CHAPTER 6

Applications to Alkaloid Synthesis

Daniel L. Comins*, Sergey Tsukanov**

* *Professor Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204 USA.*
** *Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204 USA.*

1. INTRODUCTION

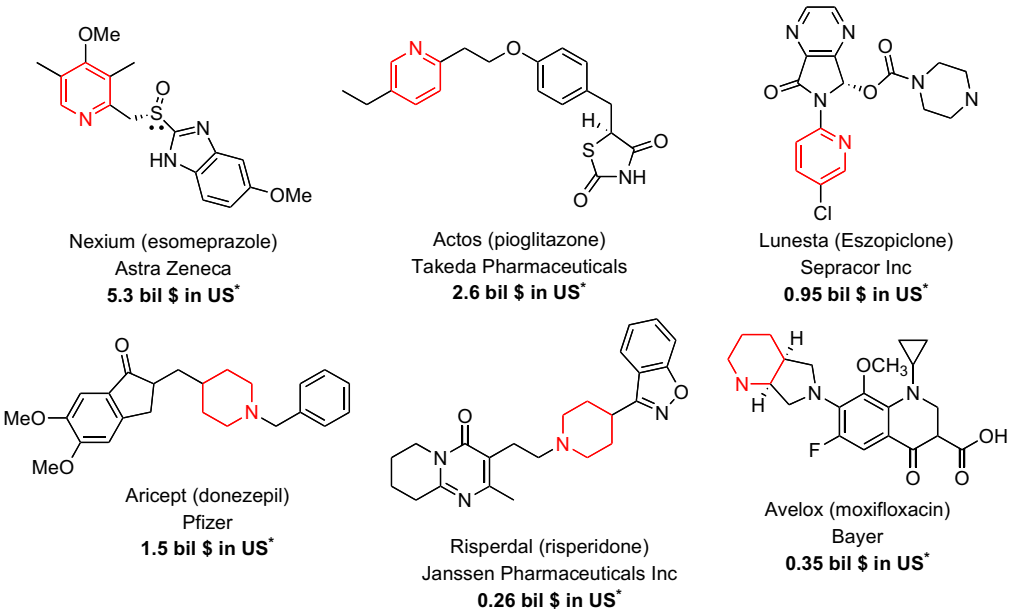
Functionalised pyridines and piperidines are very common building blocks for the synthesis of natural products and biologically active compounds. Numerous derivatives of pyridines and reduced pyridines are present in therapeutic agents, herbicides and fungicides.[1] Some of the world's top selling drugs, such as esomeprazole, pioglitazone and eszopiclone, represent a minute part of an enormous variety of medicinally important molecules that contain pyridine derivatives.[2]

A significant number of newly approved drugs over the past years are natural products themselves or synthetic derivatives of biologically active natural products.[3] Pyridine- and piperidine-containing alkaloids represent a very large class of natural products with unique frameworks and with wide-ranging biological properties.[4] Many of these alkaloids have activities relevant to the treatment of cancer, neurological disorders and other diseases, and have continued to be a valuable inspiration for drug discovery.[5] Highly efficient methods for construction of pyridines and enantiopure piperidines will remain in high demand. The stereoselective construction of functionalised piperidines with several substituents in definite positions still remains a significant synthetic challenge.[6] One of the most common and straightforward routes to access these molecules is to start from a readily available pyridine.

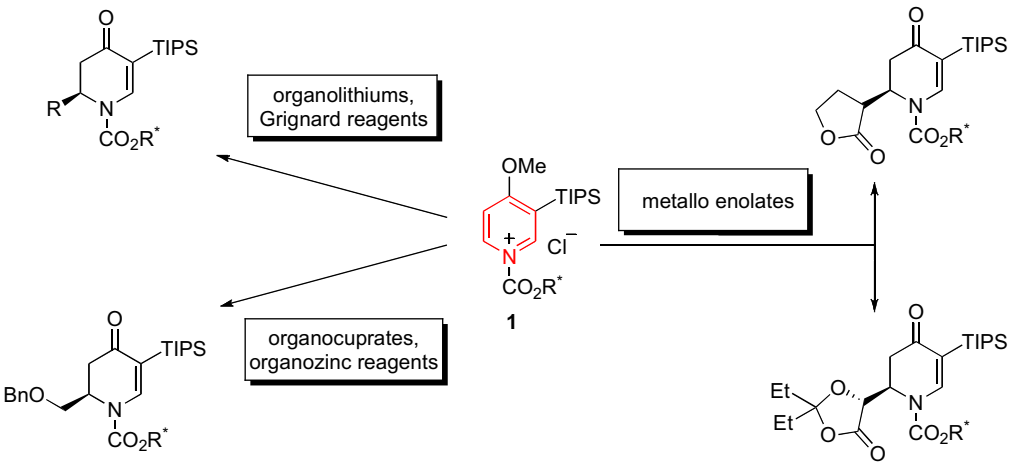
Over the years the Comins group has developed strategies for using pyridine derivatives as building blocks for synthesis. In particular, addition of nucleophiles to chiral *N*-acylpyridinium salts,[7] and the directed lithiation of functionalised pyridines,[8] have proven to be effective in the preparation of various alkaloids. A very simple and versatile method for the synthesis of enantiopure 2-substituted 2,3-dihydro-4-pyrdones from chiral *N*-acylpyridinium salts was developed. These enantiopure dihydropyridones are extremely useful synthetic intermediates. Starting from easily accessible 4-methoxy-3-(triisopropylsilyl)pyridine, chiral *N*-acylpyridinium salts **1** can be formed *in situ* upon addition of a chiral chloroformate.[7a] These salts undergo facile nucleophilic addition reactions with various Grignard reagents,[7b] organocuprates,[7c] metallo-enolates[7d] and other organometallics to provide the corresponding *N*-acyl-2,3-dihydro-4-pyridones in excellent yields and diastereoselectivity (Scheme 2).

The stereoselectivity of the process is usually very high and easily predictable on the basis of a working model. As shown in the Scheme 3, the aryl substituent of the chiral auxiliary forms a stabilising $\pi-\pi$ stacking interaction with the pyridine ring and blocks nucleophile attack at one face of

Pyridines: from lab to production
ISBN 978-0-12-385235-9, http://dx.doi.org/10.1016/B978-0-12-385235-9.00006-0

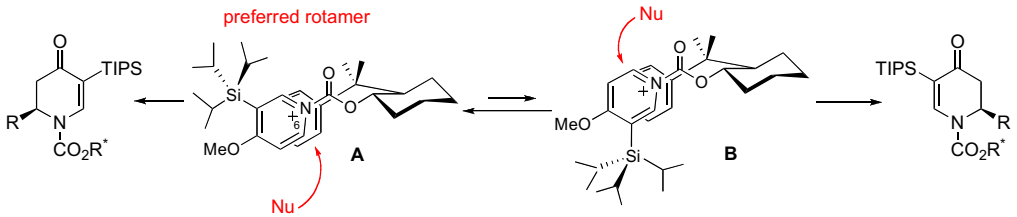


Scheme 1 Pyridine and piperidine-containing pharmaceuticals.



Scheme 2 *N*-Acylpyridinium salt reactions.

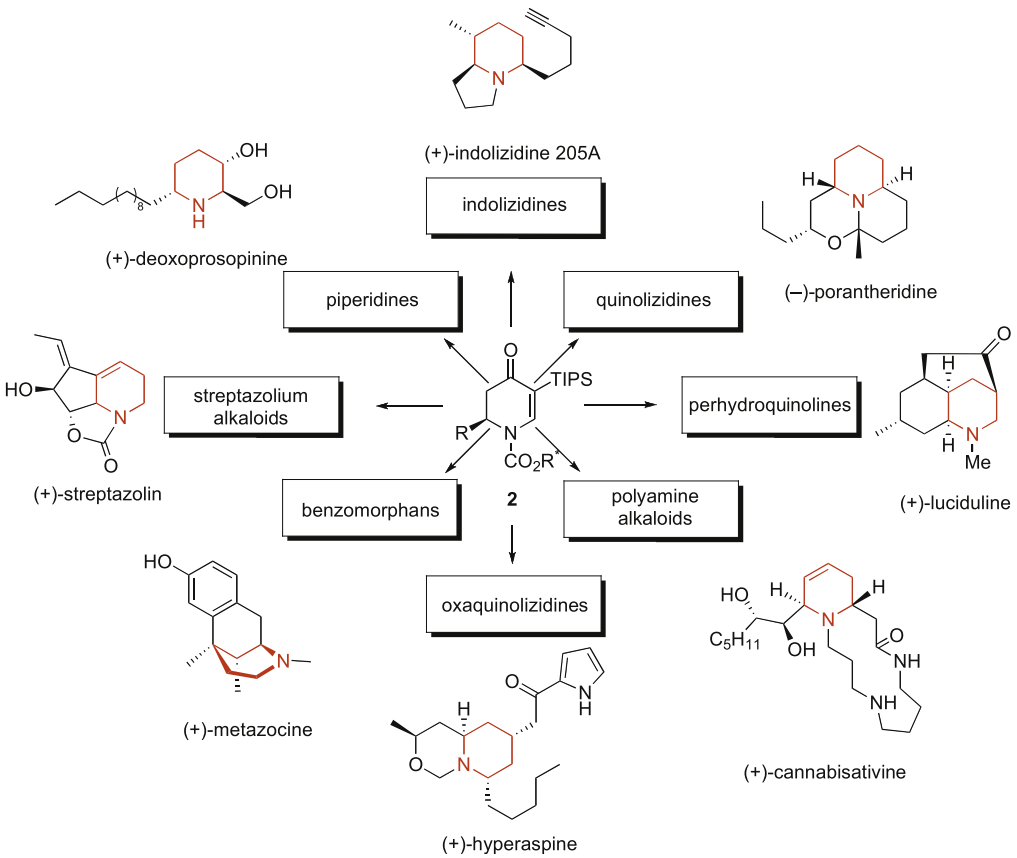
the pyridinium salt. Since the carbon—nitrogen bond of the *N*-acyl group can undergo free rotation, there are two probable rotamers, A and B, which could react with the nucleophile. The bulky TIPS group in rotamer B has unfavourable interactions with the phenyl group of the chiral auxiliary, thereby causing the rotamer population to favour A. Thus, the major diastereomeric product from the reaction is generated from addition of the nucleophile to the pyridinium C6 position of rotamer A.[7a]



Scheme 3 Mechanism of asymmetric induction.

Other methods for preparing nonracemic 2,3-dihydro-4-pyridones from *N*-activated pyridines, imines via hetero-Diels–Alder reactions, alkenyl isocyanates and amino acids have been reported.[9]

Enantiopure dihydropyridones of the type **2** are excellent building blocks for the stereoselective construction of piperidine, indolizidine, quinolizidine, perhydroquinoline and other types of alkaloids (Scheme 4). This chapter presents selected total syntheses from Comins' laboratories using



Scheme 4 Alkaloid syntheses from *N*-acyl-2,3-dihydro-4-pyridones.

chiral *N*-acylpyridinium salt chemistry and *N*-acyl-2,3-dihydro-4-pyridone building blocks. Also included are three syntheses that feature novel directed lithiations of pyridine derivatives. Useful experimental methods that can be applied to related transformations have been added to the discussion of some of the syntheses.

Preparation of 4-methoxy-3-(triisopropylsilyl)pyridine.[7a] A 1-L, three-neck, round-bottomed flask equipped with a magnetic stirring bar, a nitrogen inlet and a 100 mL pressure-equalising addition funnel was charged with a solution of diisopropylamine (23.1 mL, 0.165 mol) in 200 mL of dry tetrahydrofuran. The solution was cooled to −23 °C, and *n*-butyllithium (67.0 mL, 0.165 mol, 2.47 M in hexanes) was added dropwise over the period of 20 min. After the addition was completed, the mixture was stirred at −23 °C for 30 min, cooled to −78 °C, and then neat 4-methoxypyridine (16.0 mL, 0.158 mol) was added dropwise. The resulting mixture was stirred for additional 30 min and then a solution of triisopropylsilyl chloride (38.5 mL, 0.18 mol) in 30 mL of THF was added rapidly. The reaction mixture was allowed to warm to −23 °C, stirred for 12−16 h and quenched with saturated ammonium chloride (100 mL). The layers were separated and the aqueous phase was extracted with ether (2 × 75 mL). The combined organic extracts were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, and filtered through a thin pad of Celite. The solvents were removed under reduced pressure, and the resulting dark oil was Kugelrohr-distilled (140−160 °C, 0.5 mmHg) to yield a clear oil which was crystallised from hexanes to provide 25.2 g (60%) of 4-methoxy-3-(triisopropylsilyl)pyridine as white crystals, mp 66−67 °C.

Preparation of chiral N-acyl-2,3-dihydro-4-pyridones ***2****. Representative procedure.*[19] A solution of the chloroformate of (+)-*trans*-2-(α-cumyl)cyclohexanol (10.7 g, 38.0 mmol) in 80 mL of anhydrous toluene was added into a flask containing a solution of 4-methoxy-3-(triisopropylsilyl)pyridine (10.0 g, 37.7 mmol) in 280 mL of anhydrous toluene at −42 °C. After stirring at −42 °C for 1.5 h, 70 mL of THF was added, and the mixture was cooled to −78 °C. Freshly prepared 4-butenylmagnesium bromide (1.3 equiv, 1.2 M in THF) was added dropwise via a double-tipped stainless steel needle, and the mixture was stirred at −78 °C for 4 h. Saturated aqueous oxalic acid (100 mL) was added, and the reaction mixture was warmed to rt and then stirred overnight. The aqueous layer was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration and concentration *in vacuo* gave 23.2 g (de 90%) of the crude product. Crystallisation from 5% H_2O/MeOH yielded 15.2 g (de 100%) of the desired (2*R*)-2,3-dihydro-4-pyridone **2** (R = 4-butenyl). The mother liquor was concentrated and the residue purified by radical PLC (silica gel, 2−5% EtOAc/hexanes) to yield another 3.7 g (de 99.8%) of **2** (total yield: 18.9 g, 91%), mp 117−118 °C; $[\alpha]^{25}_D$ + 62.9 (*c* 0.34, $CHCl_3$).

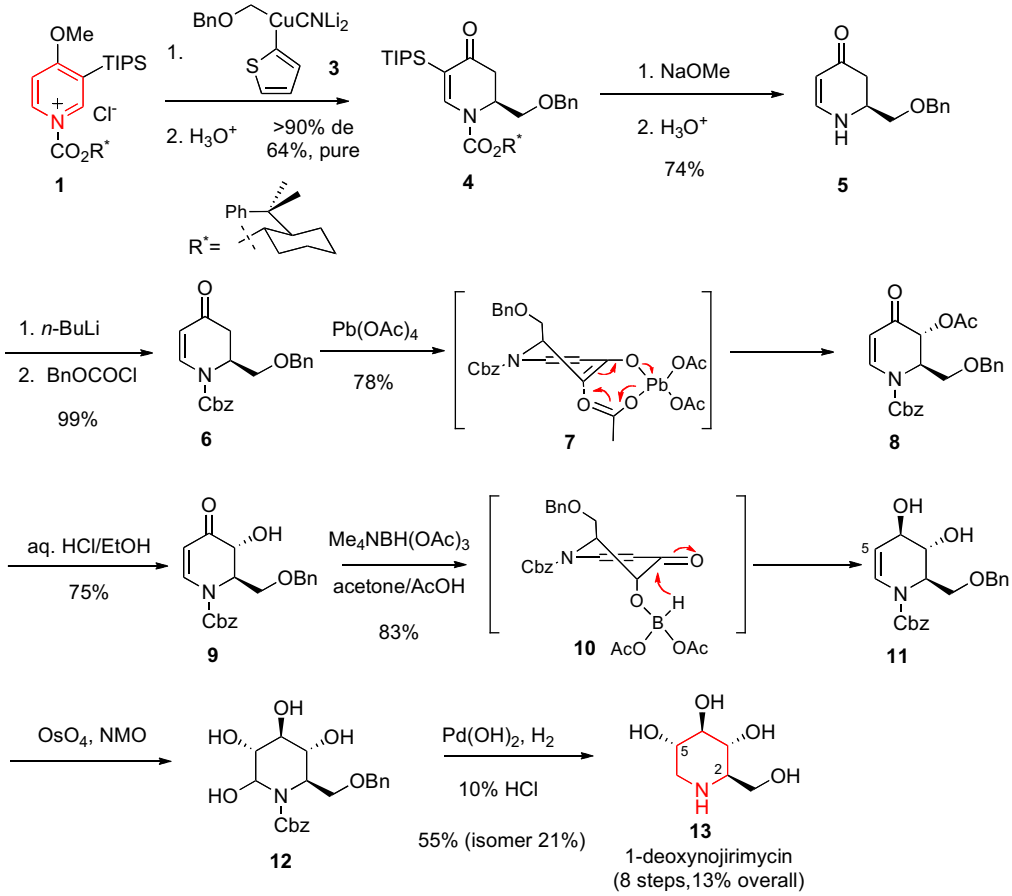
2. ALKALOID SYNTHESIS

2.1. Piperidine Alkaloids

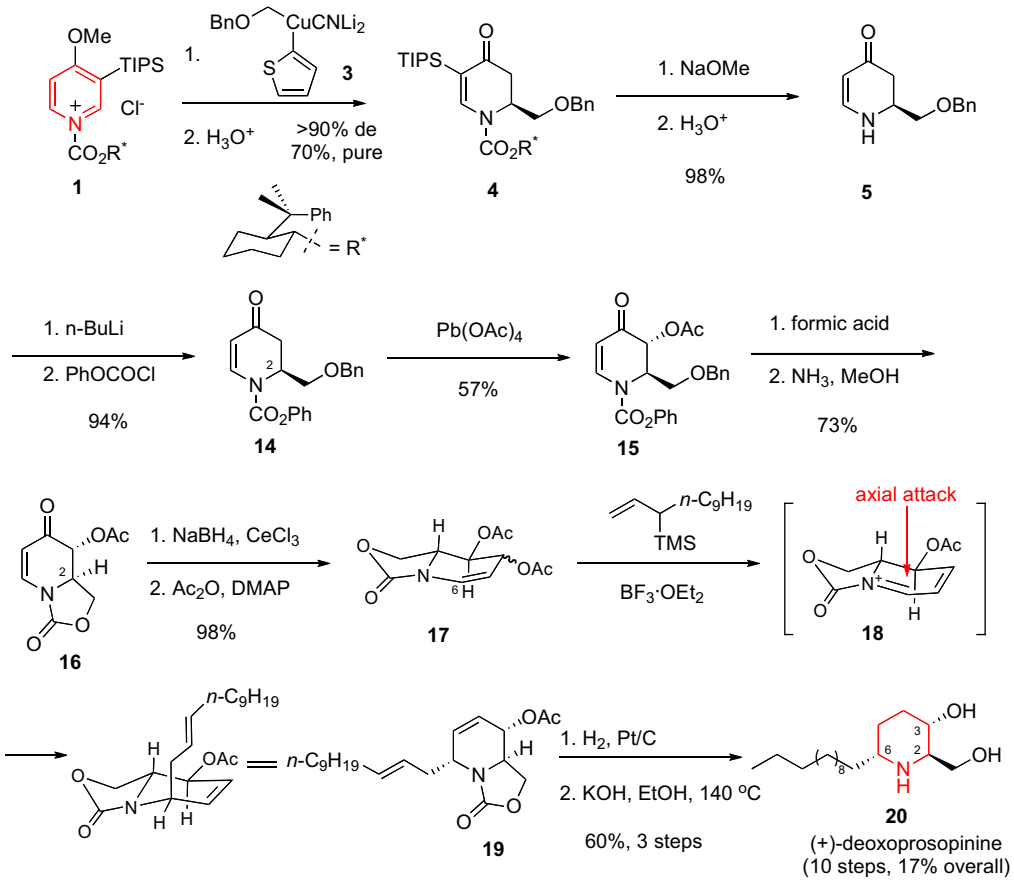
Deoxynojirimycin. Polyhydroxy piperidine alkaloid 1-deoxynojirimycin (**13**) was found to exhibit inhibitory activity against HIV *in vitro*.[10] Its potential as a pharmaceutical lead and the unusual azasugar core structure stimulated considerable interest in the preparation of this molecule. Our synthesis

commenced with an efficient introduction of the first stereocentre employing an asymmetric *N*-acylpyridinium salt reaction with (benzyloxy)methylcuprate **3** to provide dihydropyridone **4**.[11] One-pot removal of the TIPS group and chiral auxiliary from **4** gave enantiopure **5**, which was *N*-protected as the Cbz-carbamate **6**. Compound **6** was elaborated to the corresponding acetate **8** using $Pb(OAc)_4$.

The *trans* stereochemistry observed in product **8** is likely due to axial acetoxylation via a chair-like transition state (**7**) shown in Scheme 5. Hydrolysis of acetate **8** gave alcohol **9** which was reduced with tetramethylammonium triacetoxyborohydride to furnish diol **11** with complete stereocontrol. Formation of the *trans*-diol is attributed to an intramolecular hydride delivery from alkoxydiacetoxyborohydride intermediate **10**. With compound **11** lacking only a C5-hydroxy group to complete the core structure of the alkaloid, a hydroboration was attempted, but unfortunately, none of the desired product was produced. As an alternative, diol **11** was subjected to dihydroxylation with osmium tetroxide, and the crude product **12**, due to its instability, was immediately hydrogenated over



Scheme 5 Synthesis of 1-deoxynojirimycin.

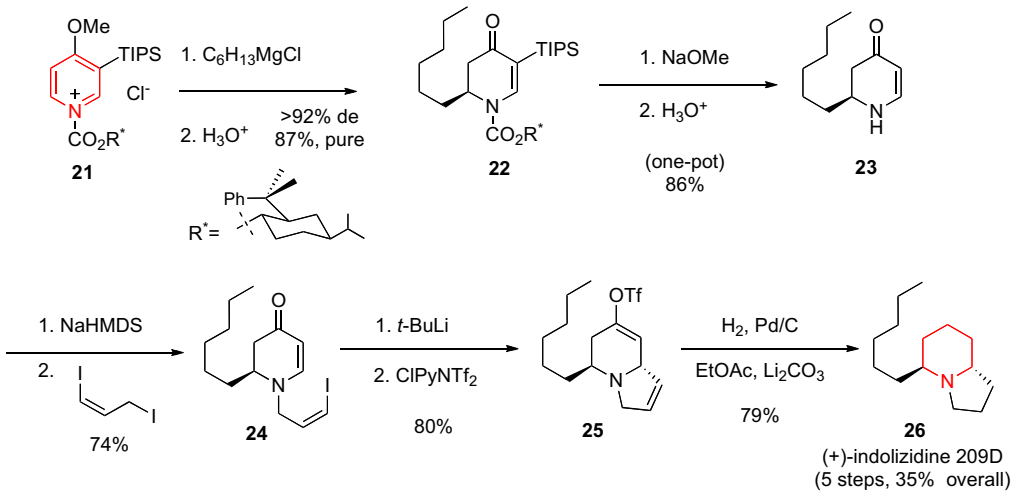


Scheme 6 Synthesis of deoxoprosopinine.

$Pd(OH)_2$ in 10% HCl to provide 1-deoxyjirimycin (**13**) as 2.7:1 mixture of diastereomers that were separated by chromatography.

C3 Acetoxylation of N-acyl-2,3-dihydro-4-pyridone ***6****. Representative procedure.*[11] To a stirred solution of **6** (250 mg, 0.71 mmol) in 25 mL of toluene at rt was added lead(IV) acetate (82.2 mg, 1.85 mmol). The resulting mixture was refluxed for 18 h. An additional 400 mg of lead(IV) acetate (0.90 mmol) was added and refluxing was continued for 4 h. After cooling to rt, the solution was filtered through Celite with methylene chloride. The filtrate was washed with saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulphate, filtered, and concentrated *in vacuo*. Purification by radical PLC (silica gel, 20−30% EtOAc/hexane) gave **8** (227 mg, 78%) as a clear colourless oil: $[\alpha]^{26}_{D}$ + 82.9 (*c* 1.37, $CHCl_3$).

Deoxoprosopinine. The dihydroxy piperidine alkaloid (+)-deoxoprosopinine (**20**) was isolated from *Prosopis africana*, whose application as the toothache treatment is deeply embedded in nontraditional medicine in the African culture.[12] This natural product has been shown to possess



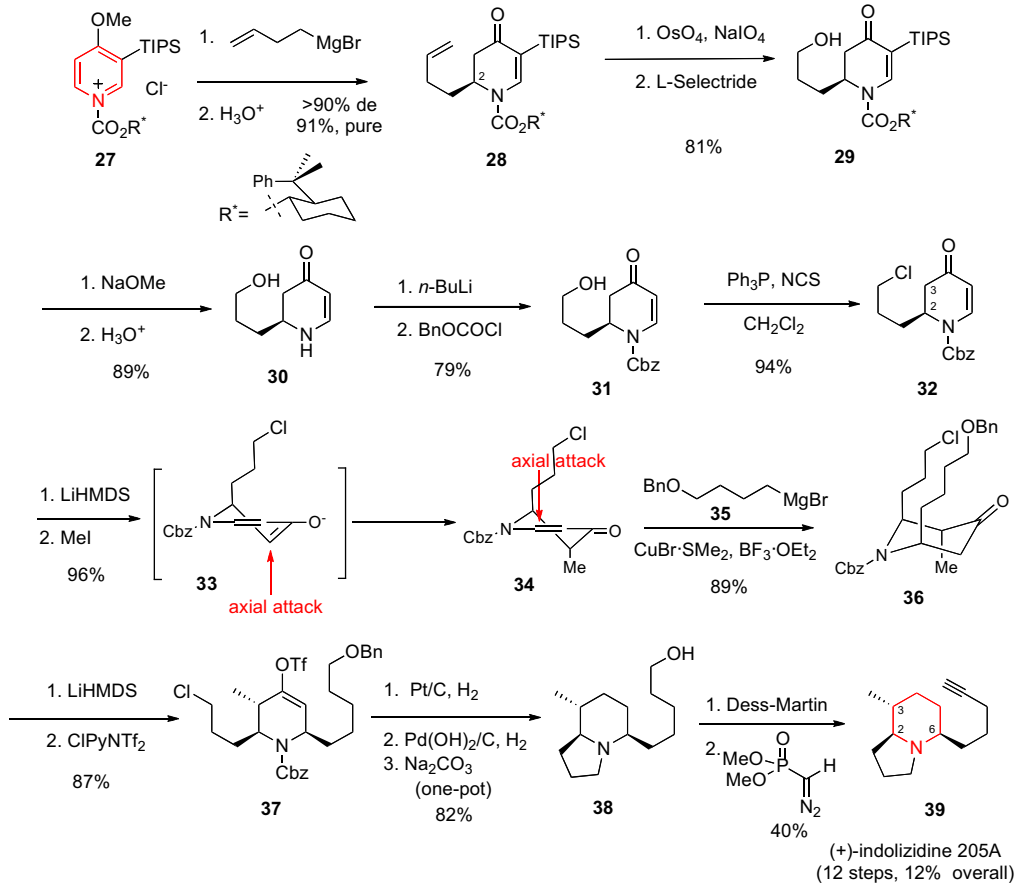
Scheme 7 Synthesis of indolizidine 209D.

antibiotic and anaesthetic activities.[13] Our synthesis started with intermediate **5** which was previously used in the synthesis of 1-deoxonojirimycin.[14] Carbamate **15** was prepared from **5** by *N*-acylation and subsequent C3 acetoxylation. Addition of a nucleophile to the vinylogous amide **15** in a 1,4-fashion would proceed through axial attack and result in a 2,6-*cis*-piperidone. To obtain the desired *trans*-stereochemistry via conjugate addition, compound **15** was converted to the bicyclic carbamate **16** using a one-pot procedure involving cleavage of the benzyl ether with formic acid followed by treatment with ammonia in MeOH at 0 °C. The C2 bond of the oxazolidinone ring is in the equatorial orientation and the overall bicyclic structure adopts a conformation in which the β-face of the alkene is open for axial attack by a nucleophile. Prepared in two straightforward steps, allylic acetate **17** undergoes Lewis acid-promoted addition of allylsilane at C6. In this reaction, upon Lewis acid activation of the C4 acetate leaving group, the highly reactive *N*-acyliminium ion **18** is formed and then attacked by the allylsilane to furnish the desired 2,6-*trans*-substituted intermediate **19**. At this point, reduction of the double bonds followed by hydrolysis of the acetate and the oxazolidinone ring with NaOH provided the target natural product (+)-deoxoprosopinine (**20**).

2.2. Indolizidine Alkaloids

▶ Alkaloid 209D

Poison-dart frog alkaloid (+)-209D[15] (**26**) was prepared in a highly concise manner using an anionic cyclisation of a 2,3-dihydro-4-pyridone.[16] The 5-step synthesis commenced with an asymmetric *N*-acylpyridinium salt reaction to install the hexyl side chain in 92% de. Removal of the chiral auxiliary and TIPS group from diastereomerically pure **22** was performed under previously developed conditions via a one-pot reaction. Dihydropyridone **23** was alkylated upon treatment with NaHMDS

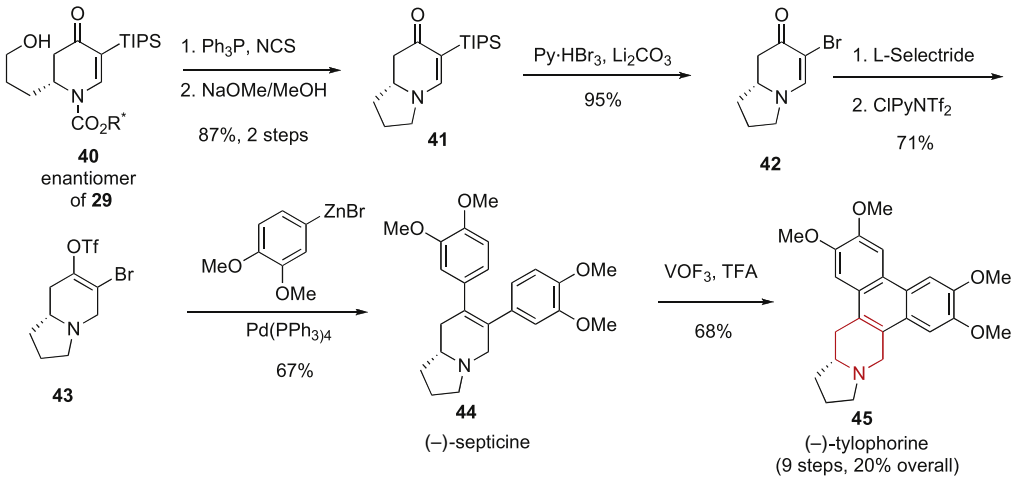


Scheme 8 Synthesis of indolizidine 205A.

and (*Z*)-1,3-diiodopropene to give vinyl iodide **24**. Lithium—halogen exchange and *in situ* cyclisation was effected through the addition of one equivalent of *tert*-butyllithium. Trapping the intermediate enolate with *N*-(5-chloro-2-pyridyl)triflimide ($ClPyNTf_2$) furnished the indolizidine **25** as one diastereomer. The stereochemical outcome of this reaction is opposite that of the corresponding intermolecular 1,4-addition reactions which generate 2,6-*cis*-disubstituted 4-piperidones. This method gives an additional way to control stereochemistry of conjugate additions and efficiently prepare 2,6-*trans*-indolizidine systems. It is noteworthy that exposure of intermediate **24** to Heck conditions failed to give any of the desired cyclised product. Finally, hydrogenation of vinyl triflate **25** provided enantiopure indolizidine 209D (**26**).

▶ Alkaloid 205A

Indolilizidine (—)-205A (**39**) is one of numerous alkaloids isolated from the skin of neotropical frogs from the family *Dendrobatidae*.[17] This indolizidine is a noncompetitive blocker for



Scheme 9 Synthesis of tylophorine.

muscle-type and ganglionic nicotinic receptor channels.[18] In contrast to alkaloid 209D, indolizidine 205A has a *cis* relationship between substituents at the C2 and C6 stereocentres. A stereoselective approach was needed and devised to address the *cis*-stereochemistry in indolizidines of this type.[19] A butenyl side chain at C2 was introduced using a chiral *N*-acylpyridinium salt reaction to provide dihydropyridone **28** in high yield. The terminal olefin was oxidatively cleaved and the resulting aldehyde was reduced with L-Selectride to generate alcohol **29**. NaOMe-mediated cleavage of the chiral carbamate followed by protodesilylation of the TIPS group gave vinylogous amide **30**, which was *N*-protected as Cbz-carbamate **31**. Treatment with *N*-chlorosuccinimide in the presence of PPh_3 converted **31** to chloride **32**. Enolate **33** was formed with LiHMDS and alkylated with MeI to provide **34** as one diastereomer in excellent yield. The desired *trans*-C2,C3 selectivity of this process is attributed to an axial methylation from the most stable enolate conformer **33** in which the C2 substituent occupies an axial position avoiding 1,3-allylic strain generated by the Cbz-carbamate. At this point, enone **34** was treated with Grignard reagent **35** in the presence of copper bromide and $BF_3 \cdot OEt_2$ to give the requisite 2,6-*cis*-disubstituted piperidone **36**. As in the previous reaction, stereoelectronically preferred axial attack on the low-energy chair conformation explains the observed stereochemistry. The resulting ketone **36** was deprotonated with LiHMDS under kinetic conditions, and the reaction was quenched with $ClPyNTf_2$ to afford triflate **37**. The vinyl triflate, Cbz and benzyl groups were reduced in tandem via hydrogenation in the presence of 5% Pt/C and 20% $Pd(OH)_2$/C.

Upon heating with sodium carbonate at reflux for 1 h, S_N2 substitution proceeded smoothly to form the desired five-membered ring of indolizidine **38** in 82% overall. Notably, all three reactions were performed in one pot without isolation of intermediates. At this stage, the only task remaining to complete the total synthesis was conversion of the primary alcohol **38** to the required alkyne. Oxidation of the alcohol was effected through the action of Dess–Martin periodinane providing an

aldehyde in 97% yield. Exposure of the transient aldehyde to methyl diazomethyl phosphate and potassium *tert*-butoxide under Gilbert–Seyferth conditions generated indolizidine 205A (**39**).

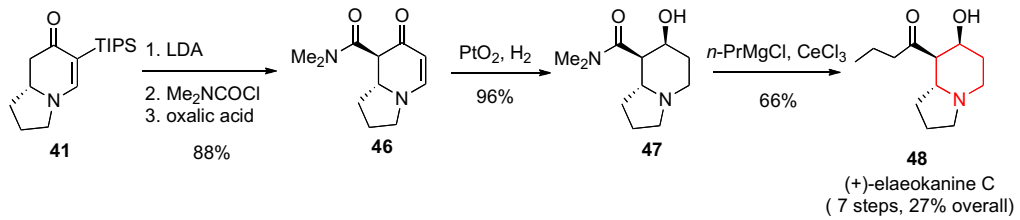
▷ Preparation of 2,6-cis-piperidone ***36***[19]

Solid copper(I) bromide–dimethyl sulphide complex (3.51 g, 17.1 mmol) was added to 70 mL of anhydrous THF and cooled to −78 °C. The Grignard of 4-(benzyloxyl)-1-bromobutane (17.1 mmol) in THF was added slowly via a double-tipped stainless steel needle. Stirring for 1 h at −78 °C produced an orange solution that appeared to be almost homogeneous. Boron trifluoride etherate (2.10 mL, 17.1 mmol) was added, and stirring was continued for 5 min. To this mixture was added (over a 1.5 h period) a solution of **34** (2.75 g, 8.55 mmol) in 35 mL of anhydrous THF. After stirring for 2 h at −78 °C, 40 mL of aqueous 20% NH_4Cl/NH_4OH (50:50) was added, and the mixture was allowed to warm to rt. After exposure to air and stirring for several minutes, the mixture turns blue. The crude mixture was extracted with diethyl ether. The organic extracts were washed with brine and dried over anhydrous K_2CO_3. Filtration and concentration *in vacuo* gave 5.26 g of the crude product as a dark oil. Purification by radical PLC (silica gel, 10–30% EtOAc/hexanes) yielded 3.70 g (89%) of the desired 2,6-*cis*-piperidone **36** as a clear oil: $[\alpha]^{24.5}_D$ -3.0 (*c* 0.46, $CHCl_3$).

Septicine and Tylophorine. An expedient and straightforward synthesis of alkaloid (−)-tylophorine[20] (**45**) was accomplished using a similar approach to that described above for the construction of the indolizidine portion of the molecule.[21] Starting from the alcohol **40**, the corresponding chloride was obtained under standard conditions in 96% yield.

The resulting chloride was treated with NaOMe in MeOH to cleave the chiral auxiliary and to provide the cyclised product **41**. Bromodesilylation was carried out using pyridinium bromide perbromide to afford the vinyl bromide **42**. The corresponding enolate generated through a conjugate reduction with L-Selectride was trapped with $ClPyNTf_2$ to deliver bromovinyl triflate **43**. At this point, the plan called for a *bis*-cross-coupling reaction. Compound **43** was exposed to the action of $Pd(PPh_3)_4$ and an excess of 3,4-dimethoxyphenylzinc bromide to give the natural product (−)-septicine (**44**) in good yield. Finally, **44** was subjected to oxidative coupling conditions employing vanadium trifluoride oxide in TFA/CH_2Cl_2 to generate (−)-tylophorine (**45**).

Elaeokanine C. The versatility and efficiency of our dihydropyridone approach towards a variety of indolizidine alkaloids was exhibited by a concise synthesis of alkaloid (+)-elaeokanine C[22] (**48**). As shown in Scheme 10, indolizidine **41**, which was prepared employing the above described protocol, was deprotonated with LDA followed by addition of excess dimethylcarbamyl chloride to afford the

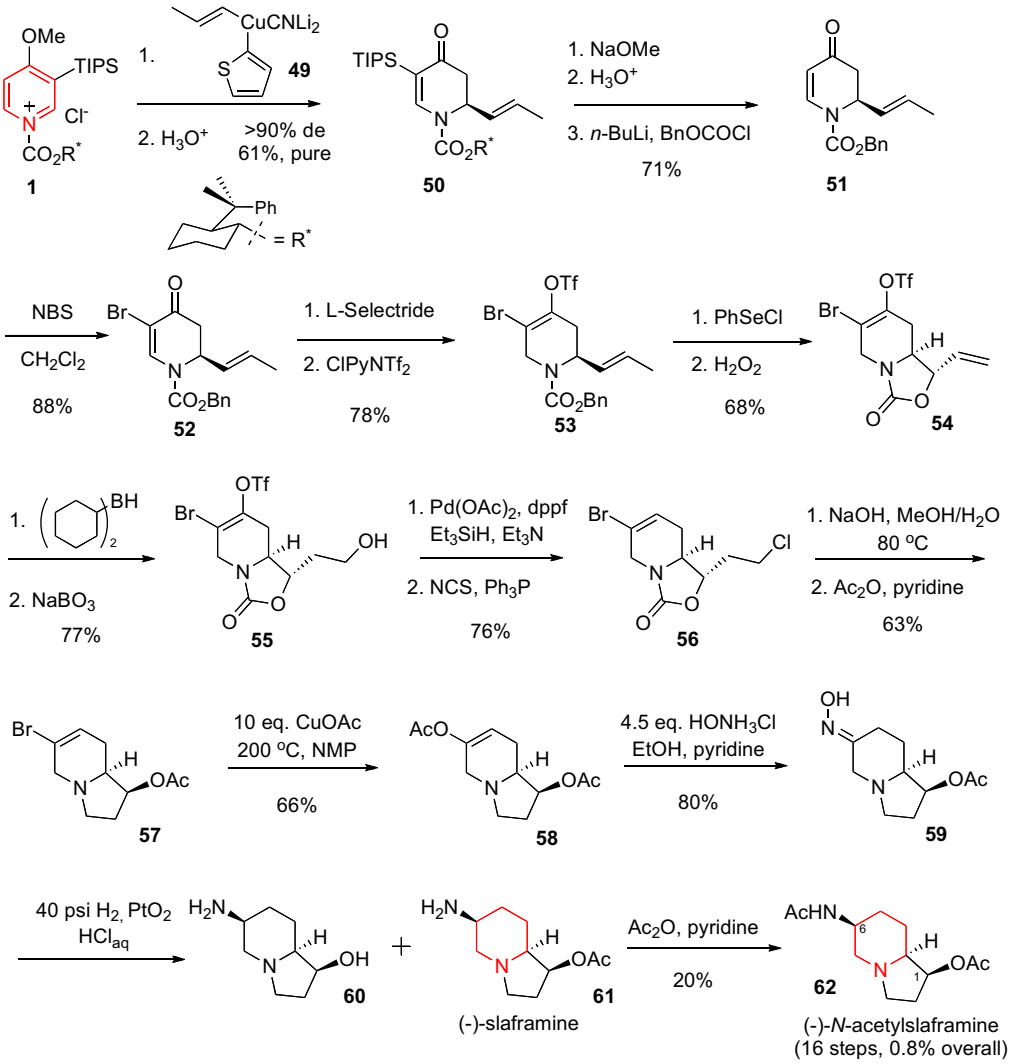


Scheme 10 Synthesis of elaeokanine C.

expected β-ketoamide.[23] Protodesilylation of the TIPS group with oxalic acid provided dihydropyridone **46**, which was reduced under hydrogenation conditions over Adams catalyst to deliver the alcohol **47** as a 95:5 mixture of diastereomers favouring the desired axial alcohol. With all three stereocentres installed, only conversion of the *N,N*-dimethylamide group to an *n*-propyl ketone remained for the completion of the total synthesis. The required propyl group was introduced through the action of *n*-propylmagnesium chloride in the presence of anhydrous cerium chloride to afford (+)-elaeokanine C (**48**).

Slaframine. The indolizidine alkaloid (−)-slaframine (**61**) was originally isolated from the fungus *Rhizoctonia leguminicola*.[24] This metabolite can infest ruminant forages, thereby causing an excessive salivation in grazing animals. Biological testing demonstrated that the natural product may be useful for the treatment of chlolinergic dysfunctions.[25] This molecule also has a potential to be a drug candidate to relieve cystic fibrosis symptoms. The biological activity and unique structure attracted a great deal of attention from the synthetic community and resulted in several synthetic efforts. Our synthesis of this natural product is shown in Scheme 11.[7c] Reaction of the *N*-acylpyridinium salt **1**, derived from (−)-TCC chloroformate and 3-TIPS-4-methoxypyridine, with alkenyl cuprate **49** provided dihydropyridone **50**, which was converted to **51** using our standard conditions. Electrophilic substitution with NBS proceeded smoothly to generate the bromide **52** in high yield. Conversion of **52** into vinyl trifltate **53** was accomplished by conjugate reduction with L-selectride and trapping of the intermediate enolate with $ClPyNTf_2$. Cyclisation via a phenylselenocyclocarbamation reaction using PhSeCl followed by oxidation with hydrogen peroxide provided terminal olefin **54**. Hydroboration with dicyclohexylborane gave alcohol **55** after oxidative work-up with sodium borate. The labile **55** was reduced to the vinyl bromide with palladium acetate, dppf and triethylsilane as a hydride source, and the terminal alcohol was converted to the chloride **56** using standard conditions. Now the stage was set for the key cyclisation reaction. Treatment of **56** with NaOH caused cleavage of the cyclic carbamate, and the resulting amine attacked the alkyl chloride to form the pyrrolidine ring. The free alcohol was protected as its acetate to afford **57**. After several unsuccessful attempts to convert the vinyl bromide in **57** directly to a ketone, an alternative plan was devised. The vinyl acetate **58** was prepared by heating **57** with copper(I) acetate in *N*-methylpyrrollidine at 200 °C. Diacetate **58** was then exposed to hydroxylamine hydrochloride in a mixture of ethanol and pyridine to obtain oxime **59**. Finally, the oxime was hydrogenated over Adams catalyst to generate the mixture of the natural product **61** and amino alcohol **60**. The mixture was acylated with acetic anhydride to provide *N*-acetylslaframine (**62**).

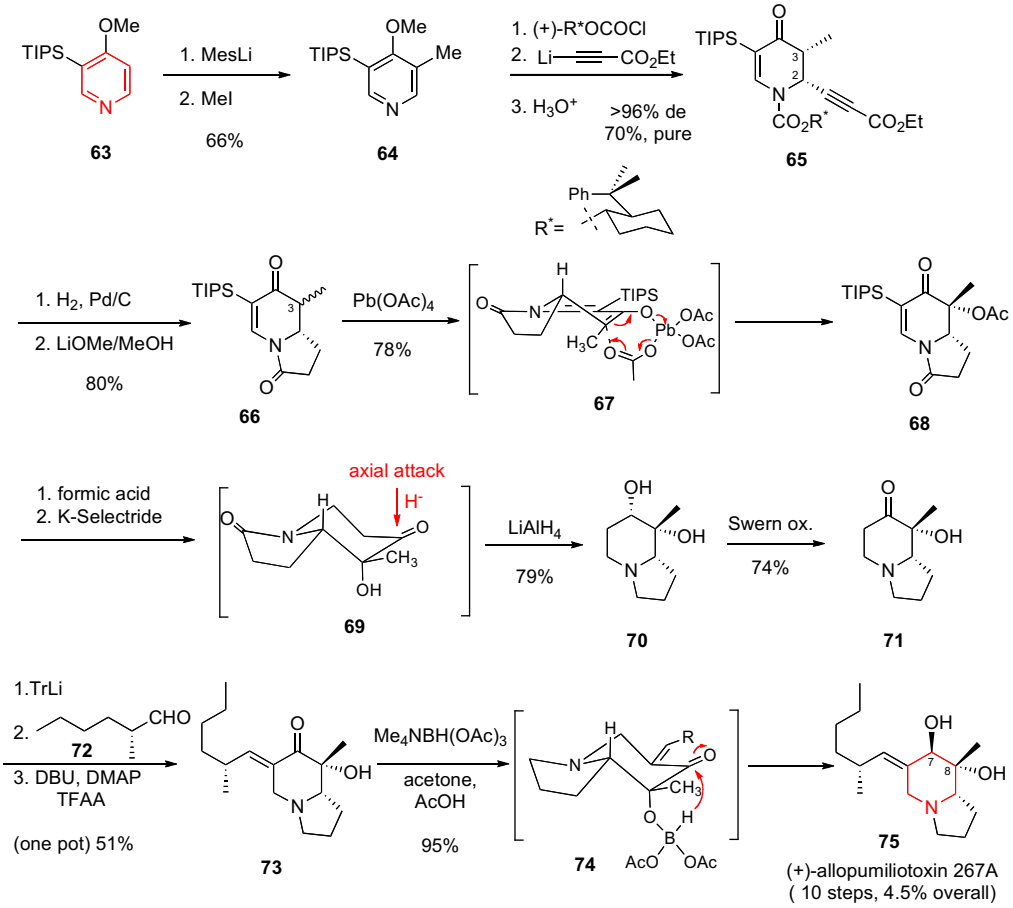
Allopumiliotoxin 267A. Pumiliotoxins belong to a large group of alkaloids containing the (*Z*)-6-alkylideneindolizidine ring system that were isolated from the skin of frogs of the family *Dendrobates*. Allopumiliotoxin 267A (**75**) is one of the most complex members of this group.[26] Its intriguing structural features include an unusual vicinal diol group in the indolizidine core. Members of this family of alkaloids were reported to possess both cardiotonic and myotonic activities.[27] The challenging architecture and potential pharmacological properties stimulated efforts towards the synthesis of this natural product. Our approach began with *ortho*-lithiation of pyridine **63** with mesityllithium followed by alkylation with methyl iodide to provide trisubstituted pyridine **64**.[28] Formation of a chiral *N*-acylpyridinium salt from **64** and (−)-TCC chloroformate followed by reaction with



Scheme 11 Synthesis of slaframine.

lithiated ethyl propiolate resulted in dihydropyridone **65** as a single diastereomer. The resulting diastereoselectivity at the C3 stereocentre of **65** can be explained by an axial protonation of the intermediate enol ether upon acid hydrolysis. The triple bond was reduced with H_2, Pd/C in quantitative yield without any consequence to the enone system due to protection by the bulky TIPS group.

Exposure of the resulting dihydropyridone to LiOMe in MeOH effected cleavage of the chiral auxiliary and formation of indolizidinone **66** as an 8:1 mixture of diastereomers due to partial epimerisation at the C3 centre. A diastereoselective acetoxylation was performed using $Pb(OAc)_4$ in refluxing AcOH/1,3-*bis*(trifluromethyl)benzene to deliver an acetoxy group under stereoelectronic

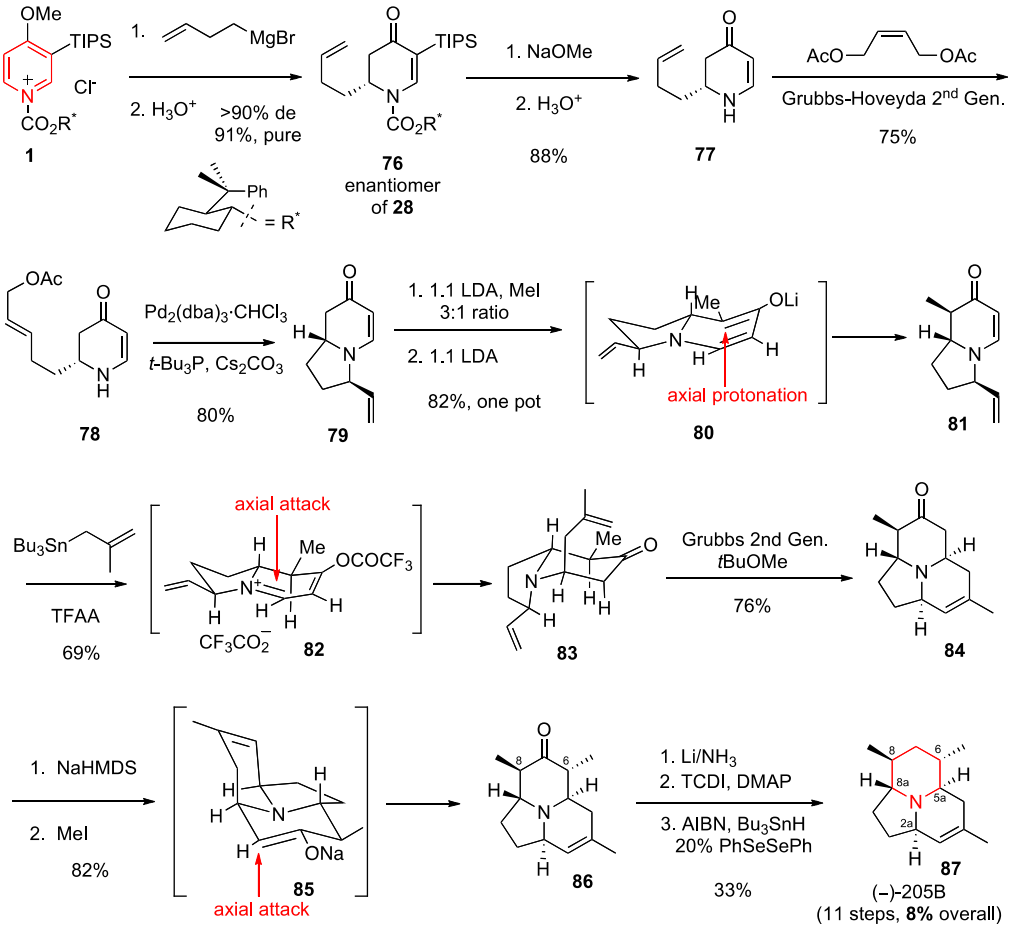


Scheme 12 Synthesis of allopumiliotoxin.

control from the axial direction preserving a chair transition state (**67**). Desilylation with formic acid, followed by a one-pot successive 1,4-, 1,2- and amide reductions utilising K-Selectride and $LiAlH_4$, provided the equatorial alcohol **70** as a single diastereomer. Subsequent oxidation of the secondary hydroxyl under Swern conditions afforded ketone **71**. Deprotonation with trityllithium to form the enolate and then addition of chiral aldehyde **72** gave an intermediate alcohol which was not isolated. Dehydration upon treatment with DMAP, DBU and TFAA delivered the desired *Z*-alkene **73** in 51% yield. Finally, transformation to (+)-allopumiliotoxin (**75**) occurred by reduction of ketone **73** with $Me_4NBH(OAc)_3$ to provide the desired axial alcohol through an intramolecular C8 hydroxyl-assisted delivery of hydride from the concave face of the molecule.

▷ Alkaloid 205B

Tricyclic alkaloid 205B (**87**) is another indolizidine isolated from the neotropical poisonous frog *Dendrobates*.[29] This alkaloid possesses an unusual 8b-azaacenonaphathylene core, and its enantiomer



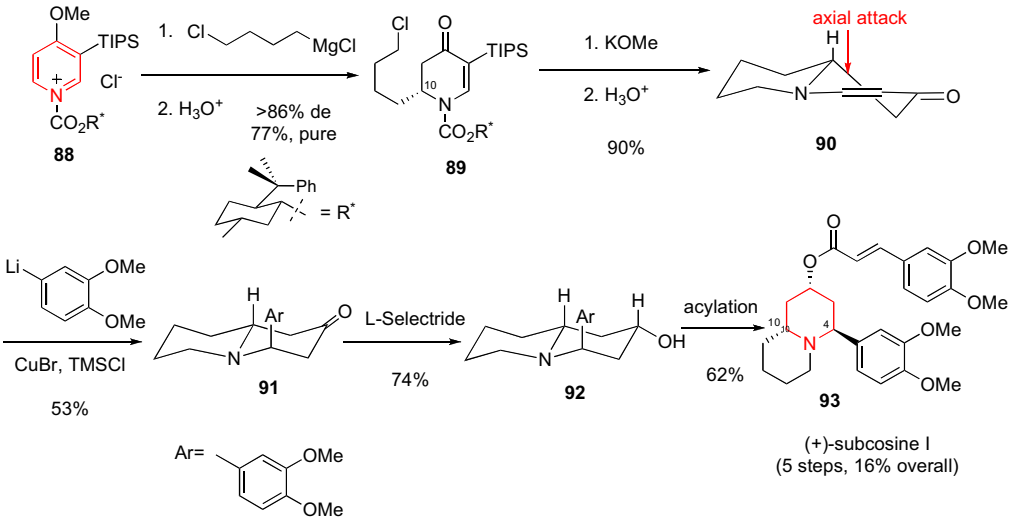
Scheme 13 Synthesis of 205B.

has shown rather promising biological activity inhibiting α7-nicotinic acetylcholine receptors.[30] In designing our synthesis plan, the highly functionalised tricyclic core was unravelled retrosynthetically to a closely related indolizidine, which appeared accessible via a simple ring-closing metathesis reaction. Our synthetic strategy for the construction of the indolizidine ring with five chiral centres would rely on substrate-controlled sequential installation of the stereocentres. In comparison with previously utilised approaches, a novel plan was devised to form the 5-membered pyrollidine ring of **87** by controlling the stereochemistry of the C2a stereocentre during the cyclisation reaction. This proposed step was key to the success of our approach.[31] The synthesis commenced with an *N*-acyl-pyridinium salt reaction of **1** and 4-butenyl Grignard to install the first stereocentre and provide **76** in an efficient manner. Our standard one-pot procedure was performed to unveil the vinylogous amide **77**. The key bicyclic motif was fashioned through a Tsuji–Trost allylic amination reaction.

Cross-metathesis of the terminal olefin **77** using Grubbs–Hoveyda 2nd generation catalyst and excess of (*Z*)-but-2-ene-1,4-diyl diacetate gave allylic acetate **78**. A tri-*tert*-butylphosphine ligand was critical for controlling the stereoselectivity of the allylic amination. Exposure of compound **78** to 5% $Pd_2(dba)_3 \cdot CHCl_3$, Cs_2CO_3 and 20% P-*t*Bu_3 in dioxane for 8 h led to the highly stereoselective formation of indolizidinone **79**. Unfortunately, alkylation of the enolate of **79** with MeI produced a 3:1 mixture of inseparable diastereomers. This problem was solved by the addition of one more equivalent of LDA to the reaction mixture to quantitatively regenerate an enolate after alkylation. Careful protonation with MeOH under kinetic conditions provided the intermediate **81** with the desired equatorial methyl group. The stereoselective 1,4-addition of a methallyl side chain to the bicyclic vinylogous amide **81** proved to be a non-trivial step. Simple cuprate additions were effective in delivering the methallyl group but were not facial selective, resulting in mixtures of diastereomers. After significant experimentation, it was found that the vinylogous amide could be activated with trifluoroacetic anhydride to produce iminium ion **82** *in situ* which was attacked at the β-face by a methallylstannane reagent in a highly stereoselective fashion. Finally, the intermediate vinyl trifluoroacetate was easily hydrolysed upon aqueous bicarbonate work-up to give ketone **83** as the desired single diastereomer. With both the methallyl and vinyl groups in place, the stage was set for the key ring-closing metathesis reaction. Reaction of **83** with Grubbs 2nd generation catalyst in *t*BuOMe resulted in efficient conversion to the tricyclic structure **84**. The last stereocentre was introduced through the action of NaHMDS followed by quenching the enolate with excess MeI to give **86** as a single diastereomer. The rigid tricyclic frame of the molecule causes a substrate-controlled stereoinduction to occur, and the outcome of the reaction is attributed to the axial alkylation from the less-hindered face of the enolate **85**. The presence of two tertiary stereocentres at C6 and C8 significantly limited the reactivity of ketone **86** and thereby made its required reduction to a methylene a formidable challenge. Finding an appropriate protocol for this transformation proved to be extremely arduous. After an exhaustive screen of commonly employed conditions, the ketone **86** was reduced to the equatorial alcohol with lithium/ammonia and then converted into its thiocarbamate through the action of 1,1'-thiocarbonyldiimidazole (TCDI) in the presence of DMAP. After many failures, radical deoxygenation was performed employing modified Barton–McCombie conditions in the presence of diphenyldiselenide. *In situ* generated PhSeH, from PhSeSePh and Bu_3SnH, has a significantly higher potential in reducing radicals. Rearrangements and fragmentations of the unstable secondary radical formed from thiocarbamate degradation were suppressed and 205B (**87**) was isolated in 60% yield.

2.3. Quinolizidines

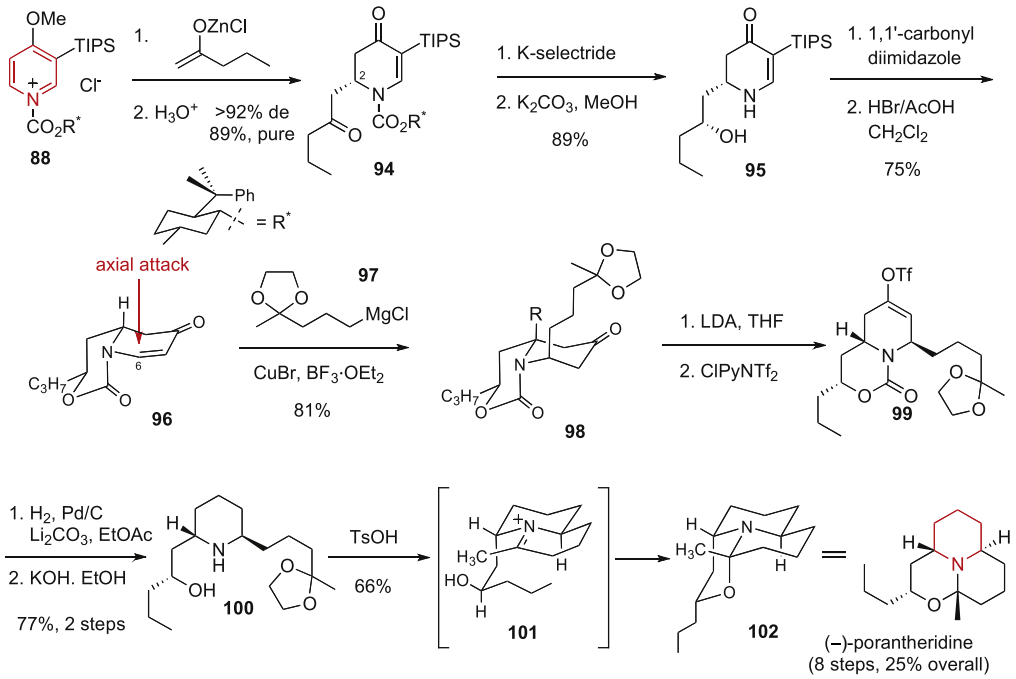
Subcosine. As effective as our chiral *N*-acylpyridinium salt chemistry is for the synthesis of indolizidine alkaloids, it is even more efficient in the case of quinolizidines. This tactic allows an easy two-step assembly of the simple framework **90**, an attractive building block for the enantioselective synthesis of a variety of alkaloids. As shown in Scheme 14, the C10 stereocentre of the quinolizidine was easily introduced through addition of 4-chlorobutylmagnesium bromide to chiral *N*-acylpyridinium salt **88**.[32] Subsequent acidic work-up provided diastereomerically pure dihydropyridone **89**.



Scheme 14 Synthesis of subcosine.

Under the influence of potassium methoxide, the chiral auxiliary was removed and cyclisation occurred to form the desired bicyclic ring system. The TIPS group was removed upon acidic work-up with oxalic acid. Quinolizidine **90** has an extremely versatile vinylogous amide functionality which allows further elaboration for the preparation of various natural products. Only three more steps were required to accomplish a concise synthesis of (+)-subcosine I[33] (**93**). Copper-mediated 1,4-addition of (3,4-dimethoxyphenyl)lithium in the presence of chlorotrimethylsilane generated the *trans*-product **91**. Stereoselective reduction of the ketone was effected with L-Selectride providing the desired equatorial alcohol **92** as one diastereomer. Finally, compound **92** was acylated with 3,4-dimethoxycinnamic anhydride in the presence of pyridine and DMAP to furnish (+)-subcosine.

Porantheridine. Our approach towards the novel tricyclic natural product (−)-porantheridine[34] (**102**) involved an addition of a metallo-enolate to chiral *N*-acylpyridinium salt **88** to set the first stereocentre in the molecule.[35] The pyridinium salt **88** was exposed to the zinc enolate of 2-pentanone. After acidic work-up, the corresponding dihydropyridone **94** was obtained as one diastereomer in 89% yield after purification. Upon treatment with K-Selectride, the ketone was reduced stereoselectively to the alcohol. Having established two stereocentres, attention was turned to the introduction of the critical C6 centre that would initiate the late-stage formation of the tricyclic ring system. To this end, the chiral auxiliary was removed with Na_2CO_3/MeOH to give **95**. To introduce the desired stereochemistry at C6, the bicyclic carbamate **96** was prepared by acylation with 1,1'-carbonyldiimidazole in excellent yield followed by TIPS cleavage with HBr/HOAc in CH_2Cl_2. A copper-mediated conjugate addition of organocopper reagent **97** proceeded without incident to provide *trans*-2,6-disubstituted piperidone **98** as a 19:1 mixture of diastereomers. As anticipated, the excellent stereocontrol of the addition is consistent with stereoelectronically preferred axial attack of the Grignard reagent. With piperidone **98** in hand, the stage was set for the ketone reduction, which was accomplished in two steps. Vinyl triflate

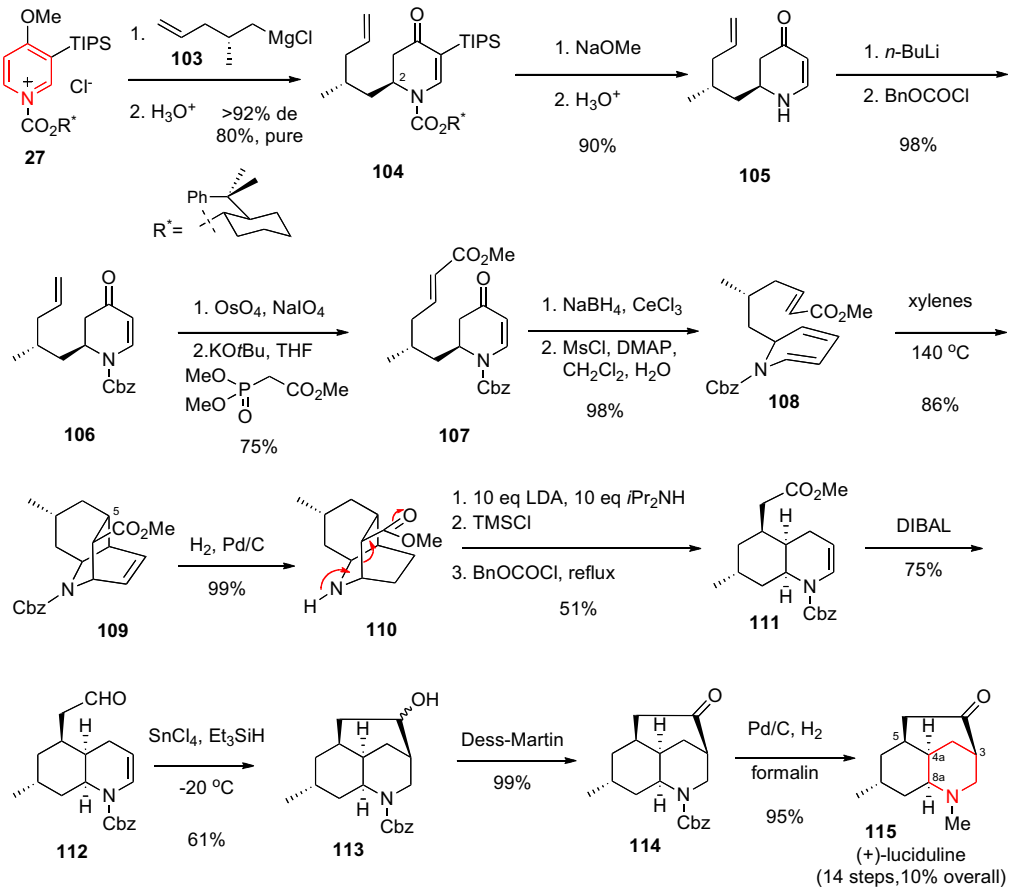


Scheme 15 Synthesis of porantheridine.

99 was prepared with LDA and $ClPyNTf_2$ and immediately subjected to hydrogenation in the presence of Li_2CO_3 and Pd/C. Subsequent hydrolysis of the resulting carbamate unveiled the alcohol and amine functions for the key final step to form the alkaloid ring system. Treatment of **100** with $TsOH \cdot H_2O$ in benzene initially hydrolyses the ketal to a ketone which then undergoes reaction with the secondary amine to provide iminium ion **101**. Due to the inherent conformation of the quinolizidine intermediate, the alcohol attacked the iminium ion from the α-face of the ring system and correctly introduced the last stereocentre to furnish (−)-porantheridine (**102**).

2.4. Perhydroquinolines

Luciduline. The *cis*-perhydroquinoline alkaloid luciduline (**115**) was isolated from *Lycopodium lucidulum*.[36] The molecular architecture of luciduline is characterised by 3 rings and 5 stereocentres. A *cis*-perhydroquinoline was chosen as a primary synthetic intermediate since it was anticipated that the last ring could be easily assembled through control from the preexisting stereocentres.[37] The required *cis*-perhydroquinoline structural motif was proposed to arise from an intramolecular Diels–Alder reaction of a 1,2-dihydropyridine containing a functionalised alkene side chain at the C2 position. This transformation would not only set both stereocentres at the ring juncture but also introduce the C5 centre of the perhydroquinoline with the proper configuration and functionality to form the last ring of the alkaloid target. As shown in Scheme 16, addition of the enantiopure Grignard



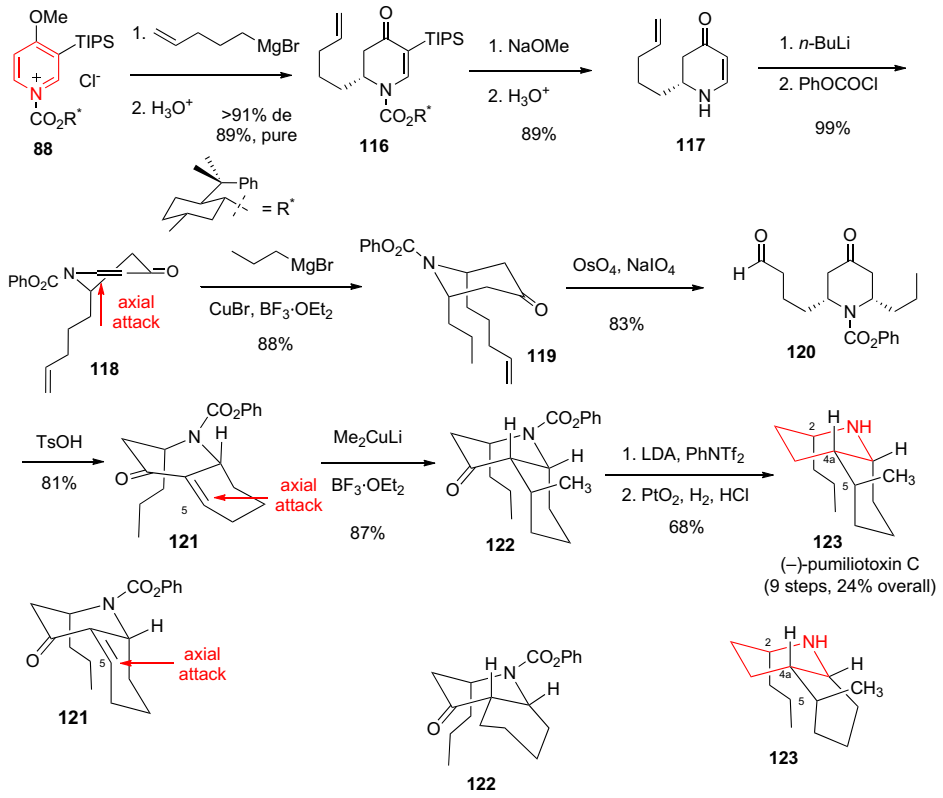
Scheme 16 Synthesis of luciduline.

reagent **103** to the *N*-acylpyridinium salt **27** gave after acidic work-up dihydropyridone **104** in 80% yield. Having served their intended purposes, the chiral auxiliary and TIPS group were smoothly removed utilising the standard one-pot protocol, and the dihydropyridone **105** was then protected as the Cbz-carbamate **106** in excellent yield.

The terminal olefin was oxidatively cleaved with catalytic OsO_4 and $NaIO_4$, and the resulting aldehyde was subjected to a Horner–Wadsworth–Emmons reaction to deliver the α,β-unsaturated ester **107**. Reduction of **107** under Luche conditions and subsequent dehydration of the secondary alcohol with Furukawa's reagent formed the desired triene **108**. The intramolecular Diels–Alder reaction proceeded smoothly in boiling xylene generating the *endo* product **109** and installing four stereocentres in a highly efficient way. Hydrogenation of the double bond and concurrent reductive cleavage of the Cbz-carbamate of **109** unmasked the secondary amine **110** and set a stage for a crucial fragmentation reaction. It was found that the desired retro-Mannich ring opening could be promoted in the presence of 10 equiv of LDA and 10 equiv of iPr_2NH at −50 °C. The reaction mixture was quenched with chlorotrimethylsilane to give

a mixture of silylated products. The resulting mixture was simply exposed to benzyl chloroformate and, after acidic work-up, the Cbz-protected enecarbamate **111** was isolated in 51% overall yield. Having established the *cis*-perhydroquinoline system, attention was turned to the introduction of the last ring. Since compound **111** has all the necessary functionality in place, the stage was set for the planned intramolecular acylation. Methyl ester **111** was carefully reduced to the aldehyde **112** using DIBAL. Satisfyingly, upon exposure of **112** to $SnCl_4$ the enecarbamate successfully attacked the activated carbonyl group and formed an *N*-acyliminium ion which was reduced *in situ* by triethylsilane to afford the desired ring with full regio- and stereocontrol. The alcohol **113** was oxidised with Dess–Martin periodinane to the corresponding ketone **114** without incident. Finally, the Cbz-carbamate was converted to the *N*-methyl group using a one-pot procedure to afford (+)-luciduline (**115**) in excellent yield.

Pumiliotoxin C. The *cis*-perhydroquinoline pumiliotoxin C (**123**) is another natural product isolated from skin secretions of neotropical frogs *Dendrobatidae*.[38] In comparison with luciduline, it has the same *cis* ring juncture but the tertiary centre at C5 has the opposite stereochemistry; therefore, a conceptually distinct strategy had to be devised to access this type of alkaloid.[39] Intermediate **118** was prepared utilising a similar sequence of steps as in our synthesis of luciduline. At this stage, dihydropyridone **118** underwent a facile copper-mediated 1,4-conjugate addition with propylmagnesium bromide and $BF_3 \cdot OEt_2$ to provide the *cis*-2,6-disubstituted piperdone **119**. Further analysis suggested



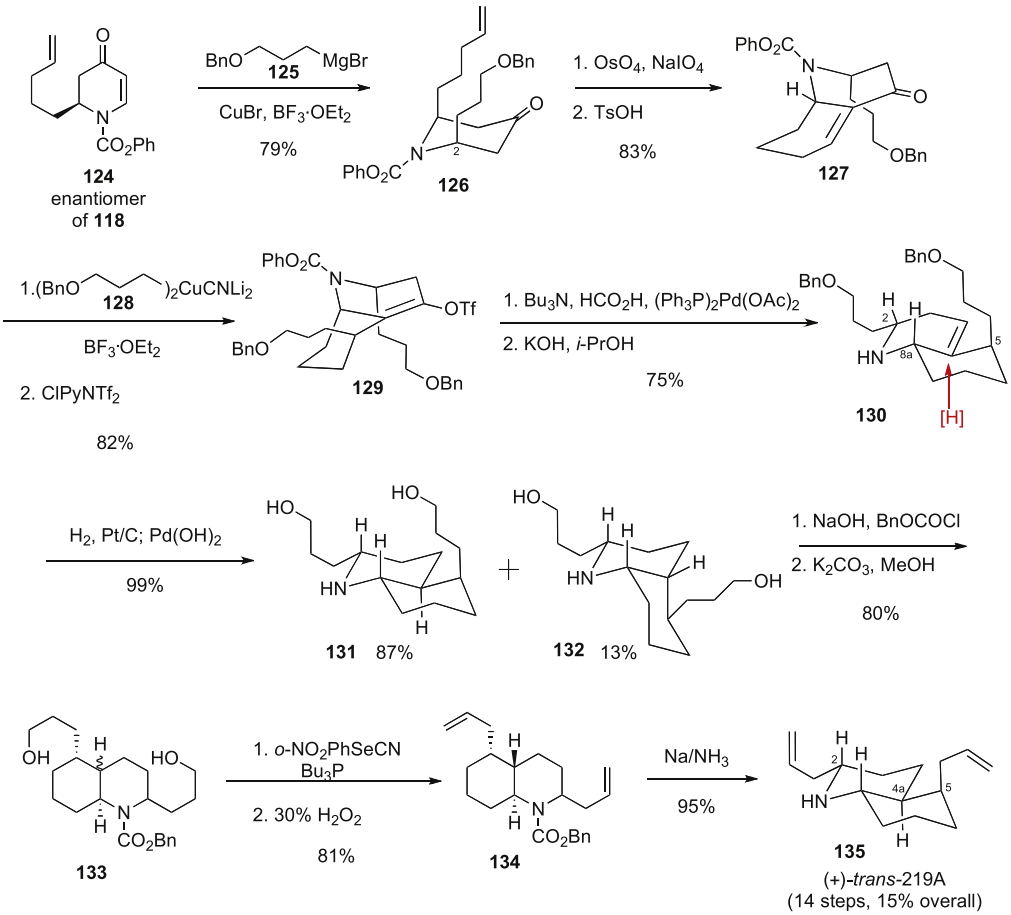
Scheme 17 Synthesis of pumiliotoxin C.

that oxidative cleavage of the olefin and subsequent aldol reaction of the newly generated aldehyde would form a bicyclic system with an α,β-unsaturated enone (see **121**). Careful consideration of the conformation of the enone revealed an appealing opportunity that simple conjugate addition with methyl cuprate followed by protonation of the enolate would give the perhydroquinoline system with the desired relative stereochemistry at both of the newly introduced stereocentres. The terminal alkene **119** was converted to aldehyde **120** through exposure to catalytic OsO_4 and $NaIO_4$. Use of a TsOH-promoted aldol reaction resulted in formation of the α,β-unsaturated enone **121**. The anticipated stereoelectronically controlled axial 1,4-conjugate addition of methyl cuprate in the presence of $BF_3 \cdot OEt_2$ proceeded smoothly, and protonation of the intermediate enolate gave the desired thermodynamically more stable *cis*-perhydroquinoline **122** in 97:3 selectivity. Treatment of the ketone **122** with LDA and $PhNTf_2$ effectively furnished the vinyl trfilate. Reduction of the vinyl triflate and concomitant cleavage of the phenyl carbamate group was accomplished upon catalytic hydrogenation over Adams catalyst to deliver (−)-pumiliotoxin C (**123**).

▶ Alkoloid 219A

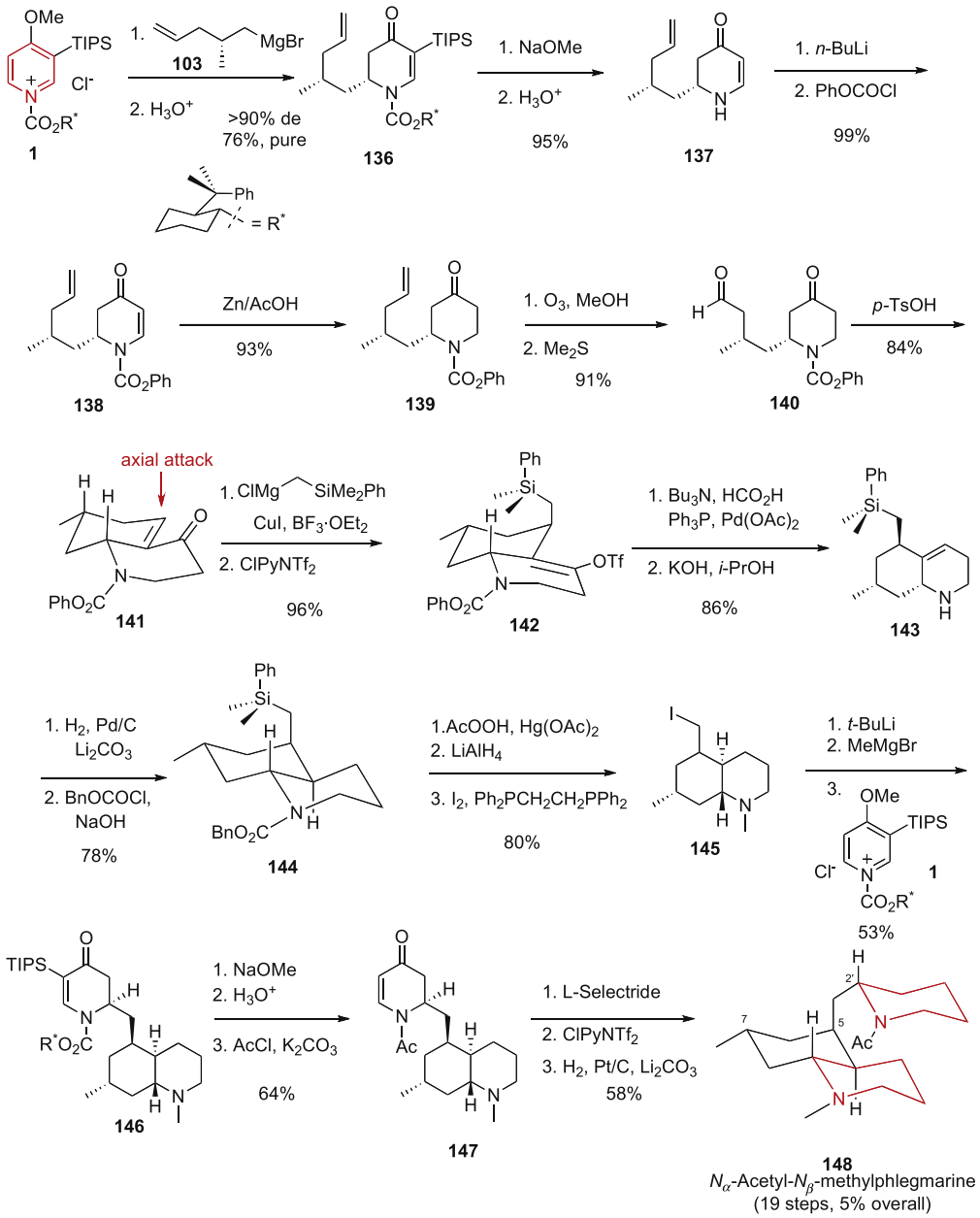
Having developed an efficient way to access *cis*-decahydroquinoline alkaloids, the challenge was to develop a complimentary strategy that would provide a concise entry into *trans*-decahydroquinoline natural products. Several alkaloids with this type of framework were isolated from the same family of neotropical frogs *Dendrobatidae*. Alkaloid (+)-*trans*-219A[40] (**135**) is one of the interesting members, and its synthesis is shown in Scheme 18.[41] Since intermediate **124** intercepts with our synthesis of pumiliotoxin, its preparation followed the previously disclosed route with the exception that the enantiomer was prepared. The side chain at the C2 position of **126** was introduced stereoselectively using a copper-mediated addition of [3-(benzyloxy)propyl] Grignard **125**. Oxidative cleavage of the oletin followed by acid-mediated cyclisation provided **127**. The cuprate addition to the enone system of **127** proceeds from the desired axial direction; however, protonation of the resulting enolate affords the *cis*-hydroquinoline. To reverse this undesired stereochemical outcome, an alternative plan was devised. After addition of the cuprate **128**, the enolate was trapped as triflate **129** with $ClPyNTf_2$. The vinyl triflate was reduced to the alkene under Cacchi's conditions, and the phenyl carbamate was hydrolysed with potassium hydroxide to furnish **130** in 75% yield for the two steps. Cleavage of the carbamate group relieves the 1,3-allylic strain and causes a conformational change so that both the C2 and C8a substituents adopt equatorial positions. The axial C5 side chain served as a stereocontrol element to direct the next crucial reduction, blocking one of the double bond faces. Hydrogenation over 5% platinum on carbon and palladium hydroxide generated an 87/13 mixture of the diols **131** and **132** favouring the desired *trans* isomer. Triacylation of the mixture, followed by deprotection of the alcohols with potassium carbonate, gave a mixture of carbamates **133**. The conversion of both diols to selenides was accomplished with *o*-nitrophenyl selenocyanate and tributylphosphine. At this point the desired *bis*-selenide was separated by chromatography and subsequently oxidised with hydrogen peroxide to furnish *bis*-alkene **134**. The benzyl carbamate was cleaved under dissolving metal conditions to give (+)-*trans*-219A (**135**).

Phlegmarines. The phlegmarines are alkaloids with intriguing and challenging architectures from the family *Lycopodium*.[42] In contrast to luciduline and pumiliotoxin, the structure of the phlegmarines

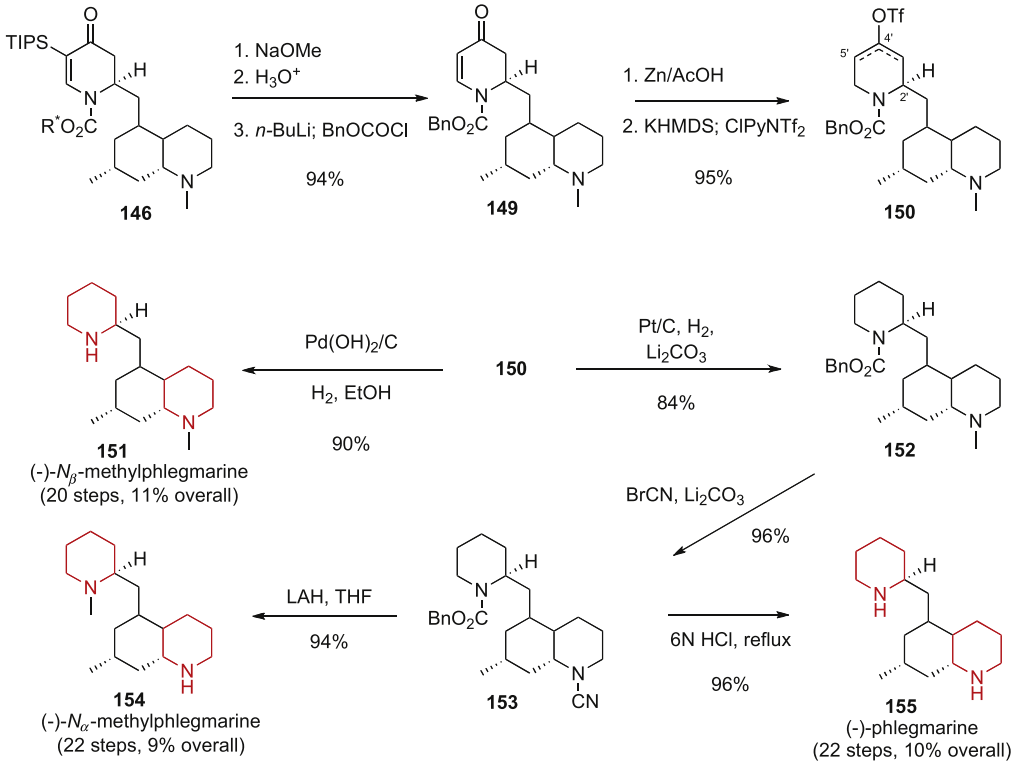


Scheme 18 Synthesis of *trans*-219A.

features a more rare *trans*-perhydroquinoline fragment. Furthermore, an additional piperidine ring attached at the C5 position of the hydroquinoline frame sufficiently increases the complexity of this molecule and adds one more stereocentre at C2′. In the light of the potential difficulties of installing the remote piperidine ring, our plan was to access it through an *N*-acylpyridinium salt reaction of a chiral *N*-acylpyridinium salt and a Grignard reagent prepared *in situ* from a corresponding perhydroquinoline intermediate.[43,44] This proposed maneuvre was highly attractive since it would couple the perhydroquinoline core and piperidine ring precursor in one step while reliably setting the desired C2′ stereocentre. Moreover, the resulting dihydropyridone product could be easily converted to a piperidine in just three well-established steps. The synthesis starts with reaction of *N*-acylpyridinium salt **1** and the chiral Grignard reagent **103** to provide after recrystallisation a 76% yield of the corresponding dihydropyridone **136** as one diastereomer. The next task, namely removal of the TIPS group and exchange of the chiral auxiliary for a phenoxycarbonyl group, was accomplished in two

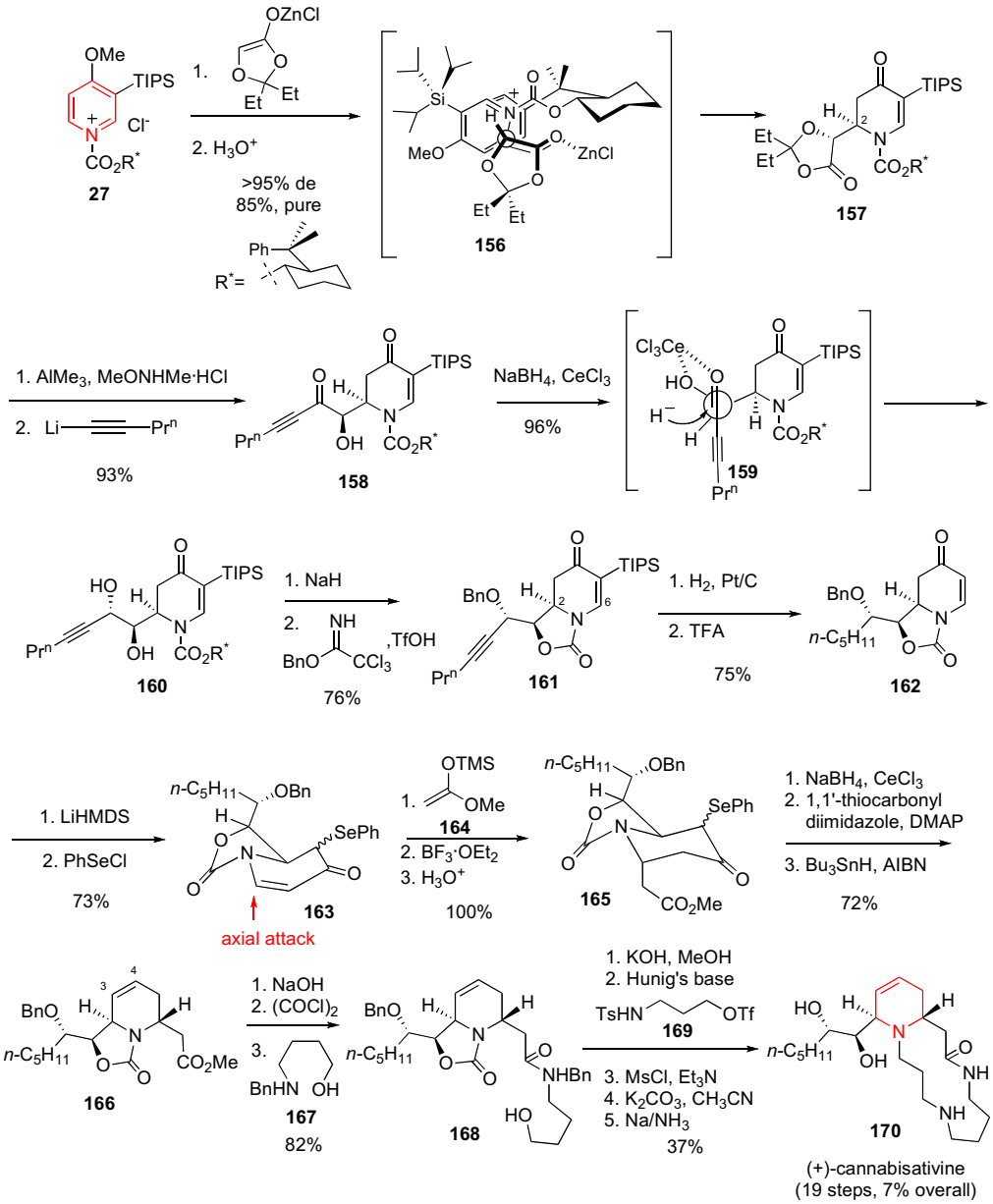


Scheme 19 Synthesis of N_α-acetyl-N_β-methylphlegmarine.



Scheme 20 Synthesis of three other phlegmarine alkaloids.

steps. Refluxing a MeOH solution of **136** in the presence NaOMe, followed by acidification with 10% HCl, provided **137**. *N*-Acylation with *n*-BuLi and PhOCOCl gave dihydropyridone **138** which underwent Zn/AcOH conjugate reduction to form the ketone **139**. Ozonolysis of the terminal double bond followed by reductive work-up with dimethyl sulphide resulted in aldehyde **140**. TsOH-promoted aldol condensation proceeded smoothly to produce the α,β-unsaturated ketone **141**. Stereoelectronically controlled conjugate addition of (dimethylphenylsilyl)methylmagnesium chloride in the presence of CuI provided an enolate which was trapped by $ClPyNTf_2$ to afford the desired vinyl triflate **142**. At this stage of the synthesis, introduction of the *trans* ring fusion in the hydroquinoline was addressed. The Pd-catalysed partial reduction of the triflate **142** was accomplished by using formic acid, tributylamine and Ph_3P as a ligand. The phenyl carbamate was hydrolysed under the action of KOH in refluxing isopropanol. The resulting alkene **143** was subjected to hydrogenation conditions with 5% of Pd/C and Li_2CO_3 in ethyl acetate. As anticipated, key stereoselective reduction of the trisubstituted olefin proceeded uneventfully delivering hydrogen mainly from the desired more accessible face of the molecule and generating the crude product as an 89:11 mixture of diastereomers. Acylation with benzyl chloroformate and purification gave a 78% yield of **144**. The β-face of the hydroquinoline **143** was more sterically shielded due to presence of the axial phenyldimethylsilyl



Scheme 21 Synthesis of cannabisativine.

group. With the core carbon framework and all four stereocentres secured, focus was turned to the challenging *N*-acylpyridinium salt reaction. With compound **144** in hand, the silyl group was oxidised using Fleming's conditions to provide the alcohol, the Cbz-carbamate was converted to an *N*-methyl group with $LiAlH_4$, and finally the alcohol was transformed into the corresponding iodide **145** with 1,2-

bis(triphenylphosphino)ethane tetraiodide. Having executed the preparation of the appropriate halide **145**, the completion of the N_α-acetyl-N_β-methylphlegmarine synthesis required the introduction of the remote 2′-substittuted piperidine ring. After significant experimentation, it was found that only a mixed Grignard reagent could be added to the pyridinium salt. The powerful *N*-acylpyridnium salt chemistry allowed installation of the fifth stereoecentre with near complete stereocontrol in 53% yield. Our standard conditions were utilised to remove both the chiral auxiliary and TIPS group. The resulting vinylogous amide was *N*-acylated with acetyl chloride and potassium carbonate to give **147**. Finally, 1,4-conjugate reduction and vinyl trfilate formation followed by hydrogenation over Pt/C furnished enantiopure N_α-acetyl-N_β-methylphlegmarine (**148**).

The other three known phlegmarine alkaloids were prepared in a concise manner from the common intermediate **146**.[44] Standard removal of the auxiliary and the TIPS group followed by reprotection with benzyl chloroformate led to dihydropyridone **149**. A conjugate reduction with zinc in acetic acid and trapping the intermediate enolate with $ClPyNTf_2$ provided vinyl triflate **150** in a 3:1 ratio favouring the isomer with the double bond at the 4′,5′ position. Hydrogenation of **150** over Pearlman's catalyst delivered (−)-N_β-methylphlegmarine (**151**). To access the two remaining target alkaloids, a careful hydrogenation of **150** with platinum on carbon in the presence of lithium carbonate was employed to generate carbamate **152** selectively. *N*-Demethylation was accomplished under von Braun conditions with cyanogen bromide giving an excellent yield of cyanamide **153**. Exposure of **153** to aqueous hydrogen chloride resulted in cleavage of both the cyano and Cbz-carbamate groups to afford natural product (−)-phlegmarine (**155**) in high yield. Finally, to our delight, reduction of the same intermediate **153** with LAH converted the benzyl carbamate to a methyl group and removed the cyano group to furnish enantiopure N_α-methylphlegmarine (**154**).

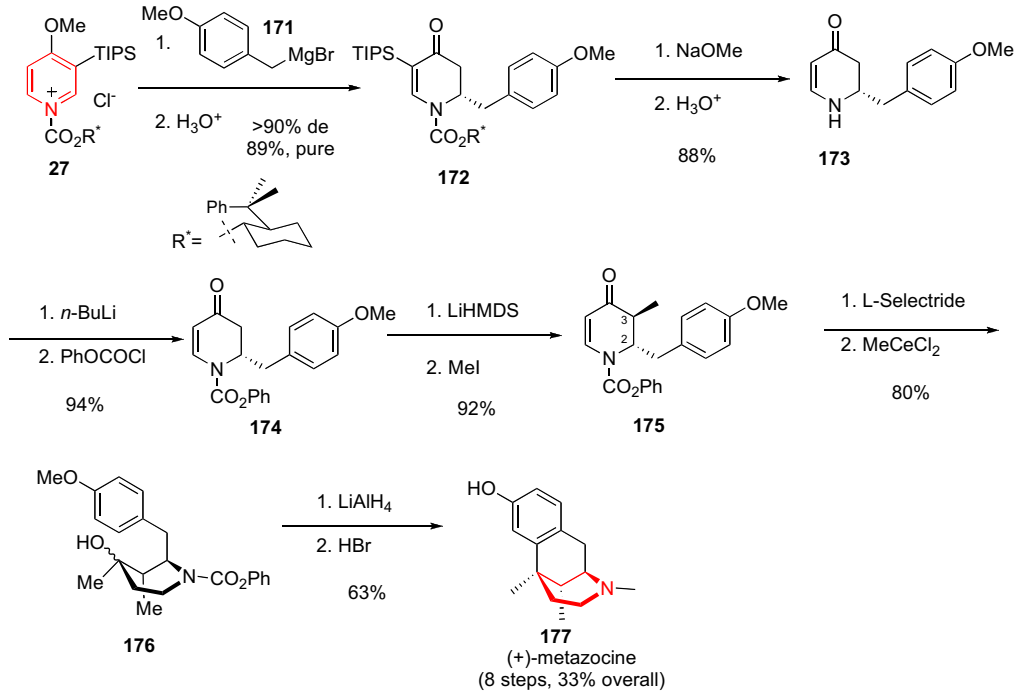
2.5. Polyamine Alkaloids

Cannabisativine. The polyamine alkaloid (+)-cannabisativine (**170**) was isolated from *Cannabis sativa* L. and contains a 13-membered lactam ring system that is annulated to a disubstituted tetrahydropyridine ring.[45] A key transformation in our synthesis of this natural product involved addition of a zinc enolate to chiral *N*-acylpyridinium salt **27** to form intermediate **157** containing two new chiral centres with excellent diastereoselectivity.[46] The facial selectivity of the process could be attributed to addition via the acyclic transition state **156** with synclinal orientation where all nonbonding interactions between the pyridine ring and incoming nucleophile are minimised. Lactone **157** was converted to the Weinreb amide followed by addition of pentynyllithium to form the desired ketone **158**. Reduction of the ketone under Luche conditions generated Cram-chelate product **160** as a single diastereomer in excellent yield. Treatment of **160** with NaH provided a 5-membered carbamate. It is worth mentioning that none of the six-membered carbamate formed under these reaction conditions. The remaining secondary hydroxyl group was protected as the benzyl ether to give **161**. The side-chain alkyne could be selectively hydrogenated over Pt/C in 97% yield since the enone system was protected by the bulky TIPS group. Removal of the TIPS group was accomplished via protodesilylation in refluxing TFA/$CHCl_3$ mixture to provide **162**. It was envisioned that the C3−C4 double bond would arise from radical elimination of

a phenylselenide. To this end, phenylselenyl chloride was added to the lithium enolate of **162** to afford a mixture of diastereomeric selenides **163**. Diastereoselective conjugate addition of *O*-TMS ketene acetal **164** under standard Mukaiyama–Michael conditions generated ketone **165** in quantitative yield. Introduction of the double bond was accomplished employing a Barton–McCombie protocol. Reduction of the ketone with $NaBH_4$, reaction of the resulting alcohols with 1,1'-thiocarbonyldiimidazole in the presence of catalytic DMAP and treatment with Bu_3SnH/AIBN resulted in formation of **166**. With all stereocentres and the alkene in place, a careful ordering of transformations was necessary for the macrocyclisation and completion of the synthesis. The methyl ester of **166** was hydrolysed to the acid and converted to an acid chloride upon exposure to oxalyl chloride. Coupling under Schotten–Baumann conditions with N-benzyl-protected amino alcohol **167** gave the expected amide **168**. The oxazolidinone ring was hydrolysed and the amine was treated with triflate **169** to furnish the desired N-alkylated product. The primary alcohol was mesylated and subjected to macrocyclisation in K_2CO_3/acetonitrile. Finally, cleavage of the benzyl and tosyl groups under dissolving metal conditions provided (+)-cannabasativine (**170**).

2.6. Benzomorphans

Metazocine. As shown in Scheme 22, the synthesis of the benzomorphan, (+)-metazocine, commenced with an introduction of the first stereocentre and methoxybenzyl group.[47] Grignard



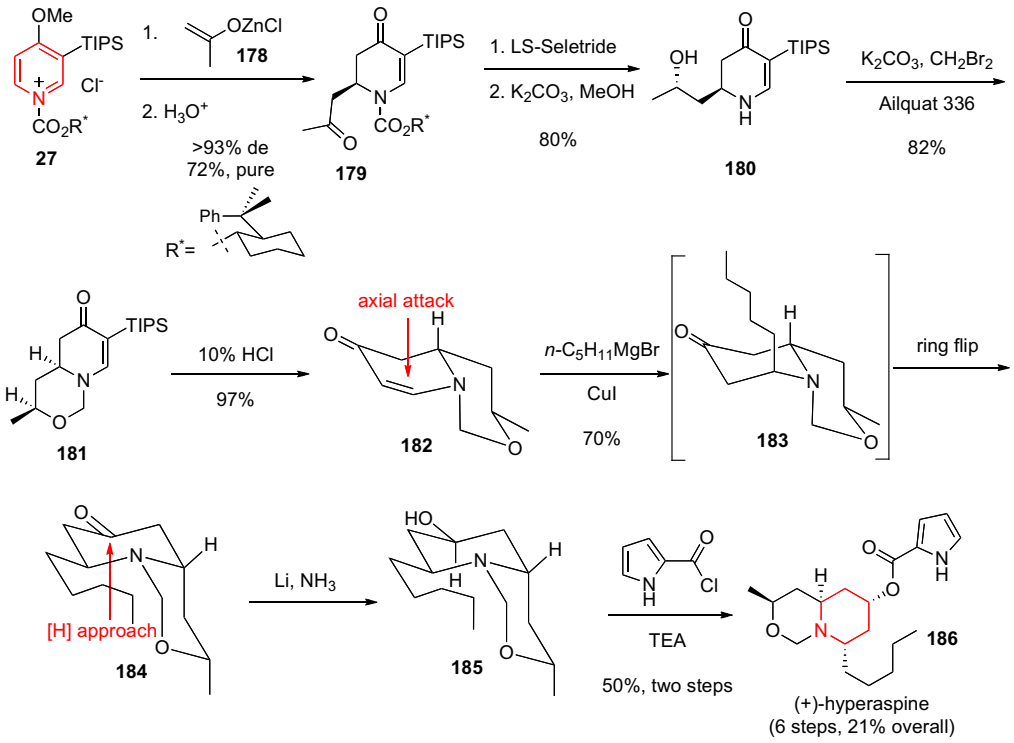
Scheme 22 Synthesis of metazocine.

reagent **171** was added to chiral *N*-acylpyridinium salt **27** to give after acidic work-up and purification dihydropyridone **172**. The TIPS group and chiral auxiliary were removed and *N*-acylation of the intermediate provided the enantiopure phenyl carbamate **174** in 2 steps. Stereoselective alkylation at C3 was effected by LiHMDS followed by addition of MeI generating the corresponding 2,3-*trans*-dihydropyridone **175**. Conjugate reduction with L-Selectride followed by 1,2-addition of methylcerium chloride to the ketone led to a mixture of diastereomeric alcohols **176** in 3.75:2 ratio.

It should be noted that the diastereomers could be separated using preparative chromatography, but they were used as a mixture in the next reaction directly since the stereochemistry of the alcohol is inconsequential to the following transformation. The phenyl carbamate **176** was converted to the *N*-methyl derivative upon treatment with $LiAlH_4$. Subsequent heating with 48% HBr caused formation of a transient tertiary carbocation which cyclised to the phenyl ring to provide (+)-metazocine (**177**).

2.7. Oxaquinolizidine Alkaloids

Hyperaspine. The unique alkaloid (+)-hyperaspine (**186**) was isolated from the European Coccinellidae *Hyperaspis campestris*.[48] The intriguing structure of this natural product includes



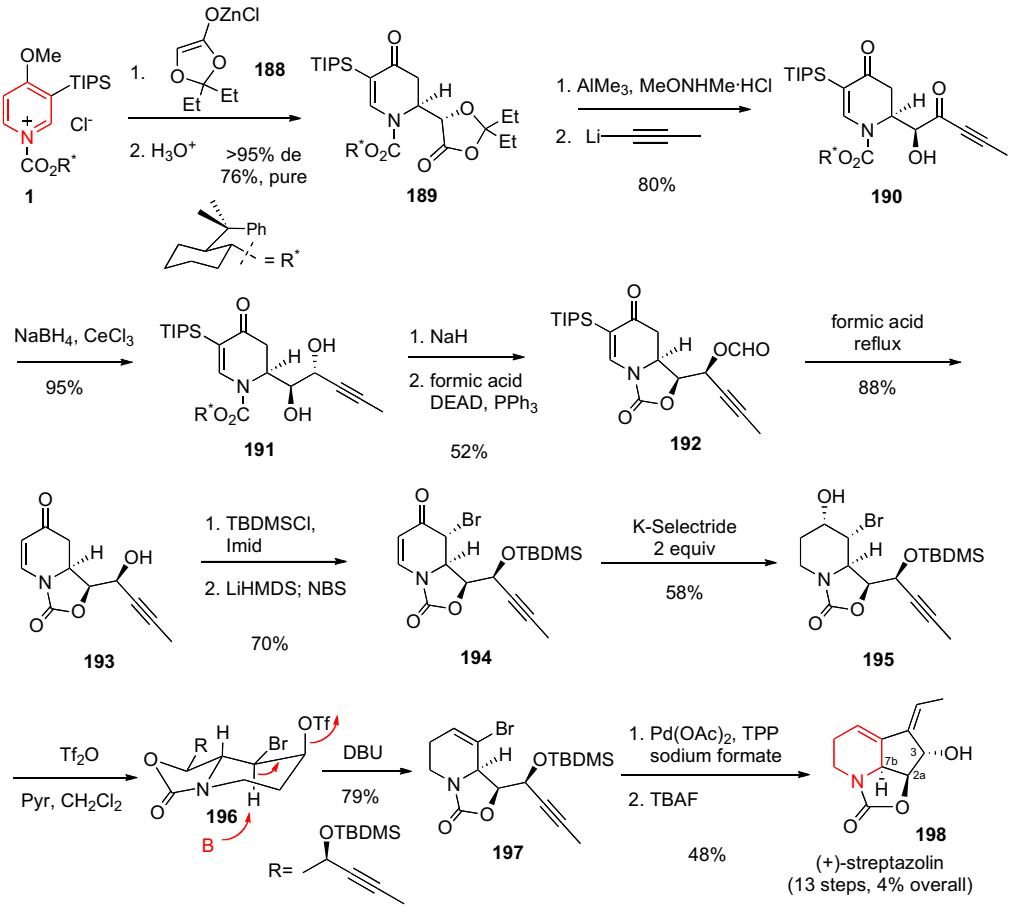
Scheme 23 Synthesis of hyperaspine.

a 3-oxaquinolizidine system. Our total synthesis of hyperaspine commenced with addition of the zinc enolate **178**, prepared from acetone and LDA followed by transmetallation with $ZnCl_2$, to chiral *N*-acylpyridinium salt **27** to furnish *N*-acyldihydropyridone **179** upon acidic work-up in 72% yield.[49] The carbonyl was reduced selectively with LS-Selectride, and the chiral carbamate was cleaved through hydrolysis to provide vinylogous amide **180**. Formation of the oxazinane ring proved to be nontrivial and required considerable effort to develop optimal conditions. The use of a catalytic amount of phase-transfer catalyst, Aliquat 336, 3 equiv of dibromomethane, and 6 equiv of Cs_2CO_3 provided the desired product **181**. Protodesilylation was accomplished with 10% HCl in THF. Now the stage was set for introduction of the pentyl side chain. Exposure of vinylogous amide **182** to the action of pentyl Grignard reagent in the presence of CuI delivered compound **184**.

This stereochemical outcome of this reaction was in accord with previously described transformations of this type. It is worth mentioning that after the initial formation of **183**, the conformation of the molecule changes and the pentyl side chain adopts the equatorial position. To obtain an equatorial alcohol, the ketone **184** should be reduced from the axial direction and more importantly from the hindered concave side of the molecule. After screening several conditions, it was found that Li in liquid ammonia could accomplish this transformation with 93:7 selectivity. Finally, acylation with pyrrole-2-carbonyl chloride furnished (+)-hyperaspine (**186**).

2.8. Streptazolium Alkaloids

Streptazolin. Streptazolin (**198**) was first isolated from cultures of *Streptomyces viridochromogenes* in 1981.[50] This molecule was identified as having antibacterial and antifungal activity.[51] The intricate molecular architecture of this natural product creates an opportunity to develop innovative strategies for its synthesis. The major causes for concern were not the three stereocentres, which of course require sufficient attention, but the regio- and stereocontrolled incorporation of the diene system. Enantiopure *N*-acyldihydropyridone chemistry was employed in the development of a concise route towards this molecule. The initial steps of the synthesis are closely related to those used in the above described synthesis of the polyamine cannabisativine.[52] As shown in Scheme 24, chiral *N*-acylpyridinium salt **1** was treated with zinc enolate **188** to provide dihydropyridone **189**. This compound was converted to the Weinreb's amide followed by treatment with propynyllithium to afford ketone **190**. Reduction of the ketone proceeded smoothly under Cram-chelate control to generate diol **191** in excellent yield; however, the newly generated centre had the opposite stereochemistry needed for the natural product and required correction at a later stage. A NaH-promoted cyclisation reaction gave exclusively a five-membered oxazolidinone with concomitant removal of the chiral auxiliary. The remaining secondary alcohol was subjected to Mitsunobu conditions to produce formate ester **192** with complete inversion of configuration. Having correctly established all three contiguous stereocentres, attention was turned to the preparation of proper functionality for the key palladium-catalysed cyclisation to install the diene system of the natural product. Exposure of bicyclic carbamate **192** to formic acid cleaved both the formate ester and TIPS groups. The TIPS group had served a dual role of guaranteeing high selectivity in the pyridinium salt

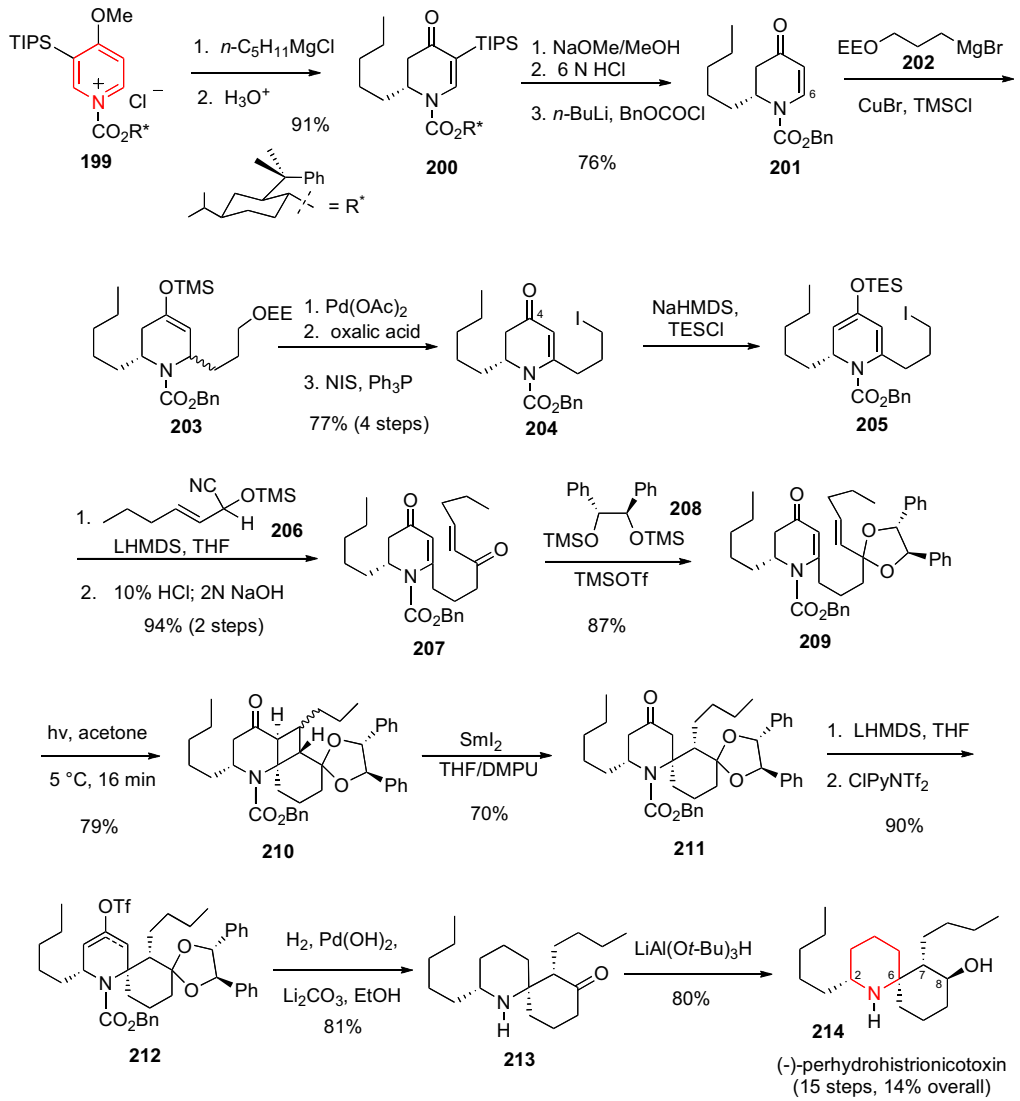


Scheme 24 Synthesis of streptazolin.

reaction and protecting the enone system throughout several crucial transformations. The alcohol **193** was immediately reprotected as a TBDMS silyl ether. At this stage the plan was to transform the enone into a vinyl bromide with a halogen in the C3 position. The lithium enolate was formed and brominated with NBS to provide bromide **194**. The dihydropyridone **194** was subjected to 2 equiv of K-Selectride to afford *cis*-bromohydrin **195**. Preparation of the axial alcohol was critical for the subsequent elimination reaction. After screening a variety of conditions, it was found that the corresponding vinyl bromide **197** could be obtained efficiently through the action of triflic anhydride to form the triflate **196** followed by *anti*-elimination induced *in situ* upon addition of DBU to the reaction mixture. With all functionality in the proper place, the cyclisation was anticipated to proceed regio- and stereoselectively. Indeed, this proved to be the case. Exposure of **197** to Grigg's conditions with $Pd(OAc)_2$ as catalyst at 130 °C for 20 h generated the desired diene. Removal of the silyl protecting group delivered (+)-streptazolin (**198**).

2.9. Spirocyclic Alkaloids

Perhydrohistrionicotoxin. Perhydrohistrionicotoxin (**214**) is a non-natural reduced analogue of histrionicotoxin, which was isolated by Witkop in 1971 from the skin secretions of the neotropical poison frogs *Dendrobates histrionicus*.[53] Both of these molecules are noncompetitive blockers of the neuromuscular, ganglionic and central neuronal acetylcholine receptors.[54] The ability of these compounds to interrupt the transsynaptic transmission of neuromuscular impulses attracted significant

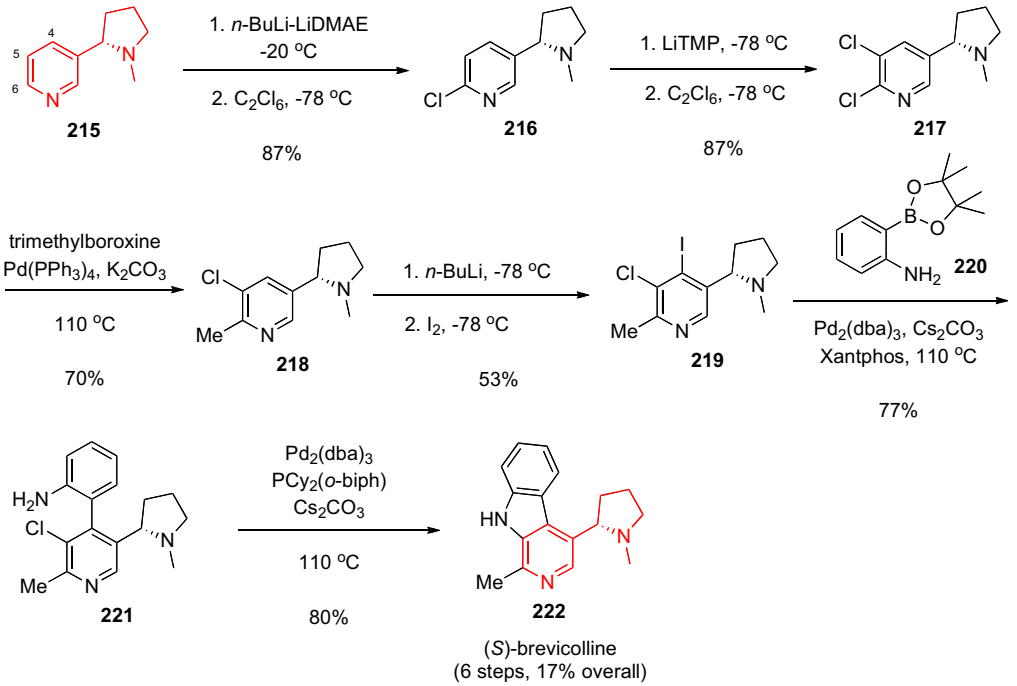


Scheme 25 Synthesis of perhydrohistrionicotoxin.

attention from the research community as they could be used as a neurophysiological tool to study cholinergic receptor mechanisms. Furthermore, the incredible low availability of the material from its natural sources and the challenging spirocyclic architecture generated considerable synthetic efforts. The strategic design element of our unique approach towards this molecule is an intramolecular [2+2]-photocycloaddition reaction to form the spirocyclic stereocentre.[55] Our synthesis started with a preparation of **209** as the desired precursor for the planned photoreaction. An asymmetric *N*-acylpyridinium salt reaction was used to introduce the pentyl side chain in dihydropyridone intermediate **200**. The TIPS group and the chiral auxiliary were removed using the standard one-pot protocol, and the resulting vinylogous amide was *N*-protected as Cbz-carbamate **201**. A side chain needed to be installed at the C6 position. This transformation was best achieved by the addition of the corresponding Grignard reagent **202** in the presence of copper bromide and TMSCl to provide silyl enol ether **203.** Saegusa oxidation of the crude product generated the corresponding dihydropyridone. Deprotection with oxalic acid to give the free alcohol and subsequent conversion to the iodide **204** under standard conditions occurred in good overall yield. The further elaboration of the side chain required protection of the C4 carbonyl. This was successfully accomplished with NaHMDS deprotonation followed by the addition of TESCl to provide the silyl enol ether **205**. The assembly of the side chain proceeded uneventfully by treatment of **205** with the anion of **206**, prepared from commercially available aldehyde, to deliver enone **207** in excellent yield. Enantiopure ketal **209**, which plays an essential role as a conformational controlling element securing the facial selectivity of the photoaddition reaction, was prepared using mild conditions with the *bis*-TMS-ether **208** and TMSOTf as an activating agent. Photolysis in acetone (460W Hanovia Hg lamp) generated cycloadduct **210** as a 7:1 mixture of diastereomers. Most notable, this reaction allowed stereospecific introduction of three stereocentres in the molecule including a quaternary spirocentre. Upon treatment with SmI_2, the cyclobutane ring was opened to afford ketone **211**. The routine cleavage of the ketone group was achieved by conversion to the mixture of vinyl triflates **212** followed by the catalytic hydrogenation over Pearlman's catalyst, which also effected the concomitant cleavage of the ketal to provide known ketone **213**. Finally, the synthesis was completed by reduction of the ketone group with $LiAl(OtBu)_3H$ according to a literature procedure from the Winkler group.

2.10. Pyridine-Type Alkaloids

Brevicolline. The β-carboline alkaloid (*S*)-brevicolline (**222**) was isolated from the plant *Carex brevicollis* D. C. (Cyperacee).[56] Its biological activities range from a phototoxic effect on bacteria and fungi to an oxytoxic effect in mammals.[57] Our synthesis, the shortest to date, starts with C-6 lithiation of (*S*)-nicotine to provide 6-chloronicotine (**216**) in high yield.[58] A subsequent C-5 lithiation−chlorination afforded the 5,6-dicholoronicotine (**217**). The C-6 methyl derivative **218** was formed in good yield *via* a Suzuki cross-coupling using trimethylboroxine. The iodination at C-4 of **218** proved to be difficult due to competitive deprotonation of the C-6 methyl group; however, addition of *n*-BuLi to **218** and quenching the resulting heteroaryllithium with iodine gave the desired 4-iodo intermediate **219** in acceptable yield. A cross-coupling reaction with boronate ester **220**



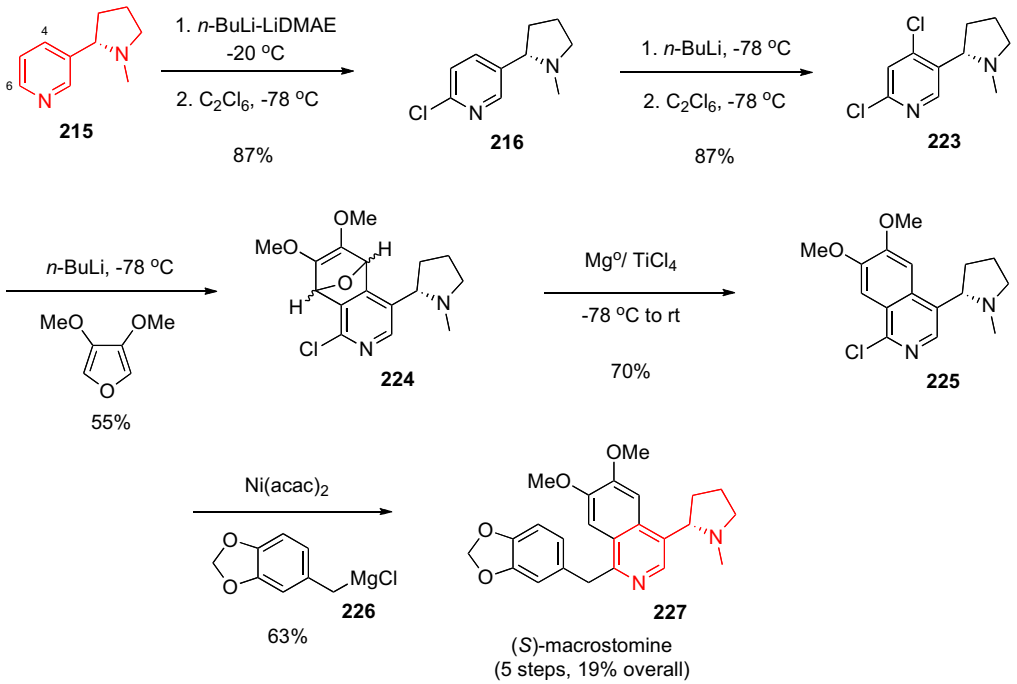
Scheme 26 Synthesis of (*S*)-brevicolline.

afforded the C-4 arylated derivative **221**. Modified Buchwald amination conditions effected the desired cyclisation to afford (*S*)-brevicolline (**222**). This synthesis was carried out in only six steps from (*S*)-nicotine with an overall yield of 17%.

Macrostomine. The alkaloid (*S*)-macrostomine (**227**) has been isolated from plants *Papaver macrostomum* and *Pacpaver arenarium*.[59] The alkaloid's biological activities include a spasmolytic effect on smooth muscle and an effect on the cardiovascular function of rabbits.[60] Our synthesis of macrostomine was accomplished in 5 steps from natural nicotine in 19% overall yield.[61]

The synthesis starts by converting natural nicotine to 6-chloronicotine (**216**) via our lithiation–chlorination procedure. A second lithiation–chlorination was effected at C-4 in high yield using *n*-BuLi/hexachloroethane to afford 4,6-dichloronicotine (**223**). After lithiation at C-5 with *n*-BuLi, and addition of excess 3,4-dimethoxyfuran, the mixture was warmed to effect pyridyne formation and subsequent Diels–Alder reaction. This process delivered the adduct **224** as a 1:1 mixture of diastereomers. Reductive aromatisation of this mixture was accomplished on addition to a solution of Mg/$TiCl_4$ in THF to furnish key intermediate **225**. Finally, Kumada cross-coupling with piperonylmagnesium chloride (**226**) afforded the enantiopure natural product **227**.

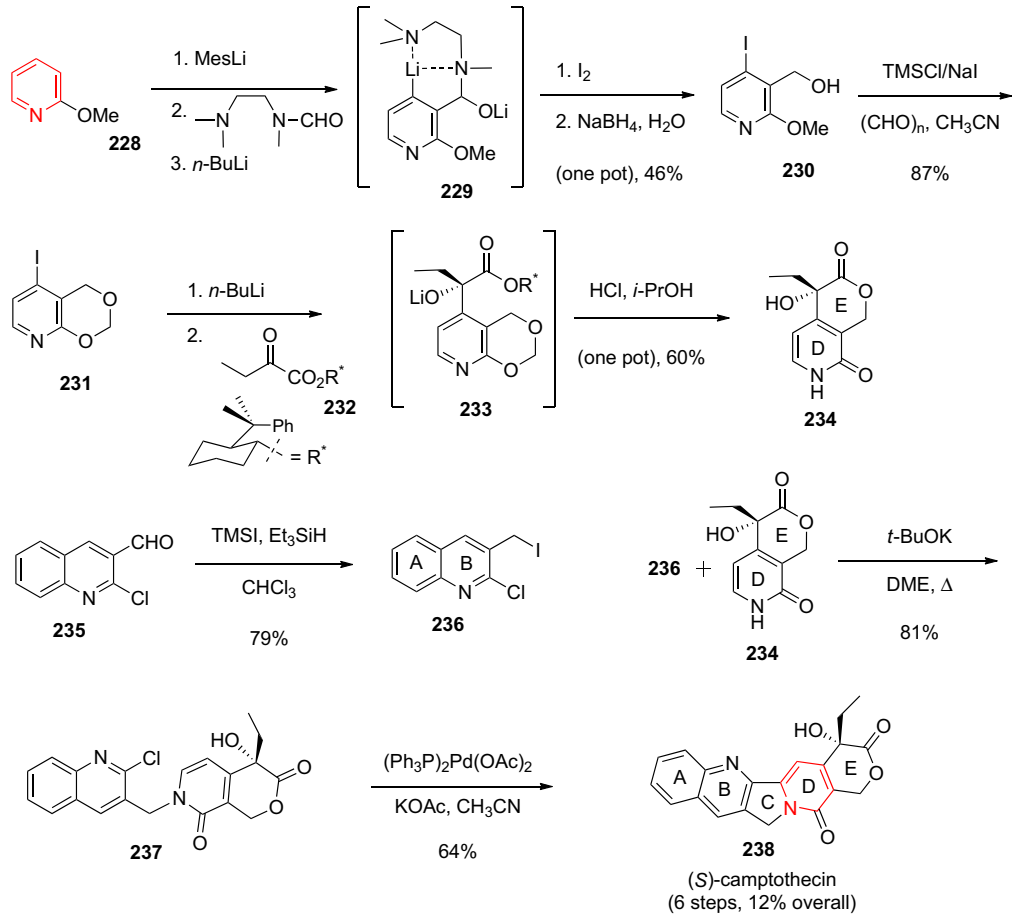
*Aromatisation of Diels–Alder adduct **224** to isoquinoline **225**.*[61] Magnesium powder (89 mg, 3.66 mmol, 10.0 equiv) was dried at 120 °C for 2 h while stirring under vacuum. The powder was allowed to cool to rt and 3 mL of THF was added under an argon atmosphere. The mixture was cooled



Scheme 27 Synthesis of (*S*)-macrostomine.

to −78 °C and neat $TiCl_4$ (0.20 mL, 1.83 mmol, 5.0 equiv) was added dropwise. The mixture was stirred at −78 °C for 30 min and then allowed to warm to rt. After stirring for 20 h, a fine black suspension was obtained. The mixture was cooled to −78 °C and treated with a solution of **224** (118 mg, 0.366 mmol) in dry THF (2 mL). After 30 min at −78 °C, the mixture was allowed to warm to rt. The mixture was stirred for 21 h at rt, then quenched by pouring it into an ice cold aqueous solution of saturated K_2CO_3 (15 mL). After stirring for 30 min at rt, the mixture was extracted with Et_2O (2 × 15 mL) and CH_2Cl_2 (1 × 15 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered through Celite, and concentrated under reduced pressure to provide the crude product. Purification by radial PLC (silical gel, 1% TEA/20% EtOAc/hexanes) afforded 78 mg (70%) of **225** as a pale yellow oil. $[\alpha]^{27}_D$ -128 (*c* 0.67, CH_2Cl_2).

Camptothecin. (*S*)-Camptothecin (CPT, **238**) is an important lead compound for the preparation of selective anticancer drugs.[62,63] Since numerous syntheses of CPT have been reported, our efforts were directed at developing short, practical routes. A 6-step synthesis was accomplished from two commercially available heterocycles.[64] A 3-step preparation of the DE ring fragment **234** started with a C-3 lithiation of 2-methoxypyridine (**228**) with mesityllithium. Addition of *N*-formyl-*N*-*N*′,*N*′-trimethylethylenediamine gave an α-amino alkoxide *in situ* which was lithiated with *n*-BuLi at C-4 to provide dianion **229**. Quenching with iodine and work-up with aqueous $NaBH_4$ provided alcohol **230** via a one-pot process. On treatment with



Scheme 28 Synthesis of (*S*)-camptothecin.

NaI/TMSCl/paraformaldehyde, **230** was converted to the 1,3-dioxane **231**. Lithium–halogen exchange followed by addition of chiral ketoester **232** afforded alkoxide **233** *in situ*. Work-up with HCl/iPrOH effected protonation, acetal hydrolysis, and lactonisation to provide the desired intermediate **234**. The AB ring fragment **236** was prepared from commercially available quinoline derivative **235** in one step by treatment with Et_3SiH and TMSI. The two fragments were coupled under basic conditions to afford **237**. After recrystallisation from methanol, an 81% yield of enantiopure material was obtained. The synthesis was completed using a Heck cyclisation to give CPT (**238**) by the shortest route to date.

*Preparation of 2-chloro-3-(iodomethyl)quinoline (**236**).*[64] To a stirred solution of 2-chloro-3-quinoline-carboxaldehyde (**235**) (36 mg, 0.19 mmol) in dry $CHCl_3$ (4 mL) was added neat Et_3SiH (0.9 mL, 0.56 mmol) and TMSI (0.13 mL, 0.94 mmol). The reaction was allowed to stir at ambient temperature for 12 h before quenching with water (2 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 5 mL),

and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude yellow oil was purified via radial PLC (silica gel, EtOAc/hexanes, 5:95) to give 45 mg (79%) of **236** as a yellow solid, mp 139 °C.

3. SUMMARY

The powerful versatility of *N*-acyl-2,3-dihydro-4-pyridones as synthetic building blocks has been abundantly demonstrated in our laboratories and others.[65] These heterocycles are ideal intermediates for synthesis due to their facile preparation from pyridine derivatives, the useful functionality present in their structure, their availability as either enantiomer, the ease of regio- and stereocontrolled introduction of ring substituents, good air and acid stability, and their potential for transformation into a wide range of heterocyclic and acyclic structures. Application of this chemistry towards the concise, stereocontrolled total syntheses of several alkaloid natural products has been described in this chapter. As new and improved methods, especially catalytic asymmetric reactions, for the preparation of 2,3-dihydro-4-pyridones develop, the utility of these heterocycles as chiral building blocks will expand even further.

Pyridine-containing natural products are abundant in nature and many have interesting biological activities. Selective lithiation of pyridine derivatives has attracted much attention as a method for the preparation of synthetic intermediates on way to natural product targets. The simplicity and high regioselectivity of this metallation chemistry allow the expedient synthesis of useful, functionalised pyridines. Some of our own work in this area was applied to the concise total syntheses of three alkaloids described at the end of the chapter.

REFERENCES

1. (a) Henry, G. D. *Tetrahedron* **2004,** *60*, 6043−6061; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003,** *103*, 893−930.
2. "Pharmaceuticals Sales 2010". Drug information online, Drugs.com December 2011: http://www.drugs.com/top200.html
3. (a) Buss, A. D.; Butler, M. S. *Natural Product Chemistry for Drug Discovery*; The Royal Society of Chemistry: Cambridge, UK, 2010.
4. For reviews, see: (a) Daly, J. A.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005,** *68*, 1556−1575; (b) Michael, J. P. *Nat. Prod. Rep.* **2008,** *25*, 139−165; (c) Michael, J. P. *Nat. Prod. Rep.* **2008,** *25*, 166−187; (d) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009,** *77*, 679−729.
5. (a) Pizzolato, J. F.; Saltz, L. B. *Lancet* **2003,** *361*, 2235−2342.
   (b) Morita, H.; Hirasawa, Y.; Shinzato, T.; Kobayashi, J. *Tetrahedron* **2004,** *60*, 7015−7023.
   (c) Daly, J. W. *J. Med. Chem.* **2003,** *46*, 445−452.
   (d) Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004,** *66*, 1061−1069.
   (e) Katavic, P. L.; Venables, D. A.; Rali, T.; Carroll, A. R. *J. Nat. Prod.* **2007,** *70*, 872−875.
   (f) Schneider, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed. *Alkaloids: Chemical and Biological Perspectives*; Pergamon: Oxford, 1996; vol. 10, p 155.
6. For reviews, see:
   (a) Buffat, M. G. P. *Tetrahedron* **2004,** *60*, 1701−1729.
   (b) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003,** *60*, 2953−2989.

7. (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994,** *116*, 4719–4728.
   (b) Comins, D. L.; LaMunyon, D. H. *Tetrahedron. Lett.* **1994,** *35*, 7343–7346.
   (c) Comins, D. L.; Fulp, A. B. *Org. Lett.* **1999,** *1*, 1941–1943.
   (d) Comins, D. L.; Kuethe, J. T.; Hong, H.; Lakner, F. L. *J. Am. Chem. Soc.* **1999,** *121*, 2651–2652.
   (e) Huang, S.; Comins, D. L. *J. Chem. Soc. Chem. Commun.* **2000,** 569–570.
   (f) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993,** *58*, 5035–5036.
8. (a) Comins, D. L.; King, L. S.; Smith, E. D.; Fevrier, F. C. *Org. Lett.* **2005,** 7, 5059–5062.
   (b) Young, D. W.; Comins, D. L. *Org. Lett.* **2005,** 7, 5661–5664.
   (c) Fevrier, F. C.; Comins, D. L. *Eur. J. Org. Chem.* **2006,** *16*, 3562–3565.
   (d) Smith, E. D.; Fevrier, F. C.; Comins, D. L. *Org. Lett.* **2006,** *8*, 179–182 For recent reviews, see.
   (e) Gros, C. P.; Fort, Y. *Curr. Org. Chem.* **2011,** *15*, 2329–2339.
   (f) Gros, C. P.; Fort, Y. *Eur. J. Org. Chem.* **2009,** 4199–4209.
   (g) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2011,** *50*, 9794–9824.
9. (a) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012,** ASAP.
   (b) Niphakis, M. J.; Turmen, B. J.; Georg, G. I. *J. Org. Chem.* **2010,** *75*, 6793–6805 and references cited therein.
   (c) Comins, D. L.; O'Connor, S.; Al-awar, R. S. Chemistry of Pyridines at Ring Positions In. *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2008; vol. 7, pp 41–100.
10. Grutes, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; PLoegh, H. L. *Nature* **1987,** *330*, 74–77.
11. Comins, D. L.; Fulp, A. B. *Tetrahedron Lett.* **2001,** *42*, 6839–6841.
12. Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972,** *81*, 425–441.
13. Ayer, W. A.; Habgood, T. E. In *The Alkaloids*; Manske, R. H., Ed. *The Alkaloids*; Academic Press: London, 1968; vol. 11, p 492.
14. Comins, D. L.; Sandelier, M. J.; Grillo, T. A. *J. Org. Chem.* **2001,** *66*, 6829–6832.
15. Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed. *The Alkaloids*; Academic Press: San Diego, CA, 1993; vol. 43, pp 185–288.
16. Comins, D. L.; Zhang, Y.-M. *J. Am. Chem. Soc.* **1996,** *118*, 12248–12249.
17. (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed. *Alkaloids: Chemical and Biological Perspectives*; Wiley: New York, 1986; vol. 4; Chapter 1, pp 1–274.
18. Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991,** *16*, 1213–1218.
19. Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1997,** *62*, 8182–8187.
20. (a) Gellert, E. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed. *Alkaloids: Chemical and Biological Perspectives*; John Wiley & Sons: New York, 1987; vol. 5, p 55.
   (b) Suffness, M.; Cordell, G. A. In *The Alkaloids*; Brossi, A., Ed. *The Alkaloids*; Academic Press: Orlando, FL, 1985; vol. 25; Chapter 1, pp 3–355.
21. Comins, D. L.; Chen, X.; Morgan, L. A. *J. Org. Chem.* **1997,** *62*, 7435–7438.
22. (a) Hart, N. K.; Johns, S. R.; Lamberton, J. A. *Aust. J. Chem.* **1972,** *25*, 817–835.
   (b) Johns, S. R.; Lamberton, J. A. In *The Alkaloids*; Manske, R. H. F., Ed. *The Alkaloids*; Academic Press: New York, 1973; vol. 14, p 325; Review.
23. Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991,** *113*, 6672–6673.
24. Harris, C. M.; Schneider, M. J.; Ungemach, F. S.; Hill, J. E.; Harris, T. M. *J. Am. Chem. Soc.* **1988,** *110*, 940–949.
25. Croom, W. J.; Hagler, W. M.; Froestschel, M. A.; Johnson, A. D. *J. Anim. Sci.* **1995,** *73*, 1499–1508.
26. Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed. *Alkaloids: Chemical and Biological Perspectives*; Wiley: New York, 1999; vol. 13, Chapter 1.
   (b) Daly, J. W. *J. Nat. Prod.* **1998,** *61*, 162–172.
27. (a) Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996,** *96*, 505–522.
   (b) Okamoto, S.; Iwakubo, M.; Kobayashi, K.; Sato, F. *J. Am. Chem. Soc.* **1997,** *119*, 6984–6990.
   (c) Tan, C. H.; Stork, T.; Feeder, N.; Holmes, A. B. *Tetrahedron Lett.* **1999,** *40*, 1397–1400.
   (d) Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000,** *122*, 6950–6954.
28. Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett.* **2001,** *3*, 469–471.
29. (a) Tokuyama, T.; Nishimori, N.; Shimada, A.; Edawards, M. W.; Daly, J. W. *Tetrahedron* **1987,** *43*, 643–657.

(b) Tokuyama, T.; Garraffo, H.; Spande, T. F.; Daly, J. W. *An. Asoc. Quim. Argent.* **1989,** *86*, 291−298.
30. Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004,** *66*, 1061−1069.
31. Tsukanov, S. V.; Comins, D. L. *Angew. Chem. Int. Ed.* **2011,** *50*, 8626−8628.
32. Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992,** *57*, 5807−5809.
33. Elbein, A. D.; Molyneua, R. J. In ;; Pelletier, S. W., Ed.; Alkaloids: Chemical and Biological Perspectives; Wiley: New York, 1987; vol. 5, Chapter 1.
34. Denne, W. A.; Johns, S. R.; Lamberton, J. A.; Mathieson, A. M.; Suares, H. *Tetrahedron Lett.* **1972,** *13*, 1767−1769.
35. Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993,** *115*, 8851−8852.
36. (a) Ayer, W. A.; Trifonov, L. S. In *The Alkaloids*; Cordell, G. A., Brossi, A., Eds. *The Alkaloids*; Academic Press: San Diego, 1994; vol. 45, pp 233−274.
(b) Blumenkopf, T. A.; Heathcock, C. H. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed. *Alkaloids: Chemical and Biological Perspectives*; Wiley: New York, 1985; vol. 3, pp 185−240.
37. Comins, D. L.; Brooks, C. A.; Al-awar, R. S.; Goehring, R. R. *Org. Lett.* **1999,** *1*, 229−231.
38. (a) Daly, J. W. *Fortschr. Chem. Org. Naturst.* **1982,** *41*, 205−340.
(b) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed. *Alkaloids: Chemical and Biological Perspectives*; Wiley: New York, 1986; vol. 4; Chapter 1, pp 1−274.
39. Comins, D. L.; Dehgani, A. *J. Chem. Soc. Commun.* **1993,** *1*, 1838−1839.
40. (a) Tokuyama, T.; Nishimori, N.; Karle, I. L.; Edwards, M. W.; Daly, J. W. *Tetrahedron* **1986,** *42*, 3453−3460.
(b) Tokuyama, T.; Tsujita, T.; Shimada, A.; Garraffo, H. M.; Spande, T. F.; Daly, J. W. *Tetrahedron* **1991,** *47*, 5401−5414.
41. Comins, D. L.; Dehgrani, A. *J. Org. Chem.* **1995,** *60*, 794−795.
42. Nyembo, L.; Goffin, A.; Hootele, C.; Braekman, J.-C. *Can. J. Chem.* **1978,** *56*, 851−856.
43. Comins, D. L.; Libby, A. H.; Al-awar, R. S.; Foti, C. J. *J. Org. Chem.* **1999,** *64*, 2184−2185.
44. Wolfe, B. H.; Libby, A. H.; Al-awar, R. S.; Foti, C. J.; Comins, D. L. *J. Org. Chem.* **2010,** *75*, 8564−8570.
45. (a) Lotter, H. L.; Abraham, D. J.; Turner, C. E.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. J. *Tetrahedron Lett.* **1975,** 7, 2815−2818.
(b) Turner, C. E.; Hsu, M. F. H.; Knapp, J. E.; Schiff, P. L.; Slatkin, D. L. *J. Pharm. Sci.* **1976,** *65*, 1084−1085.
46. (a) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000,** *2*, 855−857.
(b) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004,** *69*, 5219−5231.
47. Comins, D. L.; Zhang, Y. M.; Joseph, S. P. *Org. Lett.* **1999,** *1*, 657−659.
48. Lebrun, B.; Braekman, J. C.; Daloze, D.; Kalushkov, P.; Pasteels, J. M. *Tetrahedron Lett.* **2001,** *42*, 4621−4623.
49. Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005,** 7, 5227−5228.
50. Drautz, H.; Zachner, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981,** *64*, 1752−1765.
51. Karrer, A.; Dobler, M. *Helv. Chim. Acta* **1982,** *65*, 1432−1435.
52. Huang, S.; Comins, D. L. *Chem. Commun.* **2000,** 569−570.
53. Daly, J. W.; Karle, I.; Myers, C. W.; Tokuyama, T.; Waters, J. A.; Witcop, B. *Proc. Natl. Acad. Sci. U. S. A.* **1971,** *68*, 1870−1875.
54. Spivak, C. E.; Maleque, M. A.; Oliveiria, A. C.; Masukawa, L.; Tokuyama, T.; Daly, J. W.; Alburquerque, E. X. *Mol. Pharmacol.* **1982,** *21*, 351−361.
55. Zhang, Y.-M.; Zheng, X.; Comins, D. L. *Chem. Commun.* **1998,** 2509−2510.
56. (a) Vember, P. A.; Terenteva, I. V.; Lazurevskij, G. *Khim. Prir. Soedin.* **1967,** *3*, 249.
(b) Terenteva, I. V.; Lazurevskij, G. V.; Shirshova, T. I. *Khim. Prir. Soedin.* **1969,** *5*, 397.
(c) Vember, P. A.; Terenteva, I. V.; Uljanova, A. V. *Khim. Prir. Soedin* **1968,** *4*, 98.
57. Marcu, G. A. *Tr. Tret'ei Nauchn. Konf. Molodykh Uch. Mold., Biol. S'kh. Nauki* **1965,** *2*, 243 Chem Abstr. 1965, 63, 2297a.
58. Wagner, F. F.; Comins, D. L. *Org. Lett.* **2006,** *8*, 3549−3552.
59. (a) Mnatsakanyan, V. A.; Preininger, V.; Simanek, V.; Klasek, A.; Dolejs, L.; Santavy, F. *Tetrahedron Lett.* **1974,** *10*, 851−852.
(b) Israilov, I. S.; Manushakyan, M. A.; Mnatsakanyan, V. A.; Yusunov, M. S. *Chem. Nat. Compd.* **1984,** *20*, 71−73.
60. (a) Muller-Schweinitzer, E.; Hasse, J.; Swoboda, L. *J. Asthma* **1993,** *30*, 451−457.
(b) Siuciak, J. A.; Chapin, D. S.; Harms, J. F.; Lebel, L. A.; McCarthy, S. A.; Chambers, L.; Shrikhande, A.; Wong, S.; Menniti, F. S.; Schmidt, C. J. *Neuropharmacol* **2006,** *51*, 386−396.
(c) Tang, Y.; Luan, J.; Zhang, X. *Plast. Reconstr. Surg.* **2004,** *114*, 1166−1169.

61. Enamorado, M. F.; Ondachi, P. W.; Comins, D. L. *Org. Lett.* **2010,** *12*, 4513−4515.
62. (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966,** *88*, 3888−3890.
(b) Wall, M. E.; Wani, M. C. *J. Ethnopharmacol.* **1996,** *51*, 239−254.
(c) Holm, C.; Covey, J. M.; Kerrigan, D.; Pommier, Y. *Cancer Res.* **1989,** *49*, 6365−6368.
63. Recent reviews:
(a) Wall, M. E.; Wani, M. C. *Alkaloids* **1998,** *50*, 509−520.
(b) *The Camptothecins: from Discovery to the Patient*; Pantaziz, P.; Giovanella, B. C., Eds.Ann. N. Y. Acad. Sci.; 1996; vol. 803.
(c) *Camptothecins: New Anticancer Agents*; Potmesil, H.; Pinedo, H., Eds.; CRC Press: Boca Raton, FL, 1995.
(d) Li, Q.-Y.; Zu, Y.-G.; Shi, R.-Z.; Yao, L.-P. *Curr. Med. Chem.* **2006,** *13*, 2021−2039.
64. Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001,** *3*, 4255−4257.
65. For recent total syntheses using related methods, see:
(a) Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000,** *122*, 5017−5024.
(b) Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2001,** *123*, 8851−8853.
(c) Wilson, M. S.; Padwa, A. *J. Org. Chem.* **2008,** *73*, 9601−9609.