GALANTHAMINE

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Abstract. *This review provides a summary of syntheses of galanthamine since 2006, the time of publication of the last major review on this topic. Some landmark syntheses that were reported prior to 2006 are mentioned here as well for completeness. A brief review of biosynthesis of galanthamine is also provided.*

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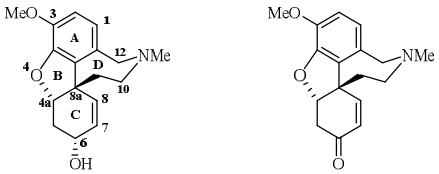
1. Introduction

Galanthamine (**1**), (Figure 1; alternate spelling as galantamine) is an alkaloid belonging to the Amaryllidaceae family that contains several diverse structural types, as shown in Figure 2. The alkaloid was isolated from *Galanthus woronowii*[1] and occurs in several other genera of Amaryllidaceae[2] such as Narcissus (daffodil) and Lycoris, where it occurs to the extent of <2%, along with narciclasine (**3**, see Figure 2). Because of its unique activity as acetylcholine esterase (AChE) inhibitor it serves in the treatment of Alzheimer disease and is marketed as such worldwide. The useful biological activity of galanthamine coupled with its scarcity from natural sources has led to increased interest in approaches to its total synthesis. Several reviews are available that cover the chemistry and pharmacology of this natural product.[3]



galanthamine (**1**) narwedine (**2**)

Figure 1. Structures of galanthamine (**1**) and narwedine (**2**).

Even though a viable synthesis of galanthamine on an industrial scale is available[4] the interest in new approaches continues. The intent of our article will be primarily the discussion of various approaches to total synthesis of galanthamine (**1**) and its immediate precursor, narwedine (**2**) (see Figure 1; carbon numbers as used throughout this chapter are added to the structures). An overview of the biosynthesis of galanthamine is also provided.

2. Biological properties

Because of the activity of galanthamine as an inhibitor of AChE and its potential in the treatment of Alzheimer disease the interest in its derivatives as well as other biological activities continues. A detailed list of additional biological activities, such as moderation of γ-aminobutyric acid (GABA) and glutamate release, has been published.[3a] The clinical use of galanthamine is significant especially in view of its neuroprotective activities.

3. Biosynthesis

As mentioned above, galanthamine (**1**) belongs to the Amaryllidaceae family of natural products that shows a fascinating diversity of different skeletal arrangements. Examples of different sub-groups of Amaryllidaceae alkaloids are displayed in Figure 2. A recent article classifies Amaryllidaceae alkaloids into nine distinct groups: norbelladine, lycorine, homolycorine, crinine, haemanthamine, narciclasine, tazettine, montanine and galanthamine.[5] In addition, narciclasine is sometimes referred to as lycoricidinol.[6] Biosynthetically, all Amaryllidaceae alkaloids are derived from the amino acid tyrosine (**11**) via a series of enzymatic steps. The structural diversity becomes possible by means of a variation of the regiochemistry of the key oxidative aromatic coupling reaction.

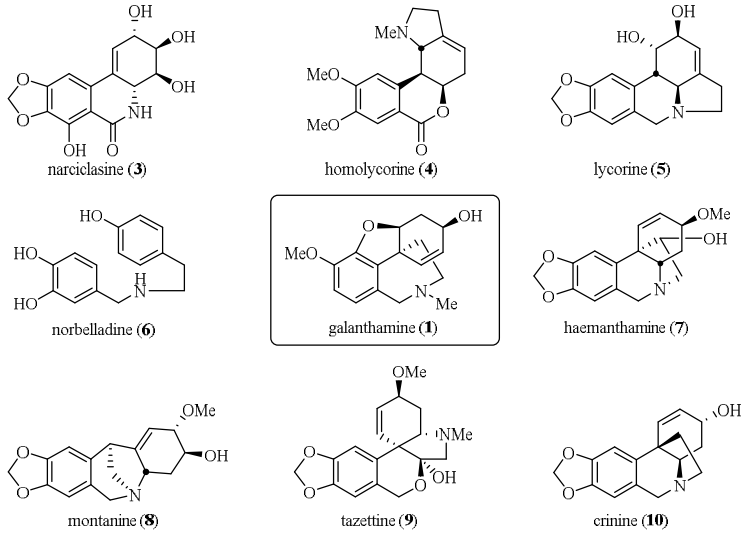
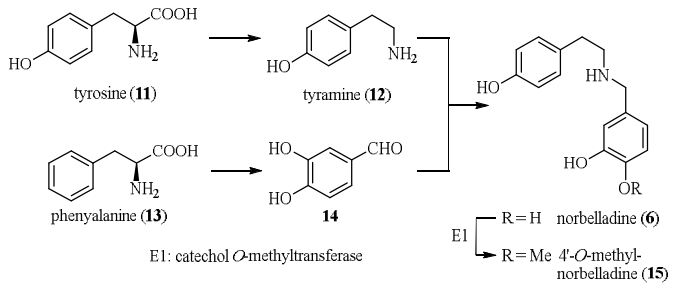


Figure 2. Examples of Amaryllidaceae alkaloids with different carbon skeletons.

The investigation of the biosynthetic pathway leading to galanthamine dates back to the early 1960's when Barton and co-workers suggested that the title compound and structurally related Amaryllidaceae alkaloids are biosynthetically derived from norbelladine (**6**), Scheme 1, via an oxidative coupling reaction.[7] Barton then succeeded in applying an oxidative phenol coupling protocol to the synthesis of racemic galanthamine.[8] This endeavor is briefly discussed in the subsequent section of this chapter. Later, Kirby and Fuganti confirmed these findings in independent studies.[9] Additionally, the addition of ^{13}C-labelled 4'-*O*-methylnorbelladine (**15**) to *Leucojum aestivum* and analysis of metabolic products improved our understanding of the biosynthesis of this important Amaryllidaceae alkaloid.[10] Nevertheless, the exact course of the biosynthetic route towards galanthamine (or other Amaryllidaceae alkaloids) still remains to be elucidated.

The findings discussed above can be summarized as shown in Scheme 1 and Scheme 2. The biosynthetic route commences with tyrosine-decarboxylase catalyzed decarboxylation of tyrosine (Scheme 1). Tyramine (**12**) then reacts with phenylalanine derived aldehyde **14**. The precursor for the oxidative phenol coupling, namely 4'-*O*-methylnorbelladine is obtained after methylation of one of the phenolic hydroxyl groups in secondary amine **6**.

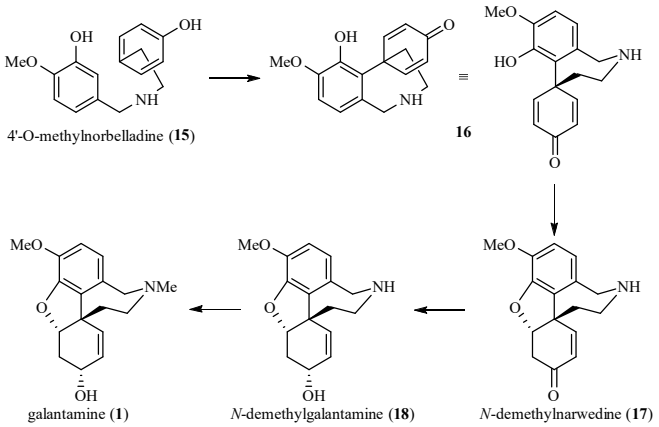


Scheme 1. Biosynthesis of galanthamine – part 1.

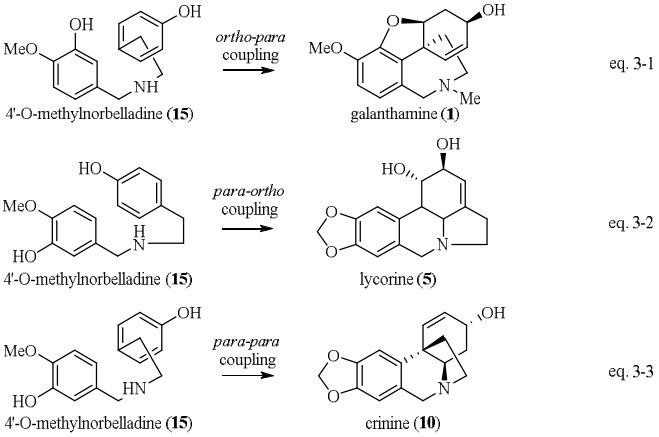
The crucial oxidative coupling reaction between both aromatic rings proceeds in an *ortho-para* fashion as shown in Scheme 2. The reaction, probably catalyzed by a cytochrome P-450 dependent enzyme, delivers a highly reactive dienone (**16**). The phenolic hydroxyl moiety in intermediate **16** then spontaneously undergoes nucleophilic 1,4-addition of the phenolic hydroxyl group onto the enone moiety and benzofuran **17** is obtained. The biosynthesis of galanthamine is completed after reduction of the carbonyl functionality and final N-methylation.

The biosynthesis of Amaryllidaceae alkaloids (and other tyrosine derived natural products) is an impressive example of Nature's ingenuity. Starting from common intermediates, only small variations in the biosynthetic pathway provide access to highly differing secondary metabolites. The point of divergence lies in the nature of the key oxidative phenol coupling reaction. Depending on the regiochemistry of this reaction, a variety of structurally intriguing classes of alkaloids are obtained. Some representative examples in the Amaryllidaceae family are shown in Scheme 3. While the aforementioned *ortho-para* coupling of 4'-*O*-methylnorbelladine (**15**) ultimately results in the biosynthesis of galanthamine (**1**), alkaloids of the lycorine skeleton (**5**) are obtained via *para-ortho* coupling, and alkaloids of the crinine skeleton (**10**) are

accessible via *para-para* oxidative phenol coupling.



Scheme 2. Biosynthesis of galanthamine – part 2.

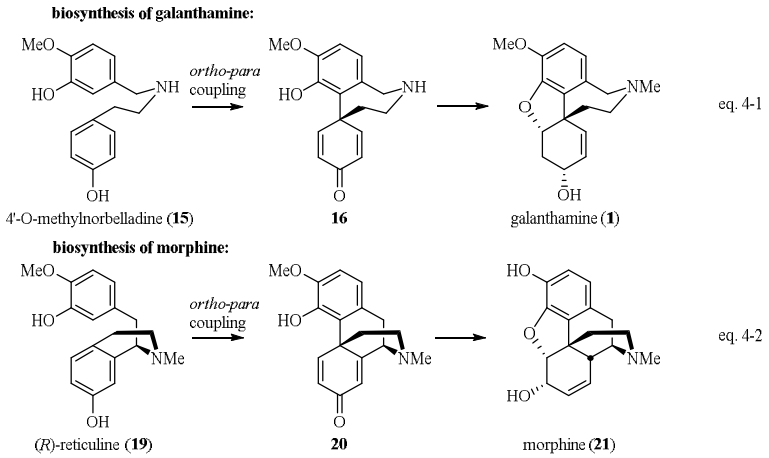


Scheme 3. Oxidative phenolic coupling in the biosynthesis of different Amaryllidaceae alkaloids.

Oxidative phenol coupling reactions also play an important role in the biosynthesis of other tyrosine-derived secondary metabolites. The biosynthesis of morphine and related opioids proceeds in a similar fashion. The requisite dienone **20** is obtained by means of a cytochrome P-450-mediated oxidative *ortho-para* coupling of (*R*)-reticuline (**19**) as shown in Scheme 4.

4. Syntheses

Since the first synthesis of galanthamine by Barton and Kirby in 1960,[8] galanthamine has attracted the attention of the synthetic community. The on-going fascination of this relatively simple, but structurally intriguing spirocyclic natural product is also in no small way related to its promising biological properties, especially its application in the treatment of Alzheimer's disease.



Scheme 4. Comparison of the biosynthesis of galanthamine (**1**) and morphine (**21**).

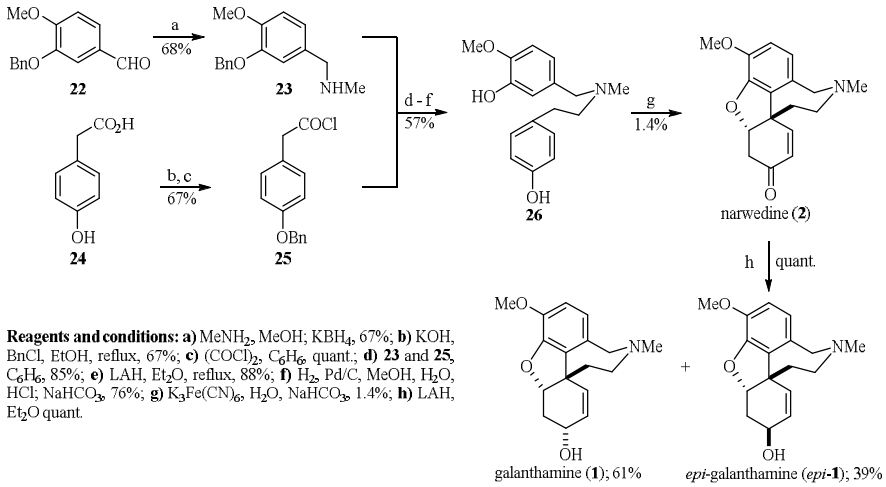
This chapter is divided into two sections. While the first part is devoted to a brief discussion of Barton's seminal biomimetic synthesis of galanthamine, and the development of oxidative coupling protocols, the second part describes in detail efforts that have been published since the last major review article by Marco-Contelles and co-workers, summarizing the syntheses of the title compound.[3a]

4.1. Landmark achievements reported prior to 2006

In 1960, Barton and Kirby published the first total synthesis of (±)-galanthamine.[8] The strategy was based on the assumption that the biosynthetic route toward this class of alkaloids (galanthamine, narwedine, and others) proceeds via an oxidative phenol coupling as the key step. With this seminal disclosure, outlined in Scheme 5, the authors also initiated serious efforts towards the development of protocols for this important synthetic operation. Because of the pioneering nature of this publication and its importance to this field of research, Barton and Kirby's synthesis is included in this chapter.

As outlined in Scheme 5, the synthesis commenced with reductive amination of *O*-benzylisovanillin (**22**), which delivered the secondary amine **23** as precursor of the A-ring of the alkaloid. This material was then reacted with acid chloride **25**, readily accessible from *p*-hydroxyphenylacetic acid (**24**) in a two-step protocol, and **26** was obtained after reduction of the amide and hydrogenolytic cleavage of the benzyl ether.

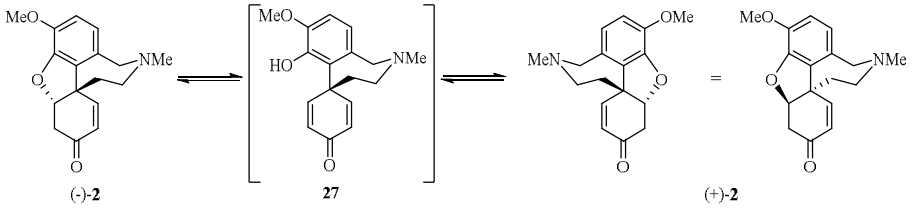
With a short route to tertiary amine **26** at hand, the stage was set to develop conditions for the crucial oxidative phenol coupling reaction to establish the galanthamine skeleton. A variety of different conditions was screened for this key transformation; however, the oxidative protocols applied afforded the desired compound in only minute quantities. Oxidation of **26** with MnO_2 seemed to be the most promising set of conditions to access narwedine (**2**), which nevertheless was isolated in only 0.3% yield. Barton and Kirby also reported the use of potassium ferricyanide, $K_3[Fe(CN)_6]$, and found evidence of narwedine formation via a radiotracer method with ^{14}C labelled material. However, **2** could not be isolated from the complex reaction mixture. Two years later, both researchers reported the successful utilization of potassium ferricyanide and were able to isolate narwedine (**2**) in 1.4% yield.[11]



Scheme 5. Barton and Kirby's synthesis of (±)-galanthamine (**1**).

The first total synthesis of galanthamine was accomplished after reduction of narwedine with lithium aluminum hydride. The natural product was obtained in 61% yield, along with 39% of *epi*-galanthamine. The authors observed the distinct difference of physical properties of the epimers. Galanthamine (**1**) was found to have higher solubility than its epimer (*epi*-**1**) and this was explained by hydrogen bonding of the hydroxyl group in galanthamine (**1**) to the oxygen of the ether ring.

Most syntheses of galanthamine proceed via its direct precursor narwedine. In 1994, Shieh reported (based on the initial finding by Barton)[11] a remarkable spontaneous resolution of racemic narwedine.[12] When treated with catalytic amounts of optically pure narwedine (only few seed crystals are required to initiate the resolution), enantiomerically enriched narwedine is obtained after several hours of equilibration time. The transformation, outlined in Scheme 6, proceeds via a retro-Michael intermediate **27**. The intermediary formed dienone **27** subsequently cyclizes to form the enantiomerically enriched material in an autocatalytic fashion. Interestingly, the chiral resolution also proceeds when seed crystals of galanthamine are added to the reaction mixture.

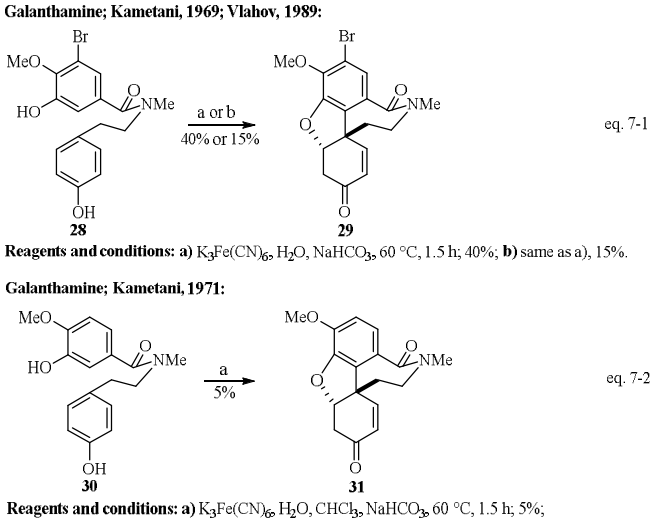


Scheme 6. Autocatalytic resolution of narwedine.

This remarkable protocol is well suited for large scale applications and decreases the overall costs of synthetic galanthamine as racemic routes can be employed in the preparation of enantiomerically pure galanthamine. Jordis and Fröhlich took advantage of this autocatalytic resolution technique and employed

the reaction in their multi-kilogram scale route to the Amaryllidaceae alkaloid.[4]

Following the seminal reports by Barton and co-workers, a lot of attention was devoted to the development of efficient protocols for oxidative coupling reactions. In 1969, Kametani reported the use of $K_3[Fe(CN)_6]$ as oxidant in the key step (eq. 7-1, Scheme 7).[13] In analogy to previous syntheses of morphine,[14] the *para* position at the aromatic ring was blocked by a bromine to force the coupling reaction to proceed at the desired *ortho* position. Additionally, the substrate did not contain a basic nitrogen as Franck[15] and Abramovitch[16] reported that the presence of the basic nitrogen atoms decrease the yield in oxidative coupling reactions. Kametani reported an impressive 40% yield in the oxidative coupling reaction. However, this result could not be confirmed by other groups and upon carrying out the same reaction with the identical substrate, Vlahov was able to isolate only 15% of **29** from the reaction mixture.[17] However, despite these discrepancies, the modifications developed by Kametani provided for a significant progress in this important area. A few years after his initial report, he was also able to show the importance of the bromine on the aromatic ring, as the substrate lacking the halide (**30**) provided the desired product in drastically reduced yield (eq. 7-2, Scheme 7).[18]



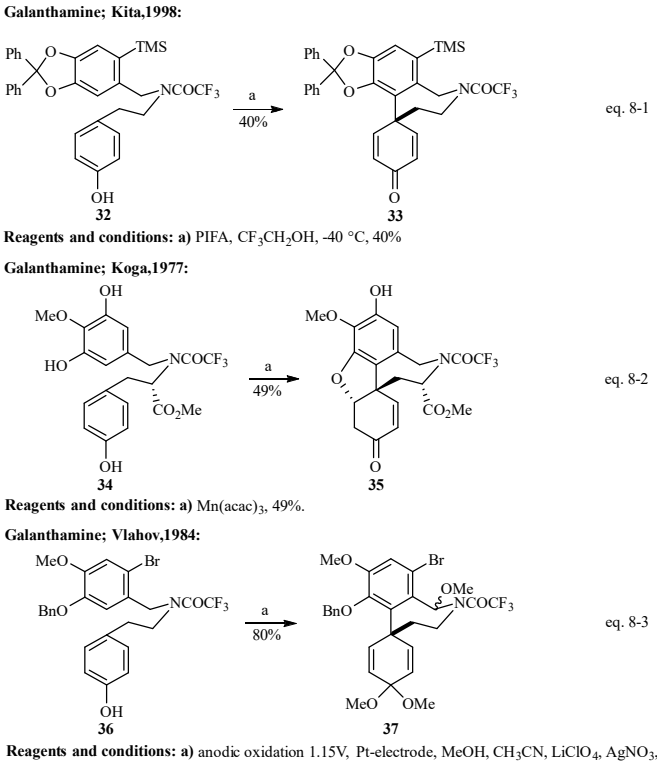
Scheme 7. Oxidative coupling reactions to establish the galanthamine skeleton – part 1.

Hypervalent iodine species, such as phenyliodine(III) bis(trifluoroacetate) (PIFA), were shown to be effective oxidants which delivered the product in 40% yield (eq. 8-1, Scheme 8).[19] The authors mentioned the importance of the fluorinated solvent as the reaction did not proceed in either benzene or dichloromethane. The oxidative protocol with hypervalent iodine was also used by Kita and Schlenk in the preparation of other Amaryllidaceae alkaloids.

Koga reported the first enantioselective total synthesis of galanthamine.[20] The key oxidative phenol coupling was achieved upon addition of an excess of $Mn(acac)_3$ to chiral ester **34** in acetonitrile (eq. 8-2, Scheme 8). The authors reported excellent 49% yield for this crucial transformation.

In 1984, Vlahov also reported the application of an electrochemical method for the oxidative phenol

coupling reaction.[21] Again, the bromide on **36** served to block the more active *para* position of the A-ring of the alkaloid. The anodic oxidation was carried out in acetonitrile, with small amounts of methanol and lithium perchlorate as the electrolyte, and yielded adduct **37** in excellent 80% yield.



Scheme 8. Oxidative coupling reactions to establish the galanthamine skeleton – part 2.

Other developments in the oxidative coupling were reported over the years primarily in connection with approaches to morphine. In 1963, Barton published a route towards morphine which, in analogy to his contribution to galanthamine, featured an oxidative phenolic coupling as the key step.[22] In this study, MnO_2 was used to trigger the cyclization and the desired product was obtained in marginal 0.012%. A few years later, Schwartz employed $Tl(TFA)_3$ as the oxidizing agent[23] and achieved a 23% yield in the oxidative coupling reaction. In another study by this group, published in 1988, $PhI(OAc)_2$ was used and the isolated yield of the coupling adduct reached 25%.[24] Also, $VO(acac)_2$ was used as oxidizing reagent in phenol coupling reactions. In 1969, Holton and Schwartz were able to obtain satisfying 76% yield for the desired coupled adduct and a more recent report outlined the potential of $VO(acac)_2$ for the coupling of 2-naphthols and phenols in excellent 90% yield.[25]

4.2. Recent syntheses of galanthamine

The main intent of this book chapter is the focus on the detailed discussion of recent syntheses of

galanthamine. The following section summarizes total synthetic efforts towards this important Amaryllidaceae alkaloid that have been published since the last major review on this topic was published by Marco-Contelles and co-workers in 2006.[3a]

As evidenced by the numerous scientific contributions in this area, the interest in galanthamine did not wane over the past few decades. On the contrary, especially in the last few years, the alkaloid received increased attention from the synthetic community. Since 2006, several total syntheses have been reported, and numerous partial synthetic efforts have been published, leading to more or less complex sub-structures of the natural product. Additionally, a great number of research groups succeeded in the preparation and biological evaluation of structural analogs and derivatives of galanthamine with the ultimate goal to improve on the biological profile of the natural product, which is currently in use as medication against Alzheimer's disease.

In order to allow the reader to efficiently compare the different strategies towards galanthamine, all syntheses discussed within this section are briefly outlined in a retrosynthetic fashion, showing the most important operations. This brief outline is then followed by a detailed discussion of all syntheses published in the reporting period.

The first synthesis discussed below was published by Chida in 2007.[26] The route, retrosynthetically outlined in Scheme 9, commenced with the conversion of glucose to chiral cyclohexanone **41** via a Ferrier carbocyclization reaction. A subsequent Grignard reaction then connected enone **41** with the aromatic portion of the alkaloid. The crucial all-carbon quaternary center was established in a stereoselective fashion by means of a [3,3]-sigmatropic rearrangement.

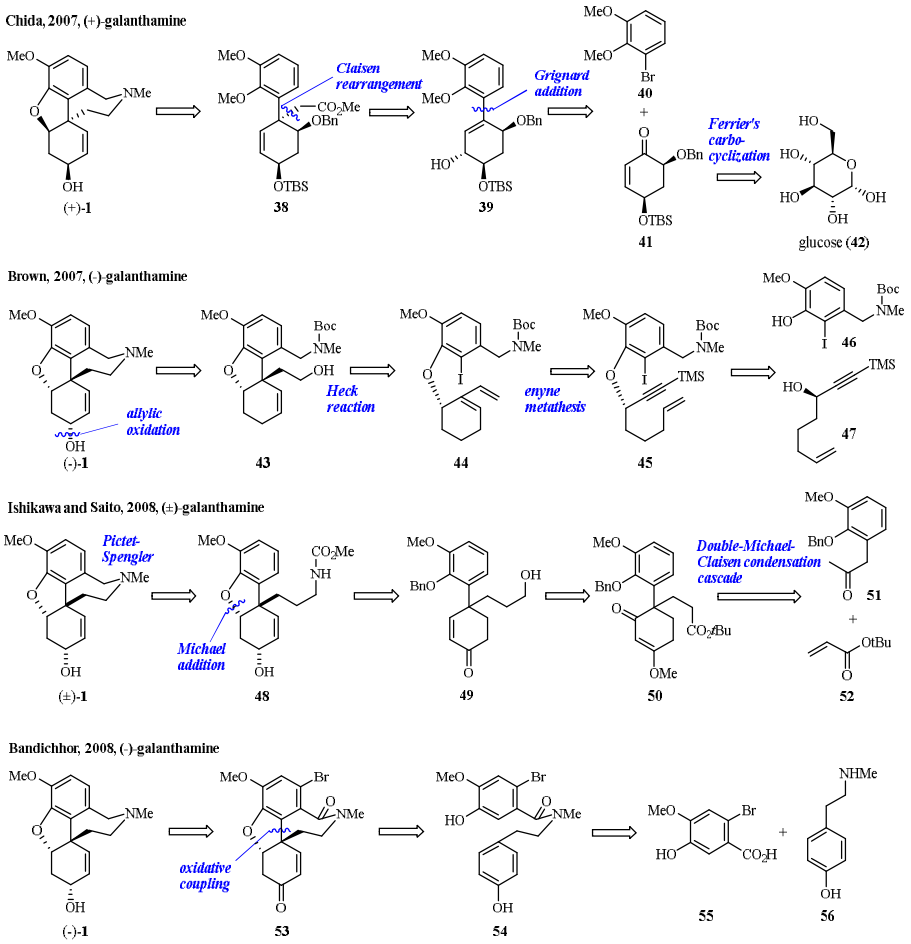
In the same year, also Brown reported a route towards (–)-galanthamine (Scheme 9).[27] The route featured an enyne-metathesis reaction as key step to elaborate the C-ring and to simultaneously provide a side chain which was elaborated into the heterocyclic D-ring of galanthamine. Allylic oxidation and the installation of the secondary allylic alcohol concluded the synthesis of the title compound.

Ishikawa and Saito completed their racemic synthesis of the title Amaryllidaceae alkaloid in 2008 that featured a double-Michael-Claisen condensation cascade reaction as the key step to deliver advanced intermediate **50** (Scheme 9).[28] The benzofuran moiety was then elaborated via a Michael reaction. A late-stage Pictet-Spengler reaction concluded the synthesis of the natural product.

Bandicchor and co-workers route was based on the application of an oxidative phenol coupling as key step (Scheme 9).[29] Chirality was introduced by means of a resolution of an advanced intermediate.

Another route that started with aromatic precursors was reported by Magnus in 2009 (Scheme 10).[30] This route toward racemic narwedine takes advantage of the previously mentioned spontaneous resolution of narwedine (see Scheme 6)[11-12] and thus constitutes a formal synthesis of (–)-galanthamine. The synthesis features a phenol alkylation as the key step for the elaboration of the all-carbon quaternary center and a Suzuki coupling to link the A-ring with the C-ring of the alkaloid.

Banwell reported several syntheses of the Amaryllidaceae alkaloid. His first synthesis of (+)-galanthamine took advantage of biocatalytically generated *cis*-cyclohexadiene diol **64** as the homochiral starting material (Scheme 10).[31] The route, also shown in Scheme 10, was based on the application of an Eschenmoser-Claisen reaction to establish the crucial quaternary center.

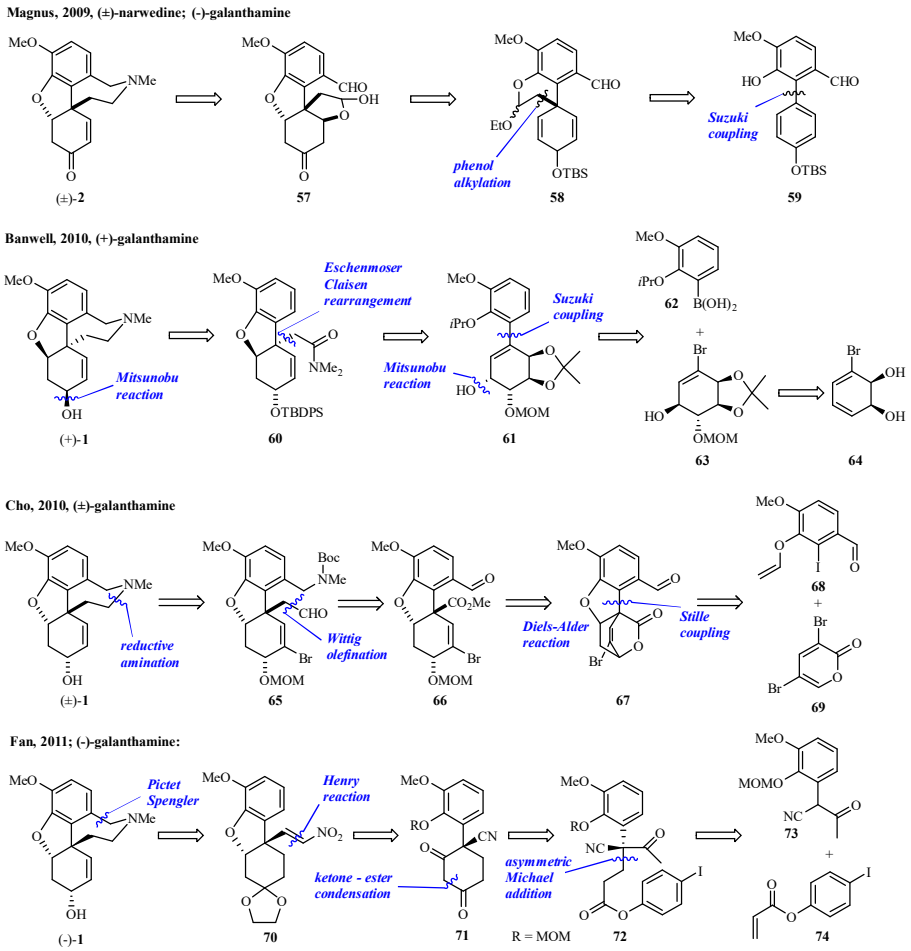


Scheme 9. Retrosynthetic analysis of recent routes towards galanthamine – part 1.

In 2010, Cho published a synthesis of racemic galanthamine (Scheme 10).[32] In this effort, the nitrogen-containing heterocycle was closed as the last major operation by means of a reductive amination. The requisite starting material for this reaction was obtained via Wittig olefination of the aldehyde in substrate **65**. Key steps in the preparation of this material were a Diels-Alder reaction and a Stille coupling to link aromatic precursor **68** with pyrone **69**.

Fan reported a synthesis of (–)-galanthamine in 2011 (Scheme 10). The route featured an asymmetric Michael addition as key step. Chiral intermediate **72** was then employed in a ketone-ester-condensation reaction to deliver **71**. Closure of the D-ring was achieved by means of a Pictet Spengler reaction.

Xie and Zhou reported completed a synthesis of (–)-galanthamine in 2012 (Scheme 11).[33] The authors planned a Pictet-Spengler reaction as one of the final key steps for the elaboration of the nitrogen heterocycle in the natural product. The precursor for this transformation was envisaged to be accessed via a reductive Heck cyclization of readily available unsaturated ester **77**.



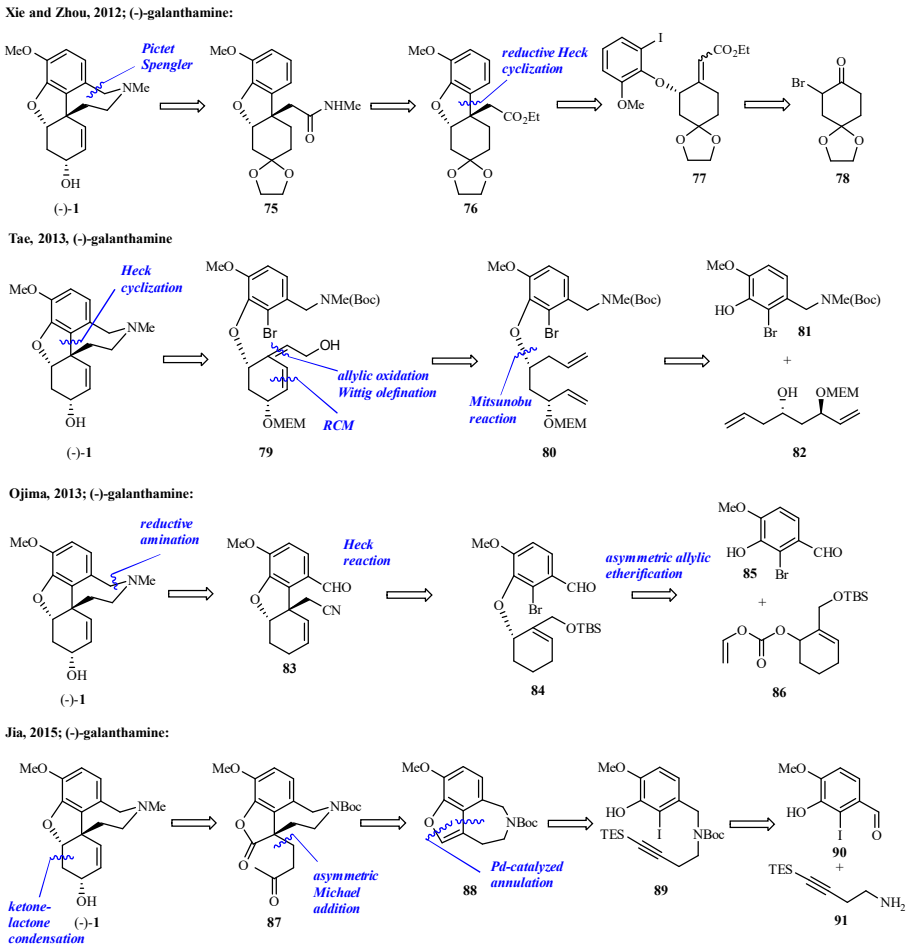
Scheme 10. Retrosynthetic analysis of recent routes towards galanthamine – part 2.

Tae's route is based on the utilization of a ring-closing-metathesis (RCM) reaction as key step for the elaboration of the C-ring of the (–)-galanthamine (Scheme 11).[34] Thus, the preparation of alkene **80** was envisaged which could be accomplished via a Mitsunobu reaction of phenol **81** and optically pure secondary alcohol **82**. The aforementioned RCM reaction then delivered intermediate **79** after allylic oxidation and Wittig olefination of the intermediary formed ketone. A Heck reaction then concluded the synthesis of the natural product.

Ojima accomplished a formal synthesis of (–)-galanthamine in 2013, Scheme 11.[35] The authors envisaged the preparation of advanced intermediate **83** which has previously been reported by Trost and co-workers.[36] The asymmetric reaction of **85** and **86** constitutes the key step on route to substrate **83**.

A rather unique route towards (–)-galanthamine was published by Jia in 2015, Scheme 11.[37] The synthetic strategy envisaged the construction of the C-ring at a late-stage via an asymmetric ketone-lactone condensation reaction. The substrate for this final operation was prepared by means of a Pd-catalyzed

annulation reaction of readily available alkyne **89**.



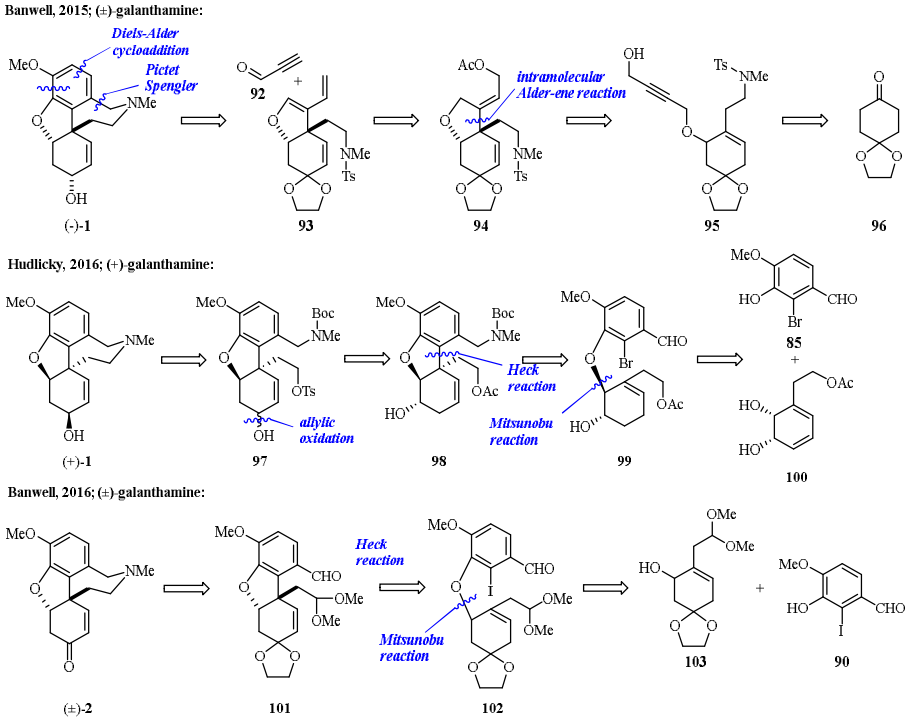
Scheme 11. Retrosynthetic analysis of recent routes towards galanthamine – part 3.

In 2015, Banwell reported his second synthesis of racemic galanthamine (Scheme 12). This route somehow seems to be the counterpart of Jia's efforts as the Australian group devised a plan for the *de-novo* construction of the aromatic A-ring of the Amaryllidaceae alkaloid via a Diels-Alder reaction between advanced intermediate **93** and propynal (**92**).[38] Diene **93** was envisaged to become accessible from tetrahydrofuran **94**, which was prepared from alkyne **95**. Commercially available achiral ketone **96** served as starting material for the synthesis of galanthamine.

Hudlicky described a route to the enantiomer of the natural product from phenethyl acetate, which was converted into optically pure cyclohexadiene diol **100** by the whole cell oxidation with a recombinant microorganism expressing toluene dioxygenase (Scheme 12).[39] Key steps include the connection of the A- and C-ring by means of a Mitsunobu reaction, and the application of a Heck reaction to establish the

quaternary center.

So far the latest contribution to the field was reported by the research group of Banwell, who reported his third synthesis of racemic galanthamine in 2016, Scheme 12.[40] The eleven-step procedure started with the reaction of phenol **90** with the allylic alcohol **103**. A Heck reaction then served to close the B-ring of the alkaloid and the synthesis was completed with a reductive amination reaction.

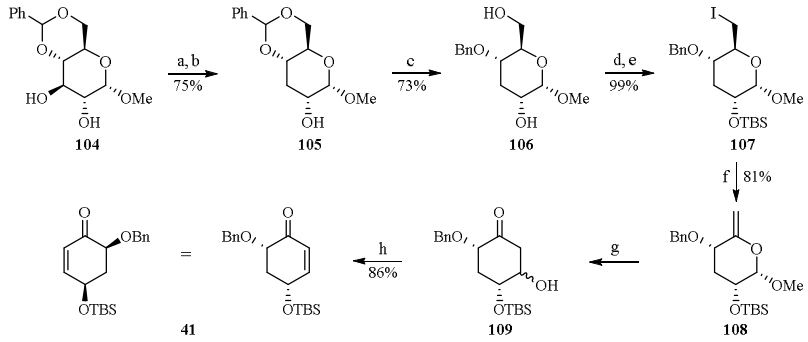


Scheme 12. Retrosynthetic analysis of recent routes towards galanthamine – part 4.

In 2007, Chida reported the synthesis of (+)-galanthamine from D-glucose.[26] A year before this synthesis of the Amaryllidaceae alkaloid was published, the route depicted in Scheme 13 was utilized for the preparation of actinobolin, a compound with pronounced antibacterial and anti-cancer properties.[41] A little later, the very same intermediate, enone **41** was also successfully employed in the enantioselective preparation of morphine.[42]

The route toward this highly versatile chiral intermediate commenced from commercially available 4,6-*O*-benzylidene-α-D-glucopyranoside **104** as shown in Scheme 13. Tosylation of the C-3-oxygen and subsequent exposure to lithium aluminum hydride afforded **105** in good yield. Reductive cleavage of acetal **105** and installation of the iodine at C-6 under Appel condition with subsequent silylation of the remaining C-2 hydroxy moiety then provided **107**. This material was exposed to basic conditions and endopyranoside **108** was obtained in good yield to serve as starting material for a catalytic Ferrier's carbocyclization reaction. Elimination of the resulting secondary alcohol via a standard two-step protocol then concluded the

route to chiral key-intermediate **41**.



Reagents and conditions: a) TsCl, py; **b)** $LiAlH_4$, THF, 75% (2 steps); **c)** DIBAL-H, toluene, 73%; **d)** I_2, PPh_3, ImH, 99%; **e)** TBSCl, ImH, DMF, quant.; **f)** *t*-BuOK, THF, 81%; **g)** $Hg(OCOCF_3)_2$ (30 mol%), acetone, acetate buffer (pH 4.8); **h)** MsCl, NEt_3, CH_2Cl_2, 0 °C, 86% (2 steps).

Scheme 13. Chida's synthesis of galanthamine – part 1.

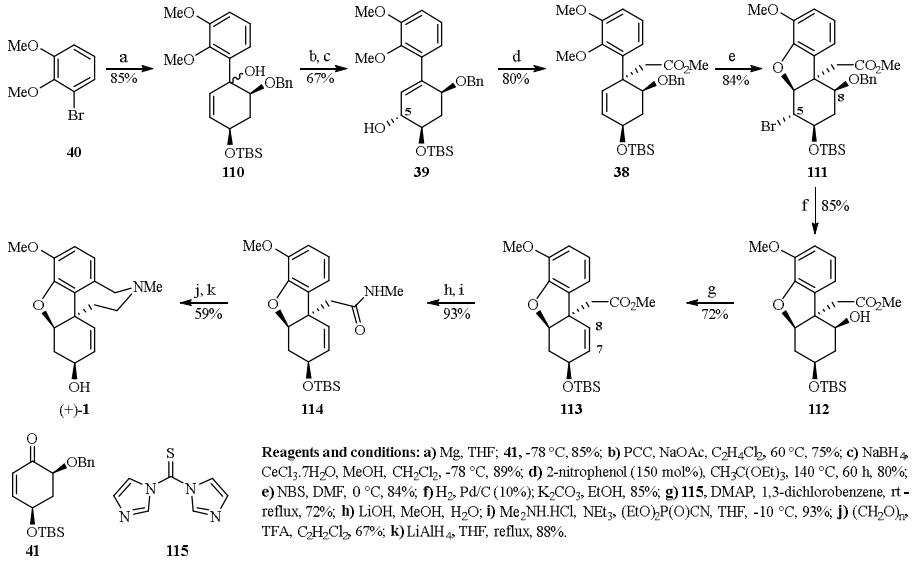
With substantial amounts of enone **41** in hand, the stage was set for the elaboration of the galanthamine skeleton. Addition of 2,3-dimethoxyphenylmagnesium bromide to enone **41** at low temperature smoothly afforded 1,2-adduct **110** as a mixture of diastereomers as outlined in Scheme 14. Addition of pyridinium chlorochromate (PCC) to enol **110** then allowed the isolation of the corresponding cyclohexanone with the carbonyl at C5. Reduction of the enone moiety under Luche conditions mainly afforded unsaturated secondary alcohol **39** with the correct stereochemical configuration of the hydroxy moiety for the subsequent key Claisen rearrangement.

When heated with triethyl orthoacetate (in the presence of 2-nitrophenol as acid catalyst) to 140 °C in a sealed tube, **39** underwent the desired Johnson-Claisen rearrangement and stereoselectively afforded ester **38** in satisfying yield. It seems worthy of mentioning that the pK_a of the acid catalyst was of crucial importance for the outcome of the reaction. The commonly used propionic acid was too acidic (pK_a of 4.62) which triggered decomposition of the substrate, while the use of the less acidic 2-nitrophenol (pK_a of 7.04) catalyzed the formation of the required ketene acetal and allowed the isolation of 80% of ester **38** after 60 hours of reaction time.

Next, the installation of the benzofuran moiety was accomplished by treatment of alkene **38** with *N*-bromosuccinimide (NBS), which resulted in the formation of bromobenzofuran **111** in 84% isolated yield. A similar approach for the installation of the benzofuran moiety has previously been reported by Mulzer and co-workers in their synthesis of morphine.[43] The material thus obtained was then hydrogenated to simultaneously remove the halide at C-5 and to cleave the benzyl group at C-8. This two-step one-pot procedure was best achieved when the reaction was initiated under neutral conditions that are required to efficiently affect the O-debenzylation. As soon as this was accomplished, potassium carbonate was added to the reaction flask as this was required for a fast cleavage of the halide in the substrate. Elimination of the C-8 hydroxyl moiety and concomitant formation of the C-7–C-8 double bond then allowed the isolation of the advanced intermediate **113** in good yield.

The final task was the installation of the B-ring of the natural product. This reaction sequence started with the conversion of the methyl ester **113** to the corresponding methyl amide. Amide **114** was then exposed to Pictet-Spengler conditions, which allowed the isolation of the desired tetracyclic material that was converted to (–)-galanthamine (**1**) via reduction of the intermediary formed amide functionality with lithium aluminum hydride.

Chida and co-workers presented an interesting route to the natural product with a highly efficient [3,3]-sigmatropic rearrangement as the key step. The authors were able to utilize inexpensive and readily available glucose as chiral pool starting material for the preparation and achieved a competitive overall yield of 4.9% in 19 synthetic steps. The only drawback of the route is the somehow lengthy conversion of glucose into the commonly used building block **41**.



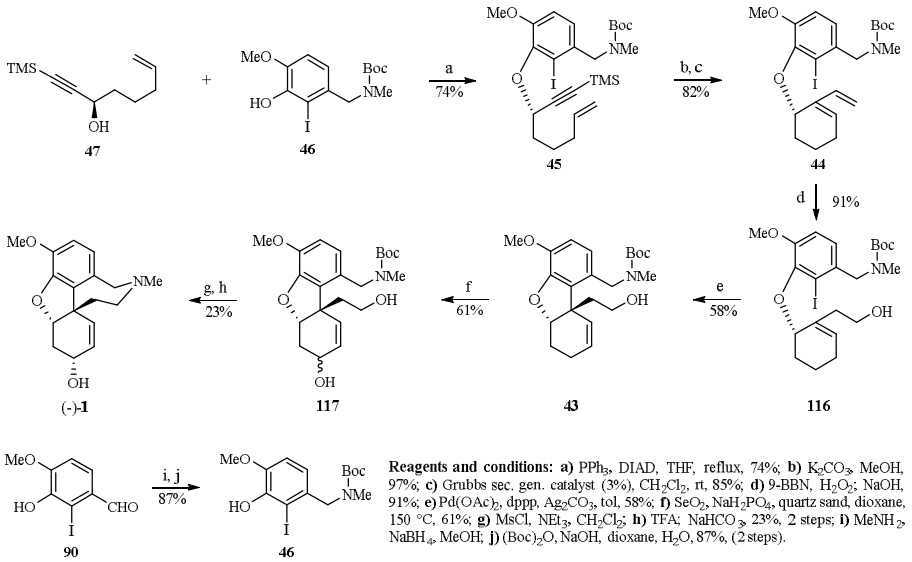
Scheme 14. Chida's synthesis of galanthamine – part 2.

Brown and co-workers reported a synthesis of (–)-galanthamine in 2007.[27] The route, outlined in Scheme 15, featured an enyne-metathesis as key step and commenced with the reaction of the enantiomerically enriched propargylic alcohol **47** with phenol **46** under Mitsunobu conditions. Next, the key enyne metathesis reaction was performed. Cleavage of the TMS group under basic conditions and exposure of the corresponding terminal alkyne to the Grubbs first generation catalyst allowed the isolation of **44** in good yield.

With substantial amounts of advanced intermediate **44** in hand, Brown could prepare the compound for the formation of the nitrogen heterocycle. Selective hydroboration and oxidation of the terminal double bond yielded primary alcohol **116**, which was subjected to Heck reaction conditions, producing the tricyclic intermediate **43**. Reaction with selenium dioxide using conditions previously employed by Trost and co-workers[36] then delivered the allylic alcohol **117** as 4.8:1 mixture of diastereomers, favoring the desired isomer. Mesylation of the primary alcohol and spontaneous closure of the 7-membered heterocyclic ring

completed the synthesis of galanthamine.

Brown was able to access the natural product in eleven linear steps and provided a beautiful example of the synthetic versatility of the enyne metathesis reaction, which established the C-ring of galanthamine and furthermore provided the side chain required for the elaboration of the nitrogen-containing ring of the natural product.

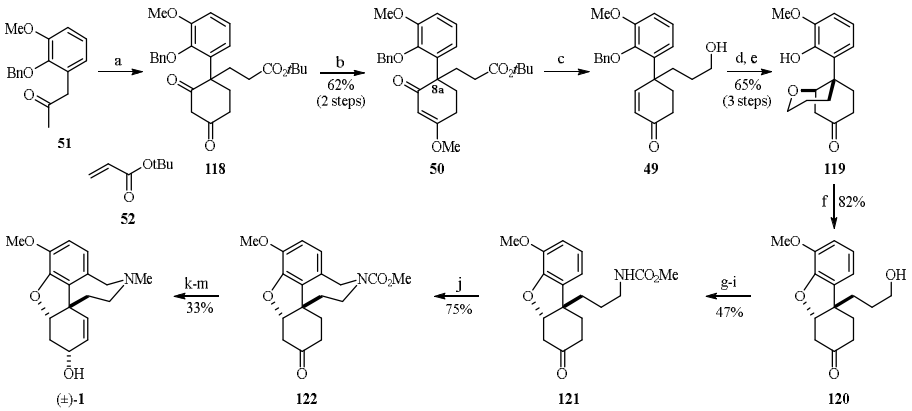


Scheme 15. Brown's synthesis of (–)-galanthamine.

In the early 2000s, Ishikawa and Saito developed a domino Michael-Claisen cyclization reaction.[44] A few years later, the authors reported the application of this reaction cascade in the total synthesis of members of different classes of alkaloids. Ishikawa and Saito's route to the title alkaloid is outlined below.[28]

As shown in Scheme 16, the synthetic route was initiated with the above-mentioned domino Michael-Claisen cyclization reaction. Reaction of commercially available ketone **51** with acrylic acid ester **52** in the presence of *tert*-butoxide delivered intermediate **118**, which then afforded **50** upon reaction with TMSCl in methanol. With this cascade reaction the authors not only established the C-ring of the natural product, but also installed the quaternary carbon (C-8a) in **50**, which was obtained in an impressive 62% yield.

Next, the authors intended to elaborate the benzofuran moiety of the title compound. Reduction of the ester in **50** with DIBAL-H afforded primary alcohol **49**. As the synthetic plan required debenzylation at this point, the enone had to be protected. Reaction of **49** with TsOH triggered an oxy-Michael addition reaction, protecting the double bond and allowing the required debenzylation to proceed smoothly, affording ketone **119** in good yield. With this material in hand, the stage was set for the envisaged closure of the benzofuran ring of galanthamine. Exposure of **119** to $MgCl_2$ resulted in the desired retro-Michael reaction, re-establishing the enone, which subsequently underwent a conjugate addition by the phenolic hydroxyl group, establishing the heterocyclic benzofuran moiety in **120** as present in the natural product.



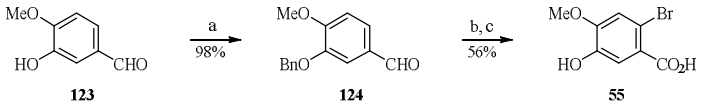
Reagents and conditions: a) **52**, *t*BuOK, tBuOH, THF, 0 °C - rt; **b)** MeOH, TMSCl, rt, 62% (2 steps); **c)** DIBAL-H, PhMe, -78 °C; **d)** TsOH, THF, rt; **e)** Pd/C, MeOH, rt, 65% (3 steps); **f)** $MgCl_2$, THF, 50 °C, 2 d, 82%; **g)** SO_3•py, DMSO, DCM, 74%; **h)** $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*BuOH, 80%; **i)** DPPA, Et_3N, PhMe, reflux, 80%; **j)** $(CH_2O)_n$, TFA, DCE, 60 °C, 75%; **k)** TBDMSOTf, Et_3N, DCM; **l)** $Pd(OAc)_2$, *p*-benzoquinone, MeCN, rt, 2 d, 66% (2 steps); **m)** L-Selectride, THF; LAH, 50%.

Scheme 16. Ishikawa and Saito's synthesis of (±)-galanthamine.

After having established the benzofuran motif of the Amaryllidaceae alkaloid, Ishikawa and Saito turned their attention to the elaboration of the D-ring of galanthamine. Now, the great advantage of the key strategy becomes even more obvious as the side-chain introduced in the key domino Michael-Claisen cyclization reaction could be smoothly converted to the heterocyclic D-ring. Oxidation of the primary alcohol in **120**, followed by a Curtius rearrangement of the intermediary formed azide allowed the isolation of carbamate **121** in good overall yield. Next, the heterocyclic ring was closed by means of a Pictet-Spengler reaction. The final steps towards galanthamine included silyl ether formation, Pd-mediated oxidation of the silyl enol ether to the corresponding enone, and concomitant reduction of the enone and the carbamate moiety.

In summary, Ishikawa and Saito presented a beautiful route toward racemic galanthamine. The advantage of the key strategy, namely the domino Michael-Claisen cyclization is clear. The reaction establishes the six-membered C-ring of the alkaloid and introduces the crucial C-8a quaternary center. Additionally, the side-chain paved the way for the elaboration of the heterocyclic D ring of the natural product.

Also in 2008, Bandichhor and co-workers reported a concise route to (–)-galanthamine[29] that is closely related to the biosynthetic route outlined in a previous section of this chapter (Scheme 17).



Reagents and conditions: a) BnBr, K_2CO_3, DMF, 30 °C, 98%; **b)** Br_2, MeOH, 30 °C, 80%; **c)** $KMnO_4$, acetone, 60 °C, 70%.

Scheme 17. Bandichhor's synthesis of (–)-galanthamine – part 1.

The synthetic strategy envisaged the coupling of two readily available aromatic substrates. The synthesis of the A-ring of the alkaloid, outlined in Scheme 17, commenced with benzylation of the phenolic

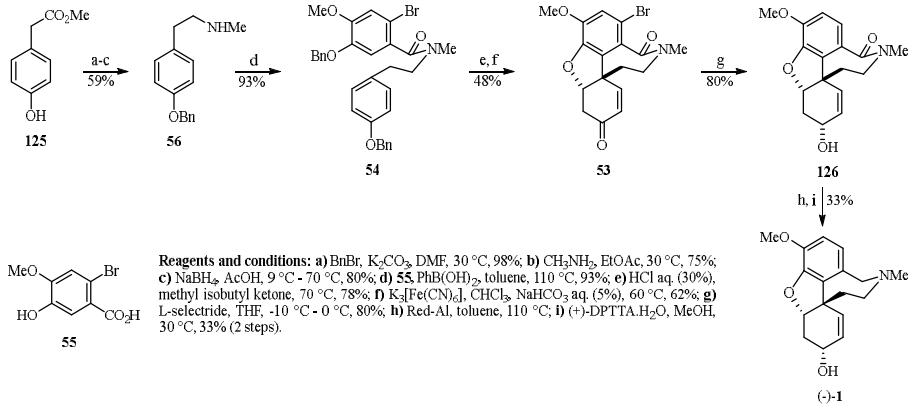
hydroxy moiety of isovanilline (**123**). Bromination of the aromatic substrate and oxidation of the aldehyde functionality to the corresponding carboxylic acid **55** completed the short route to the A-ring portion of galanthamine.

Benzylation of phenol **125**, which served as a precursor of the C-ring of galanthamine, was followed by amidation and reduction to the corresponding secondary amine **56** (Scheme 18). This material was reacted with the previously prepared building-block of the A-ring, namely acid **55**. The resulting amide was exposed to methyl isobutyl ketone and aqueous HCl at elevated temperature, which allowed for the isolation of the corresponding debenzylated material in good yield.

The key oxidative coupling reaction was accomplished when the requisite debenzylated material was exposed to an excess of potassium ferricyanide in a biphasic mixture of chloroform and aqueous sodium bicarbonate. As pointed out in the previous section, the amide present in the substrate played an important role in ensuring a satisfactory yield. The intermediary formed enone then serves as a Michael acceptor for the phenolic hydroxy group and, as a consequence, the benzofuran moiety is established and highly advanced intermediate **53** is isolated in 48% yield.

The endgame consists of the reduction of the enone using L-selectride, followed by the reduction of the amide group to the corresponding tertiary amine. Finally, the enantimoermically pure (–)-galanthamine was obtained after performing chiral resolution with a derivative of tartaric acid.

Bandichhor's synthesis of galanthamine is a nice example of the great advantages of biomimetic syntheses. By mimicking the natural process, the group presented a short and efficient route to this important alkaloid. The only drawback is the racemic nature of the process. However, Bandichhor and co-workers corrected this issue by performing classical chiral resolution technique. Because of the aromatic character and achiral properties of the early synthetic intermediates, this chiral resolution with a derivative of tartaric acid was carried out in the final step of the synthesis.

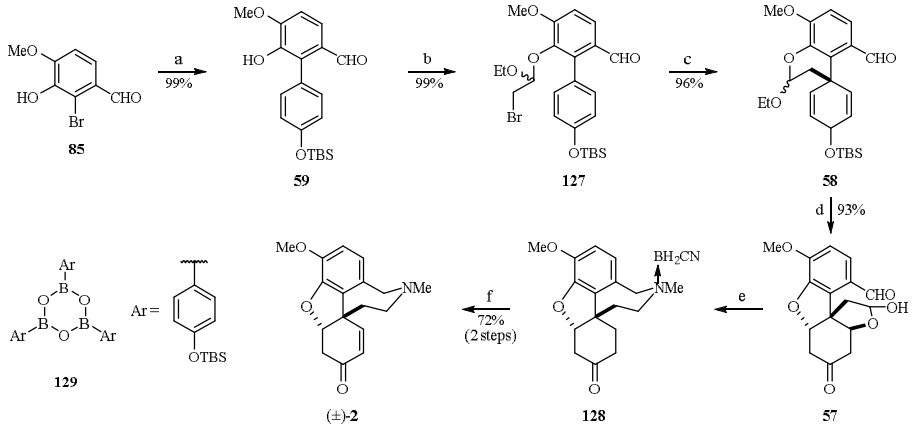


Scheme 18. Bandichhor's synthesis of (–)-galanthamine – part 2.

Magnus' route towards (–)-galanthamine featured an intramolecular phenol alkylation as the key step.[30] The synthesis was carried out in a racemic fashion and took advantage of the spontaneous resolution of racemic narwedine that was described by Shie[12] and based on initial findings of Barton.[11]

As shown in Scheme 19, the synthesis commenced with Suzuki coupling of commercially available aromatic halide **85** and boronic acid tris anhydride **129**, which delivered adduct **59** in nearly quantitative yield. Next, the free phenol in **59** was reacted with ethyl vinyl ether and bromine and acetal **58** was obtained. Exposure of this material to cesium fluoride resulted in the cleavage of the silyl ether which triggered the key phenol alkylation and installed the crucial all-carbon quaternary center. Acid-catalyzed hydrolysis of the acetal initiated the conjugate addition of the phenol and the acetyl oxygen and allowed the isolation of highly advanced intermediate **57** in excellent yield.

The synthesis of racemic narwedine (**2**) and the formal synthesis of (–)-galanthamine was concluded after reductive amination of **57** and addition of methanesulfonic acid to the intermediary formed boron adduct **128**.



Reagents and conditions: a) 129, $Pd_2(dba)_3$, PCy_3, BHT, K_2CO_3, dioxane, H_2O, 80 °C, 99%; **b)** ethyl vinyl ether, Br_2, *i*Pr_2NEt, CH_2Cl_2, 0 °C, 99%; **c)** CsF, DMF, 130 °C, 96%; **d)** 2M HCl, dioxane, reflux, 93%; **e)** $MeNH_2$.HCl, *i*Pr_2NEt, $NaCNBH_3$, AcOH, dioxane, 23 °CM **f)** $MeSO_3H$, dioxane, reflux, 72% (2 steps).

Scheme 19. Magnus' synthesis of (–)-galanthamine.

In 2010, Banwell reported his first synthesis of (+)-galanthamine.[31] In the later section of this chapter, another synthetic achievement reported by this group is discussed.

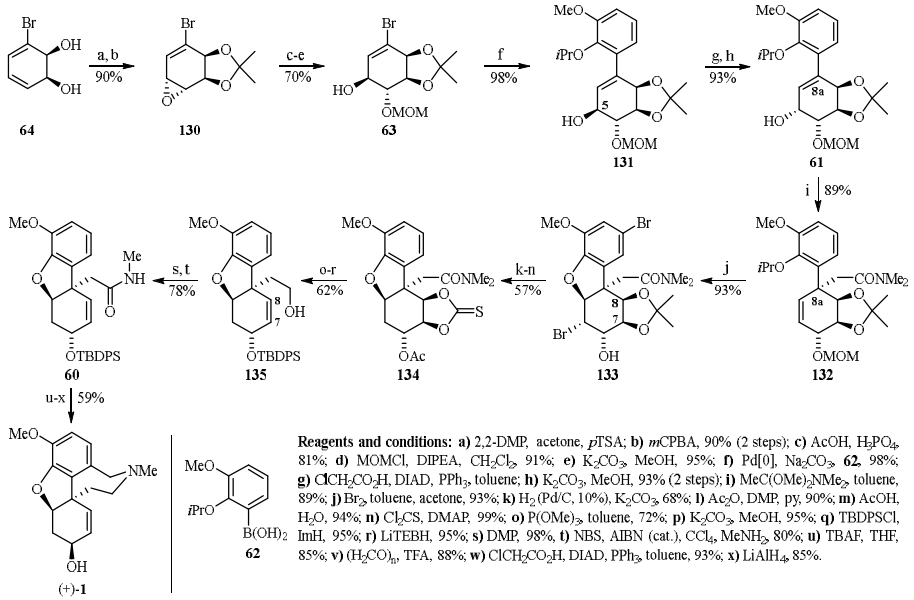
As mentioned above, Banwell's first synthesis of galanthamine is based on the application of enzymatically derived optically pure cyclohexadiene diol **64** as the starting material and the source of chirality. Cyclohexadiene diols have served as ideal starting point for the preparation of a variety of polyhydroxylated natural products, including various Amaryllidaceae constituents.[45] Banwell's synthesis provides another proof of the synthetic value of these enzymatically derived chiral synthons.

The route, outlined in Scheme 20, commenced with the protection of the vicinal hydroxy groups as acetonide in diol **64**, and selective epoxidation from the less hindered bottom face of the diene **130**. Next, a nucleophilic attack of acetic acid with concomitant opening of the epoxide, protection of the remaining hydroxy group as its MOM-ether, and cleavage of the acetate allowed for the isolation of the highly functionalized vinyl bromide **63** as building-block for the C-ring of galanthamine, in good overall yield.

Banwell's synthetic strategy relied on the facile coupling of the A-ring and the C-ring moieties by means of a palladium-catalyzed protocol. At this point, the full advantage of enzymatically derived

cyclohexadiene diol **64** for the success of the synthetic endeavor becomes obvious. The halide in **64** not only serves as an element of polarization to differentiate between both double bonds in the epoxidation step, it also defines the position at which to connect both six-membered rings via the key palladium-catalyzed reaction. In this respect, Suzuki coupling of halide **63** with boronic acid **62** allowed for the isolation of adduct **131** in nearly quantitative yield.

With a reliable route towards intermediate **131** in hand, the stage was set for the installation of the C-8a quaternary center. The hydroxy group present at C-5 presented itself as ideal handle for a [3,3]-sigmatropic rearrangement. However, before this reaction could take place, the stereochemical configuration of the hydroxy moiety had to be corrected to guarantee the correct configuration of the newly installed quaternary center. Mitsunobu inversion and cleavage of the intermediary formed ester under basic conditions afforded the requisite starting material **61** for the intended Claisen rearrangement in excellent yield. Next, treatment of the allylic alcohol **61** with *N,N*-dimethylacetamide dimethylacetal in refluxing toluene triggered the aforementioned Eschenmoser-Claisen rearrangement and a highly advanced dimethyl amide **132** was obtained after a reaction time of 7 days.



Scheme 20. Banwell's first synthesis of (+)-galanthamine.

The closure of the benzofuran moiety succeeded following the hydrobromination strategy developed by Mulzer[43] and also employed by Chida and co-workers[26] in their preparation of galanthamine (see previous section). The addition of bromine to the reaction mixture not only resulted in the desired benzofuran formation but also affected bromination of the aromatic ring, and bis-bromide **133** was obtained in excellent yield. Having fulfilled the purpose of triggering the formation of the oxygen-containing D-ring of the alkaloid, hydrogenolytic debromination simultaneously removed both halides from the substrate.

Next, Banwell's synthetic strategy called for the conversion of the acetonide moiety into the Δ^7 double bond present in the natural product. This was achieved using the Corey-Winter olefination reaction. Before this protocol could be employed, the free hydroxy group was protected as its acetate and the acetonide was converted to the corresponding cyclic thiocarbonate **134**. Exposure of this material to trimethylphosphite then triggered the formation of the cyclic carbene and the decomposition of this reactive intermediate with concomitant release of the desired double bond.

The key strategy employed in the elaboration of the seven-membered heterocycle was a Pictet-Spengler reaction. The sequence started with the saponification of the acetate and installation of a silyl ether at the C6 hydroxy group in order to achieve the reduction of the amide to the primary alcohol in the subsequent step. Addition of the Dess-Martin periodinane to the primary alcohol delivered the corresponding aldehyde, which was reacted with *N*-bromosuccinimide (NBS) and methylamine, allowing the isolation of amide **60** in excellent yield. Next, the silyl ether in **60** was cleaved and the resulting material was employed in the aforementioned key Pictet-Spengler reaction. Subjecting to the intermediate paraformaldehyde and trifluoroacetic acid (TFA) delivered the desired skeleton of (+)-galanthamine and the synthesis was concluded after Mitsunobu inversion of the secondary alcohol at C-6.

Banwell's route toward (+)-galanthamine serves as another proof for the great versatility of cyclohexadiene diols in the preparation of complex natural products. Minor drawback in the synthesis is the somewhat lengthy endgame with multiple functional group manipulations. Additionally, both hydroxy groups present in the starting material, namely those present in diol **64**, had to be removed, reducing their synthetic relevance solely to chirality transfer.

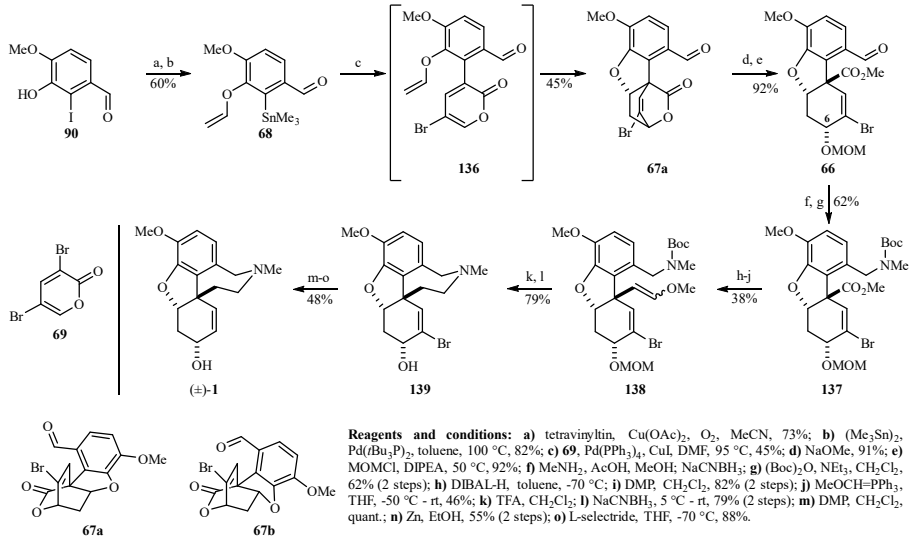
In 2010, Cho reported a route to racemic galanthamine.[32] With the application of an intramolecular Diels-Alder (IMDA) reaction, Cho introduced a new synthetic element to the area of galanthamine research. The synthesis, shown in Scheme 21, commenced with the preparation of aryltin intermediate **68**. Copper-catalyzed reaction of the commercially available phenol **90** with tetravinyltin was followed by palladium-mediated stannylation of the iodide and **68** was obtained in good overall yield. Next, Stille coupling with 3,5-dibromo-2-pyrone (**69**) delivered the desired coupling adduct **136**, which immediately underwent the intramolecular Diels-Alder reaction and lactones **67a** (*endo*-adduct) and **67b** (*exo*-adduct) were obtained from the reaction mixture. Careful screening of the reaction conditions revealed a dependence of the outcome (yield and ratio of **67a** and **67b**) on solvent, catalyst, and temperature of the reaction. The best results were obtained when the substrate was heated to 95 °C in DMF as solvent with 5 mol% of $Pd(PPh_3)_4$ and 10 mol% CuI.

Reaction of the *exo*-adduct **67a** with sodium methoxide mediated the opening of the δ-lactone and formation of the corresponding methyl ester, which was converted into intermediate **66** via protection of the C-6 hydroxy moiety as MOM ether.

The remaining steps of the synthesis of galanthamine were carried out by adopting a strategy described by Trost and co-workers in 2005 (prior to the reporting period of this chapter).[36] The sequence started with reductive amination of the aromatic aldehyde and installation of a Boc-protecting group. Next, the ester moiety attached to the quaternary center was converted to the corresponding aldehyde via a standard reduction/oxidation protocol, and subsequent chain elongation upon reaction of the carbonyl with methoxymethyl phosphorus ylide delivered vinyl ether **138**. Hydrolysis of this labile functionality and the

Boc-group under acidic conditions yielded the substrate for the final reductive amination reaction to close the seven-membered heterocycle (**139**). Galanthamine was then isolated after Dess-Martin oxidation of the C-6 hydroxyl group, Zn-mediated debromination, and reduction of the enone with L-selectride.

Cho presented a concise route with a beautiful Stille coupling/IMDA cascade. Noteworthy is the careful selection of the starting material (presence of the aldehyde in aromatic precursor **68**; concomitant installation of the quaternary center and future handle for the nitrogen heterocycle in the IMDA reaction) reduced the necessity for extensive functional group manipulations.



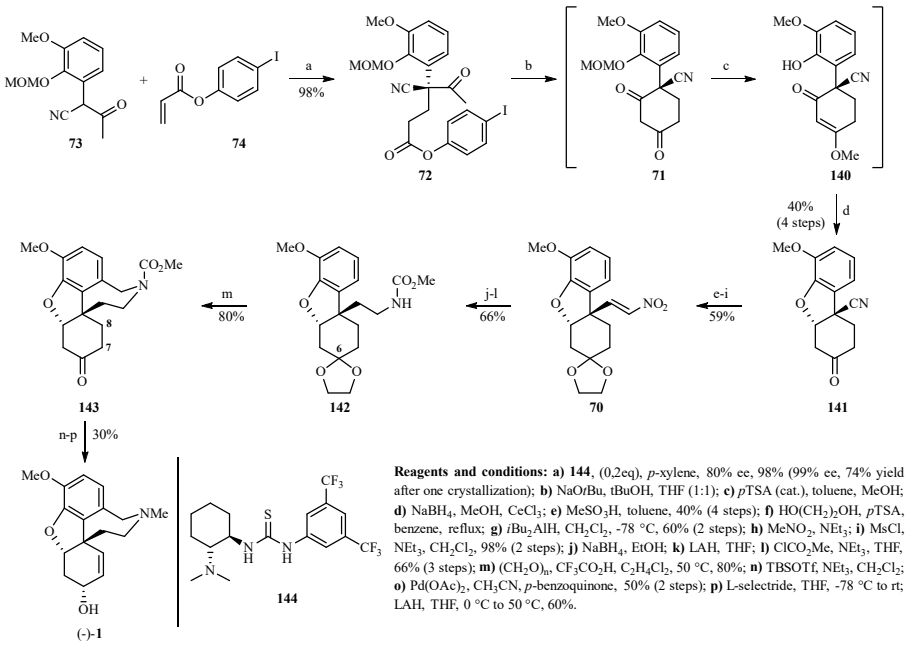
Scheme 21. Cho's synthesis of (±)-galanthamine.

Fan's synthesis of (–)-galanthamine features an asymmetric Michael reaction as the key step at an early stage.[46] Several catalysts were evaluated in this asymmetric conjugate addition reaction and thiourea **144** was identified to be the most promising candidate. When allowed to react in the presence of catalytic amounts of **144**, methyl ketone **73** and α,β-unsaturated ester **74** afforded adduct **72** in excellent yield and 80% ee., even on a multi-gram scale. A simple recrystallization of the reaction product significantly improved the enantiomeric excess and allowed the continuation of the synthesis in an enantiomerically pure fashion.

Next, adduct **72** underwent an intramolecular ketone-ester condensation, which established the C-ring of the natural product, along with the crucial C-8a quaternary center **71**. This material was then converted to the labile methyl enol ether **140** which, after Luche reduction and subsequent acidic hydrolysis, underwent an oxa-Michael reaction with concomitant formation of the benzofuran motif **141**.

With advanced intermediate **141** in hand, the stage was set for the elaboration of the D-ring of the natural product. Ketalization of the C-6 carbonyl was followed by reduction of the nitrile to the corresponding aldehyde, and subsequent chain elongation by means of a Henry reaction, which established the building block for the future D-ring of galanthamine.

Reduction of the nitroalkene and conversion of the requisite amine into carbamate **142** afforded the starting material for the Pictet-Spengler reaction, which established the galanthamine skeleton in good yield. The synthesis of the natural product was concluded after deketalization, α-silylation, and installation of the C-7–C-8 double bond and reduction of the carbamate moiety.



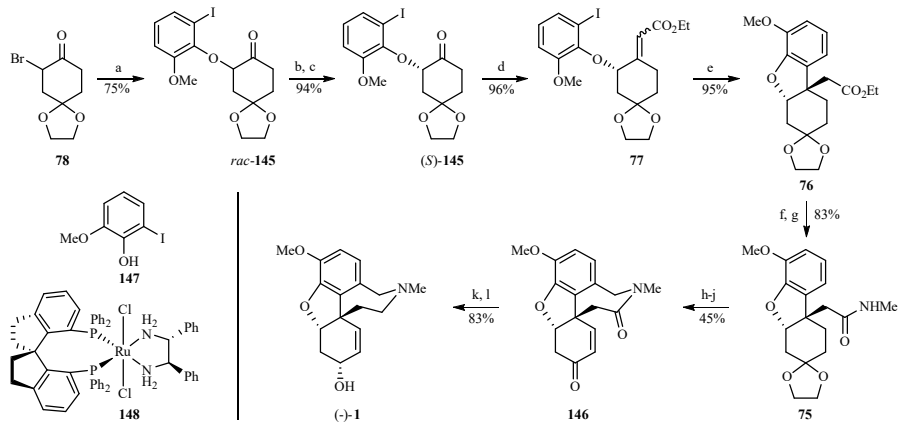
Scheme 22. Fan's synthesis of (–)-galanthamine.

In 2012, Xie, Zhou, and co-workers reported a synthesis of (–)-galanthamine featuring a catalytic asymmetric hydrogenation and a reductive Heck cyclization as key steps.[33] The route to the natural product is outlined in Scheme 23.

Alkylation of 2-iodo-6-methoxyphenol (**147**) with bromide **78** afforded racemic aryl ether *rac*-**145** in good yield. The resolution of the racemic material was then achieved via an enantioselective hydrogenation and subsequent oxidation of the intermediary reduced carbonyl group. Exposure of the enantiomerically pure aryl ether (*S*)-**145** to a Wittig olefination delivered the starting material for the key reductive Heck cyclization, namely α,β-unsaturated ester **77** in excellent yield.

The conditions of the key cyclization reaction were carefully optimized to prevent the previously reported palladium-catalyzed ionization of the aryloxy group, which would result in the undesired formation of the phenol as side product.[36, 47] When carried out in DMF in the presence of $Pd_2(dba)_3$ and two equivalents of sodium formate at 60 °C, adduct **76** was obtained in an excellent 95% yield. The great advantage of this approach becomes obvious as the reductive Heck cyclization not only serves to connect the A-ring with the C-ring of the alkaloid, and to elaborate the crucial quaternary center, it also establishes the ester side chain which serves as precursor for the nitrogen-containing moiety.

With a facile route to advanced intermediate **75** in hand, the stage was set for the completion of the carbon skeleton of galanthamine. The ester in **76** was converted in the requisite amide **75** and, the carbon skeleton of galanthamine was established by a Pictet-Spengler cyclization. Cleavage of the acetal **146** and reduction of the amide and the ketone then concluded the synthesis of the title Amaryllidaceae alkaloid.



Reagents and conditions: a) K_2CO_3, **147**, DMF, 80 °C, 75%; **b)** 30 atm H_2, **148,** KO*t*Bu, *i*PrOH, 30 °C, 99%; **c)** $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C to rt, 95%; **d)** $(EtO)_2P(O)CH_2CO_2Et$, *n*BuLi, THF, -60 °C to rt, 96%; **e)** $Pd_2(dba)_3$, HCO_2Na, DMF, 60 °C, 95%; **f)** NaOH, MeOH, H_2O; **g)** $ClCO_2Et$, NEt_3, $CHCl_3$; $MeNH_2$, -15 °C; 83% (over 2 steps); **h)** $(HCHO)_n$, TFA, $C_2H_4Cl_2$, rt, 89%; **i)** TBSOTf, NEt_3, CH_2Cl_2, -78 °C; **j)** $Pd(OAc)_2$, *p*-benzoquinone, CH_3CN, 50 °C, 51% (2 steps); **k)** K-selectride, THF, -78 °C, 93%; **l)** $Zn(OAc)_2$, $(EtO)_3SiH$, THF, 40 °C, 89%.

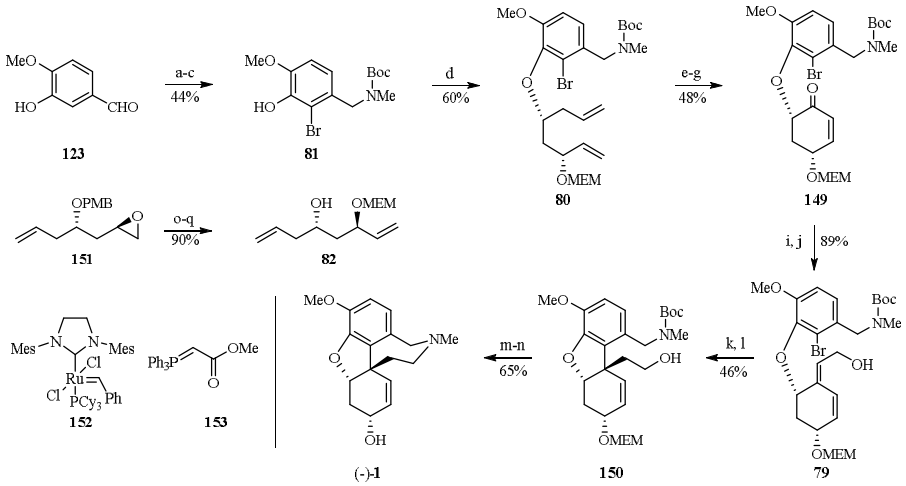
Scheme 23. Xie and Zhou's synthesis of (–)-galanthamine.

One year after Xie and Zhou's synthesis of (–)-galanthamine, Tae and co-workers also reported a synthesis of the title compound using a ring closing metathesis (RCM) reaction as one of the key steps.[34] While Tae used the metathesis reaction to elaborate the C-ring of the alkaloid, the aromatic moiety and the precursor for the C-ring were connected via the Heck reaction after initial coupling of both fragments by means of a Mitsunobu protocol.

As outlined in Scheme 24, the sequence started with bromination of isovanillin (**123**) and subsequent reductive amination of the carbonyl moiety. Boc-protection of the nitrogen then released **81**, which served as building-block for the A-ring of the galanthamine.

The preparation of the coupling partner and synthon of the C-ring was carried out starting from the previously known epoxide **151**.[48] This material was converted to the secondary alcohol **82** via addition of dimethylsulfonium methylide to introduce the allylic alcohol moiety, MEM-protection, and oxidative cleavage of the PMB-ether.

Next, the aryl bromide **81** and C-ring building-block **82** were connected through the Mitsunobu protocol affording **80**, which corrected the stereochemical configuration at C-4a and prepared the substrate for the key RCM reaction to establish the C-ring of the alkaloid. The yield of this reaction, however, was found to be quite low, mainly because of the elimination of the homoallylic alcohol in substrate **82** with the concomitant formation of the corresponding, more stable, diene. Carefully controlled reaction conditions such as low temperature, use of Bu_3P instead of Ph_3P, and application of 1,1'-(azodicarbonyl)dipiperidine (ADDP) allowed the isolation of **80** in acceptable 60% yield.



Reagents and conditions: a) Br_2, NaOAc, cat. Fe, AcOH, 12 h, rt, 75%; **b)** $MeNH_2$, MeOH; $NaBH_4$; **c)** $(Boc)_2O$, NaOH, 1,4-dioxane, H_2O (2:1), 58% (2 steps); **d)** **82**, Ph_3P, 1,1'-(azodicarbonyl)dipiperidine (ADDP), 60%; **e)** **152** (10 mol%), CH_2Cl_2, reflux, 95%; **f)** SeO_2, 1,4-dioxane, reflux; **g)** IBX, DMSO, 51% (2 steps); **h)** **152**, toluene, reflux, 95%; **i)** DIBAL-H, toluene, -78 °C, 94%; **j)** $Pd(OAc)_2$, dppp, Ag_2CO_3, toluene, reflux; **k)** $NaBH_4$, THF, H_2O, 46% (2 steps); **l)** NEt_3, MsCl, THF, 0 °C; **m)** TFA, CH_2Cl_2; **n)** $NaHCO_3$ (aq); 65% (3 steps); **o)** Me_3SI, *n*BuLi, THF, 96%; **p)** MEMCl, DIPEA, CH_2Cl_2, 96%; **q)** CAN, MeCN, H_2O (4:1), 98%.

Scheme 24. Tae's synthesis of (–)-galanthamine.

With *bis*-alkene **80** in hand, Tae and coworkers could carry out the envisaged RCM reaction with second-generation Grubbs catalyst **152** which delivered the desired product in excellent yield. Allylic oxidation with selenium dioxide in refluxing dioxane, followed by reaction with IBX proved to be the best choice of reagents as traces of the ruthenium catalyst used in the previous step turned out to be problematic in other, commonly used, methods. Reaction of enone **149** with ylide **153** then delivered exocyclic allyl alcohol **79** in good yield after reduction of the methyl ester. With this Wittig reaction, Tae and co-workers not only installed the double bond required for the intended palladium catalyzed Heck cyclization, the newly installed group also served as a precursor for the 7-membered heterocyclic C-ring of the alkaloid.

Exposure of intermediate **79** to catalytic amounts of $Pd(OAc)_2$ and 1,3-bis(diphenylphosphino)propane (dppp) and excess of silver carbonate in refluxing toluene afforded the desired cyclization product **150** after reduction of the intermediary aldehyde (via double bond shift during the Heck cyclization).

With advanced intermediate **150** in hand, the synthesis of galanthamine was completed as planned. Mesylation of the primary alcohol was followed by cleavage of the Boc-group under acidic conditions, which simultaneously removed the MEM-ether. As the final step the aza-cycle was closed upon basification of the reaction mixture with sodium bicarbonate.

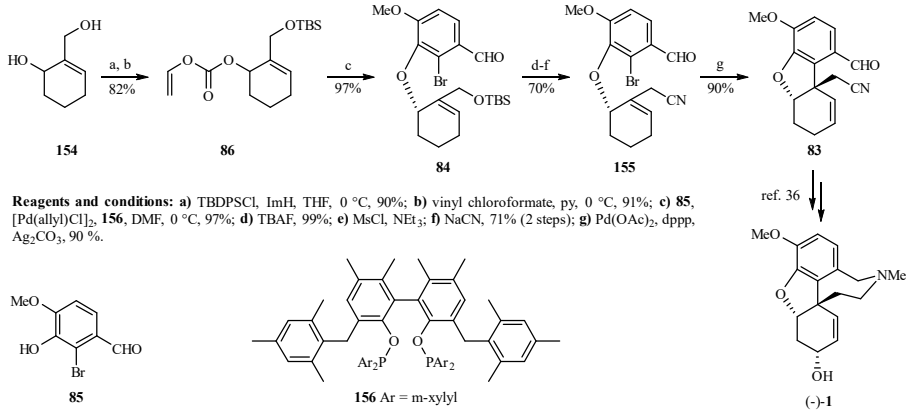
Tae's strategy differs from previously discussed endeavors as it is based on the elaboration of the C-ring via the RCM reaction. Overall, the group presented a concise and efficient route to the Amaryllidaceae alkaloid.

In 2013, Ojima and co-worker reported a formal synthesis of (–)-galanthamine.[35] The route, shown in Scheme 25, is based on the application of a Pd-catalyzed asymmetric allylic etherification reaction and ultimately delivers an intermediate previously published by Trost and co-workers in 2005.[36]

The route commenced with the preparation of allylic carbonate **86** from diol **154** via initial silylation of

the primary alcohol, followed by the reaction of the remaining hydroxyl moiety with vinyl chloroformate. With the starting material for the key asymmetric etherification in hand, Ojima and co-works carefully optimized reaction conditions for the Pd-catalyzed step. When allowed to react with phenol **85** in the presence of a palladium(II) species and chiral ligand **156**, adduct **84** was obtained in excellent yield and enantioselectivity.

The conversion to Trost's intermediate proceeded uneventfully. The silyl ether in **84** was cleaved, followed by mesylation of the resulting primary alcohol and exposure to sodium cyanide. The Heck reaction then established the quaternary center and concluded the formal synthesis of galanthamine.



Scheme 25. Ojima's formal synthesis of (–)-galanthamine.

Jia and co-workers designed a synthesis of (–)-galanthamine based on the palladium-catalyzed Larock annulation reaction as the key step for the elaboration of the ABD ring system.[37] This interesting strategy, significantly different from previously reported routes, required the installation and functionalization of the nitrogen-containing sub-unit at an early stage. The synthesis is outlined in Scheme 26.

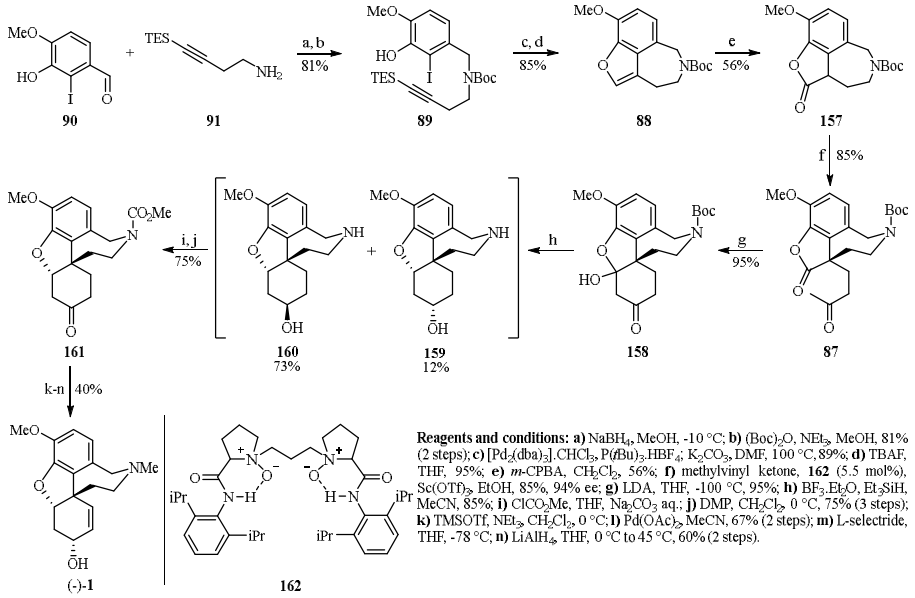
The known aldehyde **90**[36] was reacted with primary amine **91**[49] under reductive conditions and alkyne **89**, the precursor for the key palladium-catalyzed cyclization reaction was obtained after Boc-protection of the nitrogen. This alkyne was then exposed to a catalytic amount of $[Pd_2(dba)_3]$•$CHCl_3$ and P(*t*Bu)$_3$•HBF_4 and excess potassium carbonate in DMF at 100 °C, which triggered the aforementioned key Larock annulation reaction and afforded tricyclic intermediate **88** in excellent yield after cleavage of the TES group. Oxidation of the enol ether with *m*-CPBA then delivered lactone **157**.

Next, the authors turned their attention to the construction of the chiral quaternary center. This task could elegantly be solved by means of an asymmetric Michael addition. Addition of methyl vinyl ketone to lactone **157** in the presence of chiral catalyst **162** and $Sc(OTf)_3$ allowed the isolation of adduct **87** in good yield and excellent enantioselectivity (94% ee).

With an enantioselective route toward **87** available, the stage was set for the completion of the galanthamine skeleton. Methyl ketone **87** smoothly cyclized under basic conditions and delivered **158**. Reaction of the hemiketal in 158 with triethylsilane then afforded a mixture of **159** and **160** with simultaneous reduction of the ketone moiety and cleavage of the Boc-group. Protection of the nitrogen and

subjection of the mixture to the Dess-Martin periodinane (DMP) then provided ketone **161** which served as key intermediate in Fan's synthesis of galanthamine.[46]

The final task in the preparation of the natural product was the installation of the C-7 – C-8 double bond and the corresponding operations were carried out in analogy to Fan's route.[46] Ketone **161** was treated with LDA and trimethylsilyl triflate (TMSOTf) and the product was exposed to palladium acetate in acetonitrile. Stereoselective reduction of the ketone and subsequent conversion of the carbamate to the corresponding methyl amine completed Jia's synthesis of the Amaryllidaceae alkaloid.



Scheme 26. Jia's synthesis of (–)-galanthamine.

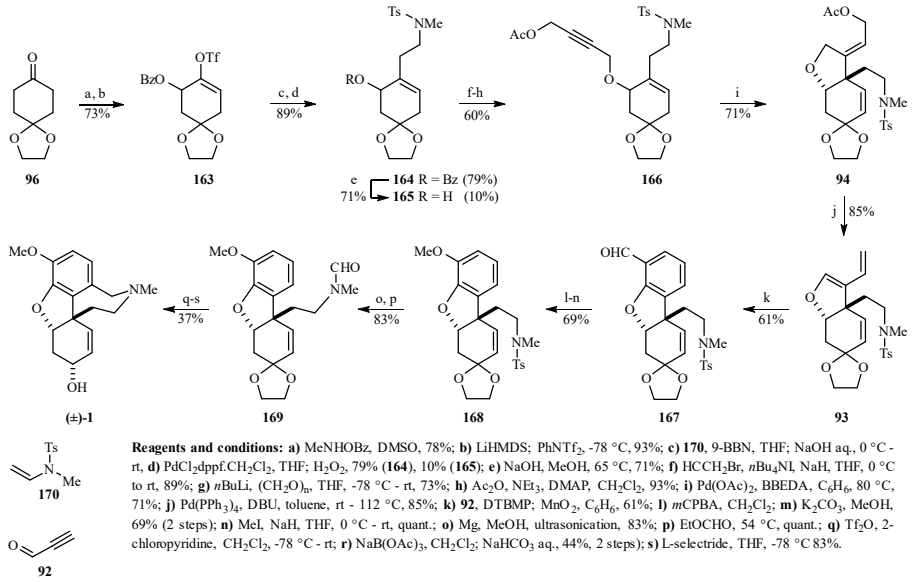
In contrast to his previous contribution, Banwell opted for the application of achiral ketone **96** as starting material and building-block for the C-ring of the alkaloid.[38] The synthetic plan devised a *de-novo* construction of the aromatic A-ring of the alkaloid with a Diels-Alder reaction as one of the key steps. The route to racemic galanthamine is shown in Scheme 27.

The initial phase of the synthesis was devoted to the construction of the tetrahydrofuran moiety and the preparation for the Alder-ene and subsequent Diels-Alder reaction. The installation of a benzoyl moiety in commercially available monoprotected diketone **96** was followed by the formation of the corresponding enol triflate under standard conditions. With this material in hand, the palladium-catalyzed cross coupling with an *in-situ* generated organoborane provided a mixture of benzoate **164** and secondary alcohol **165** in good yield. Hydrolysis of the benzoate in **164** increased the overall yield of the desired alcohol **165** and the material was converted to **166** via exposure to propargyl bromide, addition of paraformaldehyde to the deprotonated alkyne and acetylation of the resulting primary alcohol. Addition of palladium acetate to **166** then triggered the Alder-ene reaction and afforded tetrahydrofuran **94** in good yield.

Next, Banwell and co-workers installed the diene required for the key Diels-Alder reaction to establish

the aromatic portion of the galanthamine. This was achieved simply by exposure of **94** to $Pd((PPh_3)_4$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) which provided diene **93** in excellent 85% yield. The cycloaddition reaction then proceeded smoothly and **167** was obtained with the correct regiochemical orientation of the carbonyl group as precursor for the methoxy functionality present in the galanthamine.

Oxidation of the aldehyde moiety in **167**, followed by saponification of the aryl formate delivered **168** after alkylation of the free phenol. With advanced intermediate **168** in hand, the preparation of the natural product was concluded after the elaboration of the nitrogen heterocycle by means of a Bischler-Napieralski reaction.

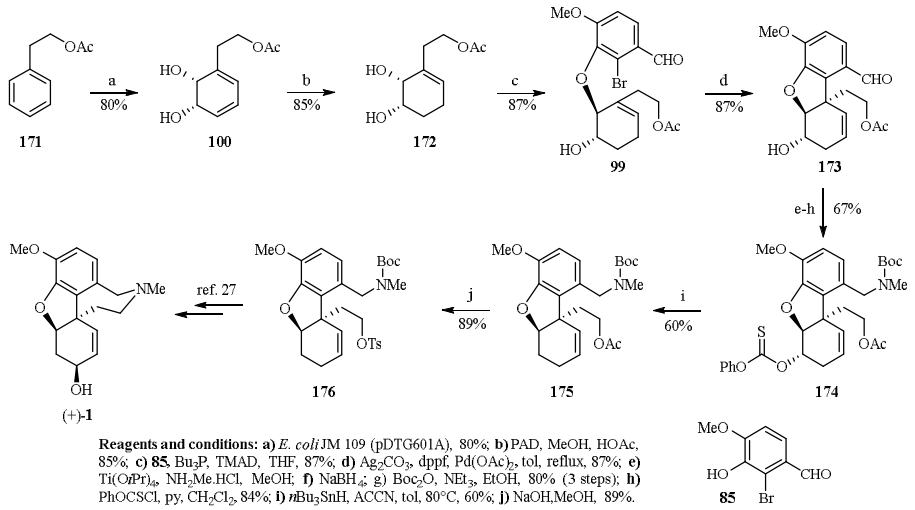


Scheme 27. Banwell's second synthesis of galanthamine.

A chemoenzymatic synthesis of (+)-narwedine and (+)-galanthamine from phenethyl acetate **171** was reported by Hudlicky.[39] The synthesis began with the whole cell fermentation of aromatic compound **171** with *E. coli* JM109(pDTG601A), a recombinant organism developed by Gibson and overexpressing toluene dioxygenase.[50] The *cis*-arene diol **100** was obtained in 80% yield (>3-5 g/L, 30-50 grams in 10 L fermentor)[51] and was subjected to a selective reduction with potassium azodicarboxylate (PAD) to provide the partially saturated diol **172**, Scheme 28. Mitsunobu reaction of this material with bromoisovanillin **85** furnished the aryl ether **99**, whose Heck cyclization provided the tricyclic aldehyde **173**. Reductive amination and protection led to the corresponding Boc-carbamate, which was converted to thiocarbonate **174** in order to remove the C-5 hydroxyl group (galanthamine numbering). This process was accomplished under Barton-McCombie conditions to provide olefin **9** along with the fully saturated byproduct (not shown) in a 4:1 ratio. Hydrolysis of the acetate gave **176**, which formalized the synthesis of *ent*-galanthamine (+)-**1**.[27]

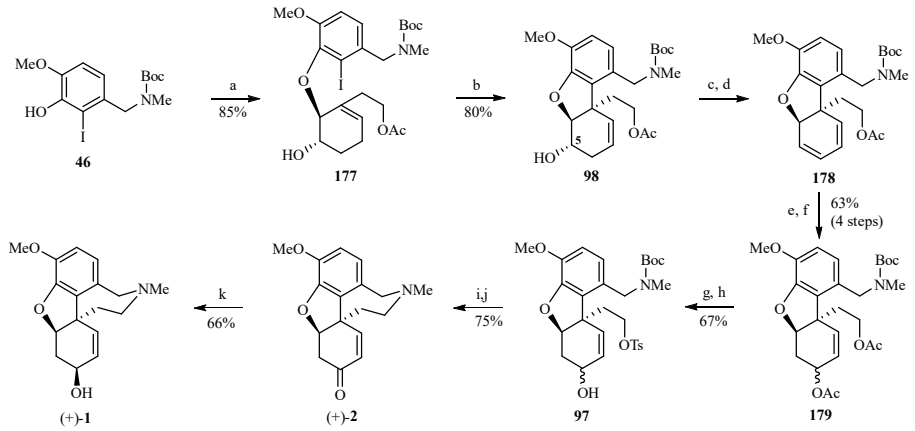
The synthesis was further improved by changing some of the operations (Scheme 29). First, Boc-carbamate **98** was prepared by the Heck cyclization of **177**, derived by the Mitsunobu reaction of diol **100**

with iodophenol **46**, in which the aldehyde had already been subjected to reductive amination, as shown in Scheme 28.



Reagents and conditions: a) *E. coli* JM 109 (pDTG601A), 80%; **b)** PAD, MeOH, HOAc, 85%; **c) 85**, Bu_3P, TMAD, THF, 87%; **d)** Ag_2CO_3, dppf, $Pd(OAc)_2$, tol, reflux, 87%; **e)** $Ti(OiPr)_4$, $NH_2Me.HCl$, MeOH; **f)** $NaBH_4$; g) Boc_2O, NEt_3, EtOH, 80% (3 steps); **h)** PhOCSCl, py, CH_2Cl_2, 84%; **i)** nBu_3SnH, ACCN, tol, 80°C, 60%; **j)** NaOH,MeOH, 89%.

Scheme 28. Hudlicky's synthesis of (+)-galanthamine.

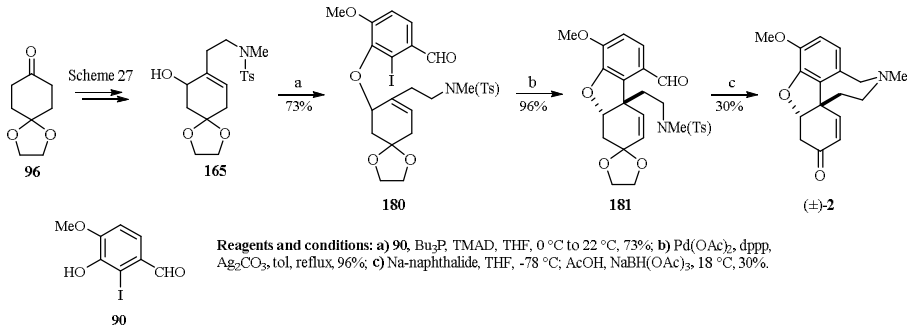


Reagents and conditions: a) 172, TMAD, nBu_3P, THF, 85%; **b)** bis(diphenylphosphino)propane, Ag_2CO_3, DMF, 150 °C, 80%; **c)** MsCl, NEt_3, CH_2Cl_2; **d)** DBU, tol, reflux; **e)** I_2, AgOAc, HOAc, THF; **f)** $NaBH_4$, DMSO, 80 °C, 63% (4 steps); **g)** NaOH, pTsCl, NEt_3, DMAP, CH_2Cl_2, 67%; **h)** TFA, CH_2Cl_2; **i)** K_2CO_3, EtOH, reflux; **j)** PCC, CH_2Cl_2, 75% (3 steps); **k)** L-selectride, THF, -60 °C, 66%.

Scheme 29. Hudlicky's synthesis of (+)-galanthamine – modified route.

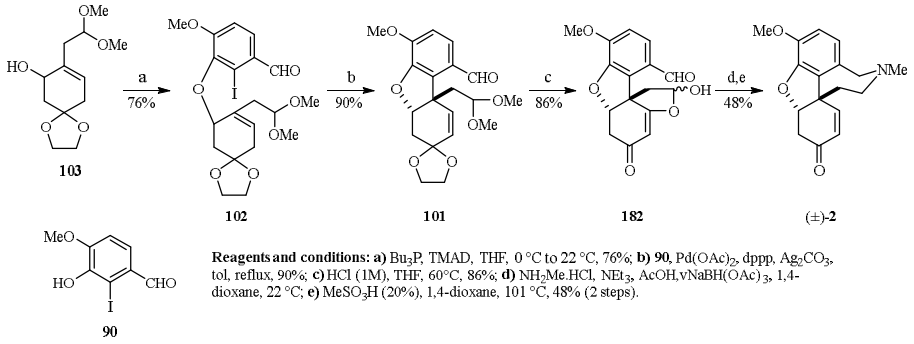
Second, the deoxygenation protocol of the C-5 hydroxyl in **98** was replaced by an elimination/hydroxylation sequence. The conjugated diene **178** was converted to a mixture of diastereomeric acetates **179**. Hydrolysis of both acetyl groups, followed by regioselective tosylation of the primary alcohol provided tosylate **97**. Acid-catalyzed release of the side-chain amine led directly to the mixture of epimeric *ent*-galanthamines ((+)-**1**). Oxidation of this mixture provided *ent*-narwedine (+)-**2**, whose reduction gave *ent*-galanthamine (+)-**1**.

Late in 2016 Banwell[40] reported the synthesis of racemic galanthamine in eleven steps from tosylamide **165**, which is accessible in four steps from the commercially available mono-protected dione **96**, Scheme 30. Mitsunobu reaction of previously reported allylic alcohol **165**[38] (for preparation see Scheme 27) with the isovanillin derivative **90** provided the aryl ether **180**, which was subjected to the intermolecular Heck reaction to furnish **181**. Detosylation of this material followed by reductive amination provided racemic narwedine (**2**), whose reduction gave racemic galanthamine in moderate 30% yield.



Scheme 30. Banwell's third synthesis of galanthamine – part 1.

In a second-generation approach, outlined in Scheme 31 the location of the aldehyde and the methyl amine functionalities was "switched" as shown in acetal **102** obtained also by Mitsunobu reaction of the isovanillin derivative **90** with the allylic alcohol **103** followed by the Heck cyclization of aryl ether **102** to produce acetal-aldehyde **101**. Reductive amination of the aryl aldehyde provided **182** and further reductive amination gave narwedine (**2**).



Scheme 31. Banwell's third synthesis of galanthamine – part 2.

The ultimate improvement was realized converting acetal **103** to lactol **182**, an intermediate used by Magnus[30] in his synthesis of narwedine. Reductive amination of **182** provided narwedine in 48% over two steps. Reduction of narwedine then yielded racemic galanthamine.

5. Conclusion

In this chapter we have provided a survey of recent syntheses of galanthamine. The interest of the synthetic community in this target has not waned, as indicated by the number of creative approaches to this alkaloid that were published during the last decade. We hope that this review will stimulate further interest in designing additional syntheses in the future.

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