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Keywords

CMMB

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Asymmetric Synthesis of Polyfunctionalized Pyrrolidines and Related Alkaloids

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Abstract: This account describes our recent studies on the development of a general method of preparing polyfunctionalized pyrrolidine, indolizidine, pyrrolizidine and pyrrolo[1,2-*a*]azepines and their related alkaloids.

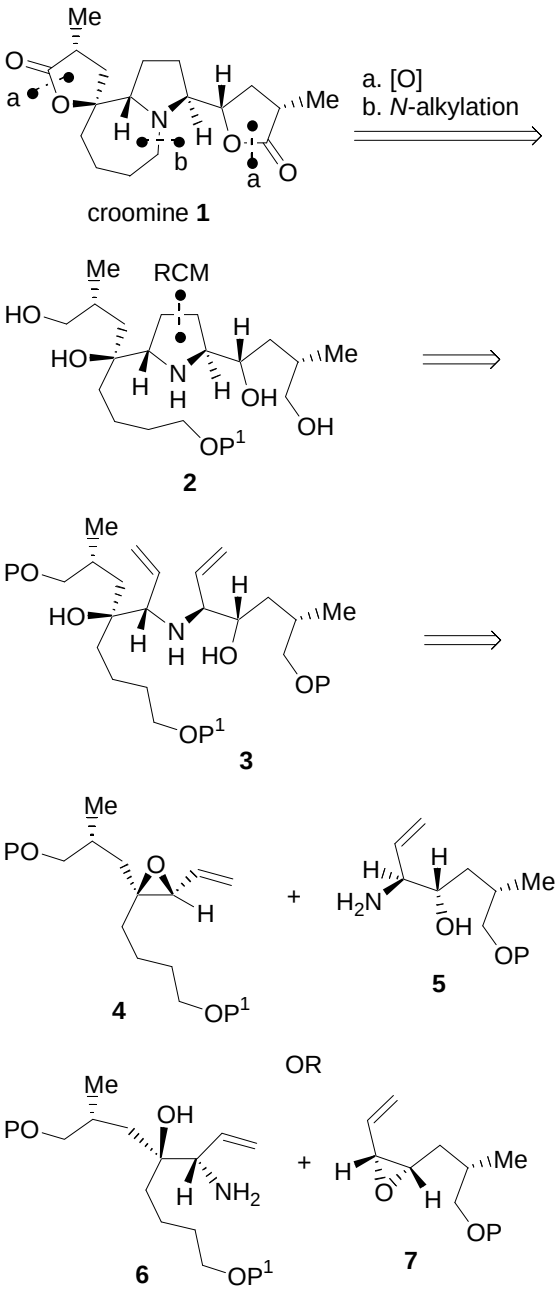
Key words: Vinyl epoxides, aminolysis, oxazolidinones, ring-closing metathesis, pyrrolidines, indolizidine, pyrrolizidine and pyrrolo[1,2-*a*]azepines, Petasis reaction.

Introduction

In early 2000, we started a project concerned with developing a general synthesis of polyfunctional pyrrolidines with the initial intention of developing a synthesis of the *Stemona* alkaloid, croomine **1**. This project was given to a fresh PhD student, Karl Lindsay, who was keen to tackle a challenging natural product target. Our general retro-synthetic analysis is outlined in Scheme 1. The key reactions of this analysis were the ring-closing metathesis (RCM) reaction of the diene **3** and the regioselective aminolysis of the vinyl epoxides **4** or **7** with the chiral allylic amines **5** and **6**, respectively. At the start of this project the regioselective ring-opening of vinyl epoxides with ammonia and benzyl and cyclohexyl amine had been reported by Somfai's group.[1,2] However, the regioselectivity of the aminolysis of more complex chiral vinyl epoxides and more hindered amines was uncertain at the time, and required closer examination. The RCM reaction was well established as a versatile and efficient process for making heterocyclic rings.[3,4] While both these key reactions had been well documented, we thought that their application in tandem appeared to be a novel way to allow ready access to our target molecule.

In the first year of Karl's project we realized that this tandem-methodology could also be applied to the synthesis of the more relatively simpler polyhydroxylated indolizidine and pyrrolizidine alkaloids like swainsonine **8** and australine **9** (Schemes 2 and 3, respectively). Thus Karl temporarily stopped

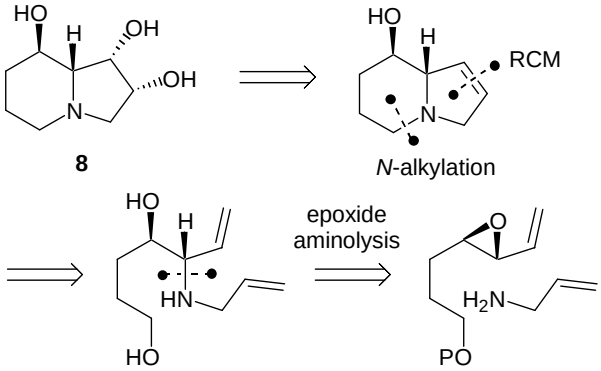
Scheme 1. Retrosynthetic analysis of croomine (**1**).



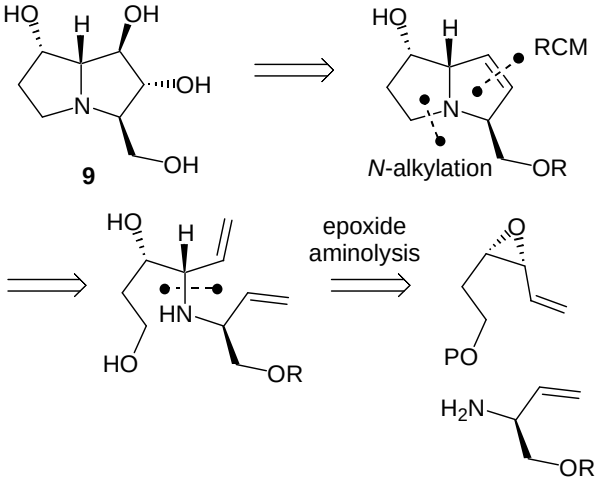
working on croomine and then focused on the synthesis of swainsonine **8**.

In early 2001, Minyan Tang joined my research group as a PhD student and she was given the task of synthesizing australine **9** and its epimers. These target molecules required access to both chiral *trans*- and *cis*-vinyl epoxides.

Scheme 2. Retrosynthetic analysis of swainsonine (**8**).



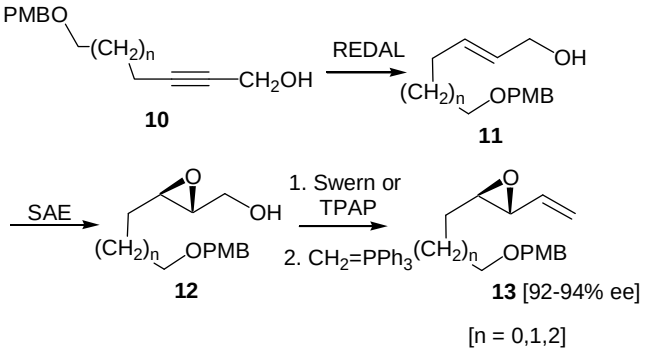
Scheme 3. Retrosynthesis of australine (**9**).



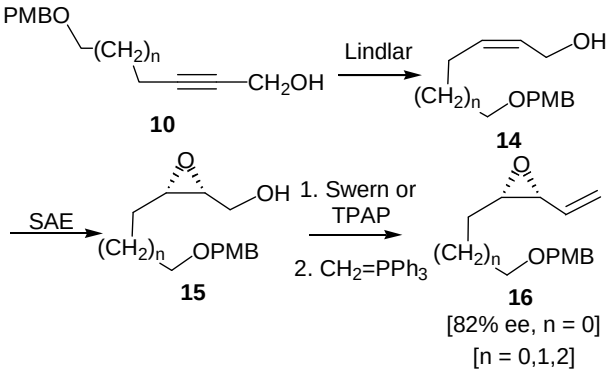
Tandem Vinyl Epoxide Aminolysis/Ring-closing Metathesis

In order to test our proposed synthetic strategy, Karl and Minyan prepared a number of chiral vinyl epoxides using the Sharpless asymmetric epoxidation (SAE) to introduce the epoxide functions on *E*- and *Z*-allylic alcohols. These were readily obtained from the differentially protected propargyl alcohols **10**, by either REDAL reduction to the *E*-allylic alcohols (Scheme 4) or Lindlar reduction to give the *Z*-allylic alcohols (Scheme 5). The resulting epoxy alcohols were then converted to chiral vinyl epoxides via TPAP or Swern oxidation followed by Wittig olefination.

Scheme 4. Asymmetric Synthesis of *trans*-vinyl epoxides.

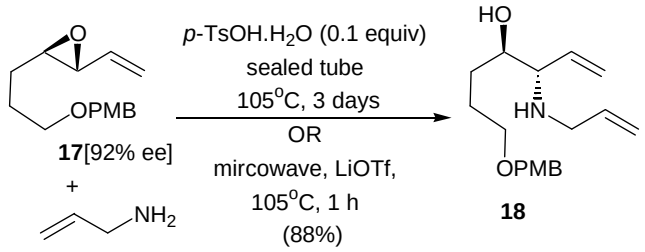


Scheme 5. Asymmetric Synthesis of *cis*-vinyl epoxides

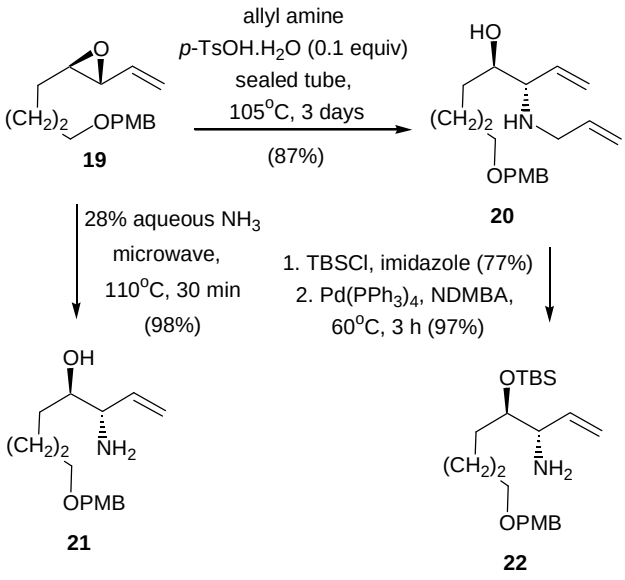


Initial vinyl epoxide-ring opening studies using allyl amine employed the methodology reported by Somfai.[1] In a typical reaction this involved heating a solution of the vinyl epoxide (e.g. **17**, Scheme 6) in the presence of allyl amine (10 equiv) and *p*-TsOH.H_2O (0.1 equiv) in a sealed tube for 3 days at 105°C. Surprizingly these seemingly harsh conditions provided the desired 1,2-amino alcohols (e.g. **18**) in good to excellent yields.[5] Furthermore these reactions were highly regioselective and gave the expected S_N2 products. We latter found that these reactions were accelerated by changing the protic acid catalyst *p*-TsOH.H_2O for the Lewis acid catalyst LiOTf (1-1.5 equiv) without any detrimental effects on the regioselectivities or chemical yields. With the combination of LiOTf and microwave heating[2] then these aminolysis reactions were complete after 1 h of heating at 110°C.[5] The purchase of a microwave reactor in 2002 allowed us to perform aminolysis reactions of vinyl epoxides using aqueous ammonia[2] which was difficult to perform in a sealed tube and often resulted in only cleavage of primary OTBS groups on the vinyl epoxide. Prior to this purchase we had to prepare amino alcohols like **22** in two steps, first vinyl epoxide aminolysis with allyl amine followed by regioselective *N*-deallylation with Pd(0) and *N*,*N*-dimethylbarbituric acid (NDMBA) (Scheme 7).[6]

Scheme 6

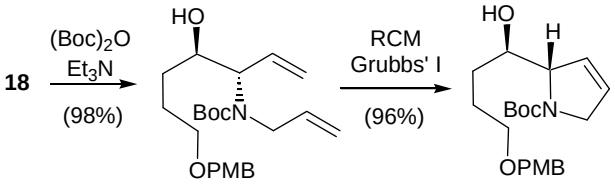


Scheme 7



With 1,2-amino alcohols in hand we were in a position to attempt RCM reactions. These were first converted to their corresponding *N*-Boc derivatives and not unexpectedly their RCM reactions proceeded readily using Grubbs' 1st generation catalyst (benzylidene *bis*(tricyclohexylphosphine)-dichlororuthenium, Grubbs' I, 5-10 mol%) and high dilution in dichloromethane solution at reflux for 18-20 h (Scheme 8).[5]

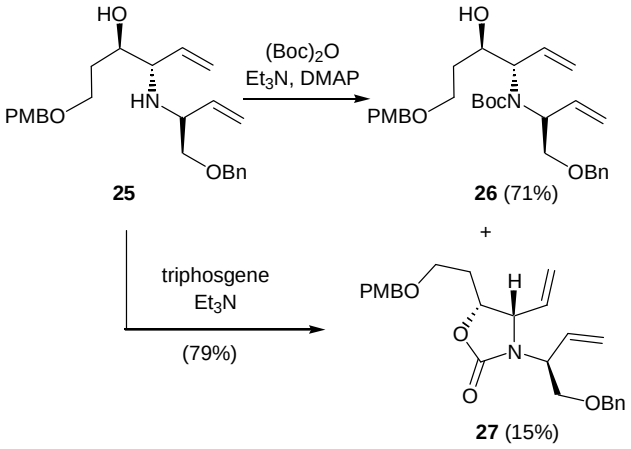
Scheme 8



All Routes Lead to Oxazolidinones

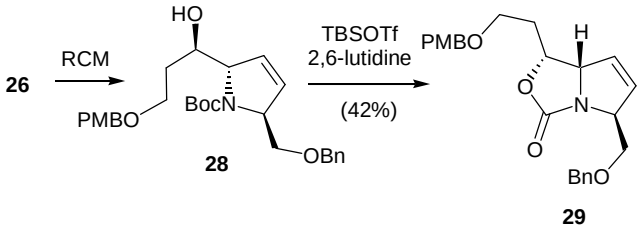
When Minyan attempted to protect the amino group of more hindered amino alcohols like **25** we found that DMAP was required to enhance the rate of reaction. Under these conditions we obtained a mixture of the desired *N*-Boc derivative **26** (71%) and the oxazolidinone **27** (15%) (Scheme 9).[7] The oxazolidinone **27** could be obtained as the exclusive product by treating **25** with triphosgene under basic conditions (Scheme 9).[8]

Scheme 9



The RCM reaction of **26** gave the expected 2,5-dihydropyrrole **28** but upon treatment with TBSOTf, for the purpose of preparing the corresponding secondary TBS ether, we obtained the oxazolidinoe **29** in 42 % yield (Scheme 10).[7]

Scheme 10

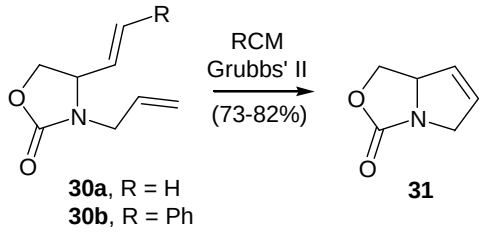


Since all Minyan's reactions were producing oxazolidinones we thought we should 'go with the flow' and use the oxazolidinone as a protectiong group for the 1,2-amino alcohol moiety. Fortunately this proved to be a viable protecting group and allowed us to perform much more diastereoselective *syn*-dihydroxylations on the resulting pyrrolo[1,2-*c*]oxazol-3-ones (e.g. **29**).[8]

At about this time Nicole Gates joined my group in 2002 to start a laboratory based 3rd year chemistry subject. Her project initially involved the synthesis of the 3-allyl-4-vinyloxazolidinones **30a,b** and an examination of their RCM reactions. Compound **30a** had been prepared before, however it was claimed to not undergo the RCM reaction with Grubbs' I catalyst in benzene at RT.[3a] We had thought that by running this reaction in refluxing dichloromethane then we would obtained the pyrrolo[1,2-*c*]oxazol-3-one **31** (Scheme 11). In the event, heating a dilute dichloromethane solution of **30a** and Grubbs' I catalyst (10 mol%) at reflux for 24 h resulted in only 50% conversion to **31** by GC analysis.[9] Indeed the RCM reaction of **30a** was slow compared to that of dienes like **23**. However a yield of 73% could be obtained for **31**, after 24 h,

when the more reactive, and expensive, Grubbs' II catalyst (10 mol%) was employed.[9] The styrene derivative **30b** underwent a RCM reaction under the same conditions to give **31** in 82% yield.[9]

Scheme 11

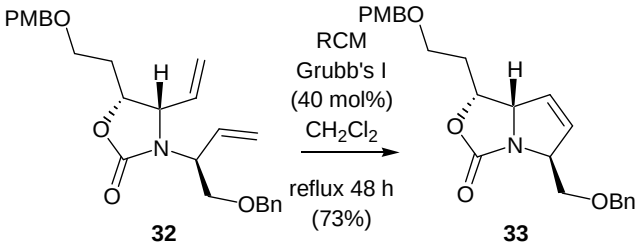


30a, R = H
30b, R = Ph

31

The more heavily substituted 3-allyl-4-vinyloxazolidinones like **32** were even more sluggish in their RCM reactions than **30a** and **30b**. For example, the RCM reaction of **32** required a total catalyst (Grubbs' I) loading of 40 mol% and heating for 48 h. The yield of the pyrrolo[1,2-*c*]oxazol-3-one **33**, however was an acceptable 73% (Scheme 12).[8]

Scheme 12

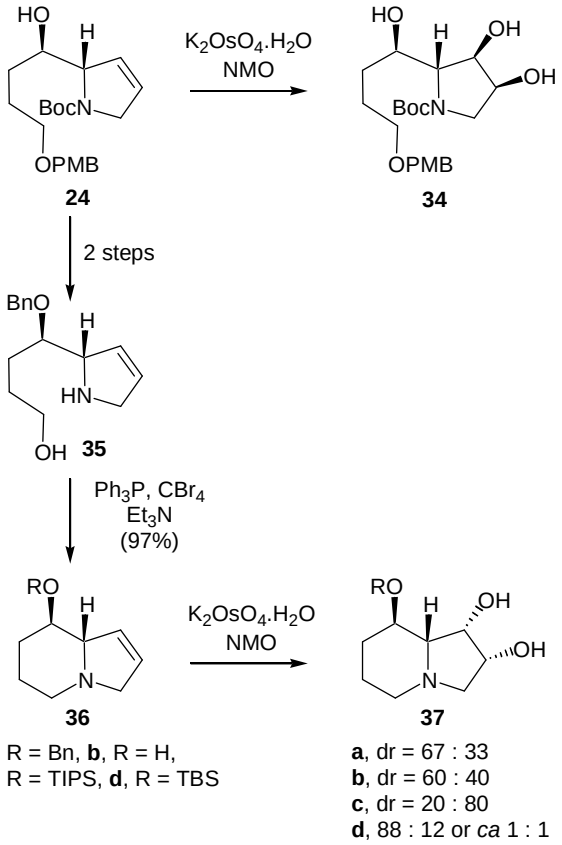


32 **33**

Syn-Dihydroxylation Reactions of 2,5-dihydropyrroles, indolizidines and pyrrolo[1,2-*c*]oxazol-3-ones

Syn-dihydroxylation (DH) of 2-substituted-2,5-dihydropyrroles like **24** with catalytic potassium osmate.dihydrate ($K_2OsO_4.2H_2O$) and stoichiometric NMO in acetone-water is a highly diastereoselective reaction (dr >98 : <2) with the C-2 substituent acting as the stereochemical control element (Scheme 13).[10] *Syn*-dihydroxylations of indolizidines **36a-d** were less diastereoselective under similar conditions. For example, we found the DH reaction of **36a** gave a 67 : 33 mixture of diastereomers in favour of the diastereomer **37a**, having the same absolute stereochemistry as swainsonine (**8**). Other investigators have found similar diastereoselectivities for the DH reactions of **36b-d** (Scheme 13).[11-13] Surprizingly, the TIPS derivative **36c** is reported to undergo DH to give a mixture in favour of 1,2-diepi-**37c** (structure not shown). The diastereoselectivities of these reactions are greatly enhanced using the Sharpless asymmetric DH conditions. Under these conditions using AD-mix-α the diastereoselectivities for the DH of **36a** by us[10] and **36d** by Blechert's group[13] were enhanced to 98 : 2 and 95 : 5, respectively. The stereochemical outcomes for these reactions were consistent with addition of the osmium reagent to the less hindered α-face of **36**. Approach to the β-face being hindered by the pseudo-axial allylic protons H8a and H3β (Scheme 14).[10-13]

Scheme 13

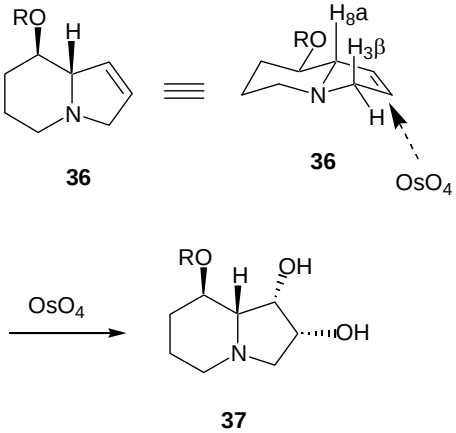


24 **34** **35** **36** **37**

a, R = Bn, **b**, R = H,
c, R = TIPS, **d**, R = TBS

a, dr = 67 : 33
b, dr = 60 : 40
c, dr = 20 : 80
d, 88 : 12 or *ca* 1 : 1

Scheme 14

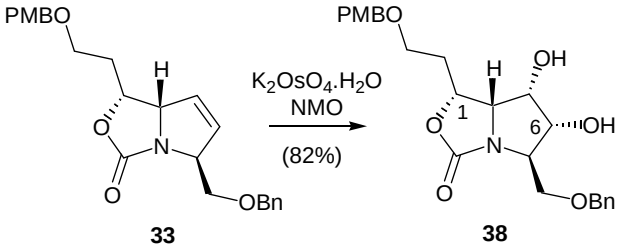


36 **36**

37

The DH reaction of Minyan's pyrrolo[1,2-*c*]oxazol-3-one **33** using $K_2OsO_4.2H_2O$/NMO was highly diastereoselective (dr >95 : <5) and gave the pure 6,7-α,α-diol **38** in 82% yield (Scheme 15).[8]

Scheme 15



The DH reaction of Nicole's pyrrolo[1,2-*c*]oxazol-3-one **31** using $K_2OsO_4.2H_2O$/NMO was also highly diastereoselective (dr >95 : <5) and gave the pure 6,7-α,α-diol **39** in 76% yield (Scheme 16). This diol resulted from attack of the oxidizing agent from the concave face of the molecule (Figure 1) due to the pseudo-axial allylic protons H5β and H7a that sterically hinder the β-face to attack by the osmium reagent (Figure 1).[9] This argument is similar to that proposed to account for the facial selectivity of DH reactions on the related indolizines **36** (Scheme 14). Thus the C-5 β-benzyloxymethyl substituent in **33** was not entirely responsible for the facial selectivity in the DH reaction of **33**.

Scheme 16

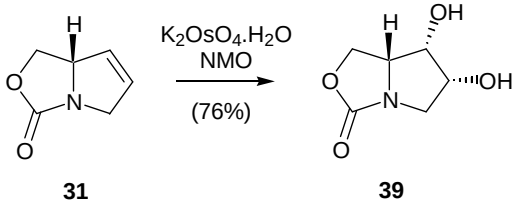


Figure 1

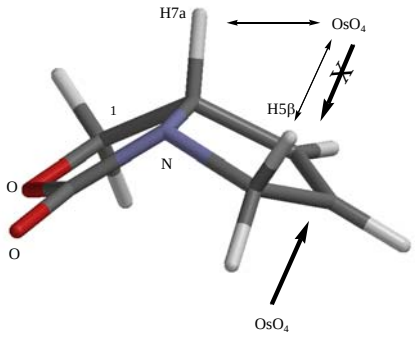


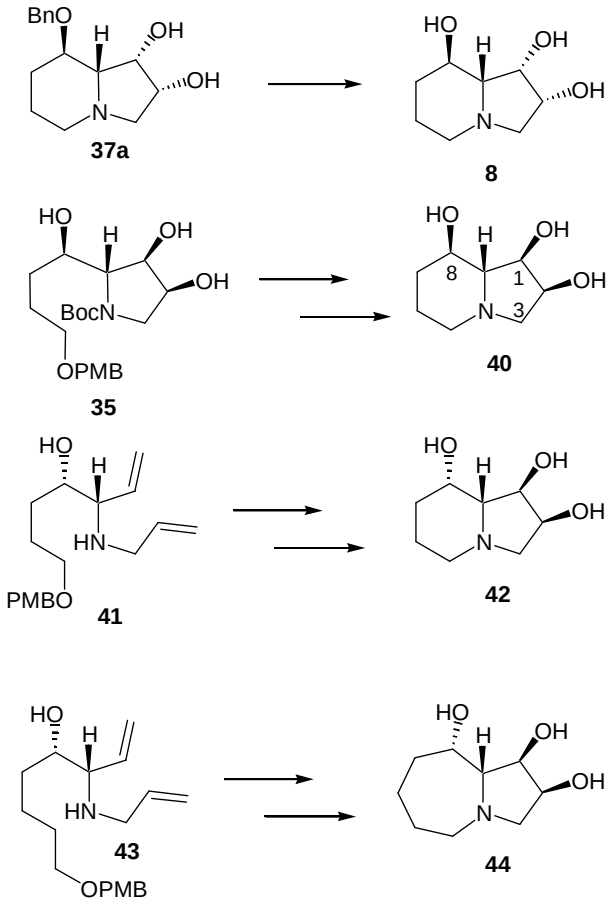
Figure 1. Stereochemical model of **31** (Spartan PC AM1).

Asymmetric Synthesis of Swainsonine and Epiaustalines

Polyhydroxylated indolizidines (e.g. (-)-swainsonine **8**) and pyrrolizidine natural products (e.g. australine **9**) are potent glycosidase inhibitors and have potential applications as anti-cancer, antiviral and anti-retroviral drugs. These interesting biological properties coupled with the polyfunctional and stereochemically rich nature of these compounds have attracted the attention of synthetic chemists resulting in many total syntheses of these and related compounds.[14,15]

In 2002 we reported Karl's successful synthesis of (-)-swainsonine **8** from the deprotection of the diol **37a** and (+)-1,2-diepi-swainsonine by intramolecular *N*-alkylation of the activated primary alcohol of **35** after removal of the *N*-Boc and *O*-PMB groups (Scheme 17).[10] In principle, the tandem vinyl epoxide aminolysis/RCM method could allow the synthesis of all possible stereoisomers of swainsonine. For example, we also reported the synthesis of (+)-1,2,8-triepi-swainsonine **42** by starting from the *cis*-vinyl epoxide **16** (n = 1). Karl also extended his method to the preparation of the novel 1*H*-pyrrolo[1,2-*a*]azepine analogue **44** of swainsonine by starting with **43** the homologue of **41** (Scheme 17).[16]

Scheme 17

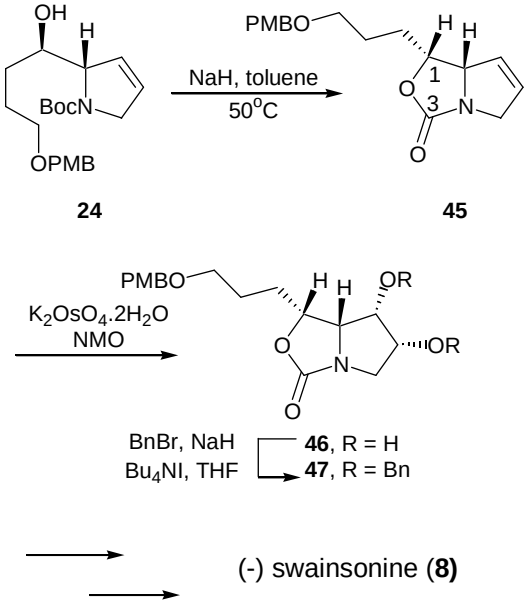


In 2003 Karl developed an alternative synthesis of (-)-swainsonine that was inspired by the success of Nicole and Minyan's DH reactions of the pyrrolo[1,2-*c*]oxazol-3-ones **31** and **33**, respectively.[17] Base catalysed cyclization of **24** gave the pyrrolo[1,2-*c*]oxazol-3-one **45**. With **45** in hand, Karl next examined its DH reactions. To this end **45** was treated with $K_2OsO_4.2H_2O$/NMO in acetone-water, which gave a 3 : 1 inseparable mixture of the diols **46** and 6,7-diepi-**46** (structure not shown) in

85% yield. A pure sample of the major diol **46** was isolated by careful crystallisation from hot dichloromethane and petroleum spirit. This crystallisation was not necessary however, because benzylation of the mixture of diols, gave the corresponding *bis*-benzyl ethers **47** and 6,7-diepi-**47** (structure not shown) in quantitative yield, and these were readily separable by column chromatography. Conducting the same DH reaction at 0^oC resulted in an improved diastereoselectivity and yield (3.5 : 1 and 92%, respectively). Thus the diastereoselectivities for the DH reaction of **46** were similar to those found for the DH reactions of indolizidine **36**. These DH reactions however were far less diastereoselective than those of the unsubstituted pyrrolo[1,2-*c*]oxazol-3-one **31**. The C-1 α-substituent present in **45** is most likely responsible for this reduced α-face diastereoselectivity. With the aim of increasing the steric bulk of the oxidant, and perhaps the diastereoselectivity, the DH reaction was repeated in the presence of the coordinating ligand pyridine (10 equiv.). Unfortunately, the use of pyridine extended the reaction time to 7 d and resulted in a significant reduction in the diastereoselectivity to 1.5 : 1. When AD-mix-α was used at RT the reaction did not go to completion within 6 d, and the diastereoselectivity was only slightly improved (3.7 : 1). Surprisingly, when AD-mix-β was used a 20 : 1 ratio of diastereoisomers was obtained, albeit at low conversion after 6 days at RT, giving a 46% yield of product diols **46** and 6,7-diepi-**46** (and 45% recovered starting material). We attribute the disparencies between the α and β AD-mixes to be a result of a matched/mismatched situation.[18]

Conversion of **47** into (-)-swainsonine **8** proved to be relatively straight forward (Scheme 19).

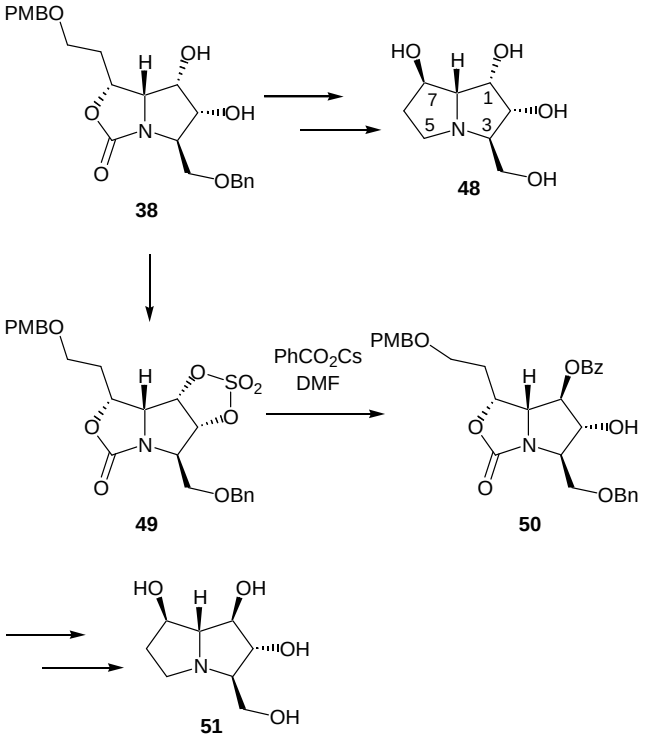
Scheme 18



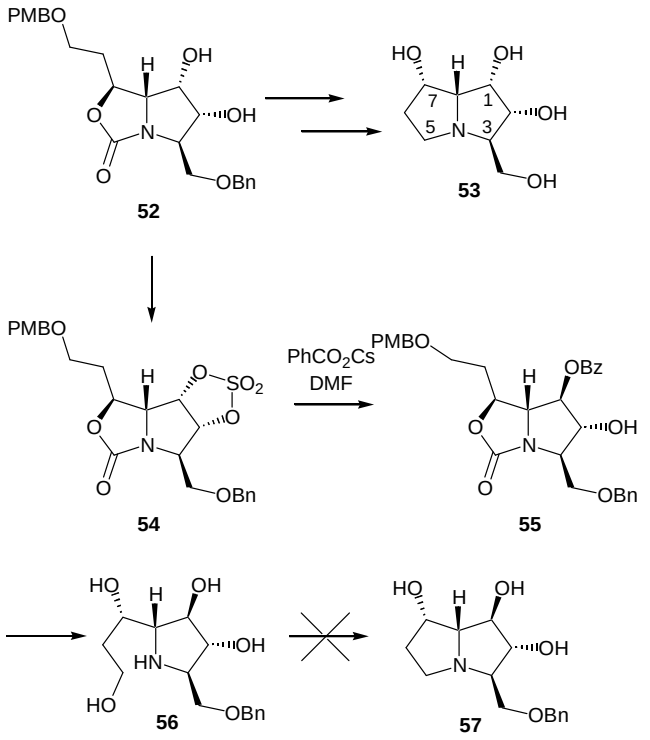
24 **45**

In 2003 we reported Minyan's synthesis of (+)-1,7-diepiaustraline **48** and (-)-7-epiaustraline **51** and from the diol **38** (Scheme 18).[8] The synthesis of (-)-7-epiaustraline **51** required us to invert the stereochemistry at C-1 (australine numbering) in the diol **38**. This was achieved in a regioselective manner via ring-opening of the derived cyclic sulfate **49** with cesium benzoate. The regioselectivity being controlled by the C-3 (australine numbering) benzyloxymethyl group in **49** (Scheme 19). In 2004 we reported Minyan's synthesis of the natural product (+)-1-epiaustraline **53** and her attempted synthesis of australine **9** (Scheme 20).[19] Starting with the *cis*-vinyl epoxide **16** (n = 0) we prepared the C-4 epimer of **25** which eventually provided the diol **52**. This was readily converted to the alkaloid (+)-1-epiaustraline **53**. Compound **52** was converted to the amino tetraol **56** using similar chemistry as shown in Scheme 19. Cyclization of **56** was anticipated to give **57**, the *O*-benzyl ether of our target australine **9** (Scheme 20). Unexpectantly, the cyclization of **56** under the Mitsunobu reaction conditions, that had provided **48**, **51** and **53**, failed to work in this case. Unfortunately we had run out of time and compound to try this cyclization again as Minyan had to commence the writing of her PhD thesis in March 2004. The reasons why this molecule failed to cyclize are not clear, however this step had been a relatively low yielding process in our synthesis of **48**, **51** and **53**. In contrast, we have had relatively little difficulty preparing analogous 5,6- and 5,7-bicyclic heterocyclic systems (c.f. Schemes 13 [conversion of **35** to **36**a] and 17) by formation of the heterocyclic 6- or 7-membered ring using the Appel cyclization conditions (Ph_3P, CBr_4, Et_3N).[20] Unfortunately this method has not been successful in our hands to prepare pyrrolizidines.

Scheme 19



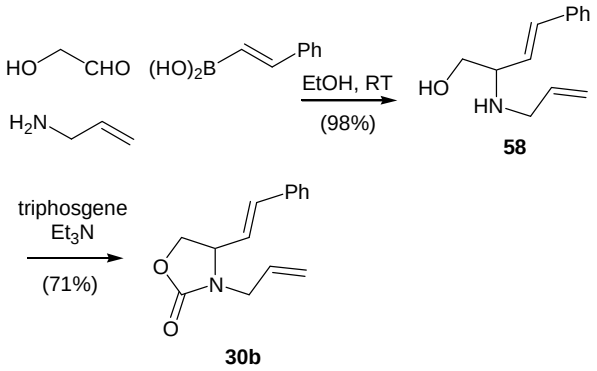
Scheme 20



Synthesis of 1,2-amino alcohols and Putative Uniflorine A using the Petasis Reaction

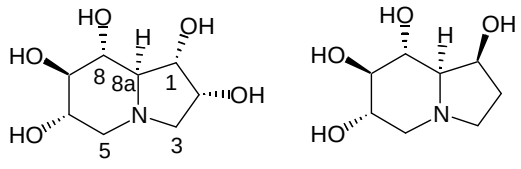
While we had successfully demonstrated the tandem aminolysis of vinyl epoxides/RCM stategy in the synthesis of several alkaloids, we were not happy that the required 1,2-amino alcohols required seven synthetic steps from commercially available alkynes. A novel one-pot, three-component method of preparing 1,2-amino alcohols is the Petasis reaction (boronic acid-Mannich reaction).[21] Indeed Nicole used the Petasis reaction in her synthesis of the 1,2-amino alcohol **30b** (Scheme 21).

Scheme 21



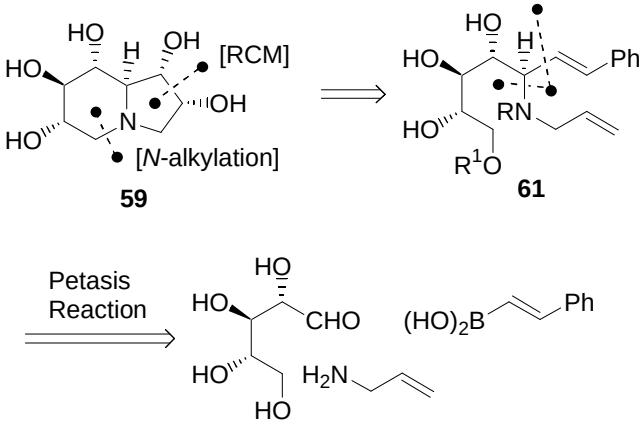
To test this method for alkaloid synthesis we targeted the synthesis of the polyhydroxylindolizidine alkaloid, uniflorine A **59** which was isolated in 2000 from the leaves of the tree *Eugenia uniflora* L.[22-24] The water-soluble extract of these leaves has been used as an antidiabetic agent in Paraguayan traditional medicine. Uniflorine A was found to be an inhibitor of the α-glucosidases, maltase and sucrase, with IC_{50} values of 12 and 3.1 μM, respectively. The structure of uniflorine A was deduced from NMR analysis to be that shown as structure **59**.[22] The proposed structure of uniflorine A is similar to that of castanospermine **60**, except for the stereochemistry at C-1 and the extra hydroxyl substitution at C-2 (Figure 2).

Figure 2



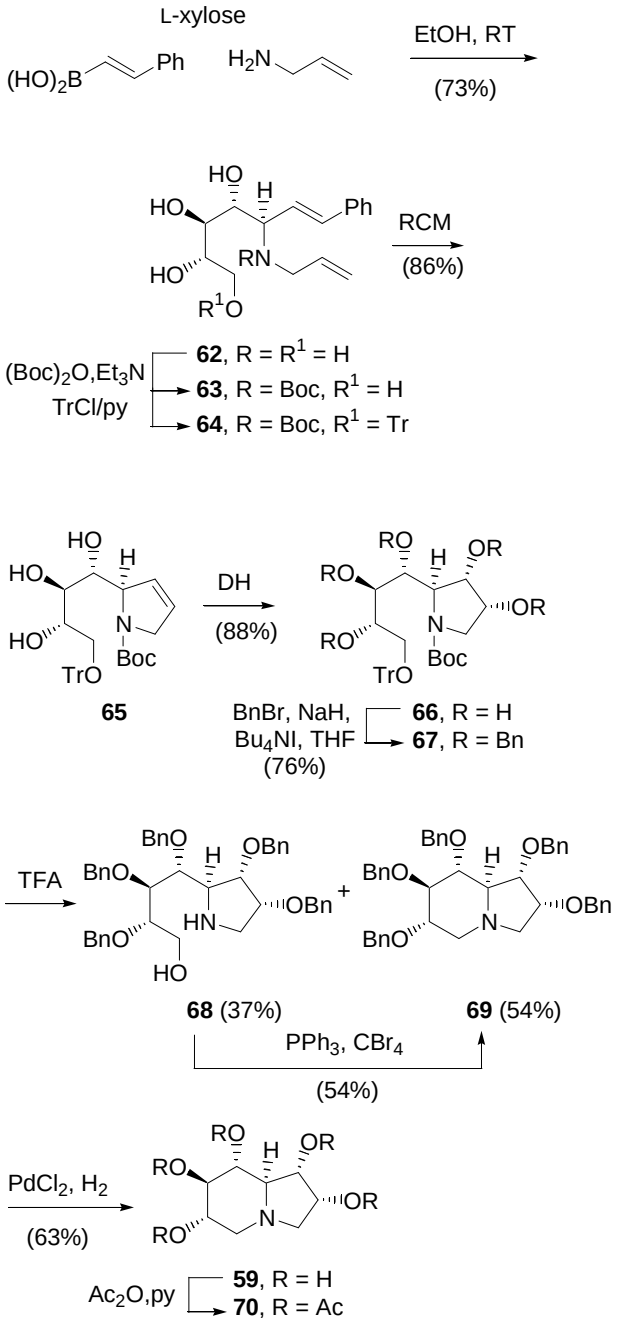
In April 2003 Andrew Davis joined our group as a new PhD student to work on the synthesis of uniflorine A and related alkaloids. Our retrosynthetic analysis of **59** (Scheme 22) suggested that the target compound could be acquired from the precursor **61** using a RCM reaction and *N*-alkylation to prepare the 5- and 6-membered rings of **59**, respectively.[25] The 1,2-*anti* amino alcohol **61** would be expected to be readily obtained from the Petasis reaction of L-xylose, allylamine and (*E*)-styrene boronic acid, followed by chemo- and regioselective *N*- and *O*-protection reactions.

Scheme 22. Retrosynthetic analysis of **59**

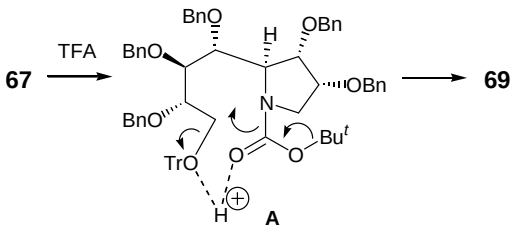


In the event, the requisite Petasis reaction gave the desired amino-tetraol **62** in 73% yield as a single diastereomer after purification by ion-exchange chromatography (Scheme 23). The amino-tetraol **62** was converted to its *N*-Boc derivative **63** (51 % yield) and then the primary alcohol was regioselectively protected as its *O*-trityl compound **64** (68 % yield). A RCM reaction of **64** using Grubbs' I catalyst (10 mol %) smoothly gave the 2-substituted-2,3-dihydropyrrole **65** in 86% yield. *Syn*-dihydroxylation of **65** furnished the pentaol **66** as a single diastereomer in 88% yield. The stereochemical outcome of this DH reaction was expected due to the stereodirecting effect of the C-2 substituent in **65** and was later confirmed from the single crystal X-ray analysis of the pentaacetate derivative of **59** (**70**). The pentaol **66** was readily converted to its penta-*O*-benzyl derivative **67** in 76% yield under standard conditions. Selective liberation of the secondary amino and primary hydroxyl groups of **67** was achieved by exposure of **67** to TFA in the presence of anisole, as a cation scavenger, at RT. Surprisingly, this reaction gave a mixture of the desired amino-alcohol **68** (37%) and the indolizidine **69** (54%) (Scheme 23). When this reaction was performed at 0°C a mixture of **68** and the mono-deprotected trityl derivative of **67** was obtained. Treatment of this compound or **68** with TFA/anisole at RT gave only a very poor yield (<5% from ^{1}H NMR analysis) of **69** after 2 days. We suggested that **69** arises by cyclization of an incipient amide anion **A** with activation of the *O*-trityl group by protonation by TFA, as shown in Scheme 24. The amino-alcohol **68** underwent smooth cyclization to give the same indolizidine **69** using $Ph_3P/CBr_4/Et_3N$ (54%). Debenzylation of **11** under hydrogenolysis conditions using $PdCl_2/H_2$ gave **59** in 63% after ion-exchange chromatography and then recrystallization in a total of 8 synthetic steps from L-xylose. The structure of **59** was unequivocally established by a single-crystal X-ray study of its pentaacetate derivative **70**. The ^{1}H and ^{13}C NMR data for synthetic **59**, however did not match with those reported for uniflorine A; the latter showed many more downfield peaks in the ^{1}H NMR, perhaps consistent with the amine salt. The ^{1}H NMR of the hydrochloride salt of synthetic **59** however, did not match the literature spectral data either. We therefore concluded that the structure assigned to uniflorine A was not correct.[25]

Scheme 23

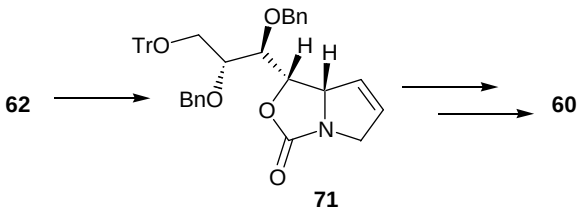


Scheme 24



In 2003 Theeraphan joined our group for 12 months as a visiting scientist from Thailand. He and Andew have prepared the pyrrolo[1,2-*c*]oxazol-3-ones **71** from the tetraol **62** which they are attempting to convert to castanospermine **60** (Scheme 25).

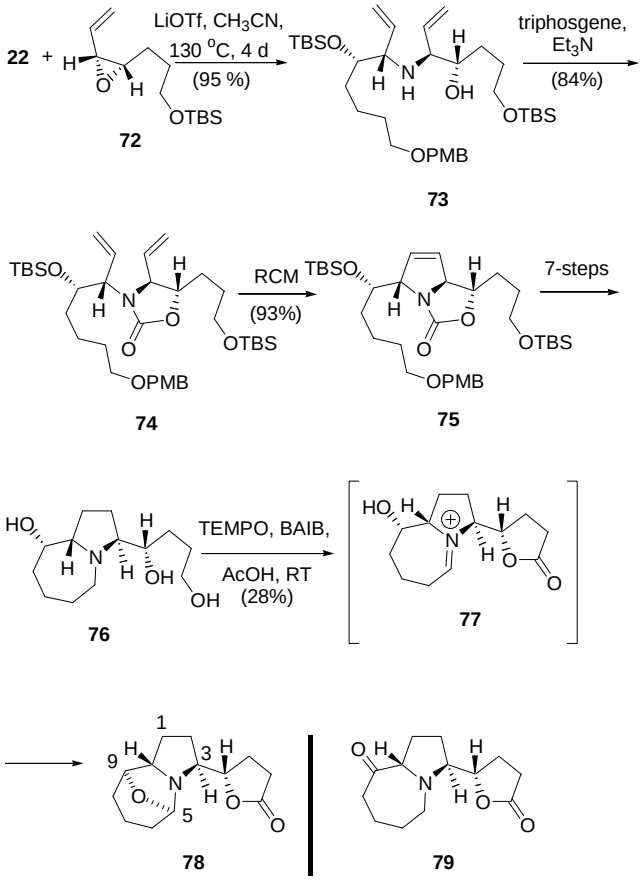
Scheme 25



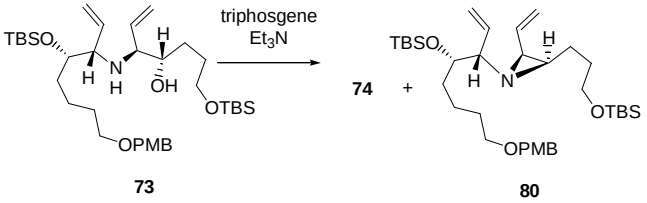
Croomine Revisited

In 2002 Karl returned to the croomine synthesis project. As model studies to test the viability of our proposed synthesis he prepared the chiral allylic amine **22**, a structurally simpler analogue of **6**, and the vinyl epoxide **72**, the nor-methyl analogue of **7**, and used them as building blocks to prepare a molecule having the tricyclic B,C,D-ring core structure of croomine (**1**).[26]

Scheme 26



Scheme 27



Heating a mixture of **22** (ee 92%) and **72** (ee >82%) and lithium triflate (1.5 equiv) in acetonitrile solution at 130 °C for 4 days in a sealed tube provided the amino alcohol **73** in 78% yield. The ee of this compound was estimated *ca* 95% due to removal of most of the undesired enantiomers of **22** and **72** as the diastereomer of **73**, since **73** and its diastereomer (not shown, 17%) were readily separated by column chromatography (Scheme 26). The unwanted diastereomer (a mixture of enantiomers) arises from the reaction of *ent*-**22** with **72** and **22** with *ent*-**72**. Treatment of **73** with triphosgene at –40 °C in the presence of base (Et_3N) gave the oxazolidinone **74** in 84% yield, along with an aziridine **80** (14%, Scheme 27) that arises from reaction of triphosgene with the secondary hydroxyl group of **73** followed by intramolecular S_N2 displacement by the nitrogen atom at the carbon bearing the activated hydroxyl. The low temperature was required to minimise the formation of this aziridine. The oxazolidinone **74** underwent a RCM reaction with Grubbs' I catalyst. The reaction was slow requiring 7 days of heating at reflux and high catalyst loading (50 mol %), however the yield of the 2,5-dihydropyrrole **75** was excellent (93%). Compound **75** was converted to the 1*H*-pyrrolo[1,2-*a*]azepine **76** in seven synthetic steps. Oxidation of this triol to give the desired keto-lactone **79** proved difficult. For example, the use of TPAP/NMO, a reagent combination that we have used successfully before to prepare a lactone from a related 1,4-diol,[5] gave a mixture of products including ones that showed aldehyde signals in the ^1H NMR spectra. When the oxidizing system 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO, catalytic)/*bis*-acetoxy iodobenzene (BAIB, stoichiometric)[27] was employed in acetic acid as solvent, the unexpected product **78** was isolated in 28% yield having a novel 5,9-epoxy-1*H*-pyrrolo[1,2-*a*]azepine tricyclic ring structure. This structure was thought to arise from oxidation of the tertiary amine to the corresponding cyclic iminium ion **77** followed by ring closure through the secondary hydroxyl in the azepine ring.

In 2003 Joe Hartley joined our group as a post-doctoral research fellow to work on the croomine project. In light of Karl's work described in Scheme 26 we went back to the drawing board and planned a modified approach to croomine that would carry the extra methyl substituents required for the natural product syntheses and would avoid oxidation reactions in the presence of the free tertiary amino group in the azepine ring. Joe will soon have epoxides **4** and **7** in hand (Scheme 1) and be in a position to prepare **3** and hopefully croomine before Christmas 2004.

In conclusion, we have demonstrated the successful application of the tandem aminolysis of chiral vinyl epoxides/RCM reaction for the synthesis of both natural and unnatural products. We have demonstated that 3-allyl-4-vinyloxazolidinones undergo slow but efficient RCM reactions to give pyrrolo[1,2-*c*]oxazol-3-ones that are useful substrates for diastereoselective manipulations because of their bicyclic nature. The combination of the Petasis reaction and the RCM allows more rapid access to these molecules and this tandem process is being keenly examined by Andrew, Nicole and Theeraphan for use in alkaloid synthesis.

Acknowledgment. We thank the Australian Research Council and the University of Wollongong for financial support of our projects and Brian Skelton and Allan White (University of Western Australia) for X-ray structural analyses.

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Asymmetric Synthesis of Polyfunctionalized Pyrrolidines and Related Alkaloids

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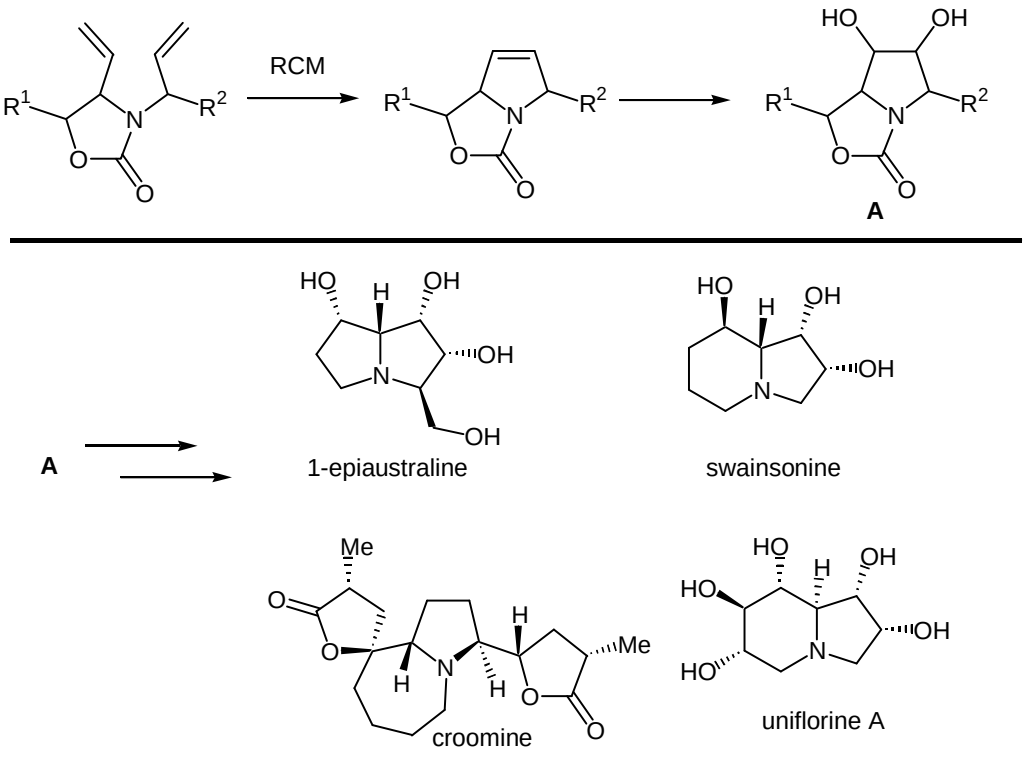

Stephen Pyne was born in Melbourne, Australia. He obtained his BSc (Hons) degree from the University of Adelaide in 1975 and his PhD in 1979 at the Australian National University under the supervision of Prof. Lew Mander. After postdoctoral fellowships at Purdue (with Phil Fuchs) and Harvard (with E. J. Corey) Universities he started his academic career as a lecturer at the University of Wollongong in 1985 and was appointed to Professor of Chemistry at the same institution in 1998. He was a Von Humboldt Research Fellow (Marburg University, 1992-3), Young Researcher of the Year Award for 1992 (offered by the Australian Research Council and the Von Humboldt Foundation) a Rhone Poulenc Fellow (University Louis Pasteur, Strasbourg, 1994), a visiting Professor, Max Planck Institute fur Kohlenforschung, Mulheim, Germany in 1998, an ARC Senior Research Fellow in 1994-1999 and Subprogram Leader for Organic and Petrochemistry, Thai-Australian Science and Engineering Assistance Program (TASEAP), 1998-2000. His early research interests were in the areas of, chiral sulfur chemistry and their rearrangement reactions with Pd(0), the asymmetric synthesis of nonproteinogenic amino acids and chiral organometallic chemistry. In 2000 his research interests changed to the asymmetric synthesis of bioactive natural products, especially alkaloids, phytochemistry of Thai medicinal plants and medicinal and fullerene chemistry**.**

Andrew Davis was born in Sydney, Australia and obtained his BSc (Hons) degree from the University of Wollongong in 2000. He has worked as a research assistant at the University of Wollongong, 2001-2 and is currently pursuing a PhD degree under Prof. Stephen Pyne.

Nicole Gates was born in Wollongong, Australia in 1981. She joined the research group of Professor Stephen Pyne in 2002 for a third year research project. After completing her BSc (Hons) in 2003 at the University of Wollongong, she began a PhD in 2004 in the same group working towards the synthesis of polyhydroxylated pyrrolidines.

Joseph Hartley was born in Bournemouth, England in 1977. His undergraduate chemistry studies at the University of Bath, England included a year spent at Rhone-Poulenc Rorer's Dagenham Research Centre, and he obtained his MChem (Hons) degree in 1999. He stayed on at the University of Bath for postgraduate studies on the use of Indium(III) salts as catalysts for electrophilic aromatic substitution reactions, under the supervision of Chris Frost, and was awarded his PhD in 2002. In 2003, he moved Down Under to Australia to begin a postdoctoral research fellowship with Stephen Pyne at the University of Wollongong.

Karl Lindsay was born in Invercargill, New Zealand and obtained his BSc (Hons) degree from the University of Otago in 1998 under the supervision of David Larsen. In 1999 he joined the Pyne group as a research assistant for 1 year and then commenced his PhD in 2000. In 2003 he submitted his PhD degree and he will formally graduate in July 2004. In early 2004 he took up a post-doctoral position in the Department of Chemistry, University of Aarhus in Denmark**.**

Theeraphan Machan was born in Phitsanulok, Thailand. He obtained his BSc (Hons) degree from Rajabhat Institute Pibulsongkram, Thailand in 1996 and MSc degree from Chiang Mai University in 2000. He is currently studying a PhD in the Faculty of Pharmacy, Chiang Mai University under The Royal Golden Jubilee PhD program. In 2003 he has joined the Pyne group as a visiting fellow for 1 year to work on natural products chemistry and synthesis.

Minyan Tang was born in Jingdezhen, China. She obtained her BSc (1995) and MSc (1998) degrees at the Jiangxi Normal Univesity, China from which she obtained 2 academic awards. In 1998-2000 she was employed at the same University in the Department of Chemistry as a lecturer in organic chemistry and a researcher in natural products chemistry. In 2001 she moved to the University of Wollongong, Australia, to start a PhD in the Pyne group. She is currently writing her PhD thesis.

Photo caption:

The Alkaloid Synthesis group: Theeraphan, Minyan, Nicole, Stephen, Andrew, Joe and Karl (inset).