, 77%). Spectroscopic data are consistent with those published in the literature.[188]

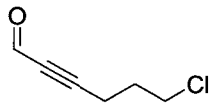
FT-IR ν_{max} (neat) 2976 (w), 2884 (w), 2247 (w), 1047 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.24 (1H, t, *J* = 1.7 Hz, C**H**), 3.72 (2H, qd, *J* = 9.5, 6.9 Hz, OC**H$_2$**CH$_3$), 3.57 (2H, qd, *J* = 9.3, 6.9 Hz, OC**H$_2$**CH$_3$), 2.49 (2H, t, *J* = 7.2 Hz, C**H$_2$**CN), 2.44 (2H, td, *J* = 6.9, 1.6 Hz, C≡CC**H$_2$**), 1.89 (2H, qn, *J* = 7.0 Hz, C**H$_2$**CH$_2$CN), 1.23 (6H, t, *J* = 7.0 Hz, CH$_2$C**H$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 119.2 (**C**N), 91.6 (**C**H), 83.4 (CHC≡**C**), 78.2 (CH**C**≡C), 61.1 (O**C**H$_2$CH$_3$), 24.6 (**C**H$_2$CN), 18.1 (**C**H$_2$CH$_2$CN), 16.5 (C≡**C**CH$_2$), 15.4 (OCH$_2$**C**H$_3$) ppm.

LRMS (ES+) *m/z* 218.2 (100%, $[M+Na]^+$).

6-Chloro-hex-2-ynal (5.33)



C_6H_7ClO
Mw = 130.57 $gmol^{-1}$
Colourless oil

Following the procedure described by Willis *et al.*,[192] 5-chloropent-1-yne (4.8 mL, 45.8 mmol) was dissolved in THF (100 mL) and cooled to –78 °C before *n*-BuLi (18.3 mL of 2.5 M soln. in hexanes, 45.8 mmol) was added dropwise. The reaction was stirred for 30 min before DMF (17.7 mL, 22.9 mmol, 5.0 eq.) was added over 10 min. The reaction was stirred for 1.5 h before it was warmed to 0 °C and stirred for a further 1 h. The reaction was quenched by pouring on to a rapidly stirred sat. soln. of NH_4Cl (200 mL). The aqueous phase was extracted with EtOAc (3 x 80 mL) and the combined organic layers were washed with H_2O (5 x 200 mL), brine (200 mL) and dried ($MgSO_4$). Purification by a plug of silica gel 60A (19:1 hexane/EtOAc) yielded the title product (2.6 g, 44%). Spectroscopic data are consistent with those published in the literature.[192]

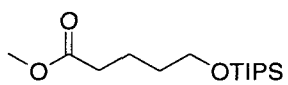
FT-IR ν_{max} (neat) 2964 (w), 2864 (w), 2022 (m), 1662 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.19 (1H, t, *J* = 0.9 Hz, **CH**O), 3.66 (2H, t, *J* = 6.0 Hz, **CH_2**Cl), 2.64 (2H, td, *J* = 7.0, 0.7 Hz, C≡C**CH_2**), 2.07 (2H, qn, *J* = 6.2 Hz, **CH_2**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2 (**C**HO), 96.9 (**C**≡CCHO), 82.4 (C≡**C**CHO), 43.4 (**CH_2**Cl), 30.6 (C≡**C**CH_2), 16.9 (**CH_2CH_2**Cl) ppm.

LRMS (EI) *m/z* 101.9 (100%, [M-CHO$^+$]), 129.0 (48%, [M-H$^+$]).

Methyl 5-[1,1,1-tri(1-methylethyl)silyl]oxypentanoate (5.36)



$C_{15}H_{32}O_3Si$
Mw = 288.50 $gmol^{-1}$
Pale yellow oil

Following the procedure described by Huckstep *et al*,[193] conc. H_2SO_4 (2 drops) was added to a stirred solution of δ-valerolactone (0.50 g, 5.0 mmol, 1.0 eq.) in distilled MeOH (10 mL). The reaction was heated to reflux for 5 h then cooled to 0 °C before

$NaHCO_3$ (0.2 g) was added. The suspension was stirred for 10 min before being filtered and the solvent removed *in vacuo*. The crude alcohol was redissolved in dry THF (10 mL) and treated with TIPSCl (1.17 mL, 5.5 mmol, 1.1 eq.) and imidazole (0.85 g, 12.5 mmol, 2.5 eq.). The reaction mixture was stirred at rt for 16 h. Next, 1 N HCl (15 mL) was added and the product extracted with Et_2O (3 x 15 mL). The combined organics were washed sequentially with a sat. soln. of $NaHCO_3$, H_2O and brine (30 mL of each) before being dried ($MgSO_4$). Purification by column chromatography (silica gel 60A, gradient elution 19:1 to 9:1 hexane/Et_2O) yielded the desired product as a pale yellow free flowing oil (1.20 g, 83%).

FT-IR ν_{max} (neat) 2942 (m), 1741 (s) cm^{-1}.

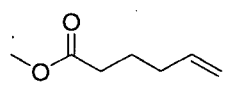
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (2H, t, J = 6.2 Hz, C(O)C**H**$_2$), 3.67 (3H, s, OC**H**$_3$), 2.35 (2H, t, J = 7.3 Hz, C**H**$_2$OTIPS), 1.77-1.67 (2H, m, C**H**$_2$), 1.62-1.53 (2H, m, C**H**$_2$), 1.5-1.15 (21H, m, Si(C**H**(CH$_3$)$_3$)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (**C**O), 63.3 (**C**H$_2$OTIPS), 51.8 (O**C**H$_3$), 34.2 (C(O)**C**H$_2$), 32.7 (**C**H$_2$CH$_2$OTIPS), 21.8 (C(O)CH$_2$**C**H$_2$), 18.4 (Si(CH(**C**H$_3$)$_3$)$_3$), 12.3 (Si(**C**H(CH$_3$)$_3$)$_3$) ppm.

LRMS (ES+) *m/z* 310.9 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{15}H_{33}O_3Si$, requires 289.2193 found 289.2197 Da.

5-Hexenoic acid methyl ester (5.38)



$C_7H_{12}O_2$
Mw = 128.17 $gmol^{-1}$
Pale yellow oil

AcCl (0.46 mL, 6.0 mmol, 0.1 eq.) was added to MeOH (30 mL) at rt and stirred for 5 min before 5-hexenoic acid (7.3 g, 64.0 mmol) was added in MeOH (20 mL). The reaction was heated to 65 °C for 3 h before a further aliquot of AcCl (0.2 mL, 2.8 mmol, 0.05 eq.) was added. The reaction was then heated at 85 °C for a further 3 h. Once cooled to rt, Et_2O (60 mL) and H_2O (60 mL) were added. The layers were separated

and the organic layer was washed with H_2O (4 x 40 mL). The combined organic layers were washed with brine (70 mL) and dried (Na_2SO_4). The solvent was removed by distillation (atm. pres.). Purification was achieved by fractional distillation (atm. pres., 220 °C) to yield the title compound as a pale yellow oil (6.8 g, 83%).

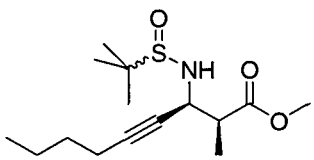
FT-IR ν_{max} (neat) 3079 (w), 2951 (w), 1736 (s), 1641 (w) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.8 Hz, C**H**=CH_2), 5.06-4.96 (2H, m, CH=C**H$_2$**), 3.67 (3H, s, OC**H$_3$**), 2.32 (2H, t, *J* = 7.3 Hz, C**H$_2$**CO), 2.13-2.05 (2H, m, C**H$_2$**CH=CH_2), 1.73 (2H, qn, *J* = 7.3 Hz, C**H$_2$**CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (**C**O), 138.0 (CH=**C**H_2), 115.7 (**C**H=CH_2), 51.8 (O**C**H_3), 33.7 (**C**H_2C(O)), 33.4 (**C**H_2CH=CH_2), 24.4 (**C**H_2) ppm.

LRMS (EI) *m/z* 41.1 (96%, [$CH_2CHCH_2^+$]), 55.1 (44.6%, [CH_2=$CHCH_2CH_2^+$]), 74.1 (100%, [$^+CH_2COOCH_3$]), 97.1 (31%, [M-OMe]$^+$).

(±)-Methyl 3-[(1,1-dimethylethyl)sulfinyl]amino-2-methyl-4-nonynoate ((±)-5.40)



$C_{15}H_{27}NO_3S$
Mw = 301.44 $gmol^{-1}$
Pale yellow oil

Using the procedure described (*vide supra*), the reaction of *i*-Pr_2NH (0.31 g, 3.1 mmol, 2.2 eq.), *n*-BuLi (1.64 mL, 3.0 mmol, 2.1 eq.), methyl propionate (0.27 mL, 2.8 mmol, 2.0 eq.), TiCl(O*i*-Pr)$_3$ (5.91 mL of a 1.0 M soln. in THF, 5.9 mmol, 4.0 eq.) and sulfinyl imine **(±)-5.15** (0.30 g, 1.4 mmol, 1.0 eq.) stirred at –78 °C yielded an inseparable mixture of two diastereomers of sulfinyl amine **(±)-5.40** (pale yellow oil, 0.37 g, 87%) after purification by column chromatography (silica gel 60A, gradient elution 9:1 to 1:3 hexane/EtOAc).

FT-IR ν_{max} ($CDCl_3$) 2957 (m), 1728 (m), 1055 (s) cm^{-1}.

Selected peaks for major diastereomer:

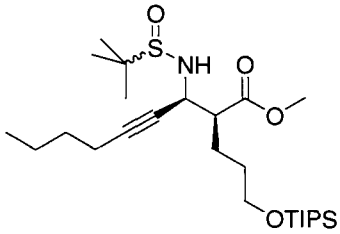
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (1H, br d, J = 4.0 Hz, N**H**), 4.31 (1H, td, J = 3.8, 2.1 Hz, C**H**NH), 3.73 (3H, s, OC**H$_3$**), 2.95 (1H, dq, J = 7.4, 4.0 Hz, **C**HCOOCH$_3$), 2.21 (2H, td, J = 7.0, 2.1 Hz, C≡CC**H$_2$**), 1.52-1.36 (4H, m, 2 x C**H$_2$**), 1.31 (3H, d, J = 7.2 Hz, CHC**H$_3$**), 1.26 (9H, s, C(C**H$_3$**)$_3$), 0.91 (3H, t, J = 7.2 Hz, CH$_2$C**H$_3$**) ppm.

^{13}C NMR (75 MHz, d$_4$-MeOH) δ 176.7 (**C**O), 89.0 (C≡**C**CH), 78.9 (**C**≡CCHN), 58.1 (**C**(CH$_3$)$_3$), 53.3 (O**C**H$_3$), 52.5 (C≡C**C**H), 48.1 (**C**HCOOCH$_3$), 32.6 (**C**H$_2$), 23.9 (C(**C**H$_3$)$_3$), 23.7 (**C**H$_2$CH$_3$), 19.8 (C≡**C**CH$_2$), 14.7 (**C**H$_3$ and CH**C**H$_3$) ppm.

LRMS (ES+) *m/z* 324 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{15}H_{28}NO_3S$, requires 302.1785 found 302.1780 Da.

(±)-Methyl 3-[(1,1-dimethylethyl)sulfinyl]amino-2-(3-[1,1,1-tri(1-methylethyl)silyl]oxypropyl)-4-nonynoate ((±)-5.41)



$C_{26}H_{51}NO_4SSi$
Mw = 501.84 gmol^{-1}
Pale yellow oil

Using the procedure described (*vide supra*), the reaction of *i*-Pr$_2$NH (0.29 mL, 2.1 mmol, 2.2 eq.), *n*-BuLi (1.1 mL, 2.1 mmol, 2.0 eq.), ester **5.36** (0.54 g, 1.9 mmol, 2.0 eq.), ClTi(O*i*-Pr)$_3$ (4.0 mL of a 1.0 M soln. in THF, 4.0 mmol, 4.0 eq.) and sulfinyl imine **(±)-5.15** (0.20 g, 0.9 mmol, 1.0 eq.) stirred at –78 °C for 2 h yielded sulfinyl amine **(±)-5.41** (pale yellow oil, 0.31 g, 66%) as a partially separable mixture of diastereomers. Purification was achieved by column chromatography (silica gel 60A, gradient elution 19:1 to 9:1 to 7:3 hexane/EtOAc).

FT-IR ν_{max} ($CDCl_3$) 2946 (m), 1736 (m), 1066 (m) cm^{-1}.

Major diastereomer:

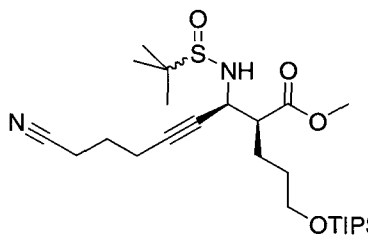
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (1H, ddt, J = 6.0, 4.4, 2.1 Hz, C**H**NH), 4.24 (1H, d, J = 5.9 Hz, N**H**), 3.72-3.68 (5H, m, O**CH$_3$** and **CH$_2$**OTIPS), 2.80 (1H, ddd, J = 8.2, 6.6, 4.8 Hz, **CH**COOCH$_3$), 2.19 (2H, td, J = 6.8, 2.0 Hz, C≡CC**H$_2$**), 1.88-1.81 (2H, m, C(O)CHC**H$_2$**), 1.65-1.54 (2H, m, **CH$_2$**CH$_2$OTIPS), 1.54-1.35 (4H, m, 2 x **CH$_2$**), 1.23 (9H, s, C(**CH$_3$**)$_3$), 1.08-1.05 (21H, m, Si(**CH**(**CH$_3$**)$_2$)$_3$), 0.90 (3H, t, J = 7.1 Hz, **CH$_3$**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (**C**O), 87.3 (C≡CCH), 76.8 (**C**≡CCH), 63.3 (**CH$_2$**OTIPS), 56.2 (**C**(CH$_3$)$_3$), 52.2 (O**CH$_3$**), 51.2 (**CH**COOCH$_3$), 49.5 (C≡**C**CH), 31.3 (**CH$_2$**CH$_2$OTIPS), 30.9 (**CH$_2$**), 25.2 (C(O)CH**CH$_2$**), 23.0 (C(**CH$_3$**)$_3$), 22.2 (**CH$_2$**), 18.7 (C≡C**CH$_2$**), 18.4 (Si(CH(**CH$_3$**)$_2$)$_3$), 13.9 (**CH$_3$**), 12.3 (Si(**CH**(CH$_3$)$_2$)$_3$) ppm.

LRMS (ES+) *m/z* 524 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{26}H_{52}NO_4SSi$, requires 502.3381 found 502.3383 Da.

(±)-Methyl-8-cyano-3-[(1,1-dimethylethyl)sulfinyl]amino-2-(3-[1,1,1-tri(1-methylethyl)silyl]oxypropyl)-4-octynoate ((±)-5.42)



$C_{26}H_{48}N_2O_4SSi$
Mw = 512.82 gmol^{-1}
Yellow oil

Following the general procedure described (*vide supra*), *i*-Pr$_2$NH (1.26 mL, 9.0 mmol, 2.2 eq.), *n*-BuLi (3.9 mL of a 2.2 M soln. in hexane, 8.6 mmol, 2.1 eq.), ester **5.36** (2.36 g, 8.2 mmol, 2.0 eq.), TiCl(O*i*-Pr)$_3$ (16.4 mL of a 1 M soln. in THF, 16.4 mmol, 4.0 eq.) and sulfinyl imine **(±)-5.16** (0.92 g, 4.1 mmol, 1.0 eq.) afforded an inseparable mixture of two diastereomers of sulfinyl amine **(±)-5.42** (yellow oil, 1.80 g, 85%). Purification was achieved by column chromatography (silica gel 60A, gradient elution: 19:1 to 1:1 hexane/EtOAc).

FT-IR ν_{max} (neat) 3220 (w), 2941 (m), 2863 (m), 2246 (w), 1735 (m), 1062 (s) cm^{-1}.

Major diastereomer (1.0 g, 47%) (selected peaks):

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23-4.20 (1H, m, C**H**N), 3.71-3.68 (5H, m, CH_2OTIPS and OCH_3), 3.61 (1H, d, *J* = 6.8 Hz, N**H**), 2.71 (1H, dt, *J* = 8.2, 6.1 Hz, C**H**COOCH$_3$), 2.55 (2H, t, *J* = 7.1 Hz, CH_2CN), 2.39-2.36 (2H, m, C≡CCH_2), 1.84-1.78 (4H, m, 2 x CH_2), 1.61-1.51 (2H, m, CH_2CH_2OTIPS), 1.19 (9H, s, C(CH_3)$_3$), 1.05-1.04 (21H, m, Si(C**H**(CH_3)$_3$)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (**C**O), 84.2 (C≡**C**CH$_2$), 80.2 (**C**≡CCH$_2$), 63.2 (**C**H$_2$OTIPS), 56.8 (**C**(CH$_3$)$_3$), 52.1 (O**C**H$_3$), 51.7 (**C**HN), 50.4 (**C**HCOOCH$_3$), 31.0 (**C**H$_2$CH$_2$OTIPS), 25.5 (**C**H$_2$CH$_2$CN), 24.7 (**C**H$_2$CHCO), 22.9 (C(**C**H$_3$)$_3$), 18.4 (Si(CH(**C**H$_3$)$_2$)$_3$), 18.2 (**C**H$_2$C≡C), 16.3 (**C**H$_2$CN), 12.3 (Si(**C**H(CH$_3$)$_2$)$_3$) ppm. No **C**N peak observed.

LRMS (ES+) *m/z* 535 (100%, $[M+Na]^+$).

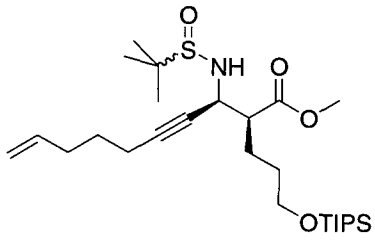
HRMS (ES+) for $C_{26}H_{49}N_2O_4SSi$, requires 513.3177 found 513.3182 Da.

Selected peaks for minor diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60 (1H, d, *J* = 9.0 Hz, N**H**), 2.81 (1H, ddd, *J* = 10.9, 6.1, 4.9 Hz, C**H**COOCH$_3$), 2.52 (1H, t, *J* = 7.1 Hz, CH_2CN), 1.19 (9H, s, C(CH_3)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) 174.1 (**C**O), 79.0 (**C**≡C), 56.3 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 51.0 (**C**HN), 49.2 (**C**HCOOCH$_3$), 31.2 (**C**H$_2$CH$_2$OTIPS), 24.8 (**C**H$_2$), 22.9 (C(**C**H$_3$)$_3$), 18.2 (Si(CH(**C**H$_3$)$_2$)$_3$), 16.3 (**C**H$_2$CN) ppm.

(±)-Methyl 3-[(1,1-dimethylethyl)sulfinyl]amino-2-(3-[1,1,1-tri(1-methylethyl)silyl]oxypropyl)-9-decen-4-ynoate ((±)-5.43)



$C_{27}H_{51}NO_4SSi$
Mw = 513.85 $gmol^{-1}$
Pale yellow oil

Following the general procedure described (*vide supra*), the reaction of *i*-Pr_2NH (0.2 mL, 1.32 mmol, 2.2 eq.), *n*-BuLi (0.63 mL of a 2.3 M soln. in hexane, 1.39 mmol, 2.1 eq.), ester **5.36** (0.38 g, 1.32 mmol, 2.0 eq.), $TiCl(O\textit{i}\text{-}Pr)_3$ (2.64 mL of a 1.0 M soln. in THF, 2.64 mmol, 4.0 eq.), sulfinyl imine **(±)-5.17** (0.15 g, 0.66 mmol) stirred at –78 °C for 2.5 h yielded sulfinyl amine **(±)-5.43** (pale yellow oil, 0.26 g, 77%) as a partially separable mixture of two diastereomers. Purification was achieved by column chromatography (silica gel 60A, gradient elution: 19:1 to 4:1 hexane/EtOAc).

Major diastereomer:

FT-IR ν_{max} (neat) 2940 (m), 2863 (m), 1736 (m), 1065 (m) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.8 Hz, C**H**=CH_2), 5.07-4.95 (2H, m, CH=C**H$_2$**), 4.28 (1H, ddt, *J* = 8.1, 6.0, 2.2 Hz, C**H**N), 3.70-3.67 (5H, m, C**H$_2$**OTIPS and OC**H$_3$**), 3.55 (1H, d, *J* = 8.2 Hz, N**H**), 2.69 (1H, dt, *J* = 5.9, 2.6 Hz, C**H**$COOCH_3$), 2.20 (2H, td, *J* = 7.1, 2.0 Hz, C≡CC**H$_2$**), 2.17-2.10 (2H, m, C**H$_2$**$CH=CH_2$), 1.85-1.77 (2H, m, C**H$_2$**CH), 1.63-1.54 (4H, m, C≡CCH_2C**H$_2$** and C**H$_2$**CH_2OTIPS), 1.20 (9H, s, $C(CH_3)_3$), 1.06-1.05 (21H, m, $Si(CH(CH_3)_2)_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (**C**O), 137.2 (**C**H=CH_2), 114.5 ($CH=CH_2$), 85.8 (C≡**C**CH_2), 77.2 (**C**≡CCH_2), 62.3 (**C**H_2OTIPS), 55.8 (**C**$(CH_3)_3$), 51.0 (OCH_3), 49.3 (**C**H$COOCH_3$), 32.1 (**C**$H_2CH=CH_2$), 30.1 (**C**H_2CH_2OTIPS), 27.1 (**C**$H_2CH_2CH=CH_2$), 24.3 (**C**H_2CHCO), 21.9 ($C(CH_3)_3$), 17.5 (**C**H_2C≡C), 17.4 ($Si(CH(CH_3)_2)_3$), 11.3 ($Si(CH(CH_3)_2)_3$) ppm. Peak for **C**HN is masked by another.

LRMS (ES+) *m/z* 536 (100%, $[M+Na]^+$).

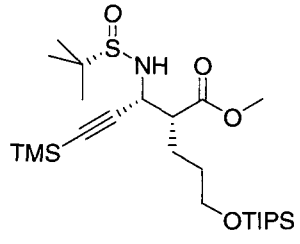
HRMS (ES+) for $C_{27}H_{52}NO_4SSi$, requires 514.3381 found 514.3384 Da.

Minor diastereomer (selected peaks):

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, C**H**=CH_2), 5.06-4.96 (2H, m, CH=C**H$_2$**), 4.35 (1H, ddt, *J* = 6.0, 4.2, 2.1 Hz, C**H**N), 4.25 (1H, d, *J* = 5.9 Hz, N**H**), 3.71-3.68 (5H, m, C**H$_2$**OTIPS and O**CH$_3$**), 2.69 (1H, dt, *J* = 6.1, 4.4 Hz, C**H**$COOCH_3$), 2.21 (2H, td, *J* = 7.0, 2.0 Hz, C≡CC**H$_2$**), 2.16-2.11 (2H, m, C**H$_2$**CH=CH_2), 1.89-1.81 (2H, m, C**H$_2$**CHCO), 1.63-1.54 (4H, m, C≡CCH_2C**H$_2$** and C**H$_2$**CH_2OTIPS), 1.23 (9H, s, C(C**H$_3$**)$_3$), 1.06-1.05 (21H, m, Si(C**H**(C**H$_3$**)$_2$)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2 (**C**O), 138.1 (**C**H=CH_2), 115.5 (CH=**C**H_2), 86.9 (C≡**C**CH_2), 77.2 (**C**≡CCH_2), 63.3 (**C**H_2OTIPS), 56.2 (**C**(C**H$_3$**)$_3$), 52.2 (O**C**H_3), 51.2 (**C**H$COOCH_3$), 49.4 (**C**HN), 33.0 (**C**H_2CH=CH_2), 31.3 (**C**$H_2$$CH_2$OTIPS), 28.1 (**C**$H_2$$CH_2$CH=$CH_2$), 25.2 (**C**$H_2$CHCO), 22.9 (C(**C**$H_3$)$_3$), 18.4 (**C**$H_2$C≡C), 18.4 (Si(CH(**C**$H_3$)$_2$)$_3$), 12.3 (Si(**C**H(C**H$_3$**)$_2$)$_3$) ppm.

(*S*$_S$)-Methyl-3-[(1,1-dimethylethyl)sulfinyl]amino-2-(3-[1,1,1-tri-(1-ethylethyl)silyl]oxypropyl)-5-(1,1,1-trimethylsilyl)-4-pentynoate (5.44)



$C_{25}H_{51}NO_4SSi_2$
Mw = 517.91 gmol^{-1}
Yellow oil

Following the procedure described (*vide supra*), *i*-Pr_2NH (0.27 mL, 1.92 mmol, 2.2 eq.), *n*-BuLi (1.01 mL of a 1.82 M soln. in hexane, 1.83 mmol, 2.1 eq.), ester **5.36** (0.5 g, 1.75 mmol, 2.0 eq.), $TiCl(O$*i*$-Pr)_3$ (3.49 mL of a 1.0 M soln. in THF, 3.49 mmol, 4.0 eq.) and sulfinyl imine **(+)-5.19** (0.2 g, 0.87 mmol, 1.0 eq.) in THF (9.5 mL, 0.2 M) stirred at –78 °C for 3 h afforded the title product as a mixture of three diastereomers

(yellow oil, 0.30 g, 69%). Purification was achieved by column chromatography (silica gel 60A, gradient elution 19:1 to 4:1 hexane/EtOAc).

Major diastereomer (0.21 g, 47%):

FT-IR ν_{max} ($CDCl_3$) 2945 (m), 2866 (m), 1741 (m), 1094 (m), 844 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (1H, dd, *J* = 8.0, 6.0 Hz, C**H**N), 3.69-3.67 (5H, m, C**H$_2$**OTIPS and OC**H$_3$**), 3.59 (1H, d, *J* = 7.9 Hz, N**H**), 2.71 (1H, dt, *J* = 7.1, 7.0 Hz, C**H**COOCH$_3$), 1.84-1.77 (2H, m, C**H$_2$**CHCO), 1.63-1.52 (2H, m, C**H$_2$**CH$_2$OTIPS), 1.19 (9H, s, C(C**H$_3$**)$_3$), 1.05-1.04 (21H, m, Si(C**H**(C**H$_3$**)$_2$)$_3$), 0.15 (9H, s, Si(C**H$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 (**C**O), 103.2 (C≡**C**TMS), 91.2 (**C**≡CTMS), 63.3 (**C**H$_2$TIPS), 56.9 (**C**(CH$_3$)$_3$), 52.0 (O**C**H$_3$), 51.9 (**C**HN), 50.2 (**C**HCOOCH$_3$), 31.1 (**C**H$_2$CH$_2$OTIPS), 25.2 (**C**H$_2$CHCO), 22.9 (C(**C**H$_3$)$_3$), 18.4 (Si(CH(**C**H$_3$)$_2$)$_3$), 12.3 (Si(**C**H(CH$_3$)$_2$)$_3$), 0.1 (Si(**C**H$_3$)$_3$) ppm.

LRMS (ES+) *m/z* 518.2 (18%, $[M+H]^+$), 540.2 (100%, $[M+Na]^+$), 1057.6 (8%, $[2M+Na]^+$).

HRMS (ES+) for $C_{25}H_{51}NO_4SSi_2Na$, requires 540.2926 found 540.2974 Da.

Second diastereomer (89.0 mg, 20%), selected peaks:

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (1H, dd, *J* = 6.2, 4.4 Hz, C**H**N), 4.27 (1H, d, *J* = 6.2 Hz, N**H**), 3.72-3.70 (5H, m, C**H$_2$**OTIPS and OC**H$_3$**), 2.83 (1H, ddd, *J* = 10.1 8.8, 5.7 Hz, C**H**COOCH$_3$), 1.88-1.79 (2H, m, C**H$_2$**CHCO), 1.64-1.23 (2H, m, C**H$_2$**CH$_2$OTIPS), 1.20 (9H, s, C(C**H$_3$**)$_3$), 1.06-1.05 (21H, m, Si(C**H**(C**H$_3$**)$_2$)$_3$), 0.15 (9H, s, Si(CH$_3$)$_3$) ppm.

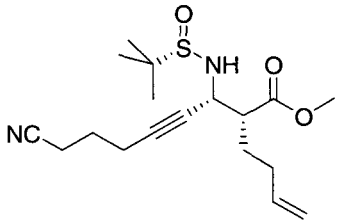
^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0 (**C**O), 103.0 (C≡**C**TMS), 91.8 (**C**≡CTMS), 63.7 (**C**H$_2$TIPS), 57.1 (**C**(CH$_3$)$_3$), 52.0 (O**C**H$_3$), 51.3 (**C**HN), 50.4 (**C**HCOOCH$_3$), 31.4 (**C**H$_2$CH$_2$OTIPS), 25.4 (**C**H$_2$CHCO), 22.9 (C(**C**H$_3$)$_3$), 18.4 (Si(CH(**C**H$_3$)$_2$)$_3$), 12.3 (Si(**C**H(CH$_3$)$_2$)$_3$), 0.0 (Si(**C**H$_3$)$_3$) ppm.

Minor diastereomer (15.0 mg, 3%):

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (1H, t, *J* = 7.5 Hz, **CH**N), 4.02 (1H, d, *J* = 7.1 Hz, N**H**), 3.72 (3H, s, O**CH$_3$**), 3.70 (2H, t, *J* = 6.2 Hz, **CH$_2$**OTIPS), 2.76 (1H, ddd, *J* = 12.8, 9.0, 4.9 Hz, **CH**COOCH$_3$), 1.94-1.72 (2H, m, **CH$_2$**CHCO), 1.62-1.52 (2H, m, **CH$_2$**CH$_2$OTIPS), 1.21 (9H, s, C(**CH$_3$**)$_3$), 1.06-1.05 (21H, m, Si(**CH**(**CH$_3$**)$_2$)$_3$), 0.16 (9H, s, Si(CH$_3$)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (**C**O), 103.3 (**C**≡CTMS), 91.5 (**C**≡CTMS), 63.3 (**CH$_2$**TIPS), 56.4 (**C**(CH$_3$)$_3$), 52.2 (O**CH$_3$**), 51.8 (**CH**N), 50.6 (**CH**COOCH$_3$), 30.6 (**CH$_2$**CH$_2$OTIPS), 26.6 (**CH$_2$**CHCO), 22.9 (C(**CH$_3$**)$_3$), 18.4 (Si(CH(**CH$_3$**)$_2$)$_3$), 12.3 (Si(**CH**(CH$_3$)$_2$)$_3$), 0.1 (Si(**CH$_3$**)$_3$) ppm.

Methyl (*S*$_S$,2*S*,3*R*)-2-(3-butenyl)-8-cyano-3-[(1,1-dimethylethyl)sulfinyl]amino-4-octynoate (5.45)



$C_{18}H_{28}N_2O_3S$
Mw = 352.49 gmol^{-1}
Yellow oil

Using the procedure previously described (*vide supra*), the reaction of *i*-Pr$_2$NH (0.15 mL, 1.1 mmol) in THF (5.5 mL, 0.2 M), *n*-BuLi (0.50 mL of a 1.9 M soln., 1.05 mmol), ester **5.38** (0.14 mL, 1.0 mmol), TiCl(O*i*-Pr)$_3$ (2.00 mL of a 1.0 M soln. in THF, 2.0 mmol, 4.0 eq.), $TiCl_4$ (22 μL, 0.2 mmol, 0.4 eq.) and sulfinyl imine **(+)-5.16** (0.11 g, 0.5 mmol, 1.0 eq.) afforded the title compound as an inseparable mixture of two diastereomers (0.13 g, 72% combined yield) after column chromatography (silica gel 60A, 4:1 to 1:4 hexanes:EtOAc). Note: the same procedure was used when 6.0 and 8.0 eq. of Lewis acid were used.

FT-IR ν_{max} (neat) 2952 (w), 1733 (s), 1056 (s) cm^{-1}.

Major diastereomer (selected peaks):

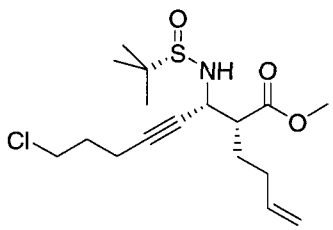
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 17.0, 10.2, 6.8 Hz, C**H**=CH_2), 5.10-5.00 (2H, m, CH=C**H$_2$**), 4.33 (1H, ddt, *J* = 6.2, 4.8, 2.2 Hz, C**H**N), 4.21 (1H, br d, *J* = 6.1 Hz, N**H**), 3.74 (3H, s, O**CH$_3$**), 2.83 (1H, dt, *J* = 8.8, 4.8 Hz **CH**COOCH_3), 2.59-2.50 (2H, m, **CH$_2$**CN), 2.42 (2H, td, *J* = 6.6, 2.2 Hz, **CH$_2$**C≡C), 2.20-2.03 (2H, m, **CH$_2$**), 1.99-1.80 (4H, m, 2 x **CH$_2$**), 1.25 (9H, s, C(**CH$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (**C**O), 137.5 (**C**H=CH_2), 119.4 (**C**N), 116.1 (CH=**C**H$_2$), 84.4 (C≡**C**CH$_2$), 79.0 (**C**≡CCH$_2$), 56.4 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 50.4 (**C**HCOOCH$_3$), 49.3 (**C**HN), 31.7 (**C**H$_2$CH=CH$_2$), 28.1 (**C**H$_2$CH$_2$CH=CH$_2$), 24.8 (**C**H$_2$CH$_2$CN), 22.9 (C(**C**H$_3$)$_3$), 18.1 (C≡**C**CH$_2$), 16.3 (**C**H$_2$CN) ppm.

LRMS (ES+) *m/z* 375.2 (100%, $[M+Na]^+$).

HRMS (ES+) for $C_{18}H_{29}N_2O_3S$, requires 353.1893 found 353.1884 Da.

(+)-Methyl-(*S*$_S$,2*R*,3*R*)-2-(but-3-en-1-yl)-8-chloro-3-(*tert*-butylsulfinyl)amino)-oct-4-ynoate ((+)-5.46)



$C_{17}H_{28}ClNO_3S$
Mw = 361.93 $gmol^{-1}$
Yellow oil

According to the procedure described (*vide supra*), the reaction of *i*-Pr_2NH (93 μL, 0.68 mmol, 2.2 eq.), *n*-BuLi (0.28 mL of a 2.5 M soln. in hexanes, 0.63 mmol, 2.1 eq.), sulfinyl amine **(+)-5.18** (70 mg, 0.3 mmol), ester **5.38** (85 μL, 0.6 mmol, 2.0 eq.), $TiCl(O$*i*$-Pr)_3$ (2.4 mL of 1.0 M soln. in THF, 2.4 mmol, 8.0 eq.) pre-treated with $TiCl_4$ (13 μL, 0.12 mmol, 0.8 eq.) in THF (3.4 mL) afforded the title compound as a partially separable mixture of diastereomers. Purification was achieved by column chromatography (silica gel 60A, gradient elution 1:1 to 4:6 hexane/EtOAc).

Major diastereomer: 87.8 mg (81%):

$[\alpha]_D^{29}$ +55.0 (*c* 1.52, $CHCl_3$).

FT-IR ν_{max} (neat) 2952 (w), 2360 (w), 1734 (s), 1053 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 16.8, 10.3, 6.6 Hz, C**H**=CH_2), 5.09-5.00 (2H, m, CH=C**H$_2$**), 4.33 (1H, ddt, *J* = 6.2, 4.4, 2.2 Hz, C**H**N), 4.22 (1H, d, *J* = 6.0 Hz, N**H**), 3.73 (3H, s, O**CH$_3$**), 3.65 (2H, t, *J* = 6.2 Hz, **CH$_2$**Cl), 2.82 (1H, dt, *J* = 5.0, 4.7 Hz, **CH**$COOCH_3$), 2.41 (2H, td, *J* = 6.8, 2.0 Hz, C≡C**CH$_2$**), 2.20-1.70 (6H, m, 3 x **CH$_2$**), 1.23 (9H, s, C(**CH$_3$**)$_3$) ppm.

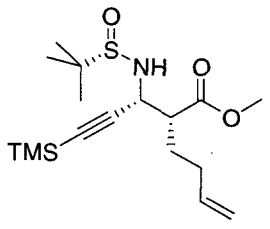
^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 (**C**O), 137.6 (**C**H=CH_2), 116.1 (CH=**CH$_2$**), 85.3 (C≡**C**CHN), 78.0, (**C**≡CCHN), 56.4 (**C**$(CH_3)_3$), 52.3 (O**CH$_3$**), 50.5 (**C**HN), 49.4 (**CH**$COOCH_3$), 43.8 (**CH$_2$**Cl), 31.8 (**CH$_2$**), 31.5 (C≡**C**CH_2), 28.0 (**CH$_2$**), 23.0 (C(**CH$_3$**)$_3$), 16.5 (**CH$_2$CH$_2$**Cl) ppm.

LRMS (ES+) *m/z* 362.4 (100%, $[M+H]^+$), 384.3 (55%, $[M+Na]^+$).

HRMS (ES+) for $C_{17}H_{28}ClNO_3SNa$, requires 384.1376 found 384.1371 Da.

Inseparable mixture: 7.9 mg (7%). Ratio 1:3 (major:minor).

(*S*$_S$)- Methyl (2*S*)-2-[(1*R*)-1-[(1,1-dimethylethyl)sulfinyl]amino-3-(1,1,1-trimethylsilyl)-2-propynyl]-5-hexenoate (5.47)



$C_{17}H_{31}NO_3SSi$
Mw = 357.58 $gmol^{-1}$
Pale yellow oil

Following the procedure (*vide supra*), the reaction of *i*-Pr_2NH (0.15 mL, 1.10 mmol, 1.2 eq.) in THF (5.5 mL, 0.2 M), *n*-BuLi (0.55 mL of a 1.9 M soln. in hexanes, 1.05 mmol,

1.1 eq.), 5-hexenoic acid methyl ester **5.38** (128 mg, 1.00 mmol), $TiCl(O\textit{i}\text{-}Pr)_3$ (2.0 mL of a 1.0 M soln., 2.00 mmol, 4.0 eq.), $TiCl_4$ (22 μL, 0.20 mmol, 0.4 eq.) and sulfinyl imine **(+)-5.19** (115 mg, 0.5 mmol, 1.0 eq.) yielded the title product as a mixture of 3 diastereomers. Purification was achieved by column chromatography (silica gel 60A, gradient elution 8:2 to 7:3 hexane/EtOAc).

Major diastereomer: 90.3 mg (50%)

Mixed: 21.0 mg (12%)

Minor diastereomer: 8.6 mg (5%)

Overall recovery: 67%

Major diastereomer:

FT-IR ν_{max} (neat) 2956 (w), 1737 (m), 1058 (m), 840 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (1H, ddt, *J* = 17.0, 10.2, 6.6 Hz, C**H**=CH_2), 5.08-5.00 (2H, m, CH=C**H$_2$**), 4.33 (1H, dt, *J* = 6.6, 4.6 Hz, C**H**NH), 4.27-4.26 (1H, dd, *J* = 6.2, 4.3 Hz, N**H**), 3.73 (3H, s, O**CH$_3$**), 2.86 (1H, ddd, *J* = 8.5, 5.2, 4.9 Hz, C**H**$COOCH_3$), 2.22-2.06 (2H, m, **CH$_2$**$CH=CH_2$), 2.00-1.75 (2H, m, CH**CH$_2$**), 1.25 (9H, s, $C(\mathbf{CH_3})_3$), 0.17 (9H, s, $Si(\mathbf{CH_3})_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (**C**O), 137.6 (**C**H=CH_2), 116.0 (CH=**C**H_2), 102.5 (C≡**C**TMS), 91.4 (**C**≡CTMS), 56.5 ($\mathbf{C}(CH_3)_3$), 52.3 (O**C**H_3), 50.4 (**C**HN), 50.2 (**C**H$COOCH_3$), 31.8 ($\mathbf{C}H_2CH=CH_2$), 27.8 (**C**H_2), 22.9 ($C(\mathbf{C}H_3)_3$), 0.1 ($Si(\mathbf{C}H_3)_3$) ppm.

LRMS (ES+) *m/z* 380.2 (100%, $[M+Na]^+$).

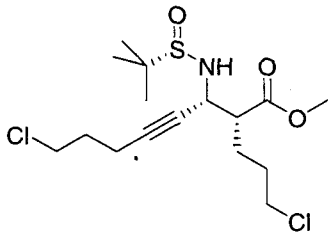
Second diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, ddt, *J* = 17.0, 10.4, 6.5 Hz, C**H**=CH_2), 5.08-5.00 (2H, m, CH=C**H$_2$**), 4.20 (1H, t, *J* = 8.6 Hz, C**H**NH), 3.70 (3H, s, O**CH$_3$**), 3.64 (1H, d, *J* = 8.6 Hz, N**H**), 2.71 (1H, td, *J* = 8.9, 4.8 Hz, C**H**$COOCH_3$), 2.13-2.01 (2H, m, **CH$_2$**$CH=CH_2$), 1.91-1.75 (2H, m, CH**CH$_2$**), 1.20 (9H, s, $C(\mathbf{CH_3})_3$), 0.17 (9H, s, $Si(\mathbf{CH_3})_3$) ppm.

Minor diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz, C**H**=CH_2), 5.08-4.99 (2H, m, CH=C**H$_2$**), 4.33 (1H, dd, *J* = 7.8, 5.9 Hz, C**H**NH), 3.71 (3H, s, OC**H$_3$**), 3.61 (1H, d, *J* = 7.8 Hz, N**H**), 2.86 (1H, dt, *J* = 9.2, 5.3 Hz, C**H**COOCH_3), 2.19-2.02 (2H, m, C**H$_2$**CH=CH_2), 1.96-1.79 (2H, m, CHC**H$_2$**), 1.20 (9H, s, C(C**H$_3$**)$_3$), 0.17 (9H, s, Si(C**H$_3$**)$_3$) ppm.

Methyl-(S_S,2*R*,3*R*)-3-[(*tert*-butylsulfinyl)amino]-8-chloro-2-(3-chloropropyl)oct-4-ynoate (5.48)



$C_{16}H_{27}Cl_2NO_3S$
Mw = 384.36 $gmol^{-1}$
Yellow oil

According to the procedure described (*vide supra*), the reaction of *i*-Pr_2NH (1.51 mL, 10.8 mmol, 4.2 eq.), *n*-BuLi (4.21 mL of a 2.5 M soln. in hexanes, 10.5 mmol, 4.1 eq.), sulfinyl amine **(+)-5.18** (0.60 g, 2.6 mmol), ester **4.76** (1.44 mL, 10.3 mmol, 4.1 eq.), TiCl(O*i*-Pr)$_3$ (20.6 mL of 1.0 M soln. in THF, 20.6 mmol, 8.0 eq.) and $TiCl_4$ (2.06 mL of a 1 M soln. in CH_2Cl_2, 2.06 mmol, 0.8 eq.) in THF (54 mL, 0.2 M) afforded the title compound as a mixture of three diastereomers after column chromatography (silica gel 60A, 6:4 to 4:6 hexane/EtOAc).

Major diastereomer: 0.59 g (60%)

Mixed: 0.12 g (12%)

Minor diastereomer: 0.12 g (12%)

Overall recovery: 84%

Major diastereomer:

FT-IR ν_{max} (neat) 2956 (m), 2869 (w), 2359 (w), 1735 (s), 1054 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.34 (1H, ddt, *J* = 6.4, 4.4, 2.1 Hz, C**H**NH), 6.39 (1H, d, *J* = 6.4 Hz, N**H**), 3.74 (3H, s, OC**H$_3$**), 3.66 (2H, t, *J* = 6.4 Hz, C**H$_2$**Cl), 3.56 (2H, t, *J* = 6.2 Hz, C**H$_2$**Cl), 2.83 (1H, ddd, *J* = 8.9, 5.8, 4.9

Hz, C**H**COOCH$_3$), 2.42 (2H, td, J = 6.8, 2.0 Hz, C≡CC**H$_2$**), 2.00-1.80 (6H, m, 3 x C**H$_2$**), 1.25 (9H, s, C(C**H$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7 (**C**O), 85.6 (C≡**C**CHN), 77.6 (**C**≡CCHN), 56.4 (**C**(CH$_3$)$_3$), 52.4 (O**C**H$_3$), 50.6 (**C**HN), 49.6 (**C**HCOOCH$_3$), 44.7 (**C**H$_2$Cl), 43.8 (**C**H$_2$Cl), 31.5 (C≡**C**CH$_2$), 30.7 (**C**H$_2$), 26.2 (**C**H$_2$), 23.0 (C(**C**H$_3$)$_3$), 16.5 (**C**H$_2$CH$_2$Cl) ppm.

LRMS (ES+) *m/z* 384.3 (100%, $[M+H]^+$), 406.3 (35%, $[M+Na]^+$), 767.5 (30%, $[2M+H]^+$).

Second diastereomer (selected peaks):

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (1H, d, J = 7.2 Hz, N**H**), 3.73 (3H, s, O**CH$_3$**), 2.72 (1H, ddd, J = 8.7, 7.7, 4.6 Hz, C**H**COOCH$_3$), 1.21 (9H, s, C(C**H$_3$**)$_3$) ppm.

Minor diastereomer:

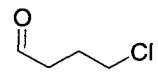
FT-IR ν_{max} (neat) 2955 (w), 2869 (w), 2360 (w), 2342 (w), 1734 (s), 1054 (s) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (1H, ddt, J = 8.2, 6.0, 2.2 Hz, C**H**N), 3.72 (3H, s, O**CH$_3$**), 3.66 (2H, t, J = 6.2 Hz, C**H$_2$**Cl), 3.62-3.55 (3H, m, C**H$_2$**Cl and N**H**), 2.67 (1H, ddd, J = 9.0, 6.0, 4.3 Hz, C**H**COOCH$_3$), 2.41 (2H, td, J = 6.8, 2.0 Hz, C≡CC**H$_2$**), 2.00-1.77 (6H, m, 3 x C**H$_2$**), 1.21 (9H, s, C(C**H$_3$**)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (**C**O), 85.5 (C≡**C**CHN), 78.9 (**C**≡CCHN), 56.9 (**C**(CH$_3$)$_3$), 52.3 (O**C**H$_3$), 51.4 (**C**HN), 50.1 (**C**HCOOCH$_3$), 44.8 (**C**H$_2$Cl), 43.9 (**C**H$_2$Cl), 31.4 (C≡**C**CH$_2$), 30.7 (**C**H$_2$), 26.0 (**C**H$_2$), 22.9 (C(**C**H$_3$)$_3$), 16.5 (**C**H$_2$CH$_2$Cl) ppm.

LRMS (ES+) *m/z* 384.3 (20%, $[M+H]^+$), 406.3 (100%, $[M+Na]^+$), 791.6 (20%, $[M+Na]^+$).

4-Chlorobutanal (6.02)

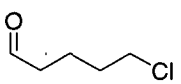


C_4H_7ClO
Mw = 106.55 $gmol^{-1}$
Yellow oil

Following the procedure described by Witiak *et al.*,[194] methyl-4-chlorobutyrate (1.8 mL, 14.6 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and cooled to –78 °C and treated with DIBAL-H (16.0 mL of a 1 M soln. in hexanes, 16.0 mmol) over 10 min. The reaction mixture was stirred at this temperature for 1 h. The reaction was quenched by pouring on to a sat. soln. of NH_4Cl (50 mL) and H_2O (25 mL). The suspension was filtered through Celite® and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were washed with brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow oil (0.92 g, 59%). No further purification was attempted. ^{1}H NMR spectroscopic data is consistent with that published in the literature.[194]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.83 (1H, s, **CHO**), 3.61 (2H, t, *J* = 7.0 Hz, **CH_2**Cl), 2.68 (2H, t, *J* = 7.0 Hz, **CH_2**CHO), 2.12 (2H, qn, *J* = 7.0 Hz, **CH_2**) ppm.

5-Chloropentanal (6.03)

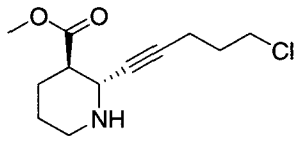


C_5H_9ClO
Mw = 120.58 $gmol^{-1}$
Yellow oil

Following the procedure described by Witiak *et al.*,[194] methyl-5-chloropentanoate (1.9 mL, 13.3 mmol) was dissolved in CH_2Cl_2 (40 mL), cooled to –60 °C and treated with DIBAL-H (14.6 mL of a 1 M soln. in hexanes, 14.6 mmol) over 10 min. The reaction mixture was stirred at this temperature for 2 h. The reaction was quenched by pouring on to a sat. soln. of NH_4Cl (50 mL) and H_2O (25 mL). The suspension was filtered through Celite® and extracted with CH_2Cl_2 (2x). The combined organic layers were washed with brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a yellow oil (1.0 g, 64%). No further purification was attempted. ^{1}H NMR spectroscopic data is consistent with that published in the literature.[195]

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (1H, t, *J* = 1.5 Hz, **CHO**), 3.62-3.53 (2H, m, **CH_2**Cl), 2.60-2.44 (2H, m, **CH_2**CHO), 1.90-1.75 (4H, m, 2 x **CH_2**) ppm.

(+)-Methyl (2*R*,3*R*)-2-(5-chloropent-1-yn-1-yl)piperidine-3-carboxylate ((+)-6.10)



$C_{12}H_{18}ClNO_2$
Mw = 243.73 $gmol^{-1}$
Orange oil

Sulfinyl amine **4.48** (1.45 g, 3.77 mmol) was dissolved in MeOH (30 mL) before 4 N HCl/dioxane (2.9 mL) was added in one portion. The reaction mixture was stirred for 30 min at rt before the solvent was removed *in vacuo*. The resulting oil was redissolved in DMF (60 mL) and the solution was treated with K_2CO_3 (2.64 g, 19.10 mmol, 5.1 eq.) and heated to 100 °C for 1 h. Once cooled to rt the reaction mixture was diluted with EtOAc (200 mL) and washed with H_2O (6 x 150 mL), brine (150 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield an orange oil (0.85 g, 92% recovery). No further purification was attempted.

$[\alpha]_D^{28}$ +3.0 (*c* 1.26, $CHCl_3$).

FT-IR ν_{max} (neat) 2948 (w), 2859 (w), 2359 (w), 2342 (w), 1732 (s) cm^{-1}.

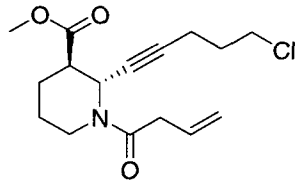
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (1H, d, *J* = 8.5 Hz, C**H**N), 3.73 (3H, s, OC**H$_3$**), 3.64 (2H, t, *J* = 6.3 Hz, C**H$_2$**Cl), 3.11 (1H, dt, *J* = 12.3, 3.8 Hz, C**H**HN), 2.70 (1H, ddd, *J* =12.3, 10.3, 3.0 Hz, CH**H**N), 2.55 (1H, appt. td, *J* = 9.3, 3.8 Hz, C**H**COOCH$_3$), 2.38 (2H, td, *J* = 6.5, 1.7 Hz, C≡CC**H$_2$**), 2.04-2.00 (1H, m, C**H**HCH), 1.93 (2H, qn, *J* = 6.5 Hz, C**H$_2$**CH$_2$Cl), 1.73-1.64 (2H, m, CH**H**CH and C**H**HCH$_2$), 1.57-1.51 (1H, m, CH**H**CH$_2$) ppm. No N**H** resonance observed.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4 (**C**O), 82.5 (C≡**C**CH), 81.0 (**C**≡CCH), 52.1 (O**C**H$_3$), 49.9 (**C**HN), 49.2 (**C**HCH), 45.3 (**C**H$_2$N), 43.9 (**C**H$_2$Cl), 31.7 (**C**H$_2$CH$_2$Cl), 27.4 (**C**H$_2$), 24.9 (**C**H$_2$), 16.4 (C≡**C**CH$_2$) ppm.

LRMS (ES+) *m/z* 244.3 (100%, $[M+H]^+$).

HRMS (ES+) for $C_{12}H_{19}ClNO_2$, requires 244.1099 found 244.1099 Da.

Methyl (2*R*,3*R*)-1-but-3-enoyl-2-(5-chloropent-1-yn-1-yl)piperidine-3-carboxylate (6.11)



$C_{16}H_{22}ClNO_3$
Mw = 311.80 $gmol^{-1}$
Colourless oil

Primary amine **6.09** cyclised prior to use in this reaction. Following the procedure described by Cropper *et al.*,[196] butenoic acid (41 μL, 0.48 mmol, 2.0 eq.) was dissolved in dry CH_2Cl_2 (1.5 mL) before DMF (1 drop) and oxalyl chloride (41 μL, 0.47 mmol, 1.95 eq.) were added at 0 °C. The reaction was stirred at rt for 3 h. The HCl salt of piperidine **6.10** (66.4 mg, 0.27 mmol) was added in dry CH_2Cl_2 (1 mL). The yellow reaction mixture was then stirred at rt for 18 h. The reaction was quenched by the addition of H_2O (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were washed with a sat. soln. of $NaHCO_3$ (20 mL), H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a yellow oil. Purification by column chromatography (silica gel 60A, gradient elution 3:2 hexane/EtOAc to 99:1 EtOAc:MeOH) yielded the title product as a colourless oil (14.5 mg, 19%) and piperidine **6.10** (34.4 mg, 59%).

FT-IR ν_{max} (neat) 2951 (w), 2864 (w), 1732 (s), 1647 (s) cm^{-1}.

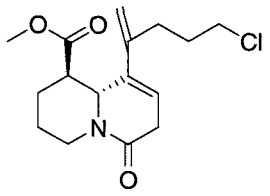
^{1}H NMR Data unresolved. Spectrum shows resonances indicating a terminal double bond.

^{13}C NMR Data unresolved.

LRMS (ES+) *m/z* 312.3 (40%, $[M+H]^+$), 334.3 (100%, $[M+Na]^+$), 645.4 (95%, $[2M+Na]^+$).

HRMS (ES+) for $C_{16}H_{22}ClNO_3Na$, requires 334.1180 found 334.1182 Da

Methyl-(1*R*,9a*R*)-9-(5-chloropent-1-en-2-yl)-2,3,4,6,7,9a-hexahydro-6-oxo-1*H*-quinolizine-1-carboxylate ((–)-6.12)



$C_{16}H_{22}ClNO_3$
Mw = 311.80 $gmol^{-1}$
Colourless oil

Enyne **6.11** (14.5 mg, 47 μmol) was dissolved in dry CH_2Cl_2 (1.5 mL) and degassed for 25 min before Grubbs' II catalyst (8.0 mg, 9 μmol, 19 mol%) was added under Ar. The reaction mixture was heated to 40 °C for 2 h over which time the dark red solution turned dark brown in colour. The solvent was removed *in vacuo* to afford a dark brown oil. Purification by column chromatography (silica gel 60A, 1:4 hexane/EtOAc) yielded the title compound as a dark yellow oil (13.9 mg, 96%).

$[\alpha]_D^{26}$ –186.0 (*c* 0.65, $CHCl_3$).

FT-IR ν_{max} (neat) 2995 (w), 2947 (w), 2864 (w), 1732 (s), 1651 (s) cm^{-1}.

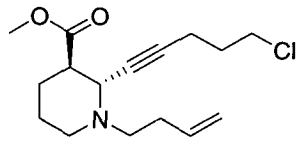
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, dd, *J* = 4.8, 3.2 Hz, C=C**H**), 4.98 (1H, s, CH=C**H**H), 4.91 (1H, s, CH=CH**H**), 4.79 (1H, ddt, *J* = 13.0, 4.5, 1.8 Hz, C**H**HN), 4.26 (1H, dt, *J* = 10.3, 2.3 Hz, C**H**N), 3.57-3.48 (5H, m, O**CH$_3$** and **CH$_2$**Cl), 3.07-3.04 (2H, m, **CH$_2$**CON), 2.64 (1H, td, *J* = 13.0, 3.0 Hz, CH**H**N), 2.45-2.27 (3H, m, =C(CH$_2$)**CH$_2$** and **CH**COOCH$_3$), 2.05-1.50 (6H, m, 3 x **CH$_2$**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (**C**O), 167.9 (**C**ON), 145.6 (**C**=CH$_2$), 137.0 (HC=**C**), 122.2 (C=**C**H), 114.0 (C=**C**H$_2$), 59.9 (**C**HN), 51.9 (O**C**H$_3$), 50.7 (**C**HCHN), 44.7 (**C**H$_2$Cl), 44.5 (**C**H$_2$N), 32.7 (=CH**C**H$_2$), 31.3 (=C**C**H$_2$ and **C**H$_2$), 29.4 (**C**H$_2$), 24.0 (**C**H$_2$CH$_2$Cl) ppm.

LRMS (ES+) *m/z* 312.3 (100%, $[M+H]^+$), 375.3 (30%, $[M+Na(MeCN)]^+$), 623.5 (40%, $[2M+H]^+$).

HRMS (ES+) for $C_{16}H_{23}ClNO_3$, requires 312.1366 found 312.1363 Da.

(+)-Methyl (2*R*,3*R*)-1-but-3-en-1yl-2-(5-chloropent-1-yn-1-yl)piperidine-3-carboxylate ((+)-6.13)



$C_{16}H_{24}ClNO_2$
Mw = 297.82 $gmol^{-1}$
Colourless oil

Following the procedure described by Schmidt *et al.*,[197] piperidine **6.10** (0.85 g, crude), 18-crown-6 (50 mg, 0.19 mmol, 5 mol%) and K_2CO_3 (0.78 g, 5.6 mmol) were placed under vacuum and the reaction vessel was then purged with Ar before MeCN (4.5 mL) and bromobutene (0.57 mL, 5.6 mmol) were added. The orange solution was heated to 70 °C for 16 h after which time the solution had turned brown. The reaction was allowed to cool to rt and was quenched by the addition of H_2O and EtOAc. The layers were separated and the organic layer was washed with H_2O (20 mL), brine (20 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Purification by column chromatography (silica gel 60A, 17:3 *iso*-hexane/EtOAc) yielded the title compound as a mixture of diastereomers: Major diastereomer (0.60 g, 53% over 3 steps) and mixed (0.15 g, 13% over 3 steps).

Major diastereomer:

$[\alpha]_D^{27}$ +16.0 (*c* 0.91, $CHCl_3$).

FT-IR ν_{max} (neat) 2948 (w), 2819 (w), 1735 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (1H, ddt, *J* = 13.5, 10.3, 6.8 Hz, C**H**=CH_2), 5.01 (2H, ddt, *J* = 13.5, 10.1, 1.3 Hz, CH=C**H$_2$**), 3.95-3.94 (1H, br s, NC**H**), 3.71 (3H, s, OC**H$_3$**), 3.66 (2H, t, *J* = 6.5 Hz, C**H$_2$**Cl), 2.68-2.33 (7H, m, C**H**CHN, 2 x C**H$_2$**N and C≡CC**H$_2$**), 2.26-2.17 (2H, m, C**H$_2$**CH=CH_2), 1.96 (2H, qn, *J* = 6.5 Hz, C**H$_2$**CH_2Cl), 1.88-1.68 (3H, m, C**H$_2$**CH and C**H**HCH_2N), 1.55-1.45 (1H, m, CH**H**CH_2N) ppm.

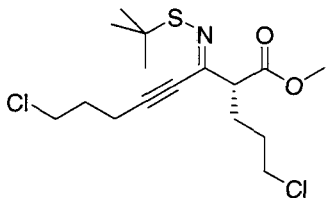
^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6 (**C**O), 137.1 (**C**H=CH_2), 115.7 (CH=**C**H_2), 85.11 (C≡**C**CH), 55.4 (**C**H_2N), 53.2 (O**C**H_3), 52.1 (**C**HCOOCH_3), 49.7 (**C**H_2N), 46.7 (**C**HC≡C), 43.9 (**C**H_2Cl), 31.9 (**C**H_2), 31.5 (**C**H_2), 23.5

(CH_2), 23.3 (CH_2), 16.4 ($C{\equiv}CCH_2$) ppm. Other $C{\equiv}C$ quaternary peak not observed.

LRMS (ES+) *m/z* 298.4 (100%, $[M+H]^+$).

HRMS (ES+) for $C_{16}H_{25}ClNO_2$, requires 298.1568 found 298.1563 Da.

Methyl (*Z*)-3-[(*tert*-butylsulfanyl)imino]-8-chloro-2-(3-chloropropyl)oct-4-ynoate (6.18)



$C_{16}H_{25}Cl_2NO_2S$
Mw = 366.35 $gmol^{-1}$
Yellow oil

Following the general procedure described (*vide supra*), *i*-Pr_2NH (0.15 mL, 1.1 mmol, 2.2 eq.) was dissolved in THF (5.0 mL, 0.2 M) and cooled to 0 °C. Next, *n*-BuLi (0.42 mL of a 2.5 M soln. in hexane, 1.05 mmol, 2.1 eq.) was added slowly dropwise. The solution was stirred for 30 min before being cooled to –78 °C. Ester **4.76** (0.14 mL, 1.0 mmol, 2.0 eq.) was added in THF (1 mL) and stirred for 30 min. This was followed by the slow addition of $TiCl(O\textit{i}\text{-}Pr)_3$ (4.0 mL of a 1.0 M soln. in THF, 4.0 mmol, 8.0 eq.) pre-treated with $TiCl_4$ (0.4 mL of a 1 M soln. in CH_2Cl_2, 0.4 mmol, 0.8 eq.) to form an orange solution. This was stirred for 30 min before sulfinyl imine **(+)-5.18** (120 mg, 0.5 mmol) was added slowly as a solution in THF (0.2 mL). The reaction was stirred for 3 h at –78 °C before it was allowed to warm to rt over 16 h. The deep orange coloured solution turned clear and bright yellow at –40 °C then darkened to orange and turned opaque as it warmed further. Citric acid (0.96 g, 5.0 mmol, 10 eq.) was added as an aqueous sat. soln. The layers were separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were washed with water (1x), brine (1x) and dried ($MgSO_4$). The solvent was removed *in vacuo*. Purification by Biotage chromatography (silica gel, 19:1 *iso*-hexane/EtOAc) yielded the title compound as a yellow oil (80 mg, 44%).

FT-IR ν_{max} (neat) 2959 (w), 2924 (w), 2863 (w), 2213 (w), 1737 (s) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74-3.71 (5H, m, OCH_3 and CH_2Cl), 3.56 (2H, t, *J* = 8.1 Hz, CH_2Cl), 3.45 (1H, t, *J* = 9.3 Hz, $CHCOOCH_3$), 2.68 (2H, t, *J* = 8.5 Hz, $C{\equiv}CCH_2$), 2.09-2.02 (4H, m, 2 x CH_2), 1.85-1.79 (2H, m, CH_2CH), 1.55 (9H, s, $C(CH_3)_3$) ppm.

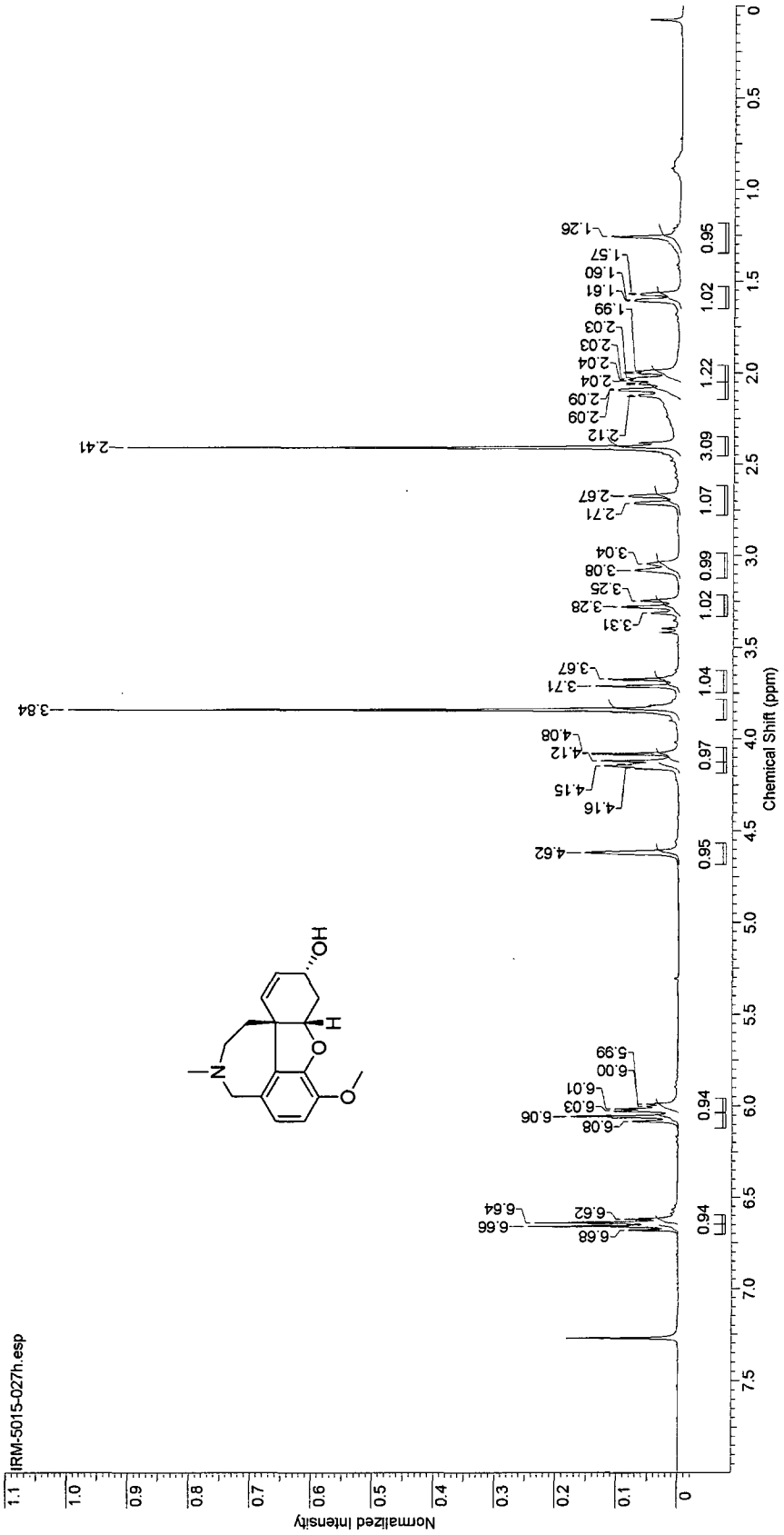
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6 (**C**O), 143.4 (**C**N), 101.9 (**C**≡CCN), 73.6 (C≡**C**CN), 55.4 (OCH_3), 52.4 ($CHCOOCH_3$), 47.2 ($C(CH_3)_3$), 44.7 (CH_2Cl), 43.7 (CH_2Cl), 31.2 ($C{\equiv}CCH_2$), 30.3 (CH_2), 29.4 ($C(CH_3)_3$), 27.1 (CH_2), 17.3 (CH_2CH_2Cl) ppm.

LRMS (ES+) *m/z* 366.3 (60%, $[M+H]^+$), 388.3 (100%, $[M+Na]^+$).

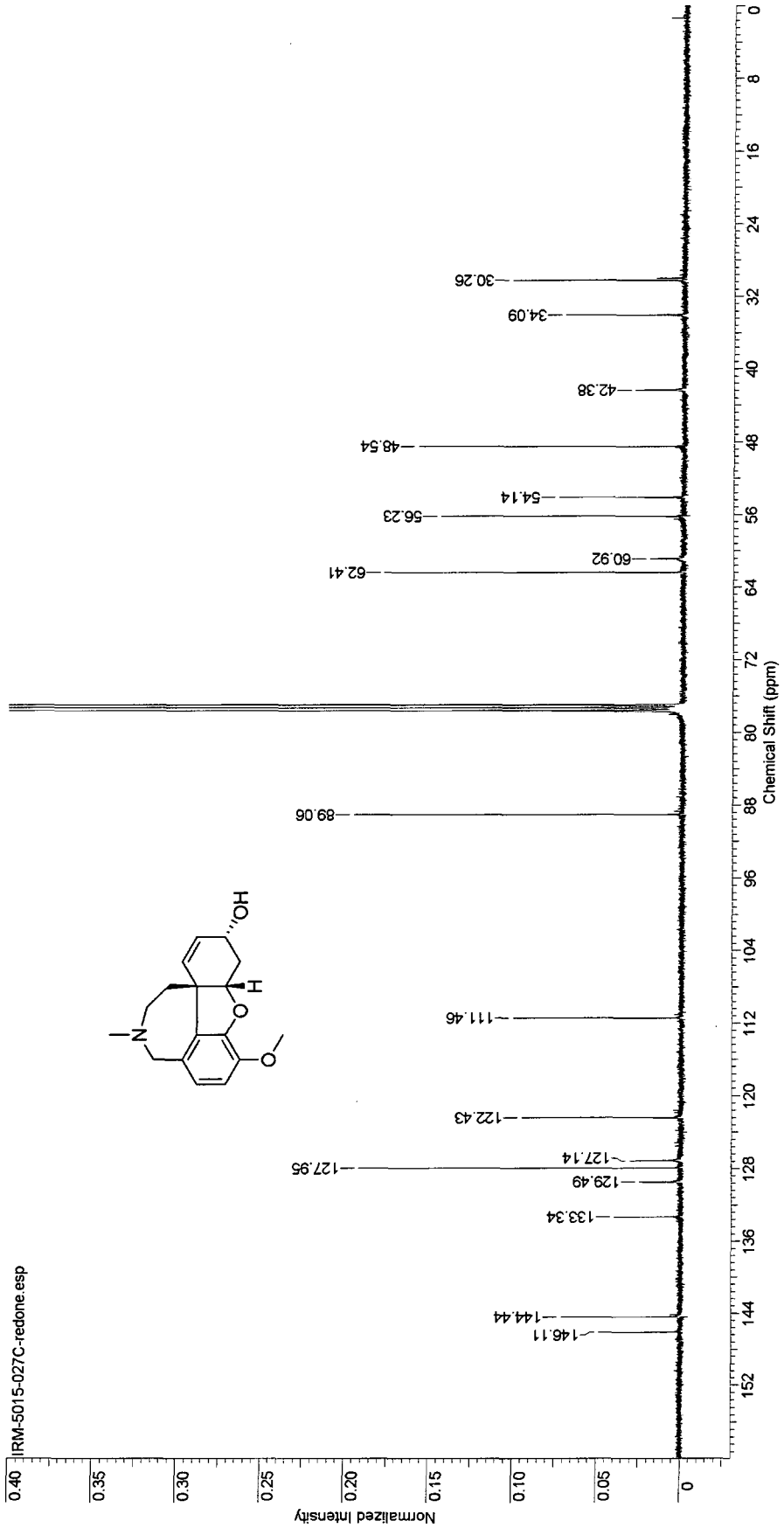
HRMS (ES+) for $C_{16}H_{25}Cl_2NO_2SNa$, requires 388.0881 found 388.0878 Da.

Appendix

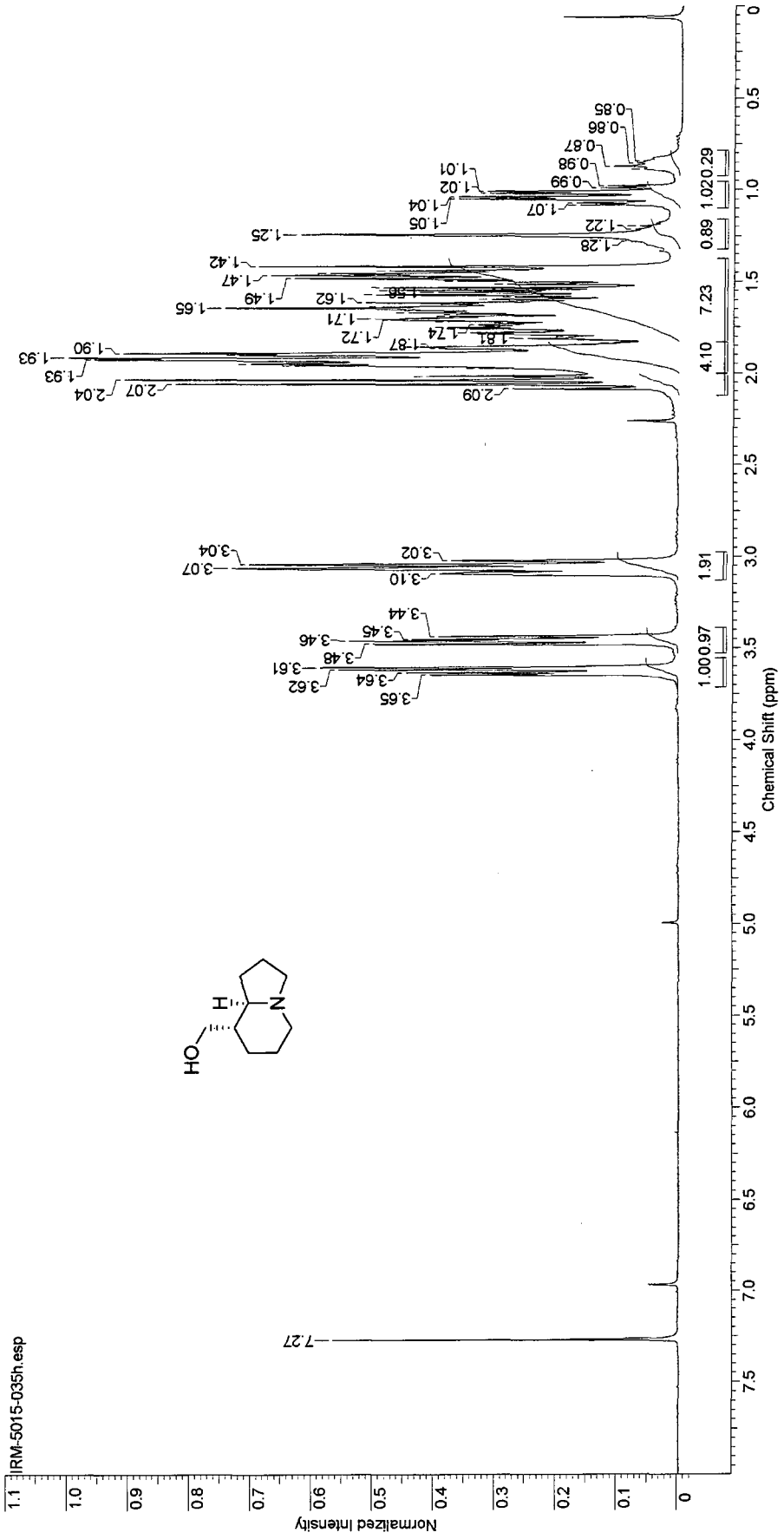
^{1}H NMR (–)-galanthamine **(1.01)**



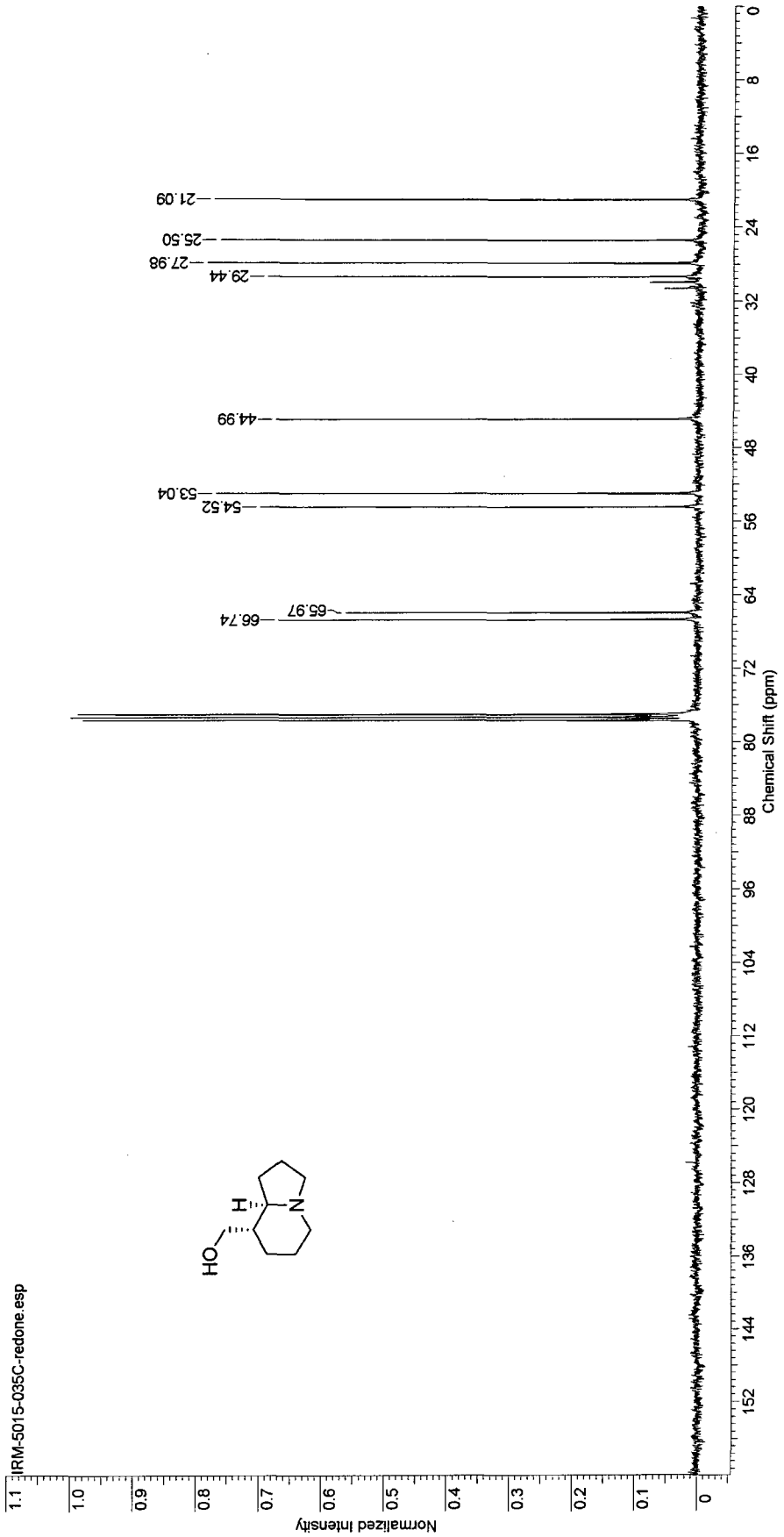
^{13}C NMR of (–)-galanthamine (**1.01**)



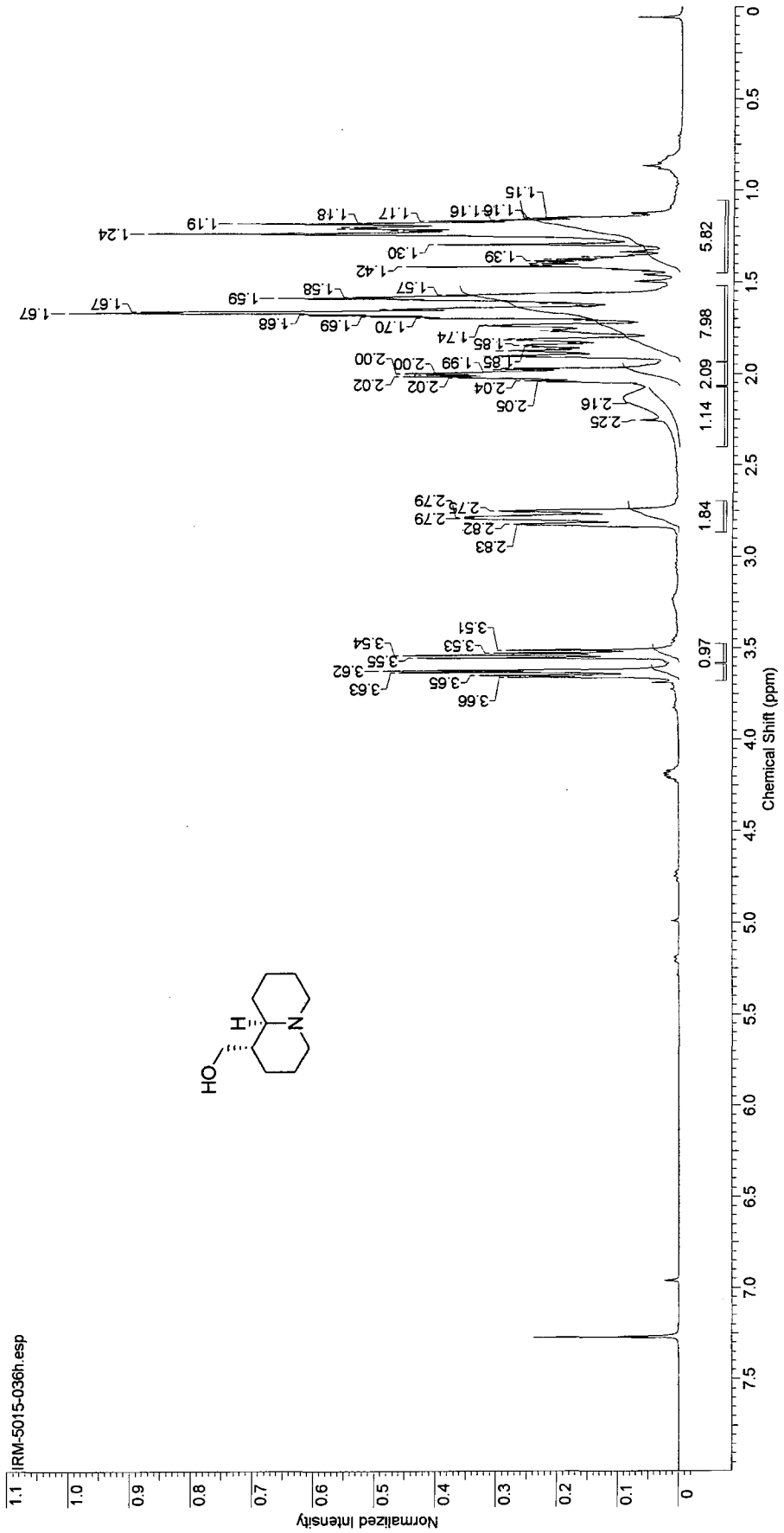
^{1}H NMR for tashiromine (**3.01**)



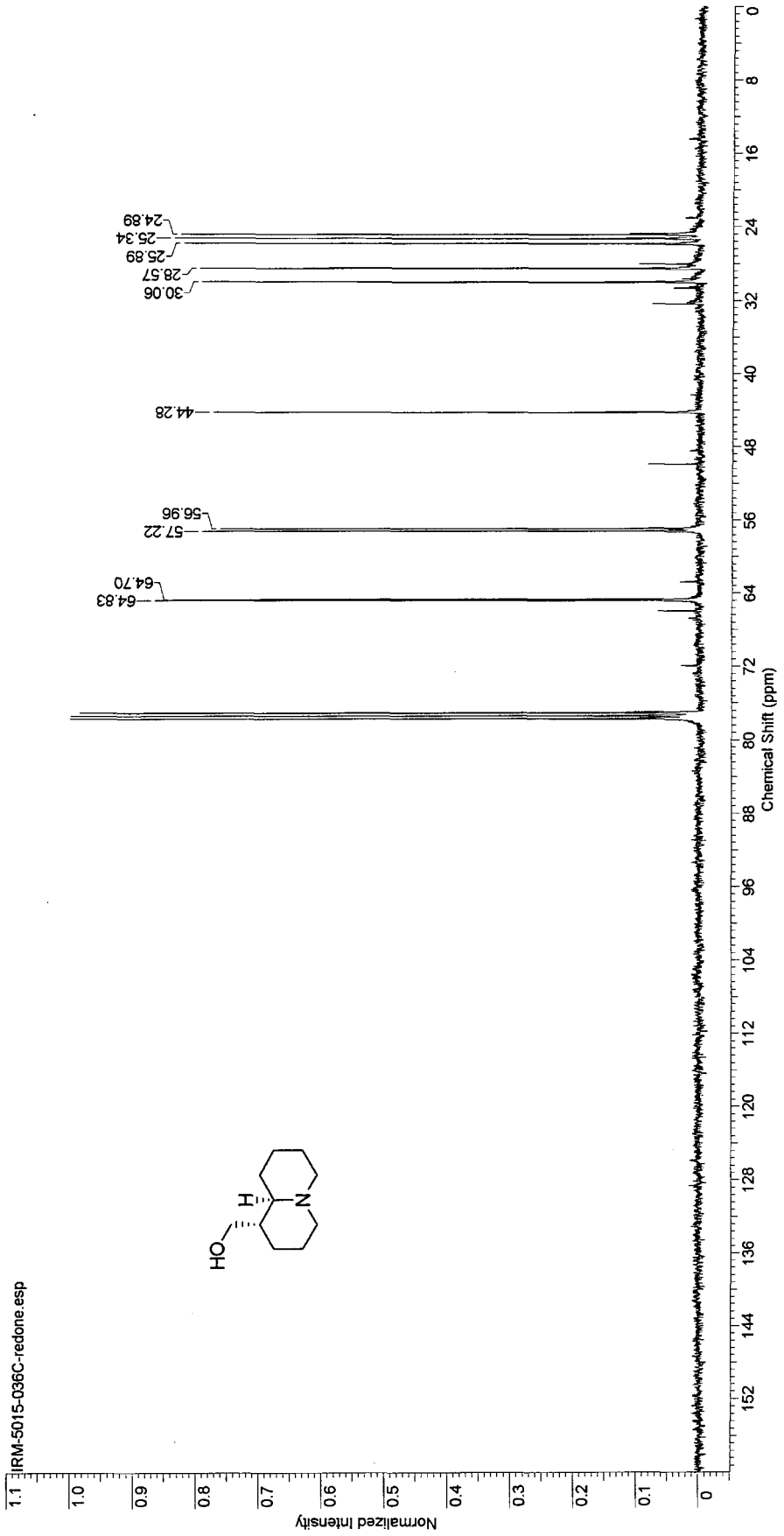
^{13}C NMR for tashiromine (**3.01**)



^{1}H NMR of epilupinine (**3.02**)



^{13}C NMR of epilupinine (**3.02**)



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