

Galanthamine, a Natural Product for the Treatment of Alzheimer's Disease

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Abstract: (-)-Galanthamine is a selective, reversible competitive acetylcholinesterase inhibitor that has been recently approved for the symptomatic treatment of Alzheimer's disease. Galanthamine is a natural product belonging to the *Amaryllidaceae* family of alkaloids. The pharmacological history of galanthamine shows that the bioactive compound was discovered accidentally in the early 1950s, and the plant extracts were initially used to treat nerve pain and poliomyelitis. In addition, galanthamine had since been tested for use in anesthesiology, from facial nerve paralysis to schizophrenia. Galanthamine is a long-acting, selective, reversible and competitive AChE inhibitor that has recently been tested in AD patients and found to be readily absorbed, to be a performance enhancer on memory tests in some patients, and to be well tolerated, although some cholinergic side effects were observed. A number of total synthetic approaches have been reported, and a method for the industrial scale-up preparation of galanthamine is now being developed and patented. A variety of galanthamine derivatives have also been synthesized aiming to develop an agent free from cholinergic adverse effects. Galanthamine is a natural product that complements other synthetic drugs for the management of AD. In this account we will review the recent patent literature showing the most important advance on the chemistry of galanthamine.

Keywords: Biogenetic-type synthesis, total synthesis, phenolic oxidative coupling, *para-ortho* coupling, PIFA, potassium ferricyanide, intramolecular Heck reaction, acetylcholinesterase inhibitors, neuronal nicotinic receptor for acetylcholine.

1. INTRODUCTION

(-)-Galanthamine (**1**) (Fig. 1), an alkaloid isolated from the Caucasian snow-drop (*Galanthus woronowii*) and from the bulbs of different species of the *Amaryllidaceae* family, is a selective, reversible, competitive acetylcholinesterase (AChE) inhibitor [1], and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine [2]. Galanthamine, commercially available as Reminyl, is the most recently approved AChE inhibitor in USA by the FDA, and in Europe by the European registration bureau for the symptomatic treatment of Alzheimer's disease (AD) [3]. Owing to the scarce supplies and the high cost of its isolation from botanical sources [4-6], several total synthetic approaches have been reported.

This review focuses on the different recent patents in the period 2001-2004, and the total syntheses of galanthamine.

2. SYNTHESSES OF GALANTHAMINE

The current synthetic approaches to galanthamine are based either on the biomimetic approach *via* the phenolic oxidative coupling [7] or on the intramolecular Heck reaction [8].

Barton was the first to recognize that *Amaryllidaceae* alkaloids, including galanthamine, could be derived from

norbelladine (**2**) (Fig. 1) *via* intramolecular oxidative phenol-coupling reaction [9]. Feeding experiments established norbelladine as the biogenetic precursor for galanthamine biosynthesis [10]. After the oxidative phenol coupling, a dienone was assumed to be the key intermediate producing narwedine (**3**) (Fig. 1), postulated as the precursor of galanthamine.

Barton and Kirby prepared racemic narwedine (**3**) in a very poor yield by phenol oxidation of diphenolic amine (**4**) (Fig. 1) using potassium ferricyanide; subsequent reduction of narwedine (**3**) with lithium aluminium hydride (LAH) constituted the first published synthesis of racemic galanthamine and *epi*-galanthamine [9]. Compound (**4**) was obtained starting from *p*-hydrophenylacetic acid (**5**) and *O*-benzylisovainillin (**6**); the corresponding acyl chloride (**7**) and the *N*-methylamine derivatives (**8**) (Fig. 1) were easily combined into the required precursor (**4**) for the oxidative phenol coupling reaction [10]. Major modifications of this approach were directed to the protection of the *para* position in order to promote more efficient coupling reactions, or to the introduction of a third phenol group in order to avoid problems of regioselectivity during the aromatic ring functionalization, and to the use of other oxidant such as PIFA [phenyliodine(III)bis(trifluoroacetate)].

For instance, in 1969 Kametani *et al.* proposed the key diphenol (**9**) with the assumption that the bromine atom would prevent the *para* coupling to the hydroxy group, and favor the *ortho* coupling. This compound was synthesized from *p*-*O*-benzylhydroxyphenylacetic acid (**10**) and 2-bromo-*O*-benzylisovainillin (**11**), *via* *N*-methylamine (**12**) and acyl chloride (**13**) derivatives, respectively (Fig. 2). This

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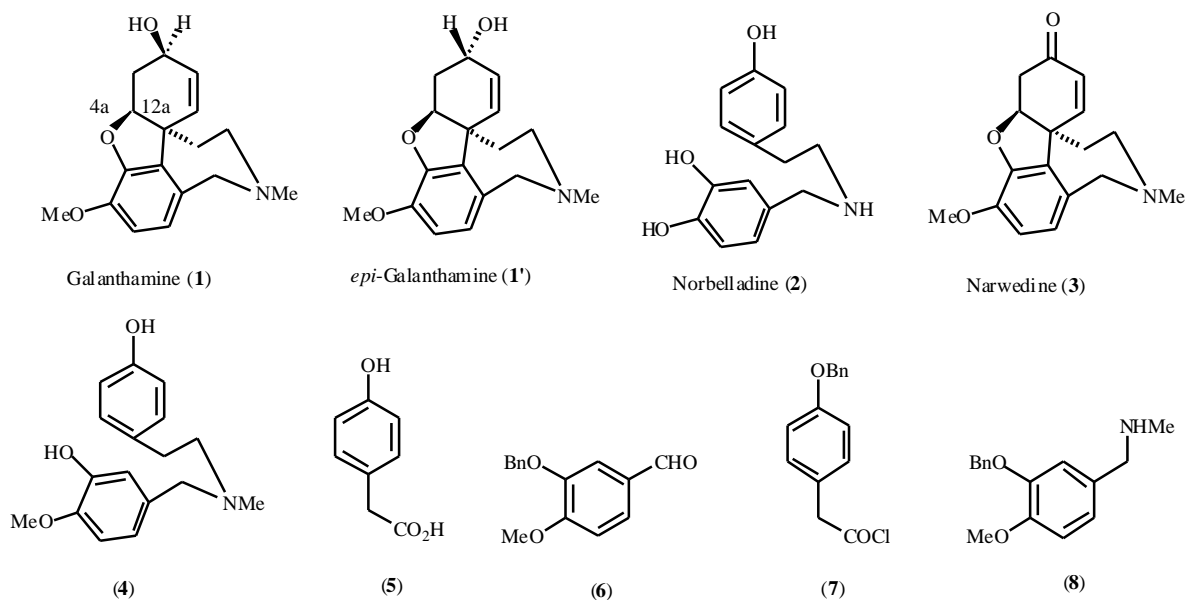


Fig. (1). Molecular structure of galanthamine (1), *epi*-galanthamine (1'), norbelladine (2), narwedine (3), and synthetic intermediates (4-8).

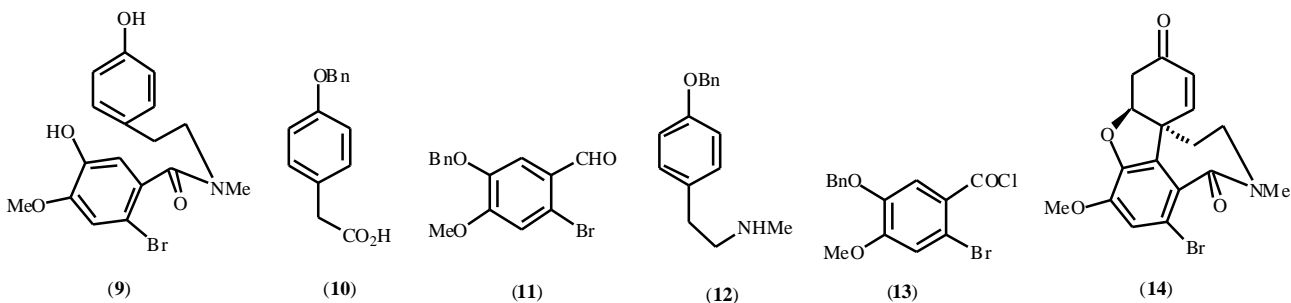


Fig. (2). Molecular structure of synthetic intermediates (9-14).

hypothesis was acceptable since the phenol oxidation of compound (9) (Fig. 2) afforded compound (14) (Fig. 2) in a better 40% yield. Final reduction of the keto group produced a mixture of galanthamine (1) and *epi*-galanthamine (1') (Fig. 1) in 50% and 40% yield, respectively [11].

In a recent patent, Vlahov has reported the preparation of (-)-galanthamine (1), which involved the cyclization of 2-bromo-5-hydroxy-*N*-[2-(4-hydroxyphenyl)ethyl]-4-methoxy-*N*-methylbenzamide (9) to form racemic 9-bromo-8-oxonarwedine (14) (Fig. 2), a ketone protection-debromination-amide reduction-resolution sequence to generate (-)-narwedine (3), and finally, the stereoselective ketone reduction leading to (-)-galanthamine (1) [12].

In 1998, Kita reported the use of PIFA in order to promote the diphenol coupling on trifluoroacetamide (15) (Fig. 3) in 36% yield. Finally, the acid hydrolysis of the acetal, followed by *O*-methylation, *N*-deprotection and *N*-methylation, afforded only galanthamine in a very stereoselective ketone reduction using L-Selectride. Using this strategy this group had patented the synthesis of a series of galanthamine derivatives such as (16) (Fig. 3) [13].

Carroll *et al.* have described the synthesis of racemic galanthamine using formamide derivatives (18) [14] and (19)

[15] (Fig. 4), obtained by bromination of a common amide precursor (17). Their oxidative (18, 19) using potassium ferricyanide afforded compounds (20) (21%) and (21) (38-43%), respectively. Finally, as it was expected, the reduction of compound (20) with LAH produced mixtures of galanthamine and *epi*-galanthamine [14]. With regard to compound (21), the final steps consisted in the reduction of the carbon-bromine bond with zinc in ethanol, the stereoselective reduction with L-Selectride, and the LAH-promoted reduction of the second bromine-carbon bond.

Node *et al.* reported a very interesting synthetic approach to galanthamine [16]. The key features in this synthesis were the use of 3,5-dibenzyloxy-4-methoxybenzaldehyde as precursor, the PIFA-promoted oxidative coupling reaction of *N*-formamide (22) in 2,2,2-trifluoroethanol at room temperature rendering a dienone (23) in 85% yield, the selective *O*-debenzylation using boron trichloride providing the narwedine-type product (24) and, finally, the required *O*-deoxygenation of the extra phenol group on the corresponding triflate by palladium(0)-catalyzed reduction with formic acid (Fig. 5).

In 2002, a patent was published where an efficient synthetic method for galanthamine-type alkaloids was

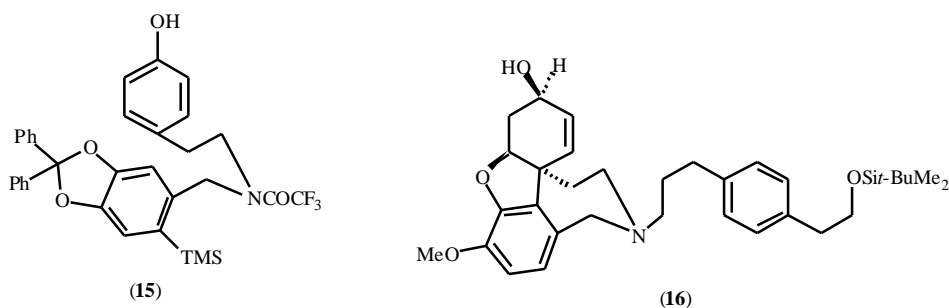


Fig. (3). Molecular structure of synthetic intermediates (15, 16).

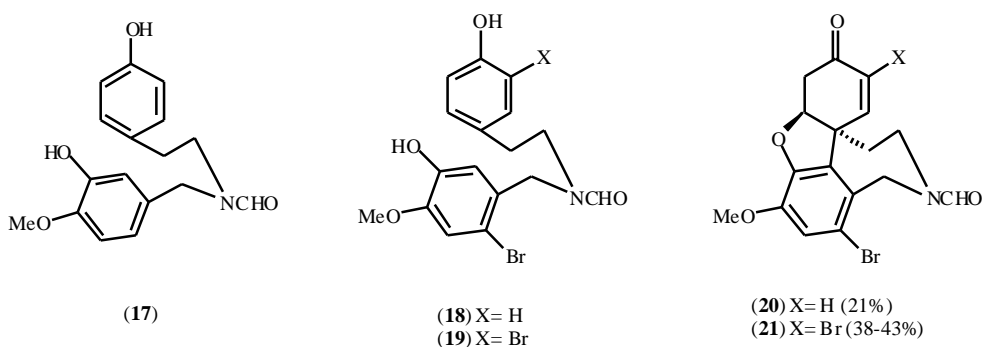


Fig. (4). Molecular structure of synthetic intermediates (17-21).

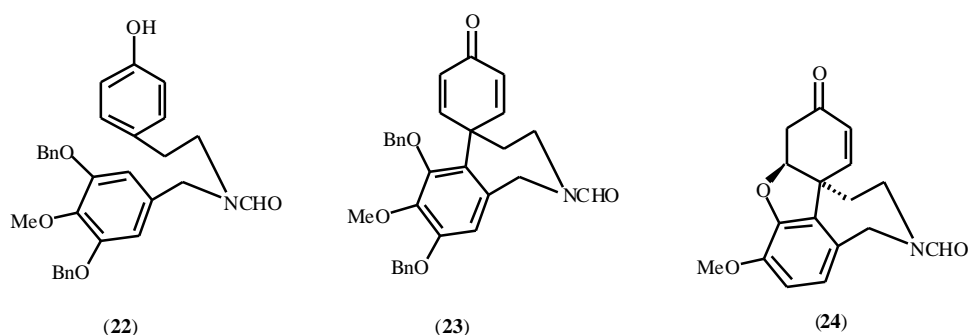


Fig. (5). Molecular structure of synthetic intermediates (22-24).

disclosed. The process involved intramolecular coupling of *N*-(3,4,5-trihydroxybenzyl)-2-(4-hydroxyphenyl)ethylamine derivatives by reaction with phenyliodine(III)bis (trifluoroacetate), to spiro[benz[*c*]azepine-cyclohexadien-4-one] and conversion of this intermediate into other galanthamine-type *Amaryllidaceae* alkaloids, such as narwedine (**3**) (Fig. 1) [17]. Chaplin *et al.* have also reported the resolution of narwedine (**3**) (Fig. 1), using the same agent, and its transformation to (-)-galanthamine [18].

Koga *et al.* reported the first asymmetric synthesis of enantiomerically pure (+) and (-)-galanthamine [19]. Compound (**25**), obtained by reduction of the Schiff base produced from 3,5-dibenzyloxy-4-methoxybenzaldehyde and L-tyrosine methyl ester, followed by reduction with sodium borohydride, was protected as a trifluoroacetamide and submitted to hydrogenation to afford compound (**26**) (Fig. 6) for the phenol oxidative *para-ortho* coupling reaction. This reaction was carried out with manganic tris(acetylacetonate)

in acetonitrile, and proved quite efficient since the expected tetracyclic compound, isolated in 49% yield when submitted to phenol protection as the diethyl phosphonate, gave a mixture of compounds (**27**) (81%) and (**28**) (traces). The absolute configuration at the new stereogenic center, the quaternary spiro-carbon, in the major isomer (**27**), was established after completion of the total asymmetric synthesis of the final product that resulted to be (+)-galanthamine (**1**). This was achieved in a series of reactions, involving the reduction of the ketone, *N*-methylation, amidation, acetylation and dehydration of the amide (**29**) to afford an unstable amino nitrile, reduction with LAH and final deoxygenation with sodium in liquid ammonia. For the synthesis of (-)-(**1**), compound (**27**) (Fig. 6) was reduced with sodium borohydride, (*O*- and *N*-)-bis-trifluoroacetylated and, selectively hydrolyzed the *O*-trifluoroacetate to produce the amide (**30**). Next, lithium diisopropylamide-promoted epimerization gave compound (**31**) (11%), which after oxidation by pyridinium chlorochromate afforded a ketone

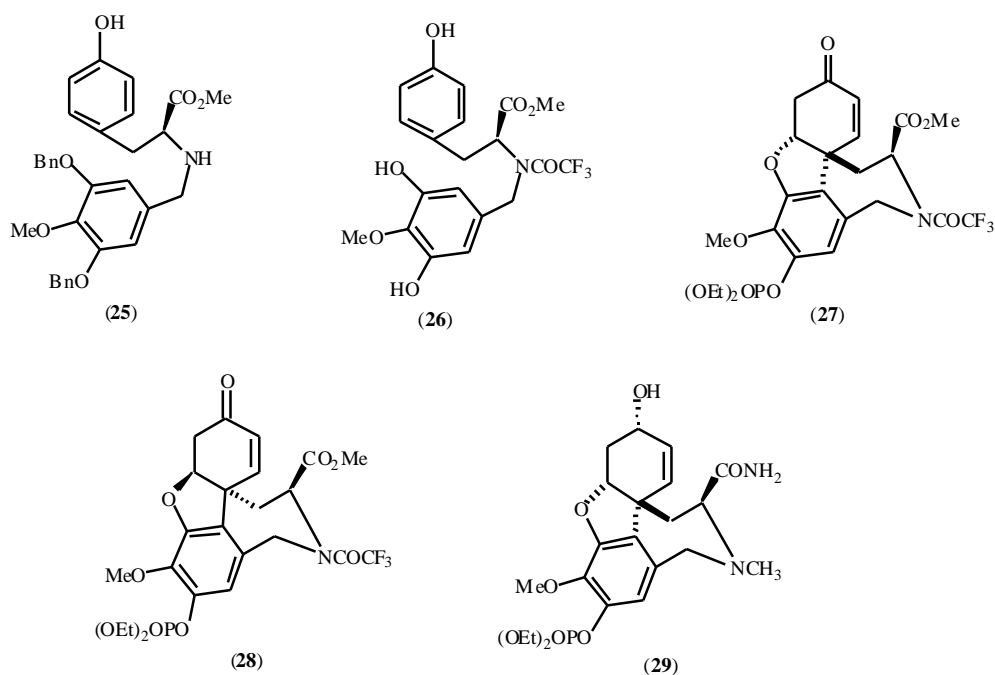


Fig. (6). Molecular structure of synthetic intermediates (25-29).

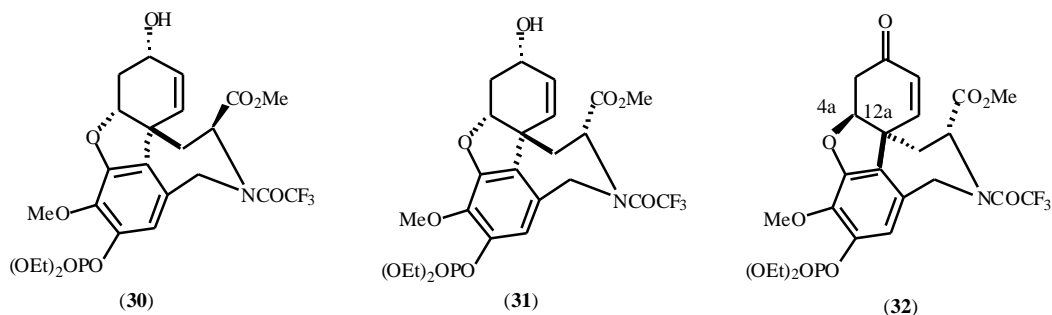


Fig. (7). Molecular structure of synthetic intermediates (30-32).

that slowly epimerized to the more stable ketone (32) (Fig. 7) with the correct and same configuration at carbons 4a and 12a, as in the natural product (-)-(1).

In 1989, Vlahov *et al.* reported his investigations on the asymmetric reduction of compound (14) (Fig. 2) for the synthesis of advanced intermediates driving to enantiomerically pure galanthamine [20]. More than 400 species of microorganisms were screened, but only five gave reproducible results. *Septomyxa affinis* DSM 6737 produced pure compound (33) (Fig. 8) in 50% yield. *Nematospira corylii* CBS 2608 rendered racemic (34) (Fig. 8) in 50% chemical yield. *Ashybya gossypii* IFO 1355 afforded enantiomerically pure (34) and racemic (33) in a 1:2 ratio, in total yield over 45%. Finally, *Nocardia alba* DSM 43130 and *Bacillus cereus* DSM 508 hydrogenated the double bond to provide derivative (35) (Fig. 8).

Jordis has achieved the synthesis of (-)-galanthamine starting from compound (18) (Fig. 4), in nine steps from 3,4-dimethoxybenzaldehyde, and in an overall yield of 18-21%. This group has deposited a patent for the industrial scale-up

executable methods for producing nor-galanthamine derivatives, based on the oxidative demethylation and a catalytic demethylation of the corresponding galanthamine compounds [21].

In 2004, another report on synthesis of (-)-galanthamine was published by Node *et al.* [22] starting with the reaction of tyramine with (*R*)-*N*-(*tert*-butoxycarbonyl)-*D*-phenylalanine providing compound (36) (Fig. 9), whose reaction with 3,5-dibenzyloxy-4-methoxybenzaldehyde gave an imine, which after acid treatment cyclized to yield imidazolidinone (37), isolated as the diastereomerically pure *trans* isomer. Next, the oxidative phenol coupling reaction provided dienone (38) in a notorious 61% yield. The final steps of the synthesis of compounds (38) to (41), via intermediate (40), were based upon the previous report of this group on the synthesis of the racemate [16].

In 2001, Guillou reported the total synthesis of racemic galanthamine by using the intramolecular Heck reaction as the key step. The French group has patented this invention [23]. In this approach the aryl iodide partner (42) was devoid

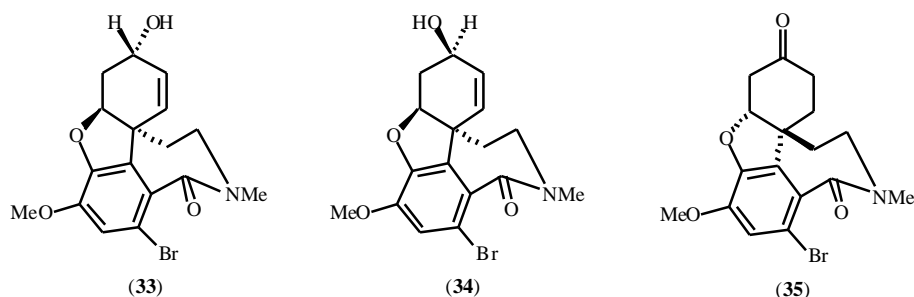


Fig. (8). Molecular structure of synthetic intermediates (33-35).

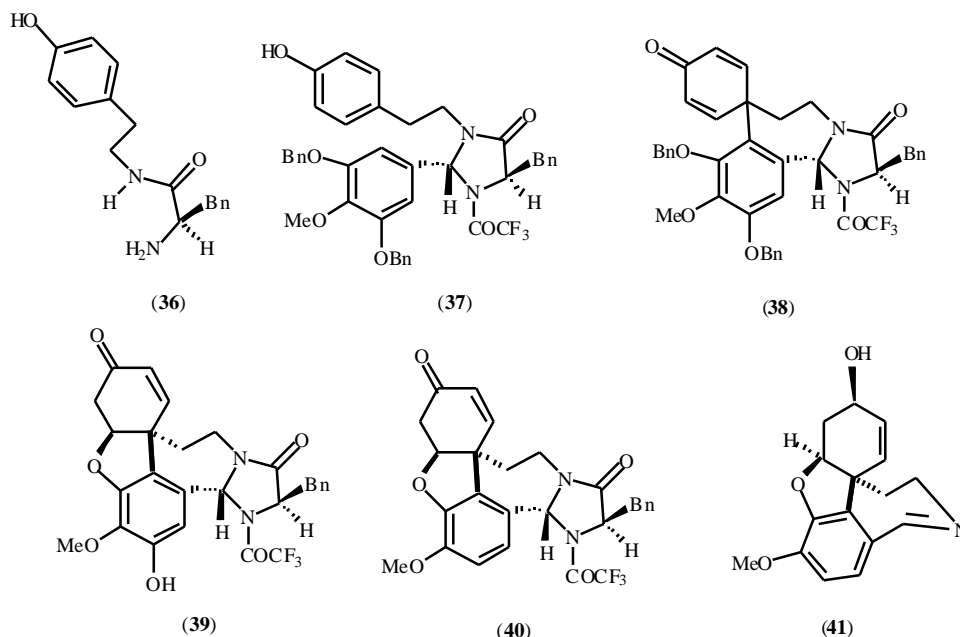


Fig. (9). Molecular structure of synthetic intermediates (36-41).

of any carboxaldehyde moiety and the α,β -unsaturated ester (43) did not have an allylic alcohol, but a protected ketone on carbon C5 (Fig. 10). This selection of functional groups completely changed the structure of the precursor (44) for the intramolecular Heck reaction. In addition, the known high stereoselectivity in the reduction of the ketone with L-Selectride secured the efficient formation of the expected allylic alcohol with the correct relative configuration. The Heck reaction, promoted by palladium-*trans*-dibenzylideneacetone in the presence of 1,2-bis(diphenylphosphanyl)ethane and thallium acetate, afforded compound (45) in 67% yield. The formation of dienone (46) was more difficult than envisaged, but the use of benzeneseleninic acid anhydride in the presence of molecular sieves solved the problem affording the product in 50% yield. The stereoselective transformation of dienone (46) into benzofurane (47) is one of the most interesting and original contributions of this synthetic approach. Thus, this product is the result of the reaction of lactone (46) with methylamine which rendered opening of the ring and formation of the corresponding amide with a free phenol group that spontaneously attacked the α,β -unsaturated ketone. Finally, the tetracyclic ring system of galanthamine was formed by electrophilic aromatic substitution of an iminium ion formed in the

reaction of amide (47) with paraformaldehyde in the presence of trifluoroacetic acid. The resulting ketone (48) was reduced with L-Selectride, and galanthamine was obtained by LAH reduction of amide (49).

In 2002, Trost and Tang published the synthesis of (-)-galanthamine [24], starting from an intermediate (50), formed in the reaction of 2-bromovainillin (51) and a carbonate derivative (52) (Fig. 11). All attempts to carry out the intramolecular Heck reaction on compound (50) failed, leading to phenol (51). In order to prevent this undesired reaction, the authors prepared compound (53) by total reduction with diisobutylaluminum hydride, followed by persilylation, whose Heck reaction was still problematic, but reaction conditions provided the expected product as a mixture of (54) and (55). Thus, compounds (54) + (55) (Fig. 12) were submitted to a total desilylation reaction, followed by selective benzylic oxidation in order to generate an intermediate that was treated with methylamine, followed by reduction with sodium cyanoborohydride and protection with the *N*-(*tert*-butoxycarbonyl) group. Next, oxidation of the other alcohol, Wittig olefination, and acid hydrolysis afforded an aldehyde that was submitted to the reductive Mannich amination to produce compound (56) in 16%

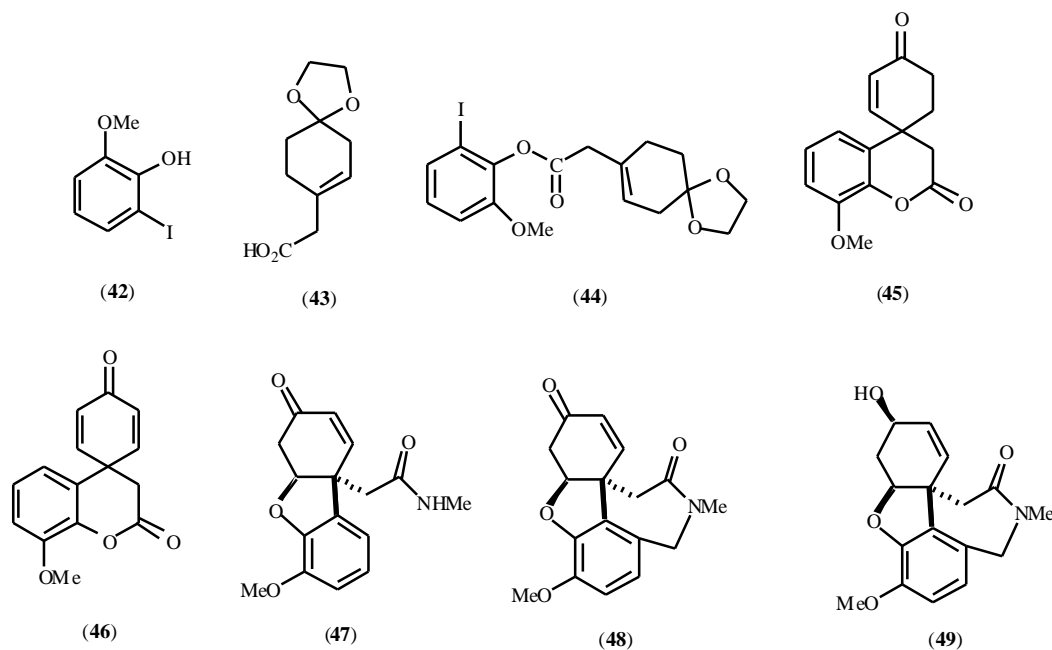


Fig. (10). Molecular structure of synthetic intermediates (42-49).

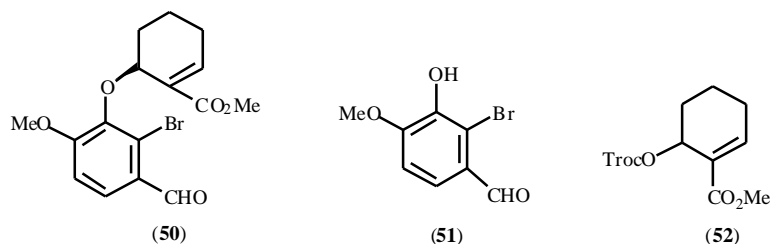


Fig. (11). Molecular structure of synthetic intermediates (50-52).

overall yield from compounds (54) + (55) (Fig. 12). At this stage of the synthetic sequence, it was only necessary to functionalize the C ring. Then, the allylic oxidation was investigated, but without success. Thus, a four-step protocol was developed to incorporate the C3 hydroxyl group in place, which ended with the synthesis of alcohol 57 (Fig. 12). Finally, when this compound was treated with Osborn's rhenium(VII) catalyst a product was obtained, identical to natural galanthamine.

After all, some galanthamine analogs have been synthesized such as the galanthamine sulfur-analog (58) (Fig. 13) [25], unfortunately devoid of any noticeable AChE inhibitory activity. The same group has also transformed galanthamine into compound 59 (Fig. 13) which showed no inhibition towards AChE [26]. More recently, Jordis communicated the synthesis of the 10-aza analogue 60 (Fig. 13), using the oxidative phenol coupling reaction promoted by potassium ferricyanide [27]. A patent on the preparation of galanthamine analogs for pharmaceutical use has also been published [28].

Janssen Pharmaceutica patented an oral solution formulation, containing galanthamine and a sweetening agent, for the treatment of various CNS disorders including AD [29].

3. CURRENT AND FUTURE DEVELOPMENTS

Galanthamine is a natural product belonging to the *Amarylidaceae* family of alkaloids. The pharmacological history of galanthamine shows that the bioactive compound was discovered accidentally in the early 1950s, and the plant extracts were initially used to treat nerve pain and poliomyelitis. Galanthamine is a long-acting, selective, reversible and competitive AChE inhibitor that has recently been tested in AD patients and found to be readily absorbed, to be a performance enhancer on memory tests in some patients, and to be well tolerated, although some cholinergic side effects were observed. It is important to highlight that preliminary results from two large clinical trials of galanthamine have not shown a significant difference between galanthamine and placebo in the rate of progression from mild cognitive impairment to AD over a two-year period [30].

A number of total synthetic approaches have been reported, and a method for the industrial scale-up preparation of galanthamine is being developed and patented. A variety of galanthamine derivatives have also been synthesized aiming to develop an agent free from cholinergic adverse effects, which complements other drugs for the management of AD.

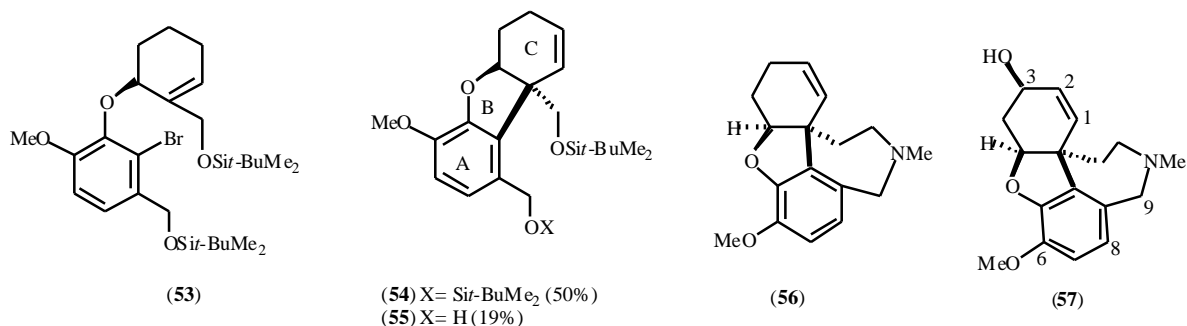


Fig. (12). Molecular structure of synthetic intermediates (53-57).

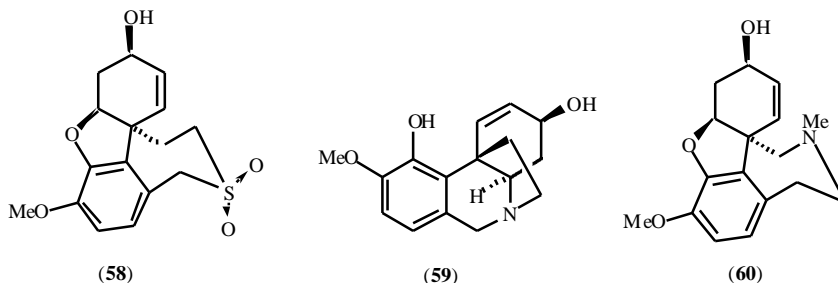


Fig. (13). Molecular structure of synthetic intermediates (58-60).

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