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A Regio- and Diastereoselective Anodic Aryl-Aryl-Coupling in the Biomimetic Total Synthesis of (–)-Thebaine

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Abstract: The biosynthesis of thebaine is based on the regioselective, intramolecular, oxidative coupling of (*R*)-reticuline. For decades, chemists have sought to mimic this coupling using stoichiometric oxidants. However, all approaches suffered from low yields or the formation of undesired regioisomers. Electrochemistry would represent a sustainable alternative in this respect but all attempts to accomplish an electrochemical synthesis of thebaine have failed so far. Herein, a regioselective and diastereoselective anodic coupling of 3',4',5'-trioxygenated laudanosine derivatives is presented, which finally enabled an electrochemical access to (–)-thebaine.

Thebaine is a minor opium alkaloid which has long been in the focus of organic chemists as it is the biosynthetic progenitor of codeine and morphine as well as a suitable precursor for the industrial semisynthetic production of relevant pharmaceuticals such as naloxone, oxycodone or buprenorphine.[1] Since the discovery that the biosynthesis of thebaine and morphine proceeds through an intramolecular oxidative coupling of reticuline,[2] many attempts towards mimicking this process in the laboratory were undertaken.[3] However, this intramolecular coupling is highly challenging as it can lead to four different regioisomers out of which only the 4a-2'-coupled product, salutaridine, can be further converted to thebaine (Scheme 1A). Coupling at C8 furnishes either corytuberine (8-2'-coupling) or isoboldine (8-6'-coupling) which share the aporphine skeleton and do not serve as precursors for thebaine. In contrast, coupling at C4a grants access to the desired morphinandienones comprising salutaridine (4a-2'-coupling) as well as isosalutaridine (4a-6'-coupling). The latter cannot be transformed into thebaine since it lacks the hydroxyl group *ortho* to the newly formed bond which is a requirement for the subsequent formation of the E-ring.

In the past decades, many researchers have faced this challenging coupling employing conventional oxidants such as $K_3Fe(CN)_6$, MnO_2-silica, Ag_2CO_3-Celite or $VOCl_3$.[3] However, these approaches suffered from relatively low yields and wrong regioisomers, mainly isoboldine and isosalutaridine, were obtained. The first report of a successful 4a-2'-coupling was published in 1963/7 by Barton and co-workers who were able to detect a vanishingly low yield of the desired product (≤ 0.03%) via isotope dilution techniques.[4] In 1975, Schwartz and Mami reported a 23% yield of a 4a-2'-coupled salutaridine derivative from *N*-ethoxycarbonylnorreticuline and its conversion to racemic thebaine, thereby completing their biomimetic approach.[1l] However, stoichiometric quantities of a highly toxic thallium(III) reagent were required. There have been a few attempts to utilize organic iodine based oxidants and the desired 4a-2'-coupled salutaridine-type products were obtained in some cases, albeit in low yield.[1o-q, 5]

Electrochemistry represents a versatile synthetic tool and offers a sustainable alternative to the use of stoichiometric quantities of chemical oxidants.[6] In 1971, Miller and co-workers published their seminal report on the anodic coupling of laudanosine on a platinum anode in a divided cell under potentiostatic conditions (52% isolated yield).[7] In the following years, improvements to the coupling procedure with respect to optimized anolyte composition, acidic additives or strict control of the total amount of passed current led to significantly improved yields and the method was transferred to an undivided cell (galvanostatic electrolysis).[8] The anodic coupling is selective for the 4a-position, thereby eliminating all aporphine-type structures as side products (Scheme 1B). However, due to steric and electronic reasons, the anodic coupling is inherently 6'-selective, which gives rise to the undesired isosalutaridines. These lack the alkoxyl group *ortho* to the newly formed bond that is required for the closure of the E-ring. So far, all attempts to enforce the desired 4a-2'-coupling by blocking the favored 6'-position either by installation of blocking groups at C6' or through adjacent substituents at C5' failed and the impedimental 4a-6'-selectivity of the anodic coupling could not be overcome.[8b-d, 9] A brief overview of previous achievements in the long struggle for a biomimetic oxidative approach to thebaine is provided in the Supporting Information.

If laudanosine derivatives with a 3',4',5'-trioxygenated benzylic moiety are employed in the anodic coupling,[1n] the formed morphinandienones always carry an oxygen substituent in the right place and thus, the problems associated with the inherent 6'-selectivity can be overcome (Scheme 1C).[8c, 9a] Even though our groups have been intrigued by this strategy for more than 15 years,[8c, 10] thebaine could never be obtained due to problems with deprotection of the coupling products. Herein, the doubly regio- and fully diastereoselective anodic coupling of 3',4',5'-trioxygenated laudanosine derivatives is described, which finally provides a viable solution for an electrochemical access to thebaine.

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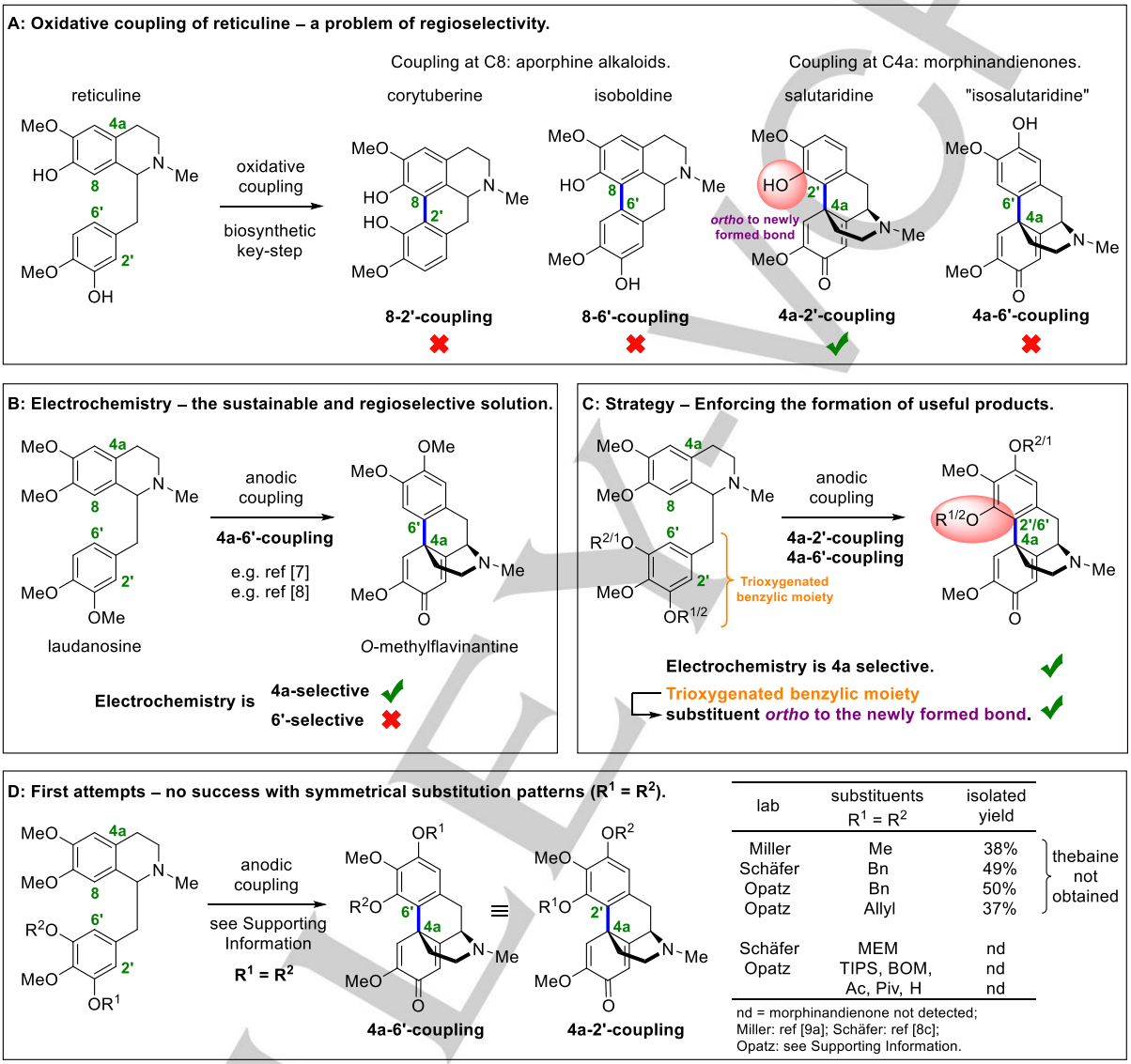
First attempts were undertaken with a symmetrical substitution pattern ($R^1 = R^2$) which would avoid the occurrence of isomeric morphinandienones (Scheme 1D). Even though these trioxygenated laudanosine derivatives proved to be prone to oxidative side reactions (such as over-oxidation or C–C bond cleavage),[11] some substitution patterns permitted a successful coupling. However, the obtained morphinandienones could not be further converted to thebaine since it was not possible to remove the O-protection without harming the C-ring. Unfortunately, all attempts to employ easily removable protecting groups failed in the anodic coupling. A detailed description of these experiments ($R^1 = R^2$ in Scheme 1D) is provided in the Supporting Information.



Scheme 1. A) The oxidative coupling of reticuline and its derivatives can lead to four different regioisomers out of which only one (4a-2') can be further converted to thebaine. **B)** Electrochemistry is 4a-selective but suffers from an inherent 6'-selectivity. **C)** Outlining the strategy – the formation of useful coupling products can be enforced by employing 3',4',5'-trioxygenated laudanosine derivatives. **D)** Unsuccessful attempts using 3',4',5'-trioxygenated laudanosine derivatives with a symmetrical substitution pattern ($R^1 = R^2$).

Due to these disappointing results, it was decided to focus on 3',4',5'-trioxygenated laudanosine derivatives with an unsymmetrical substitution pattern ($R^1 \neq R^2$ in Scheme 1D). The use of orthogonal protecting groups would allow a sequential liberation of the phenolic hydroxyl groups, which would be beneficial in view of the sensitivity of the synthetic intermediates. However, the occurrence of isomeric morphinandienones was expected which would have a negative impact on subsequent operations. Since an electronic differentiation within the trioxygenated moiety might still ensure complete regioselectivity,[8c] the combination of benzyl ether and ester protecting groups was tested. Gratifyingly, it proved to be very fruitful and led to a doubly regioselective and fully diastereoselective anodic coupling (Scheme 2). The C–C bond formation requires an initial approach of both π systems of the aromatic moieties. Moving these two rings in a parallel position that allows a sufficient π orbital overlap automatically creates the

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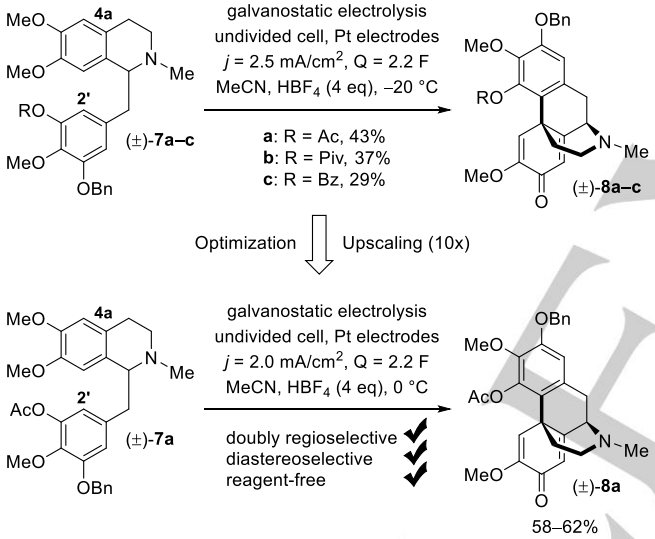
diastereoselectivity found. A rationale for the observed regioselectivity is provided in the Supporting Information.

After an extensive optimization (see Supporting Information), the desired 4a-2'-coupled morphinandienone (±)-**8a** could be obtained in relatively high yield using a simple undivided cell at constant current conditions. Except for acetonitrile as solvent and a small amount of aqueous tetrafluoroboric acid as an acidic electrolyte to prevent amine oxidation, no further reagents or supporting electrolytes are required. The use of acyl protecting groups is ideal for the subsequent synthesis as they can easily be removed under basic conditions or simultaneous to the reduction of the morphinandienone's carbonyl group. The mechanism of the oxidative coupling of laudanosine has been investigated by Miller and co-workers.[12] Under acidic conditions, the initial oxidation takes place at one of the oxygenated and thus electron-rich aromatic rings furnishing an aryl radical cation which might then be trapped via an intramolecular nucleophilic attack by the other aromatic moiety. A mechanistic discussion and cyclic voltammetry data are provided in the Supporting Information.



Scheme 2. Key-finding: A doubly regioselective and fully diastereoselective anodic coupling of 3',4',5'-trioxygenated laudanosine derivatives with unsymmetrical benzylic moieties using a combination of benzyl ether and ester protecting groups.

The selective anodic coupling (Scheme 2) serves as key-step in the presented biomimetic synthesis of thebaine (Scheme 3). Starting from homoveratrylamine and methyl gallate, this approach is based on naturally occurring and inexpensive starting materials.[13] The latter were converted to α-aminonitrile **3** and benzyl bromide **4** using standard operations (see Supporting Information). The 1-benzyltetrahydroisoquinoline core was synthesized from these two building blocks via a deprotonation-alkylation-reduction sequence furnishing (±)-**5**.[1x, 14] After installing the correct protecting groups, the trioxygenated laudanosine derivative (±)-**7a** was subjected to the anodic coupling providing morphinandienone (±)-**8a**. In order to debenzylate without harming the enol ether or enone moieties, a transfer hydrogenation employing 1,4-cyclohexadiene was performed. The superfluous hydroxyl group was removed via Pd-catalyzed transfer hydrogenation of the corresponding triflate (±)-**10**. Subsequent deacetylation followed by the selective 1,2-reduction of the carbonyl group under *Luche*-conditions furnished intermediate (±)-**11**. (±)-Thebaine was obtained upon closure of the E-ring via a biomimetic conjugate nucleophilic substitution (S_N2') through activation of the allylic alcohol with *N*,*N*-dimethylformamide dineopentyl acetal.[1o] An alternative route comprising the reduction of the carbonyl group in morphinandienone (±)-**8a** with subsequent S_N2'-cyclization to furnish (±)-**14** was unsuccessful as the 2-hydroxyl group could not be removed without affecting the dienol ether moiety.

Since both biomimetic cyclizations (Scheme 3A, steps d and j) were entirely diastereoselective, an enantioselective synthesis of natural (–)-thebaine can be accomplished starting from (*R*)-**5** (Scheme 3B). The latter could easily be prepared from α-aminonitrile **16** and benzyl bromide **4** via a similar deprotonation-alkylation-reduction sequence in combination with a *Noyori*-type asymmetric transfer hydrogenation.[15]

In summary, a biomimetic total synthesis of thebaine relying on a regio- and diastereoselective, anodic, intramolecular coupling of a 3',4',5'-trioxygenated laudanosine derivative was developed. The electrolytic conversion can be easily conducted in a very simple undivided constant current setup. This selective anodic coupling finally enabled a biomimetic, electrochemical synthesis of (±)-thebaine and its natural (–)-enantiomer, thereby solving a long-standing electrochemical challenge.

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Keywords: electrochemistry • alkaloids• thebaine • morphine • biomimetic synthesis

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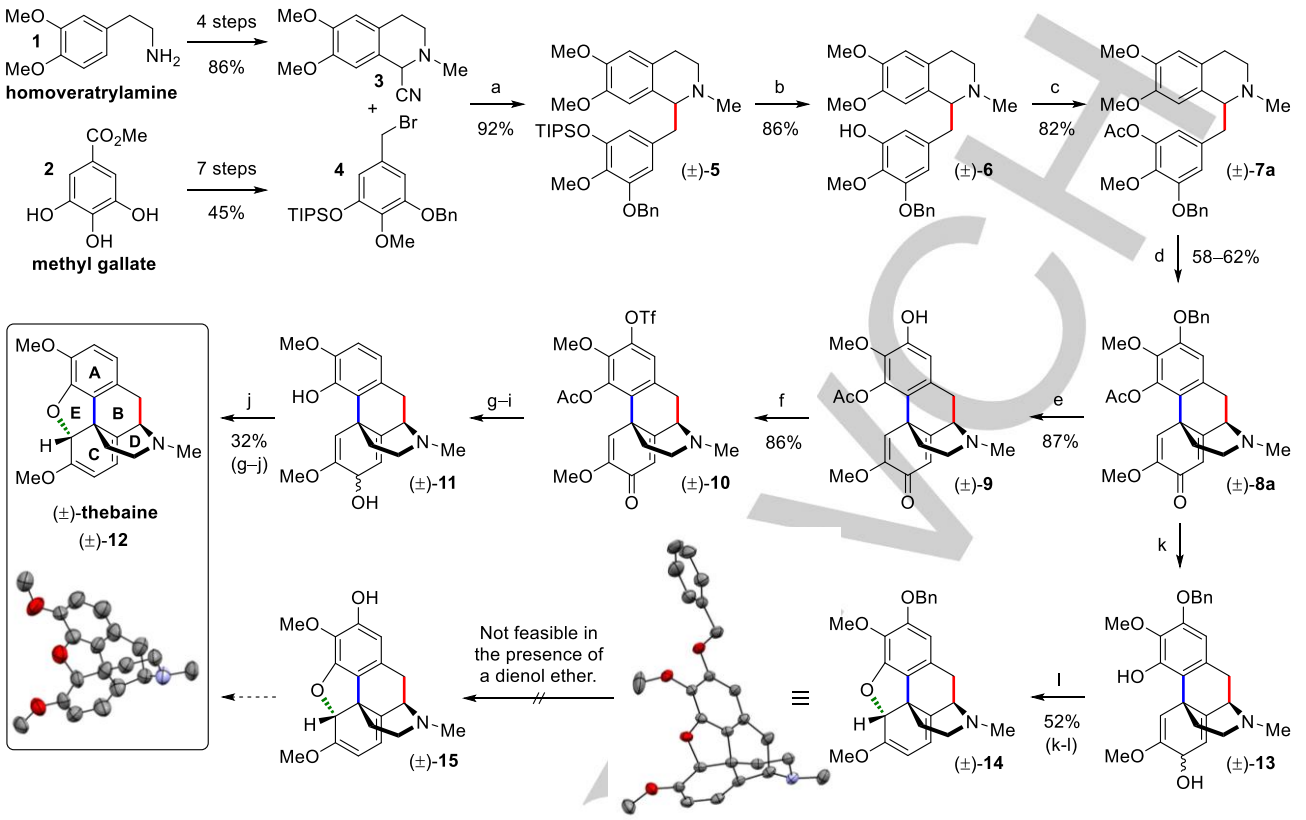
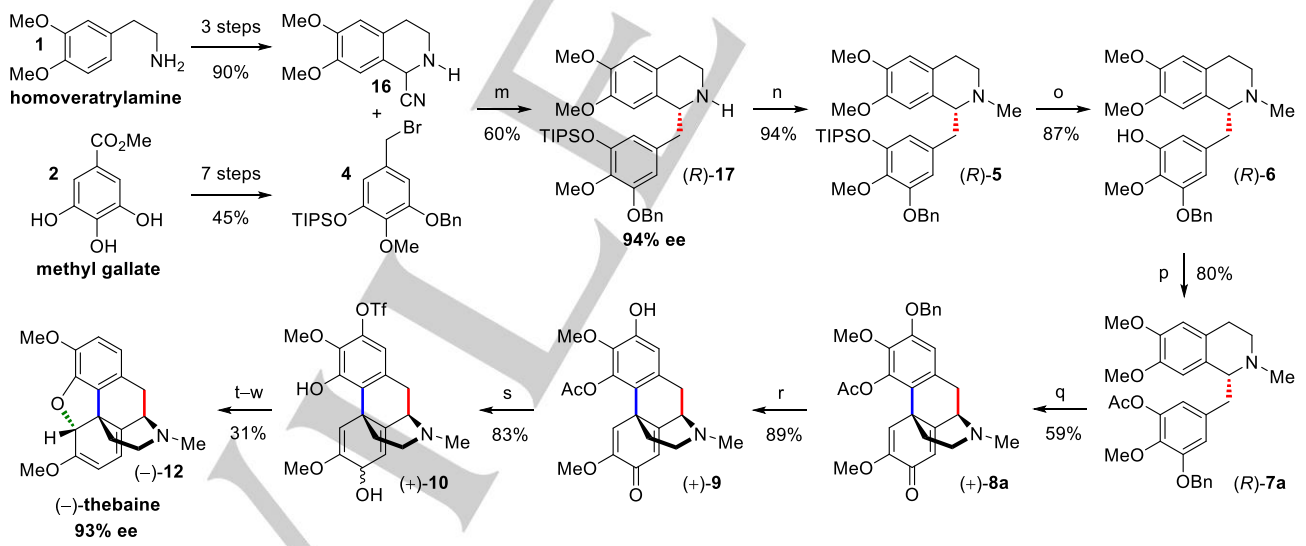
A: Synthesis of (±)-thebaine from naturally occuring starting materials.



B: Application to the stereoselective synthesis of (–)-thebaine.



Scheme 3. A) Biomimetic synthesis of (±)-thebaine from naturally occurring homoveratrylamine and methyl gallate: a) one-pot with i) KHMDS, THF, 0 °C; ii) bromide **4**, 0 °C → rt; iii) $NaCNBH_3$, EtOH, HOAc, rt; b) TBAF, THF, rt; c) AcCl, Et_3N, DMAP, CH_2Cl_2, rt; d) constant current electrolysis, undivided cell, Pt electrodes, j = 2.0 mA/cm^2, Q = 2.2 F, MeCN, HBF_4, 0 °C; e) Pd/C, 1,4-cyclohexadiene, EtOH, 35 °C; f) Tf_2O, pyridine, 0 °C; g) $Pd(PPh_3)_4$, Et_3N, HCO_2H, DMF, 60 °C; h) K_2CO_3, MeOH, rt; i) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, MeOH, 0 °C; j) *N*,*N*-dimethylformamide dineopentyl acetal, dioxane, 80 °C; k) $LiAlH_4$, THF, 60 °C; l) as in j; **B)** Synthesis of (–)-thebaine: m) one-pot with i) KHMDS, THF, –78 °C; ii) bromide **4**, –78 °C → rt; iii) RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN], HCO_2H, Et_3N, DMF, 0°C → rt; n) HCHO, $NaBH_4$, MeOH, 0 °C; o) as in b; p) as in c; q) as in d; r) as in e; s) as in f; t) as in g; u) as in h; v) as in i; w) as in j. X-ray molecular structures (ORTEP), ellipsoids displayed with 50% probability. CCDC 1831232 – CCDC 1831236 contain the supplementary crystallographic data for this paper. These data are provided free of charge by *The Cambridge Crystallographic Data Centre*. For the syntheses of **3**, **4** and **16** refer to the Supporting Information.

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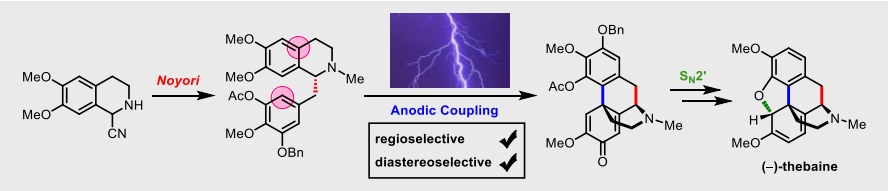

Enforcement of selectivity through a combination of electrochemistry and substrate design was used as elegant strategy to solve a long-standing electrosynthetic challenge. Herein, a regio- and diastereoselective anodic coupling of 3',4',5'-trioxygenated laudanosine derivatives is presented which enables a biomimetic, electrochemical access to (–)-thebaine.

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A Regio- and Diastereoselective Anodic Aryl-Aryl-Coupling in the Biomimetic Total Synthesis of (–)-Thebaine