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Biomimetic total synthesis of (–)-galanthamine *via* intramolecular anodic aryl–phenol coupling†

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(–)-Galanthamine as a drug for the treatment of Alzheimer's disease has attracted synthetic chemists for decades. However, previous total synthetic and biomimetic approaches often use stoichiometric oxidants (metal oxidants or hypervalent iodine) to prepare the target product. Anodic oxidative coupling offers a sustainable alternative method which is, for the first time, successfully applied to the total synthesis of (–)-galanthamine. We report a new asymmetric total synthesis of (–)-galanthamine by using an anodic aryl–phenol coupling as the key synthetic step.

Introduction

(–)-Galanthamine 1 (Fig. 1), an *Amaryllidaceae* alkaloid, has attracted the focus of synthetic chemists since 1952 when it was first isolated from the plant Caucasian snowdrop.[1] (–)-Galanthamine **1** has an interesting and synthetically challenging structure which contains a strained tetracyclic framework with an all-carbon quaternary stereocentre and has a unique activity as an acetylcholine esterase (AChE) inhibitor.[2] In 2001, (–)-galanthamine was approved by the FDA as a drug for the symptomatic treatment of Alzheimer's disease.[3]

Numerous synthetic studies of (–)-galanthamine and its analogues have been performed and a number of total syntheses of **1** have been reported.[4–11] In the early stages of (–)-galanthamine syntheses, the biomimetic intramolecular oxidative coupling was the key step to build up the tetracyclic skeleton.[4] These methods typically require stoichiometric metal or hypervalent iodine reagents as oxidants and provide the products in only low to moderate yields. The stereoselectivity of these methods mainly rely on a resolution process where the precursor (–)-Narwedine **2** is crystallized in 70–80% yield (Fig. 1).[5] Aside from the biomimetic intramolecular coupling protocol, Trost and co-workers reported an intramolecular Heck reaction to assemble a tricyclic precursor and the associated quaternary carbon centre of galanthamine.[6a] Inspired by his work, several related approaches have been published later.[6] These approaches focus on forming the ABC ring system first before assembling the D ring.[5,7] Two recent examples achieved a final construction of the C ring after installing the ABD ring skeleton.[8] A recent report by Xu and co-workers uses a Rh-catalyzed C–C activation to form the tetracyclic carbon framework directly,[9] while Brown[10] and Zhao[11] have used other transition-metal mediated approaches. Although a variety of synthetic strategies have been reported so far, the commercial supplies of **1** are still using the Fröhlich–Jordis route[4f] in which the key phenolic oxidation coupling reaction proceeds in 40–54% yield by using 2 equivalents $K_3Fe(CN)_6$ as the oxidant. A similar approach has been reported by electrochemically regenerating the ferrocyanide oxidant.[12]

In 1984, Vlahov and co-workers reported an electrochemical method for oxidative phenol couplings to synthesise products with a galanthamine skeleton.[13] Recently Opatz and co-workers have published the total syntheses of (–)-Thebaine[14] and (–)-Oxycodone[15] by using an anodic aryl–aryl coupling as the key step. However, more than 3 decades have passed and an electrochemical coupling reaction has still not been successfully applied to the total synthesis of (–)-galanthamine. Herein, we report the optimisation of an anodic aryl–aryl coupling reaction using an effective electrochemical approach with a recently developed electrochemical flow reactor[16] and its application to the asymmetric synthesis of (–)-galanthamine **1**.

Electrochemical synthesis offers a tunable, cost effective and environmentally friendly alternative to carry out redox reactions using only electrons as traceless reagents, thus obviating the need for dangerous and toxic stoichiometric oxidants.[17] Building on the advantages of flow electrochemical

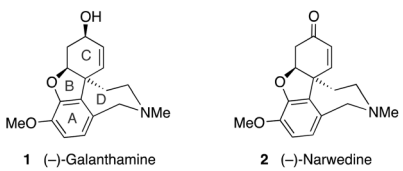

Fig. 1 (–)-Galanthamine **1** and (–)-Narwedine **2**.

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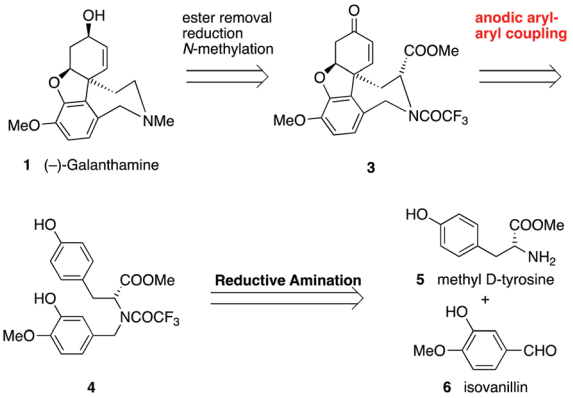


Scheme 1 Retrosynthetic strategy to access (–)-galanthamine **1** using an anodic aryl–aryl coupling reaction.

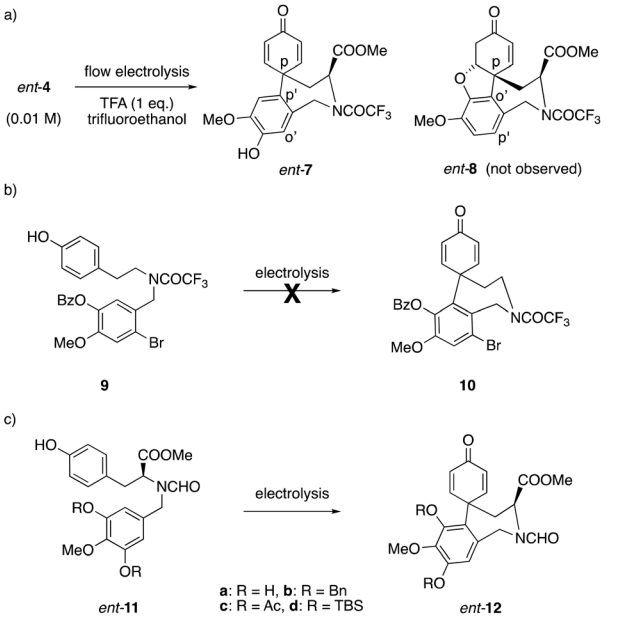
approaches,[18] we have initially developed a simple and short synthetic plan (Scheme 1).

It is based around the key norbelladine intermediate **4** which has a methylester[19] substituent designed to set up the required stereochemistry by the intramolecular anodic aryl–aryl coupling reaction leading to compound **3**. We sought to access **1** from the (–)-Narwedine derivative **3** through removal of the methylester, reduction of the enone and amide moieties of **3** followed by an *N*-methylation. The norbelladine intermediate **4** could be obtained by the reductive amination of commercially available methyl D-tyrosine **5** and isovanillin **6**.

Results and discussion

Initial synthetic investigations began with the much cheaper L-tyrosine and compound *ent*-**4** was obtained by following Yamada's work.[19] However, the electrolysis of *ent*-**4** under flow conditions generated only the *para–para*′-coupled product **7** while the desired *para–ortho*′-coupled product *ent*-**8** was not observed (Scheme 2a). In order to block the apparently favored *para* position, the electrolysis substrate was modified to **9** inspired by Vlahov's substrate.[13] Unfortunately, all attempted electrolysis reactions of **9** failed to give any products (Scheme 2b). Probably due to the difference in equipment, even Vlahov's work could not be repeated in our hands. Considering the Br group may deactivate the aromatic ring for the coupling reaction, we then redesigned the substrate to *ent*-**11** which contains a 3′,4′,5′-trioxygenated aromatic moiety (Scheme 2c). This was inspired by Node's approach,[4g] where the symmetrical configuration makes both coupling positions identical to generate a single product.

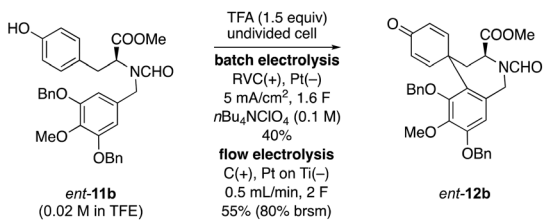
For the first attempt, a batch electrolysis of *ent*-**11b** (c = 0.02 M) in MeCN with 0.1 M nBu$_4$NClO$_4$ as supporting electrolyte (graphite anode and platinum cathode) was performed and 8% of product *ent*-**12b** was obtained. Encouraged by this result, different parameters of the electrolysis such as electrode material, solvent, temperature, current density and reaction time were scanned (see ESI†). It was found that trifluoroethanol is a very good solvent for this anodic oxidation and that a RVC



Scheme 2 (a) Initial anodic coupling of norbelladine derivative *ent*-**4**; (b) unsuccessful anodic coupling attempts of substrate **9**; (c) coupling of 3′,4′,5′-trioxygenated norbelladine derivatives **11**.

anode and platinum cathode is the best electrode material combination. Compared to room temperature, higher or lower temperatures gave worse results. Other electrolytes have only minor effects on the yield. Lower concentrations usually lead to cleaner reactions, but the yield was limited to only 20%. When more than 1.6 F was applied under these conditions, only decomposition of the starting material was observed. To increase the yield, different additives were investigated. The addition of an acidic additive such as trifluoroacetic acid successfully increased the yield of the electrolysis to 40% in batch mode (Scheme 3).

This reaction was then examined using a flow electrochemical reactor,[20] where typically the addition of supporting electrolytes is not necessary due to the close distance of the electrodes.[13] Although the addition of supporting electrolyte decreases the potential, surprisingly even the addition of only small amounts of supporting electrolyte (0.5% mol) reduced the yield of the product *ent*-**12b** under flow conditions. After further optimization of the flow system, the yield was improved to 55% (80% based on recovered starting material) as shown in Scheme 3. The difference is due to chromatographic purifi-

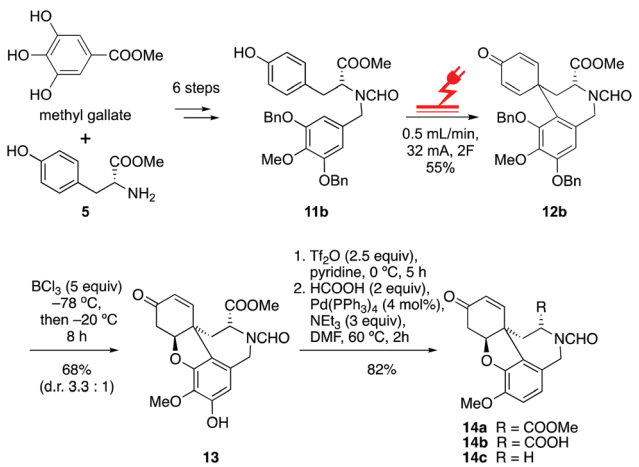


Scheme 3 Anodic coupling of 3′,4′,5′-trioxygenated norbelladine derivative *ent*-**11b**.

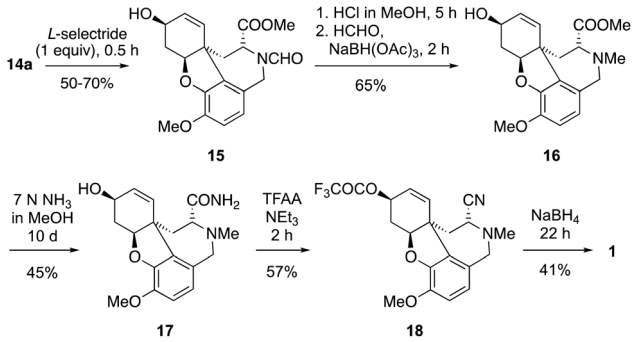
cation as both, starting material and product are not completely recovered. There are no other products observed in the electrochemical step. The unprotected substrate *ent*-**11a**, acetate *ent*-**11c** and silylether *ent*-**11d** were also examined in this anodic coupling. However, due to the very low solubility of *ent*-**11a** in TFE, MeCN or AcOH, no product was formed. Substrates *ent*-**11c** and *ent*-**11d** were unreactive and did not cyclise under the electrolytic reaction conditions. The mechanism of the anodic coupling reaction has already been investigated and discussed.[21]

After optimisation of the electrolysis conditions, **11b** was then synthesized from methyl D-tyrosine **5** and methyl gallate through 6 steps (see ESI† and Scheme 4). The cyclisation of **11b** gave similar results as *ent*-**11b** under the electrolysis conditions. With gram amounts of the key intermediate **12b** in hand, the deprotection of the benzyl groups was then attempted. The oxa-Michael addition has been shown to proceed spontaneously upon deprotection of **12b** of related substrates, and with high diastereoselectivity. Due to the steric hinderance through the methyl ester group, the oxa-Michael addition will be more favoured from the opposite side. However, after investigating different reaction conditions (Scheme 4),[4g] it was found that the reported combination of dimethyl sulfide with trifluoroacetic acid or methanesulfonic acid led to decomposition. Only the use of BCl_3 at −78 °C gave clean results, but irrespective of the reaction time, an inseparable mixture of a mono-debenzylated product and the desired product 13 was obtained (Table S6†). At temperatures above −20 °C the ester is being hydrolysed while at temperatures below −40 °C the reaction does not go to completion. An improved yield of 68% with a ratio of formamide rotamers of 3.3 : 1 was obtained by a mono-debenzylation at −78 °C, followed by one additional equivalent of BCl_3 at −20 °C (see ESI†).

The free hydroxyl moiety in **13** was then efficiently transformed into a triflate for a subsequent Pd-catalysed deoxygenation by using HCOOH/Et_3N as the transfer hydrogen reductant to give **14a** in 82% yield over two steps. The hydrolysis of the methyl ester in **14a** with LiOH also proceed in high yield (90%)



Scheme 4 Synthetic route to compounds **14**.



Scheme 5 Final stages in the synthesis of (−)-galanthamine **1**.

to generate **14b**. Converting **14b** to the narwedine derivative **14c** was then attempted by the Barton–McCombie decarboxylation.[22] However, this reaction failed to provide the desired product **14c** even after many attempts under a variety of reaction conditions. The nickel-catalyzed Barton decarboxylation reported by Baran's group[23] and a photocatalytic decarboxylation[24] were also trialed multiple times without success.

It was then decided to convert the ester group into a cyanide group for a reductive decyanation to remove the undesired functional group in analogy to a reported natural product synthesis.[19] To achieve this reductive decyanation, an initial reduction of the formamide group to the methylamine is necessary to provide an α-aminonitrile as the decyanation substrate. However, direct methods for decyanations of α-aminonitriles require usually strong reductants such as alkali metals or $LiAlH_4$ as they proceed after cyanide loss *via* the corresponding iminium ions.[25] Such reagents would also affect the enone moiety and the ester group, especially as it was found that the enone moiety is a very sensitive and therefore problematic functional group at a later stage. The L-selectride reduction of the enone was carried out initially to give the alcohol **15** in up to 70% yield. In order to convert the formamide group to a methyl substituent, it was hydrolysed to the amine by methanolic HCl followed by reductive amination with formaldehyde and $NaBH(OAc)_3$ and **16** was obtained in 65% yield over these two steps. The subsequent amidation of **16** with 7 N ammonia in MeOH was very clean but took a long time. After an increase of the reaction time from 2 to 10 days, the yield of **17** was improved from 25% to 45% and 20% starting material was recovered. The following dehydration of the amide by using trifluoroacetic anhydride (TFAA) and Et_3N gave the desired α-aminonitrile **18** in 57% yield. The final reduction was initially attempted with $LiAlH_4$ at −20 °C, but this reaction did lead to many side products. $NaBH_4$ gave a much cleaner reaction to provide 41% of (−)-galanthamine **1**, while 43% starting material was recovered (Scheme 5).

Conclusions

In summary, a new biomimetic total synthesis of (−)-galanthamine **1** was achieved in 16 steps with a 0.7% overall yield by

using an anodic aryl–aryl coupling as the key synthetic step which was optimised in a flow electrochemical setup. To our knowledge, this demonstrates the first successful application of electrochemistry in the total synthesis of (−)-Galanthamine.

Author contributions

T.W. conceptualized the work. Z.X. developed the methodology. Z.X., F.W. and C.S. performed all the experiments and analyzed the data. Z.X. and T.W. prepared the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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