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Recent advances in the synthesis of naturally occurring pyrrolidines, pyrrolizidines and indolizidine alkaloids using proline as a unique chiral synthon

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The present article describes the synthesis of a wide spectrum of natural products of the class pyrrolidines, pyrrolizidines and indolizidines using proline as a viable synthetic precursor. The review emphasizes the versatility of the basic unit of proline as a useful chiral synthon confined for the synthesis of only natural products of the above mentioned families. The vast coverage of the synthesis of these natural products is presented for a period from 1990 onwards. The synthesis of all ranges of alkaloids from simple to complex molecules is presented under the groups of alkaloids.

1. Introduction

Over the last few decades, asymmetric synthesis of natural products has gained major importance from an industrial and academic relevance.[1] Asymmetric synthesis mainly involves; carrying out the reaction with the integrity of the chiral centre *viz.* "chiral pool" strategy, introducing new chiral centres by chiral induction methods, use of chiral auxiliaries and organocatalysis. It is always difficult to carry out selective transformation of the molecules to generate new chiral centres. Although the use of organocatalysis is soaring nowadays, selectivity towards the substrates, efficacy of the systems and cost of organocatalysts make this cumbersome from an economic point of view. On the other hand, the "chiral pool" approach, being an effectual paradigm, plays a very prominent role from synthetic relevance[2] as the starting materials are easily carved from readily available materials like amino acids, carbohydrates, terpenes and organic acids. A vast number of natural products are derived from different amino acids[3] due to the availability of the functional groups suitable for various transformations to effect the required modifications and constitute new appendages. As a consequence, several amino

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acids have prompted synthetic chemists to contemplate designing various synthetic routes to embody different natural products and their structural entities.

Proline is a bifunctional, non-essential amino acid prevalent in various natural and synthetic bioactive molecules. It is the only cyclic amino acid, synthesized in our body. Despite being structurally an imino acid, it is popularly called an amino acid. L-Proline, is abundant in nature, cheaply available commercially, and finds application in various pharmacological and biotechnological applications due to its osmoprotectant behaviour. Proline is a widely distributed osmolyte found to accumulate in several environmentally stressed plants as well as microorganisms.[4] It is also used as a nitrogen source during fermentation of grape musts for the production of wine. It is the only amino acid which attains *cis* configuration in peptides unlike other amino acids which normally exist in *trans* form. Due to this unique behaviour, it assisted the detail study of protein folding and *cis–trans* isomerisation. L-Proline is one of the two amino acids which disobeys the popular "Ramachandran plot", the other being glycine.

The unique structure of proline, having both carboxylic and imino groups (Fig. 1) prevails as a versatile organocatalyst through enamine and iminium ion mechanism. Consequently, over the last few decades various proline derived organocatalysts with a multitude of embellishments have been articulated by appropriate transformation of its functional groups and efficiently applied for enantioselective and diastereoselective reactions.[5] Proline enunciates its effect as a profoundly versatile ligand by complexing with the various metals for the synthetic transformation of organic molecules.[6] The availability of the five member ring with a stereogenic nitrogen centre and the two functional groups (Fig. 2) in combination inflict the transformation of the molecule into a myriad of naturally occurring pyrrolidines, pyrrolizidines, piperidines, quinolizidines, indolizidines and macrocycles ranging from simple to complex molecules. Proline being a natural product; conversion of it to other natural products reflects the competency in adaptation of one natural product into another. The biosynthesis of L-proline is derived from L-glutamate and L-ornithine (Scheme 1).[4] Synthetic proline was reported by Willstätter in 1900 using sodium salt of diethyl malonate and 1,3-dibromopropane.

The present review delineates the use of (*R*) and (*S*) proline for the synthesis of the aforementioned types of alkaloids. The comprehensive coverage of the syntheses of these alkaloids has been done (since 1990 to 2013) using proline as a starting material or the major synthetic precursor. The synthetic applications of numerous C-substituted proline units, namely hydroxyl-prolines, also found as useful precursors for the synthesis of these alkaloids is not within the scope of this review. The synthesis of several macro cyclic compounds, generally polypeptides, was also ventured using proline as a precursor, and is also not included in this review. The review focuses directly only on the application of proline transforming to natural products and not on the isolation and biological assays of the synthesized natural product.

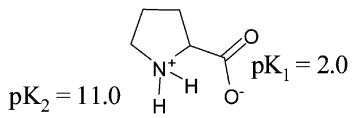


Fig. 1 Proline; a cyclic amino acid.

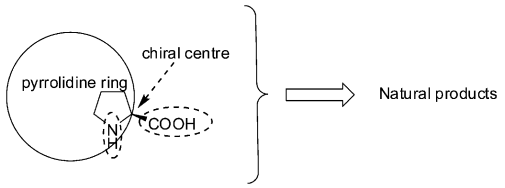
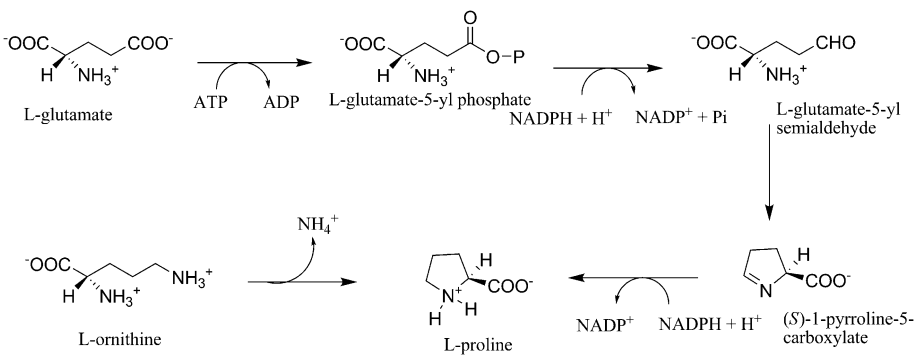


Fig. 2 Proline as a chiral source for natural products.

2. Synthesis of pyrrolidine alkaloids

2.1. Introduction

Pyrrolidine alkaloids bearing five member N-heterocycles, are enormously ubiquitous in various natural[7] and unnatural components.[8] There are about 80 pyrrolidine alkaloids known with hygrine being the simplest. These alkaloids are mainly extracted from the plants of families Colanaceae, Convolvunaceae and Erythroxylaceae. These classes of alkaloids constitute a part of the organocatalysts[9] and building blocks in organic synthesis.[10] They are endowed with a host of biological



Scheme 1 Biosynthesis of proline.

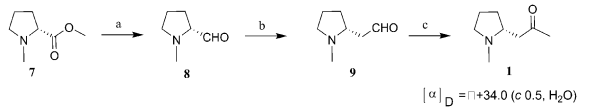
activities and pharmacological behaviours. The difficulties in the isolation and purification of these alkaloids and the global scarcity has imposed on synthetic chemists the need to contemplate the design of novel synthetic schemes. Proline, being one of the simple pyrrolidine alkaloids, has been found to be a viable precursor for the synthesis of these alkaloids through systematic transformation of the functional groups. The simplest pyrrolidine alkaloid, hygrine, acts as a biogenetic precursor for tropane alkaloids.

2.2. Tropane and sedum alkaloids

These classes of alkaloids are mainly 2-substituted pyrrolidine and piperidine members with different functional groups on the side chain and have attracted immense interest from synthetic chemists due to their intriguing pharmacological activities and hallucinogenic characteristics.[11] These alkaloids were mainly isolated from the plants *Schizanthus hookeri*, *Carallia brachiata* and *Erythroxylon coca*. Some of the representative members of five member alkaloids include (+)-hygrine **1**, (+)-hygroline **2** and (+)-pseudohygroline **3**, *etc.*

Shono *et al.* have synthesized (+)-hygroline **2** and (+)-pseudohygroline **3** starting from proline using anodic oxidation as a key step (Scheme 2).[12] The L-proline was efficiently converted to **4** as a mixture of diastereomers **4a** and **4b** according to previously reported methods.[13] The mixture was separated on column chromatography. The further reaction of either **4a** or **4b** with isopropenyl acetate in the presence of $TiCl_4$ resulted in an enantiomeric mixture of **5a** and **5b** which was as such hydrolysed using alkaline solution and electrochemically oxidised in MeOH to give a mixture of **6a** and **6b**. Further reduction of carbamate with LAH gave a mixture of isomers of hygroline **2a** and **2b** and pseudohygroline **3a** and **3b** which were separated with optical purity of 42.60% and 45.62% respectively using preparative GLC.

Arévalo-García and Colmenares synthesized the tropane pyrrolidine alkaloid (+)-hygrine **1**, mainly found in coca leaves, in six steps (Scheme 3) using (*R*)-proline derived ester **7** as a chiral precursor.[14] *N*-Methylated proline ester **7** was reduced to aldehyde **8** using DIBAL which was further homologated to **9** by

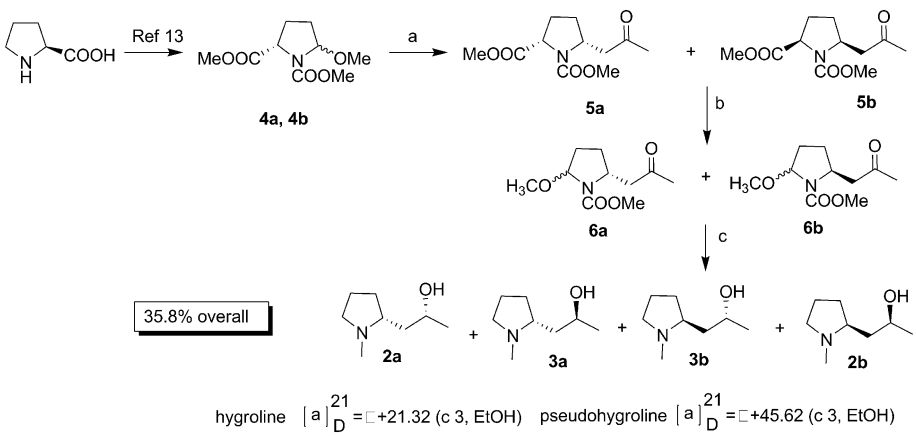


Scheme 3 *Reagents and conditions*: (a) DIBAL, DCM, −30 °C; (b) $PPh_3CH_2OCH_3Br$, KO^tBu, THF, 10% HCl–THF; (c) (i) MeMgBr, THF; (ii) DMP, DCM.

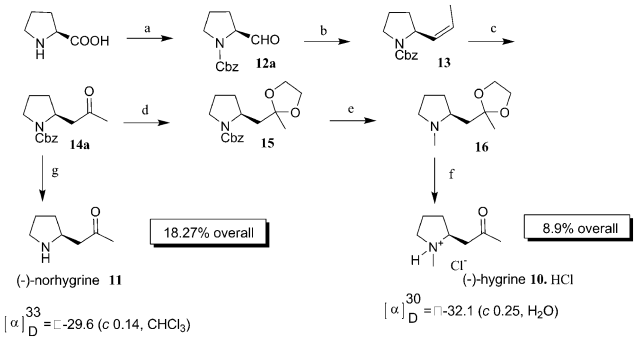
reaction with $PPh_3{=}CHOCH_3$ followed by acid hydrolysis. The Grignard reaction on **9** with MeMgBr and subsequent oxidation with DMP gave (+)-hygrine **1**.

Our research group has also approached the synthesis of the pyrrolidine alkaloids using proline as a starting material.[15] (−)-Hygrine **10** and (−)-norhygrine **11** were synthesized using regioselective Wacker oxidation as a key step (Scheme 4). The synthesis started with commercially available L-proline, converted to *N*-Cbz-prolinal **12a**. The aldehyde **12a** on Wittig reaction with ethylidinephosphorane afforded *cis* olefin **13**. The Wacker oxidation of the non-terminal double bond of **13**, performed using $PdCl_2$–CuCl in O_2 took place regioselectively at the carbon atom further away from the ring due to the bulky Cbz group, delivering the keto product **14a**. The keto group of **14a** was converted to its acetal form to give **15** before reducing the *N*-Cbz group to *N*-methyl using LAH in refluxing THF to give **16**. The amine **16** thus formed was treated with HCl to afford the natural product (−)-hygrine **10** as the hydrochloride salt. Incidentally the first synthesis of (−)-norhygrine **11** which is usually found along with hygrine in nature, was carried out by selective deprotection of the Cbz group of **14a** by hydrogenation over Pd/C.

In a continuation of our interest using proline as a synthetic predecessor, we recently reported the total synthesis of tropane and sedum alkaloids namely (−)-hygrine **10**, (−)-norhygrine **11**, (−)-hygroline **17** and (−)-pseudohygroline **18** through Henry and Nef reactions (Scheme 5).[16] The aldehydes **12a–c** prepared from proline were subjected to Henry reaction using excess nitroethane and a catalytic amount of KOH in methanol to give diastereomeric mixtures of nitro aldol products which without separation on subsequent mesylation followed by treatment



Scheme 2 *Reagents and conditions*: (a) prenyl acetate, $TiCl_4$, 85%; (b) (i) KOH, (ii) −2e, CH_3OH, NaOMe (anodic oxidation), 52%; (c) LAH, THF, refux, 81%.



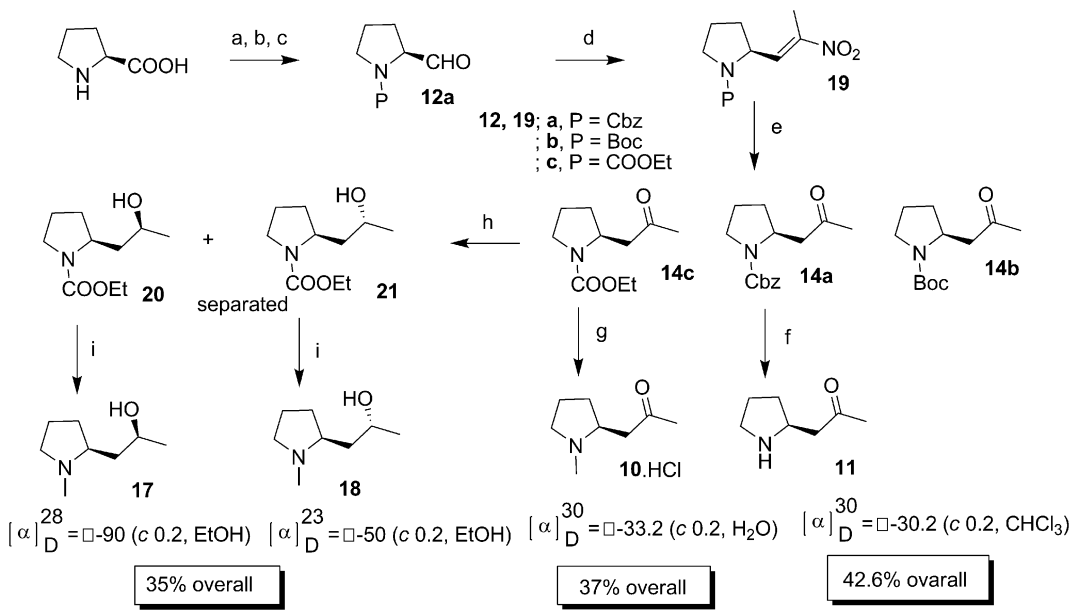
Scheme 4 *Reagents and conditions*: (a) (i) LAH, THF, reflux, 90%; (ii) CbzCl, K_2CO_3, CH_3CN, 85%; (iii) PCC, DCM, 70%; (b) ethyltriphenylphosphonium bromide, *n*-BuLi, Et_2O, 56%; (c) $PdCl_2$, CuCl, O_2, DMF–H_2O, 76%; (d) $HOCH_2CH_2OH$, *p*-TsOH, 82%; (e) LAH, THF, 66%; (f) 6 N HCl, THF, 73%: (g) H_2, Pd/C, EtOH, 81%.

with Et_3N, afforded nitro olefins **19a–c**. The pivotal Nef reaction was successfully performed using $NaBH_4$–MeOH–H_2O_2 and K_2CO_3 without racemisation to afford **14a–c**. The syntheses of aforementioned alkaloids were straightforwardly carried out by reduction of carbonyl and suitable deprotection and reduction of the protecting groups of **14a–c**. (−)-Norhygrine **11** was prepared by hydrogenolysis of the benzylcarbamate group of **14a** over Pd/C while synthesis of (−)-hygrine **10** was achieved starting from **14c** by LAH reduction followed by DMP oxidation. (−)-Hygroline **17** and (−)-pseudohygroline **18** were synthesized directly by reducing the ethyl carbamate group of **20** and **21** respectively using LAH.

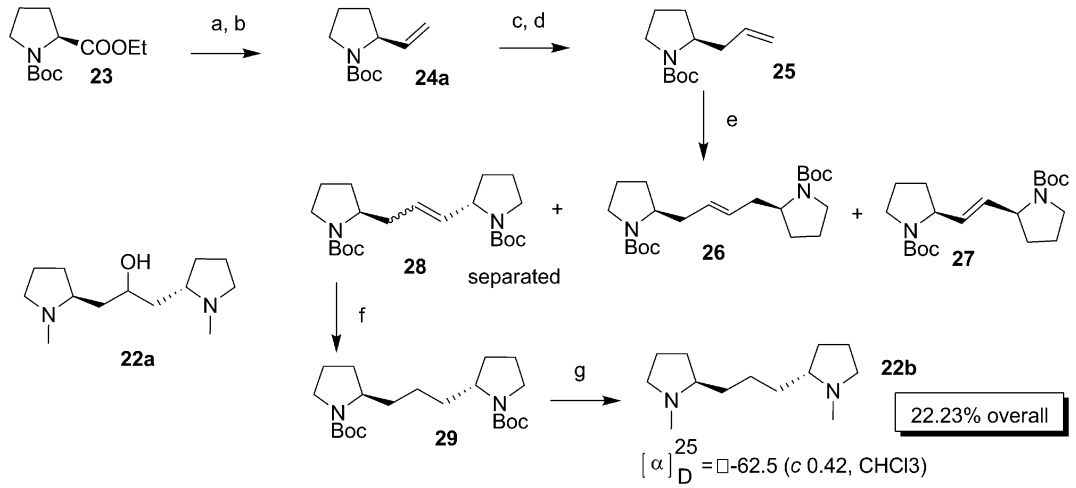
Another important pyrrolidine alkaloid (−)-dihydrocuscohygrine **22a** was isolated from *Erythroxylon coca* in 1981 by Turner.[17] Recently Yerri *et al.* synthesized (−)-deoxocuscohygrine **22b** using proline as a starting material employing cross metathesis as a key step (Scheme 6).[18] The commercially available *N*-Boc-proline ester **23** on reduction followed by Swern oxidation and Wittig olefination afforded **24a**. The alkene **24a** on hydroboration followed by subsequent oxidation and Wittig reaction produced the homologated alkene **25**, a key intermediate for metathesis. The cross metathesis of **25** and **24a** using Grubbs II catalyst resulted in the mixture of homodimers **26** and **27** along with an inseparable *cis* and *trans* mixture of required **28** in less yield. It was envisioned that the compound **24a** showed sluggish behaviour towards metathesis due to the presence of the bulky Boc group nearer to the olefin group and also the formation of the homodimer **26** was favoured due to its less reversibility. The formation of dimers was then minimised by reacting excess **25** (1.6 equiv.) with **24a**, furnishing the required product **28** in 69% yield along with dimer **26** (55% with respect to **27**). The product **28** was then separated and subjected to hydrogenation over Pd/C to give **29**, followed by LAH reduction to furnish (−)-deoxocuscohygrine **22b**.

2.3. Dolastatin: synthesis of dolaproine unit

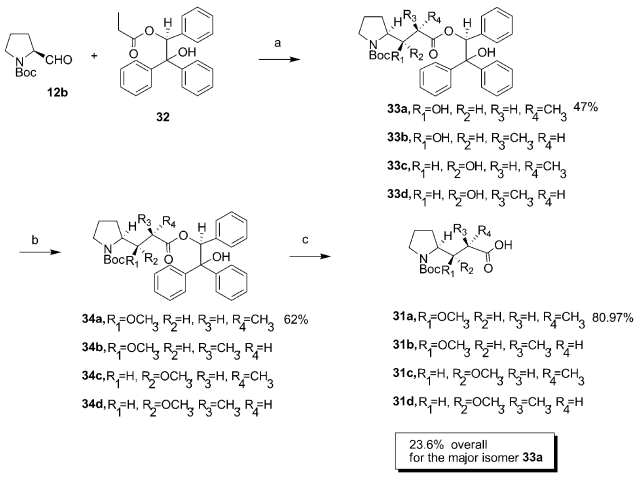
Dolastatin 10 is a marine natural product consisting of 8 chiral centres, isolated in 1984 by Petit *et al.* from the sea hare *Dolabella auricularia*.[19] After the elucidation of the structure in 1987, the first synthesis was reported by the same group in 1989.[20] The alkaloid has shown a remarkable antineoplastic activity and is under clinical trial for anticancer characteristics.[21] Dolastatin 10 is comprised of the 3-chiral centred β-methoxy-γ-amino acid, dolaproine (Dap) **30**. Most of the available reports approached



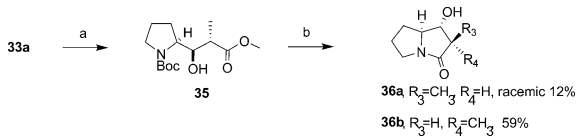
Scheme 5 *Reagents and conditions*: (a) LAH, THF, reflux, 8 h, 90%; (b) for P = −Cbz: Cbz–Cl, K_2CO_3, CH_3CN, 0 °C, 6 h, 95%; for P = −Boc: $(Boc)_2O$, Et_3N, DCM, 0 °C, 95%; for P = −COOEt: ClCOOEt, K_2CO_3, CH_3CN, 0 °C, 90%; (c) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 95%; (d) (i) $CH_3CH_2NO_2$, 2 mL of 3 N KOH, two drops of conc. H_2SO_4; (ii) $MeSO_2Cl$, Et_3N, DCM (85%, two steps); (e) $NaBH_4$, MeOH, K_2CO_3, H_2O_2, rt, 18 h (P = −Cbz, 65%; P = −Boc, 56%; P = −COOEt, 56%); (f) H_2, Pd/C, EtOH, 95%; (g) (i) LAH, THF, reflux; (ii) DMP, $NaHCO_3$, DCM, 90%; (h) $NaBH_4$–$Zn(BH_4)_2$–$LiAl(O^tBu)_3H$, 0 °C, 8 h, 95%; (i) LAH, THF, reflux, 6 h, 95%.



Scheme 6 *Reagents and conditions*: (a) LAH, THF, 0 °C to rt, 1 h, 95%; (b) (i) DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 1 h; (ii) $PPh_3{=}CH_2$, THF, −10 °C, 3 h (69% two steps); (c) $BH_3{\cdot}DMS$, THF, 0 °C, 2 h, 87%; (d) (i) DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 1 h; (ii) $PPh_3{=}CH_2$, THF, −10 °C, 3 h (70% two steps); (e) 10 mol% Grubbs II catalyst, DCM, 40 °C, 12 h, 69%; (f) H_2, Pd/C, MeOH, 2 h, 90%; (g) LAH, THF, reflux, 5 h, 77%.



Scheme 7 *Reagents and conditions*: (a) iPr_2NLi, $MgBr_2{\cdot}Et_2O$; (b) $(CH_3)_3OBF_4$, proton sponge; (c) H_2, 10% Pd/C.



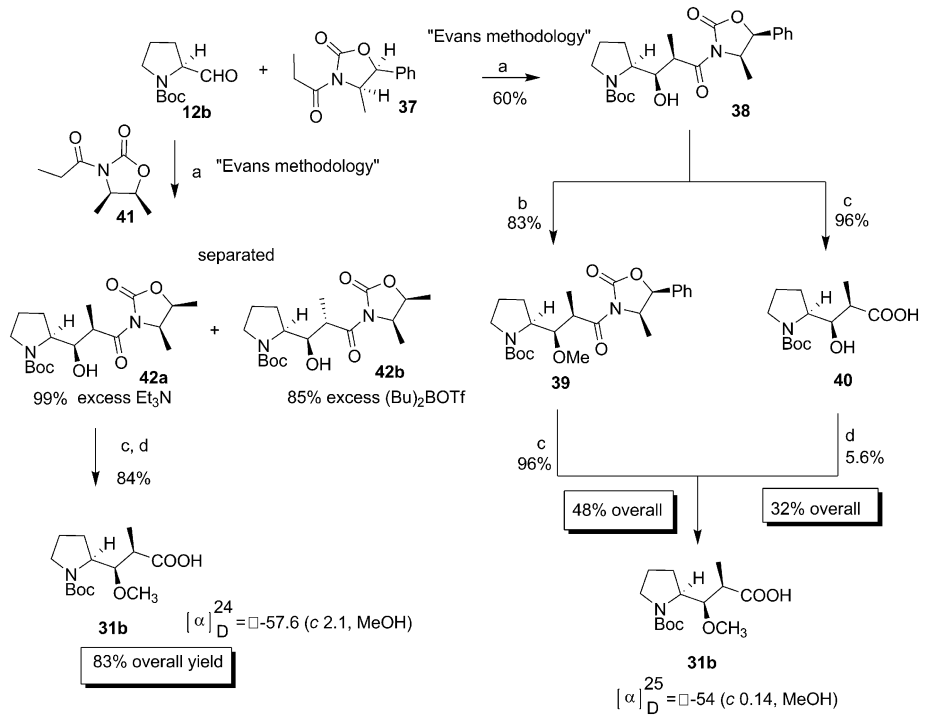
Scheme 8 *Reagents and conditions*: (a) (i) H_2–5% Pd/C, (ii) CH_2N_2; (67% for two steps); (b) (i) TFA, (ii) K_2CO_3 (71% for two steps).

the synthesis of dolastatin 10 through the synthesis of Dap **30** unit which can conveniently be accessed from proline.

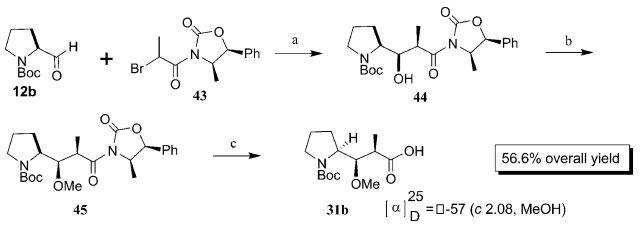
In continuation of isolation research on dolastatin 10, Petit *et al.* have synthesized the 4 isomers of Boc-Dap **31** unit through aldol condensation (Scheme 7).[22] The compound Boc-prolinal **12b** on aldol reaction with an enolate of chiral ester **32** using a strong base LDA in combination with $MgBr_2$ resulted in a mixture of diastereomers **33** separable by column chromatography. The compound **33** on treatment with $(CH_3)_3OBF_4$ afforded the methoxy compound **34** which on hydrogenolysis produced Boc-Dap isomers **31**. The configuration of the major isomer **31a** was confirmed by converting **33a** to the lactam **36** (Scheme 8) through ester **35** and systematic NMR studies. However the required isomer for the synthesis of dolaproine **30** was **33b**, found to be formed in low yield.

Petit *et al.* further improved the chiral synthesis of Dap **30**, enantioselectively and diastereoselectively through dibutyl boron triflate [$(Bu)_2BOTf$] mediated aldol condensation (Evans method) (Scheme 9).[23] The Boc-prolinal **12b** was treated with chiral oxazolidinone **37** in the presence of $(Bu)_2BOTf$ and Et_3N to furnish the compound **38** as a single diastereomer. The synthesis of the Boc-Dap **31b** was then achieved through two converging routes, either by methylation followed by hydrolysis of the chiral auxiliary (**38**–**39**–**31b**) or by hydrolysis of the chiral auxiliary followed by methylation (**38**–**40**–**31b**). In a similar way Hamada and co-workers approached the synthesis of dolastatin 10 by synthesizing using the intermediate *N*-Boc-Dap **31b**.[24] The reaction of Boc prolinal **12b** with chiral auxiliary **41** gave a separable mixture of isomers **42a** and **42b**. The compound **42a** was then converted to **31b** by hydrolysis of the chiral auxiliary followed by methylation. The configuration of the isomers was confirmed by converting them to known compounds and comparing with those reported. An interesting phenomenon was observed that only the *cis* isomer **42a** was formed with complete diastereoselection using slight excess Et_3N while the major *anti* product **42b** was formed when $(Bu)_2BOTf$ was used in excess. The required *cis* product **42a** was then converted to the dolaproine unit **31b** by hydrolysing the chiral auxiliary using LiOH and H_2O_2 and followed by methylation of –OH using MeI.

A few years later, Petit and Grealish once again succeeded in getting the required isomeric intermediate of Dap **30** in major amounts by carrying out stereoselective Reformatsky reaction assisted by a cobalt–phosphine complex (Scheme 10).[25] The reaction of the Boc protected prolinal **12b** with bromo amide **43**



Scheme 9 *Reagents and conditions*: (a) $(Bu)_2OTf$, Et_3N, −75 °C to rt; (b) $(CH)_3O^+BF_4^-$, proton sponge, 0 °C to rt, 46 h; (c) $LiOH–H_2O_2$, Na_2SO_3, 3 °C to rt, 16 h; (d) NaH, MeI, 0 °C, 48 h.



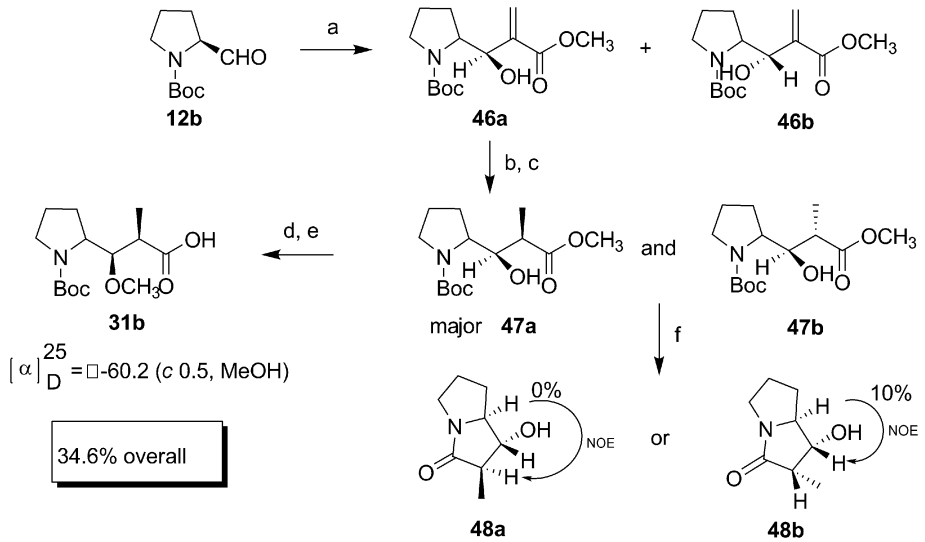
Scheme 10 *Reagents and conditions*: (a) $Co[P(PPh_3)_4]$, THF, 0 °C, 70%; (b) $BF_4O(CH_3)_3$, proton sponge, 4 Å MS, DCM, 86%; (c) LiOH, H_2O_2, 94%.

diastereoselectively led to **44**. The free –OH in **44** was methylated using trimethyloxonium tetrafluoroborate $BF_4O(CH_3)_3$ to give **45**. The chiral auxiliary unit was then hydrolysed using LiOH and H_2O_2 to furnish Boc-Dap **31b**.

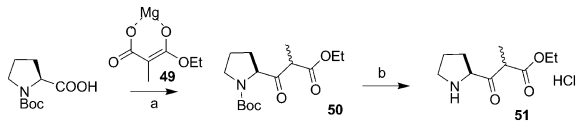
Almeida and Coelho have synthesized Boc-Dap **31b** by coupling *N*-Boc-prolinal **12b** and methyl acrylate through Baylis–Hillman reaction (Scheme 11)[26] in four steps with an overall yield of 27%. The Baylis–Hillman reaction was performed using ultrasound sonication, which without racemisation led to a mixture of diastereomers **46**, separable on column chromatography. The major isomer formed was predicted to be **46a** based on a Felkin–Ahn open-chain model which on hydrogenation afforded a mixture of isomers **47a** and **47b** in the ratio of 87 : 17. To determine the configuration of the chiral centres, the separated diastereomers of **47** were subjected to cylclisation to give lactam **48a** and **48b**, whose NOE study confirmed the formation of the required isomer in major amount. The further confirmation of the structure was done by converting **47a** to well known compound Boc-Dap **31b** by successful methylation of the hydroxyl group and hydrolysis of the ester group, which completed the formal synthesis of dolastatin 10.

Genet and co-workers approached the synthesis of dolastatin 10 *via* dynamic kinetic resolution (DKR) of **50** and **51** (Scheme 12) by performing an efficient catalytic asymmetric hydrogenation using Ru complexed with chiral ligands (Scheme 13).[27] The great discovery of manipulation of catalyst, temperature, solvent conditions and nature of protecting groups on N atom were studied for DKR of different amino substrates during the synthetic manoeuvring of γ-amino acids. For the synthesis of Boc-dap isomers, the Boc-protected and deprotected proline units showed remarkable changes in diastereoselectivity. *Anti* selectivity at the 2nd and 3rd positions was observed with unprotected proline unit **51** with Ru complexed ligands (*S*)-**52** and (*R*)-**52** to give **54a** and **54b**. The best selectivity was observed in pathway A. Surprising failure to achieve high *cis* selectivity turned attention to perform the reaction with a Boc protected unit **50**. The moderate *cis* selectivity was then achieved using (*S*)-**53** and (*R*)-**52** giving **55a** and **55b** respectively as major isomers by performing the hydrogenation under very high pressure and elongated reaction period. The product **55a** synthesized this way was efficiently transformed to Boc-dap **31** (Scheme 14) after separating it from minor isomers which on further synthetic conversion was eventually converted to dolastatin 10.

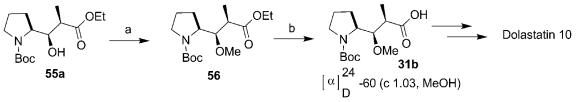
Cella *et al.* studied the diastereoselective addition of crotyl trifluoroborate salts on α-amino aldehydes and successfully synthesized Boc-dap **31b** in the presence of PTC (Bu_4NI) (Scheme 15).[28] The configuration of **57a** was confirmed by



Scheme 11 *Reagents and conditions*: (a) methyl acrylate, ultrasound sonication, 2–5 days, 70–75%; (b) H_2, 5% Pd/C; EtOAC, rt, 1 atmospheric pressure, 91% of a 83 : 17 diastereoisomeric mixture; (c) flash chromatographic separation (EtOAc–hexane 1 : 9; major isomer: 79% yield); (d) LiOH–THF, rt, 16 h, 87%; (e) Me_3OBF_4, DCM, proton sponge, rt, 18 h, 70%; (f) (i) CF_3CO_2H–DCM, 68%; (ii) K_2CO_3–MeOH, overnight (**47a** to **48a**: 82% yield; **47b** to **48b**: 71% yield).



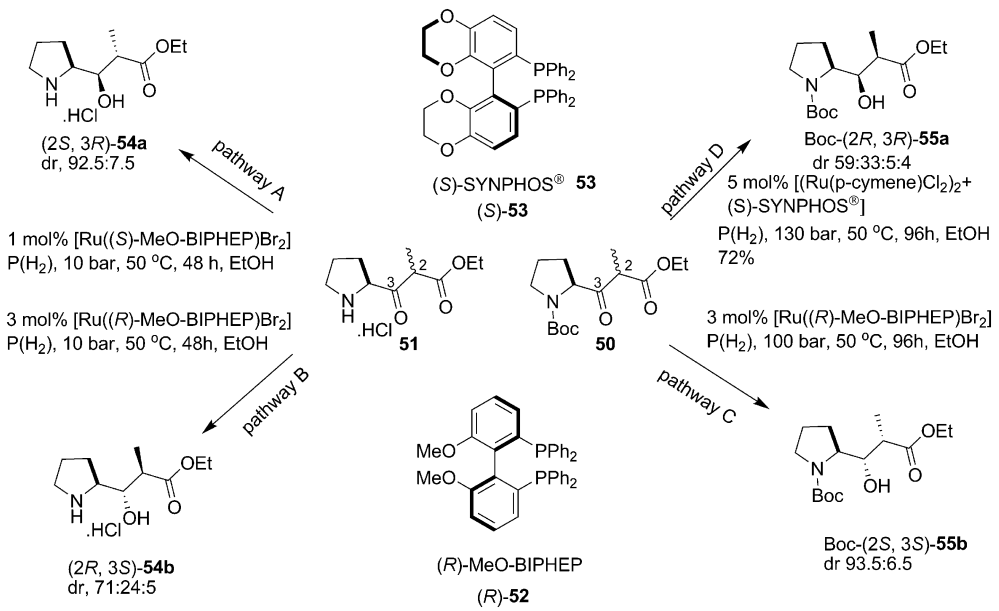
Scheme 12 *Reagents and conditions*: (a) (i) ImCOIm, THF, 0 °C–rt, 3 h; (ii) **49**, THF, Et_2O, −10 °C–rt, 4 days, (82% for two steps); (b) HCl gas, EtOH, 0 °C, 2 h.



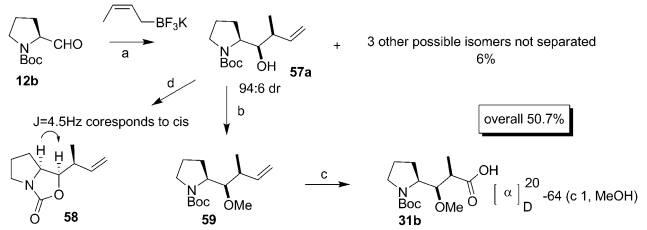
Scheme 14 *Reagents and conditions*: (a) LHMDS, HMPA, THF, −78 °C, 25 min, then MeOTf, −20 °C, 15 min, 45%; (b) LiOH, EtOH–H_2O, overnight, 59%.

converting it to **58** and measuring the proton coupling constant of vicinal protons. The compound **57a** was methylated and further converted to acid **31b** using RuO_2 which constituted the formal synthesis of dolastatin 10.

The work done by Poncet and co-workers involves the addition of crotyl boronate **61** to Boc-prolinal **12b** giving all the possible four isomers **57** with the requisite **57a** as a major



Scheme 13 Dynamic kinetic resolution by catalytic asymmetric hydrogenation.



Scheme 15 *Reagents and conditions*: (a) *n*-Bu_4NI (10 mol%), DCM–H_2O, 89%; (b) NaH, MeI, DMF, 76%; (c) RuO_2, CH_3CN–H_2O–$CHCl_3$, 75%; (d) NaH, THF, 90%.

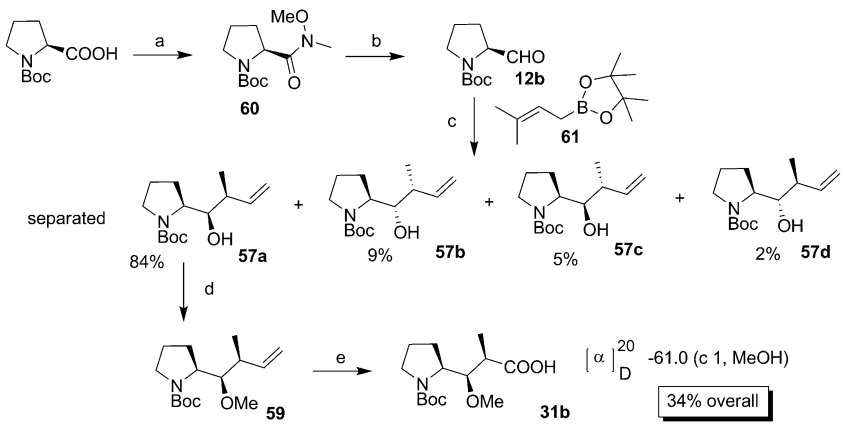
isomer.[29] The configuration of each isomer was determined by different experimentation. Compound **57a** on methylation and subsequent oxidation using RuO_2 afforded Boc-dap **31b** unit (Scheme 16).

A notable aldol condensation carried out by Koga and co-workers of boron enolate of thiophenyl propionate **62** with Boc prolinal **12b** afforded **63** as a major isomer along with other minor isomers (Scheme 17).[30] The compound **63** was then dethionated and esterified to give **55a** which on subsequent methylation and ester hydrolysis gave Boc-dap **31b.** The configuration of **56** was confirmed by preparing it from the known ester **64.**

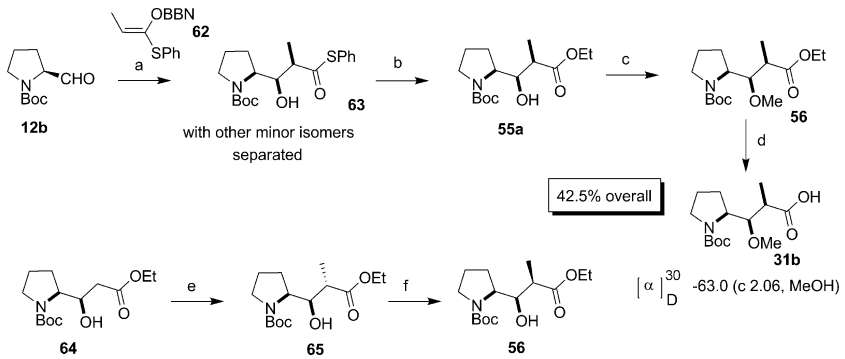
2.4. Miscellaneous examples

Jones and Woo confirmed the configuration of (−)-ruspolinone **66** as *S* by synthesizing it starting from *S*-proline methyl ester (Scheme 18).[31] The synthesis suggested that racemisation must have occurred during its isolation from the plant *Ruspolia hypercrateriformis*.[32] The NH of L-proline methyl ester on Boc protection afforded **67**. The ester group was selectively reduced to alcohol **68a** by LAH at a lower temperature and then tosylated to give **69.** The alkylation of anion of the dithiane protected 3,4-dimethoxybenzaldehyde **70** by compound **69** gave **71** in good yield. Further the removal of the dithiane group using NCS and $AgNO_3$ followed by deprotection of the Boc moiety using TFA afforded (−)-ruspolinone **66** as a pale yellow solid.

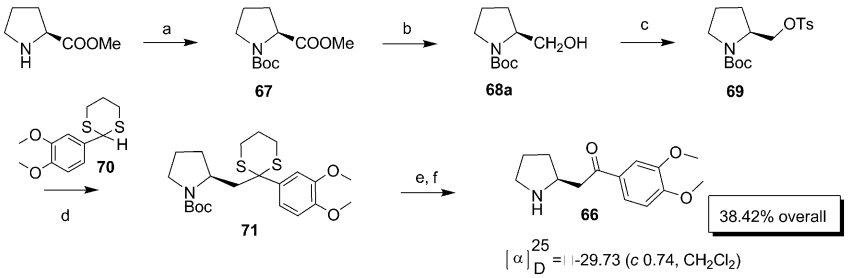
Jerrold Meinwald's group synthesized the defensive alkaloid 2-(12′-aminotridecyl)-pyrrolidine **80** (Scheme 19)[33] isolated from the Mexican bean beetle, *Epilachna varivestis.*[34] The Cbz-prolinol **72** on oxidation followed by Wittig reaction with phosphorane obtained from bromo compound **73** gave alkene **74** (*E* : *Z*/3 : 1). The acetal group was deprotected to give aldehyde **75** which on Grignard reaction with CH_3MgI gave an inseparable diastereomeric mixture of alcohol **76.** The alcoholic group of the mixture **76** was tosylated and reacted with NaN_3 to afford **78** which on reduction with H_2–Pd afforded an inseparable mixture of **79.** The separation of the isomers **79** was achieved by making



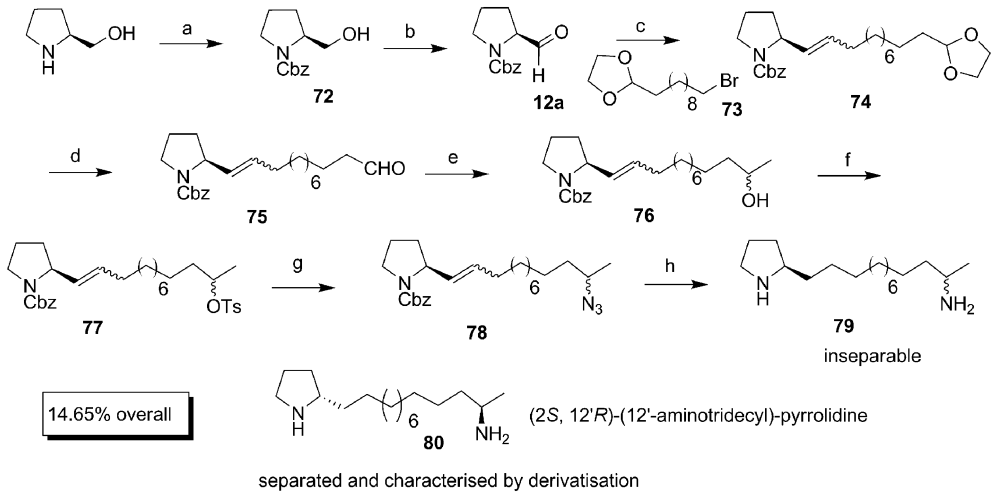
Scheme 16 *Reagents and conditions*: (a) MeNHOMe═HCl, BOP, DIEA, DCM, 82%; (b) LAH, THF, 89%; (c) **61**, THF, 64%; (d) NaH, MeI, DMF, 90%; (e) RuO_4, CCl_4, CH_3CN, H_2O, 81%.



Scheme 17 *Reagents and conditions*: (a) **62**, Et_2O, −20 °C, 64%; (b) K_2CO_3, EtOH, 88%; (c) LHMDS, MeOTf, HMPA–THF, 83%; (d) LiOH, aq. EtOH, 91%; (e) LDA, MeI, HMPA–THF, −78 °C to −20 °C, 2.5 h, 77%; (f) (i) LDA, THF, −20 °C, 1 h; (ii) MeOH, −78 °C (two steps 30%).



Scheme 18 *Reagents and conditions*: (a) $(Boc)_2O$, Et_3N, DMAP, DCM, rt, 18 h, 94%; (b) LAH, THF, 0 °C, 2 h, 90%; (c) TsCl, pyridine, DCM, rt, 4 h, 83%; (d) **70**, *n*-BuLi, −21 °C, 1 h, 76%; (e) NCS, $AgNO_3$, 2,6-lutidine, CH_3CN (80%), 1 h, 83%; (f) TFA, DCM, rt, 87%.

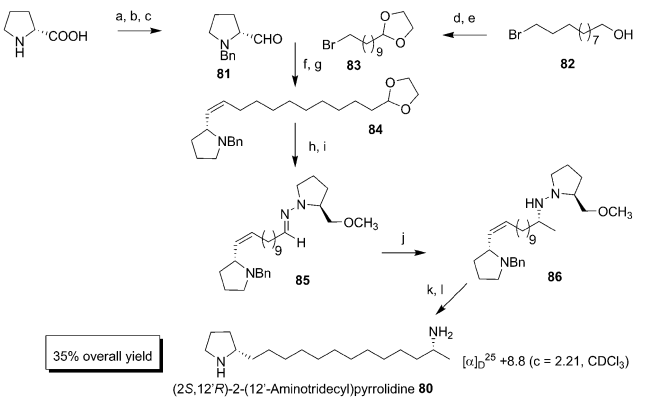


Scheme 19 *Reagents and conditions*: (a) $ClCOOCH_2Ph$–NaOH, THF, 25 °C, 20 h, 85%; (b) $(COCl)_2$, DMSO, TEA, −78 °C to 25 °C, 2 h, 95%; (c) (i) **73**, Ph_3P, CH_3CN, reflux, 60 h; (ii) *n*-BuLi, THF, −78 °C to 25 °C, 12 h; (iii) **12a**, THF, −78 °C to 25 °C, 12 h (53% three steps); (d) 1 M HCl, acetone, 25 °C, 6 h, 90%; (e) CH_3MgBr, ether, −30 °C to 25 °C, 68%; (f) TsCl, pyridine, 25 °C, 20 h, 70%; (g) NaN_3, DMF, 80 to 90 °C, 3 h, 94%; (h) H_2–Pd, THF, 25 °C, 4 h, 85%.

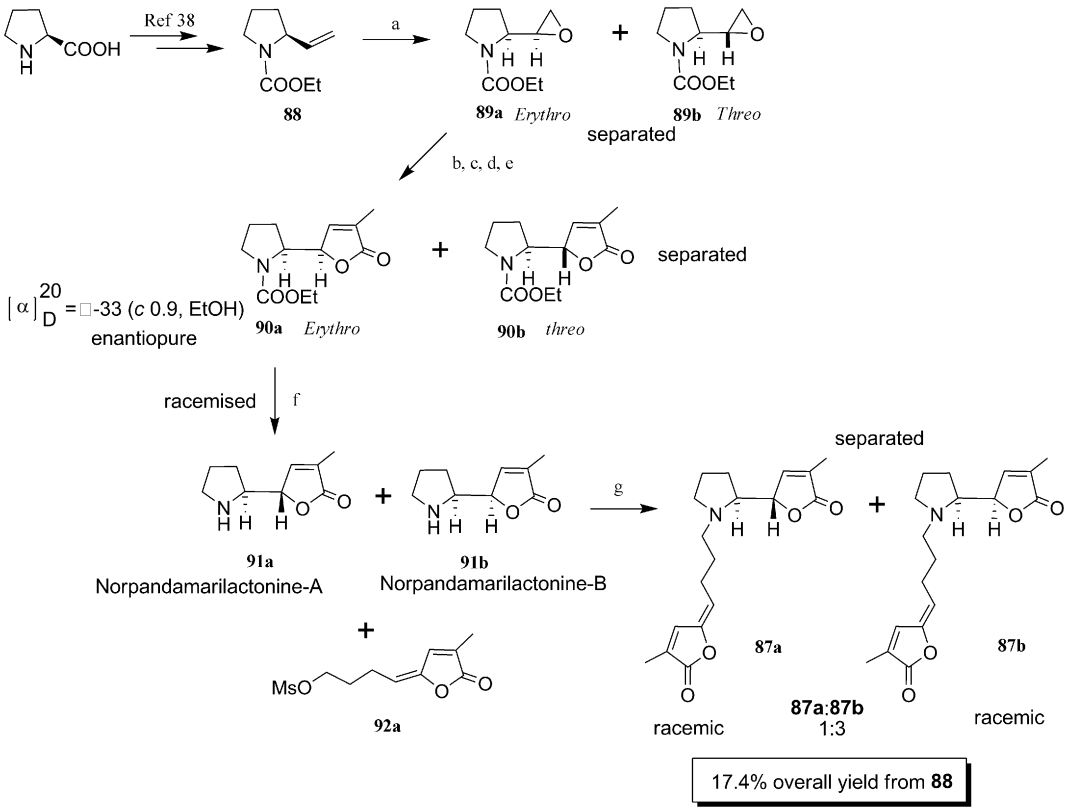
derivatives with additional chiral group attachment and further detail spectroscopic study revealed the structure of the naturally occurring compound as **80** with the configuration (2*S*,12′*R*).

Enders and co-workers encompassed the synthesis of **80** using their SAMP–hydrazone methodology[35] starting from (*R*)-proline (Scheme 20).[36] The Wittig product **84** prepared through classical synthetic steps was subjected to deprotection of the acetal followed by the trapping of the resultant aldehyde with (*S*)-1-amino-2-(methoxymethyl) pyrrolidine (SAMP) affording hydrazone **85**. The addition of methyl lithium across the nitrogen double bond took place highly diastereoselectively giving exclusively **86**. The further reduction of the double bond, benzyl deprotection and cleavage of the N–N bond afforded the natural product **80** in 35% overall yield and with high optical purity.

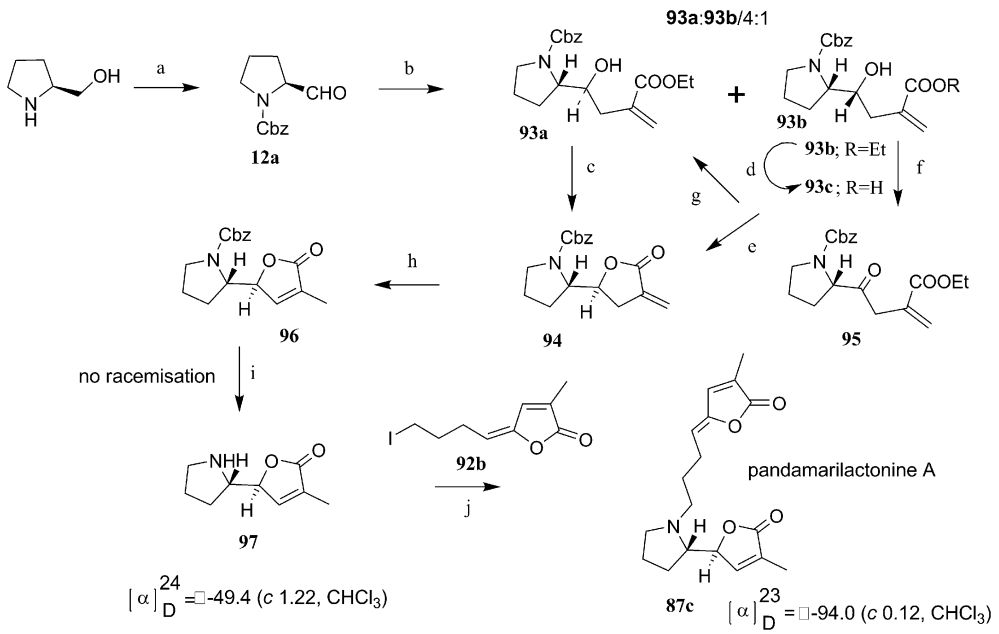
Blanco *et al.* performed studies on the configuration of the *Pandanus* alkaloids by attempting the synthesis of pandamarilactonines **87** (Scheme 21)[37] from L-proline. The requisite precursor **88** was prepared from proline according to the literature reports.[38] The alkene **88** was oxidised to oxiranes **89a** and **89b** (1.5 : 1) using MCPBA and were separated on column chromatography. The major *erythro* isomer **89a** was converted to *erythro* butenolide **90a** along with the



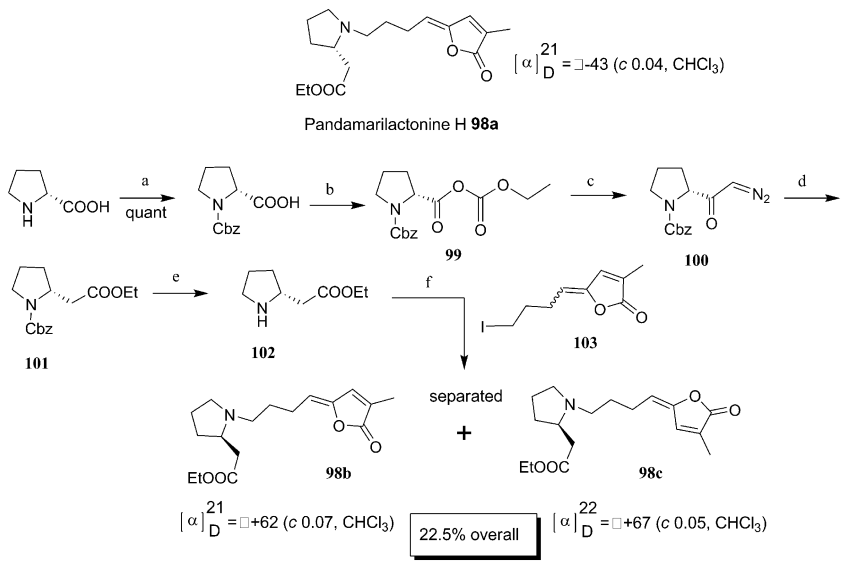
Scheme 20 *Reagents and conditions*: (a) BzCl, NaOH, H_2O, 0 °C, 2 h; (b) $LiAlH_4$, THF, reflux, 16 h; (c) $(COCl)_2$, DMSO, Et_3N, −40 to 25 °C, (78% for 3 steps); (d) $(COCl)_2$, DMSO, Et_3N, −78 to 25 °C; (e) $HOCH_2CH_2OH$, *p*-TsOH, toluene, reflux, 16 h, (96% for two steps); (f) **83**, Ph_3P, MeCN, reflux, 72 h; (g) *t*-BuLi–THF, −78 to 25 °C, 2 h; **81**, THF, −78 to 25 °C, 15 h, (80% for two steps); (h) 1 M HCl, acetone, 25 °C, 14 h; (i) SAMP, 0 to 25 °C, 30 min, (98% for two steps); (j) MeLi, THF, −78 to 25 °C, 15 h, 94%; (k) H_2–$Pd(OH)_2$-C, MeOH, 25 °C, 6 h; (l) BH_3·THF (excess), reflux, 4 h, (61% for two steps).



Scheme 21 *Reagents and conditions*: (a) MCPBA, $CHCl_3$, rt, 24 h, 77%; (b) separation of diastereoisomers; (c) $PhSeCH(CH_3)CO_2H$, LDA (2 equiv.), THF, 0 °C to rt, 1.5 h; (d) AcOH, THF, reflux, 16 h; (e) H_2O_2, AcOH, 0 °C, 45 min, 61% from **89a**; (f) TMSI, $CHCl_3$, reflux, 5 h, 84%; (g) **92a**, pyridine, DMF, 60 °C, 3 days, 44%.

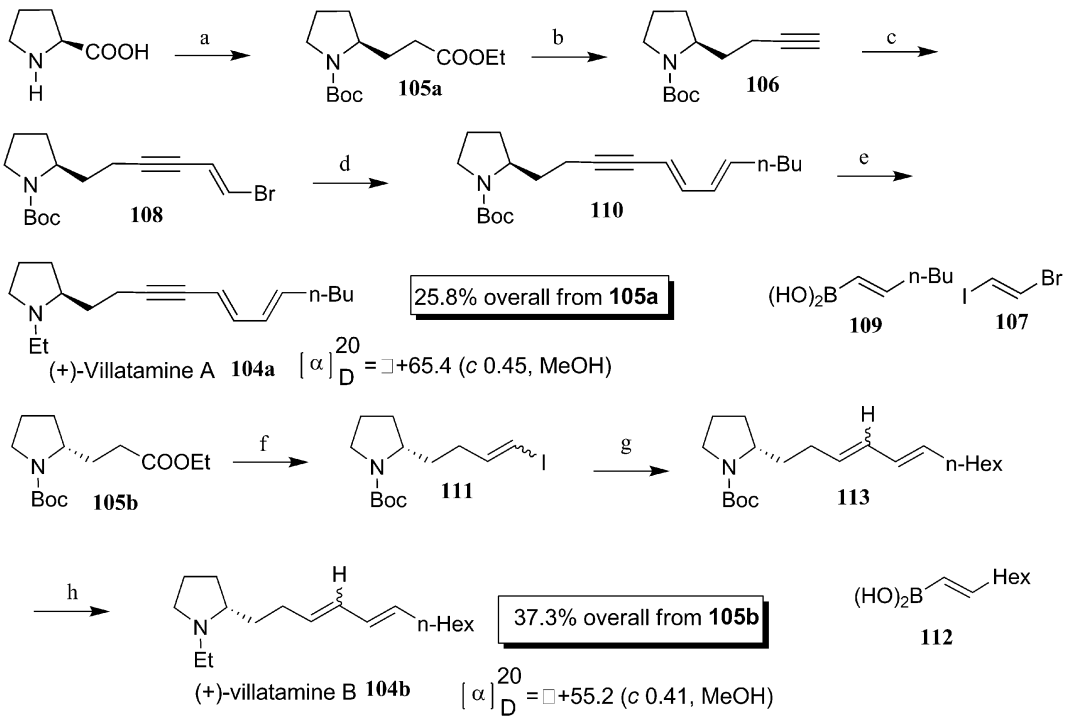


Scheme 22 *Reagents and conditions*: (a) (i) CbzCl, K_2CO_3, CH_3CN; (ii) Swern oxidation (91% two steps); (b) ethyl 2-(bromomethyl)acrylate, 2 equiv. Zn, THF–aq. satd NH_4Cl or 1.1 equiv. indium, aq. EtOH; (c) TFA, DCM, rt, 90%; (d) LiOH, aq. THF, quant.; (e) DTAD, PPh_3, THF, rt; (f) DMP, DCM, rt, quant.; (g) $NaBH_4$, MeOH, −20 °C, 86%; (h) 5 mol% Et_3SiH, 10 mol% $Rh(PPh_3)_3Cl$, toluene, reflux, 86%; (i) TMSI, CH_3CN, −15 °C, quant.; (j) Ag_2CO_3, CH_3CN, rt.

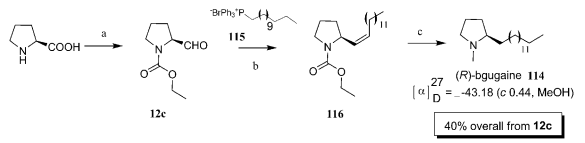


Scheme 23 *Reagents and conditions*: (a) ref. 40 quant.; (b) $ClCOOCH_2CH_3$, Et_3N, THF, −25 °C, 30 min, 71%; (c) $TMSCHN_2$, CH_3CN, 0 °C to rt, 6–19 h, 86%; (d) MeOH, $C_6H_5CO_2Ag$, Et_3N, sonication, 1 h, 83%; (e) H_2 (balloon), 10% Pd/C, MeOH, rt, 1 h, 78%; (f) Ag_2CO_3, CH_3CN, rt, 36 h, 57%.

formation of *threo* **90b** by reacting with the dianion of 2-phenylselenopropionic acid followed by lactonization and oxidation of the selenide group with consequent elimination. The selective deprotection of the carbamate group of enantiopure **90a** using TMSI in CH_3CN resulted in concomitant epimerization and racemisation to furnish two norpandamarilactonines **91a** and **91b**, each of them with a very low optical activity, separable by column chromatography. Further the 1 : 1 mixture of **91a** and **91b** was treated with mesylate **92a** in pyridine resulting in the separable mixture of **87a** and **87b** but with complete racemisation.



Scheme 24 *Reagents and conditions*: (a) ref. 44; (b) (i) DIBAL-H, toluene, −78 °C; (ii) $AcCH_2P(O)(OMe)_2$, TsN_3, K_2CO_3, CH_3CN, MeOH, rt; (63% for 2 steps); (c) *n*-BuLi, THF, −78 °C; $ZnBr_2$, −78 °C; **107**, $Pd(PPh_3)_4$, THF, rt; (d) **109**, $Pd(PPh_3)_4$, KOH, H_2O, THF, 60 °C, (66% for two steps); (e) (i) *p*-TSA, MeCN, rt; (ii) CH_3CHO, HCl, MeOH, $Na(OAc)_3BH$, rt; (62% for two steps); (f) (i) DIBAL-H, toluene, −78 °C; (ii) $CrCl_2$, CHI_3, THF, dioxane, 0 °C–rt; (65% for two steps); (g) **112**, $Pd(PPh_3)_4$, KOH, H_2O, THF, 60 °C, 91%; (h) (i) TSA, MeCN, rt; (ii) CH_3CHO, HCl, MeOH, $Na(OAc)_3BH$, rt, (63% for two steps).

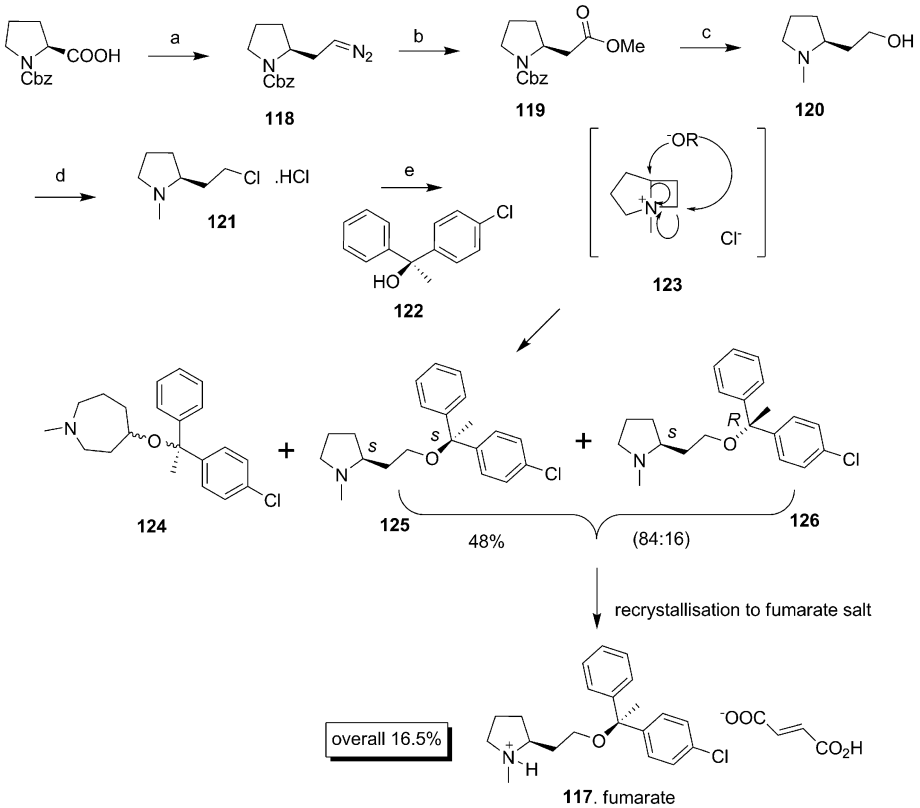


Scheme 25 *Reagents and conditions*: (a) ref. 46; (b) *n*-BuLi, THF, **115**, 0 °C to rt, 50%; (c) (i) H_2–Pd (C), EtOH; (ii) LAH, THF, reflux, 80%.

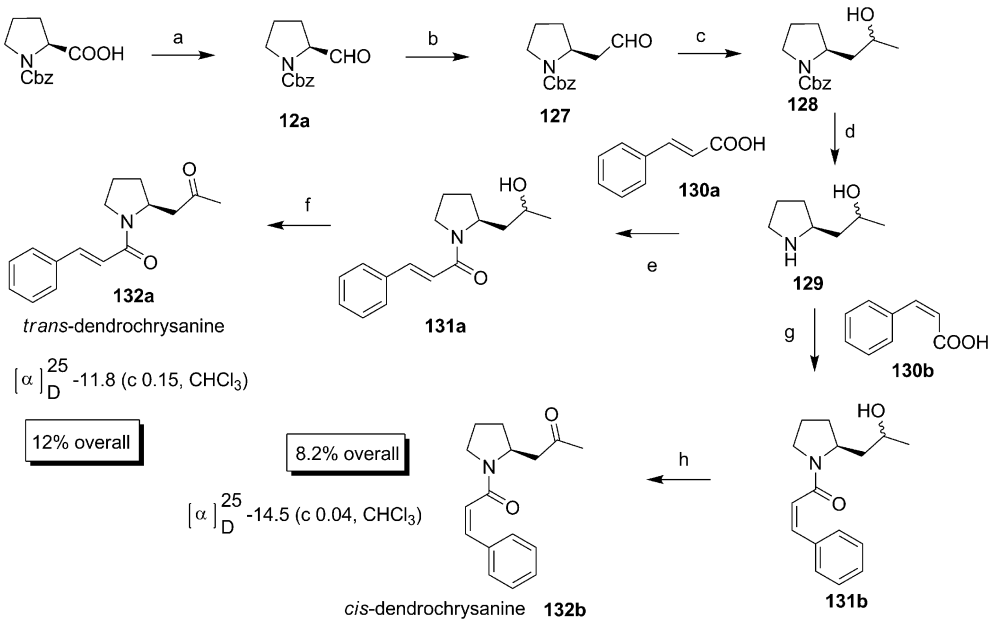
Takayama *et al.* achieved the synthesis of enantiomerically pure pandamarilactonine A **87c** (Scheme 22).[39] The synthesis commenced with Zn metallated Reformatsky reaction on Cbz protected prolinal **12a** which led to two diastereomers *threo* **93a** and *erythro* **93b** in the ratio of 4 : 1. The *erythro* **93b** isomer with unwanted stereochemistry was converted to requisite *threo* **94** either by converting the ester group of *erythro* **93b** to acid **93c** followed by intramolecular Mitsunobu reaction or by oxidising the secondary alcoholic group of *erythro* **93b** to ketone **95** using DMP followed by reduction and cyclisation. The *exo* to *endo* isomerisation of the double bond of **94** was performed using Et_3SiH (5 mol%) and tris(triphenylphosphine) rhodium chloride (10 mol%) in refluxing toluene giving α-methyl butenolide **96**. The relative stereochemistry was established using X-ray analysis. The Cbz group was selectively removed using TMSI in CH_3CN at −15 °C to give **97** maintaining the integrity of the chiral centres. The total synthesis was then achieved by coupling the amine **97** with iodo compound **92b** to afford pure pandamarilactonine A **87c** after purification. The authors speculated the reasons for the racemisation during isolation due to acidic or basic conditions and in nature it is not observed due to the participation of enzymes.

Takayama and co-workers isolated another new alkaloid pandamarilactonine-H **98a** from the roots of *Pandanus amaryllifolius.* The systematic structure elucidation was done by different spectroscopic techniques and first total synthesis of its enantiomer **98b** starting from D-proline (Scheme 23).[41] The synthesis initiated with Cbz protected D-proline converted to anhydride **99** using ethylchloroformate and Et_3N. The anhydride **99** on Arndt–Eistert reaction using trimethylsilyldiazomethane in CH_3CN afforded α-diazoketone **100** which was subjected to homologation *via* Wolf rearrangement using silver benzoate to afford **101**. The Cbz group hydrogenolysed giving **102** and further, NH was alkylated with 3 : 2 (*Z*/*E*) mixtures of iodo compound **103** to afford a mixture of diastereomers **98b** and **98c** separable on column purification. The detail spectroscopic analysis unambiguously concluded the configuration as C14-*R* for both the isomers **98b** and **98c** synthesized. The opposite optical activity of the synthesized isomer was compared to the natural product and confirmed the *S* configuration for the natural product.

Zhai and co-workers undertook an expeditious synthesis of two marine natural products villatamines A **104a** and villatamines B **104b** (Scheme 24),[42] isolated from the extract of the flatworm *Prostheceraeus vittatus*,[43] using proline as a starting material and confirmed the (*S*) configuration for the naturally



Scheme 26 *Reagents and conditions*: (a) (i) $(COCl)_2$, DMF, DCM, 0 °C, 2 h; (ii) Me_3SiCHN_2, Et_3N, THF, CH_3CN, 0 °C, 5 h (80% two steps); (b) AgOBz, Et_3N, MeOH, rt, 3 h, 78%; (c) LAH, THF, 45 °C, 45 min, 60%; (d) $SOCl_2$, $CHCl_3$, 60 °C, 2 h, 92%; (e) **122**, NaH, PhMe, 110 °C, 16 h.



Scheme 27 *Reagents and conditions*: (a) (i) MeI, K_2CO_3, DMF; (ii) LAH, Et_2O; (iii) SO_3–pyridine, Et_3N, DMSO; (30% for three steps); (b) $Cl^-PPh_3{}^+CH_2OMe$, KO^{t}Bu, THF then 1 N HCl, THF, 63%; (c) MeMgI, Et_2O, 79%; (d) HCO_2NH_4, Pd–C, MeOH; (e) HATU, HOAt, iPr_2EtN, DCM, 85%; (f) Jones reagent, acetone, 95%; (g) PyBOP, iPr_2EtN, DCM, 75%; (h) DMP, DCM, 73%.

occurring isomers. The useful intermediate **105a** was successfully prepared from proline according to the reported procedure.[44] The compound **105a** was reduced using DIBAL and subsequently converted to the terminal alkyne **106** by treating with Bestmann reagent prepared *in situ*.

The compound **106** on Zn metallation followed by Pd $(PPh_3)_4$-catalyzed Negishi coupling with **107** produced bromoenyne **108** which on subsequent Suzuki coupling with **109** afforded **110**. Finally the Boc group was deprotected using *p*-TSA in CH_3CN and the free NH was ethylated using reductive amination with CH_3CHO in the presence of $NaBH(OAc)_3$ to afford the natural product villatamine A **104a**.

For the synthesis of another isomer, the DIBAL reduced product of **105b** was subjected to Takai olefination to afford alkenyl iodide **111** which on Suzuki coupling with **112** produced the conjugated alkene compound **113**. The synthesis of villatamine B **104b** was then completed by deprotection of the Boc group followed by ethylation of the free NH as had been done earlier.

A short synthesis of 2-substituted pyrrolidine alkaloid, (*R*)-bgugaine **114** was achieved in our laboratory starting from L-proline using the existing (*S*) chiral centre (Scheme 25).[45] The Wittig condensation of **12c**[46] with *in situ* prepared phosphorane of **115** gave the olefin **116** which on hydrogenation followed by LAH reduction afforded the natural product (*R*)-bgugaine **114**.

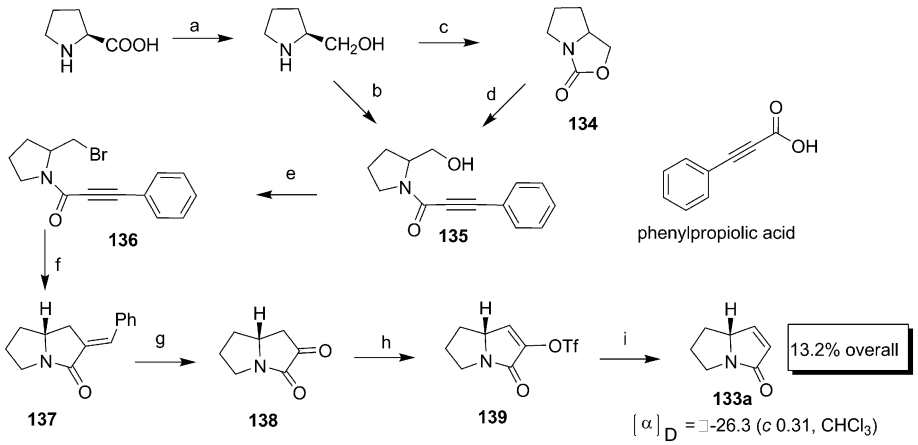
Clayden and co-workers introduced a short and concise synthesis of (−)-(*S*,*S*)-clemastine **117** by using **121** prepared by 1-carbon homologation of Cbz-proline through Arndt–Eistert method (Scheme 26).[47] The compound **119** was converted to the requisite chloro compound **121** by LAH reduction of the benzylcarbamate followed by treatment with $SOCl_2$. The labile compound **121** was immediately reacted with **122** to give a mixture of isomers **124**, **125** and **126**. After several experiments the mixture of **125** and **126** was successfully separated by transforming them to fumerates and by recrystallisation to give enentiomerically pure **117**.

Konno and co-workers synthesized *trans* and *cis* dendrochrysanine **132**,[48] Chinese traditional medicines, isolated by Wang and co-workers in 2005 from the stems of *Dendrobium chrysanthum*.[49] The synthetic strategy utilized the homologated Cbz-protected prolinal **127** synthesized from L-proline through conventional synthetic sequences. The aldehyde **127** on Grignard reaction followed by Cbz deprotection and subsequent condensation with *trans*-cinnamic acid and oxidation of the secondary alcoholic unit using Jones oxidation afforded *trans*-dendrochrysanine **132a**. Similarly treatment of alcohol **129** with *cis*-cinnamic acid and further conversion gave *cis*-dendrochrysanine **132b** (Scheme 27).

3. Synthesis of pyrrolizidine alkaloids

3.1. Introduction

Pyrrolizidine alkaloids (PAs) bearing an azabicyclic [3,3,0] octane structural motif, are a large family of natural products endowed with vast array of pharmacological and biological properties.[50] These alkaloids are generally isolated from flowering and leguminous plants while few have been found in frogs, moths, ants and butterflies.[51] The vast range of alkaloids ranging from simple to highly substituted have been found in nature. Manifolds of polyhydroxy PAs are used as potential sugar mimics and have been extensively studied for their potent glycosidase inhibitory activities, making them good candidates as new drugs for the treatment of several diseases like cancer, viral infections and diabetes.[52] Proline can contribute to the synthesis of PAs with suitable transformation on the 2nd position and subsequent 5 member cyclisation with amino group.



Scheme 28 *Reagents and conditions*: (a) LAH, THF, reflux, 71%; (b) phenylpropiolic acid, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (WSC), Et_3N, DCM, rt, overnight, 76%; (c) $(OEt)_2CO$, K_2CO_3, 120–130 °C, 70%; (d) phenylacetylene, *n*-BuLi, THF, −78 °C, 88%; (e) NBS, PPh_3, DCM, 0 °C to rt, 3 h, 86%; (f) SmI_2, HMPA, THF, 0 °C, 1 h, 90%; (g) O_3, Me_2S, MeOH–DCM, −78 °C, 94%; (h) Tf_2O, Pr_2EtN, 50%; (i) $Pd(PPh_3)_4$, LiCl, Bu_3SnH, 83%.

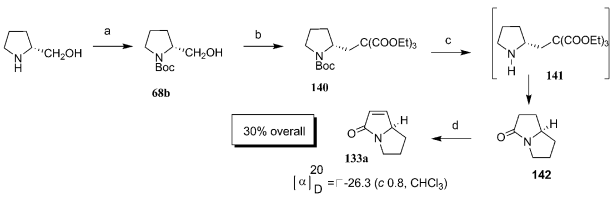
3.2. Unsubstituted pyrrolizidines

The simplest unsubstituted naturally occurring pyrrolizidine alkaloid is pyrrolam, though structurally a pyrolizidinone, included in the class of pyrrolizidine alkaloids. Pyrrolam was isolated in 1990 from *Streptomyces olivaceus*[53] in 4 different structurally related pyrrolizidinone forms, pyarrolam A–D. Of these pyrrolam A attracted considerable attention due to its biological activities and the presence of a double bond responsible for its carcinogenic and mutagenic nature.[54] Pyrrolam A, a labile alkaloid, has been synthesized in six different ways starting from proline.

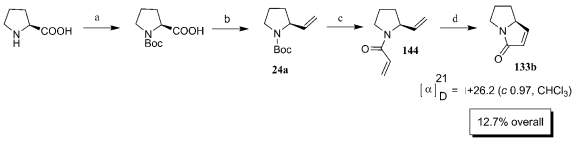
The first synthesis of (*R*)-pyrrolam (A) **133a** was achieved by Yuhara and co-workers (Scheme 28) through an intramolecular coupling reaction between a bromoalkyl and ynamide group, assisted by SmI_2.[55] Initially the (*R*)-proline was reduced with LAH to prolinol and further converted to **135** either by condensing with phenylpropiolic acid or by converting first to the cyclic carbamate **134** and then reacting with lithiumphenylacetylide. The major precursor bromo compound **136** was prepared by reacting alcohol **135** with NBS and PPh_3. The SmI_2 intramolecular cyclization was then best achieved using the additive HMPA at 0 °C to afford the *exo*-cyclic compound **137**. The olefinic part of **137** was ozonolysed to afford the diketo compound **138** which was further converted to triflate **139**. The triflate **139** was subsequently hydrogenolysed using Bu_3SnH to afford pyrrolam (A) **133a**.

The synthesis of enantiomerically pure (−)-pyrrolam A **133a** was accomplished by Giovenzana *et al.* in six steps starting from (*R*)-prolinol with an overall yield of 30% (Scheme 29).[56] The Boc protected prolinol **68b** was converted to **140** by Mitsunobu dehydrative alkylation protocol. The deprotection of Boc group, triester hydrolysis and cycloamidation were carried out in an one-pot manner without isolating the intermediate to furnish the lactam **142**. The installation of the double bond regioselectively by treatment with PhSeCl in the presence of strong base LDA followed by oxidation with H_2O_2 afforded pyrrolam A **133a**.

(+)-Pyrrolam A **133b** was successfully synthesized by Arisawa *et al.* using RCM as a key step (Scheme 30).[57] The strategy



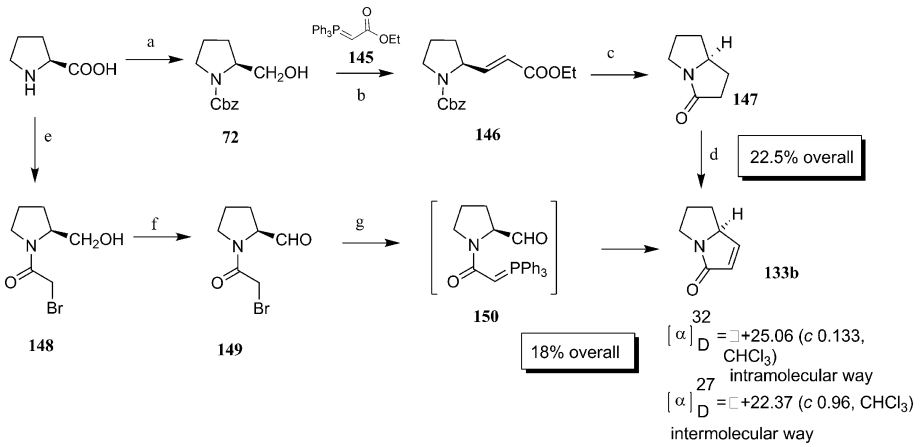
Scheme 29 *Reagents and conditions*: (a) BOC-ON®, DCM, rt; (b) TEMT, TPP, DEAD, Et_2O, rt (58% for two steps); (c) (i) TFA, DCM, rt; (ii) 12 N HC1, reflux; (iii) (i) HMDS, TMSCl (cat.), MeCN, reflux (57% for three steps); (d) LDA, THF (−78 °C), PhSeCl, then H_2O_2, THF, 0 °C.



Scheme 30 *Reagents and conditions*: (a) NaOH, $(Boc)_2O$, dioxane, 79%; (b) (i) K_2CO_3, MeI, DMF, 96%; (ii) DIBAL, toluene, −78 °C, 93%; (iii) $KN(TMS)_2$, $Ph_3PCH_3^+Br^-$, THF, 73%; (c) (i) TFA, DCM; (ii) CH_3CH_2═CHCOCl, (82% for two steps); (d) Grubbs II catalyst (0.002 M), benzene, 50 °C, 30%.

utilized the Boc-proline converted to alkene **24a** by classical synthetic steps. The TFA mediated deprotection of Boc group of **24a** and concomitant amidation with methyl acryloyl chloride gave the key intermediate **144**. RCM was then successfully performed using Grubbs II catalyst by stirring it for 3 h in benzene at 50 °C affording the pyrrolam A **133b** in 30% yield. The low yield was observed due to the instability of the product **133b** under the reaction conditions.

Two synthetic routes for (*S*)-pyrrolam A **133b** were developed in our lab by Majik *et al.* through intramolecular and intermolecular Wittig reaction using L-proline as a chiral source

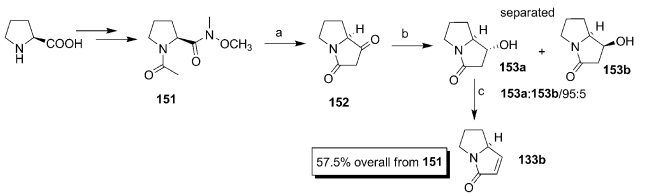


Scheme 31 *Reagents and conditions*: (a) (i) LAH, THF, reflux; (ii) CbzCl, K_2CO_3, CH_3CN, 0 °C to rt, 6 h; 72% (2 steps) (b) PCC, NaOAc, DCM, **145**, 7 h, 76%; (c) H_2, Pd/C, 10 h, rt, 67%; (d) (i) LDA, PheSeCl, 66%; (ii) H_2O_2, NaOH, 93%; (e) NaOAc, $ClCOCH_2Br$, acetone–water, 0 °C, 2 h, 65%; (f) PCC, DCM, 8 h, 68%; (g) (i) PPh_3, benzene, rt, overnight; (ii) NaH, THF, 14 h, 41% (2 steps).

(Scheme 31).[58] For the intermolecular route, alkene **146** was prepared by an one-pot oxidation and Wittig reaction of Cbz-prolinol **72** with phosphorane **145**. The concomitant deprotection of the Cbz group and reduction of the double bond afforded the cyclized product **147**. The required double bond was regioselectively established by treatment of **147** with PhSeCl and H_2O_2 to render the alkaloid pyrrolam A **133b**. The intramolecular version was achieved by converting the prolinol to acetyl bromide protected **148** followed by oxidation with PCC to afford aldehyde **149**. The further treatment with PPh_3 followed by *in situ* condensation of phosphorane **150** afforded pyrrolam A **133b**.

An approach made by Murray and Proctor[59] involved cyclization of Weinreb amide **151**, prepared from L-proline, to dione **152**. The compound **152** on diastereoselective reduction with $NaBH_4$ provided the alcohol **153** as a separable diastereomeric mixture of **153a** and **153b** (95 : 5). The compound **153a** on mesylation followed by treatment with Et_3N installed the double bond regioselectively to afford pyrrolam A **133b** (Scheme 32).

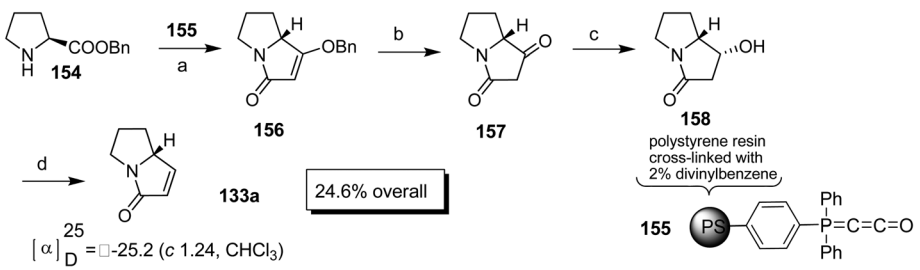
The strategy developed by Schobert *et al.*[60] involves the reaction of proline derived benzyl prolinate **154** with the polymer supported cumulated ylide **155** to give the corresponding amide **156**. The hydrogenolytic debenzylation of **156** gave the dicarbonyl key intermediate **157** which on subsequent reduction gave alcohol **158**. The mesylation of **158** followed by elimination established the double bond to afford pyrrolam **133a** (Scheme 33).



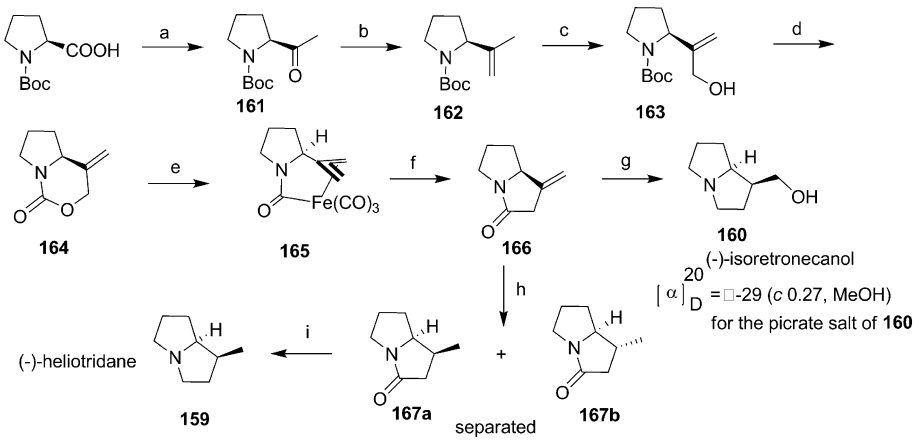
Scheme 32 *Reagents and conditions*: (a) LDA or LHMDS, THF, −78 °C; (b) $NaBH_4$, EtOH, rt, 24 h, (69% for two steps); (c) (i) MsCl, Et_3N, DCM, 0 °C–rt, 5 h, 85%; (ii) Et_3N, $CHCl_3$, reflux, 5 h, 98%.

3.3. Simple substituted pyrrolizidines

The synthesis of methyl substituted pyrrolizidine alkaloids (−)-heliotridane **159** and (−)-isoretronecanol **160** was successfully accomplished by Knight and Ley using commercially available (*S*)-*N*-Boc proline (Scheme 34).[61] The Boc-proline was converted to the keto compound **161** through the formation of Weinreb amide followed by Grignard reaction with MeMgI. The keto compound **161** on Wittig reaction with $CH_2{=}PPh_3$ afforded the alkenated product **162**. The hydroxyl product **163** was prepared by SeO_2 oxidation of **162** which on subsequent Boc



Scheme 33 *Reagents and conditions*: (a) **155**, THF, 60 °C, 16 h, 80%; (b) Pd/C, H_2, MeOH, rt, 2 h, 99%; (c) $NaBH_4$ (2.0 equiv.), DCM–AcOH (9 : 1), 0 °C, 1 h, 53% (dr 93 : 7); (d) (i) MsCl, Et_3N, DCM, rt, 16 h, 90%; (ii) Et_3N, DCM, 40 °C, 18 h, 65%.



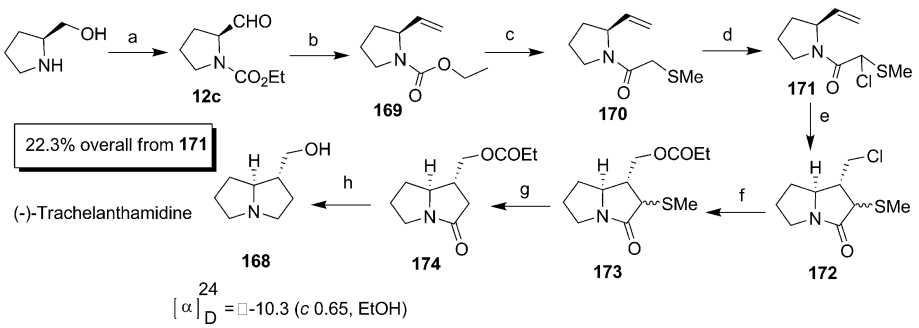
Scheme 34 *Reagents and conditions*: (a) (i) CDI, THF, rt, 1 h; (MeO)MeNH·HCl, 24 h, 98%; (ii) MeMgCl (3.0 equiv.), THF, 0 °C–rt, 16 h, 91%; (b) $Ph_3P{=}CH_2$ (2.0 equiv.), Et_2O, 0 °C, 2 h, 98%; (c) (i) SeO_2, *t*-BuOOH, DCM, 35 °C, 4 h, 58%; (d) (i) HCl, $CHCl_3$, rt, 15 min, 100%; (ii) MeOCOCl, Et_3N, DCM, rt, 4 h; NaH, PhMe, rt, 2 h, 60%; (e) $Fe_2(CO)_9$, benzene, sonication, 4 h, 98%; (f) CO (305 atm), benzene, 105 °C, 48 h, 80%; (g) BH_3·THF, reflux, 1.5 h; NaOH, H_2O_2, 1 h; HCl, MeOH, reflux, 2 h; (h) H_2, 10% Pd/C, EtOAc, rt, 16 h, 73%; (i) LAH.

deprotection of NH and reaction with CH_3COCl produced the cyclic compound **164**. The key intermediate **166** was synthesized by converting **164** to π-allyltricarbonyliron lactam complex **165** by reacting with diiron nonacarbonyl in benzene under ultrasonication followed by the exhaustive carbonylation under high pressure. The (−)-isoretronecanol **160** was synthesized from **166** by reduction of amide and hydroxylation of alkene using borane. The intermediate **166** was hydrogenated to produce the separable diastereomers **167a** and **167b** from which **167a** upon LAH reduction afforded the natural product (−)-heliotridane **159**.

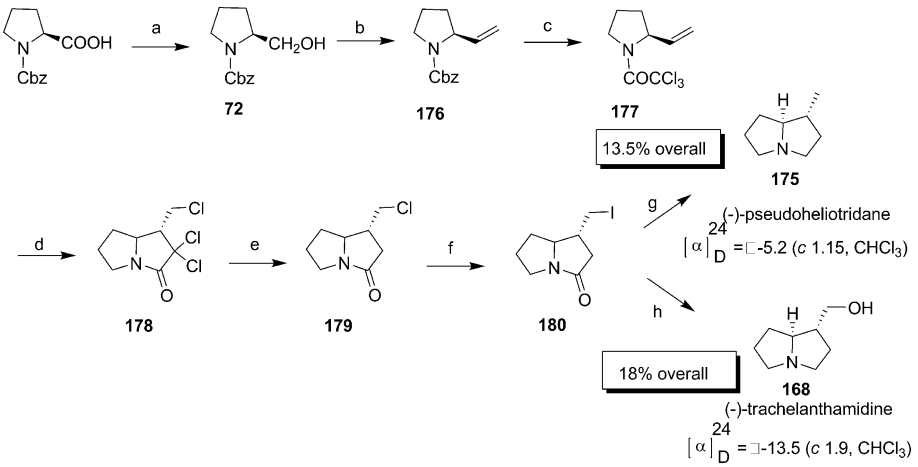
Synthesis of (−)-trachelanthamidine **168** was achieved by Ishibashi *et al. via* ruthenium catalyzed chlorine atom transfer cyclization using proline as a chiral source (Scheme 35).[62] The aldehyde **12c** prepared from prolinol was subjected to Wittig olefination to afford alkene **169**. The NH group was deprotected and further protected with methyl thio acetyl chloride to give **170**. The regioselective chlorination of **170** was accomplished using NCS to provide **171** which on cyclisation performed using $RuCl_2(PPh_3)_3$ by heating at 140 °C in benzene solution in a sealed tube afforded the bicyclic lactams **172** after removing the minor isomers by column purification. The compound **172** was subjected to nuecleophilic substitution of Cl by CsOCOEt to give **173** which underwent desulfurization on treatment with RANEY® nickel to render **174**. The LAH reduction of lactam **174** afforded the natural product (−)-trachelanthamidine **168**.

Seijas *et al.* described the synthesis of (−)-pseudoheliotridane **175** and (−)-trachelanthamidine **168**, using radical cyclization (Scheme 36).[64] The strategy utilized Cbz protected prolinol **72**, prepared by reacting Cbz-proline with ClCOOEt with concomitant reduction using $NaBH_4$. The alcohol **72** was oxidised and further converted to alkene **176** using Wittig olefination with $PPh_3{=}CH_2$. The Cbz group was hydrogenolysed and further protected with Cl_3CCOCl to afford **177**. The earlier Cbz protection was necessary since Cl_3CCOCl group was labile under $NaBH_4$ conditions. The radical cyclization of chorocompound **177** took place by refluxing with CuCN in CH_3CN in a sealed tube. The reaction was highly diastereoselective affording only **178** due to steric hindrance of the pyrrolidine nucleus. The trichloro compound **178** was further converted to monochloro compound **179** under catalytic hydrogenation condition. The nucleophilic substitution of Cl of **179** by I furnished **180** which could conveniently be transformed to the aforementioned natural products.

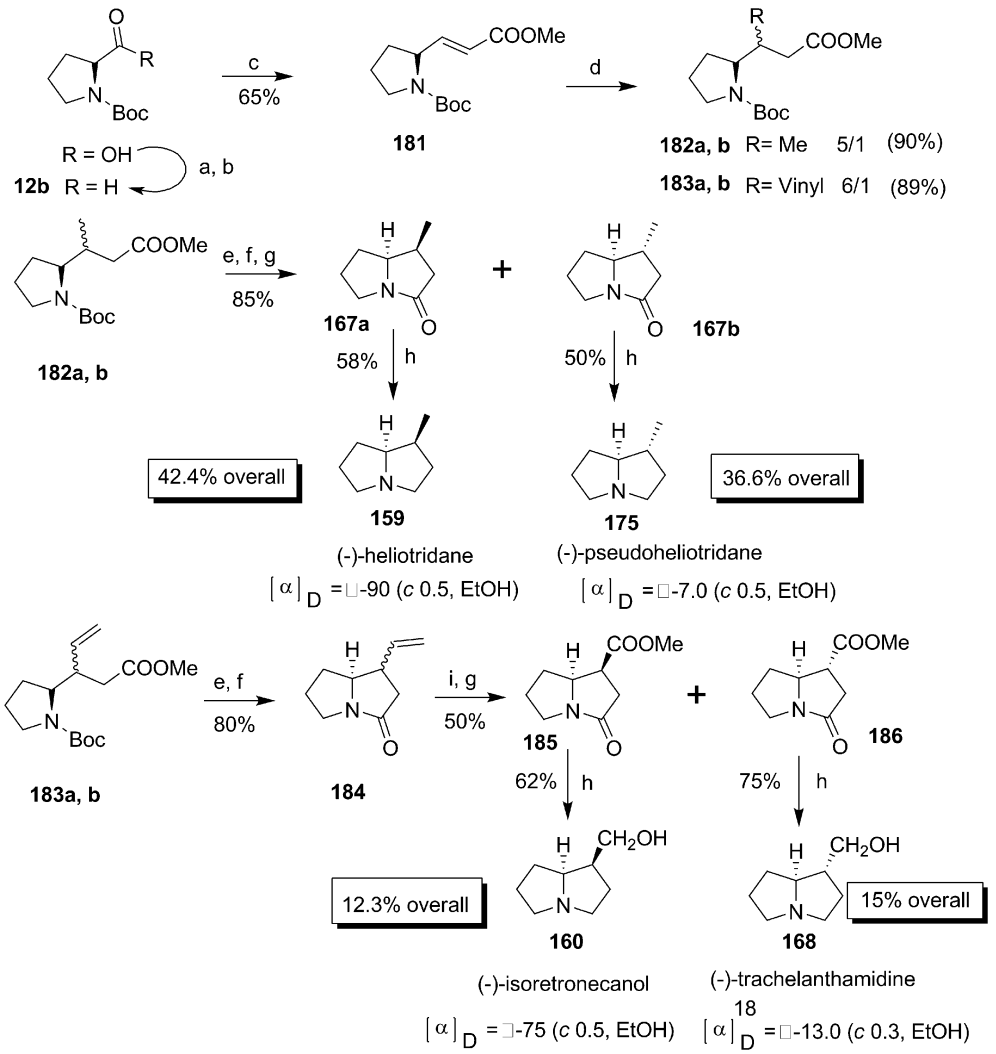
Taddei and co-workers disclosed the synthesis of (−)-heliotridane **159**, (−)-pseudoheliotridane **175**, (−)-isoretronecanol



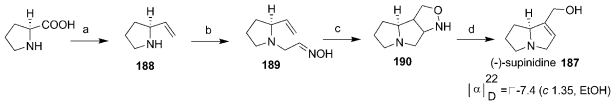
Scheme 35 *Reagents and conditions*: (a) a–d ref. 63; (e) $RuCl_2(PPh_3)_3$, 140 °C (sealed tube), 59%; (f) CsOCOEt, DMF, 80 °C, 1 h, 50%; (g) RANEY® nickel, EtOH, reflux, 2.5 h, 86%; (h) LAH, THF, reflux, 5 h, 88%.



Scheme 36 *Reagents and conditions*: (a) (i) Et_3N, ClCOOEt; (ii) $NaBH_4$ (78% for two steps); (b) (i) Swern, 98%; (ii) $PPh_3{=}CH_2$, 51%; (c) (i) HBr, AcOH; (ii) Cl_3CCOCl, DMAP (82% for two steps); (d) CuCl, CH_3CN, 150 °C, 93%; (e) H_2, Pd/C, 96%; (f) NaI, 81%; (g) (i) H_2, Pd/C, Et_3N, 86%; (ii) LAH, THF, reflux (ref. 65) 68%; (h) (i) AgOAc; (ii) LAH (ref. 65) (77% for two steps).



Scheme 37 *Reagents and conditions*: (a) TEA, pivaloyl chloride, Me(NH)(OMe), 89%; (b) LAH, 0 °C, 96%; (c) $PPh_3{=}CH_2COOMe$, THF, rt; (d) R_2CuLi, TMSCl, −30 °C; (e) HCl, AcOH; (f) pyridine, DMAP, reflux; (g) flash chromatography; (h) LAH, reflux; (i) ref. 67.



Scheme 38 *Reagents and conditions*: (a) and (b) ref. 69; (c) 180 °C, 15 h, 56%; (d) (i) LAH, 87%; (ii) 2N HCl, $NaNO_2$, 0 °C, 53%.

160 and (−)-trachelanthamidine **168** through diastereoselective Michael addition of alkyl cuprate to γ-aminocunjugated alkene (Scheme 37).[66] The synthetic strategy utilized the conversion of (*S*)-Boc-proline to aldehyde **12b** through the formation of Wienreb amide followed by LAH reduction. The olefinic compound **181** prepared by Wittig olefination was subjected to Michael addition with methyl cuprate and vinyl cuprate to afford the diastereomeric mixture **182** and **183** respectively. The mixture **182** was subjected to cyclization to give lactams **167a** and **167b** which were separable by flash chromatography. The synthesis of (−)-heliotridane **159** and (−)-pseudoheliotridane **175** was then furnished by LAH reduction of the lactams **167a** and **167b** respectively. Similarly the vinylated compound **183** was transformed to diastereomeric mixture **184** which was further converted to cyclic esters **185** and **186**. The compounds **185** and **186** were further reduced to the natural products (−)-isoretronecanol **160** and (−)-trachelanthamidine **168** respectively, using LAH.

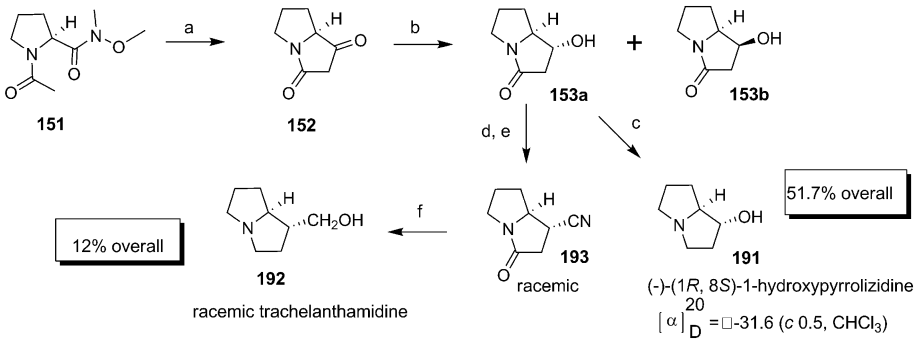
Hassner *et al.* achieved the synthesis (−)-supinidine **187** by applying intramolecular oxime-olefin cycloaddition (Scheme 38).[68] The unstable vinyl compound **188** prepared from proline was converted to oxime **189** which on heating at 180 °C afforded the cyclic product **190** along with some by-products. The compound **190** on reductive cleavage with LAH followed by diazotisation afforded the natural product (−)-supinidine **187**.

Murray and Proctor continued their earlier developed strategy, *N*-acyl anion cyclisation for the synthesis of some of the naturally occurring pyrrolizidines like (−)-(1*R*,8*S*)-1-hydroxypyrrolizidine **191** and (±)-trachelanthamidine **192** (Scheme 39).[70] The successful *N*-acyl anion cyclisation was ventured with optimal use of either LDA or LHMDS at −78 °C on *N*-methoxy-*N*-methyl amide **151** prepared from L-proline. Thus the Wienreb amide **151** cyclised to afford the diketo compound **152** with a very slight racemisation. The highly selective diastereofacial reduction with $NaBH_4$ afforded the mixture of diastereomers **153a** and **153b**. The synthesis of (−)-(1*R*,8*S*)-1-hydroxypyrrolizidine **191** was achieved by direct LAH reduction of **153a.** The major isomer **153a** was then mesylated and further treated with NaCN to afford cyano compound **193,** but surprisingly with a complete loss of enantiomeric purity. The compound (±)-trachelanthamidine **192** was then prepared on methanolysis of **193** followed by LAH reduction.

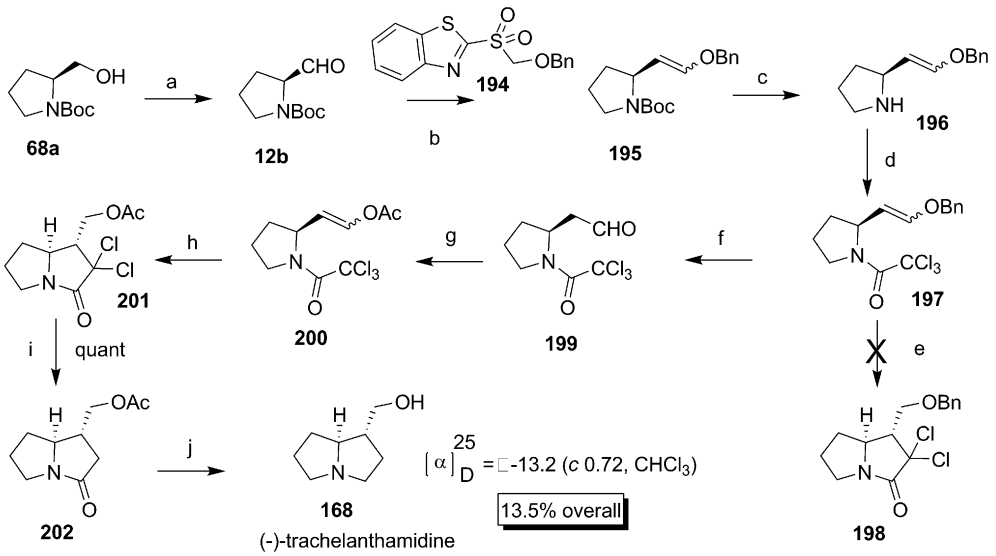
With continuing interest in radical cyclization and its applications to pyrrolizidines, Ishibashi *et al.* recently reported the synthesis of (−)-trachelanthamidine **168** through their well developed single electron transfer strategy (Scheme 40).[71] The requisite alkene **195** was prepared by Julia olefination of Boc-prolinal **12b** with α-benzyloxy sulfone **194** which on deprotection of the Boc group afforded **196.** The compound **196** on trichloroacetylation gave **197** which was subjected to cyclisation by refluxing with 1,4-dimethylpiperazine. The surprising failure of the method to give the product **198** turned the attention to prepare **200** through the formation of aldehyde **199.** The compound **200** underwent expected cyclisation affording the product **201** which on dechlorination gave the product **202.** The targeted compound (−)-trachelanthamidine **168** was achieved by direct LAH reduction of **202.**

Reddy *et al.* succeeded in the formal synthesis of (−)-isoretronecanol **160** and (−)-trachelanthamidine **168** starting from proline using ring closing metathesis (Scheme 41).[72] The alkene **24a** was prepared according to the well developed procedure from ethyl ester of Boc-proline **23** which on dihydroxylation followed by the protection of terminal –OH afforded **203.** The compound **203** was oxidised to ketone **204** and subjected to Wittig olefination to give **205.** The deprotection of the Boc group followed by reaction with acryloyl chloride afforded the ready intermediate **206** for RCM. The RCM of **206** using Grubbs II catalyst gave compound **207** which on hydrogenation followed by benzoylation afforded a separable mixture of **208a** and **208b.** The deprotection of benzoyl group of **208a** and **208b** gave **209a** and **209b** respectively which constituted the formal synthesis[73] of (−)-isoretronecanol **160** and (−)-trachelanthamidine **168.**

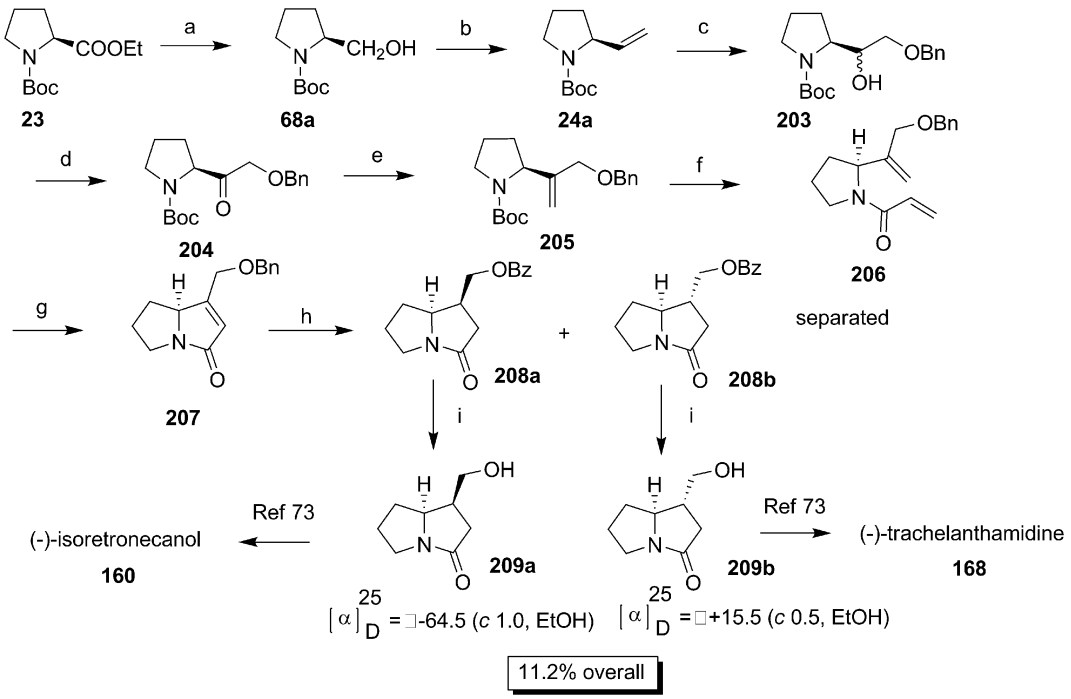
Craig and co workers successfully synthesized (−)-trachelanthamidine **168** using Pd catalysed intramolecular cyclisation (Scheme 42).[74] The methyl ester of Boc proline **67** was converted to allyl alcohol **210** by DIBAL reduction with subsequent Wittig



Scheme 39 *Reagents and conditions*: (a) LDA, THF, −78 °C; (b) $NaBH_4$, EtOH, rt, 24 h; (39–69% for two steps); (c) LAH, THF, reflux, 75%; (d) MsCl, Et_3N, DCM, 0 °C–rt, 5 h, 85%; (e) NaCN, DMSO, 90 °C, 3 h, 50%; (f) (i) HCl (gaseous), MeOH, 0 °C, 24 h, 55%; (ii) LAH, THF, reflux, 18 h, 64%.



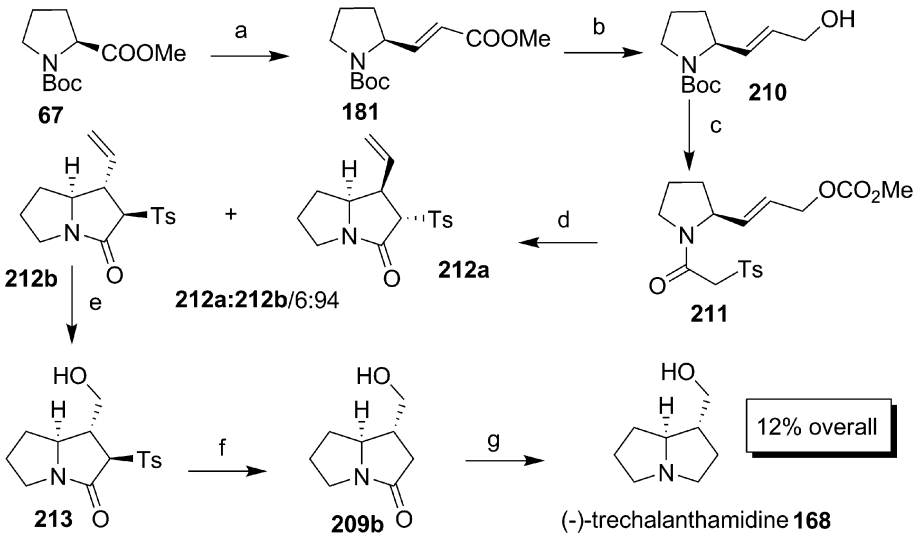
Scheme 40 *Reagents and conditions*: (a) Swern oxidation; (b) **194**, LiHMDS, THF, 0 °C, 65%; (c) TMSOTf, 2,6-lutidine, DCM, 0 °C, 92%; (d) CCl_3COCl, Et_3N, DCM, 0 °C, 95%; (e) 1,4-dimethylpiperazine, reflux; (f) 1% HCl, THF, rt, 96%; (g) Ac_2O, KOAc, Et_3N, 120 °C, 59%; (h) 1,4-dimethylpiperazine, reflux, 52%; (i) H_2, Pd/C, NaOAc, EtOH, rt, quant.; (j) LAH, THF, reflux, 86%.



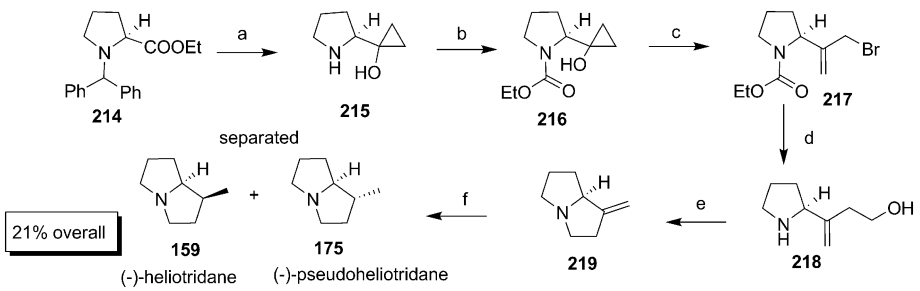
Scheme 41 *Reagents and conditions*: (a) $LiAlH_4$, THF, 0 °C to rt, 1 h, 95%; (b) (i) DMSO, $(COCl)_2$, Et_3N, DCM, −78 °C, 1 h; (ii) $Ph_3P{=}CH_2$, THF, −10 °C, 3 h (69% for two steps); (c) (i) OsO_4, NMO, monohydrate, acetone–H_2O (3 : 1), 0 °C to rt, 6 h, 89%; (ii) Bu_2SnO, toluene, reflux, 8 h, (iii) BnBr, TBAI, reflux, 16 h, (88% for two steps); (d) TEMPO, NaBr, NaOCl, $NaHCO_3$, toluene–EtOAc–H_2O (3 : 3 : 1) 0 °C, 1 h, 91%; (e) $Ph_3P{=}CH_2$, THF, −10 °C, 4 h, 61%; (f) (i) TFA–DCM (1 : 1), Et_3N, 0 °C, 1 h; 99%; (ii) acryloyl chloride, Et_3N, cat DMAP, DCM, 0 °C, 3 h, 65%; (g) 10 mol% Grubbs II catalyst, benzene, 90 °C, 36 h, 76%; based on the recovery of starting material; (h) (i) H_2, Pd/C, MeOH, rt, 2 h, 95%, (ii) benzoyl chloride, Et_3N, cat DMAP, DCM, 0 °C, 2 h, 95%; (i) K_2CO_3, MeOH, rt, 2 h, 90%.

reaction. After several experiments the ester **211** was subjected to Pd catalysed cyclisation successfully delivering the products **212** with **212b** as the major isomer after purification. The olefin **212b** was transformed to **213** by reductive ozonolysis which on subsequent detosylation uneventfully produced the lactam **209b** whose relative configurations were assigned by X-ray crystallography. The LAH reduction of **209b** gave the natural product **168.**

Kulinkovich and Lysenko accomplished the synthesis of (−)-heliotridane **159** and (−)-pseudoheliotridane **175** using



Scheme 42 *Reagents and conditions*: (a) (i) DIBAL-H (1.2 equiv.), PhMe, −78 °C, 3.5 h; (ii) $Ph_3P{=}CHCO_2Et$ (2.0 equiv.), DCM, rt, 12 h, (72% 2 steps); (b) DIBAL-H (3.0 equiv.), $BF_3{\cdot}OEt_2$ (1.0 equiv.), DCM, −78 °C to 0 °C, 3 h, 72%; (c) (i) TFA (50 equiv.), DCM, rt, 30 min; (ii) $TsCH_2CO_2H$ (1 equiv.), PyBOP (1 equiv.), Hünigs base (5.5 equiv.), DCM, rt, 12 h; (iii) methyl chloroformate (2.0 equiv.), pyridine (2.0 equiv.), DMAP (cat.), DCM, 12 h, (53% for 3 steps); (d) $Pd(dba)_3$ (5 mol%), P(Oi-Pr)$_3$ (0.5 equiv.), MeCN, 12 h, rt, 72%; (e) O_3 (g), DCM, −78 °C, 1 h; (ii) DMS (4.0 equiv.), r.t., 12 h; (iii) $NaBH_4$ (4.0 equiv.), EtOH–H_2O, rt, 1 h, 82%; (f) 6% Na(Hg) (6.0 equiv.), MeOH, −15 °C, 1 h, 75%; (g) $LiAlH_4$ (2.1 equiv.), THF, reflux, 12 h, 99%.



Scheme 43 *Reagents and conditions*: (a) 3.0 equiv. EtMgBr, 0.2 equiv. $Ti(OPr)_4$; (ii) H_2, $Pd(OH)_2/C$ (78% for two steps); (b) EtOCOCl, Et_3N, 77%; (c) (i) $MeSO_2Cl$, Et_3N; (ii) 3.0 equiv. $MgBr_2{\cdot}Et_2O$; (88% for two steps); (d) (i) Zn, $(CH_2O)n$; (ii) KOH, H_2O (52% for two steps); (e) PPh_3, CCl_4, Et_3N, DMF, 80%; (f) $NaBH_4$–$NiCl_2$, MeOH, 95%.

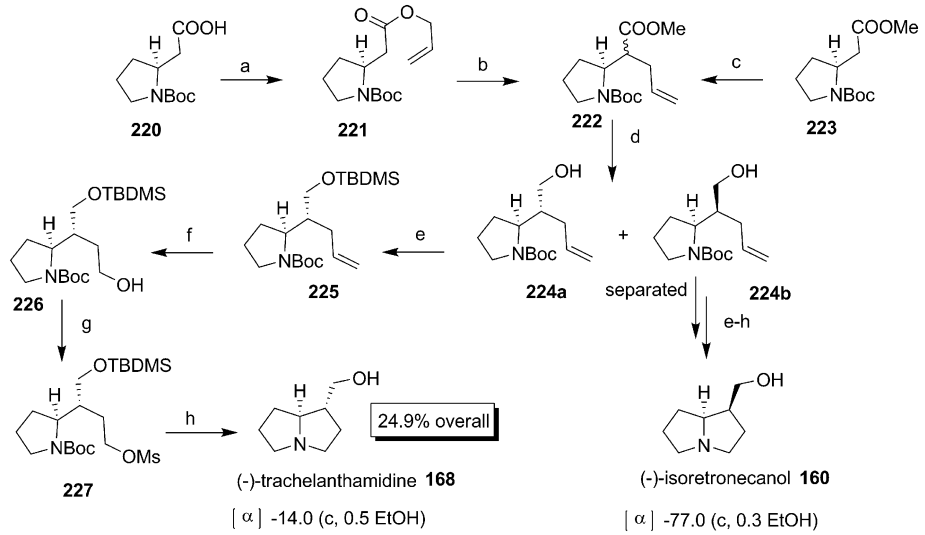
cyclopropanation of the ester group using titanium mediated Grignard reaction (Scheme 43).[75] The synthesis commenced with the cyclopropanation of proline ester **214** with $Ti(OPr)_4$ in the presence of 3.0 equiv. of Grignard reagent, followed by hydrogenolysis to afford **215**. After protecting the free NH with chloroformate, the compound **216** was subjected to mesylation in the presence of $MgBr_2$ to give **217**. The compound **217** on Reformatsky reaction with formaldehyde produced **218** which underwent cyclisation to afford **219** under Mitsunobu condition. The hydrogenation of **219** in the presence of $NiCl_2$–$NaBH_4$ gave a mixture of **159** and **175** (11 : 1) separable by column purification.

Knight and co-workers synthesized (−)-trachelanthamidine **168** and (−)-isoretronecanol **160** (Scheme 44).[76] Claisen rearrangement of ester **221** prepared from Boc-homoproline **220** gave and inseparable diastereomeric mixture of **222**. The ester **222** was also directly obtained from from Boc-homoproline methyl ester **223**. The DIBAL reduction of **222** gave a separable mixture of **224**. The less polar *erythro* isomer **224a** was successfully transformed to **168** through classical synthetic sequences. In a similar way the more polar *threo* **224b** was converted to **160**.

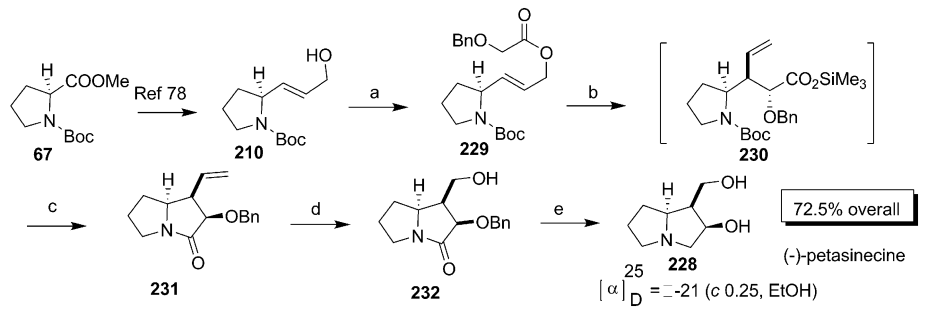
3.4. Hydroxylated pyrrolizidines

Shanyoor and Mulzer revealed a synthesis of (−)-petasinecine **228** through Ireland–Claisen type rearrangement (Scheme 45).[77] Initially Boc-proline methyl ester **67** was converted to allylic alcohol **210** by following a literature report.[78] The allyl ester **229** prepared by treatment of **210** with benzoxyacetoyl chloride was subjected to Claisen rearrangement using TMSCl and LiHMDS at −110 °C to afford the compound **231** as the only diastereomer through the intermediacy of **230**. The reductive ozonolysis of **231** with subsequent borane reduction followed by hydrogenolysis furnished the natural alkaloid **228**.

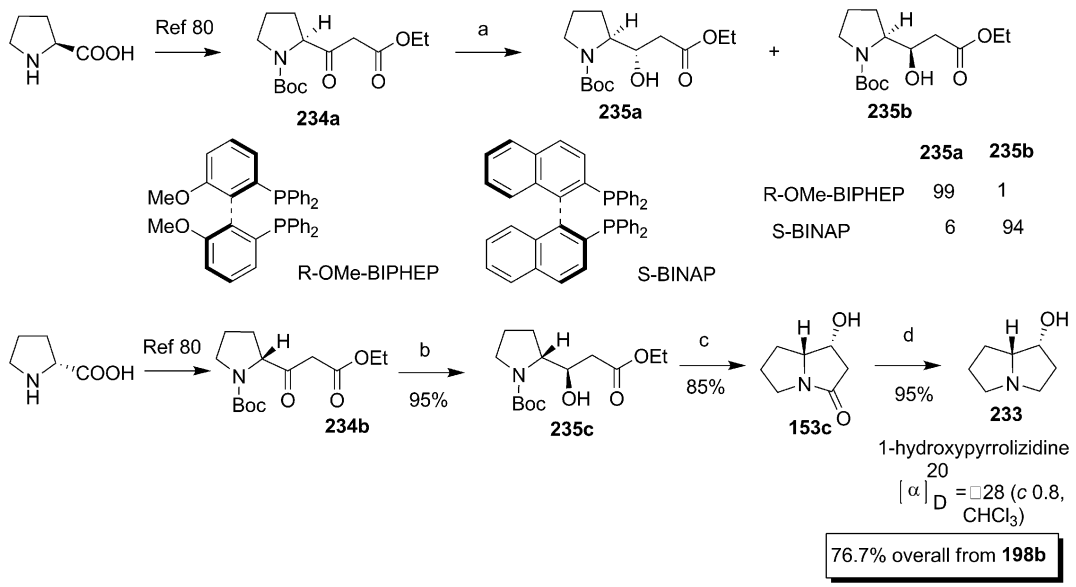
The naturally occurring alkaloid 1-hydroxyprrolizidine **233** was synthesized by Guerreiro *et al.* using diastereofacial hydrogenation of carbonyls using chiral ligands (Scheme 46).[79]



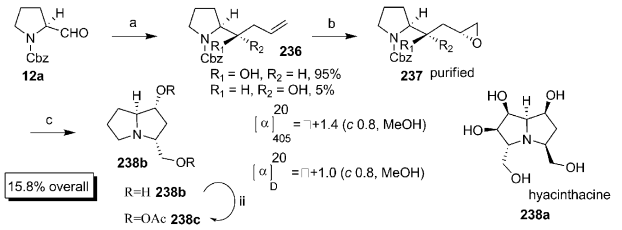
Scheme 44 *Reagents and conditions*: (a) DCC, DMAP, DCM, −20 °C, 16 h, 89%; (b) (i) LiHMDS, THF, −78 °C, 20 min, TMSI, 20 min, then +60 °C, 4 h; (ii) MeOH, H_2O, 20 °C, 0.5 h, then CH_2N_2, Et_2O, (78% two steps); (c) LHMDS, THF, 5.0 equiv., HMPA, −78 °C, 25 h, allyl bromide, −78 °C, 0.5 h, warmed to +20 °C, 1 h, 84%; (d) DIBAL, $BF_3{\cdot}OEt_2$; (e) TBDMSCl, 87%; (f) OsO_4, $NaIO_4$, $NaBH_4$, 77%; (g) MsCl, Et_3N, DCM, 0 °C, 1 h, 98%; (h) 20% TFA, DCM, 0.5 h, basified with NaOH, 65%.



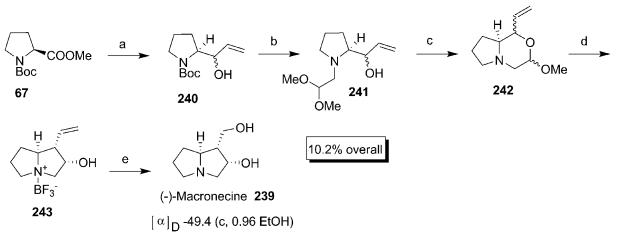
Scheme 45 *Reagents and conditions*: (a) $BnOCH_2COCl$, pyridine, rt, 5 h, 98%; (b) LiHMDS–TMSCl–THF, −110 °C, 2 h, then 5 h at 0 °C; (c) CF_3COOH, BuOH, −20 °C, 1 h, rt, 16 h, 60 °C, 48 h, 82%; (d) (i) O_3, MeOH, −78 °C, 16 h, 92%; (ii) $NaBH_4$, MeOH, −78 °C, 16 h, 92%; (e) (i) $BH_3{\cdot}$THF, 60 °C, 48 h; (ii) 10% Pd–C, H_2, MeOH, rt, 48 h, 98%.



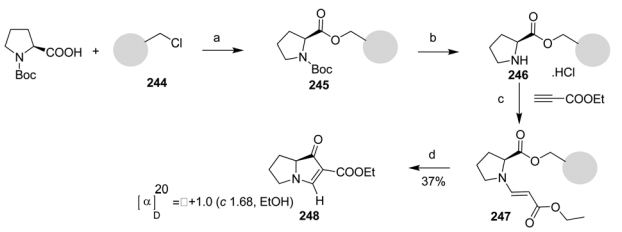
Scheme 46 *Reagents and conditions*: (a) H_2, 1% Ru catalyst, ligands, 10 bar, 50 °C, MeOH, 24 h; (b) *in situ* $RuBr_2$(*S*) Binap, 10 bar H_2, 50 °C, MeOH, 24 h, 95%; (c) TFA then K_2CO_3 EtOH–H_2O, 85%; (d) $LiAlH_4$, THF, reflux, 95%.



Scheme 47 *Reagents and conditions*: (a) $CH_2{=}CHCH_2InBr$, THF, −78 °C, 78%; (b) MCPBA, DCM, rt, 75%; (c) (i) 10% Pd/C, H_2; (ii) Ac_2O, pyridine, rt (27% two steps).



Scheme 48 *Reagents and conditions*: (a) DIBAL (1.1 equiv., −78 °C/THF), then vinylmagnesium bromide, 83%; (b) (i) TFA, 91%; (ii) α-bromoacetaldehyde dimethyl acetal, *N*,*N*-diisopropylethylamine, CH_3CN reflux, 68%; (c) TsOH, benzene reflux, 58%; (d) 'Cp_2Zr"–THF, then $BF_3{\cdot}OEt_2$, 57%; (e) (i) O_3, −78 °C, then $NaBH_4$, (ii) 10% NaOH, 60%.



Scheme 49 *Reagents and conditions*: (a) K_2CO_3, KI, reflux, 24 h; (b) DCM, Et_2O, 3 M HCl; (c) DIPEA, DMF, 4 days, rt; (d) DBU, MW, 10 min.

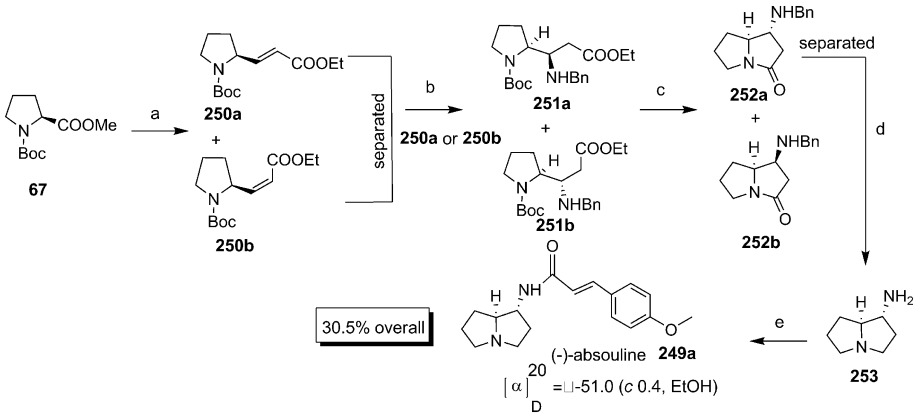
The compounds **234a** and **234b** were synthesized from L-proline and *R*-proline respectively using the literature methods.[80] The reduction of the carbonyl with chiral ligands complexed with Ru(II) under hydrogenation displayed the concept of matched and mismatched pairs. The selectivity was determined by two factors, the chirality of the proline moiety and the chirality of the ligand complexed with ruthenium. Thus the ideal case for matched pair was when (*S*)-**234a** gave diastereoselectively **235a** with (*R*)-BINAPRu(II) and (*R*)-MeO-BIPHEPRu(II) while (*R*)-**234b** gave diastereoselectively **235c** with (*S*)-BINAPRu(II). The mismatching was observed for the opposite stereoisomers. The optically pure **235c** was then subjected to Boc deprotection and subsequent intramolecular cyclization leading to the synthesis of optically pure 1-hydroxypyrrolizidine **233**.

Synthesis of the deoxy congener **238b** of the pyrrolizidine alkaloid hyacinthacine **238a** was achieved by Izquierdo *et al. via* indium mediated diastereoselective addition of allyl indium bromide to Cbz-prolinal **12a** (Scheme 47).[81] The compound **236** obtained was subjected to epoxidation using MCPBA to afford **237** whose structure was elucidated by different spectroscopic techniques. Further, catalytic hydrogenolysis of Cbz gave the cyclised product **238b** which was isolated by acetylating with acetic anhydride as **238c** for characterisation purposes.

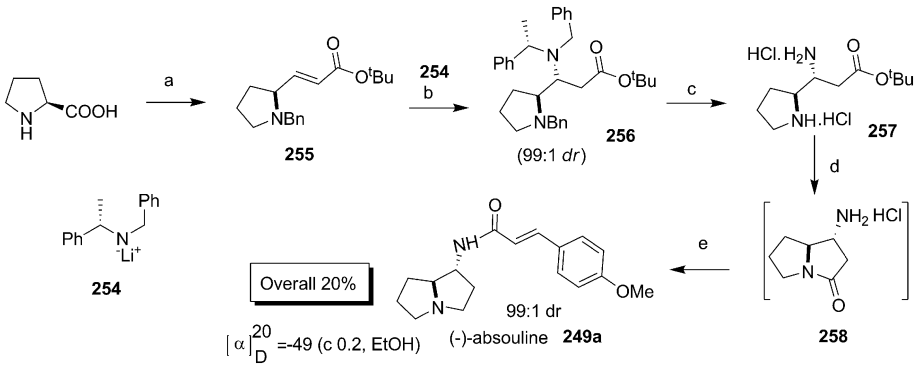
Ito *et al.* synthesized (−)-macronecine **239** during the synthetic use of zirconium mediated diastereoselective ring contraction of vinyl morpholine derivatives prepared from amino acids.[82] The proline based morpholine derivative **242** prepared from Boc-proline was reacted with "Cp_2Zr" in the presence of $BF_3{\cdot}OEt_2$ to afford pyrrolizidine–BF_3 complex **243** as a single diastereomer which on subsequent reductive ozonolysis and neutralisation gave **239** (Scheme 48).

3.5. Miscellaneous examples

Duarte *et al.* utilized L-proline as a starting material for the solid phase synthesis of **248** and claimed it as a core unit for hyacinthacine **238a** (Scheme 49).[83] The Boc-proline was coupled with Merrifield resin **244** to afford **245**. The amino salt **246**



Scheme 50 *Reagents and conditions*: (a) (i) DIBAL, PhMe, −80 °C; (ii) $(OMe)_2P(O)CH_2COOMe$, LiCl, iPr_2EtN, MeCN, 72%, (**250a** : **250b**/3 : 1); (b) **250a**, NH_2Bn, THF, 66 °C, 3 days, 73% (**251a** : **251b**/3 : 1) [**250b**, NH_2Bn, EtOH, 80 °C, 2 days, 92%, (**251a** : **251b**/7 : 2)]; (c) (i) 25% TFA, Me_2S, DCM; (ii) EtOH, Et_3N; (d) (i) $BH_3{\cdot}Me_2S$, THF, 66 °C; (ii) H_2, 10% Pd/C, MeOH, HCl; (e) DMAP, Et_3N, DCC, 4-methoxycinnamic acid, DCM; (58% for three steps).



Scheme 51 *Reagents and conditions*: (a) (i) PhCOCl, NaOH, H_2O, 0 °C, 2 h; (ii) $LiAlH_4$, THF, reflux, 18 h; (iii) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 1 h, then $Ph_3P{=}CHCO_2{}^tBu$, DCM, rt, 18 h (55% for three steps); (b) lithium-(*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **254**, THF, −78 °C, 2 h, 74%; (c) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), HCl (1.25 M in MeOH), rt, 48 h; (d) HCl (3.0 M aq.), 90 °C, 18 h [quant. for (c) and (d)]; (e) (i) DIBAL-H (1.0 M in THF), THF, 0 °C then rt, 18 h; (ii) *trans*-4-methoxycinnamic acid, DCC, DMAP, DCM, 0 °C then rt, 3 h (49% for two steps).

obtained by the deprotection of Boc was subjected to Michael reaction with ethyl propiolate to give **247**. The core unit **248** was then prepared by successful Baylis–Hillman reaction of **247** using DBU under microwave irradiation in 37% yield.

Synthesis of 1-aminopyyrolizidine alkaloid (−)-absouline **249a** was accomplished by Scheerer and co-workers using conjugate addition of amines to the unsaturated ester derived from proline (Scheme 50).[84] The authors carried out several studies to improve the heterocunjugate addition of amine to **250a** and **250b** by varying the solvents, reaction conditions and bases in producing an inseparable mixture of **251a** and **251b** which as such was subjected to cyclization to afford a separable mixture of lactams **252a** and **252b**. The absolute configuration was eventually established by X-ray analysis of salt of **252**. The synthesis of the alkaloid **249a** was then achieved by reduction of **252** to amine **253** followed by DCC coupling with 4-methoxycinnamic acid.

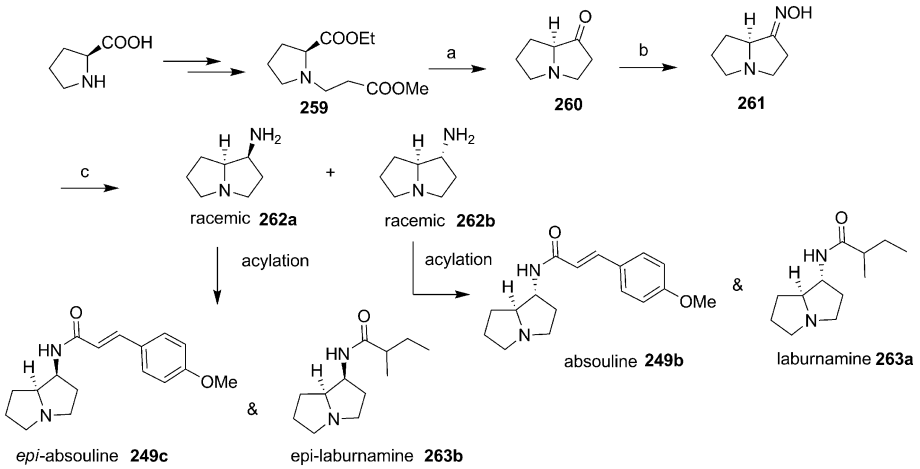
In continuation of highly diastereoselective conjugate addition studies of lithium–amide based chiral auxiliaries for the synthesis of natural products,[85] Davies *et al.* have recently reported the synthesis of (−)-(1*R*,7*a*,*S*)-absouline **249a** from L-proline (Scheme 51).[86] The conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl) amide **254** to **255** took place diastereomerically to give **256**. The hydrogenation of **256** followed by treatment under strong acidic conditions gave the cyclised amide **258** from **257**. The DIBAL reduction of **258** followed by subsequent condensation of the free amine with *trans*-4-methoxycinnamic acid afforded the natural product (−)-absouline **249a**.

Christine *et al.* achieved the synthesis of laburnamine and absouline along with their epimeric congeners.[87] The ester **259** prepared from proline was transformed to cyclic amines **262a** and **262b** in racemic forms which on condensation with the corresponding acid chlorides afforded the natural products absouline **249b**, **c** and labunamine **263a**, **b** in both the diastereomeric forms (Scheme 52).

4. Synthesis of indolizidine alkaloids

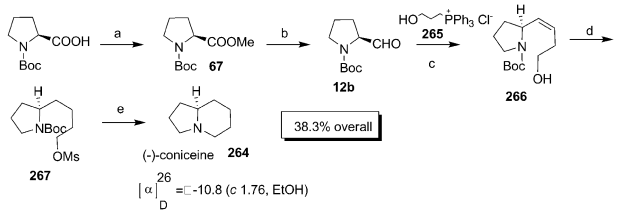
4.1. Introduction

Indolizidine alkaloids are comprised of a [4.3.0] azabicyclic nonane core, present in the numerous bioactive natural and unnatural scaffolds.[88] They are mainly isolated from skin secretions of amphibians.[89] This has attracted interest from

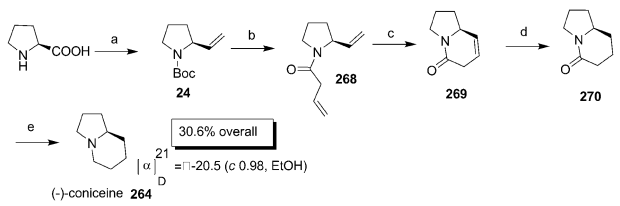


Scheme 52 *Reagents and conditions*: (a) (i) NaOEt, xylene; (ii) H^+, reflux; (b) NH_2OH, HCl; (c) $Na–NH_3$ or $H_2–PtO_2$.

synthetic chemists due to their potent biological and medicinal applications. Coniceine is the simplest indolizidine with unsubstituted 5-member and six member rings fused to each other. The indolizidine moieties even with alkyl substitution at various positions exhibit unique characteristics especially in blocking neuromuscular transmission.[90] The polyhydroxy substituted indolizidines like swainsonine, castanospermine alkaloids have attracted special interest for their anti HIV and anticancer properties and are also known for being the best mimics of sugars to act as potential glycosidase inhibitors.[91] The formulation of indolizidine alkaloids can be achieved either by starting with a six member heterocycle and then annulating a five member on to it or *vice versa*. The proline being a 5 member heterocycle can efficiently be used for the construction of indolizidines by appropriate manipulation of the side chain and wrapping it to form a six member ring around it.



Scheme 53 *Reagents and conditions*: (a) CH_3I, DBU, 89%; (b) DIBALH reduction 92% or (i) $LiBH_4$; (ii) Swern oxidation; (84% for two steps); (c) **265**, 2.0 equiv. LiHMDS, 76%; (d) (i) H_2, Pd/C, 95%; (ii) MsCl, DCM, 96%; (e) 3 M HCl, dioxane–water, overnight; NaOH, neutralized, 74%.



Scheme 54 *Reagents and conditions*: (a) (i) NaOH, $(Boc)_2O$, dioxane, 79%; (ii) K_2CO_3, MeI, DMF, 96%; (iii) DIBAL, $PhCH_3$, −78 °C, 93%; (iv) $KN(TMS)_2$, $^+PPh_3CH_3Br^-$, THF, 73%; (b) TFA, DCM, $CH_2{=}CHCH_2COCl$; (c) $Cl_2Ru(PCy_3)_2{=}CHCH{=}CPh_2$ (Grubbs II catalyst), rt, benzene, 3 days, 93% ($Cl_2Ru(PCy_3)_2{=}CHPh$, rt, benzene, 18 h, 66%); (d) PtO_2, H_2, MeOH, rt; (e) LAH, Et_2O, rt, 2 h, 96%.

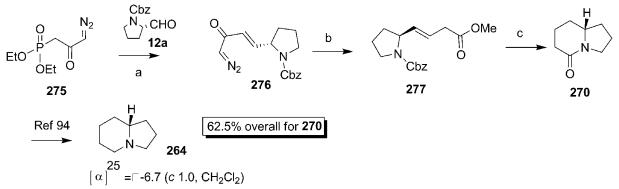
4.2. Unsubstituted indolizidines (coniceine)

Sibi and Christensen formulated the synthesis of (−)-δ-coniceine **264** from Boc-proline (Scheme 53).[92] The Boc-prolinal **12b** was prepared using conventional steps which on Wittig reaction with phosphorane of **265** afforded the olefin **266**. The hydrogenation of **266** followed by mesylation of hydroxyl group gave **267**. The compound **267** on Boc deprotection with subsequent neutralization furnished δ coniceine **264**.

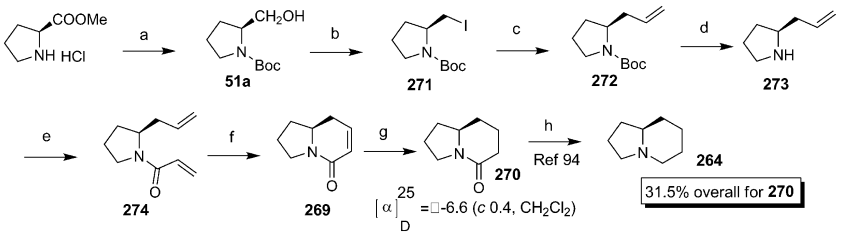
Nakagawa's group synthesized (−)-coniceine **264** using RCM as a key step (Scheme 54).[57] The method is similar to the one described earlier (Scheme 30) for pyrrolam. The compound **268** was subjected to RCM using Grubbs II catalyst to afford **269** which on hydrogenation furnished **270**. The LAH reduction of **270** gave (−)-coniceine **264**.

Chang and co-workers encompassed an efficient formal synthesis of (−)-coniceine **264** (Scheme 55)[93] using RCM strategy, similar to Nakagawa's approach. The only difference lies in nature of the side chain and the group attached to N atom. The HCl salt of methyl proline ester was converted to iodo compound **271** from alcohol **51a** with conventional synthetic sequences. The treatment of the compound **271** with vinylmagnesium bromide in the presence of CuI gave **272** which on deprotection of the –Boc afforded amine **273**. The key intermediate for RCM **274** was prepared by incorporating an acryloyl double bond over free –NH of **273**. The RCM on **274** with Grubbs II catalyst furnished **269** which on double bond reduction gave the lactam **270**, completing the formal synthesis of (−)-coniceine **264**.[94]

Recently Pinho and Burtoloso approached formal syntheses of (−)-coniceine **264** by employing an unusual Wolf rearrangement (Scheme 56).[95] The synthesis commenced with Horner–Wittig condensation of the phosphonate **275** with Cbz-prolinal **12a** to furnish **276**. The problems encountered under various



Scheme 56 *Reagents and conditions*: (a) NaH, THF, −78 °C, 70%; (b) MeOH, *hν*, 25 °C, 4 h, 97%; (c) Pd/C, MeOH, Et_3N, 48 h, 25 °C, 92%.

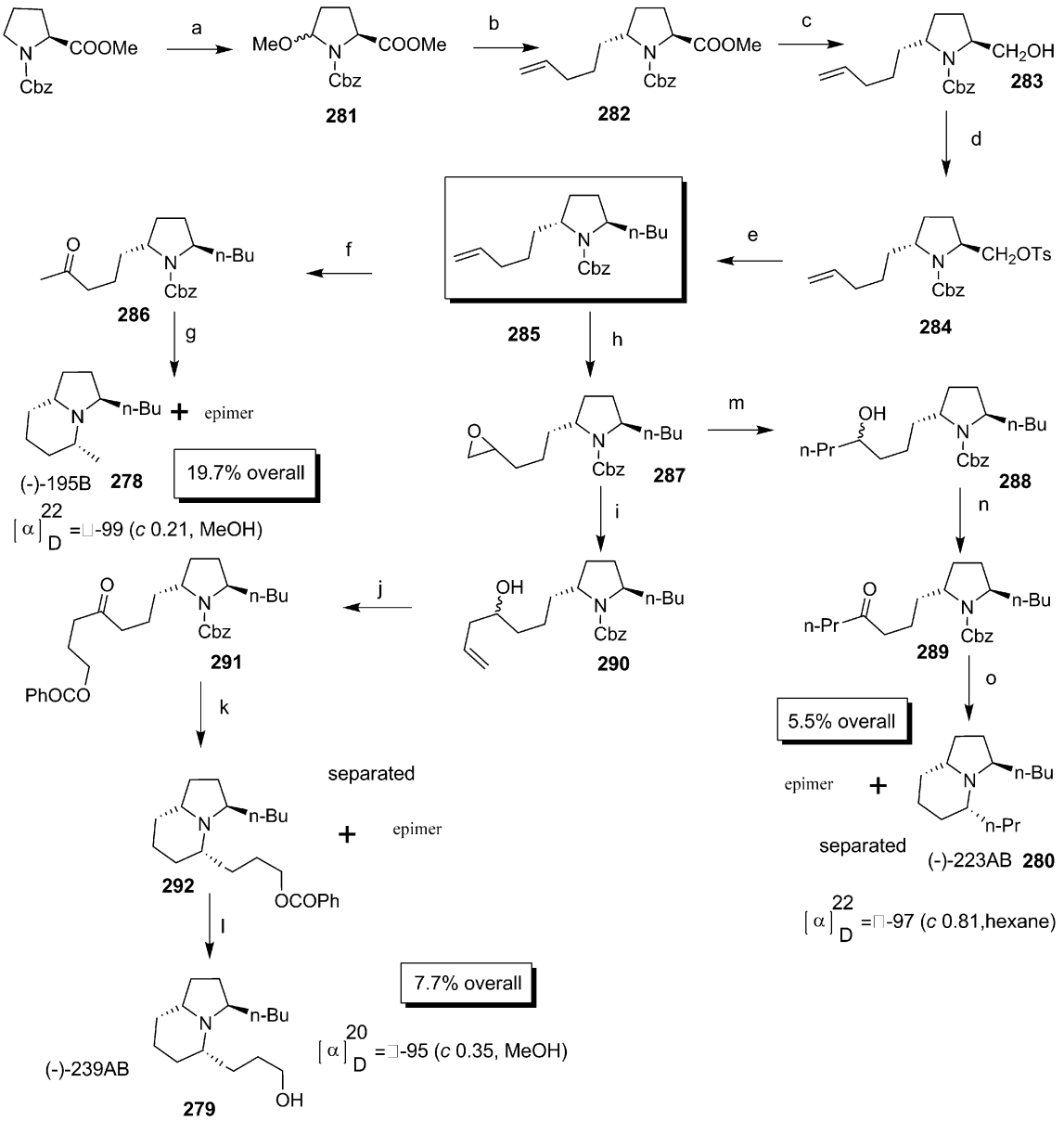


Scheme 55 *Reagents and conditions*: (a) (i) LAH (2.0 equiv.), THF, reflux, 2 h, (ii) $(Boc)_2O$ (1.2 equiv.), DCM, 60 °C, 12 h, (90% for two steps); (b) imidazole (2.0 equiv.), I_2 (1.5 equiv.), PPh_3 (1.5 equiv.), ether, rt, 12 h, 89%; (c) CuI (3 equiv.), vinylmagnesium bromide (6 equiv.), THF, −40 °C to rt, 3 h, 87%; (d) TFA–DCM (1 : 1, excess), 0 °C, 1 h, 99%; (e) acryloyl chloride (5 equiv.), Et_3N (4.0 equiv.), DCM, 0 °C to rt, 3 h, 65%; (f) (Im) $Cl_2PCy_3RuCHPh$ (Grubbs II catalyst), 5 mol%, DCM (0.05 M), rt, 3 h, 74%; (g) H_2–PtO_2 (10 mol%), EtOAc, rt, 3 h, 95%.

conditions tried for Wolf rearrangement of **276** were circumvented by employing a photochemical condition which without any epimerisation at the chiral centre afforded **277** in 97% yield. The compound **277** underwent cyclization to azabicyclic lactam **270** by hydrogenolysis of Cbz group and concomitant reduction of the double bond to complete the formal synthesis[94] of (−)-coniceine **264**.

4.3. Simple substituted indolizidines

Lhommet and co-workers explored the synthesis of three different substituted indolizidine alkaloids namely, (−)-195B **278,** (−)-239AB **279,** (−)-223AB **280,** using proline as an original chiral source by synthesizing a versatile common intermediate **285** (Scheme 57).[96] The pivotal steps involve the diastereoselective metal mediated coupling at the C-5 of the pyrrolidine and the reductive amination of the imine formed *in situ*. Initially the Cbz-proline ester was methoxylated at C-5 using anodic oxidation, a method developed by T. Shono,[97] to afford **281**. The compound **281** on BF_3 mediated coupling with pent-4-enyl copper succeeded with high diastereoselectivity to afford **282** (*trans* : *cis*/96 : 4) which was subjected to chemoselective reduction to alcohol **283** to separate as a single isomer. The compound **283** was tosylated to **284** and further, the



Scheme 57 *Reagents and conditions*: (a) electrolysis, −5 °C, 75%; (b) $CH_2{=}CH(CH_2)_3Cu$, $BF_3{\cdot}OEt_2$, −78 °C to rt, 79.5%; (c) $NaBH_4$–$CaCl_2$, THF–EtOH, −5 °C, 73.6% for *trans* isomer separated; (d) TsCl, Et_3N, 96%; (e) nPr_2CuLi, Et_2O, −20 °C, 75%; (f) O_2, $PdCl_2$, $Pd(PhCN)_2$, CuCl, H_2O–DMF (7 : 1), 60 °C, 77%; (g) H_2 (1 atm), cat. Pd/C, MeOH, 81% after separation from epimer; (h) MCPBA, DCM, $NaHPO_4$–NaH_2PO_4 (pH = 8), 69%; (i) $CH_2{=}CHMgBr$, (excess), CuI (0.05 eq.), THF, −40 °C to −20 °C, 88%; (j) (i) $BH_3{\cdot}DMS$ then H_2O_2–NaOH, 82%; (ii) PhCOCl, pyridine, −40 °C to rt, 18 h, 72%; (iii) PDC, DCM, 96%; (k) H_2, 10% Pd/C, MeOH, 82% after separation from its epimer; (l) MeONa, MeOH, 86%; (m) EtMgBr (excess), CuI (0.1 eq.), THF, −20 °C, 73%; (n) PDC, DCM, 86%; (o) H_2, 10% Pd/C, MeOH, 40%.

homologation was achieved by the nucleophilic displacement of OTs by reacting with excess of *n*-Pr_2CuLi to give the key building block **285.**

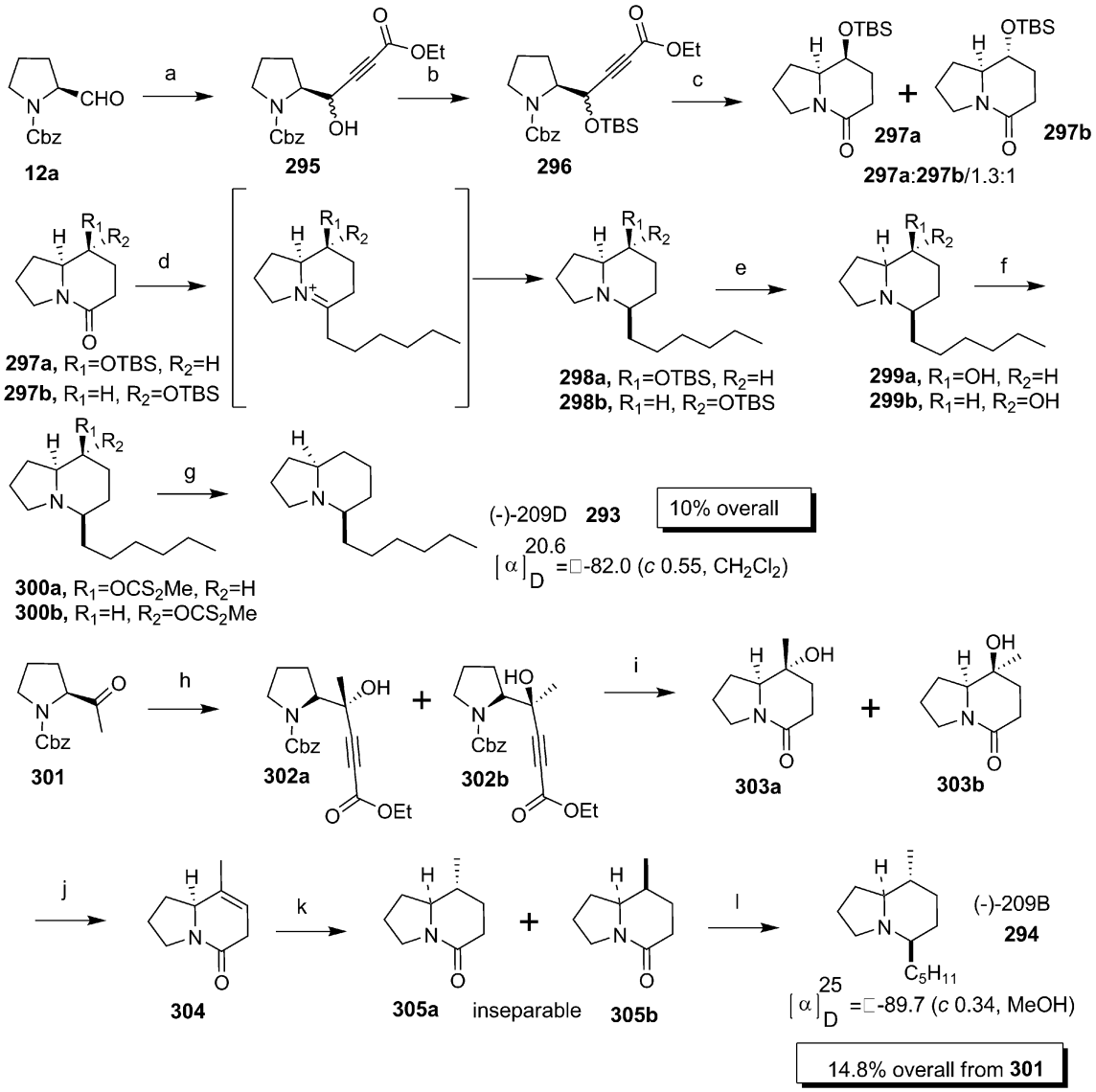
The synthesis of aforementioned indolizidines was achieved by a systematic transformation of the olefinic part of **285.**

The synthesis of **278** was furnished by Wacker oxidation of **285** followed by hydrogenolysys of Cbz group.

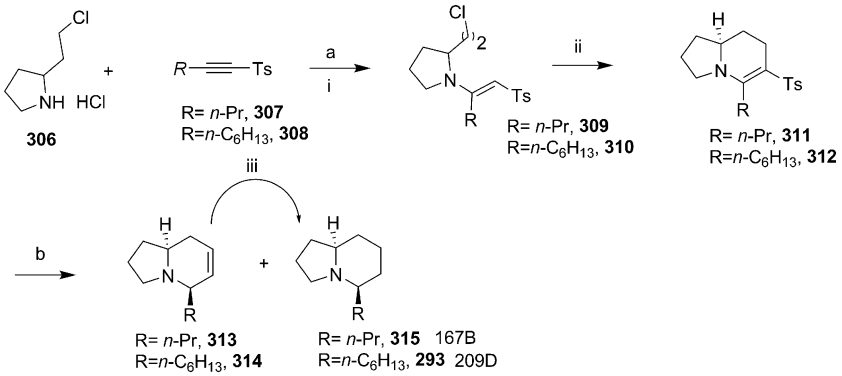
For the synthesis of **280** the olefinic part of **285** was epoxidised to **287** and further treated with excess Grignard reagent EtMgBr to give a diastereomeric mixture **288** which on direct oxidation gave the compound **289.** The hydrogenolysis of **289** as earlier afforded the compound **280** along with its separable epimer.

For the synthesis of **279** the epoxide **287** was treated with excess of vinylmagnesium bromide to afford a diastereomeric mixture **290.** The mixture **290** was as such oxidised followed by the hydroboration oxidation of the terminal double bond and protection as benzoyl group gave **291.** The compound **291** on hydrogenolysis and subsequent benzoyl deprotection of the resultant **292** provided the indolizdine **279.**

Gang and co-workers synthesized indolizidines (−)-209D **293** and 209B **294** (Scheme 58).[98] The nucleophilic addition of ethyl propiolate anion to carbonyl of **12a** afforded a mixture of diastereomers **295** which on hydroxyl protection with TBSCl afforded **296.** The subsequent hydrogenation of **296** over Pd/C in MeOH contributed the deprotection of carbamate, reduction of triple bond and the cyclisation to lactam to take place in one



Scheme 58 *Reagents and conditions*: (a) ethyl propiolate, LiHMDS, THF, −78 °C, 89%; (b) TBSCl, imidazole, DCM, rt, 24 h, 70.5%; (c) H_2, Pd/C, MeOH, 83%; (d) (i) $C_6H_{13}MgBr$; (ii) AcOH, $NaBH_4$, 63% for **298a**, 62% of **298b**; (e) 4 M HCl–MeOH, 50 °C, 92% for **299a**, 93% of **299b**; (f) NaH, CS_2, MeI, rt, 53% for **300a**, 55% for **300b**; (g) Bu_3SnH, AIBN, toluene, reflux, 60%; (h) ethyl propiolate, *n*-BuLi, THF, −78 °C, 87%; (i) H_2, 10% Pd/C, MeOH, 77% of **303a**, 77% of **303b**; (j) $SOCl_2$, Et_3N, DCM, −78 °C, 75%; (k) 506.625 kPa H_2, 10% Pd/C, MeOH, 70%; (l) (i) $C_5H_{11}MgBr$; (ii) AcOH, $NaBH_4$, 42% of **294** in two steps.



Scheme 59 *Reagents and conditions*: (a) for **311**: (i) DCM, rt, 5 h; (ii) LDA (excess), THF, −78 °C, 5–45 min; (94% with slight excess **306**; 84% with equimolar amount of **306** and **307**; for **312**: (i) DCM, rt, 40 h; (ii) LDA (excess), THF, −78 °C, 5–45 min, 86%; (b) (i) $NaCNBH_4$, TFA, DCM; (ii) Na–NH_3; (iii) H_2, Pd/C; (60% for **315** and 74% for **293** for three steps).

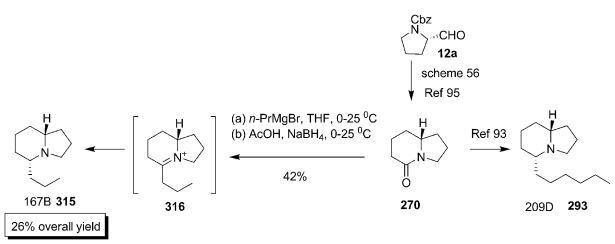
pot affording a mixture of **297a** and **297b** in a ratio of 1.3 : 1, separated by column chromatography. The compound **297a** (**297b**) was then treated with $C_6H_{13}MgBr$ followed by iminium ion reduction afforded single isomer **298a** (**298b**), the stereochemical control was attributed to the less hindered α-H atom of pyrrolidine ring which favoured the formation of β-isomer. The TBS group of **298a** (**298b**) was deprotected in acid condition to afford **299a** (**299b**). The successful synthesis of **293** was reached by converting the hydroxyl group of **299a** (**299b**) to thiocarbamate ester **300a** (**300b**) and then by deoxygenation with Bu_3SnH under Barton–McCombie deoxygenation conditions.

For the synthesis of indolizidine 209B **294**, the keto compound **301** was subjected to nucleophilic addition of lithiopropiolate-ion to afford a mixture of **302a** and **302b** (2.5 : 1) separable by column chromatography. The mixture **302** was subjected to hydrogenation furnishing **303a** and **303b** which was as such dehydrated to give the olefin **304**. The hydrogenation of **304** under high pressure afforded an inseparable mixture of **305a** and **305b** which upon addition of $C_5H_{11}MgBr$ followed by iminium ion reduction gave the pure indolizidine **294** after column purification.

Back and Nakajima developed a method to construct (−)-indolizidine 167B **315** and (−)-indolizidine 209D **293** through conjugate addition of γ-chloroamines **306** to acetylenic sulfones **307** and **308** respectively.[99] The deprotonation of chloro compounds **309** (**310**) using LDA gave cyclised product **311** (**312**). The reduction of the double bond of **311** (**312**) using $NaCNBH_4$ and subsequent desulfonation produced required products with a tiny amount of **313** (**314**). Thus the crude mixture was subjected hydrogenation over Pd/C to afford (−)-indolizidine 167B **315** (209D **293**) (Scheme 59).

Pinho and Burtoloso also approached the total synthesis of (−)-indolizidine 167B **315** and formal syntheses of (−)-indolizidine 209D **293** by employing an unusual Wolf rearrangement as described earlier under Scheme 56.[95] The synthesis of bicyclic lactam **270** constituted the formal synthesis of (−)-indolizidine 209D **293**. The synthesis of **315** was achieved by diastereoselective addition of *n*-PrMgBr to **270** followed by iminium ion reduction (Scheme 60).

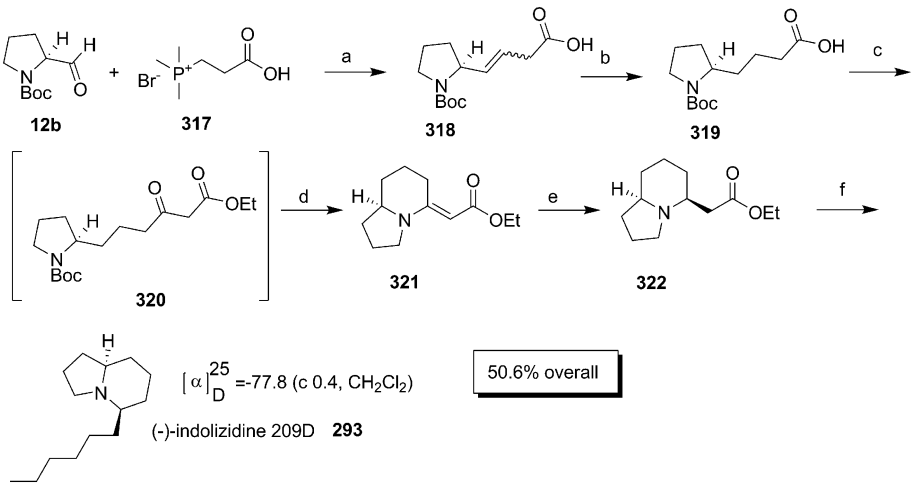
Stereoselective synthesis of (−)-indolizidine 209D **293** was furnished by Ponpandian and Muthusubramanian using sequential deprotection-cyclisation protocol (Scheme 61).[100] After overcoming the several consequences of epimerisation and inconvenient routes, the authors emerged with an appropriate sequence to bring about the deprotection and cyclisation of **320** efficiently. The compound **319** was prepared by hydrogenation of **318** which in turn was accessed from Boc-prolinal **12b** using Wittig reaction with the phosphorane of the corresponding salt **317**. The β-ketoester **320** was prepared by condensing CDI with acid **319** followed by treatment with ethyl potassium malonate in the presence of anhy. $MgCl_2$. The $BF_3 \cdot OEt_2$ mediated deprotection of the Boc group of **320** with subsequent cyclisation by treatment with $NaHCO_3$ gave the *trans* olefin **321**. The hydrogenation of **321** afforded the pure isomer **322**. The LAH reduction of **322** followed by tosylation and subsequent CuI mediated coupling with *n*-BuLi furnished indolizidine alkaloid 209D **293**.



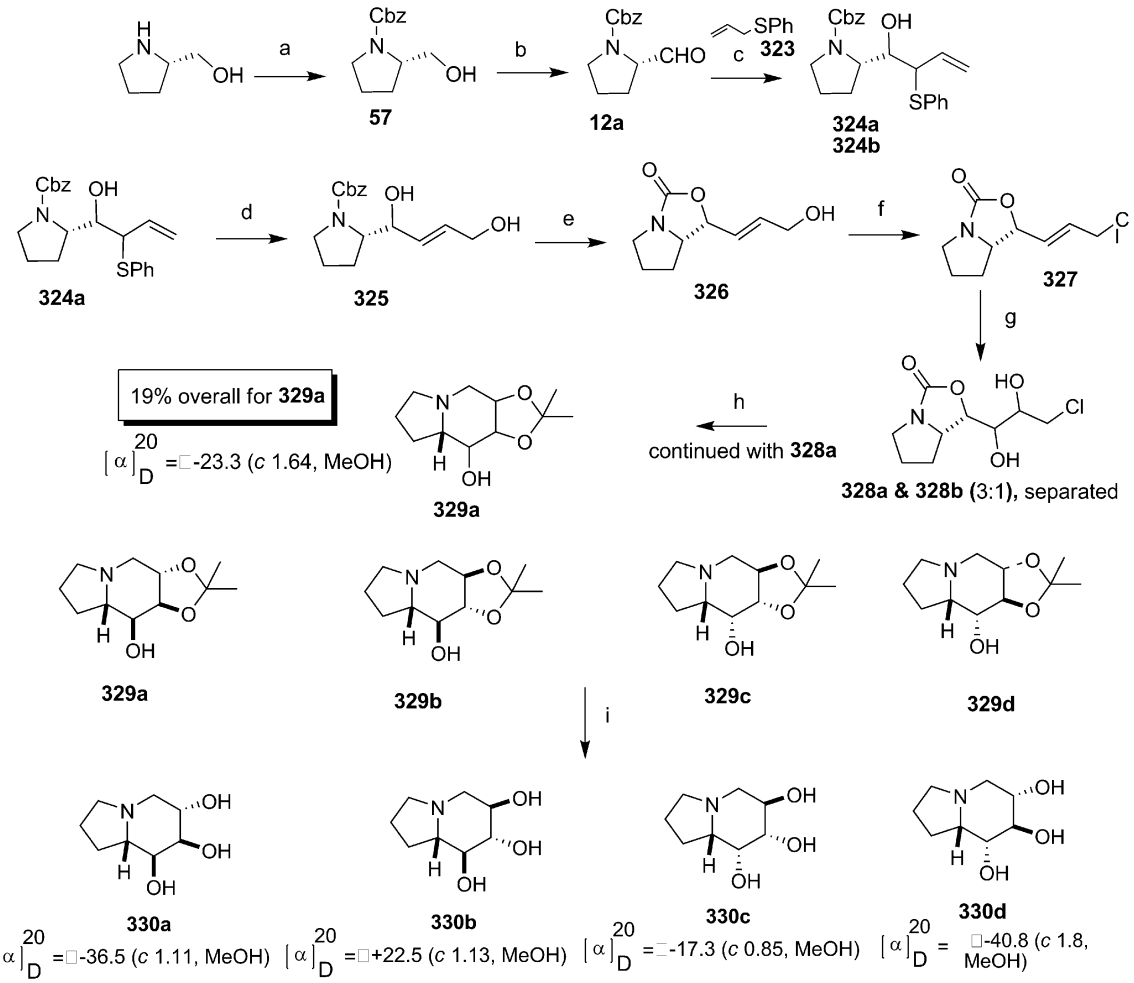
Scheme 60 Synthesis of 167B and 209D via unusual Wolf rearrangement.

4.4. Hydroxyindolizidines

St-Denis and Chan accomplished the synthesis of all four diastereomers of 1-deoxycastenospermine **330** through diastereoselective addition of anion of allyl phenyl sulphide and Sharpless dihydroxylation (Scheme 62).[101] The synthetic strategy utilized **12a** obtained from L-proline. The titanium mediated addition of anion of allyl phenyl sulphide **323** to **12a** occurred diastereoselectively affording only two isomers **324a** and **324b** out of four possible isomers. The isomers were separated by



Scheme 61 *Reagents and conditions*: (a) LiHMDS, THF, 0 °C; (b) 10% Pd/C, MeOH, 69% for (a) and (b); (c) ethyl potassium malonate, CDI, anhy. $MgCl_2$, 60 °C; (d) $BF_3{\cdot}OEt_2$, MDC, aq. $NaHCO_3$ work-up, 92% for (c) and (d); (e) H_2–PtO_2, EtOH, 95%; (f) (i) LAH, THF, rt, 30 min, 96%; (ii) TsCl, Et_3N, DCM, rt, 3 h, 92%; (iii) CuI–*n*-BuLi, ether, −30 °C, 1 h, 95%.

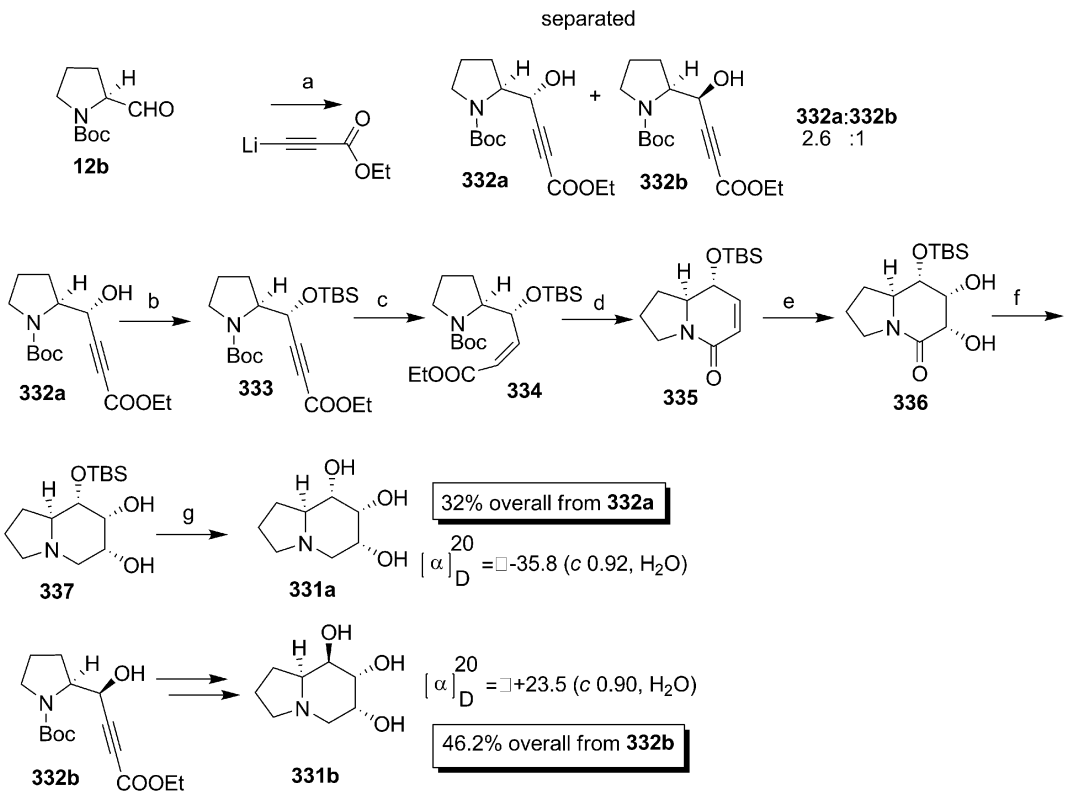


Scheme 62 *Reagents and conditions*: (a) CbzCl, K_2CO_3, CH_3CN, −20 °C, 87%; (b) Swern oxidation, 87%; (c) allyl phenyl sulphide, *n*-BuLi, Ti(i-OPr)$_4$, THF, −78 °C, 82%; (d) (i) MCPBA, DCM, −78 °C; (ii) $P(OMe)_3$, MeOH, 77%; (e) NaOH, IPA–H_2O, 70 °C, 70%; (f) PPh_3, CCl_4, reflux, 94%; (g) OsO_4, NMO, *t*BuOH, H_2O, acetone, 88%; (h) (i) 2,2-dimethoxypropane, CSA, acetone, 87%; (ii) NaOH, MeOH, H_2O, 80 °C, 79%; (i) TFA, H_2O, rt, quant.

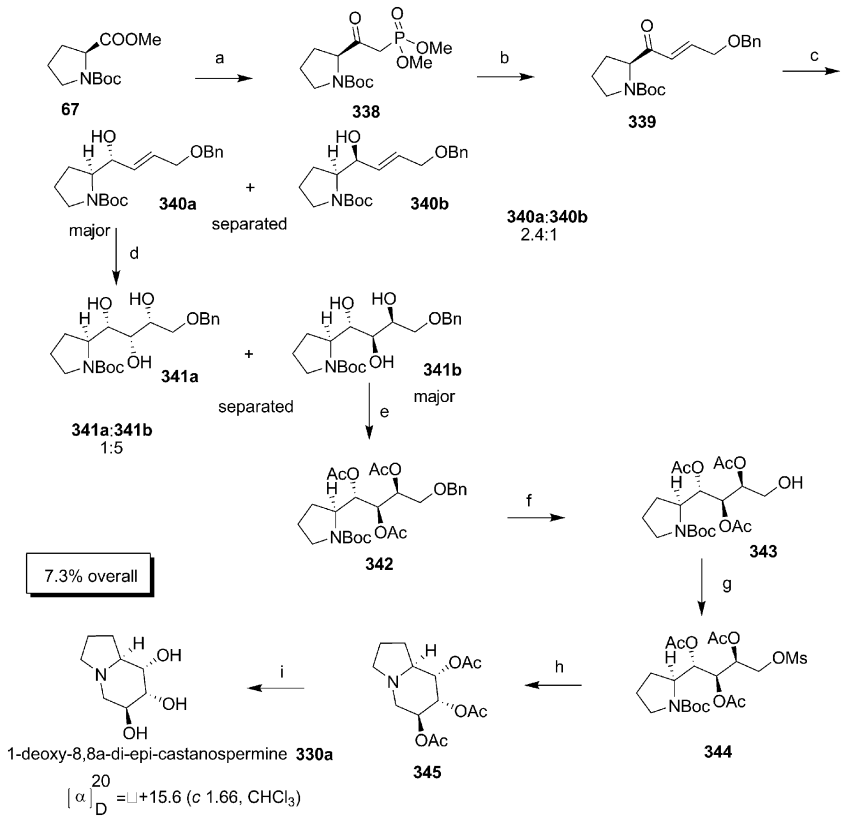
column purification and the synthesis was furthered with the major isomer **324a.** The oxidation of thio group of **324a** followed by allylic rearrangement using $P(OMe)_3$ afforded the allyl alcohol **325** which on treatment with NaOH furnished the cyclic carbamate **326.** The compound **326** was chlorinated to give **327** prior to dihydroxylation affording the diastereomers **328a** and **328b** (3 : 1), separated by column chromatography to further the synthesis with the major isomer **328a.** The protection of the diol **328a** as acetonide group followed by opening up of the carbamate using NaOH afforded the cyclised product **329a**. The stereochemistry of the compound was established at this stage through various spectroscopic techniques to confirm the structure of **329a.** In a similar way all the isomers **329b, c, d** were synthesized by utilizing the other isomers formed during the synthetic sequence. The synthesis of all four diastereomers of 1-deoxycastenospermine **330** (**a–d**) was then smoothly achieved by the deprotection of the acetonide group of **329** (**a–d**) using TFA.

Zhang *et al.* achieved the synthesis of two isomers of 1-deoxy-8*a*-*epi*-castanospermine **331a** and **331b** by diastereoselective addition of ethyl lithiopropiolate and Sharpless dihydroxylation as key steps (Scheme 63).[102] The diastereoselective addition of ethyl lithiopropiolate to carbonyl derived from Boc-prolinal **12b** in the presence of HMPA afforded the two separable diastereomers **332a** and **332b** (2.6 : 1). The secondary hydroxyl group of **332a** was then protected using TBSCl to afford **333**. The selective triple bond reduction to double bond was achieved using Lindlar's catalyst to give olefin **334** which on Boc deprotection using TFA followed by treatment with Et_3N furnished the cyclised product **335.** The compound **335** was subjected to Sharpless dihydroxylation to give diol **336** which on subsequent reduction with borane gave **337.** The deprotection of TBS group of **337** using TBAF produced the natural product **331a** whose structural elucidation was done using different spectroscopic techniques. Similar synthetic steps were repeated for the synthesis of the other isomer **331b** from **332b.**

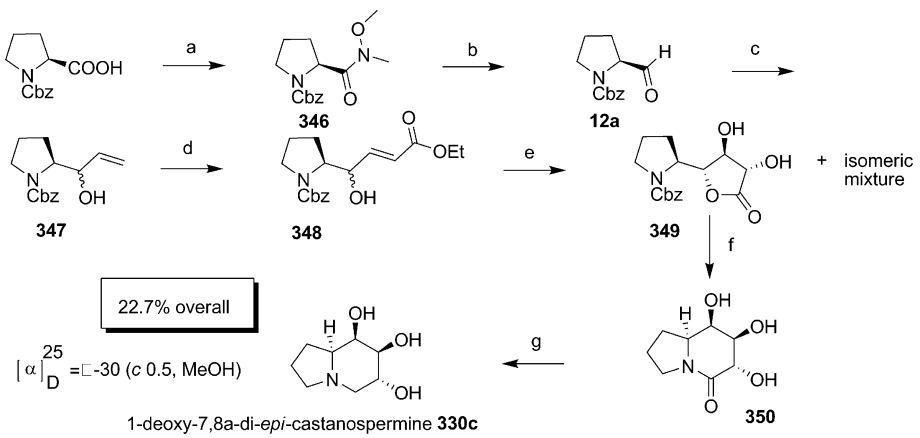
Koskinen and Kallatsa formulated the synthesis of 1-deoxy-8,8*a*-di-*epi*-castanospermine **330a** using proline as an efficient starting material (Scheme 64).[103] The phosphonate **338** was prepared from Boc-proline ester according to the procedure reported by Heathcock and von Geldern.[104] The Horner–Wadsworth–Emmons olefination was then achieved on **338** to afford **339** using mild base K_2CO_3. The stereoselective reduction of carbonyl of **339** rendered the separable mixture of **340a** and **340b**. The dihydroxyalation of isomer **340a** gave a mixture of **341a** and **341b,** separated by column chromatography. The major compound **341b** was furthered by acetylating the free hydroxyl groups to give **342** and subsequently hydrogenated to give **343.** The terminal free OH group of **343** was mesylated to give **344.** The compound **344** on Boc deprotection using TFA underwent cyclisation to give **345** which on subsequent treatment with NaOH furnished **330a.**



Scheme 63 *Reagents and conditions*: (a) Li propiolate, *n*-BuLi, THF, HMPA (2.0 equiv.), −78 °C, 3 h, (**332a** : **332 b**/2.6 : 1), 78%; (b) TBSCl, imidazole, DCM, rt, 12 h, 98%; (c) H_2, Lindlar's catalyst, 1 atm, quinoline, MeOH, rt, 3 days, 96%; (d) (i) TFA, DCM, 0 °C to rt, 1.5 h; (ii) Et_3N, DCM, rt, 2 days, 45%; (e) OsO_4, NMO, acetone–water (10 : 1), 25 °C, 8 h, 88%; (f) (i) $BH_3 \cdot Me_2S$, THF, rt, 4 h, reflux, 1 h; (ii) EtOH, reflux (95% for two steps); (g) TBAF, THF, 25 °C, 1 h, 90%.

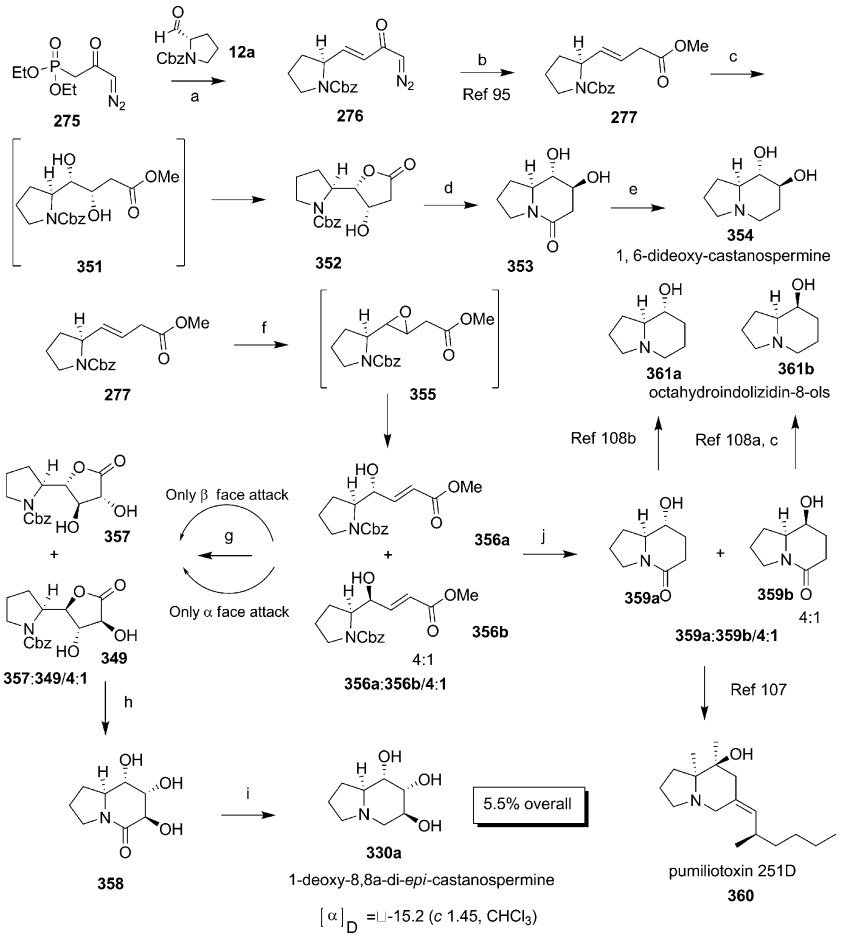


Scheme 64 *Reagents and conditions*: (a) *n*-BuLi, DMMP, THF, −78 °C, 85.2%; (b) $BnOCH_2CHO$, K_2CO_3, CH_3CN, 68%; (c) $NaBH_4$–$CeCl_3$, MeOH, rt, 63.6% for **340a**, 9.1% for **340b**; (d) OsO_4, NMO, actone–water, 57% for **341b**, 17% for **341a**; (e) Ac_2O, pyridine, DMAP, DCM, 96%; (f) H_2, Pd/C, MeOH, 94%; (g) MsCl, Et_3N, DCM, quant.; (h) (i) TFA, DCM; (ii) TEA, CH_3CN, 50%; (i) NaOMe, MeOH, 77%.

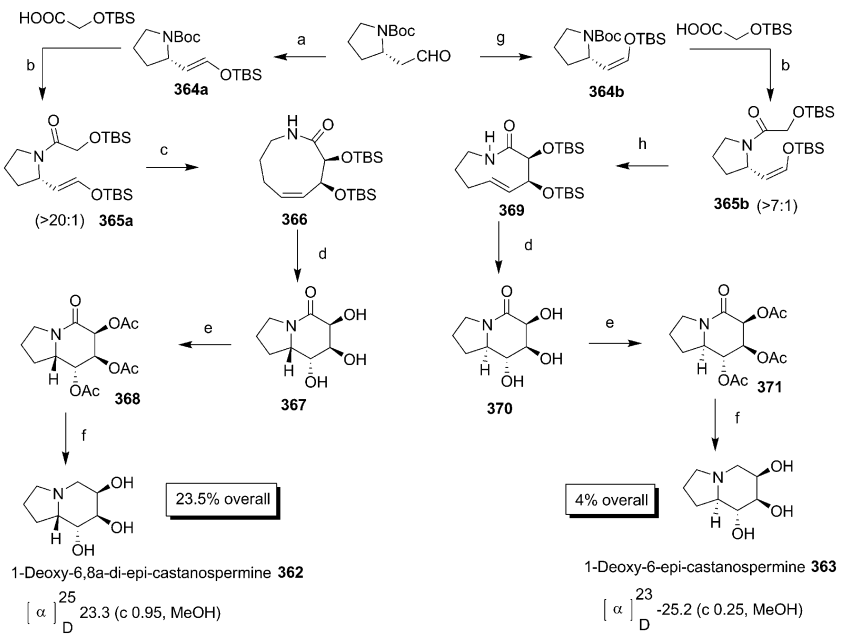


Scheme 65 *Reagents and conditions*: (a) MeNH(OMe)·HCl, DCC, HOBt, Et_3N, 0 °C to rt, 6 h, 92%; (b) LAH, THF, 0 °C, 30 min, 90%; (c) CH_2=CHMgBr, 0 °C, 3 h, 70%; (d) methyl acrylate, Grubbs II catalyst (3 mol%), toluene, rt, 2 h, 92%, (*E* : *Z*/20 : 1); (e) OsO_4, NMO, acetone–H_2O, rt, 3 h, 61% for the major isomer **349**; (f) Pd/C, H_2, MeOH, rt, 85%; (g) BH_3·Me_2S, THF, reflux, then EtOH, reflux, 82%.

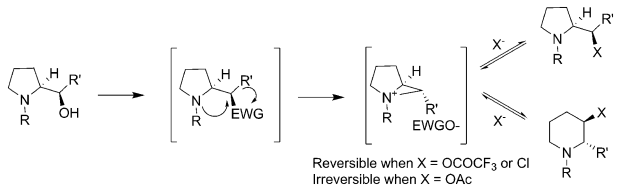
Bhat and co-workers made an entry into the synthesis of castenospermine alkaloid by synthesizing 1-deoxy-7,8*a*-di-*epi*-castanospermine **330c** through RCM and Upjohn dihydroxylation (Scheme 65).[105] The Cbz-prolinal **12a** was prepared by condensing the Cbz-proline with methoxy methyl amine chloride followed by LAH reduction of the Weinreb amide **346.** The Grignard addition of vinylmagnesium bromide on **12a** produced an inseparable mixture of diastereomers **347** which as such subjected to cross olefin metathesis with methyl acrylate in the presence of 2nd generation Grubbs II catalyst to afford **348.** The dihydroxylation of **348** gave a mixture of isomers which on purification by column chromatography afforded the major pure isomer **349,** the structure of which was confirmed by single X-ray analysis. The diol **349** without prior protection of –OH, hydrogenated to give amide **350** which on subsequent reduction using borane produced the targeted compound **330c.**



Scheme 66 *Reagents and conditions*: (a) **12a**, NaH, THF, −78 °C, 70%; (b) MeOH, *hν*, 25 °C, 4 h, 97%; (c) OsO_4, NMO, acetone–water, 25 °C, 48 h, 66%; (d) H_2, Pd, 94%; (e) $BH_3 \cdot Me_2S$, THF, 0 to 25 °C, 12 h, 71%; (f) (i) MCPBA, DCM, 25 °C, 10 h; (ii) DBU, 0 to 25 °C, 4 h, 67%; (g) OsO_4, NMO, actone–water, 6 h, 71%; (h) H_2, Pd/C, MeOH, 25 °C, 24 h, 73%; (i) $BH_3 \cdot Me_2S$, THF, 0 to 25 °C, 12 h, 70%; (j) H_2, Pd/C, MeOH, 25 °C, 24 h, 76%.



Scheme 67 *Reagents and conditions*: (a) TBSCl, DBU, DCM, reflux, 88%; (b) (i) TMSOTf, 2,6-lutidine, DCM, 0 °C; (ii) EDCI, HOBt, NMM, DCM (60% two steps); (c) LHMDS, toluene, reflux, 66%; (d) oxone, MeOH–H_2O, 63%; (e) Ac_2O, pyridine, 71%; (f) LAH, THF, reflux, 86%; (g) TBSCl, NaH, THF, 0 °C, 83%; (h) LDA, MW, benzene, 21%; (d)–(f) 38%.

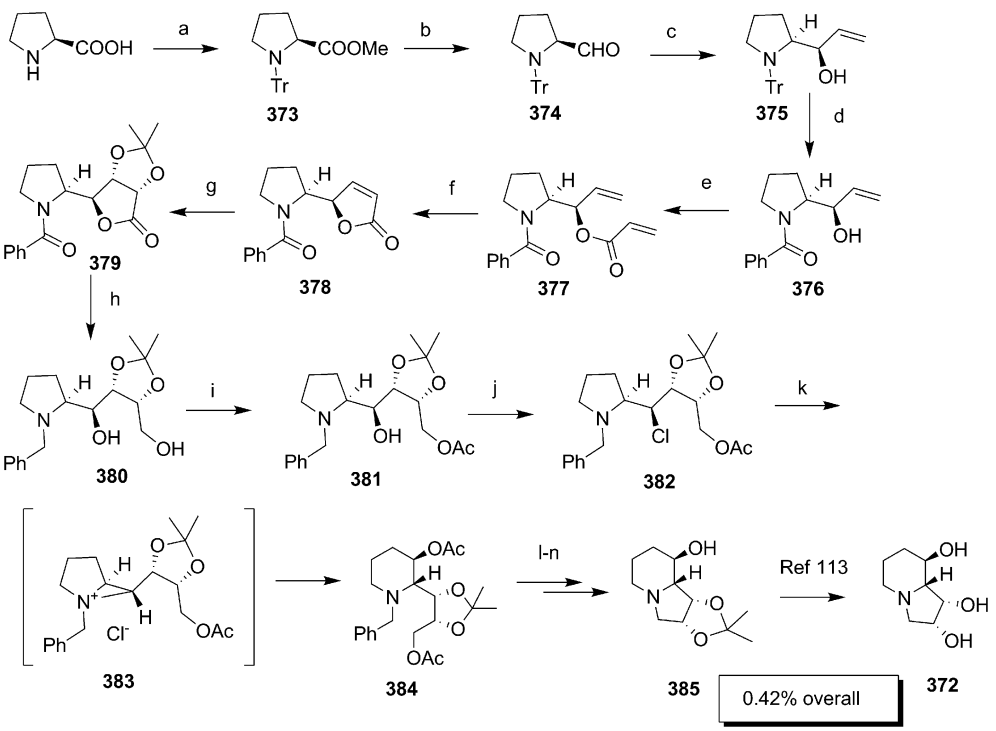


Scheme 68 Enantioselective ring expansion of prolinol derivatives.

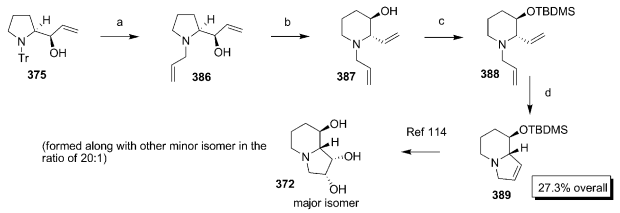
Bernardim *et al.* synthesized several castanospermine analogues by synthesizing a robust intermediate **277** (Scheme 66)[106] by well known efficient Wolf rearrangement of **276** prepared from phosphonate **275** and Cbz-prolinal **12a** under photocatalytic condition. The dihydroxylation of **277** afforded **351** which on subsequent hydrogenation gave **352**. The synthesis of 1,6-dideoxy-castenospermine **354** was completed by direct reduction of the lactam **353** using $BH_3 \cdot Me_2S$. Similarly, the compound **277** on epoxidation followed by treatment with DBU produced a diastereomeric mixture of **356a** and **356b** (4 : 1). The mixture of alkene **356** when dihydroxylated gave a mixture of **357** and **349** (4 : 1) with facial selectivity. The hydrogenation of **357** provided **358** after purification using column chromatography. The reduction of the lactam **358** afforded castanospermine analogue 1-deoxy-8,8*a*-di-*epi*-castenospermine **330a**. Interestingly the synthesis of **359a** and **359b** by hydrogenation of **356a** and **356b** constituted the formal syntheses of pumiliotoxin 251D **360** (ref. 107) and of octahydroindolizidin-8-ols **361a** and **361b**.[108]

Suh and co-workers efficiently applied their ACR-induced stereoselective ring-expansions of lactams for the synthesis of 1-deoxy-6,8*a*-di-*epi*-castenospermine **362** and 1-deoxy-6-*epi*-castenospermine **363** (Scheme 67).[109] The 1-carbon homologated Boc prolinal was converted diastereoselectively to **364a** and **364b** by differential selection of base DBU and NaH respectively. The selective deprotection of **364a** using TMSOTf and 2,6-lutidine followed by coupling with protected glycolic acid resulted **365a**. The compound **365a** on ACR execution afforded the 7 member lactam **366** which on treatment with oxone resulted in the formation of **367** *via trans* annulations and concomitant TBS deprotection. The formation of **366** was elegantly explained by the authors by invoking different transition states. The triol **367** was acetylated and reduced with LAH to afford **362**. In a similar way the *cis* isomer **364b** was transformed to **363** with ACR induced technique.

Cossy and co-workers have accomplished two formal synthesis of (−)-swainsonine **372** by enantioselective ring expansion of prolinol derivatives.[110] The ring expansion traverses through the formation of aziridinium ion (Scheme 68) which was first proposed by Fuson and Zirkle in 1948 (ref. 111) and successfully utilised by O'Brien's group.[112] The commercially available proline was converted to trityl ester **373** which on LAH reduction followed by Swern oxidation afforded the aldehyde **374**. The diastereoselective addition of vinylmagnesium chloride to the aldehyde **374** afforded the hydroxyl derivative **375** diastereoselectively (98 : 2). In order to obviate the further synthetic consequences, the trityl group was converted to



Scheme 69 *Reagents and conditions*: (a) (i) $SOCl_2$, MeOH, 36 h; (ii) Ph_3CCl, Et_3N, $CHCl_3$, (90% for two steps); (b) (i) LAH, THF; (ii) Swern oxidation; (95% for two steps); (c) vinylmagnesium chloride, Et_2O, −78 °C, 93%; (d) (i) HCl, 5 M, Et_2O; (ii) NaOH, PhCOCl (68% for two steps); (e) acryloyl chloride, DMAP, Et_3N, DCM, 65%; (f) Grubbs II catalyst, toluene, 80 °C (crude product filtered on Celite pad); (g) $RuCl_3$, $NaIO_4$ (1.5 equiv.), cat H_2SO_4, EtOAC–CH_3CN–H_2O; (ii) $Me_2C(OMe)_2$, APTS, DCM, (41% for f, g); (h) LAH, THF, reflux, 94%; (i) AcCl, 2,4,6-collidine, DCM, 88%; (j) MsCl (4.5 equiv.), Et_3N (8.0 equiv.), microwave, 100 °C, THF, 24%; (k) AgOAc, THF, 120 °C, microwave, 46%; (l) NaOMe, MeOH, THF, 83%; (m) H_2, Pd/C, EtOH, 93%; (n) DEAD, PPh_3, pyridine, 43%.



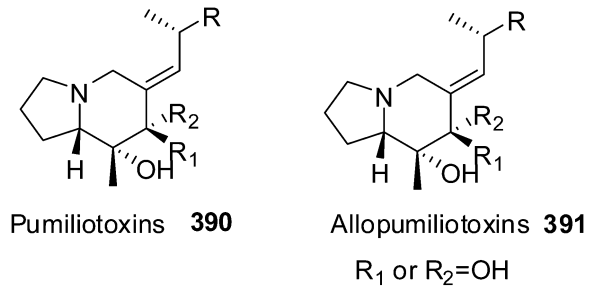
Scheme 70 *Reagents and conditions*: (a) (i) HCl, Et_2O; (ii) allylBr, K_2CO_3, *n*-Bu_4NBr, toluene, 50%; (b) (i) $(CF_3COO)_2O$, Et_3N, THF; (ii) NaOH, 95%; (c) TBDMSCl, Et_3N, DMAP, DCM, 70%; (d) (i) CSA; (ii) Grubbs I catalyst, DCM, reflux; (iii) K_2CO_3, 82%.

benzoyl to give the compound **376.** The compound **376** on treatment with acryloyl chloride produced the compound **377** which on RCM using Grubbs II catalyst afforded the product **378.** The *syn* dihydroxylation of the olefin **378** followed by diol protection provided the compound **379** which on LAH reduction gave **380.** When the attempted ring expansion of this **380** was unsuccessful, the compound **381** was prepared by protecting primary –OH with acetyl group and the secondary –OH of **381** was transformed to –Cl under microwave condition to afford **382.** The treatment of **382** with AgOAc effected the ring expansion smoothly to give **384** through the formation of aziridinium ion **383.** The further conventional synthetic steps performed over **384** gave **385** to complete the formal synthesis of (−)-swainsonine **372** (Scheme 69).[113]

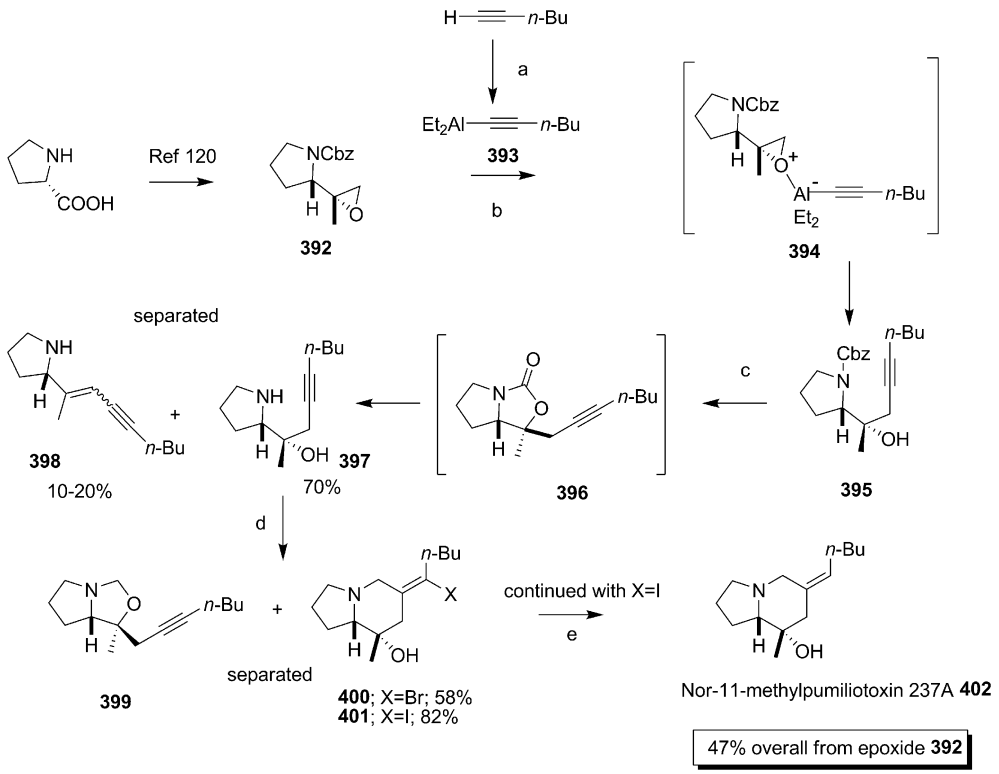
The second strategy utilized the hydroxyl allyl intermediate **375** which was converted to *N*-allylic compound **386,** suitable for ring expansion. The ring expansion of **386** was performed in the presence of $(CF_3COO)_2O$ followed by treatment with NaOH to afford **387** whose OH was further protected with TBDMS to give **388.** The RCM on HCl salt of **388** using Grubbs I catalyst gave the compound **389** which completed the formal synthesis of (−)-swainsonine **372** (Scheme 70).[114]

4.5. Pumiliotoxins

Pumiliotoxins are bicyclic indolizidine alkaloids, isolated from the amphibians *Dendrobates pumilio* in South America, in 1963.[115] They are best known for their cardiotonic activities and myotonic activities.[116] Pumiliotoxins **390** and their hydroxyl congener allopumiliotoxins **391** differ by their structure in terms of hydroxyl groups.



The designated pumiliotoxins are characterised in the general structural form **390.** There have been almost 40 members of this family isolated and found to show potent



Scheme 71 *Reagents and conditions*: (a) *n*-BuLi, Et_2AlCl (1 : 1); (b) 2.0 equiv. of **393**, toluene : hexane (7 : 1), 0 °C, NH_4Cl work up, 95%; (c) $Ba(OH)_2$, H_2O, 100 °C; (d) (*n*-$Bu)_4NBr$, $(CH_2O)n$, CSA, CH_3CN, 58%; or NaI, $(CH_2O)n$, CSA, H_2O, 100 °C, 82%; (e) *n*-BuLi (2.5 equiv., −78 °C), ether, protonation using MeOH, 83%.

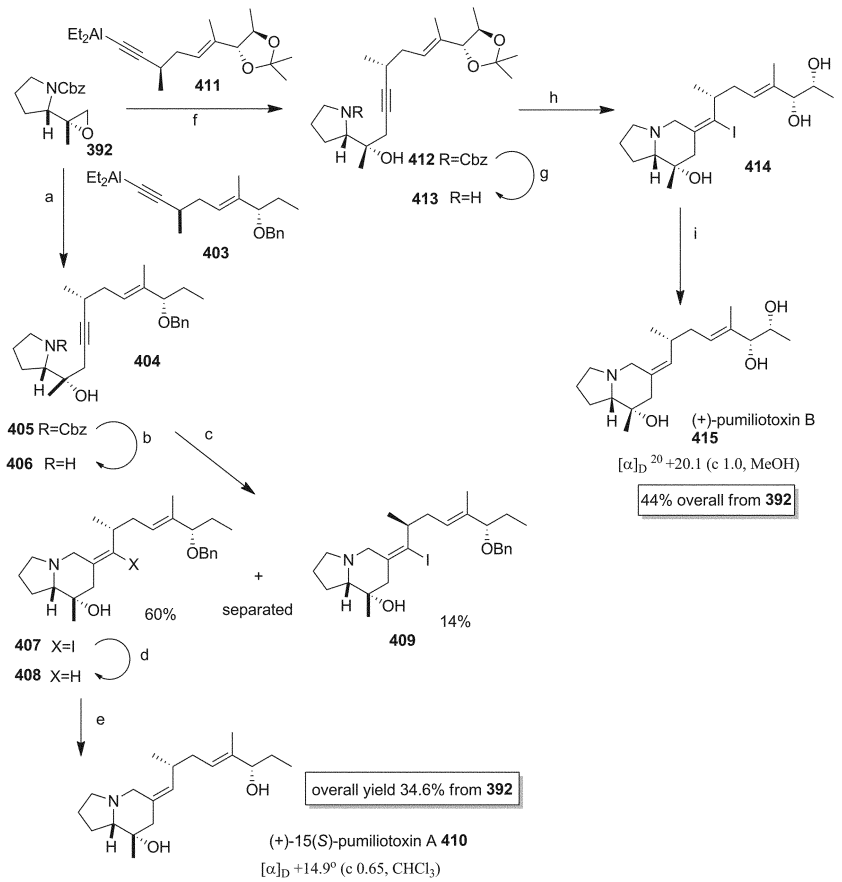
pharmaceutical behaviours. The (*Z*)-alkylidene side chain has attracted major attention in contemplating the design of the total synthesis for pumiliotoxins since the incorporation of a stereo controlled exocyclic double bond has been a formidable challenge[117] for synthetic chemists. The basic indolizidine core with a 5 member nitrogen stereo centre can be best realized using proline as a starting material. Over the last few years many chiral pool syntheses of these complex molecules have been performed and most of them involved proline as a major synthetic precursor for the construction of the chiral pyrrolidine motif.

Overmann and co-workers pioneered[118] the synthesis of heterocycles and pumiliotoxins by using their well developed iodide promoted iminium ion-alkyne cyclization strategy (Scheme 71). The epoxide **392** envisioned to be the viable precursor,[119] was synthesized from proline according to the literature reports.[120] The diastereoselective opening up of the epoxide **392** by using 2.0 equiv. of alkynylalane **393** afforded **395** exclusively. The Cbz group of **395** was subjected to deprotection using $Ba(OH)_2$ to give **397** and **398** separable on column chromatography. The plausible intermediate formed was **396** confirmed by different experimentation. The cyclization of **397** was effected either by an earlier developed strategy using 5.0 equiv. of $(n\text{-Bu})_4NBr$ or 10.0 equiv. of NaI in refluxing water to furnish **400** and **401** respectively along with separable compound **399**. The compound **401** was found to be light sensitive and thus immediately deiodinated to Nor-11-methyl-pumiliotoxin 237A **402** using *n*-BuLi.

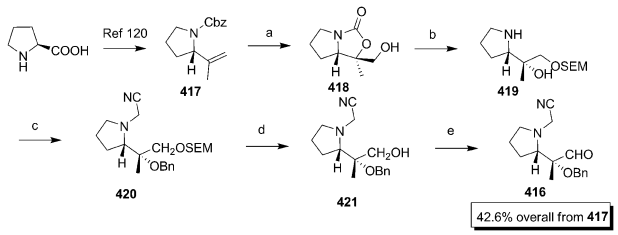
For the synthesis of (+)-15-(*S*)-pumiliotoxin A **410**, opening of epoxide **392** was effected using 2.0 equiv. of alumina derivative of **403** to furnish **404**. The deprotection of Cbz followed by iodide promoted cyclization produced **407** along with its epimeric congener **409**. The requisite **407** was deiodinated and further reacted with $Li–NH_3$ to afford pumilitoxin A **410** (Scheme 72).

In a similar way, the synthesis of (+)-pumiliotoxin B **415** was pursued using alkyne **411** (Scheme 72).

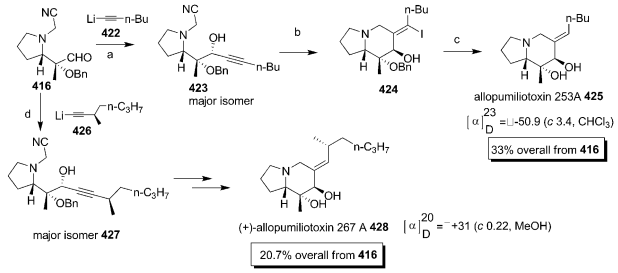
In a continuation of the synthetic interest, Overmann slightly modified the strategy for the diastereoselective addition of alkynes. This time the aldehyde **416** derived from proline proved to be a suitable chiral synthon for the pivotal step.[121] The compound **417** prepared from L-proline[120] was converted to **418** in three steps. The protection of primary –OH as SEM and subsequent hydrolysis of carbamate produced **419**. The cyanomethylation of free amine and protection of secondary –OH as benzyl ether afforded **420**. The deprotection of SEM group mediated by $LiBF_4$ gave alcohol **421** which on Swern oxidation furnished the key aldehyde intermediate **416** (Scheme 73).



Scheme 72 *Reagents and conditions*: (a) 2.0 equiv. of **403**, toluene : hexane (7 : 1), 0 °C, 95%; (b) $Ba(OH)_2$, H_2O, DME, 100 °C, 71%; (c) NaI, $(CH_2O)n$, CSA, H_2O, 100 °C, 71%; (d) *n*-BuLi, Et_2O, −78 °C, MeOH, 85%; (e) Li, NH_3, THF, MeOH–NH_4Cl, 85%; (f) 2.0 equiv. of **411**, toluene : hexane (7 : 1), 0 °C, 95%; (g) NaI, $(CH_2O)n$, CSA, H_2O, 100 °C, 68%; (h) $Ba(OH)_2$, H_2O, DME, 100 °C, 77%; (i) *t*-BuLi, NH_4Cl, H_2O, 89%.



Scheme 73 *Reagents and conditions*: (a) (i) I_2, CH_3CN; (ii) $AgNO_3$, 80 °C; (iii) Zn, MeOH, NH_4OAc; (76% for the three steps); (b) (i) SEM–Cl, $iPrNEt_2$; (ii) KOH, EtOH, H_2O, 80 °C; (c) (i) ICH_2CN, Et_3N, rt; (ii) KH, BnBr (80% overall from **418**); (d) $LiBF_4$, CH_3CN, H_2O, 78%; (e) Swern oxidation, 72–90%.



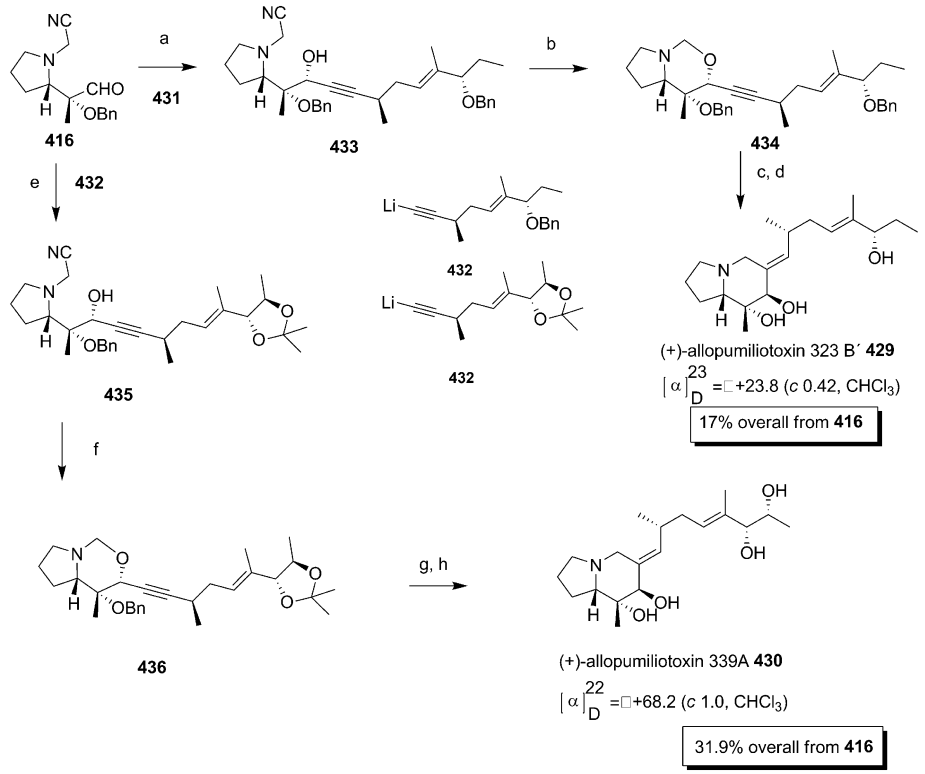
Scheme 74 *Reagents and conditions*: (a) **422**, chlorotitanium triisopropoxide, THF, −50 °C, 80% for isomer **423**; (b) (i) $AgNO_3$, EtOH, rt, 76%; (ii) NaI, $(CH_2O)n$, CSA, H_2O, 100 °C, 71%; (c) (i) *n*-BuLi, MeOH, 92%; (ii) Li, NH_3, −78 °C, 83%; (d) **426**, THF, −78 °C, 41% for **427**; for the synthesis of **428** similar steps (b and c) repeated with overall yield 50.56%.

The diastereoselective addition of lithiated alkyne **422** to aldehyde **416** favoured the *syn* product **423** (10 : 1). The iodide mediated cyclization of **423** using NaI in the presence of CSA and paraformaldehyde provided **424** which on deiodination followed by debenzylation afforded **425**, the nor-11-methyl analog of allopumiliotoxin 253A (Scheme 74).

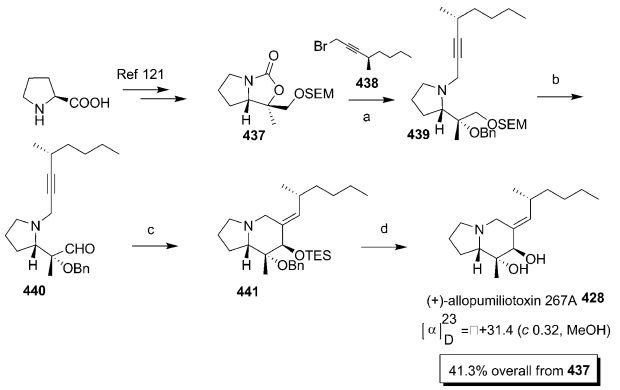
For the synthesis of (+)-allopumiliotoxin 267A **428**, the diastereoselective addition to the aldehyde **416** was performed using alkyne **426** to furnish **427**. The similar synthetic steps as described earlier were repeated to achieve the target (Scheme 74).

In similar ways (+)-allopumiliotoxin 323B′ **429** and (+)-allopumiliotoxin 339A[122] **430** were synthesized by employing diastereoselective nucleophilic addition of alkynes **431** and **432** respectively upon proline derived aldehyde **416** (Scheme 75).

Tang and Montgomery conveniently utilized the intermediate **437** prepared from proline ester according to Overman's procedure,[121] for the synthesis of (+)-allopumiliotoxin 267A **428**, (+)-allopumiliotoxin 339B **451** and (+)-allopumiliotoxin 339A **430** using Ni catalysed silane mediated diastereoselective cyclisation (Schemes 76 and 77).[123] The base hydrolysis of carbamate **437** with subsequent incorporation of the alkyne chain **438** followed by protection of the secondary –OH as benzyl ether afforded the compound **439**. The compound **439** on deprotection of SEM followed by oxidation produced the requisite aldehyde **440** which on treatment with triethylsilane in the presence of Ni $(COD)_2$ and PBu_3 underwent cyclisation to produce the single isomer **441**, confirmed by spectroscopic



Scheme 75 *Reagents and conditions*: (a) **431**, THF, −78 °C, 53% for major isomer **433**; (b) $Cu(OTf)_2$, THF, rt, 68%; (c) NaI, $(CH_2O)n$, CSA, H_2O, 100 °C, 66%; (d) (i) *n*-BuLi, MeOH, 83%; (ii) Li, NH_3, −78 °C, 86%; (e) **432**, THF, −78 °C, 68% for the major isomer **435**; (f) AgOTf, THF, 94%; (g) NaI, $(CH_2O)n$, CSA, H_2O–acetone, 100 °C, 81%; (h) (i) *n*-BuLi, MeOH, 81%; (ii) Li, NH_3, −78 °C, 76%.



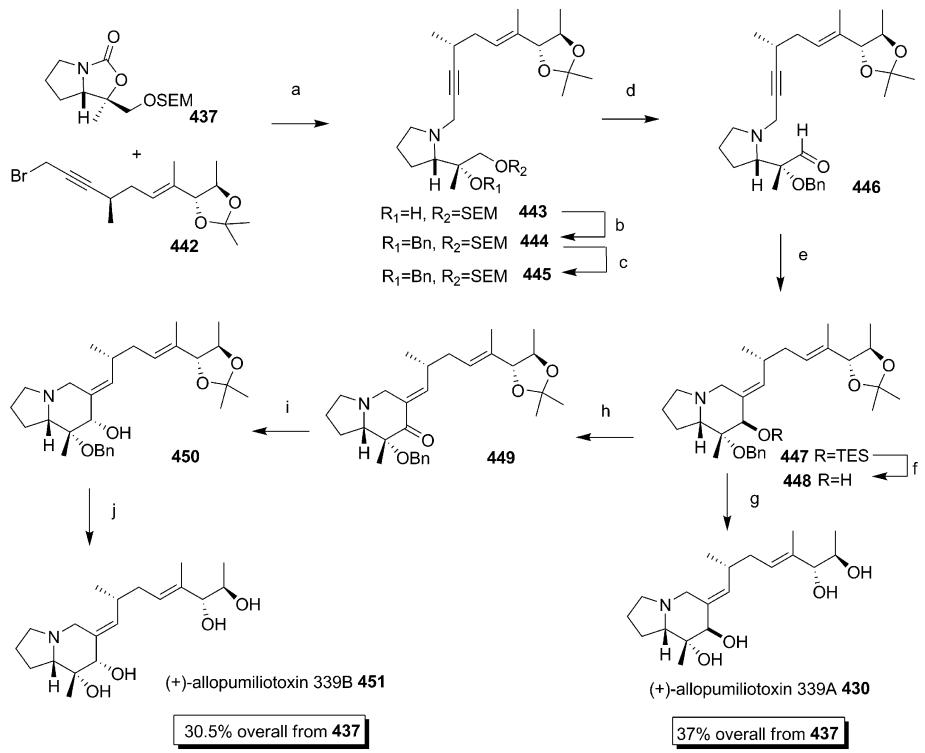
Scheme 76 *Reagents and conditions*: (a) (i) KOH, EtOH; (ii) **438**, iPr_2NEt, THF, 74% for two steps; (iii) BnBr, KH, THF, 83%; (b) (i) NBu_4F, molecular sieves, THF, 94%; (iii) Swern oxidation, 93%; (c) Et_3SiH, $Ni(COD)_2$, PBu_3, THF, 95%; (d) (i) HF·pyridine, THF, 92%; (ii) Li, NH_3, THF, 88%.

methods. The further deprotection of the protecting groups gave the target molecule (+)-allopumiliotoxin 267A **428**. The synthesis of allopumiliotoxin 339B **451** and (+)-allopumiliotoxin 339A **430** were accomplished with similar synthetic sequences (Scheme 77).

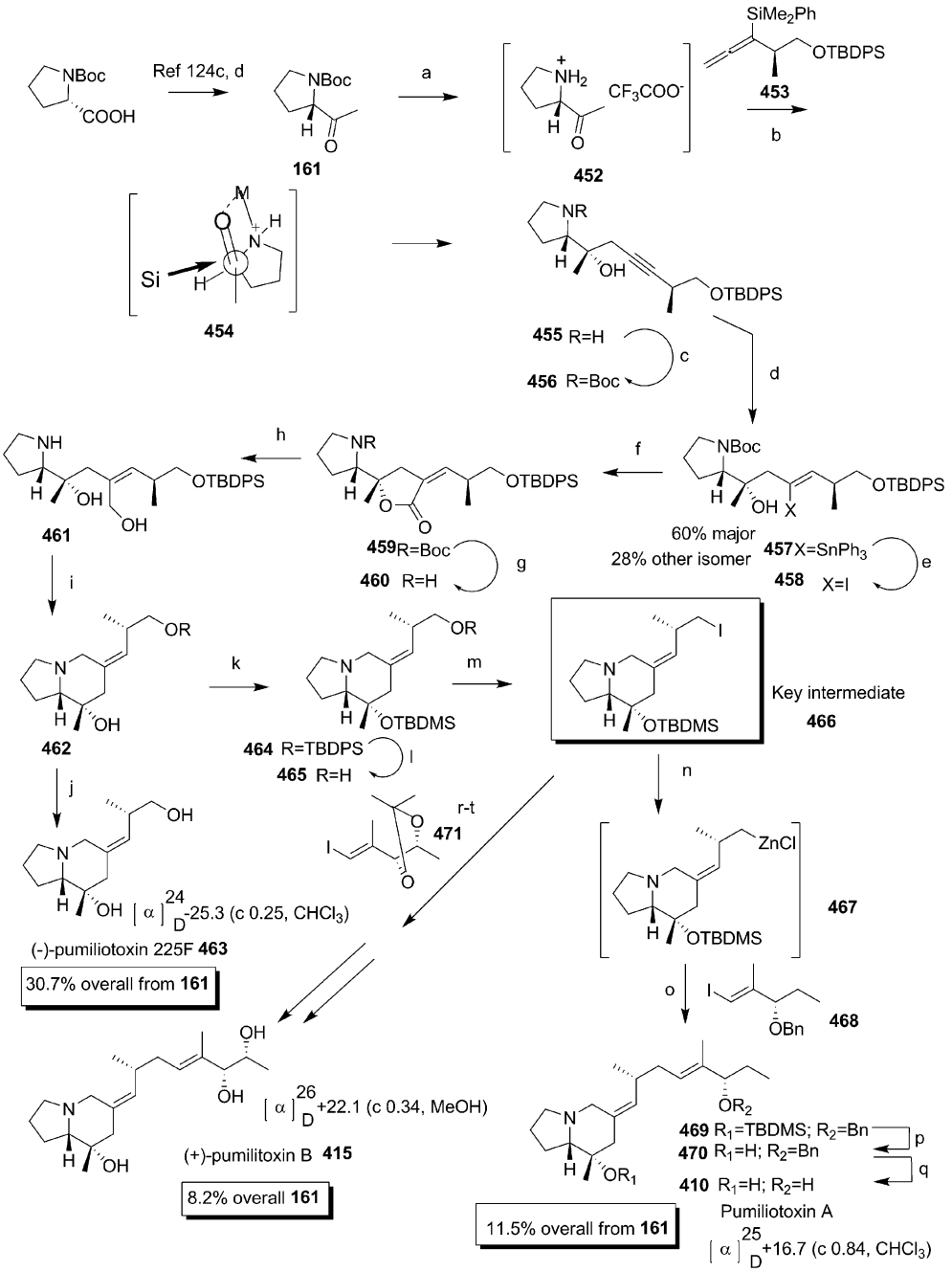
Kibayashi and co-workers achieved the synthesis (+)-pumiliotoxin A **410**, (+)-pumilitoxin B **415** and first total synthesis of (−)-pumiliotoxin 225F **463** by performing highly metal mediated diastereoselective nucleophilic addition of conjugated silylated compound **453** to the triflouro acetate salt **452** derived from proline (Scheme 78).[124] The efficiency of the nucleophilic addition of **453** to **452** was more pronounced in the presence of Hf (92% single isomer) than Ti (71%). The transition state invoked was presumed to be metal chelated **454** which could smoothly allow the complete diastereoselectivity. The hydrostannylation of the compound **456** afforded **457** with complete *trans* selectivity and with higher regioselectivity along with the other minor isomer. The requisite **457** was separated and treated with NIS to give iodinated compound **458** which on subsequent carbonyl insertion produced the lactone **459**.

The Boc deprotected **460** was subjected to DIBAL reduction to give **461**. The cyclisation to **462** was successfully performed under Mitsunobu condition which on subsequent deprotection of terminal TBDPS group using TBAF completed the first total synthesis of pumilitoxin 225F **463**. However, the optical activity observed for the synthesized compound was significantly lower than that of the natural one.

It was visualised that the intermediate **466** could be efficiently employed for the synthesis of other appendages. Thus compound **462** was transformed to iodo compound **466** through convenient synthetic sequences. After optimising the reaction conditions, a platform was set-up for the cross coupling of the iodo compound **466** with vinyl iodo compound **468** through Zn metallated halogen exchange to produce **469** by forming intermediary **467**. Further classical synthetic steps accomplished the conversion of **469** to pumiliotoxin A **410**. In a similar way the synthesis of pumiliotoxin B **415** was furnished by coupling the intermediate **466** with iodo compound **471**.

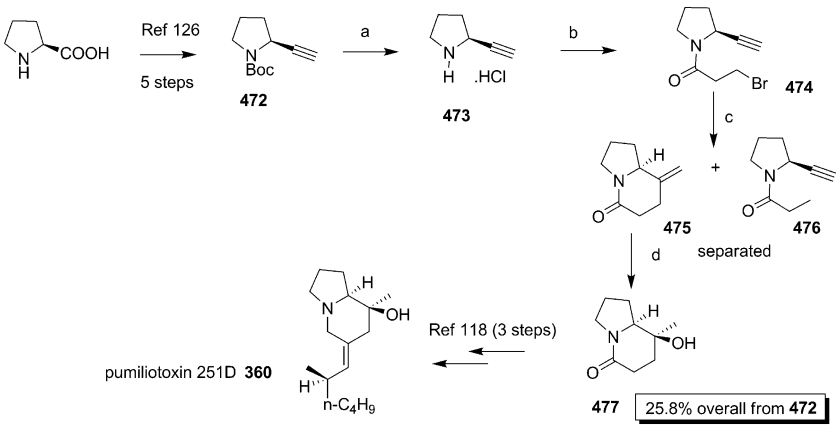


Scheme 77 *Reagents and conditions*: (a) (i) KOH, EtOH; (ii) **442**, iPr_2NEt, THF (92% for two steps); (b) BnBr, KH, THF, 82%; (c) NBu_4F, molecular sieves, THF, 92%; (d) $(COCl)_2$, DMSO, Et_3N, 89%; (e) Et_3SiH, $Ni(COD)_2$, PBu_3, THF, 93%; (f) HF·pyridine, THF, 87%; (g) (i) 3 N HCl, THF, 92%; (ii) Li, NH_3, THF, 80%; (h) $(COCl)_2$, DMSO, Et_3N, 86%; (i) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 95%; (j) (i) 3 N HCl–THF, 91%; (ii) Li, NH_3, THF, 82%.



Scheme 78 *Reagents and conditions*: (a) CF_3COOH, rt, 3 h; (b) $HfCl_4$ ($TiCl_4$), −78 °C, 30 min, **453**, −78 °C to rt, 3 h; (c) $(Boc)_2O$, 30% aq. K_2CO_3; (92% with $HfCl_4$; 71% with $TiCl_4$ for three steps); (d) Ph_3SnH, Et_3B, benzene, rt, 5 days; (e) NIS, DCM, rt, 30 min, 83%; (f) CO, 2.0 mol% $Pd(OAc)_2$, PPh_3, Bu_3N, HMPA, 100 °C, 97%; (g) TFA, DCM, 93%; (h) DIBAL-H, 71%; (i) CBr_4, PPh_3, DCM, 85%; (j) TBAF, THF, 84%; (k) TBDMSOTf, 2,6-lutidine, DMAP, 91%; (l) TAS-F, DMF, 85%; (m) I_2, PPh_3, imidazole, 95%; (n) *t*-BuLi (2.0 equiv.), Et_2O, −110 °C, then $ZnCl_2$ (1.0 equiv.), THF, −110 °C-rt; (o) $Pd(PPh_3)_4$ (10 mol%), benzene, rt, 60%; (p) $Et_3N{\cdot}3HF$, CH_3CN, 60 °C, 88%; (q) Li, NH_3, MeOH, 81%; (r) *t*-BuLi (2.0 equiv.), Et_2O, −110 °C, then $ZnCl_2$ (1.0 equiv.), THF, −110 °C-rt; $Pd(PPh_3)_4$ (10 mol%), benzene, rt, 51%; (s) $Et_3N{\cdot}3HF$, CH_3CN, 60 °C, 85%; (t) 10% HCl, THF, 70%.

Cossy *et al.* persuaded the formal synthesis of pumiliotoxin 251D **360** through chemical and photochemical induced radical cyclisation (Scheme 79).[125] The strategy utilized L-proline as a starting material to construct the requisite alkyne **472** according to the literature reports.[126] The Boc group of **472** was deprotected and the free NH was protected with bromopropenoyl group to afford key requisite **474.** The cyclisation of **474** was carried out either by chemically or photo induced radical formation to give **475** along with the debrominated product **476.** The reductive hydroxymercuration of **475** gave a mixture of epimers separable by column chromatography to give **477** which constituted the formal synthesis of pumiliotoxin 251D **360.**[127]

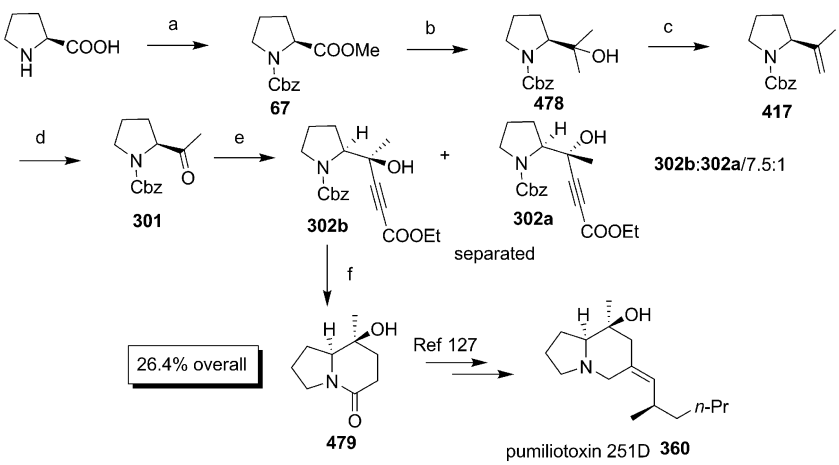


Scheme 79 *Reagents and conditions*: (a) HCl, EtOH, 8 N, reflux; (b) $BrCH_2CH_2COCl$, Et_3N, 10 min, 0 °C, 68% for the two steps; (c) Bu_3SnH, AIBN, benzene, reflux, 15 h, 40%; (d) $Hg(OAc)_2$, 3 h, rt, NaOH, $NaBH_4$, 95%.

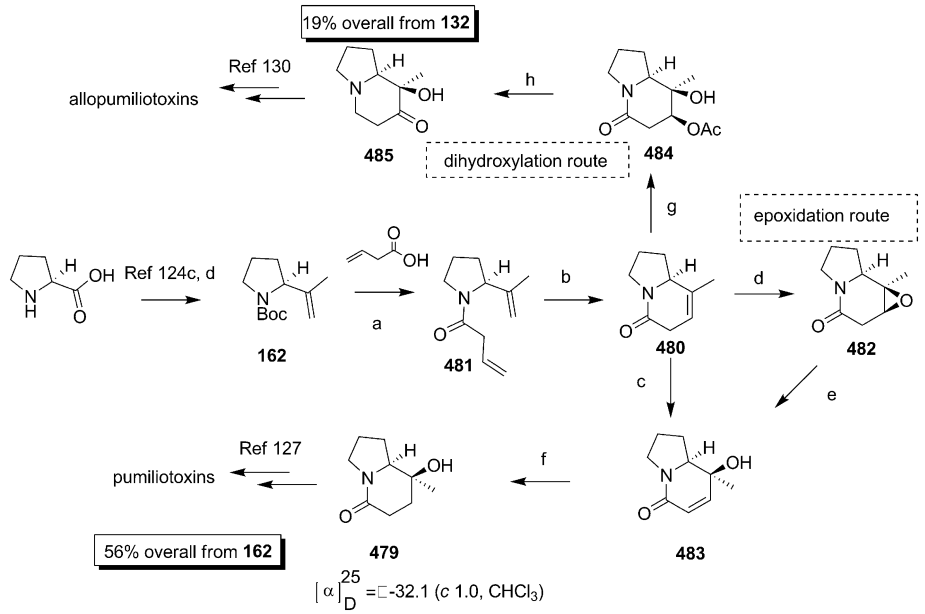
Zhao and co-workers approached the formal synthesis of pumiliotoxin 251D **360** by investigating Lewis acid mediated diastereoselective nucleophilic addition of lithiated akyne to a carbonyl group (Scheme 80).[128] The synthesis was processed by the preparation of tertiary alcohol **478** by Grignard addition of CH_3MgI on Cbz-proline methyl ester. The reaction of the alcohol **478** with $SOCl_2$ in Et_3N afforded the alkene **417** which on ozonolysis gave the keto product **301**. The metal mediated addition of ethyl lithiopropiolate to **301** gave the separable mixture of diastereomers **302a** and **302b**. The compound **302b** was subjected to hydrogenation to produce the compound **479** to complete the formal synthesis of **360**.[127]

Stevenson and co-workers demonstrated the study of epoxidation and dihydroxylation on indolizidine **480** for the synthesis of precursors of pumiliotoxin and allopumiliotoxin alkaloids respectively (Scheme 81).[129] The strategy utilized the carbamate **162** synthesised from proline according to Overmann's procedure,[124c,d] converted to diene **481** which on subsequent RCM with Grubbs II catalyst produced the robust intermediate **480**. The epoxidation of **480** followed by opening up of the oxirane **482** produced the single compound **483** whose structure was confirmed by X-ray analysis. The tertiary alcohol **483** on hydrogenation gave the precursor **479** for the synthesis of pumiliotoxins.[127] Likewise the compound **480** was subjected to dihydroxylation followed by acetylation to isolate crude acetyl ester **484**. The dihydroxylation had taken place through concave face with (*R*)-configuration at C-8 as anticipated. The reduction of the crude **484** with LAH and subsequent oxidation of the secondary alcohol afforded the key intermediate **485** used for the synthesis of allopumiliotoxins.[130]

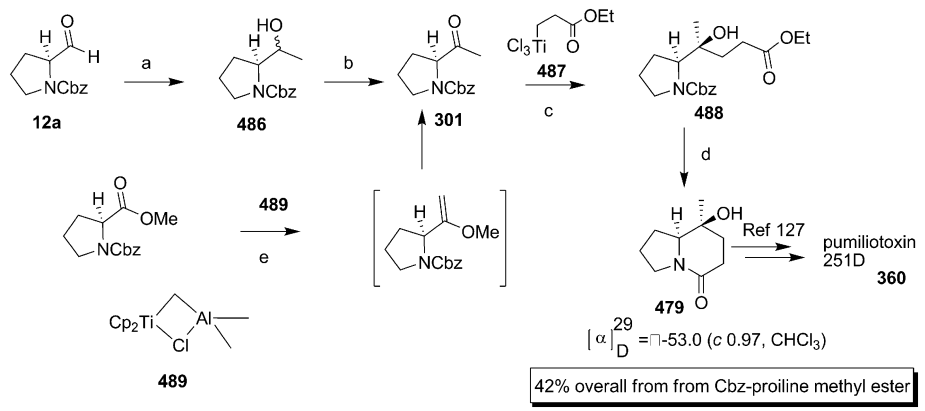
Barrett and Damiani described a very short and concise synthesis of indolizidine **479** for the formal approach of pumiliotoxin 251 D **360** (Scheme 82).[131] The synthetic strategy involved just six steps starting from Cbz-prolinal **12a**. The Grignard addition of MeMgBr on **12a** afforded the alcohol **486** which was as such oxidised using Jones reagent to give **301**. The addition of titanium homoenolate **487** to **301** furnished the single diastereomer **488** which on subsequent hydrogenolysis of Cbz group gave the indolizidine core **479**. For improvement of the yield author conveniently accessed **301** from Cbz-proline methyl ester using Tebbe reagent **489**.



Scheme 80 *Reagents and conditions*: (a) (i) $SOCl_2$, MeOH, reflux; (ii) CbzCl, K_2CO_3, CH_3CN (84% for two steps); (b) MeMgI, Et_2O, 91%; (c) $SOCl_2$, Et_3N, THF, −45 °C, 60%; (d) O_3, MeOH, Me_2S, 90%; (e) ethyl propiolate, LDA, THF, −78 °C, 80%; (f) H_2, Pd/C, MeOH, 80%.



Scheme 81 *Reagents and conditions*: (a) (i) TFA, DCM; (ii) Et_3N, diethylcyanophosphonate, but-3-enoic acid; (75% for two steps); (b) Grubbs II catalyst, toluene, MW, 15 min, 88%; (c) (i) MCPBA, DCM, 15 h, rt; (ii) Amberlite, IRA-400 (OH) resin, 85% for two steps; (d) MCPBA, DCM, 16 h, rt, 45%; (e) K_2CO_3, MeOH, 54%; (f) H_2, Pd/C, 100%; (g) (i) OsO_4, NMO, acetone–water; (ii) Ac_2O, pyridine (84% crude yield); (h) (i) LAH, $AlCl_3$, 78%; (ii) Swern oxidation, 44%.

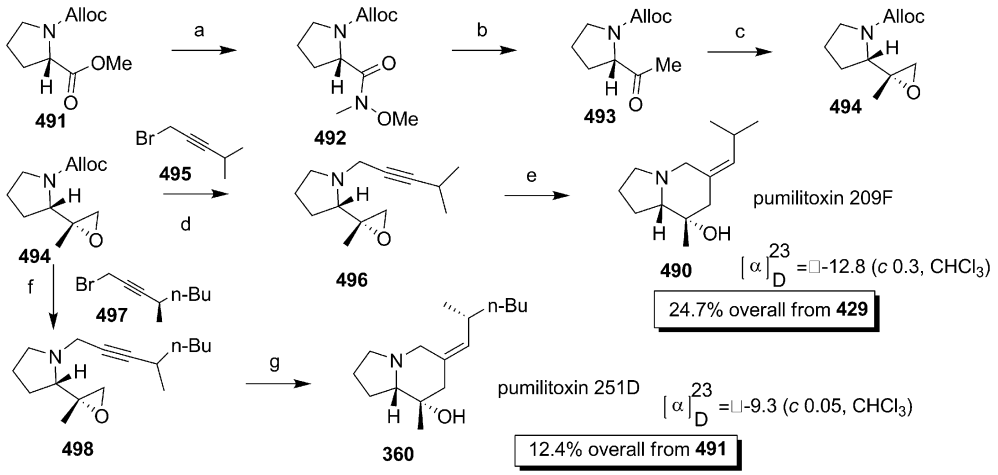


Scheme 82 *Reagents and conditions*: (a) MeMgBr, THF, −78 °C, 61%; (b) Jones reagent, 91%; (c) **487**, −78 °C, DCM, 49%; (d) H_2, Pd/C, 100%; (e) **489**, 1 M HCl, acetone, 87%.

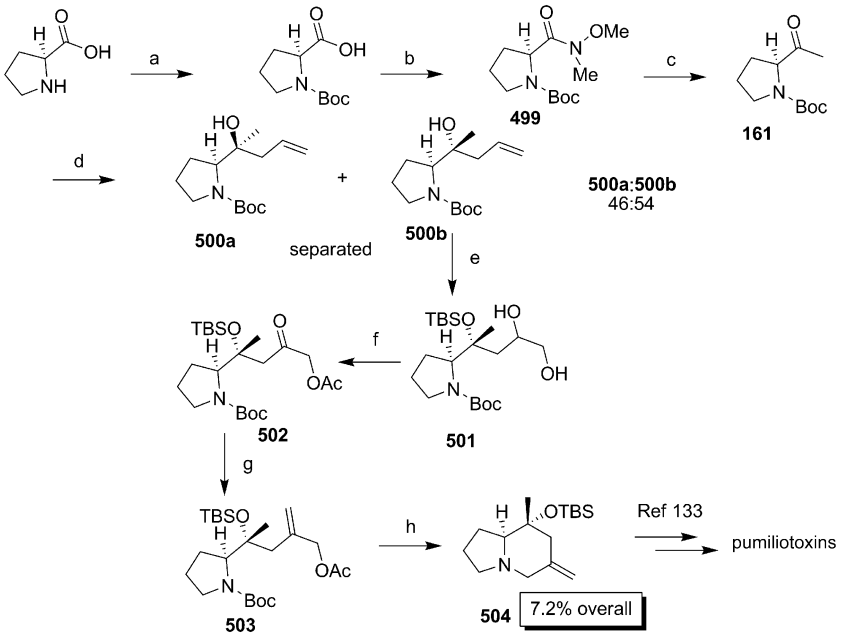
The synthesis of pumiliotoxin 209F **490** and pumiliotoxin 251D **360** was described by Woodin and Jamison involves the Ni catalysed diastereoselective epoxide-alkyne reductive cyclization (Scheme 83).[132] The Alloc protected proline methylate **491** (prepared from proline) was converted to keto compound **493** through the preparation of Wienreb amide **492** followed by addition of MeMgBr. The requisite epoxide **494** was synthesized by the treatment of **493** with trimethyl sulfonyl chloride in the presence of *n*-BuLi in high ee and de.

The effective removal of the Alloc group using catalytic $Pd(dba)_2$ and dppb in excess diethylamine followed by treatment with the suitable alkyne **495** and **497** afforded the compounds **496** and **498** respectively. The regioselective and diastereoselective cyclization of alkyne **496** and **498** was efficiently imparted using $Ni(COD)_2$ in the presence of trialkyl phosphines additives and Et_3B furnishing the indolizidines pumiliotoxin 209F **490** and pumiliotoxin 251D **360** respectively.

Martin *et al.* approached the synthesis of indolizidine core **504** as a precursor for pumiliotoxin indolizidines[133] *via* Tsuji–Trost reaction (Scheme 84).[134] The commercially available L-proline was converted to Boc-proline which on DCC coupling with (OMe)NHMe·HCl afforded the Wienreb amide **499**. The reaction of compound **499** with MeMgBr produced keto compound **161** which was transformed to an equimolar mixture of diastereomers **500** on treatment with ally magnesium bromide separable by standard column chromatography. The primary –OH of separated diastereomer **500b** was further converted to **501** by selective protection of chiral –OH as TBS group and subsequent dihydroxylation of terminal olefin with AD-mix-α. The protection of terminal –OH as acetate and oxidation of the



Scheme 83 *Reagents and conditions*: (a) MeONHMe·HCl, Me_3Al, DCM, 0 °C to rt, 95%; (b) MeMgBr, THF, 0 °C to rt, 94%; (c) Me_3SOCl, *n*-BuLi, THF, −20 °C, 72%; (d) (i) $Pd(dba)_2$ (5 mol%), dppb (5 mol%), Et_2NH, THF; (ii) **495**, Na_2CO_3, acetone, 55% (for the two steps); (e) $Ni(cod)_2$ (20 mol%), PMe_2Ph (40 mol%), Et_3B (150 mol%), 65 °C, 70%; (f) (i) $Pd(PPh_3)_4$ (5 mol%), Et_2NH, THF; (ii) **497**, Na_2CO_3, acetone; (48% for two steps); (g) $Ni(COD)_2$ (20 mol%), PMe_2Ph (40 mol%), Et_3B (150 mol%), 65 °C, 82%.



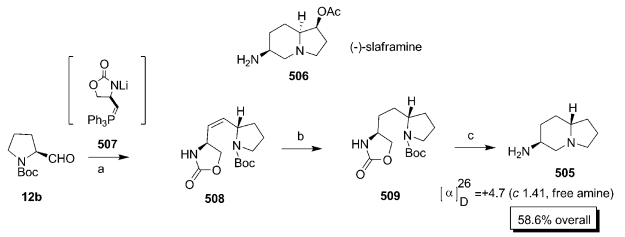
Scheme 84 *Reagents and conditions*: (a) $(Boc)_2O$, Et_3N, DCM, reflux, 24 h, 82%; (b) MeONHMe·HCl, DCC, Et_3N, DCM, reflux, 16 h, 82%; (c) MeLi, THF, −78 °C to rt, 2 h, 80%; (d) allylmagnesium bromide, THF, 0 °C, 3 h, 75%, (dr = 46 : 54 (**500a** : **500b**); (e) (i) TBS-triflate, 2,6-lutidine, DCM, 0 °C, 2 h, 83%; (ii) AD-mix-α, *t*-BuOH, H_2O, Na_2SO_3, 0 °C to rt, 48 h, 82%; (f) (i) Ac_2O, Et_3N, DCM, rt, 24 h, 86%; (ii) Dess–Martin periodinane, DCM, rt, 2 h, 72%; (g) $BrCH_3PPh_3$, NaHMDS, THF, rt, 2 h, 64%; (h) (i) TFA, DCM, rt, 2 h; (ii) $Pd(PPh_3)_4$ (10 mol%), Et_3N, THF, 60 °C, 2 h, 66%.

secondary –OH of **501** to ketone afforded the compound **502.** The Wittig olefination of **502** gave the olefinic product **503** which on Boc deprotection followed by subsequent cyclisation using Tsuji–Trost reaction in the presence of $Pd(PPh_3)_4$ and Et_3N furnished the indolizidine core **504.**

4.6. Miscellaneous examples

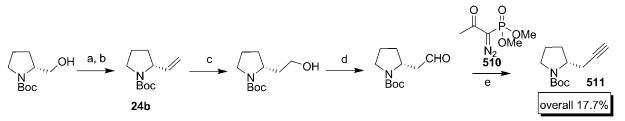
Sibi and Christensen achieved the synthesis of 6-amino-indolizidine **505,** an important indolizidine core present in various natural product, especially slaframine **506.**[92] The synthetic strategy utilized the Wittig reaction of the D-serine derived phosphorane **507** generated *in situ*; with Boc-prolinal **12b** to afford a single isomer **508** which on subsequent hydrogenation of the double bond gave **509.** The thermolytic cleavage of Boc group of **509** furnished the compound **505** (Scheme 85).

Fürstner and Kennedy efficiently synthesized some of the tylophora alkaloids through $PtCl_2$-catalyzed cycloisomerizations and tandem deprotection-Pictet–Spengler annulations.[135] The (*R*)-*N*-Boc-prolinol was subjected to 1-carbon homologation



Scheme 85 *Reagents and conditions*: (a) **507** (prepared *in situ*), THF, −78 °C, then **12b**, 72%; (b) H_2, Pd/C, 98%; (c) Heat, 83%.

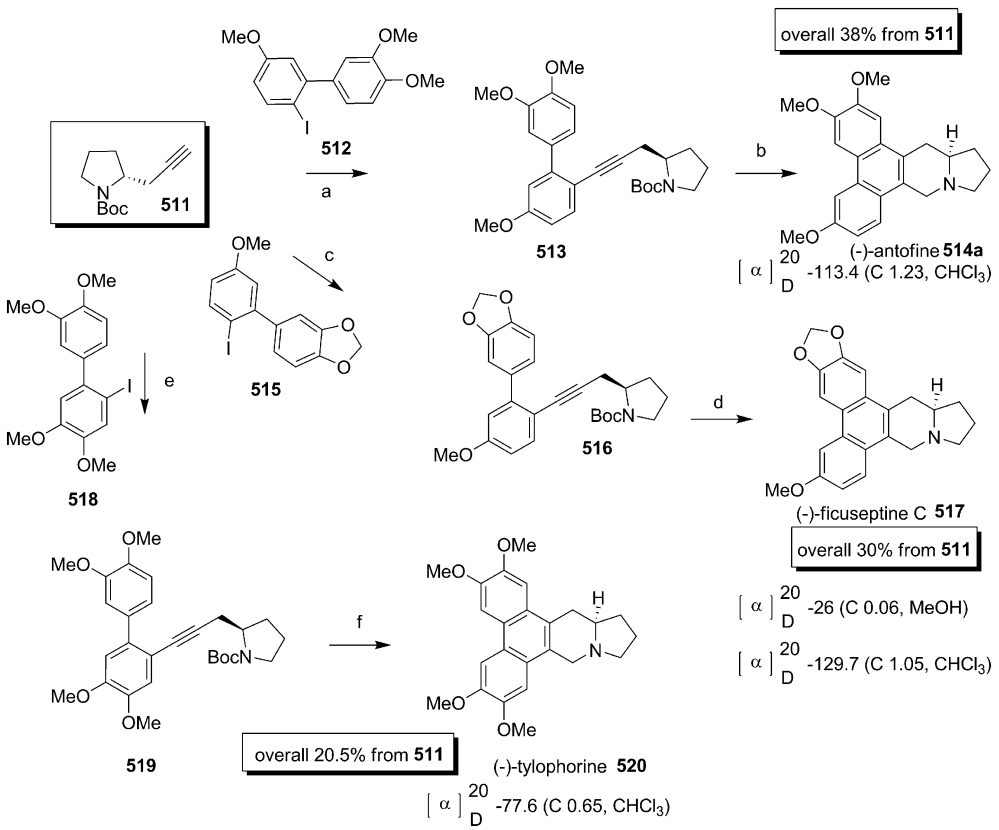
using hydroboration method and further transformed to the key alkene **511** by making use of Ohira–Bestmann reagent **510** (Scheme 86).



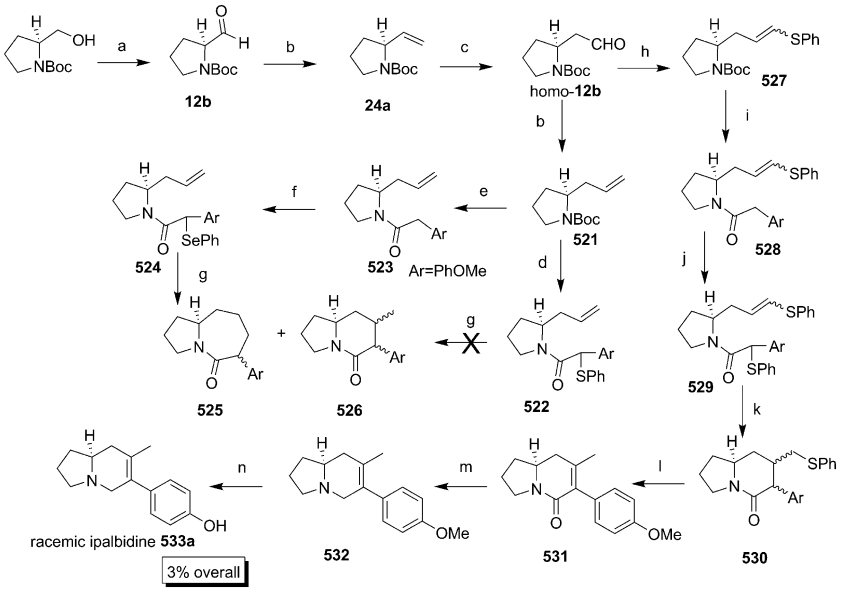
Scheme 86 *Reagents and conditions*: (a) tetra-*n*-propylammonium perruthenate (TPAP) (5 mol%), *N*-morpholine-*N*-oxide (NMO), DCM, 82%; (b) $Ph_3P{=}CH_2$, THF, 61%; (c) (i) 9-BBN, THF; (ii) $NaBO_3{\cdot}4H_2O$, H_2O, 88%; (d) TPAP (5 mol%), NMO, DCM, 73%; (e) Bestmann–Ohira reagent **510**, K_2CO_3, MeOH, 55% (ee > 99.5, chiral GC).

The alkyne **511** was subjected for coupling reaction with different iodo compounds **512, 515** and **518** to give **513, 516** and **519**. These intermediates on $PtCl_2$ catalysed cycloisomerizations followed by tandem deprotection-Pictet–Spengler cyclisation afforded the phenanthroindolizidine alakloids **514a, 517** and **520** (Scheme 87).

Ikeda *et al.* culminated in the total synthesis of (±)-ipalbidine **533a** isolated from the seeds of *Ipomoea alba* L using *exo*-trig cyclization (Scheme 88).[136] Initially the thio compound **522** synthesized from sequential homologation of Boc-prolinol was subjected to radical cyclization using Bu_3SnH and AIBN in refluxing toluene, but the starting material was recovered without any notable change. The compound **521** was then transformed into selenium compound **524** and then subjected for cyclization as described earlier. A mixture of products **525** and **526** formed with the formation of anticipated **526** in low yield. For the improvement of the synthesis, the thiovinyl compound **527** was prepared and converted to thioamide **529** which underwent the expected cyclization giving the product **530** in 65% yield. The further transformation of **530** to **532** was carried out by delsulfonation and reduction. The synthesis of ipalbidine **533a** was then achieved by hydrolysis of methoxy ether **532** using BBr_3 but with complete racemisation.

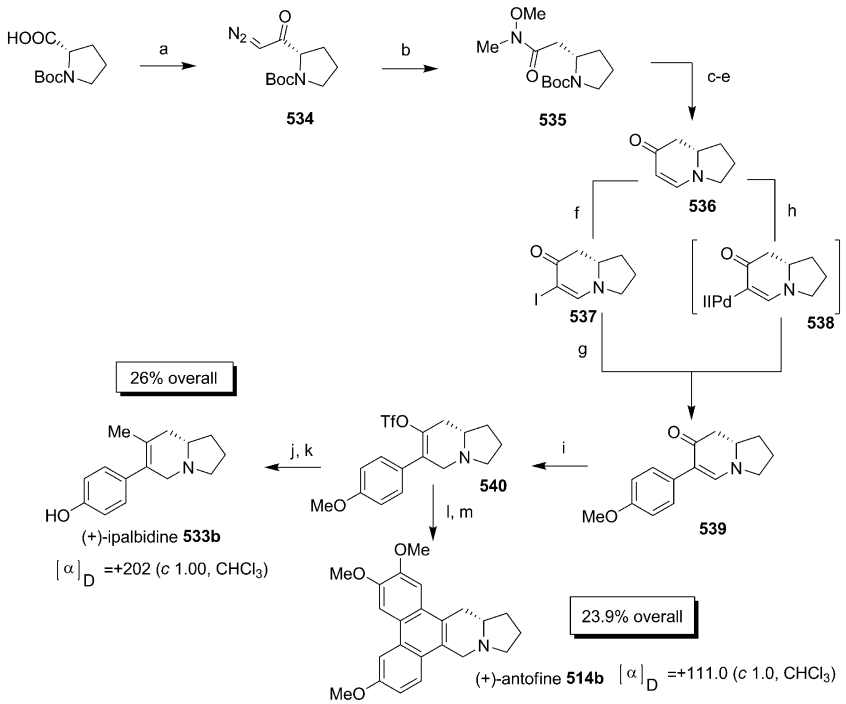


Scheme 87 *Reagents and conditions*: (a) (i) *n*-BuLi, THF, −40 °C, then 9-MeO-9-BBN, rt; (ii) iodide **512**, $[(dppf)PdCl_2]$ (5 mol%), THF, reflux, 58%; (b) (i) $PtCl_2$ (20 mol%), toluene (0.01 M), 60–80 °C, 3 h, 72%; (ii) aq. HCHO, HCl–EtOH, 80 °C, 91% (ee > 98%, chiral HPLC); (c) (i) *n*-BuLi, THF, −40 °C, 9-MeO-9-BBN, rt; (ii) iodide **515**, $[(dppf)PdCl_2]$ (5 mol%), THF, reflux, 64%; (d) (i) $PtCl_2$ (20 mol%), toluene (0.05 M), 60–80 °C, 56%; (ii) aq. HCHO, HCl–EtOH, 80 °C, 48% (ee > 98%, chiral; (e) (i), *n*-BuLi, THF, −40 °C, 9-MeO-9-BBN, RT; (ii) iodide **518**, $[(dppf)PdCl_2]$ (5 mol%), THF, reflux, 59%; (f) (i) $PtCl_2$ (20 mol%), toluene (0.05 M), 60–80 °C, 56%; (ii) aq. HCHO, HCl–EtOH, 80 °C, 62% (ee > 98%, chiral HPLC).



Scheme 88 *Reagents and conditions*: (a) SO_3·pyridine, Et_3N, DMSO, quant.; (b) $Ph_3P^+Br^-$, NaH, DMSO, 73%; (c) (i) Sia_2BH, THF, H_2O_2, NaOH, quant.; (ii) $(COCl)_2$, DMSO, Et_3N, DCM, quant; (b) 50%; (d) CF_3COOH, DCM then α-(*p*-methoxyphenyl)-α-(phenylthio)acetyl chloride, Et_3N, DMAP, DCM, 67%; (e) (i) Me_3SiI, MeCN then α-(*p*-methoxyphenyl)acetyl chloride, Et_3N; (f) LDA, PhSeCl, THF, 51% from **521**; (g) Bu_3SnH, AIBN, toluene, reflux; (h) $Ph_2(O)CH_2SPh$, NaH, DMSO, 76%; (i) Me_3SiI, CH_3CN, (*p*-methoxyphenyl)acetyl chloride, Et_3N, DCM, 57%; (j) LDA, $(PhS)_2$, THF, 81%; (k) Bu_3SnH, AIBN, benzene, reflux, 65%; (l) (i) $NaIO_4$, MeOH–H_2O, 77%; (ii) chlorobenzene, 160 °C, 53%; (m) LAH, $AlCl_3$, THF, reflux, 86%; (n) BBr_3, DCM, 51%.

George and Niphakis revealed the synthesis of aryl indolizidine alkaloids (+)-ipalbidine **533b** and (+)-antofine **514b** through *endo*-trig cyclization and CH activated aryl coupling reaction (Scheme 89).[137] The synthesis traversed with the preparation of Wienreb amide **535** from diazo compound **534** which in turn was accessed from Boc-proline. Addition of excess



Scheme 89 *Reagents and conditions*: (a) Et_3N, $ClCO_2Et$, THF; then CH_2N_2, 72%; (b) CF_3CO_2Ag (20 mol%), HN(OMe)Me, Et_3N, THF, 97%; (c) ethynylmagnesiumbromide (5 equiv.), THF, 0 °C; then $NaHSO_4$ (aq.); (d) NaI, HCO_2H; (e) K_2CO_3, MeOH, (96% for three steps c–e); (f) I_2, DMAP, DCM, 96%; (g) $Pd(OAc)_2$ (1.0 mol%), *S*-Phos (2.0 mol%), *p*-methoxyphenyl–BF_3K, K_2CO_3, MeOH, 50 °C, 5 h, 65%; (h) $Pd(OAc)_2$ (30 mol%), $Cu(OAc)_2$ (3 equiv.), *p*-methoxyphenyl–BF_3K, K_2CO_3, *t*-BuOH–AcOH–DMSO (20 : 5 : 1), 60 °C, 70%; (i) L-selectride, THF, −78 to 0 °C; then Comin's reagent, −78 to 0 °C, 76%; (j) $Pd(PPh_3)_4$ (10 mol%), MeZnBr, THF, 60 °C, 91%; (k) BBr_3, DCM, −78 °C to rt, 80%; (l) $Pd(PPh_3)_4$ (10 mol%), 3,4-dimethoxyphenylzinc bromide, THF, 60 °C; (m) $PhI(O_2CCF_3)_2$, $BF_3·Et_2O$, DCM, (67% for two steps).

ethynylmagnesiumbromide to **535** followed by subsequent Boc deprotection and neutralization furnished enaminone **536.** The aromatic coupling of enaminone **536** was effetced either by iodination to give **537** followed by Buchwald's modified Suzuki–Miyaura protocol or direct $Pd(OAc)_2$ mediated aryl coupling to furnish **539.** The treatment of compound **539** with Comin's reagent gave the requisite intermediate **540** which on Negashi coupling and dimethylation gave (+)-ipalbidine **533b** while Negashi reaction and subsequent treatment with hypervalent iodine reagent produced (+)-antofine **514b.**

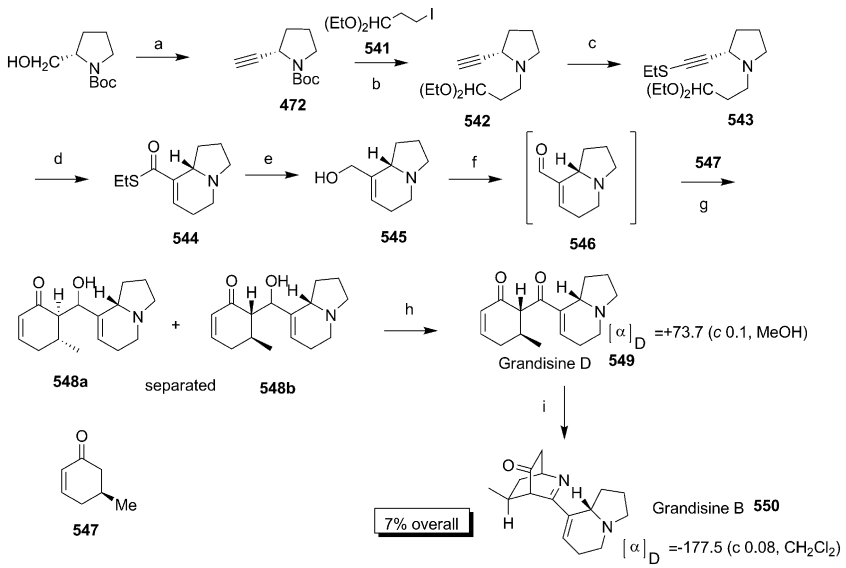
Taylor and co-workers succeeded in synthesizing grandisine B **550,** which displays a potent δ-opioid receptor affinity towards human being, using L-proline as a facile starting material (Scheme 90).[138] The synthesis began with the preparation of alkyne **472** from Boc-prolinal **12b** using CBr_4 in the presence of PPh_3 using a strong base *n*-BuLi. The deprotection of Boc group followed by reaction with iodo acetal compound **541** afforded **542.** The alkyne **542** was deprotonated and further trapped with ethyl disulfide to give **543.** The compound **543** on refluxing with formic acid underwent cyclization to **544** which on subsequent desulfurization and reduction provided the alcohol precursor **545** as a pure single isomer on column purification. The compound **545** was oxidised to aldehyde **546** which was efficiently trapped using the anion of cyclohexenone **547** to give a mixture of **548a** and **548b** separated after column chromatography. The synthesis of grandisine B **550** was then accomplished by converting **548b** to grandinisine D **549** followed by treatment with aq. NH_3.

Wang and co-workers successfully achieved the first enentioselective synthesis of 13*a*-methyl-14-hydroxyphenanthroindolizidine alkaloids **551** and suggested the structure of hypoestestatin 2 needs to be revised further (Scheme 91).[139] The requisite α-methylated proline methyl ester **554** was synthesized through Seebach's method. After several manipulations the *N*-alkylation of **554** with bromo compound **556** was eventually performed using K_2CO_3 in DCM and DMF (1 : 1), giving the product **557.** The conversion of **557** to **558** was effected *via* Parham's type cyclisation in 70% yield. After screening the several reducing agents for the diastereoselective reduction of carbonyl, Et_3BH was found to be the best in discriminating the isomers giving the separable mixture of **551c** and **551d.** In a similar way the other two possible isomers **551a** and **551b** were synthesized using ent-**554.** The detail optical activity study and NMR revealed that the physical data of none of the isomers synthesized matching with that reported for hypoestestatin 2 showcased the need of further study in this field.

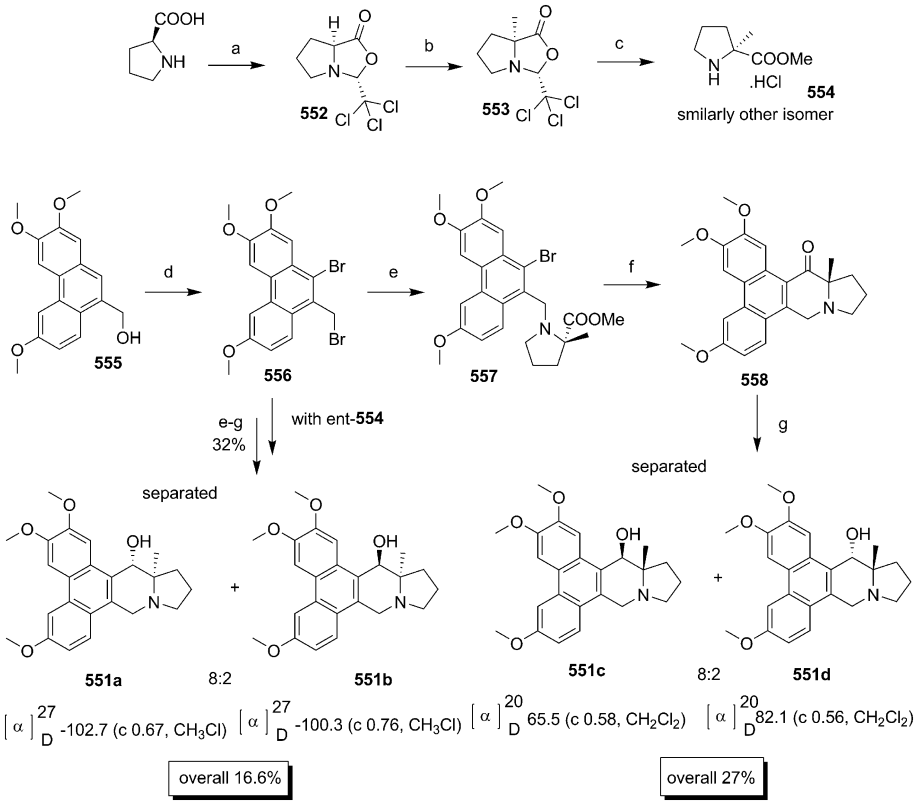
Very recently (*S*)-(+)-tylophorine **520** was synthesized by Stoye and Opatz through free-radical cyclization of an *N*-aziridinylimine (Scheme 92).[140] The starting dibromo compound **561** was prepared by condensation of homoveratric acid and veratraldehyde followed by oxidative cycization and bromination. The *N* alkylation of methyl proline ester with **561** gave **562** which on DIBAL reduction of the ester followed by subsequent condensation with amino aziridine **563** afforded **564.** The cyclisation of **564** was effected using Ph_3SnH in the presence of AIBN to furnish the natural product **520.**

5. Summary

The present review explicitly describes the versatility of proline particularly emphasizing it as a unique chiral synthon for the synthesis of naturally occurring pyrrolidines, pyrrolizidines and indolizidine alkaloids. The synthesis of a wide spectrum of natural products has been derived ranging from simple to complex molecules, that has placed proline on a cutting edge in chiral pool synthesis. The construction of various

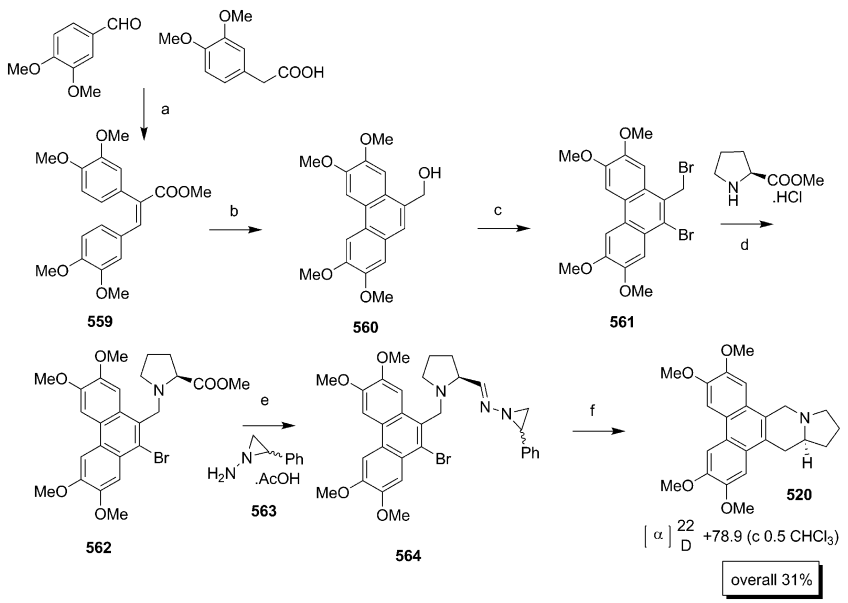


Scheme 90 *Reagents and conditions*: (a) (i) Swern oxidation; (ii) CBr_4, PPh_3, DCM, 3 h; (iii) *n*-BuLi, THF, −78 °C, 1 h; (70% for three steps); (b) (i) TFA, DCM, 0 °C to rt, 4 h; (ii) **541**, K_2CO_3, CH_3CN, reflux, 18 h; (79% for two steps); (c) (i) *n*-BuLi, THF, −78 °C; (ii) EtSSEt, −78 °C to rt, 2 h; (85% for two steps); (d) HCO_2H, 100 °C, 2 h, 97%; (e) (i) MeOH, Et_3N, AgOTf, 45 °C, 18 h; (ii) DIBALH, 0 °C to rt, 2 h; (50% for two steps); (f) Swern oxidation, 88%; (g) **547** (90 : 10 er), LDA, THF, −78 °C, 2 h, 61%, (**548a** : **548b**/1 : 5); (h) TFAA, DMSO, Et_3N, DCM, −78 °C, 1 h, 80%; (i) 35% aq. NH_3, 0 °C to rt, 2 h, 72%.



Scheme 91 *Reagents and conditions*: (a) $Cl_3CCH(OH)_2$, $CHCl_3$, reflux, 83%; (b) LDA, MeI, THF, −78 °C, 75%; (c) $SOCl_2$, MeOH, reflux, 98%; (d) Br_2, DCM, rt, 85%; (e) **554**, K_2CO_3, DCM–DMF (1 : 1), reflux, 81%; (f) *t*-BuLi, THF, −78 °C, 70%; (g) Et_3BHLi, −20 °C, 93%.

heteroatom-impregnated cyclic compounds are deemed to be useful for synthetic chemists for further tuning of these strategies. It is worth mentioning that manifolds of proline-derived heterocyclic scaffolds, similar to those natural products described in this review, have been synthesized and undoubtedly have identified proline as a robust "chiral tool" in the



Scheme 92 *Reagents and conditions*: (a) (i) Et_3N, Ac_2O, 15 h, 100 °C; (ii) AcCl, MeOH, 15 h, reflux (73% for two steps); (b) (i) $PhI(OCOCF_3)_2$, $BF_3{\cdot}OEt_2$, DCM, −40 °C, 4 h; (ii) LAH, THF, rt, 15 h (98% two steps); (c) Br_2, DCM, rt, 15 h, 98%; (d) L-ProOMe·HCl, DCM, $(iPr)_2NEt$, rt, 20 h, 92%; (e) (i) DIBAL, toluene, −78 °C, 1.5 h; (ii) **563**, DCM, MS 4 Å, −10 °C, NaOAc, 2 h (79% two steps); (f) Ph_3SnH, AIBN, toluene, 80 °C, 20 h, 61% (syringe pump).

pharmaceuticals and biotechnological fields. The review has also rationalized the synthesis of bulky alkaloids like dolastatin and pumiliotoxins using proline as a synthetic precursor which will be useful for synthetic chemists working specifically to design novel protocols for the improvement of syntheses. The collection also provides room for synthetic chemists to alleviate or obviate indigenous racemisation of the intermediates and final natural products caused by several reagents and reaction conditions during synthetic manipulation. More specifically, the present report has established proline as a competent and leading amino acid for the synthesis of asymmetric natural products besides its 'universal application' as an organocatalyst. The vast coverage of the syntheses that has taken place between 1990 and the present day will help readers to comprehend most of the proline based chiral pool synthesis of the aforementioned alkaloids, since very few syntheses have previously been reported.

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