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# VIP A General Electro-Synthesis Approach to Amaryllidaceae Alkaloids

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**Abstract:** Amaryllidaceae alkaloids appeal to organic chemists with their attractive structures and their impressive antitumor and acetylcholinesterase inhibitory properties. We demonstrate a highly versatile access to this family of natural products. A general protocol with high yields in a sustainable electro-organic key transformation on a metal-free anode to spirodienones facilitates functionalization to the alkaloids. The biomimetic syntheses start with the readily available, inexpensive biogenic starting materials methyl gallate, *O*-methyl tyramine, and vanillin derivatives. Through known dynamic resolutions, this technology provides access to both enantiomeric series of (epi-)martidine, (epi-)crinine, siculine, and galantamine, clinically prescribed for the treatment of Alzheimer's disease.

Amaryllidaceae alkaloids have attracted significant attention of synthetically oriented chemists due to their unique structures with an all-carbon chiral centre.[1] The demand for elegant synthesis strategies is based on a limited supply from natural sources and prosperous biomedical profile for clinical application. The most prominent member, (−)-galantamine (**1**, Scheme 1A), naturally occurs in the common snow-drop (*Galanthus nivalis*) and related species.[2,3] Its highly selective and reversible acetylcholinesterase inhibitory activity facilitates the clinical treatment of symptomatic Alzheimer's disease and addiction rehab, a constant societal burden.[2,4] **1**-hydrobromide is an FDA-approved active pharmaceutical ingredient (API) and sold under the brand name Razadyne.[2,5] (+)-Crinine (**2**), (+)-maritidine (**3**), or (−)-siculine (**4**), have been reported to show antitumor and anticholinergic activities. They are biosynthetically formed by different regioselective intramolecular phenol coupling reactions from a norbelladine precursor.[6] Access to the natural materials requires exploitation of limited and threatened botanical resources in economically-demanding procedures.[2,7] In the past, several synthesis approaches have targeted the attractive polycyclic skeleton of **1** employing reagent-mediated approaches (Scheme 1B).[2] Early strategies rely on elaborate protocols using Heck reactions for construction of the azepane moiety.[8] Biomimetic paths feature a hypervalent iodine-mediated oxidative intramolecular cyclization of phenolic substrates,[9–12] also performed on technical scale with $K_3[Fe(CN)_6]$ by activation of a bromo-protected arene.[13] Modern approaches rely on transition-metal catalysis.[14] Very recently, Wirth et al. accessed **1** with an anodic transformation.[15] However, these protocols employ platinum group metals, generate large amounts of reagent waste, or require hazardous reagents, challenging with residual metal impurities tolerated in APIs.[16]

Electrosynthesis has emerged as powerful and versatile technique for facing such challenges, replacing stoichiometric amounts of chemical reagents and demonstrating a high level of sustainability.[17–19] It has already proven high impact as approaches to natural products and APIs were enabled.[20] Exceptional syntheses have been demonstrated to access (−)-alliacol A,[21] dixiamycin B,[22] allocolchicines,[23] or the opioids (−)-thebaine[24] and (−)-oxycodone[25] with electro-organic key transformations. In order to become cost-efficient, simple and inexpensive starting materials, high yields, and easy to conduct protocols are crucial for a technical application of electrosynthesis.[26] In this case, also racemic syntheses with subsequent optical resolution through advanced chromatographic techniques or classical crystallization can be cost-efficient.[17,27]

The spirodienone-motif in intermediates in biomimetic syntheses of Amaryllidaceae alkaloids offers intriguing properties for electro-organic key transformations since it is conveniently prepared by phenol oxidation.[28,29] The synthesis sequence starts from the nature-derived and inexpensive compounds methyl gallate and tyramine for galantamine and vanillin derivatives for maritidine, crinine, and siculine, respectively. This approach based on natural feedstock integrates in the ascending concept of xylochemistry.[30] The experiments were inspired by literature reports for the reagent mediated biomimetic synthesis of galantamine,[12] the electrolysis conditions of Pummerer's ketone, as its structural motif appears in

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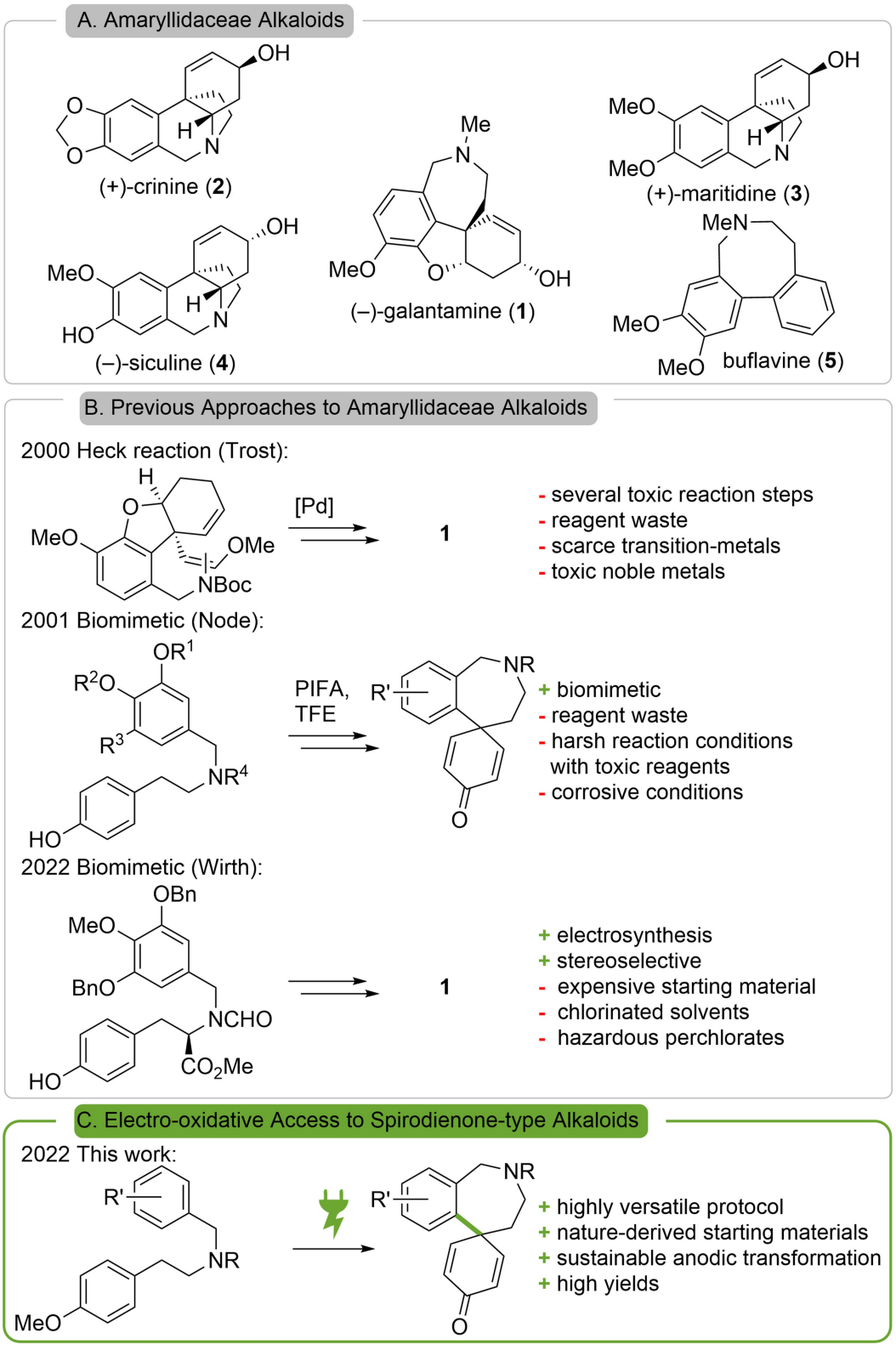
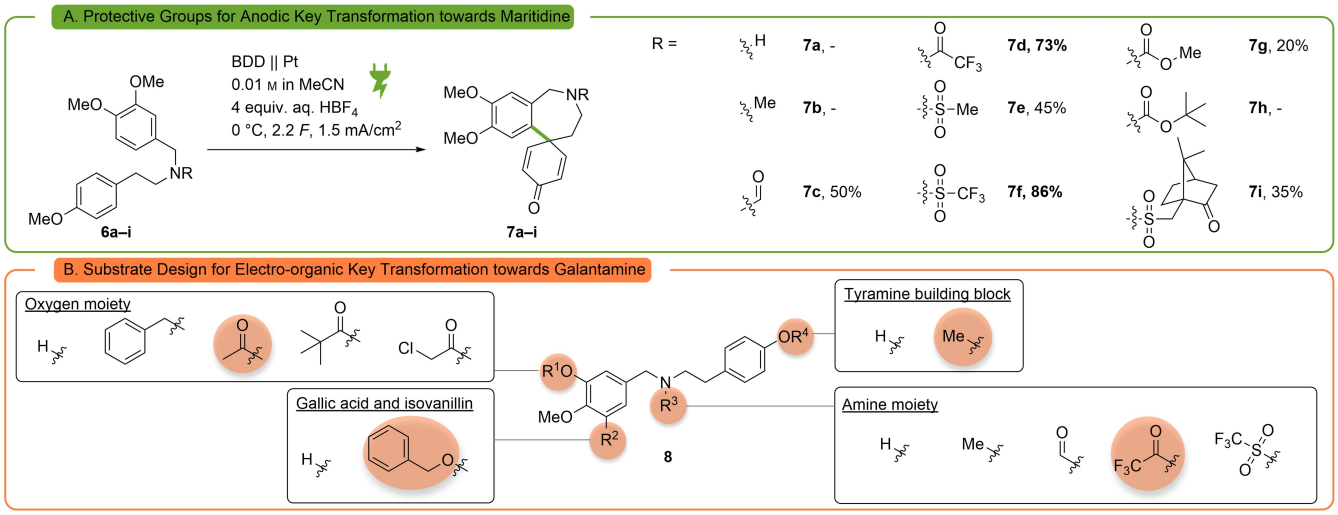



**Scheme 1.** A) Amaryllidaceae alkaloids; B) previous approaches to Amaryllidaceae alkaloids; C) electro-oxidative access to spirodienone-type alkaloids.

the electrolysis product,[29] and the reports on the synthesis of thebaine and oxycodone.[24,25] Initial experiments on the precursor **6** for functionalization towards maritidine revealed a crucial functionalization of the nitrogen moiety, since the secondary amine represents an easy-to-oxidize electrophore and resulted in decomposition during electrolysis.[18] The

comparison of different *N*-protecting groups revealed electron-withdrawing groups to be beneficial for the selective oxidation. Despite giving a lower yield, trifluoroacetyl was preferred over the triflyl group as it offers a more desirable atom economy and better cost efficiency which also proved to be the better choice for adaption and post-functionalization towards **1** (Scheme 2A). As galantamine is the compound of greatest interest for clinical application, the optimization studies have been performed with this key compound, whereby the best results of the investigations above have been verified. Further investigations on the effect of *O*-substituents revealed a superior performance in the absence of protic moieties and by using an unsymmetric substitution pattern of the gallic acid moiety, resulting in a combination of a benzyl, methyl and acetyl group with a regioselective formation of **10** (Scheme 2B). A brief overview of the biosynthesis of Amaryllidaceae alkaloids, detailed information on the extensive evaluation of suitable conditions, and studies towards the reaction mechanism can be found within Supporting Information.

The metal-free, high performance boron-doped diamond (BDD) electrode was found to be the anode material of choice (Table 1, entries 1–4).[31] Acetonitrile with acid additive, the same electrolyte system that was used in the total syntheses of thebaine and oxycodone, gave the most promising results. Any solvent change to, for example methanol, did not result in improvement product formation (Table 1, entry 5). The respective continuous parameters of the galvanostatic electrolysis were further investigated in simple undivided batch-type electrolysers using a Design of Experiments (DoE) approach[32] to achieve up to 76% isolated yield [85% based on recovered starting material (BRSM)]. Here, the amount of applied charge could be lowered to the minimum required and even less acid




**Scheme 2.** A) Protective groups in anodic key transformation to spirodienones; B) substrate design for anodic transformation towards galantamine. BDD: boron-doped diamond.

**Table 1.** Optimization studies on the anodic key transformation towards **10**.

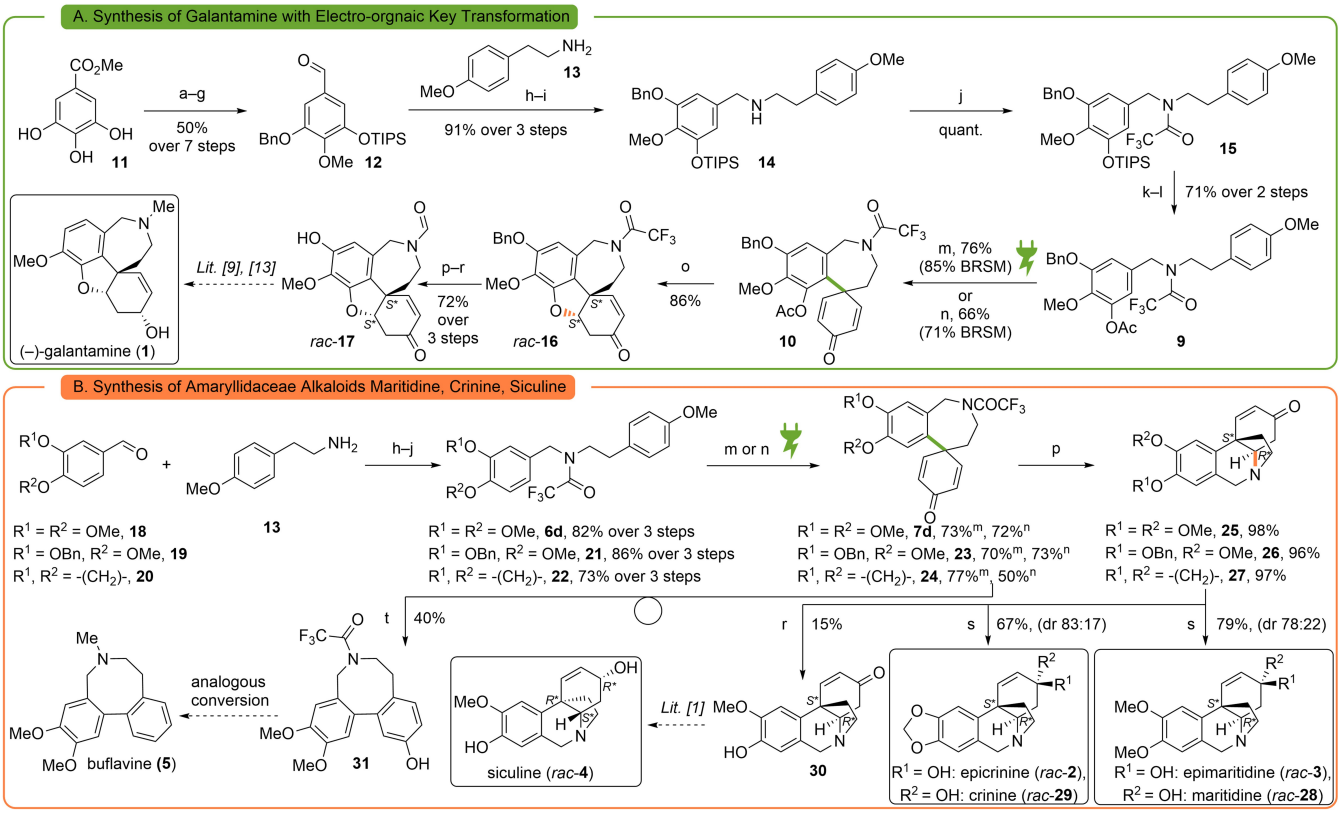

| Entry | Deviation from standard conditions[a] | Isolated yield of **10**/% (BRSM/%) |
|---|---|---|
| 1 | 10 mM in MeCN, 4.0 equiv. aq. $HBF_4$, 0 °C, 2.2 *F*, 1.5 mA/cm$^2$ | 60 (71) |
| 2 | as in 1 with Pt anode | 55 (63) |
| 3 | as in 1 with $C_{gr}$ anode | 54 (68) |
| 4 | as in 1 with $C_{gr}$ cathode | 11 (49) |
| 5 | as in 1 with MeOH | 12 (35) |
| **6** | **none** | **76 (85)** |
| 7 | flow: 20 mM, 4.0 equiv. aq. $HBF_4$, 0 °C, 2.2 *F*, 1.5 mA/cm$^2$, *d* = 0.50 mm | 56 (85) |
| **8** | **flow after DoE: 10 mM, 4.0 *F*, 1.0 mA/cm$^2$, *d* = 0.25 mm, 6.0 equiv. aq. $HBF_4$** | **66 (71)** |

as additive was required (Table 1, entry 6). Thus, less toxic waste is generated, which represents the major drawback associated with reagent-mediated procedures previously reported.

As spirodienones like **10** are prone to rearrangement under acidic conditions, even at room temperature, a continuous flow set-up was refined to neutralize the electrolyte immediately after the electrolysis.[25] This circumvents possible harm to the vinylogous Michael system, which otherwise leads to ring expansion restricting further conversion to the Amaryllidaceae alkaloids. The initial experiments in this operationally simple continuous flow set-up gave **10** in 56% yield (85% BRSM). Analogous to the batch process, the reaction parameters were investigated using a DoE approach to obtain **10** in up to 66% yield (71% BRSM) which represents an increase of 10% of isolated yield (Table 1, entry 8). Considering the complexity of the transformation, highly appreciable yields have been achieved omitting the need for redox mediators but only traceless electrons as a activator and acetonitrile as a sustainable solvent are used.[33]

To ensure further functionalization towards galantamine, the subsequent deprotection sequence of **10** had to commence with deacetylation, avoiding acidic dienone-phenol rearrangement and simultaneous liberation of the more nucleophilic nitrogen moiety. Extensive screening of conditions led to the sterically demanding and less nucleophilic amidine base 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) as superior choice to form the desired product *rac*-**16** in 86% yield. Base-mediated cleavage of the trifluoroacetamide with subsequent formylation of the nitrogen with ethyl formate and debenzylation with $BCl_3$ yielded *rac*-**17**. As the latter is a known galantamine precursor,[9,12] the presented reaction sequence represents a racemic formal total synthesis starting from methyl gallate and *O*-methyltyramine (Scheme 3A). As high yields have been obtained in the key transformation, the known dynamic optical resolution through reversible vinylogous addition becomes a viable option to access enantiomerically pure **16**.[10,13]

The versatility of the developed methodology is demonstrated as short, straightforward sequences with electro-organic key transformations of norbelladine derivatives yielded the Amaryllidaceae alkaloids *rac*-epimaritidine, *rac*-epicrinine, and *rac*-siculine as well as their diastereomers (Scheme 3B) in batch- and flow-electrolyzers. In the synthesis of *rac*-**28** the respective electrolysis product **7d** was obtained in 73% in batch-type electrolysis and in 72% in the refined continuous-flow setup. Similar results have been observed for **23** which was formed in 70% yield in batch and in 73% flow electrolysis. However, the synthesis of the electrolysis precursor towards *rac*-**24** performed best in batch-type reactors with up to 77% (88% BRSM). The




**Scheme 3.** A) Total synthesis of galantamine and B. Synthesis of Amaryllidaceae alkaloids. a. $HC(OEt)_3$, Amberlyst 15, PhMe, 48 h; b. $K_2CO_3$, BnCl, DMF, 70 °C, 20 h; c. $HCl_{aq}$, MeOH, r.t., 15 h; d. MeI, $Li_2CO_3$, DMF, 55 °C, 20 h; e. TIPSCl, imidazole, DMF, r.t., 20 h; f. $LiAlH_4$, THF, r.t., 20 h; g. IBX, MeCN, 82 °C, 1 h; h. **13**, MeOH, 80 °C, 1 h; i. $NaBH_4$, 0 °C, 1 h; j. TFAA, pyridine, 0 °C, 2.5 h; k. TBAF, THF, Ar, r.t., 18 h; l. $Ac_2O$, $NEt_3$, 0 °C - r.t., 2 h; m. BDD||Pt, 5 mM in MeCN, 3.0 equiv. aq. $HBF_4$, −20 °C, 2.0 *F*, 1.0 mA/cm², 200 rpm; n. BDD||Pt, 10 mM in MeCN, 4.0 *F*, 1.0 mA/cm², 0 °C, *d* = 0.25 mm, 6.0 equiv. aq. $HBF_4$; o. DBN (8.0 equiv.), MeCN, 50 °C, 4 h; p. 10% KOH in MeCN, r.t., 3 h; q. $HCO_2Et$, 60 °C, 1 h; r, $BCl_3$, DCM, −78 °C, 21.5 h; s, L-selectride, THF, −78 °C, 15 h; t. workup of electrolysis without basification - also by treatment with acid.

amine moiety of electrolysis products can simply be liberated in alkaline conditions resulting in the aza-Michael addition towards the tetracyclic core. A debenzylation of *rac*-**26** with subsequent reduction using L-selectride gives access to *rac*-**2**, *rac*-**3**, *rac*-**4**, *rac*-**28**, and *rac*-**29**. As the stereochemistry is not being set until the vinylogous addition to the symmetrical dienone, it is likely that (organo-)catalytic versions of this transformation can be developed while its reversibility permits powerful dynamic optical resolutions. The rearrangement of spirodienone **7d** can even be put to an advantage. The synthesis of **30** during workup of an electrolysis of **7d** without basification results in a ring expansion and thus, the skeleton to accesses a route towards the Amaryllidaceae alkaloid buflavine (Scheme 3B).

In summary, a general biomimetic approach towards the Amaryllidaceae alkaloids based on a highly versatile anodic key transformation to spirodienones was devised. Remarkably high yields achieved in the key transformation using a Design of Experiments approach for optimization studies underline the impact of this protocol. The strategy, based on simple biogenic starting materials, enables access to galantamine in only a few steps following the key transformation. Such a green electro-organic technology can even be conducted in continuous flow setups and thus be scaled up by simply increasing the number of flow electrolyzers.

## Supporting Information

The Supporting Information (PDF) including detailed optimization studies, experimental procedures, mechanistic studies, and copies of NMR spectra can be found under:

## Author Contributions

All authors have given approval to the final version of the manuscript.

## Notes

The authors declare no competing financial interest.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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