Natural Product Reports

REVIEW



Cite this: *Nat. Prod. Rep.*, 2024, **41**, 1060

Recent advances in the total synthesis of galantamine, a natural medicine for Alzheimer's disease

Bichu Cheng, 💿 ac Qi Wang, ^c Yi An 💿 ^a and Fener Chen 💿 *abc

Covering: 2006 to 2023

(–)-Galantamine is a natural product with distinctive structural features and potent inhibitory activity against acetylcholine esterase (AChE). It is clinically approved for the treatment of Alzheimer's disease. The clinical significance and scarcity of this natural product have prompted extensive and ongoing efforts towards the chemical synthesis of this challenging tetracyclic structure. The objective of this review is to summarize and discuss recent progress in the total synthesis of galantamine from 2006 to 2023. The contents are organized according to the synthetic strategies for the construction of the quaternary center. Key features of each synthesis have been highlighted, followed by a summary and outlook at the end.

Received 5th January 2024 DOI: 10.1039/d4np00001c

rsc.li/npr

- 1. Introduction
- 2. Biomimetic oxidative coupling reactions
- 2.1 Biosynthesis of galantamine
- 2.2 Previous results of oxidative phenol coupling
- 2.3 Chemoenzymatic approach (Saladino)
- 2.4 Electrosynthesis approach (Wirth, Opatz and Waldvogel)
- 2.5 Chemical resolution (Bandichhor)
- 3. Transition metal catalyzed reactions
- 3.1 Heck reaction (Trost and Guillou)
- 3.2 Enyne RCM and Heck reaction (Brown)
- 3.3 Dynamic kinetic resolution and reductive Heck (Zhou and Xie)
- 3.4 Alder-ene, Diels-Alder and Heck reaction (Banwell)
- 3.5 Microbial dihydroxylation/Heck reaction (Hudlicky)
- 3.6 $\operatorname{Rh}(1)$ -catalyzed [(3+2)+1] cycloaddition (Yu)
- 3.7 "Cut and sew" carboacylation reaction (Xu)
- 3.8 Olefin carbonylative annulation (Zhao)
- 4. Rearrangement reactions
- 4.1 Semipinacol rearrangement (Tu)
- 4.2 Johnson–Claisen rearrangement (Bisai)
- 4.3 Eschenmoser–Claisen rearrangement (Li)
- 5. Alkylation reactions
- 5.1 Cascade double Michael addition and Dieckmann reaction (Ishikawa)

- 5.2 Organocatalyzed asymmetric intermolecular Michael addition (Fan)
- 5.3 Lewis acid catalyzed asymmetric intermolecular Michael addition (Jia)
- 5.4 Organocatalyzed asymmetric Robinson annulation (Tu)
- 5.5 Aryne insertion reaction (Chandrasekhar)
- 5.6 Intramolecular phenol alkylation (Magnus)
- 6. Miscellaneous approaches
- 6.1 Tandem Stille/IMDA (Cho)
- 6.2 Radical cyclization (Yu)
- 7. Summary of the total syntheses
- 7.1 Evolution of synthetic strategy for the quaternary center
- 7.2 Assembly of the tetracyclic structure
- 7.3 Source of chirality
- 8. Conclusions
- 9. Author contributions
- 10. Conflicts of interest
- 11. Acknowledgements
- 12. Notes and references

1. Introduction

(–)-Galantamine (1) is a natural product of the Amaryllidaceae alkaloid family. It was first isolated from the plant Caucasian snowdrop in the 1950s by scientists from the Soviet Union, and later from the bulbs of several different species of the Amaryllidaceae family.^{1,2} These plants have been used in traditional herbal medicine for centuries. (–)-Galantamine (1) was found to be the major active component and has a dual mechanism of action on the cholinergic system.³ It is a centrally acting,

C ROYAL SOCIETY OF CHEMISTRY

View Article Online

View Journal | View Issue

^aEngineering Center of Catalysis and Synthesis for Chiral Molecules, Department of Chemistry, Fudan University, Shanghai 200433, China. E-mail: rfchen@fudan.edu.cn ^bCollege of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi 330022, China

^cSchool of Science, Green Pharmaceutical Engineering Research Center, Harbin Institute of Technology, Shenzhen 518055, China

selective, reversible, and competitive acetylcholinesterase (AChE) inhibitor and an allosteric modulator of the nicotinic receptor for acetylcholine (Fig. 1). It has 50-fold greater selectivity for human erythrocyte AChE than for plasma BuChE (AChE IC₅₀ = 0.35 μ M; BuChE IC₅₀ = 18.6 μ M).⁴ In 2001, after half a century of investigation, (–)-galantamine hydrobromide, commercially known as Razadyne, was approved by the FDA as a drug for the treatment of mild to moderate confusion (dementia) related to Alzheimer's disease (AD). A meta-analysis of randomized controlled trials of galantamine showed that it significantly improved cognitive, behavioral, and global performance in patients with AD.⁵

(-)-Galantamine (1) has a fascinating and synthetically challenging structure containing a strained tetracyclic framework and three stereocenters. The fused tetracyclic structure consists of an aromatic A ring, a heterocyclic B ring, a cyclohexenol C ring and an azepine D ring. The three stereocenters, including a spiro benzylic quaternary center,⁶⁻⁸ are embedded in the tetracyclic structure (Fig. 2). The structure of (-)-galantamine (1) and its close relatives narwedine (5) and lycoramine (6) is similar to that of morphine (7). These structural



Fig. 1 Structure of (-)-galantamine and AChE inhibitors.

Numerous synthetic studies of (–)-galantamine (1) and its analogues have been performed and dozens of total syntheses have been reported.⁹⁻¹² This review aims to summarize the recent synthetic achievements of this fascinating natural product and to discuss the evolution of the synthetic strategies employed during different periods.¹³⁻⁴³ Special focus is placed on the construction of the key benzylic quaternary center and the asymmetric synthesis. For the sake of brevity and completeness of this review, only a few selected key early discoveries prior to 2006 will be summarized, followed by more recent developments.

2. Biomimetic oxidative coupling reactions

The biosynthesis of galantamine with oxidative *ortho-para* phenol coupling as the key step was first proposed by Barton and coworkers and later supported by their own biomimetic synthesis. Since then, oxidative coupling of phenols⁴⁴ has become the most extensively studied method for the total synthesis of galantamine. The early efforts have been summarized in a previous review.⁹

2.1 Biosynthesis of galantamine

Barton and co-workers recognized that Amaryllidaceae alkaloids, including galantamine (1), could be derived from a common precursor, 4'-O-methylnorbelladine (8) (R=H, or its *N*-methyl congener) (Scheme 1).⁴⁵ Oxidative *ortho-para* phenol coupling of 8 forms the central C–C bond, with simultaneous generation of the quaternary center and the azepine ring. An intramolecular oxa-Michael addition of the phenol to the quinoid system generates product 10 with the tetracyclic scaffold. Further reduction of the keto group and methylation of the



Fig. 2 Structure of (-)-galantamine from different perspectives and related natural products.



amine would afford galantamine (1). The biosynthesis of Amaryllidaceae alkaloids has been investigated biochemically using labelled precursors and intermediates.^{45–47} More recently, genomic studies have identified several biosynthetic genes that encode enzymes involved in these steps.^{48,49}

2.2 Previous results of oxidative phenol coupling

Barton and Kirby were the first to report the biomimetic intramolecular oxidative coupling of **11a** with potassium ferricyanide (K₃Fe(CN)₆) as the oxidant, resulting in the desired product **12a**, albeit in very low yield (Scheme 2). Subsequent ketone reduction with lithium aluminium hydride (LiAlH₄) led to a mixture of (\pm)-galantamine and (\pm)-epigalantamine.⁵⁰ This landmark biomimetic synthesis inspired many groups to make significant contributions to improve the performance of



Scheme 2 Racemic oxidative coupling reactions.

Barton's synthesis in the following years. Subsequent modifications were made to the substrate structure, and alternative oxidants were employed to enhance the efficacy of the intramolecular oxidative phenol coupling reaction.

Kametani and co-workers found that by blocking the para position of the phenol with a bromide and using a lactam instead of an amine significantly increased the yield of the oxidative phenol coupling (11b).51,52 In 1998, Kita and coworkers reported that [bis(trifluoroacetoxy)iodo]benzene (PIFA) was a suitable oxidant for promoting the diphenol coupling.53 Krikorian and co-workers then applied PIFA to the key oxidative coupling reaction of amide 11b and obtained the tetracyclic derivative 12b in 60% yield.54 In 2001, Node and coworkers reported a synthesis of galantamine using the symmetric N-formamide 13 as the substrate.55 The PIFApromoted oxidative coupling reaction of 13 in trifluoroethanol at room temperature afforded a dienone in 85% yield, a selective O-debenzylation using BCl₃ and in situ oxa-Michael addition provided the narwedine-type product 14 in a high yield. The use of the symmetrical substrate 13 as a precursor avoided the use of bromide as a blocking group at the para-phenol position. The extra hydroxy group was later removed by a palladium-catalyzed reduction of the corresponding triflate.

The first asymmetric synthesis of enantiomerically pure (+)and (-)-galantamine was reported by Koga's laboratory (Scheme 3).⁵⁶ Compound **15** was derived from L-tyrosine methyl ester. The phenol oxidative *ortho-para* coupling reaction was carried out with 5 equiv. of manganic tris(acetylacetonate) (Mn(acac)₃) in acetonitrile. The resulting tetracyclic compound was protected as the diethyl phosphonate to give **16** in 81% yield. Compound **16** was then converted to (+)-galantamine. Node and co-workers reported in 2004 a creative synthesis of (-)-galantamine based on the concept of remote asymmetric induction.⁵⁷ Compound **17** was readily obtained from tyramine with (*R*)-*N*-BOC-D-phenylalanine. The oxidative phenol coupling reaction of **17** afforded a dienone. *O*-debenzylation and *in situ* oxa-Michael addition delivered product **18**, which was converted to (-)-galantamine.

Barton and Kirby also investigated the interconversion of galantamine and narwedine (Scheme 4).50 Oxidation of (-)-galantamine (1) with manganese dioxide, and crystallization from acetone led to (-)-narwedine (5). Serendipitously, they discovered that crystallization from ethanol (EtOH) led to (+)-narwedine. The apparently spontaneous formation of (+)-narwedine during crystallization was most likely due to the presence of small amounts of unoxidized (-)-galantamine. The process must proceed through the symmetrical dienone intermediate 9. Eventually, they obtained (-)-narwedine (5) by crystallization of (\pm) -narwedine with 0.5 equiv. of (+)-galantamine in a mixture of EtOH/Et₃N. Further reduction of the ketone group in 5 with LiAlH₄ completed a relay synthesis of (-)-galantamine. Shieh and coworkers reinvestigated this crystallization-induced dynamic resolution of narwedine.58,59 They found that resolution of (\pm) -narwedine in EtOH/Et₃N worked equally well with a catalytic amount of (-)-narwedine (2.5%) or (+)-galantamine (1%). This process is highly efficient, as evidenced by the conversion of 10 g of (\pm) -narwedine into





Scheme 3 Asymmetric oxidative coupling reactions.



Scheme 4 Crystallization-induced dynamic chiral resolution and ketone reduction.

9.02 g of (–)-narwedine in just two cycles. Shieh and coworkers also solved the issue of stereoselectivity in the final ketone reduction. The desired product was stereoselectively obtained by employing L-selectride as the reducing agent instead of LiAlH₄. These two key improvements are crucial for the pilot scale synthesis of (–)-galantamine (*vide infra*).

In the late 1990s, a collaboration between the pharmaceutical company Sanochemia and Vienna University of Technology (Johannes Fröhlich and Ulrich Jordis) resulted in a pilot-scale process for the production of (-)-galantamine (Scheme 5).^{60,61} The phenol **19** was prepared from veratraldehyde in 4 steps on a 100 kg scale. The oxidative phenol coupling reaction was optimized by a multifactorial analysis of reaction parameters, and 40–42% yield of **20** were consistently obtained on scales up to 12 kg. Compound **20** was transformed to racemic narwedine $((\pm)$ -5) in 2 steps. Racemic narwedine is then resolved according to Shieh's procedure to give enantiomerically pure (–)-narwedine.⁵⁸ Using a catalytic amount of seed crystals of (–)-5, a consistently reproducible procedure has been developed for the crystallisation-induce chiral transformation of (\pm)-5 to (–)-5 on scales up to 7 kg. (–)-Narwedine was stereoselectively reduced with L-selectride to afford (–)-galantamine (1), which was isolated as the salt of hydrobromide in nearly quantitative yield. More than 5 kg of the final product was obtained by this process in 12.4% overall yield.

From Barton's biomimetic synthesis to Sanochemia's pilot scale synthesis of galantamine, it took generations of chemists and almost four decades of effort to optimize a low-yielding but landmark reaction to an industrial scale reaction with practical values. There are continuous and ongoing interest in this biomimetic intramolecular oxidative coupling reaction, especially with the advent of new technologies. The clinical demand for (-)-galantamine also requires a sustainable and economical supply to complement the isolation of (-)-galantamine from its natural source.⁶²

2.3 Chemoenzymatic approach (Saladino)

Biocatalysis is especially useful for the preparation of novel building blocks or the late-stage modification of complex molecules, due to the high selectivity profiles of enzymes. Chemoenzymatic synthesis allows the organic chemists to combine the versatility of synthetic organic transformations with the unparalleled selectivity of biocatalysis, providing efficient access to important bioactive small molecules.⁶³

Laccases (EC 1.10.3.2) are a class of multicopper-containing oxidoreductase that catalyze the one-electron oxidation in nature ($E^0 = 0.5$ to 0.8 V vs. normal hydrogen electrode NHE), using air as the primary oxidant.^{64,65} In 2020, Saladino and coworkers reported a novel and biomimetic synthesis of galant-amine (Scheme 6).³⁶ They developed a laccase catalyzed *para*-



Scheme 5 Industrial synthesis of (–)-galantamine by Sanochemia.



Scheme 6 Saladino's chemoenzymatic synthesis of galantamine.

ortho oxidative radical coupling of a norbelladine derivative 19 to a spirocyclohexadienone 21 in the presence of the redox mediator 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO). The phenol 19 was prepared in two steps from commercially available tyramine and 2-bromoisovanillin via reductive amination and N-formylation. Treatment of 19 with laccase from Trametes versicolor (1000 U $mmol^{-1}$) and 0.6 equivalents of TEMPO as the redox mediator and oxygen as the primary oxidant led to the oxidative radical coupling product 21 in 70% yield. Product 21 is a tricyclic fused system, containing the azepine D ring and two hexadienone rings. Surprisingly, in contrast to the spontaneous oxa-Michael addition to form the B ring in the biomimetic chemical synthesis of galantamine (vide supra),60,61 this enzyme catalyzed reaction stopped at the oxidative coupling stage, reflecting the mildness of the reaction conditions. Tautomerization of 21 with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) induced an

intramolecular oxa-Michael addition to give the tetracyclic product **20** in 91% yield. Final sequential reduction of the ketone with L-selectride and reduction of the amide and debromination with LiAlH₄ afforded galantamine in 61% yield.

The entire process of this total synthesis required only 6 steps from commercial compounds, with an overall yield of 34%. Further optimization of the reaction conditions, *e.g.*, reducing the amount of TEMPO and using supported laccase for recycling, would make this route a potential candidate for scaling up the synthesis of galantamine.

2.4 Electrosynthesis approach (Wirth, Opatz and Waldvogel)

Organic electrosynthesis is an old and rich discipline that has experienced a significant renaissance in recent years. It provides a customizable, cost effective and environmentally benign alternative for conducting redox reactions using only electrons as traceless reagents, thereby eliminating the need for dangerous and toxic stoichiometric oxidants.⁶⁶ With the recent renaissance of the field, two independent reports on the electrochemical synthesis of galantamine were published almost simultaneously.^{39,40}

In 2022, Wirth and coworkers reported a new biomimetic total synthesis of (-)-galantamine (1), using an anodic aryl-aryl coupling as the key synthetic step, which was further optimized in a flow electrochemical setup (Scheme 7a).39 The substrate 22 was synthesized from methyl p-tyrosine and methyl gallate in 6 steps. Various parameters of the electrolysis were screened and optimized. It was found that RVC anode and platinum cathode is the best electrode material combination, trifluoroethanol with 0.1 M nBu₄NClO₄ as supporting electrolyte is a very good solvent, the addition of an acidic additive such as trifluoroacetic acid successfully increased the yield of the electrolysis product 23 to 40% in batch mode. This reaction was then examined using a flow electrochemical reactor. After optimizing the flow system, the yield of 23 increased to 55%. Subsequently, product 23 was converted to (-)-galantamine by adapting the strategy from Koga's synthesis.56

Review



Scheme 7 Electro-synthesis of galantamine. (a) Wirth and (b) Opatz and Waldvogel's work.

In the same year, Opatz and Waldvogel reported a biomimetic approach towards the synthesis of Amaryllidaceae alkaloids using a highly versatile anodic key transformation to spirodienones (Scheme 7b).⁴⁰ The substrate **24** for the electro oxidative coupling was prepared from methyl gallate in 11 steps. The metal-free, high performance boron-doped diamond (BDD) electrode was found to be the anode material of choice. Acetonitrile with an acid additive gave the most promising results. To prevent the rearrangement of the sensitive spirodienone moiety, a continuous flow setup was refined to neutralize the electrolyte immediately after electrolysis. Product **25** was then converted to Node's intermediate,⁵⁵ which represents a formal total synthesis of galantamine.

Electrosynthesis provided an alternative approach to traditional oxidants for this key biomimetic oxidative coupling in the total synthesis of galantamine. However, both the substrates and the reaction parameters for this key reaction required a lot of effort for careful optimization in the above two cases, making the overall syntheses less efficient.

2.5 Chemical resolution (Bandichhor)

The process for the scalable chemical synthesis of (-)-galantamine by Sanochemia^{60,61} was adapted or modified on certain steps for further improvement by all subsequent production procedures. In 2008, Bandichhor and coworkers reported an alternative scalable synthesis of (-)-galantamine via Kametani's intermediate 11b (Scheme 8).17 The acid 26 and amine 27 were both obtained in 3 steps from readily available starting materials. Coupling of these two fragments with 10 mol% of ecofriendly phenyl boronic acid afforded the amide 28 in 93% yield.67 The O-benzyl groups was removed under acidic condition to give the known phenol 11b.^{51,52} The incremental addition of 11b to Kametani's conditions $(K_3Fe(CN)_6, NaHCO_3)$ led to the key intramolecular oxidative coupling followed by a spontaneous oxa-Michael addition to give the tetracyclic product 12b in 62% yield, much higher than those reported by Kametani and the Sanochemia



process. The enone was reduced with L-selectride to afford an alcohol in good yield (80%) and diastereoselectivity (de 99.6%). The reduction of the lactam and concomitant debromination with vitride led to the racemic galantamine $((\pm)$ -1). The racemic mixture was resolved using (+)-di-*p*-tolyl tartaric acid ((+)-DPTTA) to produce the enantiomerically pure product (-)-galantamine (1) with good yield (70%, based on available enantiomer in the racemate) and chiral purity (99.91%).⁶⁸ The HBr salt of (-)-galantamine was formed conventionally using aq. HBr. All reactions in the process were performed on a decagram scale, and an overall yield of 9% was obtained from isovanillin.

By modifying the substrate and reaction conditions, they were able to obtain a good yield for the key intramolecular oxidative coupling reaction. However, half of the valuable late-stage product was lost using the classical resolution method, and they did not demonstrate the recycling of the other enantiomer, which makes the route less cost effective for scalable production of (-)-galantamine.

3. Transition metal catalyzed reactions

Transition metal catalyzed reactions play an indispensable role in modern synthetic chemistry. They have been awarded the Nobel Prize in Chemistry three times in the 21st century. For decades, oxidative phenol coupling was the only way to construct the benzylic quaternary center in the total synthesis of galantamine. Trost and coworkers were the first to break this paradigm and use a palladium catalyzed intramolecular

Natural Product Reports

Heck reaction.^{69–71} Since then, numerous applications of transition metal catalyzed reactions, including all three Nobel Prize-winning reactions (the Heck coupling reaction, asymmetric hydrogenation reaction²² and olefin metathesis reaction^{14,23,41}), have been employed in the total synthesis of galantamine.^{14,23,24,28,29}

3.1 Heck reaction (Trost and Guillou)

In 2000, Trost and Toste reported the first catalytic asymmetric synthesis of (-)-galantamine (Scheme 9).⁶⁹ They used sequential

palladium-catalyzed asymmetric allylic alkylation (AAA) and intramolecular Heck reaction to build the key vicinal stereocenters with high enantioselectivity. This is the first total synthesis that does not use an oxidative phenol coupling to construct the quaternary center of (-)-galantamine (1).

First, a palladium-catalyzed AAA reaction of allylic carbonate 29 with 2-bromovanillin (30) in the presence of the chiral ligand 31 afforded the required chiral aryl ether 32 in 72% yield and with 88% enantiomeric excess (ee). The attempted intramolecular Heck reaction of the electron-poor olefin 32 to construct the crucial quaternary center failed. Therefore, 32 was



Scheme 9 Trost and Toste's total synthesis of (–)-galantamine.



Scheme 10 Trost and Tang's total synthesis of (-)-galantamine.

Review

transformed to an electron-rich bis-TBS ether. This compound underwent the palladium-catalyzed intramolecular Heck reaction smoothly with the electron-rich bidentate ligand 1,2-bis(dicylohexylphosphino)ethane (dcpe). The reaction yielded benzofuran 33 in good yield, together with some monodeprotected product. Both the olefin isomerization reaction and the phenol ionization reaction were suppressed under this condition. Compound 33 was then converted to 34 in 6 steps, including a reductive amination to form the azepine D ring. Compound 34 was converted to allylic alcohol 35 in a further 3 steps, through an epoxide to allylic alcohol isomerization. Finally, a 1,3-transposition of the allylic alcohol provided (–)-galantamine (1).

Two years later, Trost and Tang improved the total synthesis of (–)-galantamine (1) to an 8-step process (Scheme 10).⁷² The same arylether **32** was used in their second generation total synthesis. The α , β -unsaturated ester was homologated to a β , γ -unsaturated nitrile **36** in four steps, including a Mitsunobu reaction with acetone cyanohydrin. The enantiomeric excess of **36** was improved to 96% ee after recrystallization. The palladium-catalyzed intramolecular Heck cyclization proceeded smoothly in the presence of silver carbonate (Ag₂CO₃) and provided the product **37** in high yield (91%). An allylic oxidation mediated by SeO₂ introduced the allylic hydroxy group and selectively delivered the product **38** (dr 10:1). The condensation of aldehyde **38** with methylamine, followed by subsequent reduction and intramolecular cyclization, formed the hydrobenzazepine D ring and gave (–)-galantamine (**1**) in a one-pot process.

In 2001, Guillou and Thal reported an efficient synthesis of (\pm) -galantamine from a readily available ester **39** (Scheme 11).⁷³



Scheme 11 Guillou and Thal's total synthesis of (\pm) -galantamine.

The palladium-catalyzed intramolecular Heck cyclization of **39** afforded the tricyclic compound **40** in 67% yield. Removal of the dioxolane group, followed by oxidation with (PhSeO)₂O afforded the key spirocyclohexadienone intermediate **41** in 50% yield. The ester amidation reaction of **41** with 40% aqueous methylamine was carried out at room temperature and resulted in the spontaneous phenolic oxa-Michael addition to cyclohexadienone to afford amide **42**. Compound **42** was then subjected to Pictet–Spengler cyclization with paraformaldehyde to form the azepine D ring and give tetracyclic product **43** in 63% yield. Successive stereoselective reduction of the enone **43** with L-selectride and reduction of the lactam with LiAlH₄ afforded (\pm)-galantamine in good yield.

The above three total syntheses of galantamine formed the basis for many subsequent total syntheses. The intramolecular Heck reaction has been used many times to construct the quaternary center. The reductive amination method of Trost and the Pictet–Spengler cyclization method of Guillou were employed to form the azepine D ring. The key intermediates in their total syntheses became the targets of later syntheses.

3.2 Enyne RCM and Heck reaction (Brown)

In 2007, Brown and coworkers reported their first-generation enantioselective total synthesis of (-)-galantamine in 11 linear steps from commercially available materials.¹⁴ An enantioselective reduction of a propargylic ketone 44 with (*R*)-alpine borane afforded the chiral alcohol 45. Coupling of the alcohol 45 with phenol 47 *via* Mitsunobu reaction afforded enyne 48. The C ring was closed by an efficient enyne metathesis reaction of 48 in the presence of 3 mol% of the first-generation Grubbs' catalyst, generating the diene product 49 in 85% yield at ambient temperature (Scheme 12).

The terminal olefin of **49** was selective hydroborated and oxidized to yield a homoallylic alcohol (Scheme 13). Subsequently, an intramolecular Heck reaction successfully formed the central heterocyclic five-membered B ring to give tricyclic compound **50**. Allylic oxidation of **50** using Trost's procedure led to the desired (*R*)-allylic alcohol **51** with modest selectivity.⁶⁹ The azepine D ring was generated by selectively activating the primary hydroxyl group through mesylation, followed by a one-pot Boc deprotection/*N*-alkylation process by sequential treatment with TFA and neutralization with NaHCO₃ (aq). (–)-Galantamine and its epimer were obtained after separation by column chromatography.

Fifteen years later, Brown and coworkers reported their second-generation asymmetric synthetic route to (–)-galantamine with very high levels of stereocontrol. Several transitionmetal mediated reactions were pivotal in achieving high levels of chemo and stereo-control, including the use of an enyne ring closing metathesis (RCM), two asymmetric allylation reactions and an intramolecular Heck reaction.⁴¹

Asymmetric allylation of aldehyde 52 with Hafner's titanium-TADDOL reagent (S,S)-53 provided the chiral homoallylic alcohol 54 with excellent enantioselectivity (Scheme 14).⁷⁴ The Mitsunobu coupling of phenol 47 and alcohol 54 afforded an olefin as a single enantiomer in high yield. A two-step



Scheme 12 Enyne metathesis reaction.



Scheme 13 Brown's first-generation total synthesis of (–)-galantamine.



Scheme 14 Synthesis of 48 by two asymmetric allylation reactions.

dihydroxylation/oxidative cleavage process transformed the terminal olefin to aldehyde 55. A second aldehyde allylation reaction with TADDOL reagent (R,R)-53 gave another homoallylic alcohol in good yield and excellent diastereoselectivity. Functional group manipulation provided enyne 56, which contained the full scaffold of the alkaloid and the necessary stereochemical information, ready for the key reactions.

In the presence of Grubbs' first-generation catalyst, enyne **56** underwent an RCM reaction to generate the C ring and afforded the cyclized product **57** (Scheme 15). Selective hydroboration of the terminal olefin with 9-BBN and oxidation, followed by an intramolecular Heck cyclization generated the tricyclic compound **58**.⁷⁰ Finally, formation of the azepine D ring by an *N*-alkylation reaction and *in situ* deprotection delivered (–)-galantamine (**1**). The overall process of their total synthesis of (–)-galantamine is **11** steps with 7.3% overall yield from the known enantiomerically enriched alcohol **54**.



Scheme 15 Brown's second-generation total synthesis o (-)-galantamine.

3.3 Dynamic kinetic resolution and reductive Heck (Zhou and Xie)

In 2012, Zhou and Xie reported an asymmetric total synthesis of (-)-galantamine (20.1%, 12 steps).²² Their synthetic strategy features an efficient ruthenium-catalyzed asymmetric hydrogenation of a racemic α -aryloxy cyclic ketone *via* dynamic kinetic resolution (DKR), and a palladium-catalyzed intramolecular reductive Heck cyclization to construct the benzylic quaternary center.

Previously, they developed a highly efficient rutheniumcatalyzed asymmetric hydrogenation of racemic α -aryloxy cyclohexanones *via* DKR to produce chiral β -aryloxy cycloalkanols with excellent enantioselectivity.⁷⁵ Using this methodology, the racemic α -aryloxy cyclic ketone **59** was hydrogenated with the chiral ruthenium catalyst RuCl₂-(*S*)-SDP/ (*R*,*R*)-DPEN (**60**) to afford the chiral β -aryloxy cyclohexanol **61** in high yield (99%), excellent enantioselectivity (97% ee) and *cis*selectivity (*cis/trans* > 99:1) (Scheme 16). The aryloxy cyclohexanol **61** was then converted by Swern oxidation and Horner–Wadsworth–Emmons reaction (HWE) to give the α , β -unsaturated ester **62** as an inconsequential olefin mixture (*Z*/*E* 1:5).

The construction of the key quaternary center via the intramolecular Heck reaction of aryl allyl ethers is often impeded by a competitive palladium-catalyzed ionization of the aryloxy group, leading to the formation of a phenol.⁶⁹ To address this issue, a reductive Heck reaction was investigated. After screening and optimization, it was found that the intramolecular reductive Heck cyclization successfully formed the desired product 63 in 95% yield when the Z, E-mixture of ester (S)-62 was subjected to the catalyst $[Pd_2(dba)_3]$ in the presence of sodium formate (HCO₂Na) (Scheme 17). The ester 63 was then transformed to an amide, followed by Pictet-Spengler cyclization with paraformaldehyde according to Guillou's procedure73 to give the tetracyclic intermediate 64. Stereoselective reduction of the ketone group to the alcohol with K-selectride and a further reduction of the lactam to the amine by Beller's method⁷⁶ (triethoxysilane ((EtO)₃SiH)/Zn(OAc)₂) afforded the natural product lycoramine (6). On the other hand, a Sagusa oxidation of the ketone 64 gave the known enone product 43,73 and successive reduction with K-selectride and (EtO)3SiH)/ $Zn(OAc)_2$ gave the natural product (-)-galantamine (1). (-)-Galantamine (1) was synthesized in twelve steps with 20.1% overall yield and lycoramine (6) was synthesized in ten steps with 40.2% overall yield from commercially available starting materials.

3.4 Alder-ene, Diels-Alder and Heck reaction (Banwell)

The Banwell group has been working on the total synthesis of galantamine for a long time, and has published several generations of total syntheses with different strategies.^{19,27,28,42,77} In 2015, they reported a new and distinct total synthesis of galantamine,²⁷ in which the aromatic A ring was made by a Diels– Alder reaction, the heterocyclic B ring and associated



Scheme 16 A DKR reaction to generate the oxygenated stereocenter



Scheme 17 Zhou and Xie's total synthesis of (–)-galantamine.



Scheme 18 Palladium-catalyzed intramolecular Alder-ene reaction.

quaternary carbon center were constructed by a palladiumcatalyzed intramolecular Alder-ene (IMAE) reaction, and the seven-membered D ring was then formed by a modified Bischler–Napieralski reaction. Following a literature method,⁷⁸ the commercial ketone **65** underwent an α -acyloxylation reaction with *N*-methyl-*O*-benzoylhydroxylamine (MeNHOBz) at room temperature to give the product **66** (Scheme 18). This reaction presumably proceeds *via*

Review

a concerted pericyclic rearrangement of the intermediate **65**' to give the α -benzoyloxy imine **66**', with further *in situ* hydrolysis to give the observed product. The ketone **66** was regioselectively converted to an enol triflate **67**, which underwent a *B*-alkyl Suzuki coupling reaction with the *in situ* generated boron reagent **68** to afford the coupling product alcohol **69** after ester hydrolysis. The incorporation of the alkyne moiety was completed in 3 steps to give the enyne **70**. The palladium-catalyzed IMAE reaction of enyne **70** was best performed with a strong σ -donating ligand *N*,*N*'-bis(benzylidene)ethylenediamine (BBEDA), to successfully form the heterocyclic B ring and the quaternary center and provide the desired cyclization product **72**.^{79,80}

The allylic acetate **72** underwent a palladium-catalyzed elimination reaction under basic conditions to give a diene **73** (Scheme 19). Compound **73** then participated in a regioselective Diels–Alder cycloaddition reaction with propynal, followed by immediate oxidation with manganese dioxide (MnO₂) to form the aromatic A ring and afford the aldehyde **75**. Compound **75** was converted in 5 steps to formamide **76**. A modified Bischler–Napieralski cyclodehydration reaction of **76** under Movassaghi's conditions (Tf₂O/2-Cl pyridine) formed the D ring,⁸¹ and subsequent reduction of the resulting iminium with sodium triacetoxyborohyride (NaBH(OAc)₃) afforded narwedine. A diastereoselective reduction of the ketone group with L-selectride afforded (\pm)-galantamine (**1**). The longest linear sequence of the total synthesis is 18 steps from commercial compound **66**.

Although several distinctive strategies were used, the installation of the aromatic moiety in the above synthesis was



Scheme 19 Banwell's total synthesis of (\pm) -galantamine.



Scheme 20 Banwell's improved total synthesis of (–)-galantamine.

laborious, making the overall process less efficient. After several generations of evolution,19,28 Banwell and coworkers published a concise total synthesis of (–)-galantamine in 2022 (Scheme 20).42 The synthesis commenced from the known chiral allylic alcohol 79, which was readily available from an asymmetric ketone reduction reaction with (L)-TarB-NO₂ reagent (78) derived from (L)-tartaric acid.82 Compound 79 was then subjected to a B-alkyl Suzuki cross-coupling reaction to introduce the alkyl side chain and a Mitsunobu reaction with commercial iodoisovanillin 46 to afford the coupling product 80, containing all the carbons of the natural product. An intramolecular Heck reaction of 80 under the standard conditions afforded the cyclohexene derivative 81, with concomitant formation of the quaternary center and the heterocyclic B ring. Allylic oxidation under Trost's conditions with SeO₂ diastereoselectively generated the allylic alcohol 82.72 It was proposed that SeO₂ reacted with the olefin and the axial proton H_{ax} through an ene mechanism, with Hax perfectly aligned with the π -system. Finally, closure of the azepine D ring *via* a double reductive amination reaction in the presence of formaldehyde afforded the final target (-)-galantamine (1). In the absence of formaldehyde, a related natural product (-)-norgalantamine was obtained. The whole process for the total synthesis of (-)-galantamine (1) took only 6 steps from the known chiral compound 79.



Scheme 21 Hudlicky's total synthesis of (+)-galantamine.

3.5 Microbial dihydroxylation/Heck reaction (Hudlicky)

In 2016, Hudlicky and coworkers reported a ten-step chemoenzymatic synthesis of ent-galantamine from phenethyl acetate (Scheme 21).²⁹ The synthesis began with the microbial dihydroxylation of phenethyl acetate 83 to afford an intermediate cyclohexadiene diol 84. The less hindered alkene was selective reduced, followed by a selective Mitsunobu reaction of the more reactive allylic alcohol with phenol 47, resulting in the coupling product 85. The tricyclic ABC rings of galantamine was assembled by a subsequent intramolecular Heck reaction of 85. The alcohol 86 was converted to the diene 87 by mesylation, followed by elimination with DBU. A Prevost reaction of the diene 87 gave a diastereomeric mixture of iodoacetates, which were immediately subjected to reduction with sodium borohydride in DMSO to give a 2:1 mixture of diastereomeric acetates 88. Formation of the azepine D ring and adjustment of the stereochemistry of the allylic alcohol was achieved in 5 steps from 88, resulting in the synthesis of (+)-galantamine.



Scheme 22 (a) An intramolecular Pauson-Khand reaction; (b) Rh-catalyzed $\left[(3+2)+1\right]$ cycloaddition reaction.

3.6 3.6 Rh(1)-catalyzed [(3 + 2) + 1] cycloaddition (Yu)

Vinylcyclopropanes (VCPs) have been widely used in transitionmetal-catalyzed cycloaddition reactions.⁸³ The presence of an olefin ligand directs the transition-metal for the selective C–C bond cleavage of the highly strained cyclopropane ring. In 2010, Yu and coworkers developed a Rh(1)-catalyzed [(3 + 2) + 1] cycloaddition reaction,⁸⁴ which could be regarded as a homologous Pauson–Khand reaction (Scheme 22). Highly substituted bicyclic cyclohexenones and cyclohexanones could be obtained by this method.

In 2015, they extended the scope of this methodology further and reported a Rh(i)-catalyzed [(3 + 2) + 1] cycloaddition reaction of 1-ene-vinylcyclopropane and CO to build the cis-hydrodibenzofuran skeleton. This strategy was then applied to the formal synthesis of (\pm) -galantamine and (\pm) -lycoramine (Scheme 23).26 The substituted vinylcyclopropane substrate 92 was prepared from 89 in 3 steps. The phenol 89 and alcohol 90 underwent a Mitsunobu reaction to form the allylic ether 91 in 71% yield. A Claisen rearrangement in naphthane transformed 91 to a phenol, which underwent a Cu- catalyzed O-vinylation with 2,4,6-trivinylcyclotriboroxane-pyridine complex⁸⁵ to give the 1-ene-VCP 92. The key Rh-catalyzed [(3 + 2) + 1] cycloaddition reaction under 1 atm of CO gas generated the desired tricyclic cis-hydrodibenzofuran product 93. The yield dropped slightly when the reaction was scaled up. Compound 93 was transformed to aldehyde 94 in 3 steps. Following Tu's precedent,13,86 aldehdye 94 was converted to amide 95 under radical oxidation conditions (vide infra). Install the D ring by a Pictet-Spengler cyclization using Guillou's procedure generated the tetracyclic compound 64,73 which is a key intermediate in Zhou and Xie's total synthesis of galantamine.22





Scheme 23 Yu's formal total synthesis of galantamine.

3.7 "Cut and sew" carboacylation reaction (Xu)

Transition metal-catalyzed carbon–carbon bond activation has been increasingly used as a powerful tool for devising unusual bond-disconnecting strategies. The "cut and sew" strategy uses strained rings (benzocyclobutenones and cyclobutanones) with a tethered unsaturated moiety as substrates. It starts with the oxidative addition of a transition metal into the cyclic C–C bond (the "cut" step) to give a reactive metallacycle, followed by intramolecular migratory insertion of the unsaturated unit and reductive elimination to furnish the ring (the "sew" step) (Scheme 25).^{87,88}

In 2020, Xu and coworkers reported a novel strategy for the formal total synthesis of galantamine and lycoramine.³⁵ The

concise synthesis was enabled by a Rh-catalyzed intramolecular "cut and sew" carboacylation reaction for the formation of the tetracyclic framework and a regioselective Pd-catalyzed C-H activation for double-bond introduction.

Their synthesis commenced with the preparation of substituted benzocyclobutenone **102** (Scheme 24). Lithium enolate **98** was first prepared *in situ* from THF and *n*-BuLi. Slow addition of a freshly prepared solution of lithium tetramethylpiperidide (LiTMP) to a mixture of aryl bromide **96** and lithium enolate **98** generated the highly reactive substituted aryne **97**, which underwent the [2 + 2] cycloaddition reaction with **98** to afford the benzocyclobutanol **99** regioselectively in 64% yield on a decagram scale.⁸⁹ The adjacent methoxymethyl ether (MOM) group on benzyne allowed the



Scheme 24 Preparation of benzylcyclobutenone 102

Natural Product Reports

production of **99** as a single regioisomer through the negative inductive effect.⁹⁰ Dess–Martin oxidation of the alcohol followed by removal of the MOM group under acidic conditions afforded benzocycloubutenone **100** in 79% overall yield on a decagram scale. Alkylation of **100** with the known bromide **101** followed by a selective Wittig olefination provided the key C–C activation precursor **102** in 45% yield over 2 steps.

After screening and optimization of the reaction parameters, it was found that the key "cut and sew" carboacylation reaction⁸⁷



Scheme 25 The "cut and sew" carboacylation reaction of 102.



Scheme 26 Xu's formal total synthesis of (\pm) -galantamine and (\pm) -lycoramine.

of **102** was best performed with the catalysis of $[Rh(CO)_2Cl]_2$ (5 mol%) in combination with an electronically poor monodentate phosphine ligand P(C₆F₅)₃ (22 mol%). Ring opening of the strained cyclobutenone *via* C–C bond cleavage, followed by cyclization with the tethered olefin generated the desired product **105** in 77% yield on a gram scale (Scheme 25).

Having successfully established the core structure of the target, the next goal was to form the azepine D ring by an Ninsertion reaction of the tetracyclic ketone 105 (Scheme 26). They first tried the Schmidt rearrangement, but it was unsuccessful. Instead, condensation of 105 with hydroxylamine gave the corresponding oxime quantitatively as a separable mixture of E/Z isomers (E/Z = 1 : 1.2). The E-isomer **106** was isolated and tosylated, and the Beckmann rearrangement occurred spontaneously at 30 °C in THF/water without any additives to give the desired amide. Subsequent N-methylation generated Zhou and Xie's intermediate 64,22 which underwent a Pd-catalyzed regioselective dehydrogenation reaction according to Stahl's procedure⁹¹ to give Guillou's enone 43.73 Sequential reduction of the ketone and lactam groups with L-selectride and LiAlH₄ successfully elaborated intermediates 64 and 43 to (\pm) -lycoramine (6) and (\pm) -galantamine (1), respectively. The longest linear sequences of the total synthesis of galantamine and lycoramine are 11 and 10 steps, respectively.

3.8 Olefin carbonylative annulation (Zhao)

In 2021, Zhao and coworkers reported a highly efficient formal total synthesis of galantamine and lycoramine.³⁷ A two-phase approach was used in their total synthesis, with a palladium-catalyzed carbonylative cascade annulation and a DDQ-mediated regioselective intramolecular oxidative lactamization to generate the tetracyclic skeleton in the early phase, followed by a BF₃·OEt₂-promoted selective reorganization of the bridged tetracyclic skeleton in the late phase.

Their synthesis started with the deprotonation of racemic allylic alcohol 107, followed by intermolecular O-alkylation with freshly prepared benzylic bromide 108 in the presence of a catalytic amount of NaI to provide the desired 109 in 82% yield (Scheme 27). The crucial palladium catalyzed carbonylative lactonization reaction was then investigated under a variety of conditions.92,93 It was found that the reaction could be catalyzed by Pd(OAc)₂ without additional ligand, in the presence of AgOTf and a sterically hindered base 2,6-di-tertbutylpyridine (DTBP) under 1 atm of carbon monoxide. Loss of the MOM group in situ under the reaction conditions led directly to the desired lactonization product 110 in 61% yield. In contrast to the *cis*-5,6-bicyclic products obtained in the previous total syntheses, only the trans-6,6-bicyclic product was obtained in this case. Treatment of 110 with MeNH₂·HCl in the presence of K₂CO₃, followed by one-pot deprotection of the ketal, afforded the amide 111 in 76% yield. The X-ray crystal structure of 111 confirmed the trans-6,6-bicyclic structure of 110. Although there are many precedents for similar transformations, the structural rearrangement of compound 111 to the galantamine skeleton was unsuccessful under a variety of conditions. Instead, oxidation of 111 with DDQ proceeded





Scheme 27 Palladium catalyzed carbonylative esterification.

smoothly to afford the bridged tetracyclic aza-acetal **112** in excellent yield.

Compound **112** was found to be a suitable substrate for the desired skeletal rearrangement reaction (Scheme 28). They were

pleased to find that treatment of **112** with $BF_3 \cdot Et_2O$, followed by the addition of $(EtO)_3SiH$ as the reductant, successfully converted **112** to the desired tetracyclic lactam **64** in 56% yield. Presumably, the Lewis acid $BF_3 \cdot Et_2O$ initiated the aza-acetal



Scheme 28 Zhao's formal total synthesis of (\pm) -galantamine and (\pm) -lycoramine.

Natural Product Reports

cleavage, a retro-oxa-Michael addition and a phenolic oxa-Michael addition cascade to afford the tetracyclic iminium, followed by reduction with $(EtO)_3SiH$ to give the known lactam **64**.²² Remarkably, this sequence allowed the preparation of hundreds of milligrams of late intermediate **64** in 19% overall yield in five steps from compounds **107** and **108** in a single batch. As in the previous total synthesis, further oxidation state adjustment of **64** completed the seven- and six-step syntheses of (\pm) -galantamine (**1**) and (\pm) -lycoramine (**6**), respectively.

4. Rearrangement reactions

Intramolecular rearrangement reactions are efficient ways to build sterically hindered quaternary centers. Stereospecific rearrangement reactions, such as the sigmatropic rearrangement, can transfer the chirality from a less hindered stereocenter to a sterically congested one with high fidelity. These reactions have been extensively employed in the total syntheses of natural products with quaternary centers. Several rearrangement reactions have been successfully applied in the synthesis of galantamine.^{13,15,19,38,43}

4.1 Semipinacol rearrangement (Tu)

In 2006, Tu and coworkers reported their total synthesis of (\pm) -galantamine in 13 steps from the commercially available compounds.¹³ The overall yield of their synthesis is 12%. Similar to their previous work on the total synthesis of lycoramine,⁹⁴ a semi-pinacol rearrangement reaction of an allylic alcohol was used to build the benzylic quaternary center.

A modified Shapiro reaction of hydrazone 113 with n-BuLi generated a vinyl lithium,95 which reacted a o-vanillin derivative to give an allylic alcohol 114 in 85% yield (Scheme 29). Upon treatment of 114 with NBS in DCM at 0 °C, the aldehyde 116 with a quaternary center was obtained in 95% yield as a single isomer. Presumably, a bromonium ion 115 was formed first, followed by a stereospecific semipinacol rearrangement of the aromatic group to generate the quaternary center. Reaction of 116 with DBU in DMSO initiated a one-pot desilylation and intramolecular S_N2 type cyclization reaction to form the B ring and gave the tricyclic product 117 in 90% yield.94 Compound 117 was then transformed into aldehyde 118 in 6 steps, including a one-carbon homologation of the aldehyde and oxidation state adjustment of the C ring. A radical oxidation of the aldehyde generated the corresponding acid bromide, which reacted with MeNH₂ to give an amide 119.86 A further Pictet-Spengler reaction of 119 with paraformaldehyde gave the known lactam,73 and reduction of the lactam afforded (\pm) -galantamine.

4.2 Johnson-Claisen rearrangement (Bisai)

In 2022, Bisai and coworkers reported asymmetric total synthesis of naturally occurring Amaryllidaceae alkaloids sharing dihydrobenzofuran scaffolds, including (–)-galantamine (1), (–)-lycoramine (6), and (–)-narwedine (5).³⁸ The synthesis used a key catalytic enantioselective Corey–Bakshi–Shibata (CBS) reduction of α -bromoenone (99% ee), the chirality of the resulting secondary alcohol was transferred to an all-carbon quaternary center *via* an orthoester Johnson–Claisen rearrangement.

NHTris ⁿBuLi, then MeO NBS СНО TBSO (95%) OH OTBS 115 114 OMe Ó 113 (85%) MeO MeO MeO TBSO CHO 6 steps CHO DBU Br СНО (90%) (42%) C Ω НÒ 118 116 117 MeO MeC 1) Ac₂O 1) (CH₂O)_n pyridine TFA C 2) NBS, AIBN H 2) LiAlH₄ Me then MeNH₂ (62%) (60%) ŃHMe ΗÔ НÒ (±)-1 119

Scheme 29 Tu's total synthesis of (\pm) -galantamine.



Scheme 30 The orthoester Johnson–Claisen rearrangement.



The α -bromo-3-arylcyclohexenone **120** was synthesized by a Stork–Danheiser reaction over a 10 g scale.⁹⁶ CBS reduction of **120** was carried out using the 20 mol% (*S*)-Me-CBS catalyst at 25 °C for 3 h to afford allyl alcohol **121** in 99% ee on gram scale (Scheme 30).⁹⁷ The bromo atom at the α -position was essential for the high enantioselectivity. Two sets of conditions were identified for the crucial Johnson-Claisen rearrangement.98,99 In the first approach, debromination with *n*-BuLi afforded the allylic alcohol 122, Conventional weak acidic conditions for the Johnson-Claisen rearrangement of 122 led to the product with decreased ee. Further optimization revealed that reaction in a basic medium suppressed the loss of optical purity. Under the optimized conditions, heating a solution of 122 (98% ee) and triethyl orthoacetate in DIPEA promoted the orthoester Johnson-Claisen rearrangement to produce the desired ester 123 in 68% yield in 48 h without the loss of optical purity (97.4% ee). Microwave irradiation shortened the reaction time to 20 min at 210 °C. In the second approach, the orthoester Johnson-Claisen rearrangement of 121 was carried out in the presence of onitrophenol using 20 equivalents of triethyl orthoacetate at 220 °C for 36 h. This reaction afforded the desired product without the loss of optical purity. A radical-initiated debromination with tributyltin hydride (Bu₃SnH) in the presence of catalytic AIBN provided product 123.

An allylic oxidation of **123** using CrO₃ in the presence of 3,5dimethylpyrazole (DMP) afforded the enone **124** in 71% yield (Scheme 31).¹⁰⁰ A chemoselective demethylation of **124** with 1.05 equivalent of BBr₃ resulted in a concomitant oxa-Michael cyclization to form the tricyclic structure and delivered **125** in 91% yields in a one-pot fashion. The ester was transformed to an amide, which underwent a Pictet–Spengler reaction with paraformaldehyde to generate the azepine D ring and gave compound **64**, an intermediate in Zhou and Xie's total synthesis.²² The tetracyclic compound **64** was a versatile intermediate and was converted to four Amaryllidaceae alkaloids in 2–5 steps, including (–)-galantamine.

4.3 Eschenmoser-Claisen rearrangement (Li)

In 2023, Li and coworkers reported a chemo- and regioselective 1,2reduction of arenes *via* η^6 -coordination to chromium (126), providing rapid access to 1,3-cyclohexadienes **128** (Scheme 32).⁴³ The process begins with the *in situ* generation of the hydride ion from Ph₃SiH and KOt-Bu or Me₄NF. This ion then attacks the arene ring to form the η^5 -cyclohexadienyl anion intermediate. Protonation of this intermediate results in the formation of the Cr–H species **127**. Reductive elimination completes the 1,2reduction process, and the resulting η^4 -cyclohexadiene complex quickly undergoes solvolysis to release the final 1,3-cyclohexadiene product. The reaction conditions are mild and can tolerate various reduction-sensitive functional groups. More than 50 examples



> 50 examples precise, regiodivergent deuteration

Scheme 32 Selective 1,2-reduction of chromium-bound arenes.



Scheme 33 Li's formal total synthesis of (\pm) -galantamine via 94.

have been developed to demonstrate the versatility of the reaction. Additionally, it allows for regiodivergent deuteration, with precise control over the position of deuteration and the degree of deuterium incorporation by using different sequences of (non)deuterated hydride and acid reagents.

The reaction was then applied in a formal total synthesis of galantamine (Scheme 33). The η^6 -coordinated chromium complex **130** was prepared by refluxing 4-methoxydibenzo[*b*,*d*] furan **129** with chromium hexacarbonyl. Following the standard conditions developed above, the chromium-bound complex **130** was reduced to a diene on a gram-scale. The crude 1,2-reduction product was subjected to a hydroboration/oxidation process to give the alcohol product **131**. A novel dearomative Eschenmoser–Claisen rearrangement was used to convert **131** to amide **132** with a quaternary center in 78% yield. Compound **132** was further transformed to compound **94**, an intermediate in Yu's synthesis of (±)-galantamine.²⁶

5. Alkylation reactions

The enolate alkylation reaction is a fundamental and wellestablished process for C–C bond formation, including the creation of bonds involving highly congested quaternary centers. The control of the stereoselectivity of enolate alkylation using chiral auxiliaries, chiral bases, and chiral catalysts has received considerable attention, resulting in many innovative methodologies. The enolate alkylation reaction has been successfully implemented in the construction of the congested quaternary center and C ring of galantamine. Highly efficient asymmetric enolate alkylation reactions with organocatalysts and Lewis acid catalyst were identified for the asymmetric total synthesis of (–)-galantamine.

5.1 Cascade double Michael addition and Dieckmann reaction (Ishikawa)

In 2008, Ishikawa and Saito developed a practical method for synthesizing 4,4-disubstituted cyclohexane-1,3-diones from nonactivated simple ketones (Scheme 34).¹⁶ The process involved a double Michael addition of substituted acetone derivatives **133** with excess acrylic acid ester under basic conditions, followed by a Dieckmann cyclization, resulting in the formation of 4,4-disubstituted cyclohexane-1,3-diones **134** in a single pot. Interestingly, only highly substituted enolates participate as Michael donors in the cascade process. Enol ethers **135** were selectively formed from diketones **134** under acidic conditions. Alkyl and aryl groups were successfully



Scheme 34 The cascade double Michael addition and Dieckmann reaction.



Scheme 35 Ishikawa and Saito's synthesis of (\pm) -galantamine and (\pm) -lycoramine.

introduced at the quaternary stereogenic center, which is typically challenging to achieve.

completed the enantioselective total synthesis of (-)-galantamine.

Enol ethers 135 were found to be useful intermediates for the synthesis of sterically congested natural products (Scheme 35). A hydroxy enone was obtained by reduction of the ester and ketone groups of 136. When treated with TsOH, it underwent an intramolecular oxy-Michael addition reaction, and the olefin was temporarily protected. Subsequent O-debenzylation under hydrogenolysis conditions gave a phenol derivative 137. A MgCl₂-mediated retro-Michael and a phenolic hydroxy-Michael addition reaction of 137 afforded the thermodynamically more stable dihydrobenzofuran 138. The primary hydroxy group of 138 was transformed to a carbamate 139 in 3 steps. A Pictet-Spengler cyclization of 139 with paraformaldehyde generated the D ring and gave the key tetracyclic product 140.73 As in the previous total syntheses, compound 140 served as a common intermediate for the total syntheses of (\pm) -galantamine and (\pm) -lycoramine.

Ishikawa's work opened up a new avenue for the total synthesis of galantamine. In the majority of previous total syntheses, the C ring of galantamine was obtained from commercial supplies. Ishikawa's work was one of the earliest examples to generate the C ring during the total synthesis, and it was also the first example to create the quaternary center by the classic enolate alkylation reaction. The new synthetic strategy provides many opportunities for the development of asymmetric total synthesis of galantamine. Following their racemic synthesis, several groups successfully identified highly efficient asymmetric catalytic systems for similar reactions and

5.2 Organocatalyzed asymmetric intermolecular Michael addition (Fan)

In 2011, Fan and coworkers reported total syntheses of several hydrodibenzofuran alkaloids.²¹ They first developed a method to set up the key sterically congested aryl-substituted quaternary carbon center through an organocatalytic asymmetric intermolecular Michael addition of α -aryl- α -cyanoketones **141** with acrylates **142** (Scheme 36). Compound **141** was readily prepared in 5 steps from *o*-vanillin in a good overall yield. The Takemoto catalyst **144** (ref. 101) and the cinchonidine-derived bifunctional catalyst **145** (ref. 102) gave the best results and allowed for tuning of the enantioselectivity. Among the solvents tested, *p*-xylene was found to be the optimal choice with respect to both enantioselectivity as well as the reactivity of the catalyst.

Using **144** as the catalyst, the Michael addition of **141** and **142b** yielded the functionalized δ -keto ester **143b** with an arylsubstituted all-carbon quaternary center. Iodide **143b** was selected for the final synthesis because of its ease of crystallization. An optical purity of 99% ee was obtained with a yield of 74% after a single recrystallization. The absolute configuration of the chiral all-carbon quaternary stereocenter was confirmed by X-ray crystallography.

Following Ishikawa's racemic total synthesis, compound **143b** underwent a Dieckmann condensation reaction under basic conditions. The resulting 1,3-diketone was regioselectively transformed to enol ether **146** under acidic conditions (Scheme



Scheme 36 Intermolecular asymmetric Michael addition to form the quaternary center.

37). The subsequent Luche reduction of **146**, followed by acidic workup led to the formation of an enone that underwent a further intramolecular oxa-Michael addition reaction. The tricyclic intermediate **147** with the key *cis*-hydrodibenzofuran skeleton was obtained in 40% yield over 4 steps. Subsequently, a one-carbon homologation of the nitrile group was performed in 7 further steps, converting **147** into the carbamate **148**. Compound **148** underwent a Pictet–Spengler reaction with paraformaldehyde to form the tetracyclic compound **140**, which is a key intermediate in Ishikawa's racemic total synthesis.¹⁶ Following similar reaction sequences, **140** was converted to (-)-galantamine and (-)-lycoramine after the oxidation state adjustment.

5.3 Lewis acid catalyzed asymmetric intermolecular Michael addition (Jia)

In 2015, Jia and coworkers disclosed a catalytic asymmetric total synthesis of (-)-galantamine (1) and (-)-lycoramine (6).²⁵ Two metal catalyzed reactions were developed to build the core structure of the natural products. Specifically, a palladium-catalyzed intramolecular Larock annulation reaction was employed to construct the 3,4-fused benzofuran,



Scheme 37 Fan's formal synthesis of (–)-galantamine and (–)-lycoramine via 140.

Review

while a Sc(m)/N, N'-dioxide complex catalyzed enantioselective conjugate addition of a 3-alkyl-substituted benzofuranone to methyl vinyl ketone was used to set up the quaternary carbon center.

They first investigated the synthesis of 3,4-fused benzofuran by an intramolecular Larock annulation reaction of an *ortho*iodophenol tethered with an internal alkyne.¹⁰³ The reaction of **149** under the catalysis of $[Pd_2(dba)_3]$ (5 mol%) and $P(t-Bu)_3$ · ·HBF₄ (20 mol%) afforded the desired product **150** in 95% yield (Scheme 38). This transformation was found to be quite general, with more than 15 examples of 3,4-fused benzofurans containing either carbon, oxygen, or nitrogen tethers were obtained in reasonable yields.

Having developed this method, they applied it to the total synthesis of galantamine. The substrate 151 was obtained in 2 steps from readily available materials. Under the reaction conditions developed above, the 3,4-fused benzofuran 152 was obtained from 151 in 89% yield. Removal of the TES group with TBAF followed by oxidation with *m*-CPBA afforded the lactone 153. They then explored the construction of the chiral all-carbon quaternary stereocenter. They first examined a number of organocatalysts for the reaction of 153 with methyl vinyl ketone (MVK). However, the highest enantioselectivity obtained was 55% ee. Alternatively, other catalytic reaction systems were explored, and it was discovered that a combination of the Lewis acid Sc(OTf)₃ with the chiral N,N'-dioxide ligand 154 catalyzed the asymmetric Michael addition reaction of 153 to MVK.¹⁰⁴ The reaction proceeded smoothly at room temperature to afford the desired product 155 in 85% yield with 93% ee. An intramolecular cyclization reaction of 155 yielded a hemiketal and generated the tetracyclic core structure 156. Ionic reduction of

the hemiketal with Et_3SiH resulted in simultaneous reduction of the ketone and removal of the Boc group. Protection of the amine with methyl chloroformate and oxidation of the alcohol delivered **140**, the key intermediate in Ishikawa's racemic total synthesis¹⁶ and Fan's asymmetric synthesis (Scheme 39).²¹

5.4 Organocatalyzed asymmetric Robinson annulation (Tu)

In 2019, Tu and coworkers reported catalytic asymmetric total syntheses of (-)-galantamine (1) and (-)-lycoramine (6).³³ They developed a spirocyclic pyrrolidine (SPD)-catalyzed enantioselective Robinson annulation reaction to construct the key *cis*-hydrodibenzofuran core with the all-carbon quaternary stereocenter.¹⁰⁵

Their synthesis commenced from 3-butyn-1-ol **157** (Scheme 40). A one-pot double transformation of **157** led to an internal alkyne **158**. A copper catalyzed regioselective and stereoselective hydroboration reaction of alkyne **158**, followed by a Pd-catalyzed Suzuki coupling reaction with aryl bromide **159**, selectively afforded the trisubstituted olefin **160**. Compound **160** was then converted to the α , β -unsaturated ketone **161**.

An initial effort was made to produce the tricyclic compound **164** through a direct intramolecular Robinson annulation of **161**. However, the transformation stopped at the Michael addition stage, despite numerous experimental conditions screening. The product was isolated as **163** after a Wittig olefination. Among the reaction conditions screened, it was discovered that the Michael addition/Wittig olefination product **163** was obtained in good yield and selectivity in the presence of the SPD catalyst **C** and 2,4,6-triisopropylbenzoic acid as an additive. The outcome of the reaction was further improved by decreasing the reaction temperature to -30 °C,



Scheme 38 Larock-type annulation for the synthesis of 3,4-fused benzofurans.



Scheme 39 Jia's formal total synthesis of (–)-galantamine via 140.



Scheme 40 Synthesis of α , β -unsaturated ketone 161.

resulting in the product **163** being obtained in 87% yield with 96% ee (Scheme 41).

As a direct intramolecular Robinson annulation of **161** to generate the tricyclic compound **164** was not successful, it was discovered that an acid catalyzed aldol cyclization reaction of crude Michael product **163** afforded the tricyclic compound **164** (>99% ee) (Scheme 42). Compound **164** was used as a key intermediate in their total synthesis of morphine.¹⁰⁵ A Rubottom oxidation reaction installed the hydroxy group of **165** in 3 steps from compound **164**. Followed by a further oxidation state adjustment, the aldehyde **166** was generated in 5 steps. The

tetracyclic product **167** was produced by oxidative amidation of the aldehyde and a Pictet–Spengler reaction with paraformaldehyde, following the protocol from their previous racemic total synthesis,¹³ Stereo inversion of the alcohol was achieved by Dess–Martin oxidation of the alcohol and L-selectride reduction of the ketone. A final lactam reduction with LiAlH₄ completed the total synthesis of (-)-galantamine (1).

5.5 Aryne insertion reaction (Chandrasekhar)

In 2019, Chandrasekhar and coworkers reported a racemic total synthesis of (\pm) -galantamine (1).³⁴ The process involved only two sub-critical temperature reactions and less than five chromatographic purifications. The synthesis used a key regioselective aryne insertion reaction into a GABA (γ -amino butyric acid) derivative to form the substituted aromatic A ring of galantamine.

Aryne is a highly reactive intermediate, it allows rapid functionalization of an aromatic ring by forming multiple carbon–carbon or carbon–heteroatom bonds in a single operation. The acyl–alkylation reaction of aryne with β -ketoester represents a mild and direct aryne insertion into a carbon– carbon bond (Scheme 43). The use of *o*-silyl aryl triflates, *e.g.*, **168**, as aryne precursors has allowed generation of the reactive intermediate under almost neutral conditions. The acylalkylation product **170** is the net result of aryne insertion into the α , β C–C single bond of the β -ketoester **169**, presumably by a formal [2 + 2] cycloaddition/fragmentation cascade.¹⁰⁶

The synthesis began with the β -formyl ester **171**, which was synthesized from GABA in four steps. Upon treatment with the methoxy benzyne precursor **172** and cesium fluoride (CsF), the trisubstituted aryl compound **173** was regioselectively obtained



Scheme 41 Intramolecular Michael addition/Wittig olefination of α, β-unsaturated ketone 161.



Scheme 42 Tu's total synthesis of (–)-galantamine.

in 62% yield (Scheme 44). The methoxy group on benzyne, through the negative inductive effect,⁹⁰ provided **173** as a single regioisomer. The product was transformed to the lactone **174** in 3 steps. The lactone was α -alkylated with methyl vinyl ketone, and the azepine D ring was installed with a Pictet–Spengler reaction to generate compound **175**. A further intramolecular condensation reaction gave the tetracyclic product **176**, which is a close analogue of Jia's intermediate **156**.²⁵ By carrying out similar transformations to those in Jia's synthesis, compound **176** was converted to galantamine in a further seven steps.

5.6 Intramolecular phenol alkylation (Magnus)

In 2009, Magnus and coworkers reported a distinct total synthesis of (\pm) -narwedine (5).¹⁸ The synthesis used the *para*-alkylation of a substituted phenol as the key reaction.³¹ This reaction generated the cross-conjugated 2,5-cyclohexadienone **179** with a quaternary center and avoided the phenolic oxidation reaction.

Their synthesis commenced from a Suzuki cross coupling reaction of commercially available 2-bromovanillin (**30**) with the



Scheme 43 Acyl-alkylation of aryne with β -ketoester.

boronic acid anhydride **177** (Scheme 45). The resulting biaryl phenol was treated with ethyl vinyl ether and Br_2 in the presence of *N*,*N*-diisopropylethylamine at 0 °C. The bromoetherification product **178** was obtained in excellent yield (98%). Exposure of **178** to CsF (3 equiv.) in *N*,*N*-dimethylformamide (DMF) at 130 ° C resulted in a clean desilylation and intramolecular alkylation reaction. The 2,5-cyclohexadienone **179** was obtained in high

yield, and thus confirming the viability of this strategy. Acid catalyzed hydrolysis of the acetal in **179** resulted in two oxa-Michael addition reactions to give product **180**. Reductive amination of **180** with MeNH₂ generated the azepine D ring, which was converted into narwedine (5) by treatment with MeSO₃H. The overall process was completed with an impressive yield of 63%, which is approximately five times the yield of the current commercial process.^{60,61} Since (\pm)-narwedine (5) has been converted into (-)-galantamine (**1**) by a crystallizationinduced dynamic chiral resolution, and a diastereoselective reduction with L-selectride,⁵⁸ this completes an eight-step formal total synthesis of (-)-galantamine (**1**).

6. Miscellaneous approaches

Other than the above four general approaches to the total synthesis of galantamine, there are several other miscellaneous approaches reported. Yu and coworkers reported a formal synthesis with a radical cyclization to form the quaternary



Scheme 44 Chandrasekhar's total synthesis of (±)-galantamine.



Scheme 45 Magnus' total synthesis of (±)-narwedine.

Review



center,³⁰ Cho and coworkers reported a synthesis of (\pm) -galantamine by a tandem C3-selective Stille couplingintramolecular Diels–Alder (IMDA) cascade reaction.²⁰ Nagase and coworkers finished a semi synthesis from naltrexone,³² which will not be discussed in this review.

6.1 Tandem Stille/IMDA (Cho)

In 2010, Cho and coworkers reported their synthesis of (\pm) -galantamine by using a tandem C3-selective Stille couplingintramolecular Diels–Alder (IMDA) cascade of 3,5-dibromo-2pyrone as a key strategy, which was a novel strategy and a valuable addition to the galantamine synthesis predominated by the approaches involving either oxidative phenol coupling or an intramolecular Heck reaction.²⁰

A Cu(π)-promoted *O*-vinylation of the iodophenol **46** provided the aryl vinyl ether **181** in good yield.¹⁰⁷ The Pd-catalyzed stannylation of iodide in **181** proceeded smoothly to afford the aryltin fragment **182**. Alternatively, compound **182** could be made in 2 steps from the bromo analogue **183** in a more economical way (Scheme 46).

A C3-selective Stille coupling reaction of **182** with 3,5dibromo-2-pyrone was best performed with 5 mol% of Pd(PPh₃)₄ and 10 mol% of CuI in DMF (Scheme 47). The reaction did not afford the Stille coupling product **185**, but instead gave the tandem Stille/IMDA cascade product **186** directly in modest yield and selectivity. The lactone ring opening of 6-*endo* product **186** with NaOMe and protection of the resultant secondary hydroxyl group as a MOM ether furnished ester **187** in 84% yield over two steps. From this point, they converted compound **187** to the tetracyclic intermediate **188** in 7 steps, adapting the procedures developed by Trost and co-workers for the synthesis of galantamine on the basis of the structural similarity with their tricyclic intermediate.⁶⁹ Final epimerization of the alcohol and reductive removal of the bromide afforded galantamine (**1**).

6.2 Radical cyclization (Yu)

In 2016, Yu and coworkers reported another formal total synthesis of (-)-galantamine,³⁰ shortly after the first generation.²⁶ They first investigated a Rh-catalyzed [5 + 1] cycloaddition of di- and tri-substituted allenylcyclopropanes with CO (Scheme 48). The allene derivative **191** was prepared in 5 steps



Scheme 47 Cho's total synthesis of galantamine.



Scheme 48 Rh-catalysed [5 + 1] cycloaddition of allenylcyclopropanes and CO.



Scheme 49 Yu's formal total synthesis of (–)-galantamine *via* 50.

from the propargylic alcohol **189**. Under the optimized conditions, the Rh-catalyzed cycloaddition reaction of **191** with CO afforded the functionalized 2-methylidene-3,4-cyclohexenone **192**.

CBS reduction of enone **192** led to the chiral alcohol product **193** in 79% yield and 97% ee (Scheme 49). Then alcohol **193** and the known phenol underwent the Mitsunobu reaction to form ether **194** in 86% yield. The TBS group was deprotected using TBAF and then the alcohol intermediate was oxidized to aldehyde **195** by activated MnO_2 in 86% yield over two steps. The initial attempts to form the five-membered ring in the natural product (–)-galantamine with Heck reaction of **194** or its deprotected alcohol was not successful. It was found that the starting materials decomposed slowly under the reaction conditions. Instead, ring closing cyclization of **195** under the radical conditions led to the desired product in 60% yield. Finally, reduction of the aldehyde led to Brown's intermediate **50** in total synthesis of galantamine,¹⁴ which constituted a formal total synthesis of (–)-galantamine.

7. Summary of the total syntheses

Prior to 2006, there were only two synthetic strategies available for constructing the quaternary center in the total synthesis of galantamine: oxidative phenol coupling and the intramolecular Heck reaction.⁹ The asymmetric total synthesis of galantamine relied on chiral auxiliaries or chemical resolution, with only one example of catalytic asymmetric total synthesis coming from the Trost group. However, substantial progress has been made in the synthetic chemistry of galantamine since then, with over 30 new syntheses reported (Table 1).

7.1 Evolution of synthetic strategy for the quaternary center

For almost half a century, the field has been dominated by the classical oxidative phenol coupling method, during which time some landmark achievements were discovered. The biomimetic oxidative phenol coupling reaction evolved from a low-yield, proof-of-concept experiment⁵⁰ to a high-yield, reliable synthetic strategy.^{53,55} Asymmetric versions of total synthesis were achieved with chiral auxiliary control,^{56,57} and more significantly, with the discovery of crystallization-induced dynamic resolution of (\pm)-narwedine.⁵⁸ Finally, based on these early discoveries, an impressive pilot scale chemical synthesis of (–)-galantamine was developed.^{60,61} Recent progress on this strategy involves the implementation of new synthetic technologies, including chemoenzymatic synthesis³⁶ and electrosynthesis.^{39,40}

The situation changed at the beginning of this century with the advent of transition metal catalyzed reactions.⁶⁹⁻⁷² These reactions not only introduced new synthetic strategies, but also provided new ways for the asymmetric synthesis of (–)-galantamine, which coincides with the rapid development in the field of transition metal catalyzed asymmetric reactions. Since these pioneering works, in addition to the use of the Heck coupling strategy in new circumstances,^{14,23,24,28,29,41,42} novel transition metal catalyzed reactions, such as the reductive Heck reaction,²² rhodium-catalyzed C–C bond activation,^{26,30,35} and palladiumcatalyzed cyclization reactions,^{27,37} have been successfully applied in the total synthesis of galantamine.

In addition to the advances in the two classical approaches mentioned above, several more diverse synthetic strategies have emerged in the recent total synthesis of galantamine, including enolate and phenolate alkylation reactions, several types of rearrangement reactions and other miscellaneous approaches. Highly efficient asymmetric total syntheses have been developed based on either traditional stoichiometric chiral reagents³⁸ or asymmetric Lewis acid catalysis²⁵ and organocatalysis.^{21,33}

7.2 Assembly of the tetracyclic structure

The aromatic A ring was obtained from commercial sources and was used as the starting material in most total syntheses of galantamine. The only exception was the total synthesis reported by Banwell in 2015.²⁷ They used a regioselective Diels–Alder reaction of a diene with propynal, followed by oxidation to form the A ring.

The heterocyclic B ring was formed either by C–O bond linkage *via* an intramolecular phenolic oxa-Michael addition in

Table 1 Tabulated summary of highlighted syntheses of galantamine since 2006

Strategy	Main author/Year	Key reactions	Ring forming sequence	Source of chirality	Ref.
Oxidative phenol coupling	Bandichhor/2008 Wirth/2022 Opatz, Waldvogel/2022 Saladino/2022	Phenol oxidative coupling Electrosynthesis Electrosynthesis Chemoenzymatic phenol oxidative coupling	$\begin{array}{l} A+C \rightarrow DB \\ A+C \rightarrow DB \\ A+C \rightarrow D \rightarrow B \\ A+C \rightarrow D \rightarrow B \\ A+C \rightarrow D \rightarrow B \end{array}$	Chemical resolution Chiral pool Racemic Racemic	17 39 40 36
Transition metal catalyzed reaction	Zhou, Xie/2012 Brown/2007 Brown/2022 Banwell/2015 Banwell/2015	Dynamic kinetic resolution and reductive Heck Enyne RCM and Heck reaction Enyne RCM and Heck reaction Alder-ene, Diels-Alder <i>B</i> -alkyl Suzuki <i>B</i> -alkyl Suzuki, Heck	$\begin{array}{c} A+C \rightarrow B \rightarrow D \\ A \rightarrow C \rightarrow B \rightarrow D \\ A \rightarrow C \rightarrow B \rightarrow D \\ C \rightarrow B \rightarrow A \rightarrow D \\ C \rightarrow B \rightarrow A \rightarrow D \\ A+C \rightarrow B \rightarrow D \\ A+C \rightarrow D \rightarrow D \\ A+C \rightarrow D \rightarrow D \\ A+C \rightarrow D \rightarrow D \rightarrow D \\ A+C \rightarrow D \rightarrow $	Dynamic kinetic resolution Asymmetric ketone reduction Asymmetric aldehyde allylation Racemic Asymmetric ketone reduction	22 41 27 42
Enolate alkylation	Yu/2015 Xu/2020 Zhao/2021 Ishikawa/2008 Fan/2011 Jia/2015 Tu/2019	Rh-catalyzed [(3 + 2) + 1] cycloaddition Rh-catalyzed "cut and sew" reaction Pd-catalyzed olefin carbonylative cyclization Cascade double Michael addition and Dieckmann reaction Organocatalyzed asymmetric Michael addition Lewis acid catalyzed asymmetric Michael addition Organocatalyzed asymmetric Michael addition	$\begin{array}{c} A \rightarrow BC \rightarrow D \\ A + C \rightarrow B \rightarrow D \\ A + C \rightarrow B \rightarrow D \\ A \rightarrow B D \rightarrow C \\ A \rightarrow B \rightarrow C \rightarrow D \end{array}$	Racemic Racemic Racemic Racemic Organocatalysis Lewis acid catalysis Organocatalysis	26 35 37 37 21 21 23 33
Rearrangement reaction	Chandrasekhar/2019 Magnus/2009 Tu/2006 Bisai/2022	Aryne insertion Intramolecular phenol alkylation Semipinacol rearrangement Johnson–Claisen rearrangement	$\begin{array}{c} A \ \ \to \ \ B \ \ \to \ \ D \ \ \to \ C \\ A + C \ \ \to \ \ B \ \ \to \ \ D \\ A + C \ \ \to \ \ B \ \ \to \ D \\ A + C \ \ \to \ B \ \ \to \ D \end{array}$	Racemic Racemic Racemic Catalytic asymmetric ketone reduction	34 18 38 38
Miscellaneous approaches	Li/2023 Cho/2010 Yu/2016	Eschenmoser-Claisen rearrangement Tandem Stille coupling/IMDA Rh-catalyzed [5 + 1] cycloaddition, radical cyclization	$\begin{array}{l} ABC \to D \\ A \to B + C \to D \\ A + C \to B \to D \end{array}$	Racemic Racemic Catalytic asymmetric ketone reduction	43 20 30

View Article Online Review

the oxidative coupling strategy and was the last ring formed for the tetracyclic structure, or alternatively, by C–C bond linkage *via* intramolecular Heck cyclization. Recent developments include the formation of the C–O bond by intramolecular phenolic substitution reaction,¹³ or the formation of the C–C bond *via* intramolecular reductive Heck reaction,²² Alder-ene reaction²⁷ or radical cyclization reaction.³⁰ The B ring has also been formed in intramolecular annulation reactions with concomitant formation of D or C ring.^{25,26,33}

The cyclohexene C ring has been obtained from commercial sources in many total syntheses. However, disconnection at the C ring provides new options for diverse and innovative strategies in the total synthesis of galantamine. Recent progress in the synthesis of C ring include Robinson type annulation reactions,^{16,21,25,33,34} metal catalyzed^{14,26,30,41} or thermal cycload-dition reactions,²⁰ and arene dearomatization.⁴³

The azepine D ring is typically the last ring to be formed in most total syntheses. Methods for the synthesis of this ring were mostly developed before 2006. The A and C rings were united in the intramolecular oxidative phenol coupling reaction, with simultaneous formation of the D ring. Other methods were the intramolecular C–N bond formation *via* reductive amination or *N*-alkylation reaction developed by Trost,^{69,72} and C–C bond formation *via* the Pictet–Spengler reaction first used in Guillou's total synthesis.⁷³ A recent development came from Jia's synthesis,²⁵ in which the D ring was formed by a Pd-catalyzed intramolecular Larock annulation reaction with simultaneous formation of the B ring to give 3,4-fused benzofuran. In Xu' total synthesis, a ring expansion reaction *via* Beckman rearrangement was used to form the D ring.

7.3 Source of chirality

The industrial production of (-)-galantamine currently relies on a highly efficient crystallization-induced dynamic chiral resolution of a racemic intermediate (\pm) -narwedine (5) with a catalytic amount of chiral mediator. This process may reduce the importance of asymmetric synthesis for (-)-galantamine, but it remains a valuable platform for its application. Various methodologies have been used in the asymmetric total synthesis of (-)-galantamine and its enantiomer. These include chemical resolution,¹⁷ biocatalysis,^{19,29} asymmetric ketone reduction with catalytic^{30,38} or stoichiometric^{14,42} chiral reagents, asymmetric aldehyde allylation reaction,⁴¹ and asymmetric catalysis with chiral transition metal complexes,²² chiral Lewis acid²⁵ and organocatalysis.^{21,33}

8. Conclusions

Galantamine is a bioactive natural product that was isolated from a herbal medicine and developed into a clinically approved drug for Alzheimer's disease. It is another gift of nature to mankind.¹⁰⁸⁻¹¹⁰ Because of its important bioactivities, scarcity of the natural resources and intriguing structural features, galantamine has attracted a lot of interest from the synthetic organic chemistry community, and even more so after it became a generic drug. The development of synthetic strategies for the total synthesis of galantamine parallels the advances in modern synthetic organic chemistry. It provides a good opportunity to demonstrate the interplay between targetoriented synthesis and synthetic methodology by summarizing and analyzing the total synthesis of galantamine. It is anticipated that galantamine will remain as a source of inspiration and a test for new synthetic methods and strategies.

The demand for galantamine has outstripped its natural supply. Currently, the natural product is synthesized industrially using the classic work of oxidative phenol coupling and crystallization-induced dynamic resolution. While this method is elegant and practical, there is still room for improvement. Several routes in the previously mentioned total syntheses have already surpassed the current industrial pilot-scale synthesis in terms of both step count and overall yield. The development of new chemistry and technology, as well as the pursuit of sales and profit, may lead to newer and more creative total syntheses of the natural product, potentially including a more efficient and scalable route.^{111,112}

9. Author contributions

B. Cheng wrote the manuscript with the assistance from Q. Wang and Y. An. F. Chen supervised the project.

10. Conflicts of interest

There are no conflicts to declare.

11. Acknowledgements

Financially support from Shenzhen Fundamental Research Program (GXWD20201230155427003-20200822151253001) was acknowledged.

12. Notes and references

- 1 D. A. Cozanitis, Wien. Med. Wochenschr., 2021, 171, 205-213.
- 2 B. Janssen and B. Schäfer, ChemTexts, 2017, 3, 7.
- 3 S. Lilienfeld, CNS Drug Rev., 2002, 8, 159-176.
- 4 A. L. Harvey, Pharmacol. Ther., 1995, 68, 113-128.
- 5 D. Jiang, X. Yang, M. Li, Y. Wang and Y. Wang, *J. Neural Transm.*, 2015, **122**, 1157–1166.
- 6 K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191.
- 7 C. Li, S. S. Ragab, G. Liu and W. Tang, *Nat. Prod. Rep.*, 2020, 37, 276–292.
- 8 P.-W. Xu, J.-S. Yu, C. Chen, Z.-Y. Cao, F. Zhou and J. Zhou, *ACS Catal.*, 2019, **9**, 1820–1882.
- 9 J. Marco-Contelles, M. do Carmo Carreiras, C. Rodríguez, M. Villarroya and A. G. García, *Chem. Rev.*, 2006, **106**, 116– 133.
- 10 U. Rinner, C. Dank and T. Hudlicky, *Targets Heterocycl.* Syst., 2016, 20, 283.
- 11 W. Haiming, C. Peng and T. Meng, Chin. J. Org. Chem., 2014, 34, 852.

- 12 F. Lei, G. O. U. Shao-Hua and Z. Yi-Hua, *Chin. J. Org. Chem.*, 2011, **31**, 286.
- 13 X.-D. Hu, Y. Q. Tu, E. Zhang, S. Gao, S. Wang, A. Wang, C.-A. Fan and M. Wang, Org. Lett., 2006, 8, 1823–1825.
- 14 V. Satcharoen, N. J. McLean, S. C. Kemp, N. P. Camp and R. C. D. Brown, Org. Lett., 2007, 9, 1867–1869.
- 15 H. Tanimoto, T. Kato and N. Chida, *Tetrahedron Lett.*, 2007, **48**, 6267–6270.
- 16 T. Ishikawa, K. Kudo, K. Kuroyabu, S. Uchida, T. Kudoh and S. Saito, J. Org. Chem., 2008, 73, 7498–7508.
- J. M. Reddy, K. V. Kumar, V. Raju, B. V. Bhaskar,
 V. Himabindu, A. Bhattacharya, V. Sundaram,
 R. Banerjee, G. M. Reddy and R. Bandichhor, *Synth. Commun.*, 2008, 38, 2138–2149.
- 18 P. Magnus, N. Sane, B. P. Fauber and V. Lynch, J. Am. Chem. Soc., 2009, 131, 16045–16047.
- 19 M. G. Banwell, X. Ma, O. P. Karunaratne, A. C. Willis, M. G. Banwell, X. Ma, O. P. Karunaratne and A. C. Willis, *Aust. J. Chem.*, 2010, **63**, 1437–1447.
- 20 J. H. Chang, H.-U. Kang, I.-H. Jung and C.-G. Cho, *Org. Lett.*, 2010, **12**, 2016–2018.
- 21 P. Chen, X. Bao, L.-F. Zhang, M. Ding, X.-J. Han, J. Li, G.-B. Zhang, Y.-Q. Tu and C.-A. Fan, *Angew. Chem., Int. Ed.*, 2011, **50**, 8161–8166.
- 22 J.-Q. Chen, J.-H. Xie, D.-H. Bao, S. Liu and Q.-L. Zhou, *Org. Lett.*, 2012, 14, 2714–2717.
- 23 J. Choi, H. Kim, S. Park and J. Tae, *Synlett*, 2013, 24, 379– 382.
- 24 Y. Zang and I. Ojima, J. Org. Chem., 2013, 78, 4013-4018.
- 25 L. Li, Q. Yang, Y. Wang and Y. Jia, Angew. Chem., Int. Ed., 2015, 54, 6255–6259.
- 26 Y. Feng and Z.-X. Yu, J. Org. Chem., 2015, 80, 1952–1956.
- 27 J. Nugent, E. Matoušová and M. G. Banwell, *Eur. J. Org Chem.*, 2015, 3771–3778.
- 28 J. Nugent and M. G. Banwell, *Eur. J. Org Chem.*, 2016, 5862– 5867.
- 29 M. A. A. Endoma-Arias and T. Hudlicky, *Chem.-Eur. J.*, 2016, 22, 14540–14543.
- 30 C.-H. Liu and Z.-X. Yu, *Org. Biomol. Chem.*, 2016, 14, 5945–5950.
- 31 B. Dong, B. Zhou, J. Ren, L. Lu, G. Lu, P. Hu and B.-B. Zeng, *Tetrahedron*, 2017, 73, 4719–4722.
- 32 N. Yamamoto, T. Okada, Y. Harada, N. Kutsumura, S. Imaide, T. Saitoh, H. Fujii and H. Nagase, *Tetrahedron*, 2017, **73**, 5751–5758.
- 33 Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *J. Org. Chem.*, 2019, 84, 12664–12671.
- 34 T. Venkatesh, P. S. Mainkar and S. Chandrasekhar, Org. Biomol. Chem., 2019, 17, 2192–2198.
- 35 Y. Zhang, S. Shen, H. Fang and T. Xu, *Org. Lett.*, 2020, **22**, 1244–1248.
- 36 C. Zippilli, L. Botta, B. M. Bizzarri, M. C. Baratto, R. Pogni and R. Saladino, *RSC Adv.*, 2020, **10**, 10897–10903.
- 37 Y.-P. Chang, X. Ma, H. Shao and Y.-M. Zhao, *Org. Lett.*, 2021, 23, 9659–9663.

- 38 S. Majumder, A. Yadav, S. Pal, A. Khatua and A. Bisai, J. Org. Chem., 2022, 87, 7786–7797.
- 39 Z. Xiong, F. Weidlich, C. Sanchez and T. Wirth, Org. Biomol. Chem., 2022, 20, 4123–4127.
- 40 D. Pollok, L. M. Großmann, T. Behrendt, T. Opatz and S. R. Waldvogel, *Chem.-Eur. J.*, 2022, 28, e202201523.
- I. R. Miller, N. J. McLean, G. A. I. Moustafa, V. Ajavakom,
 S. C. Kemp, R. K. Bellingham, N. P. Camp and
 R. C. D. Brown, *J. Org. Chem.*, 2022, 87, 1325–1334.
- 42 N. Hu, Y.-T. He, P. Lan, M. G. Banwell, L. V. White, N. Hu, Y.-T. He, P. Lan, M. G. Banwell and L. V. White, *Aust. J. Chem.*, 2022, 75, 974–982.
- 43 J.-Y. Qiu, W.-L. Zeng, H. Xie, M.-Y. Wang and W. Li, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218961.
- 44 M. C. Carson and M. C. Kozlowski, *Nat. Prod. Rep.*, 2024, **41**, 208–227.
- 45 D. H. R. Barton, G. W. Kirby, J. B. Taylor and G. M. Thomas, J. Chem. Soc., 1963, 4545–4558.
- 46 A. M. Takos and F. Rook, *Int. J. Mol. Sci.*, 2013, **14**, 11713–11741.
- 47 J. Eichhorn, T. Takada, Y. Kita and M. H. Zenk, *Phytochemistry*, 1998, **49**, 1037–1047.
- 48 B. B. Majhi, S.-E. Gélinas, N. Mérindol, S. Ricard and I. Desgagné-Penix, *Front. Plant Sci.*, 2023, 14, 1231809.
- 49 T. U. Jayawardena, N. Merindol, N. S. Liyanage and I. Desgagné-Penix, *Nat. Prod. Rep.*, 2024, DOI: 10.1039/ D3NP00044C.
- 50 D. H. R. Barton and G. W. Kirby, *J. Chem. Soc.*, 1962, 806–817.
- 51 T. Kametani, K. Yamaki, H. Yagi and K. Fukomuto, J. Chem. Soc. Chem. Commun., 1969, 425–426.
- 52 T. Kametani, K. Yamaki, H. Yagi and K. Fukumoto, *J. Chem. Soc. C*, 1969, 2602–2605.
- 53 Y. Kita, M. Arisawa, M. Gyoten, M. Nakajima, R. Hamada,
 H. Tohma and T. Takada, *J. Org. Chem.*, 1998, 63, 6625–6633.
- 54 D. Krikorian, V. Tarpanov, S. Parushev and P. Mechkarova, *Synth. Commun.*, 2000, **30**, 2833–2846.
- 55 M. Node, S. Kodama, Y. Hamashima, T. Baba, N. Hamamichi and K. Nishide, *Angew. Chem., Int. Ed.*, 2001, **40**, 3060–3062.
- 56 K. Koga, K. Shimizu, K. Tomioka and S. Yamada, *Heterocycles*, 1977, 8, 277.
- 57 S. Kodama, Y. Hamashima, K. Nishide and M. Node, *Angew. Chem., Int. Ed.*, 2004, **43**, 2659–2661.
- 58 W.-C. Shieh and J. A. Carlson, J. Org. Chem., 1994, 59, 5463– 5465.
- 59 N. G. Anderson, Org. Process Res. Dev., 2005, 9, 800-813.
- 60 L. Czollner, W. Frantsits, B. Küenburg, U. Hedenig, J. Fröhlich and U. Jordis, *Tetrahedron Lett.*, 1998, 39, 2087–2088.
- 61 B. Küenburg, L. Czollner, J. Fröhlich and U. Jordis, *Org. Process Res. Dev.*, 1999, 3, 425–431.
- 62 1.64–1.75 kg of galantamine was isolated per hectare of *N. pseudonarcissus*: M. D. Fraser, H. E. Vallin, J. R. T. Davies, G. E. Rowlands and X. Chang, *Sci. Rep.*, 2021, 11, 1389.

- 63 J. Li, A. Amatuni and H. Renata, *Curr. Opin. Chem. Biol.*, 2020, 55, 111–118.
- 64 M. Mogharabi and M. A. Faramarzi, *Adv. Synth. Catal.*, 2014, **356**, 897–927.
- 65 N. Cardullo, V. Muccilli and C. Tringali, *RSC Chem. Biol.*, 2022, **3**, 614–647.
- 66 S. Möhle, M. Zirbes, E. Rodrigo, T. Gieshoff, A. Wiebe and S. R. Waldvogel, *Angew. Chem., Int. Ed.*, 2018, 57, 6018–6041.
- 67 R. K. Mylavarapu, K. GCM, N. Kolla, R. Veeramalla, P. Koilkonda, A. Bhattacharya and R. Bandichhor, *Org. Process Res. Dev.*, 2007, **11**, 1065–1068.
- 68 D. A. Chaplin, N. B. Johnson, J. M. Paul and G. A. Potter, *Tetrahedron Lett.*, 1998, **39**, 6777–6780.
- 69 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 2000, **122**, 11262–11263.
- 70 P. J. Parsons, M. D. Charles, D. M. Harvey, L. R. Sumoreeah, A. Shell, G. Spoors, A. L. Gill and S. Smith, *Tetrahedron Lett.*, 2001, 42, 2209–2211.
- 71 C. Pilger, B. Westermann, U. Flörke and G. Fels, *Synlett*, 2000, 1163–1165.
- 72 B. M. Trost and W. Tang, Angew. Chem., Int. Ed., 2002, 41, 2795–2797.
- 73 C. Guillou, J.-L. Beunard, E. Gras and C. Thal, *Angew. Chem., Int. Ed.*, 2001, **40**, 4745–4746.
- 74 A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit and F. Schwarzenbach, *J. Am. Chem. Soc.*, 1992, **114**, 2321– 2336.
- 75 W.-J. Bai, J.-H. Xie, Y.-L. Li, S. Liu and Q.-L. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 81–84.
- 76 S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 1770–1771.
- 77 M. G. Banwell, J. N. Buckler, C. J. Jackson, P. Lan, X. Ma, E. Matoušová and J. Nugent, in *Strategies and Tactics in Organic Synthesis*, ed. M. Harmata, Academic Press, 2015, vol. 11, pp. 29–50.
- 78 C. S. Beshara, A. Hall, R. L. Jenkins, K. L. Jones, T. C. Jones, N. M. Killeen, P. H. Taylor, S. P. Thomas and N. C. O. Tomkinson, *Org. Lett.*, 2005, 7, 5729–5732.
- 79 L. Petit, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2011, **13**, 5800–5803.
- 80 B. M. Trost and C. Pedregal, J. Am. Chem. Soc., 1992, 114, 7292–7294.
- 81 M. Movassaghi and M. D. Hill, *Org. Lett.*, 2008, **10**, 3485-3488.
- 82 S. Eagon, C. DeLieto, W. J. McDonald, D. Haddenham, J. Saavedra, J. Kim and B. Singaram, *J. Org. Chem.*, 2010, 75, 7717–7725.
- 83 J. Wang, S. A. Blaszczyk, X. Li and W. Tang, *Chem. Rev.*, 2021, **121**, 110–139.
- 84 L. Jiao, M. Lin, L.-G. Zhuo and Z.-X. Yu, *Org. Lett.*, 2010, **12**, 2528–2531.
- 85 N. F. McKinley and D. F. O'Shea, *J. Org. Chem.*, 2004, **69**, 5087–5092.

- 86 I. E. Markó and A. Mekhalfia, *Tetrahedron Lett.*, 1990, 31, 7237–7240.
- 87 Y. Xue and G. Dong, Acc. Chem. Res., 2022, 55, 2341-2354.
- 88 P. Chen, B. A. Billett, T. Tsukamoto and G. Dong, ACS Catal., 2017, 7, 1340–1360.
- 89 P.-H. Chen, N. A. Savage and G. Dong, *Tetrahedron*, 2014, 70, 4135–4146.
- 90 P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550– 3577.
- 91 T. Diao and S. S. Stahl, J. Am. Chem. Soc., 2011, 133, 14566– 14569.
- 92 K. Ma, B. S. Martin, X. Yin and M. Dai, *Nat. Prod. Rep.*, 2019, 36, 174–219.
- 93 P. H. Gehrtz, V. Hirschbeck, B. Ciszek and I. Fleischer, *Synthesis*, 2016, **48**, 1573–1596.
- 94 C.-A. Fan, Y.-Q. Tu, Z.-L. Song, E. Zhang, L. Shi, M. Wang,
 B. Wang and S.-Y. Zhang, *Org. Lett.*, 2004, 6, 4691–4694.
- 95 A. R. Chamberlin, J. E. Stemke and F. T. Bond, J. Org. Chem., 1978, 43, 147–154.
- 96 G. Stork and R. L. Danheiser, J. Org. Chem., 1973, 38, 1775– 1776.
- 97 E. J. Corey, R. K. Bakshi and S. Shibata, J. Am. Chem. Soc., 1987, 109, 5551–5553.
- 98 W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T.-T. Li, D. J. Faulkner and M. R. Petersen, J. Am. Chem. Soc., 1970, 92, 741–743.
- 99 R. A. Fernandes, A. K. Chowdhury and P. Kattanguru, *Eur. J. Org Chem.*, 2014, **2014**, 2833–2871.
- 100 W. G. Salmond, M. A. Barta and J. L. Havens, J. Org. Chem., 1978, 43, 2057–2059.
- 101 T. Okino, Y. Hoashi and Y. Takemoto, J. Am. Chem. Soc., 2003, **125**, 12672–12673.
- 102 J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481–4483.
- 103 R. C. Larock, J. Organomet. Chem., 1999, 576, 111-124.
- 104 X. Liu, L. Lin and X. Feng, Acc. Chem. Res., 2011, 44, 574-587.
- 105 Q. Zhang, F.-M. Zhang, C.-S. Zhang, S.-Z. Liu, J.-M. Tian, S.-H. Wang, X.-M. Zhang and Y.-Q. Tu, *Nat. Commun.*, 2019, **10**, 2507.
- 106 U. K. Tambar and B. M. Stoltz, *J. Am. Chem. Soc.*, 2005, **127**, 5340–5341.
- 107 M. Blouin and R. Frenette, J. Org. Chem., 2001, 66, 9043-9045.
- 108 A. G. Atanasov, S. B. Zotchev, V. M. Dirsch and C. T. Supuran, *Nat. Rev. Drug Discovery*, 2021, **20**, 200–216.
- 109 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2020, **83**, 770–803.
- 110 Y. Tu, Angew. Chem., Int. Ed., 2016, 55, 10210-10226.
- 111 C. A. Kuttruff, M. D. Eastgate and P. S. Baran, *Nat. Prod. Rep.*, 2014, **31**, 419–432.
- 112 X.-Y. Liu and Y. Qin, Nat. Prod. Rep., 2023, 40, 1694-1700.