A Review on Recent Syntheses of Amaryllidaceae Alkaloids and Isocarbostyrils (Time period mid-2016 to 2017)

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Alkaloids from the Amaryllidaceae have become valuable targets for synthetic organic chemists, mainly due to their wide variety of bioactivities and potential for utilization in medicinal chemistry ventures. In addition, the structural complexity of a number of these alkaloids has also been a reason for the interest in these compounds. In this review, the last 18 months of literature was perused and synthetic highlights have been presented here, with the hope to further focus attention on this interesting class of compounds and to encourage others to synthesize these compounds and their derivatives and/or analogues. The review contains examples of syntheses from most of the important alkaloid scaffold classes previously isolated from the Amaryllidaceae, namely: lycorine, crinine, galanthamine, tazettine, montanine, phenanthridone, phenanthridine, plicamine, mesembrine and some minor scaffolds (like gracilamine).

Keywords: Amaryllidaceae, Alkaloids, Isocarbostyrils, Synthesis, Lycorine, Crinine, Galanthamine, Tazettine, Montanine, Phenanthridone, Phenanthridine, Plicamine, Mesembrine, Gracilamine.

The aim of this review is to present new syntheses of Amaryllidaceae alkaloids [1] published during the late period of 2016 to October 2017. This has been done to supplement and extend two recent excellent reviews, namely by Hudlicky and co-workers [2] and Jin [3], both of which extensively focus on synthetic progress in this field. In addition, other topical recent reviews on various important aspects of the Amaryllidaceae alkaloids, exemplified by Kornienko and Evidente [1a], He et al. [1b], Nair et al. [1c-e], Ding and co-workers [4], Evidente and co-workers [5] and Hotchandani and Desgagne-Penix [6] serve as testimony to the tremendous growing interest by synthetic and natural product chemists in the biological value these alkaloids possess. Our information is derived from the very latest articles we were able to source from our search engines. It should be noted that the focus will be on total and formal syntheses and not specifically on advances in enzyme-mediated approaches [7-9], in-silico-based research [10] or natural product isolation as for instance in these recent literature examples [11-13].

The syntheses are arranged and presented in such a way as to represent, as far as possible, similar classes of the Amaryllidaceae alkaloids, as utilized in recent reviews [4]. However, there could be a degree of overlap due to the very nature of the various syntheses since a particular synthetic intermediate might be a useful synthon for a number of different members of this alkaloid family. It should also be noted that, on occasion, some finer details might have been omitted from reaction schemes and these can easily be obtained from the references. We trust that our overview of these 18 months will provide evidence of the intense synthetic focus on the Amaryllidaceae alkaloids and will thus enthuse more researchers to participate in generating these compounds, their analogues and derivatives.

a) Lycorine-scaffold alkaloids:

i) Asymmetric total syntheses of (+)-lycorane, (+)-zephyranthine, and a formal synthesis of (+)-clivonine, by Sun and co-workers: Sun and co-workers developed a fairly rapid protocol for the synthesis of another pivotal intermediate 11, based on their earlier work [14], which acted as most innovative scaffold for its further transformation into a number of Amaryllidaceae alkaloids [15]. Thus, starting from the TBS-protected 4-hydroxy butanoic acid 1, E van’s auxiliary 2 was easily and efficiently introduced to give the chiral intermediate 3 (90%). This was followed by an asymmetric α-allylation on the carbonyl alkyl chain to produce 4 (68%) with a d.r. >20:1. Removal of the chiral auxiliary with LiBH4 followed by Dess-Martin periodane-mediated oxidation of the corresponding primary alcohol provided aldehyde 5 (70% for the 2 steps), which was converted into the one very important intermediate viz., 7 (96%) by treatment with (R)-N-tert-butanen sulfinyl amine 6 in the presence of Ti(0Ei)4 (Scheme 1).

Reaction between the building blocks 7 and 8 under palladium-catalysed cinnamyloration conditions, followed by a spontaneous cyclization afforded the stereospecifically desired product 9 (53%) (d.r. >20:1). As noted, this protocol generated two consecutive stereocentres, in addition to ring B in a 1-pot sequence. Removal of both protecting groups under acidic conditions then gave a lactam alcohol (96%) which was re-protected as the mesylate 10 (96%) by reaction with methane sulfonic anhydride (Scheme 2). A subsequent
RCM using Hoveyda-Grubbs II generation catalyst caused the precipitation of the product 11 (93%) which was now set up for formation of ring D and was achieved by using the relatively weaker and bulkier base tBuOK (cf NaH) to prevent any possible racemization, to form the pivotal intermediate 12 (Scheme 2).

In order to illustrate the value of intermediate 12, it was converted into three important Amaryllidaceae alkaloids illustrated in Scheme 3. Thus Pd(OH)$_2$ catalysed hydrogenation afforded lactone 13 (79%) which upon reduction with LiAlH$_4$ in THF under reflux gave the enantiomerically pure α-lycorane 14 (89%). Alternatively, Sharpless asymmetric dihydroxylation of 12 with AD-mix-β gave the C1, C2 cis-diol (73%) with a d.r. = 8:1. Reduction of the lactam with LiAlH$_4$ then afforded zephyranthine 15 (62%). On the other hand, performing the dihydroxylation with AD-mix-α followed by acetonation lead to isolation of products 16 (52%) and 17 (22%) in which the latter compound was an intermediate in the formal total synthesis of (+)-clivonine 18.

Thus treating ketoester 19 (1 mol) and nitroalkene 20 (1.5 mol) in DCM with 10 mol% of the chiral squaramide catalyst at room temperature for 6 h followed by heating under reflux for 36 h gave an 88% yield of the nitroester 21 with an ee of 92%. This represents an interesting double Michael cascade reaction stereochemically controlled by the catalyst. Treatment of nitroester 21 with dilute H$_2$SO$_4$ in DMSO, followed by heating to 120 °C for 2 h led to the removal of the ester (decarboxylation) and TBS groups to yield alcohol 22 (92%) which was converted into mesylate 23 (95%) under standard conditions. A reductive aminomethylation with zinc powder in acetic acid then afforded the octahydro-indolone 24 (94%), which was then converted into the ethyl carbonate 25 (90%) by reaction with ethyl chloroformate and TFA. The well-established Bischler-Napieralski lactam ring-closure protocol was then efficiently effected with Tf$_2$O and DMAP in DCM to produce the enol triflate lactam 26 (87%). Palladium-catalysed reduction of the enol triflate afforded the cyclohexane ring (95%) followed by amide reduction with LiAlH$_4$ which then gave the target molecule viz., (+)-δ-lycorane 27 (Scheme 4).

iii) Synthesis of (+)-γ-lycorane by intramolecular Friedel-Crafts reaction, by Bates and co-workers: Bates and co-workers employed an intramolecular Friedel-Crafts reaction to prepare racemic γ-lycorane 35 ending with a diastereoselective hydrogenation of a late stage pyrrole intermediate [18]. To this end, N-Tosyl pyrrole 28 was subjected to a Friedel-Crafts acylation with succinic anhydride followed by removal of the ketone moiety by Clemmensen
reduction to afford pyrrole 29 (72% for 2 steps). Conversion of the acid 29 into the Weinreb amide 30 was effected by treatment with Et$_3$N and N$_2$O-dimethylhydroxylamine hydrochloride in 86% yield. This intermediate was coupled with the lithiate 31 at -78 °C to give the expected ketone (74%) which was reduced to the corresponding alcohol 32 (86%) with NaBH$_4$ in MeOH at 0 °C. Treatment of the latter alcohol with Amberlyst-15 in MeCN smoothly transformed it into the next Friedel-Crafts product (not illustrated) (82%), and this was immediately followed by deotosylation with sodium ethanethiolate to afford pyrrole 33 (99%). Hydrogenation of 33 by the method of Kray and Reinicke using $\text{PO}_4$/AcOH/H$_2$ under a modest pressure produced 34 as a single stereoisomer. Finally, a Pictet-Spengler reaction with paraformaldehyde in CF$_3$CO$_2$H was immediately followed by detosylation with sodium oxoassoanine, affording γ-lycorane (72% for 2 steps). Treatment of the latter alcohol with Amberlyst-15 in MeCN smoothly transformed it into the Weinreb amide 30 in 86% yield. This intermediate was coupled with the lithiate 31 at 18 °C to give the expected ketone (74%) which was reduced to the corresponding alcohol 32 (86%) with NaBH$_4$ in MeOH at 0 °C. Treatment of the latter alcohol with Amberlyst-15 in MeCN smoothly transformed it into the next Friedel-Crafts product (not illustrated) (82%), and this was immediately followed by deotosylation with sodium ethanethiolate to afford pyrrole 33 (99%). Hydrogenation of 33 by the method of Kray and Reinicke using $\text{PO}_4$/AcOH/H$_2$ under a modest pressure produced 34 as a single stereoisomer. Finally, a Pictet-Spengler reaction with paraformaldehyde in CF$_3$CO$_2$H afforded γ-lycorane 35 (62%) (Scheme 5).

iv) Convergent synthesis of oxoassoanine by way of Rh(III)-catalyzed C-H conjugate addition/cyclization reactions, by Weinstein and Ellman: Weinstein and Ellman developed a most useful C-H catalytic addition and cyclisation cascade protocol via a Rh(III) catalyst in their synthesis of the Amaryllidaceae alkaloid, oxoassoanine 41 [19]. Thus, conjugate addition between the N-homoallylic benzamide 36 with trans-diesters 37 in the presence of a Rh(III) catalyst afforded a moderate (57%) yield of the desired product 38 (Scheme 6). Treatment of 38 with TFA afforded imide 39, which without being isolated, was treated with TFAA. This mediated the Paal-Knorr cyclisation to produce the amidofuran 40 (66% for the 2 steps) in a one pot process. Heating amidofuran 40 neat at 230 °C then gave the Diels-Alder adduct of the tetracyclic system and final decarboxylation with copper-bronze afforded oxoassoanine 41 (68% for the 2 steps).

b) Crinine-scaffold alkaloids

i) Total synthesis of rac-joubertiamine and other family members, by Bisai and co-workers: Bisai and co-workers developed a common precursor molecule, vide infra, from which they were able to synthesize joubertiamine 42, mesembrine 43 and crinine 44 scaffolds all of which have structural motifs viz., a single all carbon quaternary stereocentre [20] (Figure 2).

Figure 2: Typical mesembrane-type alkaloids.

Many alkaloids of the Amaryllidaceae family have similar structural motifs and due to their vast biological activity profiles, constitute valuable synthetic challenges. In their new approach, Bisai and co-workers developed a unified strategy to produce a common precursor which would lead to a range of Sceletium and Amaryllidaceae alkaloids [20]. Thus, the Stork-Danheiser protocol was successfully applied to cyclohexenone 45 using appropriate Grignard reagents to produce the corresponding 3-aryl-2-cyclohexenones 46-48, each of which was reduced by the Luche protocol to afford the corresponding alcohols 49-51 in excellent yields of 92-96% (Scheme 7).

Scheme 6: Synthesis of oxoassoanine 41.

39, which without being isolated, was treated with TFAA. This mediated the Paal-Knorr cyclisation to produce the amidofuran 40 (66% for the 2 steps) in a one pot process. Heating amidofuran 40

Scheme 7: Synthesis of 3-(aryl)cyclohex-2-enols.

In order to generate the pivotal quaternary centre, the authors applied the Eschenmoser-Claissen rearrangement on enols 49-51 which produced the desired rearranged amides 52-54 again in
excellent yields of 83-92%. Allylic oxidation with PDC and tert-butyl hydroperoxide afforded the enones 55-57 in 60-62% yield. Reduction of the enone amides with LiAlH₄ afforded the enol amines 58-60 in yields of 80-90%. Allylic oxidation of the latter enols to the corresponding joubertiamines 61 and 62 was achieved in 67-75% yields. Demethylation of the 4-methoxy precursor to enols to the corresponding joubertiamines 63 and 64 in 85% yields respectively. Reduction of the enone amides with LiAlH₄ afforded the enol in 89% yield. Transformation of the cyano group of 75 into the aldehyde 76 was efficiently effected with DIBAL·H in dichloromethane in 84% yield, which was followed by an equally efficient one-carbon homologation under Wittig conditions to form the diene 77 (88%). This compound was perfectly set up for a RCM using Grubbs’ II catalyst to afford the corresponding sulfide with simultaneous loss of the Boc group in 71% yield and was followed by the oxidation of the latter sulfide with mCPBA to generate the epimeric sulfoxides 78 in 89% yield (Scheme 11).

The commercially available benzylic cyanide 73 was then monoalkylated with iodide 72 under basic conditions to afford sulfide 74 in 72% yield. The crucial quaternary carbon was then generated by treatment of 74 with the powerful base KHMDS in THF containing HMPA and tosyl aziridine, followed by Boc protection to give the rather congested cyanosulfide 75 in 67% yield. Transformation of the cyano group of 75 into the aldehyde 76 was accomplished by using BBr₃ in DCM at -78 °C for 1 h in an 83% yield (Scheme 8).

In order to employ the pivotal intermediates 53 and 54 for the synthesis of mesembrane and crinane entities, the C2 position was required to be functionalised. To this end, iodolactonization of syntheses of mesembrane and crinane entities, the C2 position was best effected via a reductive amination using (Scheme 9). The all-important transformation of these latter viz, the ketoaldehydes followed by Swern oxidation to deliver the next key intermediates corresponding 1,4-diols in almost quantitative yield which was In order to employ the pivotal intermediates 53 and 54 for the synthesis of mesembrane and crinane entities, the C2 position was required to be functionalised. To this end, iodolactonization of syntheses of mesembrane and crinane entities, the C2 position was best effected via a reductive amination using (Scheme 9). The all-important transformation of these latter viz, the ketoaldehydes followed by Swern oxidation to deliver the next key intermediates corresponding 1,4-diols in almost quantitative yield which was followed by Swern oxidation to deliver the next key intermediates viz, the ketoaldehydes 65 and 66 in excellent yields of 90% (Scheme 9). The all-important transformation of these latter ketoaldehydes was best effected via a reductive amination using methylvamine and sodium cyanoborohydride in ethanol, catalysed by a mixture of either 10% AcOH or 10% TFA to afford the mesembranes 43 and 67 in yields of 86% and 90%, respectively. Finally treatment of ketoaldehyde 66 with ammonium acetate under the standard reductive amination conditions afforded an 85% yield of 68 followed by a rather ingenious usage of Eschenmoser’s salt (N,N-dimethylmethylene ammonium iodide) to complete the synthesis of crinane 44 (Scheme 9).

**ii) Synthesis of crinane utilizing an allylic sulfoxide for the construction of a hydroindole ring, by Raghavan and Ravi:** In their new approach to the crinane alkaloids, Raghavan and Ravi made use of a vinylogous Pummerer reaction to form the octahydroindole central core [21]. Their synthesis commenced by treating the monoprotected 1,3-propanediol 69 with diphenyl disulfide under conditions developed by Hata [22] to afford sulfide 70. Chlorination α- to the sulfur atom was achieved using N-chlorosuccinimide and the product was treated with vinyl magnesium bromide to afford the allylsulfide 71 in 95% yield. Acid catalysed deprotection of the silyl ether, followed by iodination of the alcohol produced the vinyl iodide 72 in 70% yield for the two steps (Scheme 10).

The commercially available benzylic cyanide 73 was then monoalkylated with iodide 72 under basic conditions to afford sulfide 74 in 72% yield. The crucial quaternary carbon was then generated by treatment of 74 with the powerful base KHMDS in THF containing HMPA and tosyl aziridine, followed by Boc protection to give the rather congested cyanosulfide 75 in 67% yield. Transformation of the cyano group of 75 into the aldehyde 76 was efficiently effected with DIBAL·H in dichloromethane in 84% yield, which was followed by an equally efficient one-carbon homologation under Wittig conditions to form the diene 77 (88%). This compound was perfectly set up for a RCM using Grubbs’ II catalyst to afford the corresponding sulfide with simultaneous loss of the Boc group in 71% yield and was followed by the oxidation of the latter sulfide with mCPBA to generate the epimeric sulfoxides 78 in 89% yield (Scheme 11).

At this point of the protocol, the sequence was developed in two different ways. Firstly, treatment of 78 with TFAA in Et₂N produced an intermediate sulfonium salt which then converted into the selenium ion 79 to undergo the Pummerer-type ring closure reaction and produce cyclohexene 80, a most valuable intermediate

**Scheme 11: Synthesis of sulfoxide 78.**

**Scheme 12: Synthesis of crinane 68 and other intermediates.**

At this point of the protocol, the sequence was developed in two different ways. Firstly, treatment of 78 with TFAA in Et₂N produced an intermediate sulfonium salt which then converted into the selenium ion 79 to undergo the Pummerer-type ring closure reaction and produce cyclohexene 80, a most valuable intermediate
for the synthesis of numerous members in the crinine family. Secondly, sulfoxide 78, when treated with triflic anhydride in 2,6-lutidine and DCM at -78 °C afforded the sulfonium salt 81, followed by stoichiometrically controlled intramolecular cyclisation with loss of sulfenyl triflate to afford the mesembrane skeleton 82 in 92% yield. Next, removal of the Ts group was effected with sodium naphthalimide, reduction of the double bond by H2/Pd and final treatment with acidified formalin resulted in an excellent yield of the natural product crinane 68 (Scheme 12).

iii) Asymmetric syntheses of (-)-crinine and (+)-4a-dehydroxycrinamine, by Wang and co-workers: Wang and co-workers employed a new approach for installation of the crucial chiral quaternary centre for the crinine-type alkaloids they described as a palladium-catalysed asymmetric allyl-allyl cross coupling reaction [23]. Their synthesis began by Friedel-Crafts acylation between commercially available 1,3-benzodioxole 83 and 3-bromopronanoic acid chloride to produce ketone 84 (78%). This was followed by transformation of the latter into the corresponding benzyloxy analogue 85 (92%). A Grignard reaction with vinyl magnesium bromide afforded alcohol 86 (80%), which when treated with (Boc)2O in Et3N afforded the rearranged olefin 87 (85%) in an E/Z ration of 4:1. The vital allyl-allyl cross coupling between 87 and allyl B(pin) 88 was then optimized with an interesting phosphorous catalyst to give the pivotal diene 89 (85%) (ee 94%). Selenium(IV) dioxide oxidation of the latter with an excess of t-butyl hydroperoxide (TBHP) gave the α,β-unsaturated ketone 90 (65%) (Scheme 13).

Michael addition of vinyl magnesium bromide to ketone 90 in the presence of CuCN at -78 °C provided the keto olefin 91 (78%). Next RCM using Grubbs’ II catalyst afforded the six-membered ring intermediate 92 (98%). Catalytic hydrogenation then removed the benzyl group and reduced the double bond to afford the keto alcohol 93 and its hemiacetal (93%). Dess-Martin periodinane oxidation of the primary alcohol 93 produced the corresponding aldehyde (92%), followed by a reductive amination with ammonium acetate and sodium cyanoborohydride. Finally, a Pictet-Spengler protocol with dimethylmethylene ammonium iodide (Eschenmoser’s salt) produced (+)-crinine 44 (55% for the 2 steps) (Scheme 14).

The authors next developed a method, using intermediate 92, for the synthesis of the more complex crinamine. Thus 92 was dihydroxylated with OsO4 and NMO to afford a single diastereomer which was protected as the acetonide 94 (88% for the 2 steps). Through an analogous set of reactions used for conversion of 93 into 44 illustrated in Scheme 14, ketone 94 was converted into (+)-4a-dehydroxycrinamine 95 in 20% yield (for 5 steps), the final one being treated with concentrated hydrochloric acid in methanol (Scheme 15).

iv) Bioinspired enantioselective synthesis of crinine-type alkaloids via iridium-catalysed asymmetric hydrogenation of enones, by Zhou and co-workers: Zhou and co-workers developed an interesting iridium catalyst viz., Ir-SpiroPAP and applied it for the bioinspired asymmetric hydrogenation of racemic oxocrinine to produce the cis and trans products 96 and 97 (Scheme 16) [24]. These compounds were then converted into their benzoyl esters in order to simplify their chromatographic separation after which hydrolysis of the pure isolates afforded (-)-crinine 96 and (-)-epivittatine 97. This process was instrumental in the group preparing an extensive library of crinine-type alkaloids on a gram scale.

v) Syntheses of (-)-crinine and (-)-aspidospermidine, and the formal synthesis of (+)-minfliensene using enantioselective intramolecular dearrangive cyclisations, by Tang and co-workers: Tang and co-workers developed a most useful asymmetric dearrangive cyclisation protocol to generate the core nucleus of the crinine type Amaryllidaceae alkaloids by employing a mixture of palladium and phosphorus catalysts [25]. Their synthetic route started by reductive amination of the product formed by reaction between 6-bromopiperonal 98 and aniline 99 to afford amine 100 (93%) after reduction of the initial imine. This was followed by conversion of the nitrogen into the phosphoramide group with LiHMDS/CIP(NMe2)2/H2O2. Subsequent treatment with KF/tetraethylene glycol selectively removed the aryl TBS group to afford the N-protected phenol 101 (64%). The pivotal intramolecular dearrangive cyclisation of the bromophenol 101

Scheme 13: Synthesis of dienone 90.

Scheme 14: Synthesis of (+)-crinine 44.
catalysed by palladium and (S)-AntPhos produced the tetracycle 102 with the desired quaternary carbon in 96% yield and with an ee of 94%. Selective enamide double bond reduction of 102 with DIBAL-H at -78 °C was followed by Luche reduction of the ketone and removal of the primary TBS protecting group with TBAF produced the allylic alcohol 103 (74% for 2 steps). A rather clever protocol involved treatment of allylic alcohol 103 with triphosgene/Et3N which removed both the N-protecting group and activated the primary alcohol as the alkyl chloride which then underwent the intramolecular cyclisation with the nucleophilic nitrogen atom to form the crinine motif 104 (93%). One needs to be aware of the inversion of stereochemistry of the secondary alcohol when converted into the chloride. This intermediate now served as a general intermediate for a number of further transformations into other crinine alkaloids (Scheme 17).

Scheme 17: Synthesis of chloride 104

Thus, after some trial and error, treatment of chloride 104 with the same palladium catalyst as earlier, PPh3 and AgOAc afforded the stereoselective allylic acetate which was hydrolysed to (-)-crinine 96 (90%). On the other hand, methanolation of allylic chloride 104 afforded buphanisine 105 (15%) and epibuphanisine 106 (40%), while reducing it with LiEt3BH at 40 °C for 8 h, followed by a cis-dihydroxylation protocol gave amabiline 107 (50% for 2 steps) (Scheme 18).

Scheme 18: Synthesis of (-)-crinine 96 and some of its analogues from a common precursor 104

vi) 5,10b-Ethanophenanthridine alkaloid-inspired novel bicyclic ring systems, by Frolova, Kornienko and co-workers: Frolova, Kornienko and co-workers made good use of a biomimetic approach for the synthesis of the crinine skeleton [26]. This approach is based on the intramolecular para-para oxidative coupling of O-methylbelloxane 108, followed by a subsequent intramolecular Michael cyclisation of the spiro bicyclic intermediate 109 to afford the noroxomaritidine skeleton 111 after aromatization of the intermediate 110 (Scheme 19).

Scheme 19: Proposed biosynthesis of the crinine skeleton.

Over the years, many laboratory methods have been developed to mimic the oxidative coupling vide infra which has proved to be one of the most efficient protocols for synthesizing crinine 5,10b-ethanophenanthridine ring systems. In their approach, Henry et al. reacted appropriate aldehydes 112 (partial structures of generic alkaloid aromatic systems illustrated) with tyramines to produce the corresponding imines which without isolation were efficiently reduced to the amines 113 in yields of between 60-97%. It was found that converting the latter amines into their trifluoroacetamides 114 in 60-95% yields served best, both to protect the molecule and to serve an important purpose later. Phenylisodine(III)bis(trifluoroaceta)te (PTFA) in 2,2,2-trifluoroethanol facilitated the regioselective oxidative para-para coupling providing the corresponding spirocyclic dienes 115 in yields ranging from 11-55%. Treatment of these dienes with KOH in aqueous methanol removed the protecting group under very mild conditions and released the nucleophilic amine nitrogen for the intramolecular Michael condensation on the α,β-ene system to afford the various 5,10b-ethanophenanthridine analogues 116 in yields of 30-90% (scheme 20).

Scheme 20: General protocol for the formation of crinine-type alkaloids. The squiggly lines represent the general aromatic systems of the alkaloids.

In order to obtain further analogues of 5,10b-ethanophenanthridenes for biological evaluation, the group debenzylated intermediate 117 by treatment with BCl3 at -78 °C in CH2Cl2, followed by the intramolecular Michael cyclisation in methanolic potassium hydroxide to afford noroxomaritidine 111, which in turn was converted under standard conditions into the benzoyl analogue 118, acetyl analogue 119 and ester 120. It was also possible to convert the carbonyl group of 111 into the oxime (not illustrated) under standard conditions in 70% yield (Scheme 21).
mesylated with mesyl chloride in pyridine to afford the mesyl ether 123. This was followed by sodium iodide treatment at 100°C in DMF and then in DBU at 100°C as well, to afford an isomeric mixture of the two possible cyclohexene products 124. Finally, reduction of this mixture using Wilkinson’s catalyst in benzene afforded the single pentacyclic molecule 125 (73% for the six steps). Hofmann elimination protocols applied to compound 125 lead to the all-important 9-17 bond cleavage to give the cyclohexene 126 (99%). Lemieux-Johnson oxidation of 126 resulted in removal of

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\text{MeO}_2\left(\text{CF}_3\right)\text{N}^+\text{Br}^- + \text{LiEt}_3\text{BH} \rightarrow \text{MeO}_2\left(\text{CF}_3\right)\text{N}^+\text{BH}^- + \text{LiBr} + \text{H}_2\text{O}
\]

the C-9 to afford keto-aldehyde 127 (80%) which upon treatment with TrocCl in disopropyl ethyl amine resulted in formation of the N-Troc analogue 128 (81%). This keto-benzaldehyde was chemoselectively protected at the ketone as the acetal 129 (90%). Removal of the Troc protecting group on the nitrogen atom was achieved with the use of Zn-acetic acid after which it subsequently underwent ring closure with the aromatic aldehyde group to form the new 7-membered ring of 130 (98%). Introduction of the double bond in the cyclohexanone ring was effected by treatment with LDA and diphenyl disulfide addition with subsequent oxidation with mCPBA at -78°C to afford the sulfoxide. This underwent the anticipated β-elimination to afford the desired α,β-unsaturated cyclohexenone 131 (41% for the 3 steps). Luche reduction of enone 131 gave a separable mixture of the anticipated diastereomers with 132 being the major (48%). Finally mesylation of 132 with MeCl in pyridine, followed by treatment with aqueous sodium hydrogen carbonate afforded a diastereomeric mixture of (-)-galanthamine 133 (major 48% and minor 23%) (Scheme 22).

**ii)** The synthesis of derivatives and analogues of (-)- and (+)-galanthamine, by Banwell and co-workers: Banwell and co-workers developed an effective and neat protocol for the synthesis of analogues of (-)- and (+)-galanthamine 133 in order to evaluate their acetylcholine esterase inhibition potential [29]. The group’s synthesis commenced by the coupling between vinyl bromide 134 and boronic ester 135 with PdCl₂ catalyst to afford the aryalted cyclohexene 136 (68%). An intramolecular Mitsunobu reaction afforded the acid-sensitive isobenzofuran 137 (33%). Subjecting the latter benzofuran to Eschenmoser-Claisen conditions afforded amide 138 (84%). Reduction of the amide 138 with LiEt₃BH in THF produced the primary alcohol (92%) which was oxidized to the corresponding carboxylic acid 139 using the Bobbit and Bailey protocol. Conversion of acid 139 into the corresponding N-methyl amide 140 (79%) was accomplished by CDI activation of the acid followed by treatment with methylamine (Scheme 23).

Exposure of amide 140 to a modified Pictet-Spengler protocol with paraformaldehyde afforded the seven-membered lactam 141 (47%) with concomitant loss of the Ley acetal moiety. Reduction of the lactam carbonyl group was effected with sodium bis (2-methoxy ethoxy) aluminium dihydride to form the azepine 142 (44%). On the other hand, hydrolysis of intermediate 140 with aqueous TFA gave diol analogue 143 (66%) while similar hydrolysis of intermediate 138 afforded the dimethylamino amide 144 (88%). By making use of the enantiomeric isomer 145, the enantiomeric analogues were synthesized using the same protocol illustrated in Scheme 24.
iii) Synthesis of Guillou’s galanthamine intermediate, by Zeng and co-workers: Zeng and co-workers developed a new synthesis for Guillou’s galanthamine intermediate 150 which requires four further known steps for the final formation of rac-galanthamine 133 [30]. This was in response to the inherent shortcomings in the original synthesis of Guillou et al. [31] Thus phenol 146 was treated with ethyl vinyl ether and Br₂ in DCM in the presence of DIPEA to afford ether 147 (97%) which subsequently underwent a Suzuki cross coupling reaction with p-hydroxybenzeneboronic acid catalysed by Pd(OAc)₂/Ph₃P in n-PrOH/H₂O/NaHCO₃ to give the diphenyl molecule 148 (90%). Deprotonation of the phenol moiety with K₂CO₃ in DMSO at 140 °C then set up conditions for the para-alkylation via an intramolecular cyclisation to form the quaternary spiro tricyclic intermediate 149 (92%). Removal of the ethoxy group from the acetyl moiety was achieved by treatment with 1.0 M HCl/1,4-dioxane at 100 °C for 2 h (83%) and subsequent oxidation of the hemiacetal with 2-iodoxybenzoic acid (IBX) in AcOH smoothly converted it into the spiro-lactone 150 (85%). Four remaining known steps applied to Guillou’s intermediate 150 provided rac-galanthamine 133 in 47% yield for the 4 steps (Scheme 25).

iv) Synthesis of galanthamine, by Banwell and Nugent: Banwell and Nugent, using commercially available cyclohexane-1,4-dione monoethyleketal to prepare 151, developed a short efficient synthesis of rac-galanthamine 133 [32]. To this end, intermolecular Mitsunobu condensation between ketal 151 and the iodated derivative of isovanilin 152 produced the expected ether 153 (76%). This was followed by an intramolecular Heck reaction with Pd(OAc)₂, dppp and Ag₂CO₃ in toluene at 110 °C for 4 h to afford the quaternary carbon-centered benzofuran 154 (90%). After some investigations, it was found that the most efficient way forward involved treatment of the doubly protected aldehyde 154 with 1 M HCl in THF at 60 °C for 2 h which hydrolysed both the acetal and ketal functionalities to afford the ketoaldehyde 155 (86%) which is the key intermediate in the synthesis of (±)-narwedine 156. In an improved protocol, it was discovered that treatment of aldehyde 155 with methylene hydrochloride in the presence of NaBH₄CN in Et₂N and AcOH resulted in formation of a boron complex of narwedine, which was subsequently cleaved with methanesulfonic acid in refluxing 1,4-dioxane to afford the rac-narwedine 156 (48%) for the 2 steps. Finally, reduction of the ketone function of narwedine 156 with L-selectride afforded rac-galanthamine 133 (83%) (Scheme 26).

v) Chemoenzymatic total synthesis of (+)-galanthamine and (+)-narwedine, by Endoma-Arias and Hudlicky: Endoma-Arias and Hudlicky made efficient use of an initial microbial dihydroxylation protocol in their synthesis of (+)-galanthamine 133 starting from phenylethylacetate 157 [33]. E.coli and potassium azodicarboxylate (PAD) were employed for the efficient microbial dihydroxylation of 157 in MeOH/AcOH to afford cyclohexanediol 158 (68%) which was followed by an intermolecular Mitsunobu reaction with 2-bromoisovanilin using Bu₃P and TMAD as reagents in THF to afford ether 159 (87%) as a result of the more reactive allylic alcohol functionality. Then followed an intramolecular Heck reaction of 159 with Pd(OAc)₂, Ag₂CO₃ and dppp under reflux in toluene to produce the tricyclic scaffold 160 (87%). Reductive amination of the free aldehyde group was effected by treatment with methylene hydrochloride and NaBH₃CN after which the amine was protected as the Boc analogue (67%) with TsCl. Hydrolysis of the acetate mixture of diastereomeric acetates 158 with MsCl in Et₃N, (70%) which is a 2:1 ratio of the primary alcohol as the OTs analogue (67%) with TsCl. Removal of the Boc group from the nitrogen with TFA in DCM and evaporation of the solvents was followed by treatment of the residue with K₂CO₃ in EtOH and then heating under reflux lead to formation of epimeric ent-galanthamines 164 (70%) in a 2:1 ratio and favouring the 6-β epimer. Oxidation of the epimeric mixture...
Recent syntheses of Amaryllidaceae alkaloids and isocarbostyrils

Reduction of lactam 171 with NaBH₄ in methanol produced a mixture of compounds, which after MnO₂ oxidation afforded a separable mixture of lactone 172 as the major product (45%), and lactam 173 as the minor product (29%). Treatment of lactone 172 with HF-pyridine in THF removed the TBS group (99%) and N-methylation was chemoselectively performed using KH and Mel in THF to afford the C-6a epimer of (±)-3-O-demethylmacronine 174 (99%). On the other hand, the haemanthidine-based hydroxylactam 173 was treated with TsOH to induce a pivotal rearrangement not yet fully understood to produce the naturally occurring rac-C-6a-stereoisomer of macronine (not illustrated) (48%) and N-methylation in this case had to be effected by a reductive methylation protocol using formaldehyde and sodium cyanoborohydride to ultimately produce (±)-3-O-demethylmacronine 175 (89%) (Scheme 29).

![Scheme 27: Synthesis of (-)-galanthamine 133.](image)

**d) Tazettine-scaffold alkaloids**

1. **Total synthesis of (±)-3-O-demethylmacronine through rearrangement of a haemanthidine alkaloid framework precursor, by Banwell and co-workers:** Banwell and co-workers established an elegant 10-step synthesis of racemic 3-O-demethylmacronine, a tazettine type alkaloid, which embodied the incorporation of a strained lactam scaffold [34]. Suzuki-Miyaura cross-coupling of the known boronate ester 165 with the known cycloalkenyl bromide 166 afforded the desired cyclohexene 167 (83%), which was readily propargylated at the nitrogen atom with 1-bromo-2-butene in the presence of NaH in DMF to give 168 (91%). An intramolecular Alder-ene (IMAE) cyclization catalysed by Pd(OAc)₂ and supported by the powerful σ-donating ligand N,N′-bis(benzylidene)ethylenediamine (BBEDA) under reflux in toluene produced the hexahydroindole 169 (73%). In a most interesting intramolecular cyclisation, the Fukuyama protocol for the removal of the nosylate protection group also encouraged lactamization with the pendant ester to afford the strained lactam 170 (79%). Chemoselective dihydroxylation of the exocyclic double bond under Bäckvall conditions, followed by oxidation with iodosobenzene diacetate gave the equally strained ketoamide 171 (51%) for the two steps (Scheme 28).

2. **Synthesis of rac-pancracine by [3+2] cycloaddition of non-stabilized azomethyne ylides, by Pandey et al.** In this paper by Pandey et al., they describe, without providing full details, their use of a [3+2] cycloaddition of a non-stabilized azomethine ylide (AMY) in a strategy for the synthesis of rac-pancracine which is provided here as an example [35]. The bis TMS amino alcohol 176 was N-alkylated with benzyl iodide 177 in refluxing MeCN in the presence of K₂CO₃, followed by benzylation of the primary alcohol to afford 178 (81%). A Heck coupling of 178 with 8 equivalents of MVK gave enone 179 (60%), which when converted into the azomethine ylide with Ag(I)F in DCM underwent the [3+2] cycloaddition, to smoothly produce the tetracyclic molecule 180 (56%). Upon debenzylation with LiOH/McOH, 180 was converted into its C12 epimeric alcohol (not shown). Conversion of the primary alcohol into the mesylate with MsCl/Et₃N was followed by intramolecular cyclisation under kinetic control using KHMDS to produce the pentacyclic 181 during which stage epimerization had occurred. This compound was converted into the enol triflate by

![Scheme 28: Synthesis of ketamide 171.](image)
treatment with LDA and Commin’s reagent after which final reduction of the latter with Pd(PPh₃)₄ and EtSiH produced the corresponding cyclohexene 182. Finally, following the known procedure, this latter compound was transformed into rac-pancracine 183 to represent a new formal synthesis for this alkaloid (Scheme 30). For another montamine-related synthesis see Scheme 48.

Figure 3: (+)-trans-Dihydrolycoridine 184 and catalyst 185.

Their synthesis commenced with the all-important enantioselective 1,4-Friedel-Crafts (FC) condensation developed by the group between enol 186 and an appropriately protected nitro-olefin 187 in the presence of 5 mol % of the organocatalyst 185 in toluene at 20 °C to produce a 75% yield of the 1,4-FC adduct 188 with a most acceptable 92% ee. To release the aldehyde, 188 was treated with 1M HCl followed by an intramolecular Henry reaction between the nitromethyl carbon and the aldehyde in methanolic sodium hydroxide to afford the nitro alcohol 189 (74% for the 2 steps) as a single diastereomer. The bonds of the three contiguous centres viz C4, C4a and C10b in ring C were all in the thermodynamically more stable equatorial positions. Both hydroxyl groups were protected as their TBS ethers followed by chemoselective hydroxylation, ketone functionality at C2 and C3 of this latter intermediate 192 and thus decided to start from a different nitro-olefin.

To this end, a similar 1,4-FC condensation between 186 and the oxygenated racemic nitro-olefin 193 was undertaken and following the proven analogous protocol employed before, the corresponding coricidine intermediate 194 was obtained. The TBS ether of 194 was selectively deprotected by treatment with catalytic PTS in methanol followed by Swern oxidation to yield the corresponding ketone 195 (68% for the two steps). In order to activate C3 for hydroxylation, ketone 195 was treated with TBSOTf in disopropylethylamine at 0 °C to form the regioselective enol ether 196 (95%). Next followed a highly stereoselective instalment of an acetoxy group at C3 on treatment with phenyliodonium diacetate for a good yield of acetate 197 (69%). NaBH₄ reduction of ketone 197 gave the corresponding C2 β-alcohol as a consequence of axial attack of the hydride. Mesylation of the C2 β-hydroxyl group with methane sulfonyl chloride followed by base-catalysed ring closure ...
afforded epoxide 198 (62% for the 2 steps). Finally, the TIPS protecting group was removed with TBAF and the resulting epoxide was both regio- and stereoselectively hydrolysed with TFA to provide (+)-184 (71% for the 2 steps) (Scheme 32).

ii) Asymmetric cinnamylation of N-tert-butanesulfonyl imines with cinnamyl acetates for the total syntheses of (+)-lycoricidine and (+)-7-deoxypancreatistatin, by Sun and co-workers: In work related to that described earlier in this review, Sun and co-workers recently described a highly diastereoselective palladium catalysed cinnamylamimation of N-tert-butanesulfonyl imines for the synthesis of two related Amaryllidaceae isocarbostyrils [14]. Thus commencing from bromide 199, the Ag₂CO₃ promoted Heck reaction afforded the cinnamyl acetate 200 (68%). This was followed by treatment with a previously prepared (S)-N-tert-butanesulfonyl imine 201 from iodoribose, which underwent a cinnamylamimation followed by a cyclisation sequence the group pioneered to afford the exo-diol 202 in an impressive 91% yield, thereby accomplishing the construction of the B ring of the target alkaloids. Ring C was then formed through a RCM reaction employing the Grubbs-Hoveyda II generation catalyst to actually suppress the loss of the acetonide protecting group. This was achieved by treatment of diol 203 from the toluene solution in 79% yield. Removal of the tert-butanesulfonyl group was achieved (99%) with 4 M HCl in dioxane during which it was necessary to add acetone to suppress the loss of the acetamide protecting group. This was followed by the cis-dihydroxylation of the C1-C2 double bond with potassium osmium tetroxide to afford the exo-diol 204 in an 86% yield with a diastereoselectivity of 13:1. The pivotal intermediate 205 was then generated by treatment of diol 204 with firstly SOCl₂ and then oxidation of the intermediate with RuCl₃/NaIO₄ to give the trans fused lactam 202 as a single diastereomer in an impressive 91% yield, thereby accomplishing the construction of the B ring of the target alkaloids. Ring C was then formed through a RCM reaction employing the Grubbs-Hoveyda II generation catalyst to actually suppress the loss of the acetonide protecting group. This was achieved by treatment of diol 203 from the toluene solution in 79% yield. Removal of the tert-butanesulfonyl group was achieved (99%) with 4 M HCl in dioxane during which it was necessary to add acetone to suppress the loss of the acetamide protecting group. This was followed by the cis-dihydroxylation of the C1-C2 double bond with potassium osmium tetroxide to afford the exo-diol 204 in an 86% yield with a diastereoselectivity of 13:1. The pivotal intermediate 205 was then generated by treatment of diol 204 with firstly SOCl₂ and then oxidation of the intermediate with RuCl₃/NaIO₄ to give the desired cyclic sulfate 205 (67%) (Scheme 33).

From the pivotal intermediate 205, two pathways were developed for further transformations as follows: a) ring opening of the sulfate moiety using n-Bu₄NI at the less hindered C1 position afforded the trans iodo intermediate which underwent an anti-elimination and acid hydrolysis to afford (+)-lycoricidine 206 (48%); b) a similar trans-dialxial ring opening of the cyclic sulfate 205 was effected with sodium benzoate at the C1 position, followed by mild acid hydrolysis to afford benzoate 207 (87%). Hydrolysis of this ester viz., 207 with sodium methoxide in MeOH gave the (+)-7-deoxypancreatistatin 208 (57%) (Scheme 34).

iii) A chiron-based approach to the total synthesis of (+)-lycoricidine, by Shaw and Saidarreddy: Shaw and Saidarreddy developed an efficient synthesis for (+)-lycoricidine 206, a member of the pancratistatin amaryllidaceae isocarbostyril family [37]. Their synthesis began with a Suzuki-Miyaura cross-coupling between boronic acid 209 and the α-iodoeneone 210, the latter being derived from methyl α-D-galactopyranoside, in the presence of Pd/C and Na₂CO₃ in DME to produce the new enone 211 (88%). Dibal-H reduction of the ketone moiety at -78 °C generated the corresponding alcohol (85%) in which the 6-OH was syn to the adjacent 5-Obn of the cyclohexene ring. Mitsunobu reaction of the latter was effected by conversion into the corresponding mesylate with MsCl and then subjecting it to an azidation with Na₂N₃ in DMF to afford the inverted azide 212 (83%). Reduction of the azide moiety to the amine was achieved by treatment with PPh₃, followed by activation with methyl chloroformate and DMAP to provide 213 (78%). A modified Bischler-Napieralski cyclisation with TfO and DMAP in DCM at 0 °C then produced the tetracycle 214 (62%), followed by debenzylation with BCl₃ in DCM at 0 °C to provide the target alkaloid, (+)-lycoricidine 206 (55%) (Scheme 35).

iv) Enantioselective total synthesis of (+)-trans-dihydronarciclasine, by Kádas and co-workers: Kádas and co-workers developed a feasible and reasonably inexpensive synthesis for the biologically active Amaryllidaceae isocarbostyril (+)-trans-dihydronarciclasine 229 [38]. Thus vanillin 215 was iodated with I₂ in an aqueous solution of KI and K₂CO₃ for 3 h to afford the desired 3-iodovanillin (99%), which was hydrolysed with aqueous NaOH in the presence of CuSO₄ to produce aldehyde 216 (64%). Treatment of 216 with CH₂Br₂ in DMF containing K₂CO₃ and CuO afforded myristic aldehyde 217 (94%). The well-known Claisen-Schmidt condensation between 217 and acetone in aqueous NaOH then afforded the butenone 218 (67%). Michael addition between nitromethane and butanone 218 with a selected catalyst 219 gave the pivotal enantiomer (−)-220 (57%, ee > 99%). The interesting Claisen-Henry condensation was then applied to 220 in order to generate the hydroxycyclohexanone 221 (38%), using ethyl formate as the carbon source. It was suggested that the reason a single enantiomer viz., (−)-221 formed, could be ascribed to intramolecular
H-bonding between the adjacent 4-nitro and 3-hydroxy groups. Protection of the ketone group was facilitated by employing ethylene glycol and a catalytic amount of anhydrous oxalic acid in anhydrous MeCN to afford dioxolane (90%). Reduction of the 4-nitro group was achieved using 10% Pd/C and H2 at 80 °C, followed by chemoselective urethane formation on the amine group with methyl chloroformate to give (-)-223 (95%, ee 95%). Release of the ketone at C1 with p-TsOH not only gave the expected ketone, but in addition, a dehydroxylation in ring C occurred and afforded the enone (99%, ee 98%) (Scheme 36).

\[
\text{Scheme 36: Synthesis of narciclasine precursor 224.}
\]

Ultimoto’s reduction of enone 224 afforded the stereoselective alcohol (-)-225 due to axial attack of the hydride coordinated to the Ca+ in 96% yield and ee 99%. It was necessary to invert the orientation of the C1 equatorial OH to the axial position. This was achieved by a Mitsunobu protocol affording benzoate (-)-226 (63%). A stereoselective Sharpless-Upjohn cis-dihydroxylation using N-methylmorpholine N-oxide in the presence of OsO4 gave the anticipated diol (99%), which was protected as its diacetate (99%). Lactam formation was efficiently achieved via the Banwell modification of the Bischler-Napieralski protocol to afford an imine-methoxy intermediate, which upon acidic treatment produced lactam (99% for 2 steps). Removal of the aromatic MeO group was effected with TMS-Cl in the presence of KI in MeCN (54%) and was followed by removal of the three acyl groups by NaOMe in THF to give (+)-229 (99%, ee 92%) (Scheme 37).

v) Total synthesis of (+)-trans-dihydronarciclasine via an asymmetric organocatalytic [3+3]-cycloaddition, by McNulty and co-workers: McNulty and co-workers developed an asymmetric synthesis of (+)-trans-dihydronarciclasine 236 employing an organocatalytic [3+3]-cycloaddition in an effective manner [39]. In this work, a two-carbon aldehyde homologation of the commercially available 5-methoxypiperonal 217 with a suitable Wittig reagent produced the alkenal 218 (82%), which was followed by the pivotal iminium ion- mediated [3+3]-Michael aldol reaction with the Jørgensen catalyst in combination with quinidine to afford the stereochemically desired chiral cycloadduct 230 (58% and ee>99%). Reduction of the azide in the presence of dimethylcarboxylate gave the Moc-protected compound 231 (74%). Dehydration of 231 was effected by mesylation of the OH in DIPEA for 3 h (88%) and was followed by reduction of the ketone to the equatorial alcohol 232 (83%) using Li(tributyl)2AlH in THF at 0 °C. Epoxidation of the olefin proved problematic, but eventually metaCPBA in benzene:dioxane (1:1) in the presence of NaHCO3 afforded a 38% yield of the β-epoxide 233. The epoxide ring was opened with treatment with sodium benzoate and immediately followed by protection as the triacetate (99%, ee 92%) (Scheme 38).

vi) Total synthesis of (+)-pancratistatin by the Rh(III)-catalyzed addition of a functionalized benzamide to a sugar-derived nitroalkene, by Potter and Ellman: Ellman and Potter developed
a remarkable diastereoselective Rh(III)-catalysed C-H bond insertion by a sugar-derived nitroalkene in their 10-step synthesis of (+)-pancratistatin 241 [40]. Their elegant synthesis commenced with the pivotal C-H bond insertion between nitroalkene 237 and amide 238 with a selected Rh(III) catalyst to afford the insertion product 239 (73%, dr > 20:1) [41]. Removal of both the acetonide and silyl groups with aqueous TFA at 50 °C gave the crude furanose imine 240 (66%, dr 10:1). Treatment of this material with Zn/AcOH/H2O at 140 °C in a sealed tube promoted reduction of the nitro group to afford (+)-pancratistatin 241 (45%). The authors suspected that H-bonding could facilitate the crucial transamidation steps and thus as an alternative, they firstly removed the benzyl group under Pd/C- seen as a key starting point in their concise synthesis of (+)-pancratistatin 241 and (+)-7-deoxypancratistatin 253 [44]. The group applied an enantioslective dearrative trans-carboamination of benzene protocol to install the first two vic stereocentres employing MTAD as the nitrogen source coupled with the appropriate aryl Grignard reagent and using Ni(cod)2 as catalyst for the synthesis of the

ii) Chemoenzymatic formal total synthesis of pancratistatin from narciclasine-type compounds via a Myers transposition, by Hudlicky and co-workers: Recently, Lapinskaite et al. published an improved synthesis of (+)-pancratistatin 241 starting from the relatively advanced intermediate 242 [42] which the group had synthesized earlier [43]. Luche reduction of enone 242 afforded the allylic alcohol 243 (75%). This was followed by a modified Myers’ reductive transposition using di-2-nitrophenylcarboxylic acid (DBAD) together with PPh3 and 2-nitro-N-(propan-2-yliide)benzenesulfonylhydroxide (IP-NBSH) which afforded the olefin 244 (64%). All attempts at trans-hydroxylation of the olefinic bond were unsuccessful and thus cis-hydroxylation via the Upjohn method with OsO4 was carried out to provide the corresponding cis-diol 245 (53%). This was readily converted into the easier-to-handle sulfonate 246 (70%) by treatment with sulfonylidimazole (SDI) under basic conditions in THF. Treatment of the sulfonate 246 with ammonium benzoate afforded the desired trans triol (73%) by preferential trans-diastilic attack of the sulfonate 246. After acidic work-up, the triol was converted into its triacetate analogue 247 (80%). Next the Banwell modification of the Bischler-Napieralski ring closure produced lactam 248 (52%), which could be transformed into (+)-pancratistatin 241 in two known steps (Scheme 40).

viii) Synthesis of (+)-pancratistatins via catalytic desymmetrization of benzene, by Sarlah and co-workers: Sarlah and co-workers developed a catalytic desymmetrization of benzene as a key starting point in their concise synthesis of (+)-pancratistatin 241 and (+)-7-deoxypancratistatin 253 [44]. The group applied an enantiosselective dearrative trans-carboamination of benzene protocol to install the first two vic stereocentres employing MTAD as the nitrogen source coupled with the appropriate aryl Grignard reagent and using Ni(cod)2 as catalyst for the synthesis of the


Scheme 40: New variation of the synthesis of (+)-pancratistatin 241 from an advanced intermediate 242.

Scheme 41: Synthesis of (+)-7-deoxypancratistatin 208 and (+)-pancratistatin 241.
pivotal diene intermediate 249, which was obtained on a 10 g scale. Chemoselective epoxidation of the more electron-rich distal alkene with mCPBA and subsequent stereoselective epoxide ring-opening with TsOH in a large excess of water containing hexafluoroisopropanol (HFIP) afforded diol 250 (74%). An Upjohn dihydroxylation of the remaining alkene was effected with OsO₄ and NMO in BuOH/H₂O at 22 °C to produce the important tetrol 251 as a single isomer in 91% yield. It should be noted that at this stage the original benzene ring had been fully functionalized into the pancratistatin core in which all the contiguous stereocentres had been installed.

Removal of the urazole protecting group with LiAlH₄ and Raney-Co under a H₂ atmosphere produced the free amine 252 (60%). Installation of the isocarbostyril framework was effected by initial bromination with Br₂/AcOH followed by NaCo(CO)₄-catalysed carbonylation under a CO atmosphere and UV irradiation and afforded (+)-7-deoxypancratistatin 208 (72% over two steps). In a new and novel C7 arené hydroxylation protocol the group developed, 208 was treated with HMDS and I₂ in MeCN at 80 °C followed by removal of solvent. The residue was then immediately treated with (TMP)₂Cu(CN)₂Li₂ in THF at -78 °C to effect C-7 cupration. Finally hydroxylation with BuO₂H in THF at this 7 position completed the synthesis of (+)-pancratistatin 241 in a 62% yield (Scheme 41).

ix) Miscellaneous: Finally, in this section on pancratistatin syntheses, a paper describing the chemoenzymatic synthesis of triazololactams somewhat structurally related to pancratistatin, by de la Sovera et al. should be noted [45].

g) Phenanthidine-scaffold alkaloids

i) Synthesis of ismine, by Chen and co-workers: Chen and co-workers developed a short and efficient synthesis for the neuroprotective and antifungal Amaryllidaceae alkaloid ismine 257 starting from 2-bromo-4,5-(methylenedioxy) benzoic acid 253 [46]. Conversion to the acid chloride with SOCl₂ followed by treatment with methylamine afforded amide 254 (78%). Coupling between the latter bromo-amide 254 and iodo benzene using a palladium catalyst gave the new lactam 255 (60%). Acid hydrolysis of this lactam afforded the amino acid 256 (75%) which was subsequently reduced by LiAlH₄ to afford the desired ismine 257 (65%) (Scheme 42).

\[
\begin{align*}
\text{MeOH} & \rightarrow \text{NMe} \\
\text{255} & \rightarrow \text{MeOH} \\
\text{256R} = \text{COH} & \rightarrow \text{NMe} \\
\text{257R} = \text{CH}_2\text{OH} & \rightarrow \text{NMe}
\end{align*}
\]

Scheme 42: Synthesis of ismine 257.

ii) Synthesis of phenanthidine skeletal alkaloids, by Fan-Chiang et al.: Fan-Chiang et al. developed a strategy which focused on the phenanthidine scaffold to develop a generalized synthetic protocol for a range of bicolorine type Amaryllidaceae alkaloids [47]. For a recent review on this particular area, see the paper by Rafiee [48]. Thus, in the Fan-Chiang work, cyanation of commercially available bromo aldehyde 98 with sodium azide in CH₂CN containing TIOH afforded an 88% yield of bromo cyanide 258. This compound was in turn converted into the corresponding boronic ester with bispinacolato-diborane in 85% yield, followed by a Suzuki coupling with 1-bromo-2-iodobenzene to form the pivotal bipheny1 intermediate 259 in 67% yield. Cu-catalysed ring closure afforded crinasiadine 260 in 72% yield, which in turn proved to be a most useful general intermediate. Thus, treatment of 260 with Tf₂O in pyridine formed the iminotriflate, which upon hydrogenation with Pd(OAc)₂ and formic acid formed trisphaeridine 261 in 68% yield for the two steps. Finally, efficient methylation of 261 with MeI, coupled with an exchange of the I by Cl afforded bicolorine 262 in 86% yield (Scheme 43).

\[
\begin{align*}
\text{Br} & \rightarrow \text{Me} \\
\text{260} & \rightarrow \text{Me} \\
\text{262} & \rightarrow \text{Me}
\end{align*}
\]

Scheme 43: Synthesis of bicolorine-type alkaloids.

Alternatively, methylation of crinasiadine 260 with MeI and Cs₂CO₃ in THF afforded N-methylcrinasiadine 255 (86%) and reduction of the latter with LiAlH₄ gave the corresponding 5,6-dihydrocrinasiadine 263 (74%). In order to reduce the number of steps for trisphaeridine 261, biaryl 259 was treated with the super hydride, Li(ET₃)BH, which gave 261 in an albeit moderate yield of 58%, but nevertheless did save two steps starting with 98. Further transformations included conversion of bicolorine 262 into either 263 by reduction with LiAlH₄ (78%), or 255 by oxidation with potassium ferricyanide (80%) (Scheme 43).

To shorten the overall number of steps even further, bromomaldehyde 98 was converted into the corresponding boronic ester 264 (95%) under the same Miyaura borylation conditions shown in scheme 43, followed by Suzuki coupling to afford aldehyde 265 (70%) for the two steps [49]. This was followed by the copper-catalysed annulation pioneered by the group to afford the bicolorine 266.
(83%) as the bromide salt, representing the shortest route to the bicolorine and its analogues to date. Finally, 5,6-dihydrobicolorine 263 was prepared through Suzuki coupling between boronic ester 264 and N-methyl-2-iodoaniline, followed by LiAlH₄ reduction in a 67% yield for the two steps (Scheme 44).

The same authors then applied their proven strategies for the synthesis of three further indole alkaloids. Thus Suzuki coupling of boronic ester 264 with bromoindole 267, followed by reduction with LiAlH₄ afforded galanthidine B 271 (74%). On reduction with LiAlH₄ this compound afforded lycosinines A 272 (92%) (Scheme 45).

iii) Copper-catalyzed annulation for the synthesis of phenantrimidine bromides, by Jiang et al.: Jiang et al. in realizing that an efficient and scalable protocol for the synthesis of N-substituted phenantrimidine alkaloids found in Amaryllidaceae plants was lacking to support phamaceutical research efforts, considered a Cu-catalyzed C-N bond formation coupled with a ring closure protocol as an option [49]. The group developed one of the shortest routes to the bicolorine Amaryllidaceae alkaloids. Thus treatment of the general diaryl system 273 with methyl amine in the presence of 5 mol % CuCl₂ in ethylene glycol at 100 °C for 24 h afforded bicolorine 274 (83%, R = H) (Scheme 46). By suitably substituting the bromo aryl ring in the starting material, i.e. the R group, a range of different bicolorines were readily synthesized.

iv) Copper-catalyzed selective ortho-C-H/N-H annulation of benzamides with arynes for the synthesis of phenantrimidine alkaloids, by Zhang et al.: Zhang et al. also interrogated application of copper-catalysed annulation protocols in their rendition of the synthesis of the phenantrimidine Amaryllidaceae alkaloids [50]. Their protocol involved a selective ortho-C-H/N-H annulation. Thus treatment of the amidines 275 and 276 with benzene generated from the Kobayashi benzene precursor shown in Scheme 47 in the presence of Cu(OAc)₂, CsF and TBAI in O₂ at 80 °C, afforded the respective N-protected amides 277 (91%) and 278 (62%) respectively. Simple removal of the nitrogen-protecting group with BB₃ and PhI(TFA)₂ produced phenaglydon 279 (62%) and crinasidane 260 (55%), representing a short and efficient synthetic protocol for these scaffolds (Scheme 47).

v) Rhodium-catalyzed denitrogenative [3+2] cycloaddition providing access to functionalized hydroindolones and the framework of montanine-type alkaloids, by Zhai and co-workers: Zhai and co-workers developed a Rh(II)-catalysed denitrogenative [3+2] cycloaddition protocol to successfully gain rapid entry into the montanine-type Amaryllidaceae alkaloid scaffold [51]. Thus reaction between the sulfonil-1,2,3-triazole 280 with the cyclic dienol TBS ether 281 in the presence of Rh₂(Oct)₃ in dichloroethane at 100 °C for 2 h afforded the aza-[3+2] cycloadduct 282 (80%) (Scheme 48).

Reduction of the ketone moiety with L-selectride in THF at -78 °C gave alcohol 283 (90%), which was followed by a poor yielding reduction of the double bond of the pyrrole ring by NaBH₄CN to yield the trans-octahydroindolone 284 (45%). Oxidation of the secondary alcohol with DMP (78%) was followed by its protection as the ketal 285 (90%). The Ts group was then removed by sodium naphthalide at -78 °C, followed by a Pictet-Spengler cyclisation with formalin to produce the all-important 5,11-methanomorphanthridine-3-one 286 (40% for the two steps), which represents the basic scaffold of the monamine alkaloids (Scheme 48).

vi) Synthesis of phenantrimidine alkaloids via Suzuki-Miyaura cross-coupling, by Tanimori and co-workers: Tanimori and co-workers extended their developed protocol for the synthesis of some new phenantrimidine alkaloids via Suzuki-Miyaura cross-coupling in the following way [52]. Reaction between ester 199 and 2-aminobenzeneboronic acid catalysed by Pd(OAc)₂, (S)-phos and K₂PO₄ in 1,4-dioxane/H₂O at 100 °C for 24 h afforded the Amaryllidaceae alkaloid crinasidane 260 (88%) in a single step which was converted into N-methyl crinasidane 255 (88%) by treatment with Mel/CsCO₃ in THF under reflux. Reduction of lactam 255 with LAH/THF under reflux afforded 5,6-dihydrobicolorine 263 (70%). On the other hand, reaction between
the same boronic acid under the same conditions as for 260, but with aldehyde 98 afforded trisphaeidine 261 (50%) which when subjected to methylation with Mel/acetone under reflux provided bicolorine 287 (71%) (Scheme 49).

![Diagram](image1)

Scheme 49: Synthesis of crinasiadine 260 and bicolorines 263 and 287.

vii) Palladium-catalyzed direct synthesis of phenanthridones from benzamides through tandem N-H/C-H arylation, by Banerji and co-workers: The group of Banerji and co-workers developed a new synthetic protocol for construction of phenanthridones related to the Amaryllidaceae alkaloids requiring no directing group nor external ligand to assist in the reaction [53]. Their protocol involved condensation between the easily accessible benzamides 288 and 289 with 1-bromo-2-iodobenzene in a sealed tube in the presence of Pd(PPh3)2Cl2 as catalyst and CsCO3 in DMF at 140 ℃/N2 for 16 h. It is clear in this instance, that the corresponding regioisomeric phenanthridones 255 and 290, as well as 291 and 292 occurred in a single step. This protocol, not only represents an amazingly short and easy route for the two Amaryllidaceae alkaloids 255 and 291, but also establishes an intriguingly new class of phenanthridone alkaloids viz., 290 and 292, in good yield (Scheme 50).

![Diagram](image2)

Scheme 50: Synthesis of N-methylcrinasiadine 255 and N-isopentylcrinasiadine 291.

viii) Total syntheses of zephycandidine III and lycosinine A, by Banwell and co-workers: Banwell and co-workers, after failing to form the important aryl-aryl bond between two relevant precursors for their synthesis of the two Amaryllidaceae alkaloids zephycandidine III, 298 and lycosinine A 272 via the anticipated Suzuki-Miyaura cross coupling protocol, resorted to the palladium-catalysed Ullmann cross coupling which proved more successful [54]. Thus reduction of aldehyde 293 with sodium borohydride and methylation of the resulting primary alcohol with methyl iodide in DMSO containing KOH, afforded methyl ether 294 (63% for the two steps). Palladium-catalysed Ullmann cross coupling with aldehyde 295 then afforded the pivotal biaryl compound 296 (70%). Reduction of the aldehyde moiety with sodium borohydride in MeOH was followed by reduction of the nitro group under catalytic hydrogenolysis to afford the amino alcohol 297 (86% for the two steps). In order to methylate the primary amine of 297 in the presence of the primary benzylic alcohol moiety, a reductive monomethylation was efficiently performed using a molar equivalent of formaldehyde in the presence of sodium cyanoborohydride to provide zephycandidine 298 (95%) (Scheme 51).

![Diagram](image3)

Scheme 51: Synthesis of zephycandidine 298.

Lycosinine A 302, on the other hand, was prepared by the Suzuki-Miyaura cross coupling protocol. Thus the C7 borylated indole 299 was successfully cross coupled with aryl iodide 300 in the presence of PdCl2(dppf) to afford the biaryl compound 301 (91%). A most interesting reductive methylation of indole 301 using paraformaldehyde and sodium cyanoborohydride was effected. Not only was the indole N-methylated, the 5-membered ring of the indole was also reduced to afford lycosinine A 272 (100%) (Scheme 52).

![Diagram](image4)

Scheme 52: Synthesis of lycosinine A 272.

h) Plicamine-scaffold alkaloids

i) Multicomponent access to indolo[3,3-a,c]-isoquinolin-3,6-diones as a formal synthesis of (+)-plicamine, by Miyangos and Miranda: (+)-Plicamine 303 is a rather novel example of a tetracyclic indolo[3,3-a,c]-isoquinoline scaffold which forms the identifying motif common to the plicamine alkaloids found in many Amaryllidaceae alkaloid families. A multistep solid support synthesis by Ley and co-workers afforded (+)-plicamine 303 (Figure 4) [55-57].

![Diagram](image5)

Figure 4: (+)-Plicamine 303.
Some 10 years later, Mijangos and Miranda developed the Ugi-4CR in their shortened protocol to successfully construct the core indolo[3,3-a]isoquinoline nucleus in an innovative way [58]. In their retrosynthetic analysis, they reasoned that the core nucleus 304 could be derived from the precursor 305, which in turn could be derived from an Ugi-4CR protocol between p-hydroxybenzaldehyde 306, piperonyl amine 307, a carboxylic acid 308 and an isocyanide 309 illustrated in Retrosynthetic Scheme 53.

Scheme 53: Retrosynthetic analysis incorporating the Ugi-4CR for the indoloisoquinoline core.

The proposed route incorporates the possibility of producing a number of analogues since various acids 308 and isocyanates 309 can be incorporated. Thus, optimum conditions derived by the group involved initial reaction between aldehyde 306 and amine 307 to pre-form the corresponding imine after which the respective isocyanide and carboxylic acid were added, followed by heating the resultant mixture in MeOH under microwave conditions at 60 °C. In this way good yields of 305 (for example R1 = tBu; R2 = CH2C6H4- pOMe, 80%) were obtained. The next step in the synthesis involved an intramolecular oxidative de-aromatization phenolic coupling protocol which was most efficiently accomplished by treatment of intermediates 305 with phenylendimine(III)bistrifluoracetate (PIFA) in 2,2,2-trifluoroethanol (2,2,2-TFE) at -25 °C. Cyclisation was rapid and almost quantitative to produce the spirodienone intermediates 310, which had to be immediately isolated due to their instability at low pH (Scheme 54).

Scheme 54: Aza-Michael products 311-anti and 311-syn of spiridienone 310.

In order for the 5-membered lactam ring to be formed for the core indoloisoquinoline scaffold, an intramolecular aza-Michael condensation was required and the quaternary spirocyclic system adjacent to the free rotatting amide R'NH supported this. Thus treatment of 310 (R1 = tBu, R2 = CH2C6H4-OMe) with 1 equivalent of DBU in MeCN at 22 °C for 5 h afforded a 61% yield of 311 (anti: syn = 1 : 5 : 1.0). In order to improve both the yield and selectivity of the protocol, it was found that removal of the solvent following the phenolic coupling of 305 should be followed by the immediate addition of 4 equivalents of DBU in MeCN in a one-pot sequence, which then afforded 311 in a 56% yield.

Finally, the conjugated ketone functional group of precursor 312 (as an example) was chemoselectively reduced under Luche conditions followed by treatment of the crude product with NaH in THF at 0 °C and then with MeI to afford a 60% yield of the endo methyl ethers 313 (d.r. 1.6:1). Fortunately, the desired stereoisomer was the major product formed. Deformylation with methanolic NaOH in a microwave oven promoted hydrolysis at 70°C and gave a 67% yield of the serendipitous thermodynamically favoured diastereomer 314 (d.r. 30:1), which upon alkylation and oxidation to the lactam using conditions developed by Ley and co-workers can be converted into (±)-plicamine 303 (Scheme 55).

Scheme 55: Conversion of precursor 312 into rac-plicamine 303.

i) Mesembrine-scaffold alkaloids

i) Total synthesis of (-)-mesembrine, by Yu and co-workers: Yu and co-workers developed a most efficient synthesis of the Amaryllidaceae alkaloid mesembrine rac-320 by making use of a [5+1] cycloaddition and an (S)-Anthphos ligand-palladium catalysed Buchwald coupling strategy [59]. For a recent review on this particular alkaloid, see the paper authored by Krstenansky [60]. The Yu synthesis started by an S2 displacement of the iodine in 315 by a BocNHMe moiety to afford the corresponding N-Boc analogue 316 (47%). This was followed by the [5+1] cycloaddition protocol involving ring-opening of the cyclopropane by the Rh(I) catalyst to form a transient intermediate which when exposed to CO gas afforded the cyclohexenone 317 (73%). Next the Buchwald coupling between the enone 317 with 0.7 equiv of bromoaryl 319 afforded racemic 319 (68%) with the installation of the all-important quaternary centre being accomplished. Racemic mesembrine 320 was then obtained by treatment of 319 with TFA to remove the Boc and facilitated the intramolecular aza-Michael ring closure in 76% yield. The authors found that by employing Tang’s (S)-Anthphos ligand (20 mol %) in conjunction with Pd(OAc)2 (20 mol %) for the critical Buchwald coupling, they were successful in isolating a 63% yield of chirally pure 319, which upon removal of the Boc group with TFA afforded (-)-mesembrine 320 (73%, ee 86%) (Scheme 56).

Scheme 56: Synthesis of (-)-mesembrine 320.
ii) Total synthesis of (+)-mesembrine by the application of asymmetric gold catalysis, by Czekelius and co-workers: Czekelius and co-workers used an asymmetric gold catalyst in their synthesis of (+)-mesembrine [61]. Their synthesis commenced with the commercially available 4-bromoveratrole 321 which was subjected to an Ullmann cross-coupling reaction with acetylacetone in the presence of CuI as catalyst to afford the expected diketone (43%). This compound was then allylated at the benzyl carbon (74%) and finally transformed into the 1,4-diyne 322 (77%) via the corresponding enol phosphate ester following an adaptation of the Negishi protocol. Chemoselective dihydroxylation (83%) using the Upjohn protocol at the alkene moiety followed by glycol oxidation with NaO4 on silica gel gave the 1,4-diyne aldehyde 323 (97%). Reduction of the aldehyde with NaBH4 afforded the expected primary alcohol (73%), which was followed by a Mitsunobu-type reaction with Boc-p-tosylamide, and by an acid-mediated deprotection of the Boc group to afford the tosyl diyne 324 (87% for the 2 steps). The gold-catalysed enantioselective desymmetrization cyclo-isomerisation protocol developed by the authors was next applied to the tosyl diyne 324 to afford the methylene pyrrolidine 325 (76%, ee 76%). Conversion of pyrrolidine 325 into the acetylide by BuLi, followed by treatment with ethyl chloroformate and chemoselective hydrogenation afforded pyrrolidine 326 (97% for the 2 steps). Removal of the Ts protecting group with sodium naphthalenide lead to the formation of the indole skeleton 327 (97%). At this vital stage, it was necessary to Boc-protect the vinylogous indole 327 in order to recrystallize it from hexane/EtOAc, which increased the ee > 99%. This compound was then transformed into the N-methyl intermediate 328 (97%), before final conjugate alkene reduction with Li/NH3 to give (+)-mesembrine 329 (77%) (Scheme 57).

j) Minor scaffolds

i) Biomimetic total synthesis of the pentacyclic alkaloid derivative Gracilamine by Gao, Banwell and Willis: Gracilamine (Figure 5) 345 is an intricately structured pentacyclic Amaryllidaceae alkaloid isolated from Galanthus gracilis from Turkey and has had its structure confirmed by single crystal x-ray analysis [62].

Banwell and co-workers commenced their synthesis by mesylation of the readily available iodocyclohexene 330 employing the Crossland-Servis protocol to form the corresponding mesylate, which was then treated with sodium azide in DMF to afford iodoazole 331 (83% for the 2 steps) [63]. The latter azide 331 was reduced under Staudinger conditions to the amine, which was then protected as the nosyl amine 332 (82% for 2 steps). Suzuki-Miyaura cross-coupling with the respective aryl borate afforded the aryl cyclohexene intermediate 333 (79%) (Scheme 58).

Scheme 58: Synthesis of hexahydroindole aldehyde 336.

Removal of the N-H proton of 333 with NaH followed by reaction with 1-bromo-2-butene (RX in scheme 58) produced the corresponding 1,6-enzyme 334 (87%). Heating the latter compound in toluene containing Pd(OAc)2 resulted in an intramolecular Alder-ene (IMAE) cyclisation to produce the hexahydroindole 335 (68%). Reduction of the ester group of 335 to the corresponding alcohol, accomplished with DIBAL-H, was followed by Dess-Martin oxidation to afford aldehyde 336 (83%) (Scheme 58). The crucial proof of concept was then undertaken by reaction of aldehyde 336 with ethyl L-leucinate in trimethylamine and MgSO4 at 22 °C to generate the pivotal transitional azomethine ylide 337. This compound was perfectly set up for the thermal [3+2] cycloaddition which was accomplished by heating it in toluene under reflux for
24 h to afford the desired product 338 (36%), together with the inevitable alternative 339 (32%), due to reaction with the exocyclic olefin residue (Scheme 59).

In order for the β-OH group to be introduced into ring E of gracilamine 345, the allylic amine 340 was treated via a similar protocol as illustrated in Schemes 58 and 59 to produce the corresponding analogue 341. Removal of the exocyclic olefinic group was achieved in 3 major steps. Firstly, the exocyclic olefin group was dihydroxylated with OsO₄ and then oxidized to the corresponding ketone 342 with iodosbenzene diacetate (79% for the two steps). Secondly, reduction of the ketone with sodium borohydride in methanol afforded the corresponding β-OH alcohol (89%) which was converted into its xanthate and thirdly this compound was treated under the Barton-McCombie protocol for deoxygenation using tri-n-butyltin hydride to afford the required perhydroindole 343 (68%). Removal of the Ts group on the nitrogen atom was accomplished by treatment with magnesium in MeOH and the resulting amine was then treated with 3 M HCl to cleave the TBS ether to afford the amino alcohol 344 (75% for the 2 steps). Finally, an Eschweiler-Clark reductive amination, using formaldehyde and sodium cyanoborohydride, produced (+)-gracilamine 345 (63%) (Scheme 60).

The group then embarked on a shorter route for the preparation of gracilamine 345 in which pyrone 349 was the starting material prepared in six steps. Microwave heating of pyrone 349 at 170 °C for 12 h facilitated the pyrone Diels-Alder cascade reaction to afford, after treatment on a silica gel column to effect hydrolysis of the vinylos chloride, the enaminone 345 in an amazing 83% yield. After some trial and error it was found that the most efficient way to reduce the olefinic bond was treatment of 345 with SmI₂ activated with HMPA at 23 °C for 10 h to afford the corresponding alcohol, together with reduction of the double bond, as a single unassigned diasteresomer of the C-OH bond but with the correct ring junction configuration. Oxidation of the alcohol using the Salmend protocol effected oxidation of both the alcohol function as well as the benzylic group of the 5-membered ring to give diketone 351 in an overall yield of 20% from 345. Removal of the Teoc group was effected by treatment with TFA and subsequent methylation with Mel and K₂CO₃ afforded the corresponding methyl diketone 352 (85% for the 2 steps). Since other workers had earlier converted diketone 352 into gracilamine 345 in 4 further steps, this synthesis requires only 10 steps from commercially available starting materials (Scheme 62).

Thus, treatment of pyrone 346 with the appropriate amine, displaced the 6-chloro group and was followed by carbobenzoxy protection of the amine under standard conditions to produce pyrone 347 with a tethered olefin at the 3-position. The aromatic moiety at the 3-position can also be changed to the 3,4-OCH₂O-group as well. Pyranone 347 was heated under microwave conditions in toluene to 160°C for 10 h to afford the Diels-Alder adduct which was gratifyingly found to undergo hydrolysis of the vinylos chloride during silica gel chromatography to afford enone 348 (85%). Removal of the Cbz group was effected by

ii) Pyrone Diels-Alder routes to indolines and hydroindolines resulting in the syntheses of gracilamine, mesembrine, and Δ⁷-mesembrone, by Snyder and co-workers: Snyder and co-workers developed an expeditious protocol they described as a “pyrone Diels-Alder route” to gracilamine, mesembrine and Δ⁷-mesembrone [64]. This group also wished to develop key building blocks for the general synthesis of Amaryllidaceae alkaloids. To this end, they developed a protocol from a single starting material viz., 4,6-dichloropyrone 346.

Thus, treatment of pyrone 346 with the appropriate amine, displaced the 6-chloro group and was followed by carbobenzoxy protection of the amine under standard conditions to produce pyrone 347 with a tethered olefin at the 3-position. The aromatic moiety at the 3-position can also be changed to the 3,4-OCH₂O-group as well. Pyranone 347 was heated under microwave conditions in toluene to 160°C for 10 h to afford the Diels-Alder adduct which was gratifyingly found to undergo hydrolysis of the vinylos chloride during silica gel chromatography to afford enone 348 (85%). Removal of the Cbz group was effected by

iii) Formal synthesis of gracilamine using a Rh(I)-catalysed [3+2+1] cycloaddition, by Bose, Yang and Yu: Yu and co-workers employed an intriguing Rh(I)-catalyzed [3+2+1] cycloaddition protocol in a new formal synthesis of the Amaryllidaceae alkaloid gracilamine [65]. Starting from bromide 353, treatment with 1,2 dibromoethane and lithium amide in DME

![Scheme 61: The pyrone Diels-Alder approach to the mesembrines.](image-url)
produced the cyclopropane 354 (71%), which in turn was treated with Dibal-H to give the corresponding aldehyde 355 (92%). A Wittig reaction with methylene triphenyl phosphorane afforded the alkene 356 (97%). Heating the latter alkene 356 with CuCN in DMF under reflux for 18 h gave the corresponding cyano alkene 357 (82%), which was hydrolysed with Dibal-H to the aldehyde 358 (93%) and then subjected to a further Grignard reaction with ethynyl magnesium bromide to produce alcohol (93%) and then subjected to a further Grignard reaction with the alcohol, followed by protection with TBDPSOTf gave 359 (94%), which was protected as its OTBS ether.

Next followed the pivotal Rh(I)-catalysed [3+2+1] cycloaddition protocol with CO at 80 °C and using a 5 mol % catalytic loading which afforded the tetracyclic ketone 360 (59%) after chromatographic separation from the cis diastereomer. LAH reduction of the ketone moiety to the alcohol, followed by protection with TBSCOTf gave 362 (78%) over 2 steps) with a d.r. = 15:7:1 (Scheme 63).

Subsequent hydroboration-oxidation of the vinylic double bond of 362 with 9-BBN afforded primary alcohol, 363 (98%). Catalytic hydrogenation with H2 on 5% Pt/C in toluene reduced the ring-junction double bond to give the syn product (56%) (structure not illustrated), which was followed by acetylation of the primary alcohol to afford acetate 364 (99%). This was subsequently treated with TBAF to chemoselectively remove the TBDPS protecting groups and both secondary alcohol groups were oxidized to the corresponding ketones with Dess-Martin periodanone. Finally, removal of the acetate protecting group afforded the diketo-alcohol 365 (59% for the 2 steps) known as Gao’s intermediate. This was finally converted by known methodology into gracilamine 345 and thus represents a new formal synthesis of this novel pentacyclic biologically active alkaloid (Scheme 64).

On the other hand, the authors’ asymmetric synthesis of gracilamine 345 commenced by oxidation of the previously synthesized alcohol 359 into the corresponding ketone in refluxing ethyl acetate containing IBX, after which the latter ketone was reduced with the (S)-CBS reagent and BH3·Me2S to give the chiral propargyl alcohol (-)-359 with ee 98.2%. Employing essentially similar synthetic protocols, both the cis and trans isomers of gracilamine 345 were synthesized (Scheme 65).

iv) Asymmetric total synthesis of gracilamine, by Zhou and co-workers: Zhou and co-workers very recently reported on a biomimetically based synthetic protocol for the first asymmetric total delivery of (+)-gracilamine 345 from the known rac-oxocrinine 366. Asymmetric hydrogenation of rac-oxocrinine 366 by a known procedure and protection of the resulting alcohol as the TBDPS protected (+)-epivittamine 367 (43%, 93% ee) was accomplished on a gram scale (Scheme 66). Next the (+)-epivittamine 367 was ring-opened by treatment with TrocCl and CHCl3 at 60°C for 3 h to afford (+)-368 (87%) on a 4 g scale. Benzyl ether oxidation was effected with NaClO2 in trichloroethene/H2O at 65°C for 4.5 h to produce the (+)-lactam (70%) (not illustrated) on a 5 g scale. Removal of the Troc group with Zn/NaOH at 0°C afforded the corresponding deprotected (+)-lactam 369 (99%) on a 3 g scale. Treatment of this lactam with NaH to remove the H from the N-H group then facilitated the intramolecular cyclisation to produce the pentacyle 370 (96%) on a 2 g scale which was then carefully reduced with LiAlH4 in THF at 0°C to produce a 4:1 mixture of the diastereomeric alcohols 371 (95%) on a 2.4 g scale. The lactol ring was then opened by treatment with TrocCl in DCM at 22°C to produce the most important intermediate viz., (+)-372 (87%) on a 2.3 g scale.
Condensation between (+)-benzaldehyde 372 and leucine ethyl ester hydrochloride, followed by an intramolecular [3+2] cycloaddition of the resulting imine (similar to Ma’s protocol) [62] afforded the hexacyclic ester (+)-373 (59%) on a 1.3 g scale and as a single isomer. Removal of the Troc group was effected with Zn/AcOH and followed by chemolective methylation of the one pyrrolidine N-atom with LiHMDS and Mel in THF at -78°C to produce the hexacycle (+)-374 (83%) for the two steps on a scale of 0.7-0.9 g.

Finally, removal of the TBDPS protecting group with NH4HF2 in DMF at 50°C for 12 h produced (+)-gracilamine 345 (99%) on a 0.6 g scale to complete the synthesis in an overall 9.9% yield in 11 steps from rac-ofoxocrinine 366 (Scheme 66).

Conclusions: The numerous new papers published in the very recent past (mid 2016 to 2017) dealing with syntheses of Amaryllidaceae alkaloids attests to the real value that these alkaloids possess as biological scaffolds and upon which many new ventures into their use in addressing medical conditions faced in all countries of the world will be conducted. Some groups have furthermore developed scaled up protocols in order to deliver the alkaloids on a gram scale for further in-depth evaluations in order to broaden the scope of evaluation and one cannot fail to wonder what these intriguing alkaloids might one day become famous for. It is also of note that the challenging structures of some of the alkaloids continue to attract the attention of synthetic chemists and will thus continue to foster developments in the area of new synthetic methods. Most of the general scaffold motifs had a reasonable number of syntheses (1-4 papers per topic), while the crinine and galanthamine scaffolds saw slightly more research interest (5-6 manuscripts). The phanthuridine and phananthridone scaffold-based investigations remain very popular with 8 papers on each. It was also very clear that the structural complexity of gracilamine has captured the imagination of a number of research groups and four impressive investigations on the synthesis of this alkaloid were detailed during the 18 month period of the review. It was also noted that relatively few biomimetic protocols have been published during the period of the review and those that have, seem to point to perhaps the future routes which might yet prove to be the most fruitful.

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References


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