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SPECIAL ISSUE | ACCOUNT
https://doi.org/10.1071/CH22144

AUSTRALIAN JOURNAL OF CHEMISTRY

My 37 years of working with nitrogen heterocycles and alkaloids

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Handling Editor:
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ABSTRACT

This account highlights work from my laboratory at the University of Wollongong (UOW), concerning nitrogen heterocycles and alkaloids, from my appointment as lecturer in Chemistry in February 1985 to the present time as an Emeritus Professor since 2022. I am thankful to the Royal Australian Chemical Institute for the recognition of my work through the recent award of a Distinguished Fellow at the national conference in Brisbane in July 2022.

Keywords: 1,2-amino alcohols, alkaloid, borono-Mannich reaction, cycloadditions, metal catalysis, structural corrections, sulfoxide, sulfoximine, vinyl epoxides.

Introduction

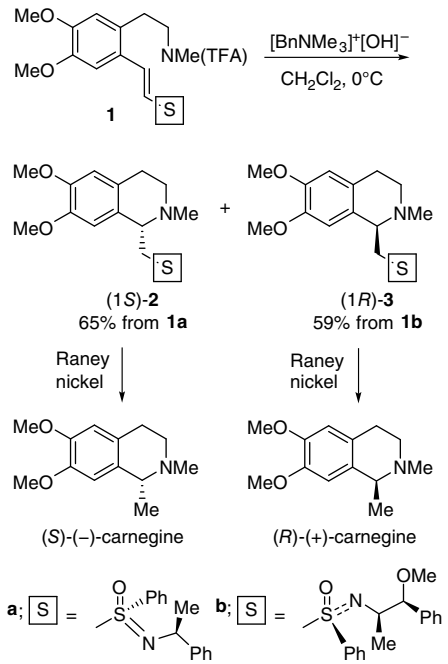
My first experience in a research laboratory was at the University of Adelaide in my BSc (Honours) year working with Dr. Ralph Massey-Westropp. My project involved the synthesis of the proline derived alkaloid odorine, isolated from a plant growing naturally in Indonesia.[1] The purpose of this work was to determine the absolute configuration of the two stereogenic centers in this molecule. This project sparked my interest in the asymmetric synthesis of natural products as a means of validating their structures and determining their configurations, a theme that continued through my academic career at Wollongong. Before my academic appointment I completed a PhD at the ANU with Lew Mander (gibberellic acid synthesis),[2] and post-doctoral fellowships with Philip Fuchs (Purdue University, on alkaloid synthesis)[3–5] and E. J. Corey (Harvard, on leukotriene synthesis and methodology).[6–9] A more senior colleague once announced at a conference 'never work with children, animals or nitrogen compounds', fortunately I did not heed that advice and spent my career working on the synthesis of such molecules and the isolation and synthesis of alkaloids.

Chiral sulfoxime and sulfoxide chemistry

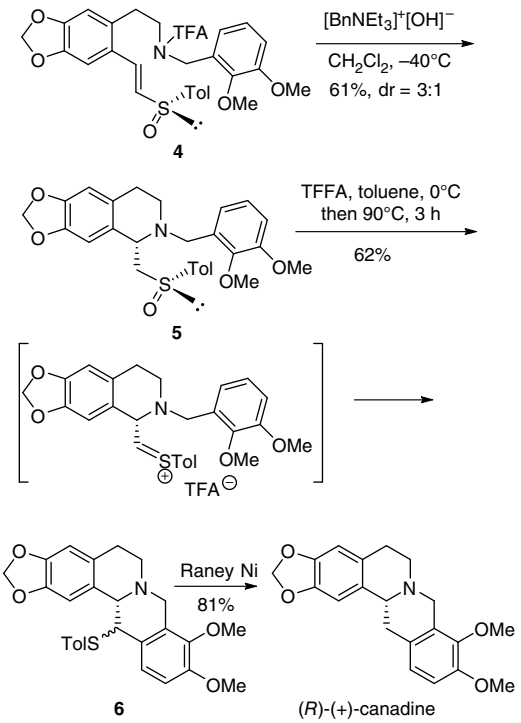
My first ARC grant supported a project on asymmetric synthesis using chiral vinyl sulfoximines and sulfoxides as chiral auxiliaries. This grant proposal was written at La Trobe University during my short time there as an independent research fellow. While my first publication resulting from this grant was on the asymmetric synthesis of chiral molecules from the addition of carbon nucleophiles (organometallic reagents) to chiral vinyl sulfoximes,[10] we soon discovered at UOW that the intramolecular addition of amine nucleophiles to these substrates was useful for the asymmetric synthesis of alkaloids. In 1986 we reported the asymmetric synthesis of (*S*)-(−)- and (*R*)-(+)-carnegine from the intramolecular addition of amine nucleophiles to chiral (*S*)- and (*R*)-vinyl sulfoximes.[11] These were prepared *in situ* from base hydrolysis of their *N*-trifluoroacetamides, **1a** and **1b**, respectively (Scheme 1). While the diastereoselectivities of these reactions were rather modest (diastereomeric ratios (dr) 74:26–71:29), the pure major diastereomers (1*S*)-**2** and (1*R*)-**3** could be isolated in respectable yields, 65 and 59%, respectively. Treatment of these individual products with Raney nickel gave (*S*)-(−)-carnegine ($[\alpha]_D$ −23.5 (~0.15, EtOH); lit. ($[\alpha]_D$ −24.9 (~4.45, EtOH));[11] and

Received: 23 June 2022
Accepted: 11 August 2022
Published: 10 November 2022

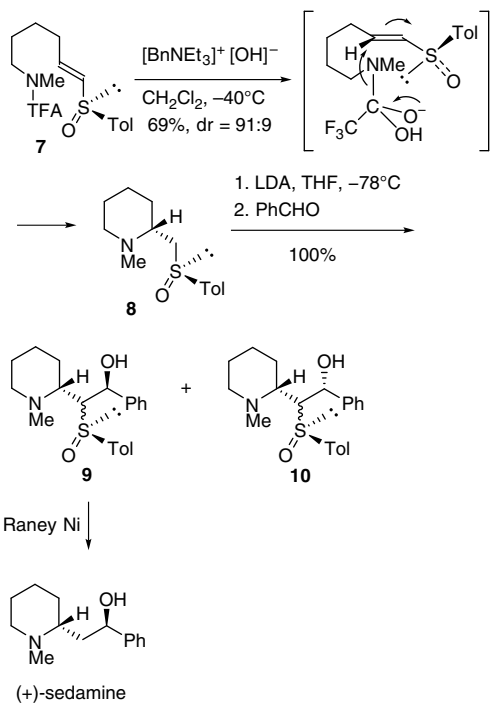
Cite this:
Pyne SG (2022)
Australian Journal of Chemistry
75(11), 923–944. doi:10.1071/CH22144



Scheme 1. Synthesis of (*S*)-(−)- and (*R*)-(+)-carnegine from chiral vinyl sulfoximes (S_S)-**1a** and (R_S)-**1b**.



Scheme 2. Synthesis of (*R*)-(+)-canadine from chiral (*E*)-vinyl (*R*)-tolylsulfoxide **4**.

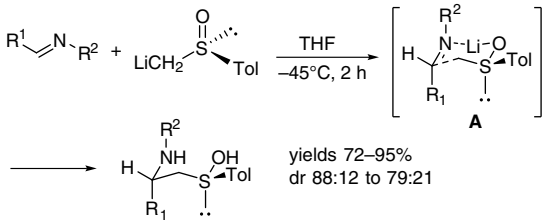


Scheme 3. Synthesis of (*R*,*R*)-(+)-canadine from chiral (*E*)-vinyl (*R*)-tolylsulfoxide **7**.

(*R*)-(+)-carnegine ([α]$_D$ +23.2 (~0.18, EtOH), respectively. The analogous reactions of the related (*E*)-vinyl (*S*)-tolylsulfoxides were less diastereoselective, however, those of the corresponding (*Z*)-vinyl (*S*)-tolylsulfoxides proceeded with enhanced diastereoselectivity (dr up to 84:16) allowing the synthesis of (*R*)-(+)-canadine.[12]

Our asymmetric synthesis of (*R*)-(+)-canadine involved a similar cyclization step of the chiral (*E*)-vinyl (*R*)-tolylsulfoxide **4** to form the 1-tolylsufinylmethyltetrahydroisoquinoline derivative **5** (dr = 3:1) which could be isolated as a pure diastereomer after purification by column chromatography (Scheme 2). In contrast to our earlier work,[12] the (*Z*)-isomer of **4** cyclized to also give **5** as the major diastereomer and with improved diastereoselectivity (dr = 4:1). The major diastereomer of **5** underwent a Pummerer reaction to give the 13-[(4-methylphenyl)thio]-6*H*-dibenzo[*a*,*g*]quinolizine derivatives **6** (dr = 1:1) which upon desulfurization over Raney nickel gave (*R*)-(+)-canadine ([α]$_D$ +273 (~0.04, $CHCl_3$); lit. ([α]$_D$ +299 (~0.04, $CHCl_3$)) (Scheme 2).[13]

A related strategy was employed to prepare (+)- and (−)-sedamine via base-catalyzed cyclization of the (*E*)- and (*Z*)-vinyl (*R*)-tolylsulfoxides (Scheme 3).[14] Cyclization of the (*E*)-vinyl (*R*)-sulfoxide **7** gave the piperidine **8** (dr = 91:9) which was isolated diastereomerically pure after column chromatography. Since these cyclization reactions proceed at low temperature (−40°C) we proposed that they occur via an incipient amide ion, as shown in Scheme 3, rather than the free amine, since we found that the intermolecular reactions of amines with vinyl sulfoxides and sulfoximine require elevated temperatures (50% conversion after 6 days in refluxing EtOH) and an excess amount of the amine.[15,16] Deprotonation of **8** with lithium diisopropylamide (LDA) at −78°C and then quenching the resulting



Scheme 4. Diastereoselective additions of lithiated (*R*)-methyltolylsulfoxide to (*E*)-imines.

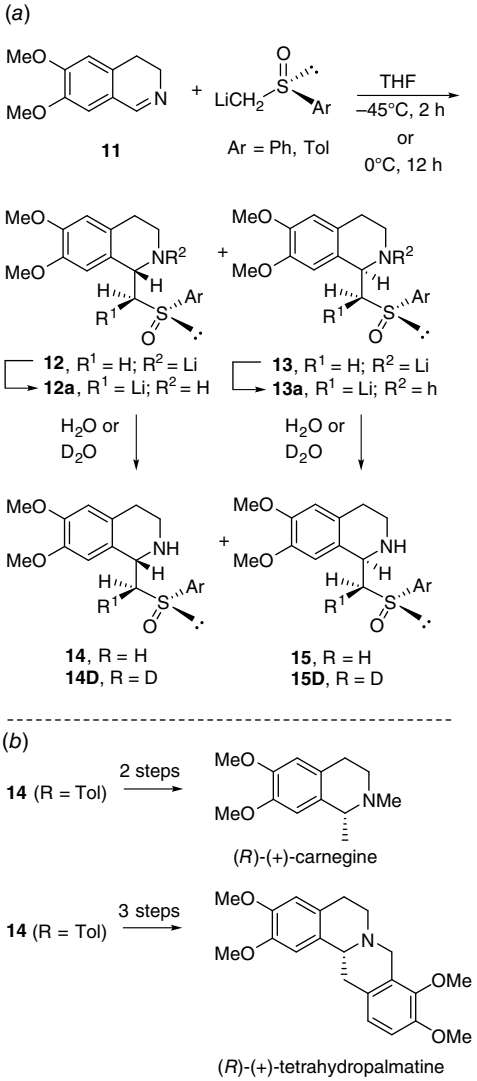
sulfoxide stabilized carbanion with benzaldehyde gave a mixture of diastereomeric aldol-like products **9** and **10**, each as a mixture of *syn*- and *anti*-isomers. Reductive desulfurization of **9** gave (+)-sedamine. The (*Z*)-vinyl (*R*)-sulfoxide analogue of **7** allowed for the synthesis of (−)-sedamine.[14]

It is noteworthy that in Schemes 2, 3 we employed the chiral sulfoxide in two diastereoselective reactions, the intramolecular addition of an amine to a vinyl sulfoxide and then in an intramolecular Pummerer cyclization reaction to form a tetracyclic product (Scheme 2) and in an aldol-like reaction to form a new C–C bond (Scheme 3).

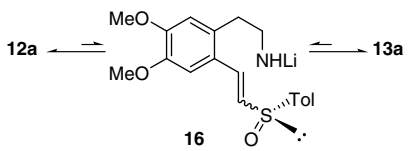
In parallel to these studies, we also studied the synthesis of related compounds via the addition of α-lithiated sulfoxides (Scheme 4) and sulfoximines to imines[17–21] and nitrones.[22] The reaction of lithiated *rac*-methylphenylsulfoxide ($LiCH_2S(O)Ar$, Ar = Ph) with 3,4-dihydro-6,7-dimethoxyisoquinolne **11** at −45°C for 2 h gave in 64% yield, a 23:77 mixture of the diastereomers **14** (R = Ph) and **15** (R = Ph), respectively (Scheme 5*a*).[18] However, when this reaction was run at 0°C for 12 h the diastereoselectivity reversed to 89:11 in favor of **14** (R = Ph). Quenching this reaction with D_2O, rather than H_2O, resulted in isolation of the deuterated derivatives **14D** and **15D** indicating proton transfer to the nitrogen of the initially formed nitrogen-anion intermediate. The reaction of **11** with lithiated (*R*)-methyltolylsulfoxide ((*R*)-$LiCH_2S(O)Ar$, Ar = Tol) at 0°C afforded a 92:8 mixture of diastereomers **14** (R = Tol) and **15** (R = Tol), respectively. These higher temperature results and the deuteration experiment suggested that products were formed under reversible (thermodynamic controlled) conditions. We suggested that the intermediates **12a** and **13a** are in equilibrium via the intermediate vinyl sulfoximine **16** (Scheme 6), allowing equilibration between the kinetically favoured intermediate **13a** and the thermodynamically more favoured intermediate **12a**. Compound **14** was converted into (*R*)-(+)-tetrahydropalmatine and (*R*)-(+)-carnagine (Scheme 5*b*).[18]

Other examples that have or could be employed in alkaloid synthesis include the addition of lithiated *rac*-*N*-*t*-butyldiphenylsilyl-*S*-benzyl-*S*-methylsulfoxime to the BF_3 complex of 3,4-dihydro-6,7-dimethoxyisoquinolne **11** to give a 1-benzyltetrahydroisoquinoline with high diastereoselectivity (dr = 92:8).[19]

We also developed a palladium-catalyzed rearrangement of chiral allylic sulfoximines for the asymmetric synthesis of

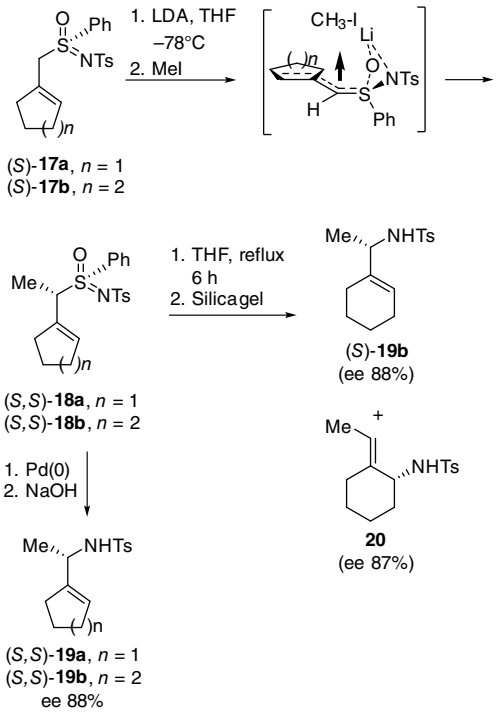


Scheme 5. (*a*) Reactions of lithiated methylarylsulfoxides with 3,4-dihydro-6,7-dimethoxyisoquinolne **11**. (*b*) Synthesis of (*R*)-(+)-carnagine and (*R*)-(+)-tetrahydropalmatine.

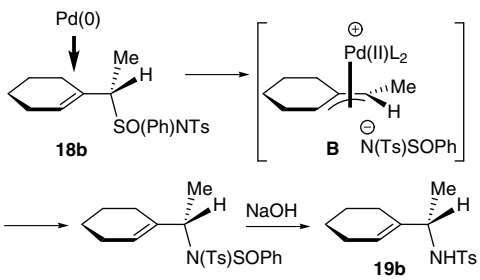


Scheme 6. Proposed intermediate vinyl sulfoximine **16**.

chiral *N*-tosylallylic amines (Scheme 7).[23–25] Treatment of allylic (*S*)-sulfoximines **17a** or **17b** with lithium diisopropylamide (LDA) and then methyl iodide gave the corresponding methylated products **18a** and **18b**, respectively (dr = 96–98%).[25] Heating a solution of **18b** in THF for 6 h and then purification over silica gel gave a 45:55 mixture of the *N*-tosyl allylic sulfonamides **19b** (88% ee or 92% ee corrected for the ee of **17b**) and **20** (87% ee or 91% ee corrected for the ee of **17b**), respectively, which were



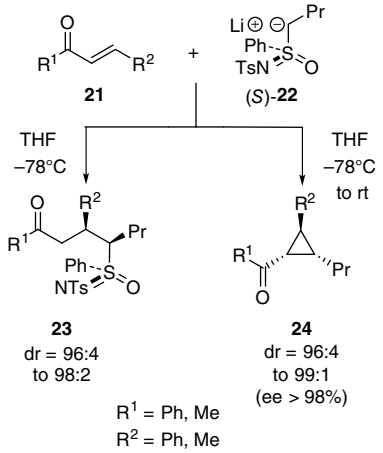
Scheme 7. Synthesis of chiral *N*-tosylallylic amines via thermal and palladium-catalyzed rearrangement of chiral allylic sulfoximines.



Scheme 8. Proposed intermediates in the Pd-catalyzed reaction of **18b** to give the *N*-Ts allylic amine **19b**.

separated by semi-preparative HPLC in a combined yield of 73%. The configuration of **18b** was established by its conversion into (*S*)-*N*-tosyl(1-cyclohexylethyl)amine **19b**, indicating the configuration of **18b** was (*S,S*), consistent with our earlier investigations.[26] In contrast, treatment of **18a** or **18b** with 5 mol% [$Pd(PPh_3)_4$] in THF at room temperature for 10 min, followed by treatment with 10% aqueous NaOH at room temperature gave only the *N*-tosyl allylic amines **19a** and **19b**, respectively, in 36 and 59% yields, both in 88% ee (92% ee corrected for the ee of **17a, b**). The intermediate **B** that we proposed to be involved in these Pd-catalyzed reactions, can account for the observed configurations of the isolated products, is shown in Scheme 8.[25]

In this period, the diastereoselective reactions of lithiated sulfoximines (e.g. (*S*)-**22** (ee 97%)) at −78°C with enones **21** was developed to give ketones **23**,[26,27] with the

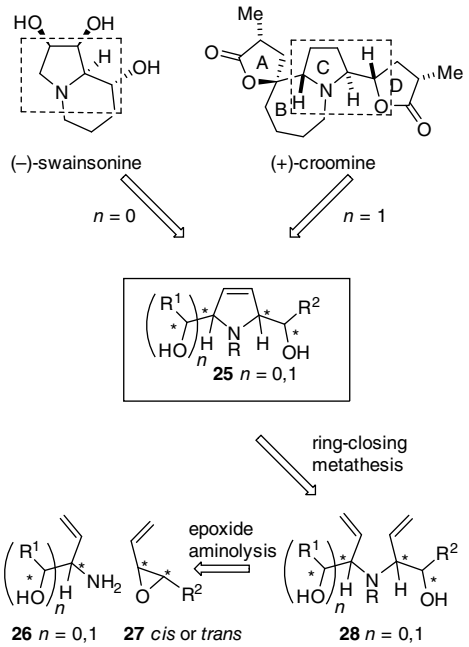


Scheme 9. Diastereoselective reactions of lithiated sulfoximines (e.g. (*S*)-**22** (ee 97%)) at −78°C with enones **21** to give ketones **23** or chiral cyclopropane products **24** at rt.

discovery that when these reactions were warmed to room temperature then chiral cyclopropane products **24** were obtained in high ee (98%) involving cyclization of the initially formed enolate intermediate with the sulfoximine moiety acting as a leaving group (Scheme 9).[27]

Diastereoselective synthesis of polyfunctional-pyrrolidines via vinyl epoxide aminolysis/ring-closing metathesis

At this point in time, Sharpless had developed the catalytic asymmetric epoxidation and asymmetric dihydroxylation (ADH) reactions and other chiral catalysts for asymmetric synthesis were being developed. Chiral auxiliaries that were not recyclable, like those that we were using, were taking second place. We therefore moved out of chiral sulfur chemistry (a much-appreciated move by my colleagues in the School of Chemistry) and explored aminolysis reactions of chiral vinyl epoxides (VE) **27**, now readily available via Sharpless asymmetric epoxidation reactions of their precursor allylic alcohols, as ways to access more complex alkaloids that had, as a common structural feature, a 1,2-amino alcohol (1,2-AA) moiety (e.g. (−)-swainsonine and (+)-croomine, Scheme 10). This method was teamed up with the newly described ruthenium-catalyzed ring-closing metathesis (RCM) reaction developed by Grubbs to provide rapid access to chiral 2,5-dihydropyrroles (e.g. **25**) and pyrrolizidines (Scheme 10).[28–30] Using this methodology the total synthesis of (−)-swainsonine, (+)-1,2,8-tri-epi-swainsonine and (+)-1,2-di-epi-swainsonine,[31,32] and (−)-7-epiaustraline, (+)-1-epiaustraline and (+)-1,7-diepiaustraline[33,34] and (+)-(1*R*,2*S*,9*S*,9a*R*)-octahydro-1*H*-pyrrolo[1,2-*a*]azepine-1,2,9-triol, a potential glycosidase inhibitor.[35] Model studies on the synthesis of croomine resulted in the synthesis of the tricyclic B,C,D-ring core structure.[36] Unfortunately, our attempted synthesis of

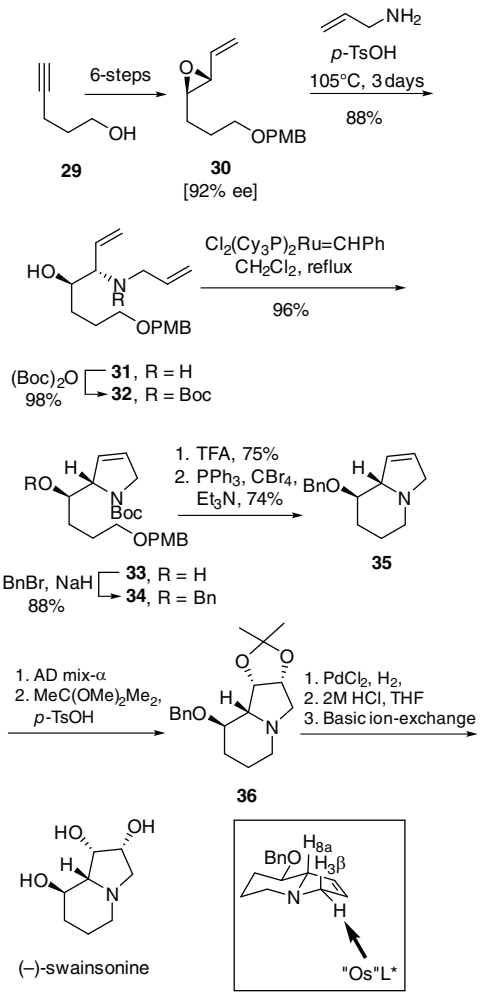


Scheme 10. Our retro-synthetic analysis of the alkaloids (−)-swainsonine and (+)-croomine.

australine was unsuccessful using this methodology,[34] however, a latter and different strategy that we developed was.

Total synthesis of (−)-swainsonine

(−)-Swainsonine is a natural product and a powerful inhibitor of α-D-mannosidase and mannosidase II. Its ability to inhibit the processing of glycoproteins is likely linked with its several biological activities, including anticancer activity.[37] For our synthesis of (−)-swainsonine, 4-pentyn-1-ol **29** was converted into the VE **30** (ee 92%) in six synthetic steps. (Scheme 11).[31] Heating a solution **30** in allylamine (10 equiv.) with *p*TsOH·H_2O (0.1 equiv.) at 105°C for 3 days gave the *anti*-1,2-AA **31** in 88% yield as a single diastereoisomer, the reaction proceeding with inversion of configuration at the allylic carbon. *N*-Boc protection of **31** gave **32** which upon RCM using Grubbs first generation catalyst ($Cl_2(Cy_3P)_2Ru$ = CHPh, Grubbs I) yielded, in 96% yield, the 2,5-dihydropyrrole **33**. The pyrrolizidine **35** was obtained after *O*-benzylation of **33** and then *N*-Boc and *O*-PMB removal with TFA/anisole and finally cyclization of the resulting amino alcohol under Appel conditions (Ph_3P, CBr_4, Et_3N, 0°C). *Cis*-dihydroxylation (DH) of **35** using OsO_4/*N*-methylmorpholine *N*-oxide (NMO), gave a 2:1 mixture of diols favouring that required for the synthesis of (−)-swainsonine. However, DH of **35** using ADmix-α was highly diastereoselective (dr = 98:2). When ADmix-β was used there was a slight reduction in diastereoselectivity (95:5), however, the same major diastereomer was formed. The diol from DH of **35** with ADmix-α was transformed to the



Scheme 11. Total synthesis of (−)-swainsonine.

known acetonide **36**. Its specific rotation ($[\alpha]_D^{26}$ −54 (~0.6, $CHCl_3$), lit. $[\alpha]_D^{26}$ −58.9 (~0.27, $CHCl_3$))[31] compared favourably with the literature value, considering the 92% ee of VE **30**. Compound **36** was then converted into (−)-swainsonine, as shown in Scheme 11, in 94% overall yield. The high diastereoselectivity in the DH reaction of **35** with either ADmix-α or β is consistent with addition of the bulky osmium reagent to the less hindered α-face of the molecule, *anti* to the sterically demanding *pseudo*-axial protons H8a and H3β (highlighted in Scheme 11).

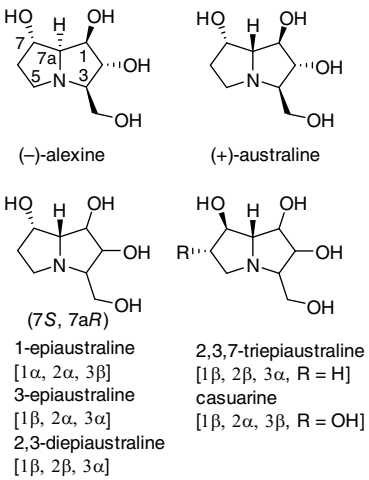
Total synthesis of (+)-1,7-di-epiaustraline and (−)-7-epiaustraline

Alexine was isolated from the seeds of *Castanospermum australe* and was the first alkaloid to be isolated with the 3-hydroxymethylpyrrolizine structure.[38] In later studies australine, 7a-epi-alexine, was described followed by the epimeric australines shown in Scheme 12.[38] 2,3,7-Triepiaustraline, having the identical configuration at C-7, C-7a as casurine,

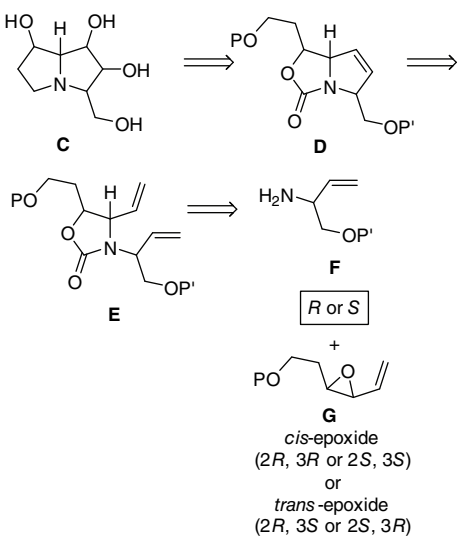
was the first 7-epiaustraline alkaloid to be isolated. Australine, 6-*O*-α-D-glucopyranosylcasurine and 2-*O*-β-D-glucopyranosyl-1-epiaustraline, were the most specific and potent glycosidase inhibitors. Further studies have shown that these and related compounds have *anti*-retroviral and antiviral activities.[38]

Towards the total synthesis of some of these compounds and their diastereomers we established a modular synthetic approach which could in principle be applied to the synthesis of any natural 3-hydroxymethylpyrrolizidine alkaloid or their diastereomers as outlined in Scheme 13. Aminolysis of an enantiomerically enriched *trans*- or *cis*-VE **G**, with the *R* or *S* enantiomer of the allylic amine **F**, could, in principle, provide the corresponding 1,2-AA with any required configuration. The 2-oxazolidinone **E** could then be obtained by protection of the 1,2-AA moiety. A RCM reaction of **E** would then provide the pyrrolo[1,2-*c*]oxazol-3-one **D**. The bicyclic nature of **D** would then allow for the stereoselective DH of the 3,4-double bond of **D**, a problem that we had experienced in our synthesis of (−)-swainsonine (Scheme 11). To examine the viability of this synthetic tactic we chose (+)-1,7-diepiaustraline and (−)-7-epiaustaline as our initial targets.[33]

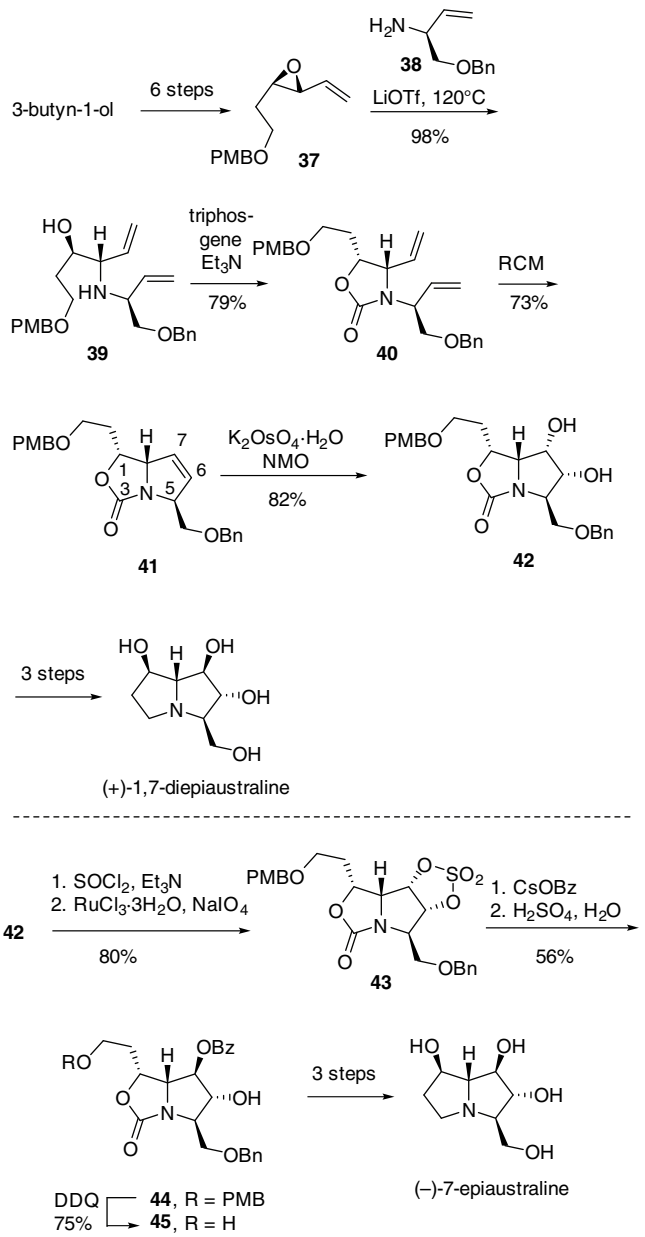
For the synthesis of 1,7-diepiaustraline the VE (+)-(2*R*, 3*R*)-**37** was prepared in six steps from 3-butyn-1-ol. These steps included the Sharpless epoxidation reaction (94% ee), the Swern oxidation and a Wittig-olefination reaction (Scheme 14).[33] Treatment of **37** with (*S*)-allylamine **38**



Scheme 12. Structures of the 3-hydroxymethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1,2,7-triol alkaloids.



Scheme 13. Our retro-synthetic modular approach to 3-hydroxymethyl-2,3,5,6,7,7a-hexahydro-1*H*-pyrrolizine-1,2,7-triol alkaloids and analogues.



Scheme 14. Synthesis of (+)-1,7-di-epiaustraline and (−)-7-epiaustraline.

(1.4 equiv) and LiOTf (1.5 equiv) at 120°C for 72 h afforded the 1,2-AA **39** in 98% yield, *via* a regioselective S_N2 ring opening reaction. A RCM reaction on the corresponding 2-oxazolidinone derivative **40** provided the pyrrolo[1,2-*c*] oxazol-3-one **41** in 73% yield. A DH reaction of compound **41** gave the diol **42** (82% yield), with the DH occurring at the least hindered face of the 6,7-alkene in **41** (cf. Scheme 11). The absolute configuration of **41** was confirmed from its conversion into (+)-1,7-di-epiaustraline. Its specific rotation matched closely with the literature value.[33]

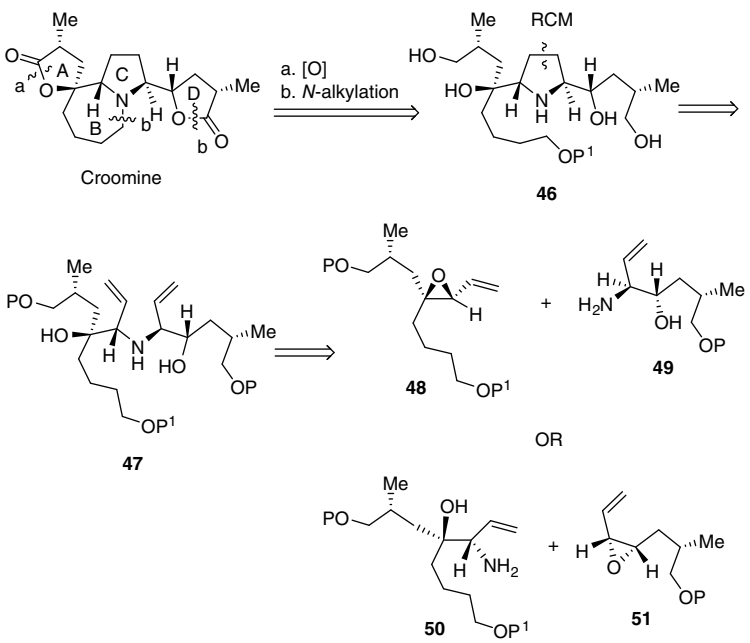
The synthesis of (−)-7-epiaustraline required an inversion of configuration at C-7 in the pyrrolo[1,2-*c*]oxazol-3-one **42**. Consequently, the diol moiety of **42** was transformed to its corresponding cyclic-sulfate **43**, which underwent regioselective ring opening with cesium benzoate, to give the benzoate **44** in 56% yield. Nucleophilic attack on **43** had occurred regioselectively at C-7 since attack at C-6 was hindered by the β-C-5 benzyloxymethyl substituent. Treatment of **44** with DDQ provided the alcohol **45** (75% yield) which was converted into (−)-7-epiaustaline in three synthetic steps. The spectroscopic data and specific rotation of this compound were consistent with those reported.[33]

The *Stemona* group of alkaloids comprises over one hundred members where the pyrrolo[1,2-*a*]azepine nucleus is shared by most of these alkaloids (e.g. croomine).[39–41] In 2003, in collaboration with scientists from Chang Mai University, we reported the isolation and structure determination of stemocurtisine from the roots of *S. curtisii*.[42] This was the first *Stemona* alkaloid having a pyrido[1,2-*a*]azepine A,B-ring system. Others having this same structural feature have since been isolated.[43,44] Extracts of the roots of *Stemona* plants have been used in traditional Chinese medicine as anthelmintic agents and for the treatment of various respiratory diseases. The relative complexity and structural diversity of these alkaloids has resulted in many synthetic studies.[40] More recently we identified some naturally occurring and some semi-synthetic stemofoline derivatives that inhibited P-glycoprotein in multidrug resistant human leukemic cells allowing for their more efficacious chemotherapeutic treatment with standard anticancer drugs.[45–47]

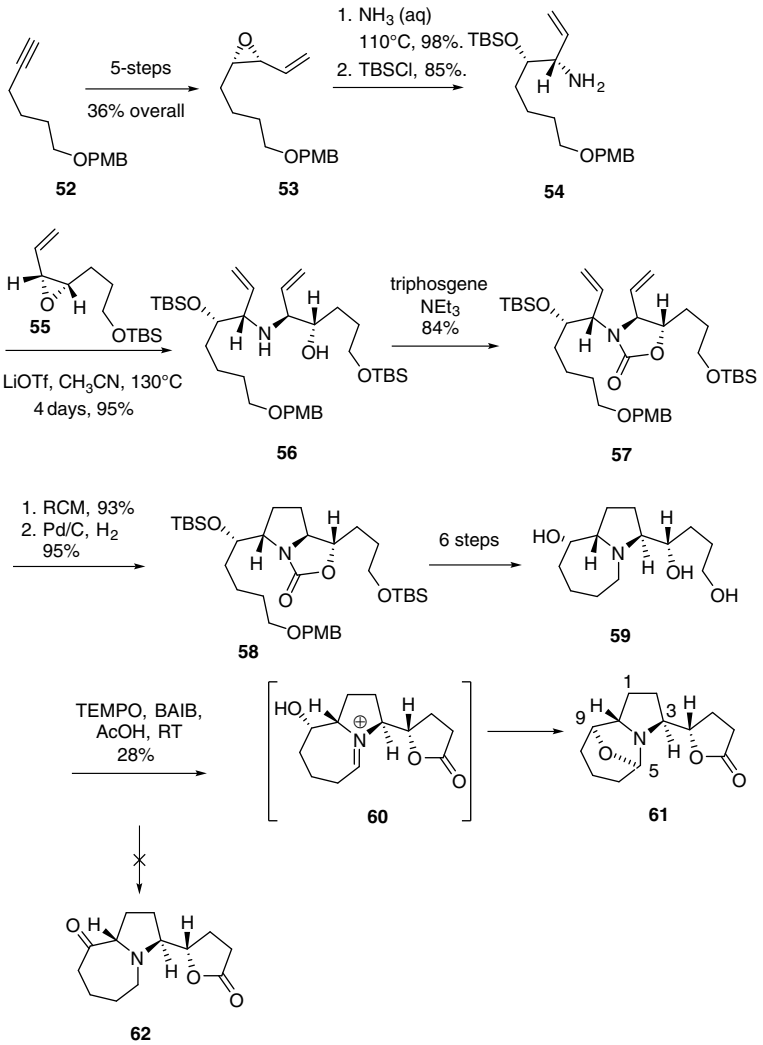
In 2004, we reported our progress toward developing a convergent synthesis of croomine.[36] Our retro-synthetic analysis (Scheme 15), indicated that the A and D rings could be realized from the tetrol **46** by an oxidative lactonization reaction, while an *N*-alkylation reaction could be used to prepare the B-ring. A RCM reaction of the diene **47** could be employed to prepare the tetrol **46**, which could be obtainable by reactions between the VPs **48** or **51** and the allylic amines **49** and **50**, respectively.

To test the feasibility of this approach a model study was performed using the allylic amine **54**, and the VP **55**, the nor-methyl analogue of **51**. Compound **54** was prepared from the chiral *cis*-VP **53** (ee 92–94%), which was readily available in five steps (38% overall) from *O*-PMB protected 5-hexyn-1-ol **52** (Scheme 16). Aminolysis of **53** in aqueous ammonia at 110°C for 30 min was highly regioselective and gave the corresponding 1,2-AA in 98% yield which was protected as its *O*-TBS ether **54** in 85% yield (Scheme 16).

Thermolysis of a mixture of **54**, **55** and LiOTf (1.5 equiv) in acetonitrile at 130°C for 4 days gave the AA **56** (78%, ee estimated ~95%) and its diastereomer (not shown, 17%) (Scheme 15). Compound **56** was converted into the oxazolidinone **57** which upon RCM gave the expected 2,5-dihydropyrrole product (93%) which upon hydrogenation over Pd/C smoothly gave the pyrrolidine **58** with the PMB group still intact. Compound **58** was then transformed to the



Scheme 15. Retro-synthetic analysis of croomine.



Scheme 16. Synthesis of the tricyclic B,C,D-ring core structure of croomine.

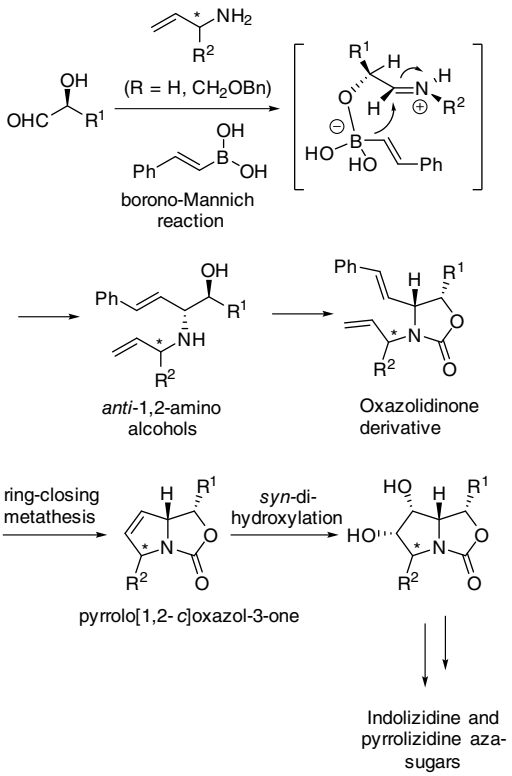
triol **59** in six synthetic steps. The realization of the keto-lactone **62** by oxidation of triol **59** was problematic. For example, the use of tetrapropylammoniumperruthenate (TPAP)/NMO gave a mixture of products while the use of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, catalytic)/*bis*-acetoxy iodobenzene (BAIB, stoichiometric) in acetic acid, gave the novel 5,9-epoxy-1*H*-pyrrolo[1,2-*a*]azepine **61** in 28% yield. This compound most likely arises from the cyclic iminium ion **60** followed by ring closure by the secondary hydroxy group.

Petasis Borono-Mannich reaction (PBMR)

While our above achievements in alkaloid synthesis using chiral VEs were valuable, one major problem was that their synthesis from commercially available starting materials often required six or more synthetic steps. Thus, an alternative, shorter method for synthesizing chiral 1,2-AAs was warranted. At this point in time Petasis had reported on the PBMR as a highly diastereoselective way of preparing *anti*-1,2-AAs from a one-pot, three-component reaction between α-hydroxyaldehydes, 1° or 2° amines and vinyl or aryl boronates or boronic acids.[48] We have pioneered the development of the PBMR in the total synthesis of many biologically important indolizidine and pyrrolizidine aza-sugar alkaloids, and the nortropane alkaloid, calystegine B_4. The α-hydroxyaldehydes that we have examined include unprotected or partially protected sugars and those prepared *in situ* from the ADH reactions of vinyl sulfones or the chemoselective oxidation of chiral 1,2-diols. The success of these achievements further demonstrated the use of an oxazolidinone as a protecting group for the *anti*-1,2-AA products for a subsequent RCM reaction of the diene moiety to build a 1,5-dihydropyrrolidine ring which then allowed diastereoselective DH of the resulting pyrrolo[1,2-*c*]oxazol-3-one (Scheme 17).

Correcting the structure of uniflorine A

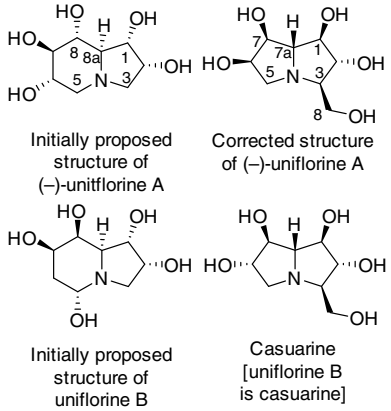
In 2003 I had a new PhD student (Andrew Davis) who was given as his synthetic target molecule the alkaloid uniflorine



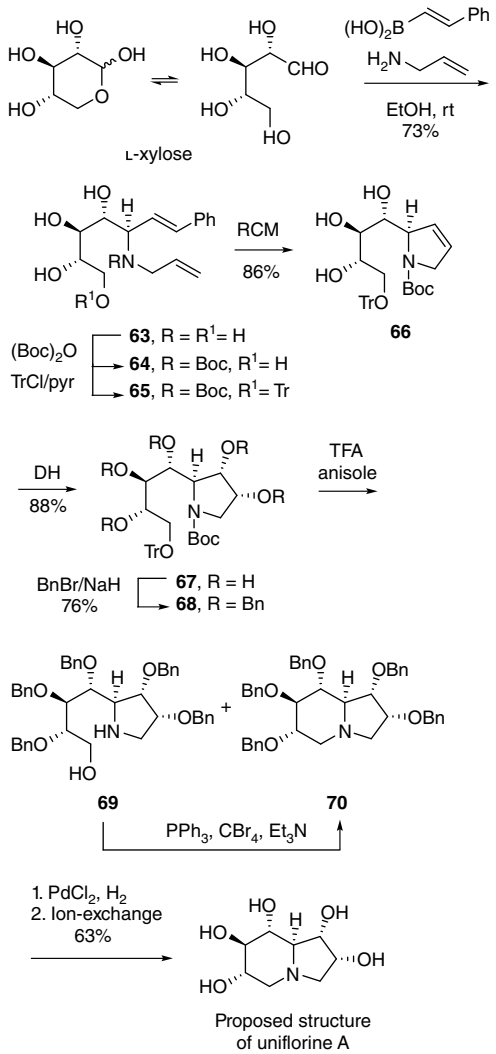
Scheme 17. Proposed diastereoselective synthesis of *anti*-1,2-amino alcohols and their conversion into indolizidine and pyrrolizidine alkaloids.

A. This proposed polyhydroxylindolizidine alkaloid was isolated from the aqueous extracts of the leaves the Paraguayan tree *Eugenia uniflora* L.[49] These extracts were used as an antidiabetic agent in Paraguayan traditional medicine. Uniflorine A was shown to inhibit the α-glucosidases, maltase (IC_{50} = 12 μM) and sucrase (IC_{50} = 3.1 μM), consistent with the antidiabetic activity of the leaf extract. Its initial chemical structure was proposed from NMR analysis to be that shown in Scheme 18.[49] This purported indolizidine structure is related to that of castanospermine, except for the configuration at C-1 and the extra hydroxy substituent at C-2.

To achieve the synthesis of this proposed structure we employed the PBMR using L-xylose as the α-hydroxyaldehyde component, allyl amine and β-(*E*)-styrenylboronic acid (Scheme 19).[50] The resulting amino-tetrol **63** was obtained in 73% yield. This was transformed to the *N*-Boc derivative **64** (51% yield) and then the primary alcohol was selectively protected as its *O*-trityl ether **65** (68% yield). A RCM reaction of **65** readily gave the 2,3-dihydropyrrole **66** which upon DH furnished the pentol **67** in 88% yield as a single diastereomer due to the stereodirecting effect of the C-2 ring substituent in **66**. The pentol **67** was readily converted into its penta-*O*-benzyl derivative **68**, then selective deprotection of the secondary amino and primary hydroxy groups of **68** was achieved by treatment of **68** with TFA/anisole. Unexpectedly, this reaction resulted in a mixture of the



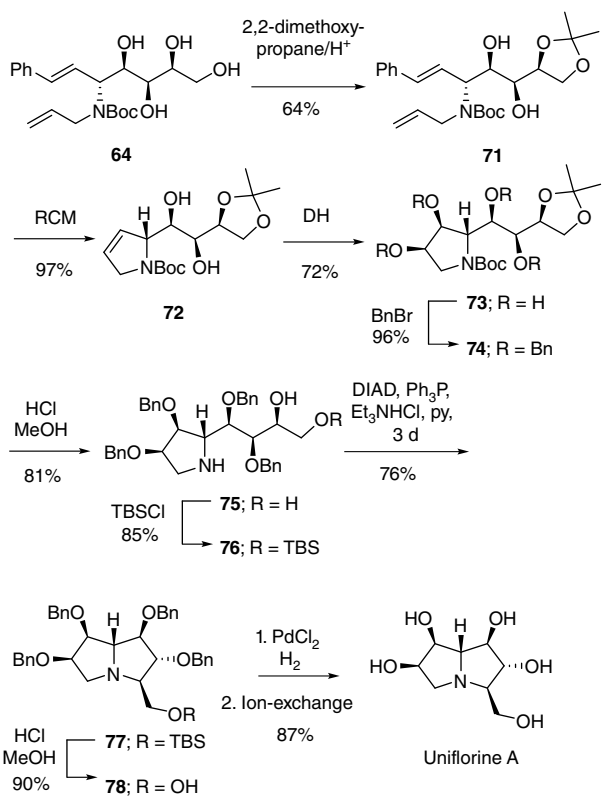
Scheme 18. Purported structures of uniflorine A and B and their corrected structures.



Scheme 19. Synthesis of the proposed structure of uniflorine A.

desired AA **69** (37%) and the indolizidine **70** (54%) (Scheme 19). The AA **69** underwent cyclization under Appel conditions ($Ph_3P/CBr_4/Et_3N$) to give the same indolizidine **70** (54%). Debenzylation of **70** over $PdCl_2/H_2$ gave the proposed structure of uniflorine A in 63% in a total of eight synthetic steps from L-xylose. The structure of this compound was confirmed from the single crystal X-ray analysis of its pentaacetate derivative. The ^1H and ^{13}C NMR spectroscopic data of this compound, however, did not match those reported for uniflorine A. We therefore concluded that the structure assigned to uniflorine A was not correct. After a more critical examination of the NMR data in the original isolation paper we proposed that uniflorines A and B were not indolizidines as originally proposed but were the pyrrolizidine alkaloids shown in Scheme 18.[51]

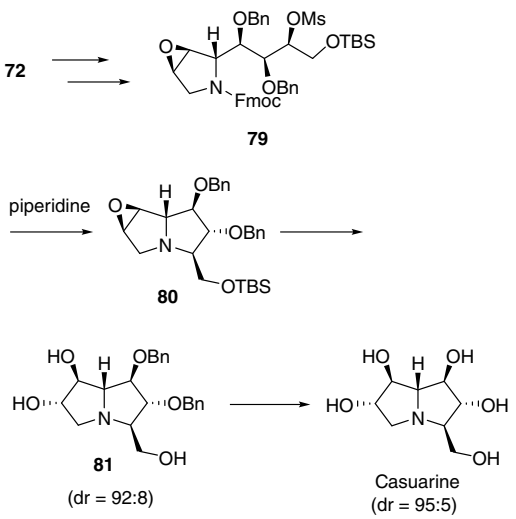
To prove our hypothesis we first prepared (+)-uniflorine A from the less expensive L-xylose[52] and then later natural (−)-uniflorine A from the more costly D-xylose (Scheme 20).[53] The terminal diol functionality of the previously prepared *N*-Boc-tetrol **64** (Scheme 19) was converted into its corresponding acetonide derivative **71**. A RCM reaction of the diene **71** afforded the 2,5-dihydropyrrole **72** (97% yield). A DH reaction of **72** furnished the tetrol **73** as a single diastereomer (Scheme 20) due to the stereodirecting effect of the C-2 pyrrolidine substituent in **72**. The tetrol **73** was then converted into its per-*O*-benzyl derivative **74** which upon acid hydrolysis resulted in the amino diol **75** in 81% yield. Regioselective *O*-silylation of **75** gave the primary silyl ether **76** in 85% yield. In our earlier synthesis of (+)-uniflorine A,[52] the compound *ent*-**76** underwent cyclization under Mitsunobu reaction conditions to give a 4:1 mixture of the desired pyrrolizidine *ent*-**77** and an undesired indolizidine product (structure not shown) in poor yield (30%). The undesired product arose from an initial base catalyzed *O*-TBS migration to the secondary hydroxy group in *ent*-**76** followed by Mitsunobu cyclization onto the primary carbon of the butyl side chain. However, by buffering the reaction mixture with $Et_3N{\cdot}HCl$[54] we found that the yield of **77** could be enhanced to 76% with undetectible amounts, by NMR analysis, of the undesired product. Acid hydrolysis of **77** gave the primary alcohol **78** (90% yield) which upon exposure to $PdCl_2/H_2$ gave uniflorine A ($[\alpha]_D^{22}$ −3.7 (~1.2, H_2O), lit. $[\alpha]_D^{22}$ −4.4 (~1.2, H_2O)),[53] in 87% yield in a total of 11 synthetic steps and 13% overall yield from L-xylose The ^1H NMR spectroscopic data of our synthetic uniflorine A and those of the natural isolate were nearly identical ($\Delta\delta_H$ = 0.00–0.02 ppm). The ^{13}C NMR signals of our synthetic uniflorine A and that of the natural product showed consistent differences ($\Delta\delta_c$ = 2.1–2.2 ppm) which we suggested were due to alternative referencing between the two samples.



Scheme 20. Total synthesis of uniflorine A.

Total synthesis of casuarine

Casuarine was prepared from the 2,5-dihydropyrrole **72** as summarized in Scheme 21. The strategy employed required a modification to that used for uniflorine A to secure the desired 6α,7β-configuration. This was achieved via the regioselective ring-opening reaction of the epoxide **80** with $NaHSO_4$ and then *O*-benzyl deprotection.[53]



Scheme 21. Total synthesis of casuarine.

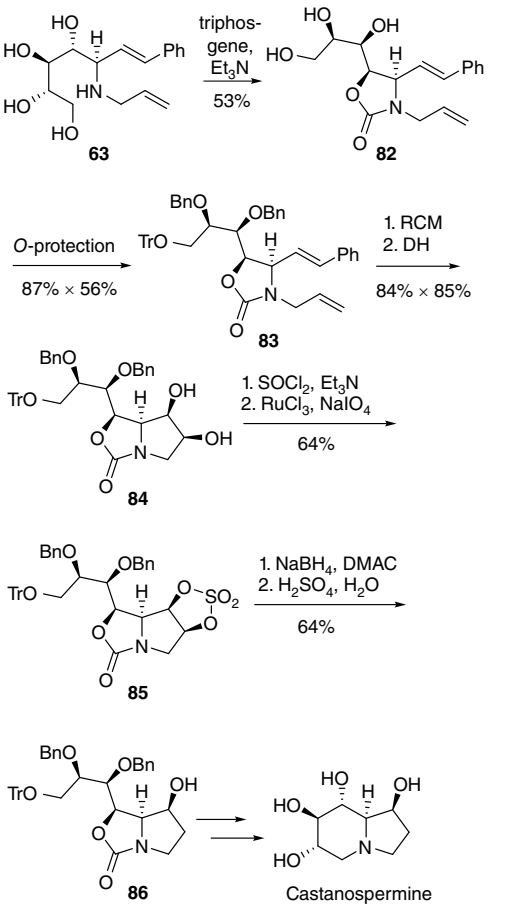
Total synthesis of castanospermine

A related synthetic strategy was applied to our synthesis of castanospermine where the amino tetrol **63** was converted into the oxazolidinone **82** which upon *O*-protection, RCM and then DH gave the diol **84** which was converted into the cyclic sulfate **85**.[55] Regioselective ring-opening of the cyclic sulfate moiety by hydride provided the alcohol **86** which was then transformed to castanospermine. This diastereoselective and regioselective synthesis once again demonstrated the utility of pyrrolo[1,2-c]oxazol-3-one intermediates (Scheme 22).

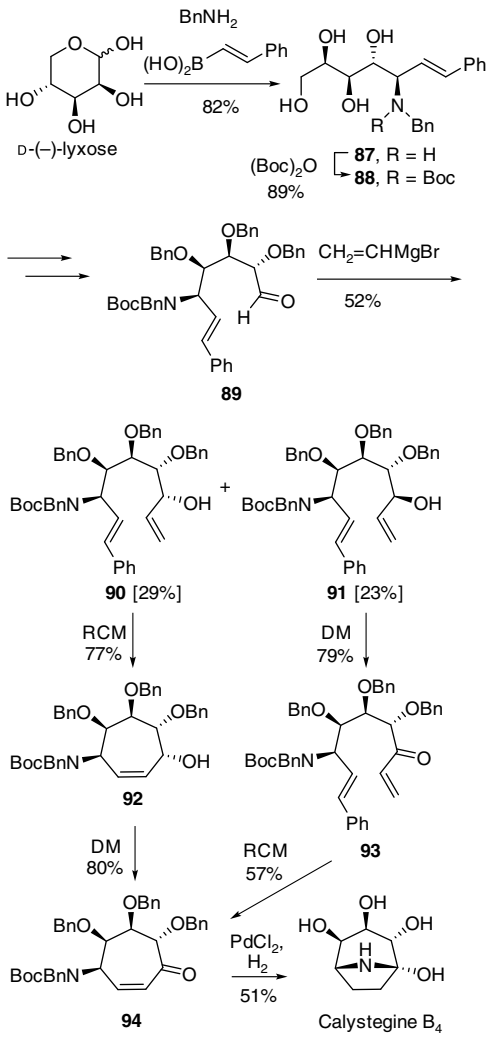
Total synthesis of calystegine B_4

The calystegine alkaloids include thirteen different polyhydroxylated, 1-hydroxy-nortropanes and one trihydroxylated 1-amino-nortropane (calystegine N_1). The *N*-methyl derivatives of calystegine B_2 and C_1 have also been isolated along with their glycoside derivatives.[56] A number of successful syntheses of these alkaloids have involved a protected di- or tri-hydroxylated 4-aminocycloheptene intermediate.[56] Hydroboration and then oxidation gives the corresponding 4-aminocycloheptanone which upon deprotection gives a 1-hydroxynorptropane structure. Unfortunately, these hydroboration reactions are poorly regioselective, leading, after oxidation to mixtures of 4-aminocycloheptanone products. We developed a synthetic strategy for the synthesis of calystegine B_4 that avoids the possibility of formation of regioisomeric ketones (Scheme 23).[57]

This synthesis starts with the PBMR reaction of D-(−)-lyxose with benzylamine and *trans*-2-phenylvinylboronic acid which gave the amino tetrol **87** in 82% yield (Scheme 23). After a series of functional group protections and a deprotection reaction this compound was converted into the aldehyde **89** which upon treatment with vinylmagnesium bromide gave a mixture (~1:1) of the alcohols **90** and **91**. This mixture was not a concern since this carbinol center was to be oxidized to the corresponding ketone in future steps. However, these diastereomers were chromatographically separated to examine their individual chemistries. The RCM reaction of **90** gave the cycloheptenol **92** in 77% yield which upon oxidation with



Scheme 22. Total synthesis of castanospermine.



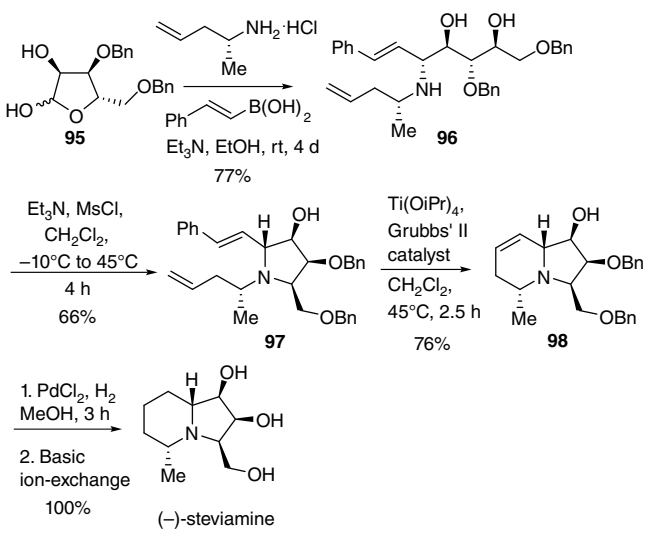
Scheme 23. Total synthesis of calystegine B_4.

Dess-Martin (DM) periodinane gave the protected aminocycloheptenone **94**. In contrast, the RCM reaction of the diastereomer **91** was much less efficient under similar reaction conditions. However, a reversal of operations involving first oxidation of **91** to the ketone **93** and then RCM was more successful and produced the same protected aminocycloheptenone **94**. Finally, treatment of **94** over $PdCl_2/H_2$ gave calystegine B_4 in 51% yield.

Total synthesis of (−)-steviamine

(−)-Steviamine is the first polyhydroxylated indolizidine to have a C-5 methyl and a C-3 hydroxymethyl substituent. It was isolated from the leaves of *Stevia rebaudiana* (Asteraceae) and the absolute configuration of its HBr salt was determined by X-ray crystallographic analysis.[58] In 2013 we reported the first synthesis of steviamine as outlined in Scheme 24.[59]

Our synthesis commenced with a PBMR between the L-β-ribofuranose derivative **95**, (*R*)-4-penten-2-amine and *E*-styrylboronic acid (Scheme 24) which gave the 1,2-AA **96** in 77% yield. Treatment of **96** with methanesulfonyl chloride (1.07 equiv) and triethylamine (3.5 equiv) at −10°C gave the corresponding *O*-mesylate intermediate which cyclized to the fully substituted pyrrolidine **97** upon warming to 40–45°C. Column chromatography then gave **97** in 66% yield. A RCM reaction of diene **97** using Grubbs' 2nd generation catalyst (18 mol%), in the presence of $Ti(O^iPr)_4$ (0.2 equiv) gave the indolizidine **98** in 76% yield. Treatment of **98**, over $PdCl_2/H_2$ gave (−)-steviamine in quantitative yield. The NMR spectroscopic data of synthetic steviamine and its specific rotation matched closely with those of the natural isolate.[58] Thus, we achieved the first synthesis of (−)-steviamine in four synthetic steps from compound **95**, which was prepared in four steps (45% overall yield) from commercially available β-L-ribofuranose-1,2,3,5-tetra-*O*-acetate. Thus, our synthesis of steviamine, involves an eight-step total synthesis in 17% overall yield, from commercially available starting materials.[59]



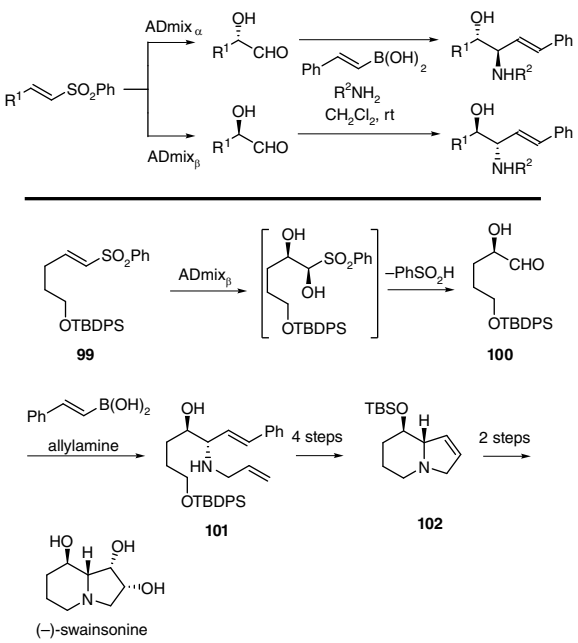
Scheme 24. Total synthesis of (−)-steviamine.

Total synthesis of (−)-swainsonine

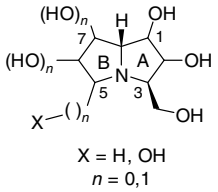
We have successfully employed the PBMR using either sugars or their partially protected derivatives as the chiral α-hydroxyaldehyde component to alkalid synthesis, however, to extend the generality of this process we required a more general method of preparing such aldehydes. To this end we examined the PBMR of *in situ* generation of α-hydroxyaldehydes prepared from the Sharpless ADH reactions of vinyl sulfones as originally described by Evans.[60] This method has allowed much more rapid access to valuable *anti*-1,2-AA chiral building blocks. The derived diene products, obtained using allylamine, allowed for a short, formal synthesis of the important natural product (−)-swainsonine (Scheme 25).[61] For example, the ADH reaction of the vinyl sulfone **99** gave the α-hydroxyaldehyde **100** (formed as its cyclic hemiacetal dimer) which upon reaction with allyl amine and *E*-styrylboronic acid gave the 1,2-AA **101** in 93% ee and 38% overall yield. This was converted into the known indolizidine **102** which has been converted into (−)-swainsonine in two synthetic steps.

Total synthesis of the hyacinthacine alkaloids

The hyacinthacine group of alkaloids comprise nineteen polyhydroxylated 3-hydroxymethylpyrrolizidine natural



Scheme 25. Total synthesis of (−)-swainsonine.



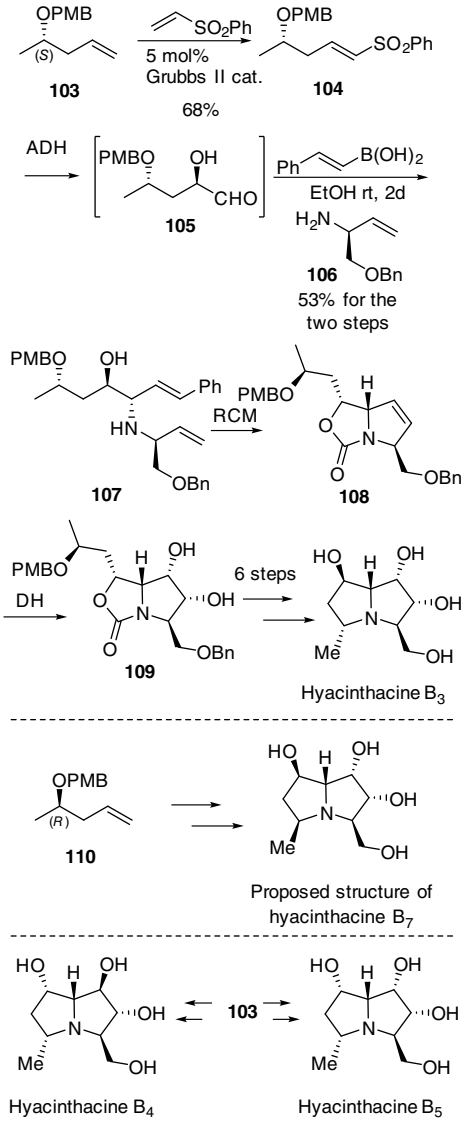
Scheme 26. General structure of the hyacinthacine alkaloids.

products of general structure shown in Scheme 26. These have been isolated from extracts of *Hyacinthoides nonscripta* (the common bluebell), *Muscari armeniacum*, *Scilla campanulata*, *S. sibirica* and *S. sociali*.[62] These alkaloids have been classified as hyacinthacines A_{1-7}, B_{1-7} and C_{1-5} based on their total number of hydroxy and hydroxymethyl groups in the ring B.[62] Their structures have been assigned based primarily on NMR spectroscopic analysis. Synthetic chemistry studies have revealed, however, that the purported structures of hyacinthacines C_3 and C_5 are incorrect.[62]

In 2010 we reported the first synthesis of hyacinthacine B_3[63] which confirmed the structure and absolute configuration of this alkaloid and the synthesis of the C-5 epimer of hyacinthacine B_3, hyacinthacine B_7, which revealed that the purported structure of the natural isolate was incorrect.[63]

The syntheses of hyacinthacine B_3 and hyacinthacine B_7 from the *O*-PMB derivatives of (*S*)- and (*R*)-4-penten-2-ol, **103** and **110**, are outlined in Scheme 27. For the synthesis of hyacinthacine B_3, **103** (ee > 98%) was converted into the (*E*)-vinyl sulfone **104** employing a cross-metathesis reaction. Vinyl sulfone **104** reacted very sluggishly under standard ADH conditions,[60] however, using the less hindered DHQD-IND chiral ligand, **104** was converted into the corresponding α-hydroxyaldehyde **105**, as a mixture of acetal derivatives, at rt in 24 h.[63] This mixture was treated with the (*S*)-allylic amine **106** and (*E*)-styrenylboronic acid, to provide the *anti*-1,2-AA **107** in 53% overall yield from **104**. Compound **107** was converted via a RCM reaction into the pyrrolo[1,2-*c*]oxazol-3-one **108** and then into the diol **109** by DH with OsO_4/NMO. This high level of diastereoselectivity in the DH reaction of **108** was explained based on stereoelectronic effects and nature of the HOMO of **108** about the alkene moiety where the non-bonding orbital of the N-atom overlaps more efficiently with the π-system of the alkene moiety on the α-face making this face more favorable to DH.[64,65] Importantly, the pyrrolo[1,2-*c*]oxazol-3-one **108** allowed us to obtain the target alkaloid with the desired 2,3-diol configuration, on essentially a *trans*-2,5-disubstituted-2,5-dihydropyrrole A-ring precursor, that would otherwise be expected to show poor diastereofacial selectivity. The diol **109** was then converted into hyachinthacine B_3 using methods described above in earlier schemes.

The purported structure of hyacinthacine B_7 was prepared from the *O*-PMB derivative of (*R*)-4-penten-2-ol (ee > 98%) using related chemistry (Scheme 27). Of import was that the NMR spectra of our synthetic compound did not



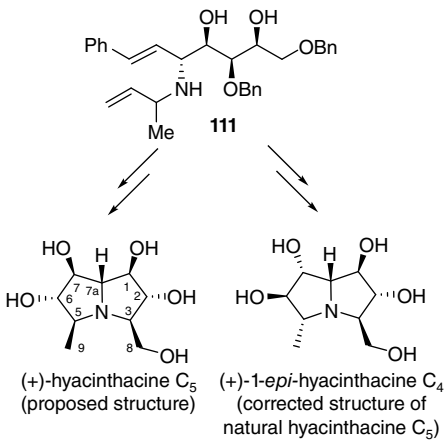
Scheme 27. Total synthesis of hyacinthacines B_3, B_4 and B_5 and the proposed structure of hyacinthacine B_7.

match with that reported for hyacinthacine B_7. NOESY NMR analysis of our synthetic compound clearly indicated that it had the correct relative configuration, with a significant correlation observed between H-5 and H-7. This correlation was not reported for the original isolate. Unfortunately, natural hyacinthacine B_7 was no longer available to make a direct comparison, however the same *Scilla socialis* plants that were used in the original isolation paper were. GC-MS analysis of a fresh plant extract indicated no hyacinthacine corresponding to the retention time of 10.71 min of our synthetic compound. The tetra-TMS derivative of our synthetic compound gave a characteristic mass spectrum with a base ion peak at *m/z* 388. Four hyacinthacines in the new plant extract showed the same fragmentation pattern indicating they were epimers of synthetic hyachinthacine B_7. One major hyacinthacine with the *m/z* 388 base ion peak

had a retention time of 11.31 min by GC-MS which was the same retention time as a standard of hyacinthacine B_5. Another epimer was also observed at 10.97 min. This GC-MS analysis indicated that our synthesized hyachinthacine B_7 is not a natural product and that epimers of this compound are. We thus concluded that the structure purported for hyacinthacine B_7 is incorrect. Later we reported the synthesis of hyacinthacines B_4 and B_5 from (2*S*)-4-penten-2-ol[66] which confirmed the structures and absolute configurations of these natural products. By comparing the NMR spectroscopic data of all our synthetic B-type hyacinthacines we proposed that naturally occurring hyacinthacine B_7 is actually hyacinthacine B_5. Unfortunately, the unavailability of these natural alkaloids did not allow us to be unequivocal about this structural reassignment.

Structurally, the hyacinthacine C-type subclass of these alkaloids is the most complex and can contain up to seven possible stereogenic centers. Consequently, there are 128 unique possible diastereomers (together with their enantiomers) containing a 3-hydroxymethyl-5-methylpyrrolizidine-1,2,6,7-tetraol core that can be potentially synthesized.[67] In 2018 we reported the total synthesis of natural (+)-hyacinthacine C_5, which allowed correction of its initially proposed structure to that of (+)-1-*epi*-hyacinthacine C_4, as well as its putative structure and five additional hyacinthacine C-type alkaloids.[68] These compounds were prepared from the PBMR product **111**, prepared using either (*R*)-2-amino-3-butene or *rac*-2-amino-3-butene as the amine component (Scheme 28).

The ^{1}H and ^{13}C NMR spectroscopic data of our synthetic 1-*epi*-hyacinthacine C_4 ($[\alpha]_D^{25}$ +5.2 (~1.00, H_2O)) were found to be identical with those of the isolate titled hyacinthacine C_5 (lit.$[\alpha]_D$ +1.5 (~0.22, H_2O)).[68] Thus the correct structure of hyacinthacine C_5 has the opposite configuration at the three contiguous stereogenic centers, C-5, C-6 and C-7, to that of the originally proposed structure (Scheme 28).



Scheme 28. Total synthesis of the proposed structure of hyacinthacine C_5 and 1-*epi*-hyacinthacine C_4 (the correct structure of hyacinthacine C_5).

Hyacinthacine C_1 and hyacinthacine C_4 were isolated from plant extracts of *Hyacinthoides non-scripta* and *Scilla socialis* in 1999 and 2007, respectively. These alkaloids were assigned the same structures (Scheme 29),[67] even though they had different ^{1}H and ^{13}C NMR spectroscopic data.

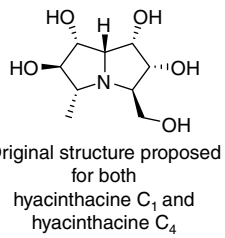
In 2019 we were able to correct the structure of hyacinthacine C_1 through its total synthesis as shown in Scheme 30.[69] Our advanced intermediate **112** was subjected to a Swern oxidation, followed by a stereoselective reduction with L-selectride. This approach led to the synthesis of (+)-5-*epi*-hyacinthacine C_1 which was identical to the original isolate named hyacinthacine C_1.

Other aza-sugar alkaloids

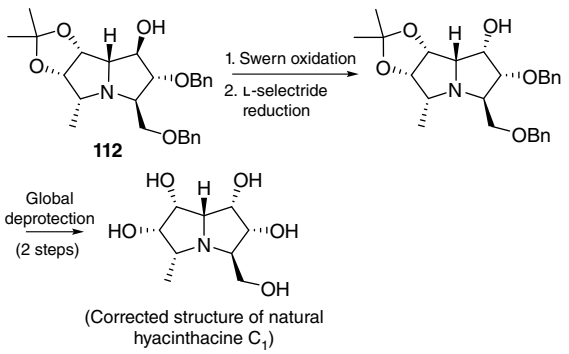
The PBMR has also been employed in a diastereoselective concise syntheses of the polyhydroxylated alkaloids DMDP and DAB[70] and progress toward the total synthesis of 9β-hydroxyvertine.[71]

Synthesis and structural correction to glyphaeaside C

The natural product glyphaeaside C was originally reported to be a derivative of the piperidine natural product 1-deoxynojirimycin. Through total synthesis of its antipode

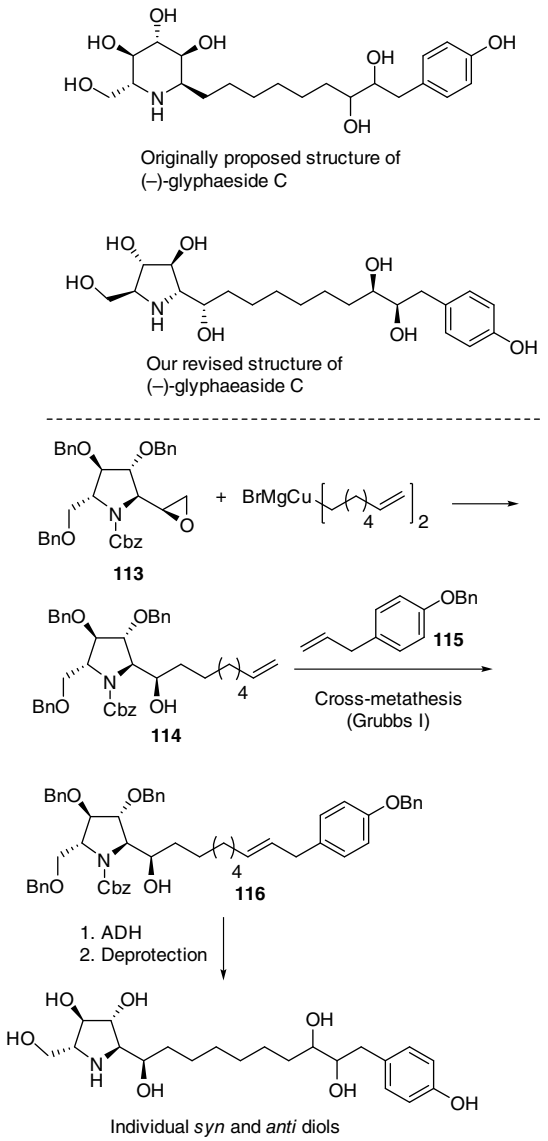


Scheme 29. The same structure was proposed for hyacinthacines C_1 and C_4.



Scheme 30. Total synthesis of the correct structure of hyacinthacine C_1.

we revised its structure to a derivative of 2,5-dideoxy-2,5-imino-L-mannitol.[72] This revised L-DMDP-derived configuration is the first of its kind to be observed in Nature. The synthesis involved ring opening of the novel epoxide **113** with a Gilman-like diorganocopper reagent to give the alcohol **114** which upon a cross-metathesis reaction with **115** gave **116** as a 4.8:1 mixture of *E* and *Z* isomers, respectively. ADH of **116** with ADmix-α or ADmix-β gave their respective 8′*S*,9′*S*-*syn* diols and 8′*R*,9′*R*-*syn* diols as the major diastereomeric products, with the *anti*-8′,9′-diols arising from ADH of the minor *Z* alkene of **116**. Deprotection and then separation by HPLC allowed the isolation of the four possible 8′,9′-diol diastereoisomers of the target alkaloid. The major 8′*S*,9′*S*-*syn* and 8′*R*,9′*R*-*syn* diols had almost identical NMR spectra in CD_3OD as each other and as glyphaeaside C, with the specific rotation of the 8′*S*,9′*S*-*syn* diol closer in magnitude, but opposite in sign to that of the natural product. Consequently, we concluded that the natural product was the enantiomer of our synthetic compound, however, without access to a sample of the natural material we could not unambiguously confirm this claim. We are currently exploiting the epoxide **113** in the synthesis of the related broussonetine alkaloids (Scheme 31).

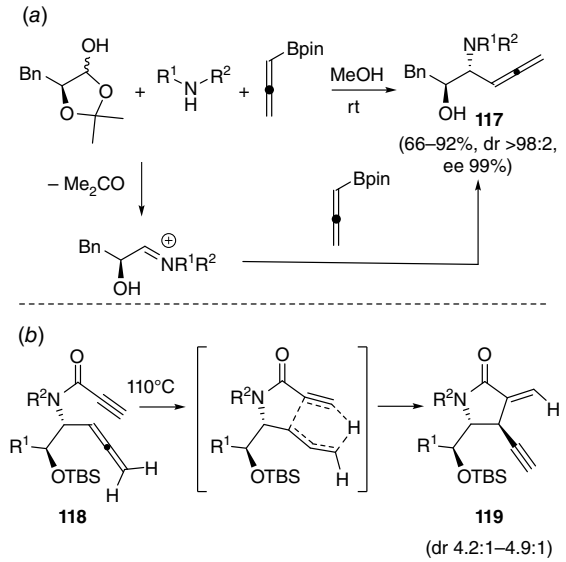


Scheme 31. Total synthesis of the enantiomer of glyphaeaside C.

Other developments on the PBMR

Other developments of the PBMR include the regioselective and diastereoselective PBMR using α-hydroxyaldehydes and pinacol allenylboronate (Scheme 32*a*) leading to highly functionalized β-allenyl-β-amino alcohols (e.g. **117**).[73] In a related study using ethyl glyoxylate as the aldehyde component, α-propargylglycinates were obtained.[74] An indium chloride catalyzed addition reaction of allenyl potassium trifluoroborate with the (*S*)-*N*-tert-butylsulfinyl imine of ethyl glyoxylate gave, after *N*-deprotection, (*S*)-ethyl α-propargylglycinate, in 97% ee.[74] In collaboration with Chris Hyland, the β-amino alcohols **117**, after first *O*-TBS protection, were acylated using propiolic acid, DCC and DMAP to give the α-allenyl propiolamides **118** (Scheme 32*b*). These substrates were found to undergo intramolecular Alder-ene reactions upon heating at 110°C to give α-methylene-γ-lactams **119** in yields ranging from 69 to 92% with dr values ranging from 4.2:1 to 4.9:1.[75] These reactions occurred via a mechanism distinct from previous [2 + 2] cycloisomerization reactions of related systems. The mechanism involves an unusual transfer of the allene-hydrogen and is favored by the electron-deficient nature of the propiolamide moiety.

In related studies with Chris Hyland we prepared the α-allenyl-β-amino alcohols **121** and **122**, which are isomeric with **117**.[76] These were prepared in a regioselective and diastereoselective manner via the Et_2Zn-catalyzed allenylation reactions of chiral *N*-protected L-α-amino aldehydes **120** with pinacol allenylboronate (Scheme 33*a*). The *N*-Boc protected L-α-amino aldehydes **120** (R^2 = H) gave the *syn* products **121**, consistent with a Cram-chelation like transition state (intramolecular H-bonding between the NH and aldehyde carbonyl) while the *N*-Boc, *N*-Bn protected L-α-amino aldehydes **120** (R^2 = Bn) gave the *anti*-products **122**, consistent with the Felkin-Ahn like transition state model. Treatment of **122** with an excess amount of NaH in THF gave the eneynes **123** in good yield which were converted into the ene-diynes **124** via Sonagashira coupling with aryl iodides (R^2I) and then an amide coupling reaction with propiolic acid. Treatment of these ene-diynes **124** with 2.5 mol% of the basic trigold oxo complex $[(Ph_3PAu)_3O]BF_4$ gave the isoindolinones **125** via a novel cycloaromatization process that involved a dual gold-catalyzed reaction pathway (Scheme 33*b*).[77] Other collaborative efforts have also uncovered a novel Rh^I-catalyzed dehydro Diels–Alder reaction of enediynes **126** proceeding



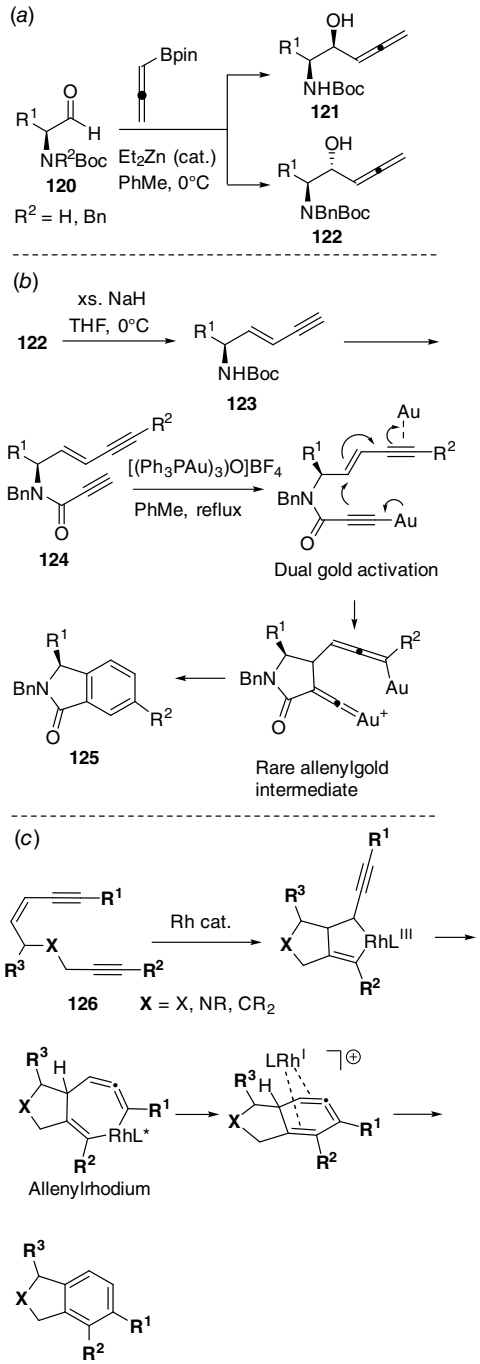
Scheme 32. (*a*) Diastereoselective borono-Mannich reactions with pinacol allenylboronate. (*b*) Intramolecular Alder-ene reactions of α-allenyl propiolamides **118**.

via a rhodium-stabilized cyclic allene (Scheme 33*c*)[78] and the Pd-catalyzed asymmetric allylic alkylation reactions of sulfamidate imines.[79] In other studies on metal-promoted or metal-catalyzed cyclization reactions we have reported cyclization-cyanation and cyclization-halogenation reactions of β-hydroxyalkynes and *o*-alkynyl-anilines and phenols, leading to valuable 3-cyano-indoles and benzofurans,[80] and cycloisomerization reactions leading to furo[3,2-*b*]pyridines and furo[3,2-*b*]pyrroles.[81]

Further studies on the PBMR resulted in the development of a highly diastereoselective synthesis of enantioenriched *anti*-α-allyl-β-fluoroamines from *in situ* prepared chiral α-fluoroaldehydes leading to 3-, 5- and 6-membered ring heterocycles, with the latter two types having an exo-cyclic alkylfluoro-substituent (Scheme 34*a*);[82] and the synthesis of enantioenriched *anti*-β-amino alcohols (Scheme 34*b*) via allylation reactions of *in situ* prepared chiral, *O*-protected α-hydroxyaldehydes.[83]

Synthesis of other heterocycles

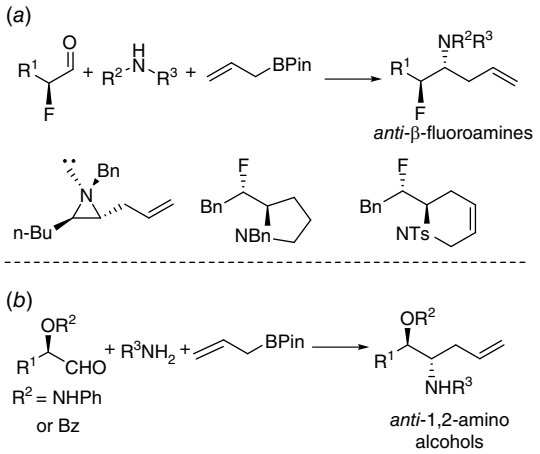
My research group also pioneered the discovery of cyclization reactions of α,β-unsaturated *N*-acyliminium ions with tethered bisnucleophiles to provide access to novel spirocyclic and bridged heterocycles and 5,5-disubstituted pyrrolidines (Scheme 35),[84–86] including those shown in Scheme 36, that have promising biological activities. The analogous reactions of α-cyclopropyl *N*-acyliminium ions with tethered bisnucleophiles were also developed leading to novel spirocycles (Scheme 37).[87] Diastereoselective Ritter reactions of chiral cyclic *N*-acyliminium ions were also developed to



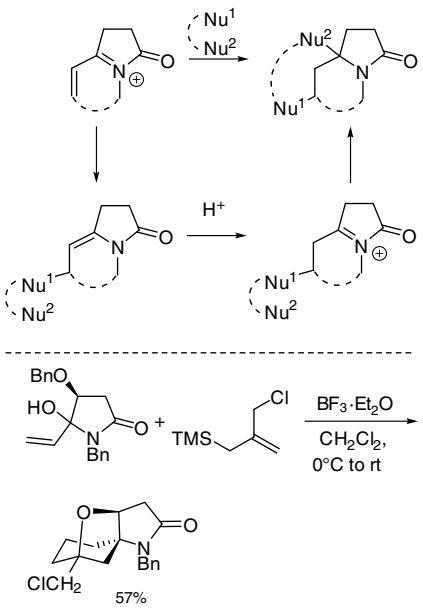
Scheme 33. (*a*) Synthesis of α-allenyl-β-amino alcohols **121** and **122** via the Et_2Zn-catalyzed allenylation reactions of chiral of *N*-protected L-α-amino aldehydes **120**. (*b*) Synthesis of isoindolinones **125** via a novel dual gold-catalyzed reaction pathway. (*c*) Tetradehydro-Diels–Alder reaction involving a low energy allenylrhodium species.

allow, after hydrolysis, rapid access to chiral, substituted, 5-*N*-acylamino pyrrolidines and 6-*N*-acylamino-piperidines.[88]

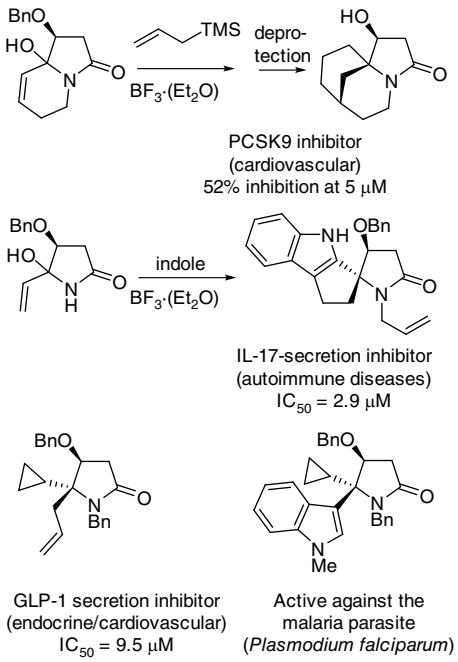
We have used chiral oxazolidinones in [4 + 2][89,90] and [3 + 2][91–93] cycloaddition reactions to prepare conformationally restricted amino acids, including conformationally



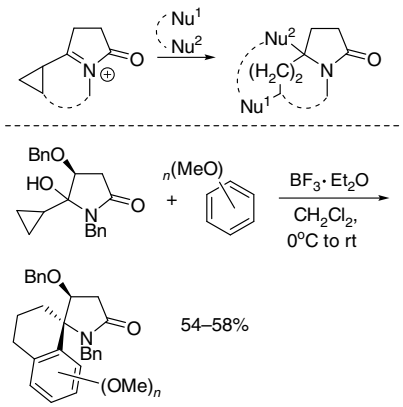
Scheme 34. (*a*) Synthesis of chiral *anti*-α-allyl-β-fluoroamines and some derived heterocycles. (*b*) Synthesis of chiral *anti*-α-allyl-β-hydroxyamines.



Scheme 35. Cyclization reactions of α,β-unsaturated iminium ions with tethered bisnucleophiles provide novel spirocyclic and bridged heterocycles and 5,5-disubstituted pyrrolidines. A typical example using 2-chloromethyltrimethylallylsilane is given.



Scheme 36. Representative products from Schemes 35, 37 are shown along with their biological activities.

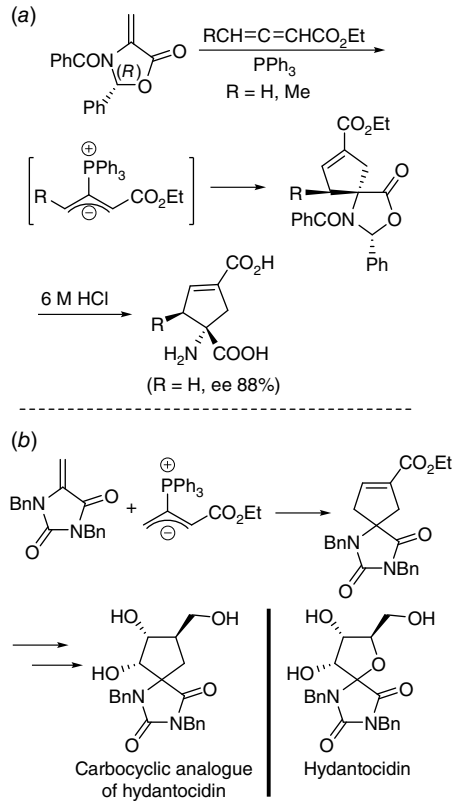


Scheme 37. Cyclization reactions of α-cyclopropyl *N*-acyliminium ions with bisnucleophiles provides novel spirocyclic heterocycles. A typical example using electron rich aromatic nucleophiles is given.

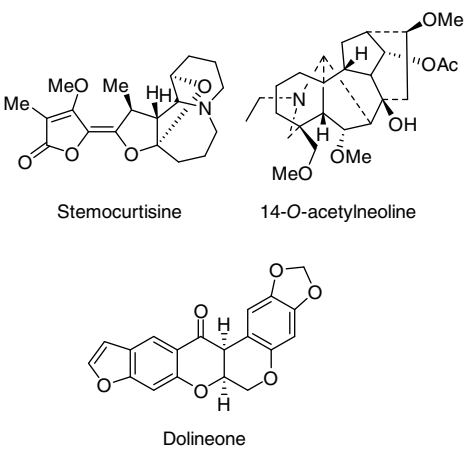
restricted glutamates (Scheme 38*a*) and the carbocyclic analogue of the proherbicide hydantocidin using the related heterocyclic substrate, *N*,*N*-dibenzyl-5-methylenehydantoin (Scheme 38*b*).[94] These methods were extended to the synthesis of 2-azaspiro[4.4]nonan-1-ones,[95] and chiral proline derivatives[96] and to reactions involving additions of 1,3-dipolar[97,98] or free radicals.[99] Along with Paul Keller we have had a productive collaboration on the preparation of mono and disubstituted fullerenes (C_{60} derivatives) functionalized with amino acid derivatives, including dihydrofullerenylpyrroles.[100,101] A peptide system comprising two tethered dihydrofullerenylpyrroles allowed for the important discovery of fullerene van der Waals oligomers as electron traps.[102]

Isolation of natural heterocycles from Nature (alkaloids)

In the area of natural products chemistry research, our group has developed strong and very productive research collaborations with chemists and biologists in Thailand,[103,104] Malaysia,[105] Bhutan[106] and Nigeria,[107] resulting in the isolation of a number of biologically active alkaloids.



Scheme 38. (*a*) Synthesis of conformationally restricted glutamates from [3 + 2] cycloaddition reactions of a chiral oxazolidinone. (*b*) Synthesis of the carbocyclic analogue of hydantocidin from [3 + 2] cycloaddition reaction of *N*,*N*-dibenzyl-5-methylenehydantoin.



Scheme 39. Structures of some bioactive natural products isolated in my lab.

A highlight of this research was the discovery of the first pyrido[1,2-*a*]azepine *Stemona* alkaloid, stemocurtisine (Scheme 39), in my lab at UOW in 2003 through a collaboration with Thai scientists.[42] We also developed a successful synthesis of the tricyclic A-B-C ring structure of stemocurtisine, however, we were not able to complete the total synthesis.[108]

A study of Bhutanese traditional medicinal plant *Aconitum laciniatum* led to the isolation of the diterpenoid alkaloid 14-*O*-acetylneoline (Scheme 39) which demonstrated mitigation of inflammation in a murine model of ulcerative colitis.[109] Work on a more recent project concerned with Nigerian traditional medicinal plants that are used in the treatment of secretory diarrhea in domestic animals and humans, led to the isolation of CFTR and TMEM16A inhibitors (chloride channel blockers) from *Neorautanenia mitis* (A. Rich) Verdcourt which validated the traditional medicinal use of this plant.[110] The most potent isolate was dolineone (Scheme 39).

Conclusions

In conclusion, this account has highlighted work from my laboratory at UOW from 1985 to 2022, concerning the synthesis of nitrogen heterocycles and alkaloids starting from the use of chiral auxiliaries (sulfoxides and sulfoximines) to chiral vinyl epoxides and the PBMR using chiral α-hydroxyaldehydes. This has resulted in the synthesis of a number of alkaloids, from different structural groups, which have often confirmed the structures and configurations of these natural products and in several cases, corrected their structures. This work has also contributed a better understanding of the stereochemical outcomes of these diastereoselective reactions. Furthermore, we have developed a number of diastereoselective reactions based on other PBMR, cycloaddition chemistry, thermal and metal-catalyzed cycloisomerization reactions and *N*-acyl iminium ion chemistry. Working in collaboration with academics in Thailand, and through PhD students from Malaysia, Bhutan and Nigeria we have isolated and identified many novel natural products, and in some cases, verified the use of their plant source in traditional medicine.

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Data availability. This is an Account of our work published in peer-reviewed journals and as such no supporting or supplementary data is provided. This information can be found within the original publications.

Conflicts of interest. The author declares no conflicts of interest.

Declaration of funding. The author thanks the Australian Research Council (DP130101968 and DP180101332) and the University of Wollongong for funding this research.

Acknowledgements. I acknowledge my academic collaborators who made valuable contributions to the work described here, Leon Kane-Maguire, Paul Keller, John Bremner, Alison Ung, Chis Hyland, Ute Wille, Alireza Ariafard, Renate Griffith, Thunwadee Limtharakul (*nee* Ritthiwigrom), Pitchaya Mungkornasawakul, Araya Jatisatienr, Surat Laphookhieo, Somdej Kanokmedhakul, Kwanjai Kanokmedhakul, Prapairat Seephonkai, Sumalee Kamchonwongpaisan, Pornngarm Limtrakul, Boonsom Liawruangrath, Saisunee Liawruangrath, Phurpa Wangchuk, Atsushi Kato, Robert Nash, Graham Ball, Brian Skelton, Allan White, Tony Willis, Chris Richardson and Wilford Lie. I also acknowledge the hard work of my many PhD students and post-doctoral fellows whose names are cited in the reference section. I thank the Australian Research Council and UOW for continuous support and the Royal Australian Chemical Institute for the recognition of my work through the recent award of a distinguished fellow at the national conference in Brisbane in July 2022.

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