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Synthesis of Morphinans through Anodic Aryl-Aryl Coupling

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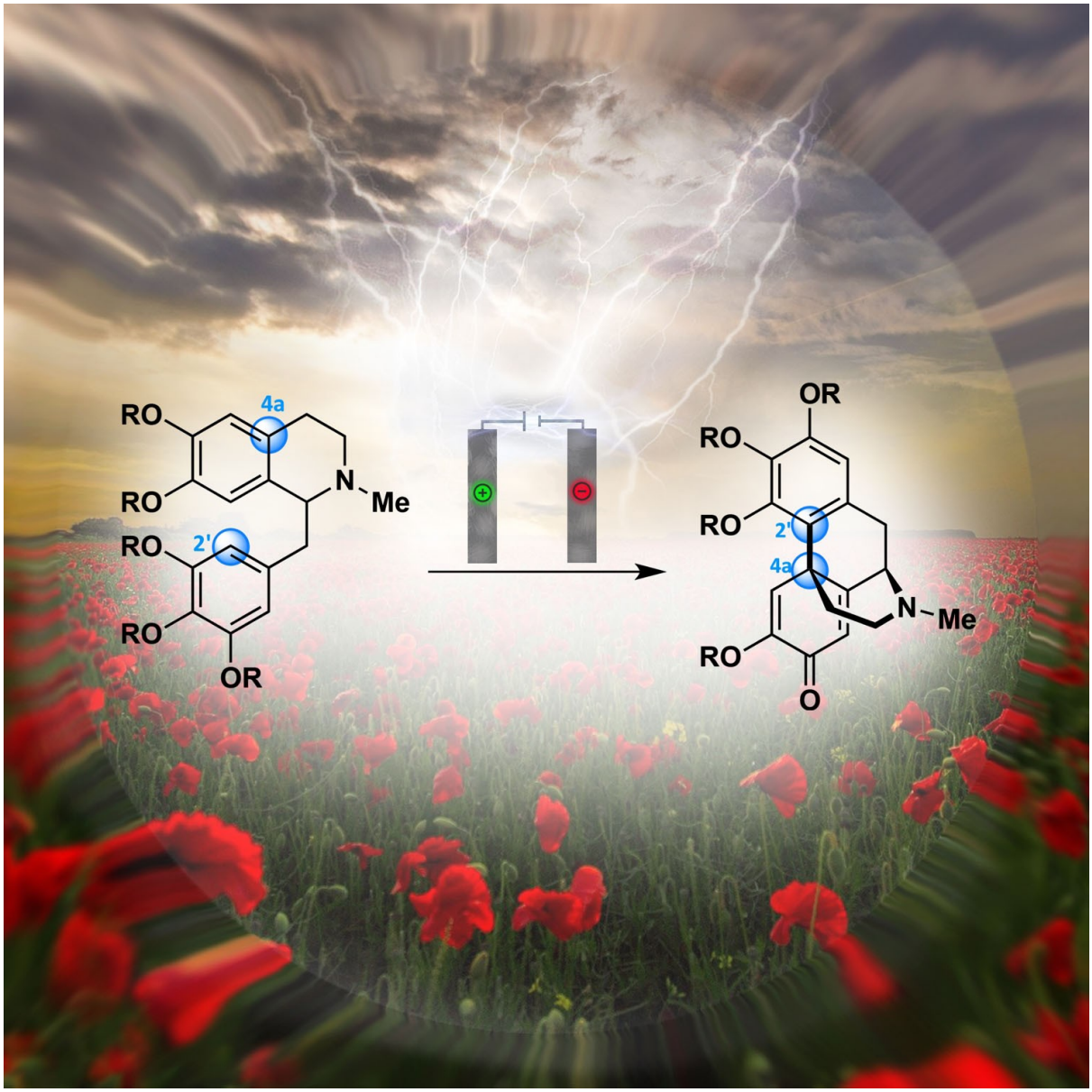
Dedicated to Professor Shigeru Nishiyama for his achievements in organic electrosynthesis.



Abstract: The morphinans are an important class of structurally fascinating and physiologically important natural products as exemplified by the famous opium alkaloids of the morphine family. Although this class of secondary metabolites from the juice of the opium poppy capsule was already used for medicinal purposes thousands of years ago, chemical modifications are still being applied to the core structure today in order to achieve the most specific effect on the various receptor subtypes possible with the fewest possible side effects. The unusual architecture of the morphinan core has also proven to be a highly challenging target for total synthesis. This review highlights electrosynthetic approaches towards natural and semisynthetic morphinan alkaloids. The historical progress in applying anodic aryl-aryl couplings to the construction of the morphinan framework is described in chronological order while particular benefits and challenges concerning the electrochemical transformations are grouped together, including the influence of substitution patterns, protecting groups, and reaction conditions.

Keywords: Electrochemistry, total synthesis, morphinans, aryl–aryl coupling, anodic oxidation

1. Introduction

1.1. Background

The morphinan skeleton, consisting of an octahydrophenanthrene framework with a bridging piperidine ring, is an important structural motif widely encountered in plant-derived alkaloids (Scheme 1A). Hundreds of representatives possessing various structural elements can be isolated from different flowering plants with the *Papaveraceae* family being the most prominent source of morphinan alkaloids.[1,2] Most of these morphinan natural products exhibit potent biological activities and were administered to humans in the form of raw opium for millennia for various pharmacological purposes.[3] Since Sertürner's pioneering isolation of morphine (**1 a**) from the complex mixture of alkaloids found in the latex of the opium poppy capsule in 1817,[4] purified natural, semi-synthetic and fully synthetic opioids are meanwhile used as analgesics, sedatives and cough suppressants on a global scale,[5] with morphine (**1 a**) still being the most famous representative of this family.[6] Semisynthetic opioids, e. g. diacetylmorphine (heroin, **1 b**), hydromorphone (**2**) or etorphine (**3**), can display an even higher activity than morphine due to a higher receptor affinity or a more rapid onset of action.[7–9] Therefore, the chemical modification and total synthesis of morphine and its derivatives continues to be a fascinating field of research for synthetic chemists. Despite the great progress in developing new protocols for the total synthesis of complex natural products over the past decades, the total synthesis of morphinan alkaloids still remains a challenging task, mainly due to regioselectivity problems in the biomimetic assembly of the B-ring (see section 1.2). However, numerous approaches have been developed to overcome these problems, including cuprate chemistry,[10] various rearrangements, and cyclization reactions.[11–14] Moreover, versatile electroorganic reactions have been devised which provide significant advantages in the construction of morphinan natural products.

1.2. Structural Challenges

In nature, the spectacular enzyme-catalyzed intramolecular oxidative coupling of reticuline (**4**) to salutaridine (**7**) represents the key step of the biosynthesis of morphinan alkaloids, in which the central tetracyclic core structure is constructed with the correct C-4a connectivity.[15] For decades, chemists have attempted to imitate this unique enzymatic transformation, but without the help of the corresponding cytochrome P450 monooxygenase, salutaridine synthase,[16] oxidative coupling of reticulin or a structurally related precursor gives rise to up to four different coupling products (Scheme 1B). C8-2' and C8-6' coupling leads to the generation of the aporphines corytuberine (**5**) and isoboldine (**6**), respectively. While these are still interesting alkaloids, they are undesirable dead ends in the intended construction of the morphinane scaffold.[17–19] Only salutaridine (**7**, 4a–2′-connectivity) can be further converted to morphine (**1 a**) (Scheme 1B). Coupling to C4a is a prerequisite for the formation of the morphinan backbone, and the position of the hydroxyl group ortho to the newly attached bond is essential for the subsequent construction of the E-ring via a conjugated nucleophilic substitution, which is the reason why C4a-6' coupling to isosalutaridine (**8**) is also an undesirable dead end in this cascade.

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After the mid-20th century, the pioneering work of Barton and Schwartz led to successful intramolecular C-4a couplings, which were effected by the use of toxic heavy metal-containing oxidants.[20–23] Despite intensive optimization including the structural modification of starting materials, variation of reaction conditions as well as testing a great number of different oxidants, the lack of regioselectivity, low yields, the need for toxic reactants and difficult purification protocols[24–27] required the exploration of more efficient alternatives.

The application of electrochemistry instead of reactions involving stoichiometric oxidants provides several advantages.[28–30] The general use of electrochemistry is beneficial from an economical and environmental perspective. Moreover, as the following synopsis will demonstrate, anodic intramolecular coupling reactions of laudanosine derivatives exclusively proceed with C-4a selectivity, thus paving an attractive, general entry to the morphinan alkaloids.

2. Miller's Initial Work (1971–1973)

In 1971, Miller described for the first time the anodic oxidative coupling of benzylisoquinolines, providing an oxidant-free alternative to the intramolecular construction of the morphinan B-ring with C-4a-6' selectivity (Scheme 2A).[31] In a first approach, laudanosine (**9a**) was anodically oxidized on a platinum electrode in a divided cell under potentiostatic conditions. In the presence of sodium carbonate or tetramethylammonium tetrafluoroborate as the electrolyte, *O*-methylflavinine (**10a**) could be isolated in 52% yield (Scheme 2A).[31] This landmark electrochemical approach proved far superior to the contemporary examples employing inorganic oxidants (for an extensive overview, the reader may be referred to ref. [32]) considering yields and the inherent selectivity problem of undesired C-8-coupling to form aporphine alkaloids instead of the desired morphinandienones (see section 1.2). Two years later, Miller was able to extend his method to the coupling of three further benzylisoquinolines **9b–d** bearing O-benzyl protection at C-2, C-3 or C-6.[33] It is important to note that the peak potentials for benzylisoquino-

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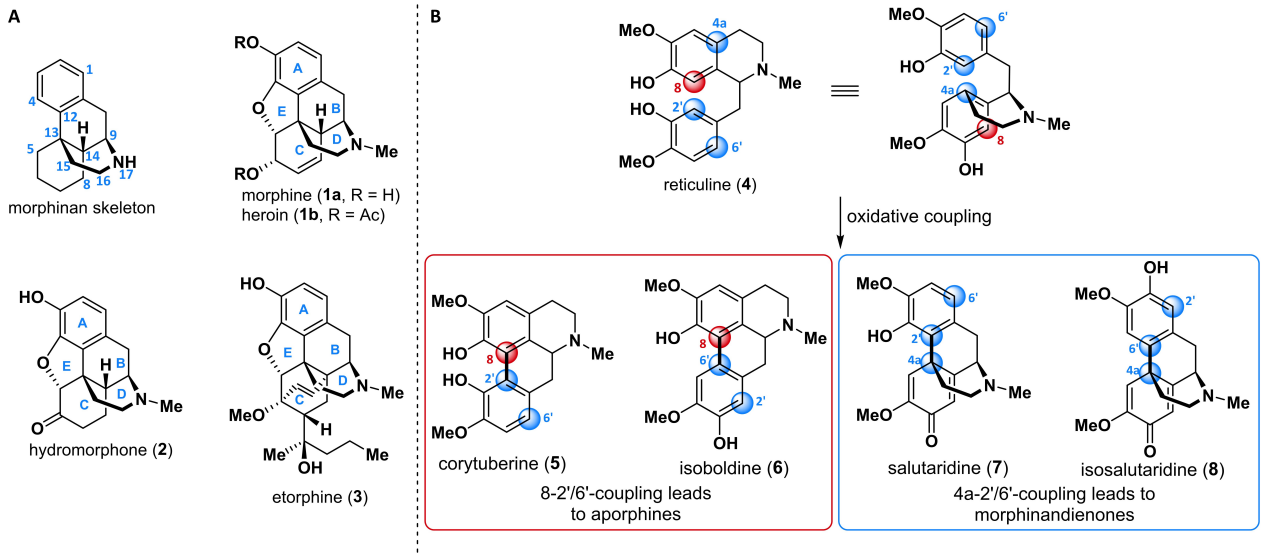
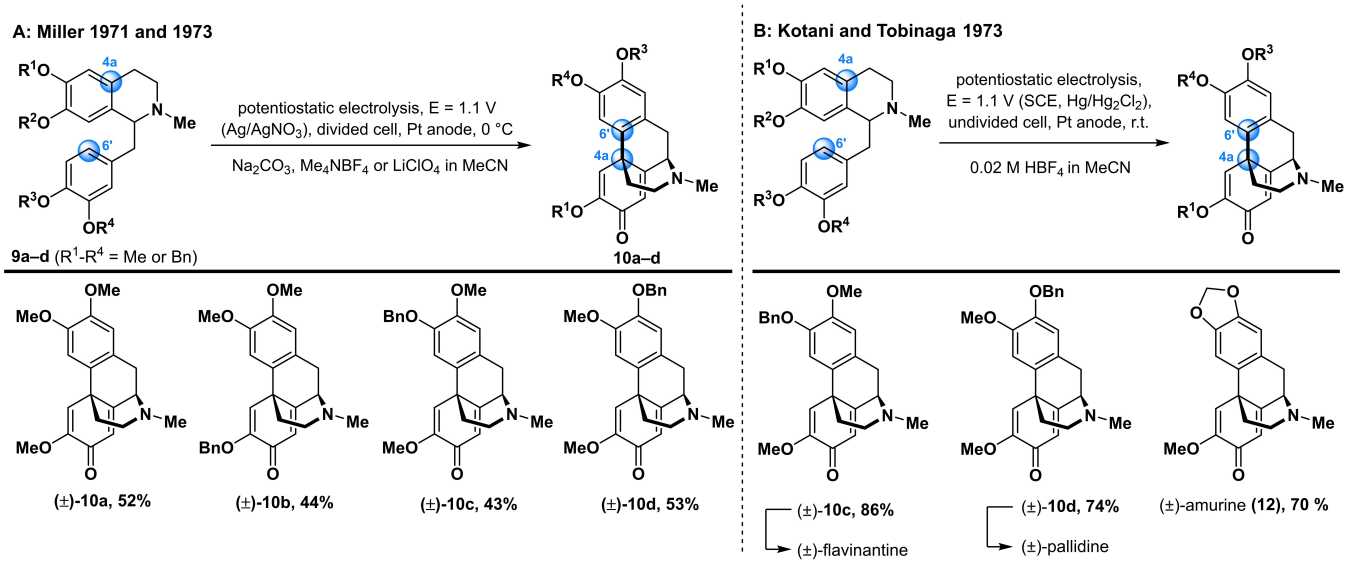
Eisuke Sato obtained his diploma in Chemistry from Keio University in 2013. In 2018, he completed his PhD under the direction of Professor Kiyotake Suenaga at the same university. After the postdoctoral study at JGU with Professor Till Opatz, he is currently working as an assistant professor at Okayama university. His research interest includes the total synthesis of natural products and the development of synthetic methods with electrochemical reactions.

Till Opatz obtained his diploma in Chemistry from Frankfurt University in 1997. In 2001, he completed his PhD at Johannes Gutenberg University under guidance of Professor Horst Kunz and, after a postdoctoral stay at Utrecht University (Netherlands) with Professor Rob Liskamp, he returned to Mainz to complete his habilitation in 2006. From 2007 on, he was associate professor at Hamburg University and returned to Mainz as a full professor in 2010. His research interests are the development of synthetic methods, the structure elucidation and total synthesis of natural products as well as sustainable chemistry.



Scheme 1. A: Structure and members of the morphinan family. B: The intramolecular oxidative coupling of reticuline (**3**) leads to the generation of four different products of which only the 4a-coupled molecules **6** and **7** possess the core morphinan framework.



Scheme 2. A: Miller's pioneering work in anodically driven intramolecular coupling reactions of laudanosine derivatives. B: By optimization of the reaction setup with an acidic electrolyte in an undivided cell, Kotani and Tobinaga significantly increased the overall efficiency.

lines **9a–d** and the corresponding morphinandienone products **10a–d** are very similar, resulting in yield-limiting overoxidation. However, the authors partly circumvented this issue by performing all reactions in acetonitrile, from which the desired products precipitate. In this way, the corresponding morphinandienones **10a–d** could be obtained in yields of 43–53% (Scheme 2A).

Remarkably, when reticulin was subjected to anodic coupling by the group of Bobbit in order to mimick the biochemical pathway, only overoxidation and fragmentation of the starting material could be observed.[34] However, these researchers described the successful anodic phenolic coupling of *N*-carbethoxy- and *N*-carbobenzyloxy norreticuline leading to the respective 4a-6'-coupled isosalutaridines, even though the yields were significantly lower.[34] All subsequent relevant work therefore focused on laudanosine as the starting material.

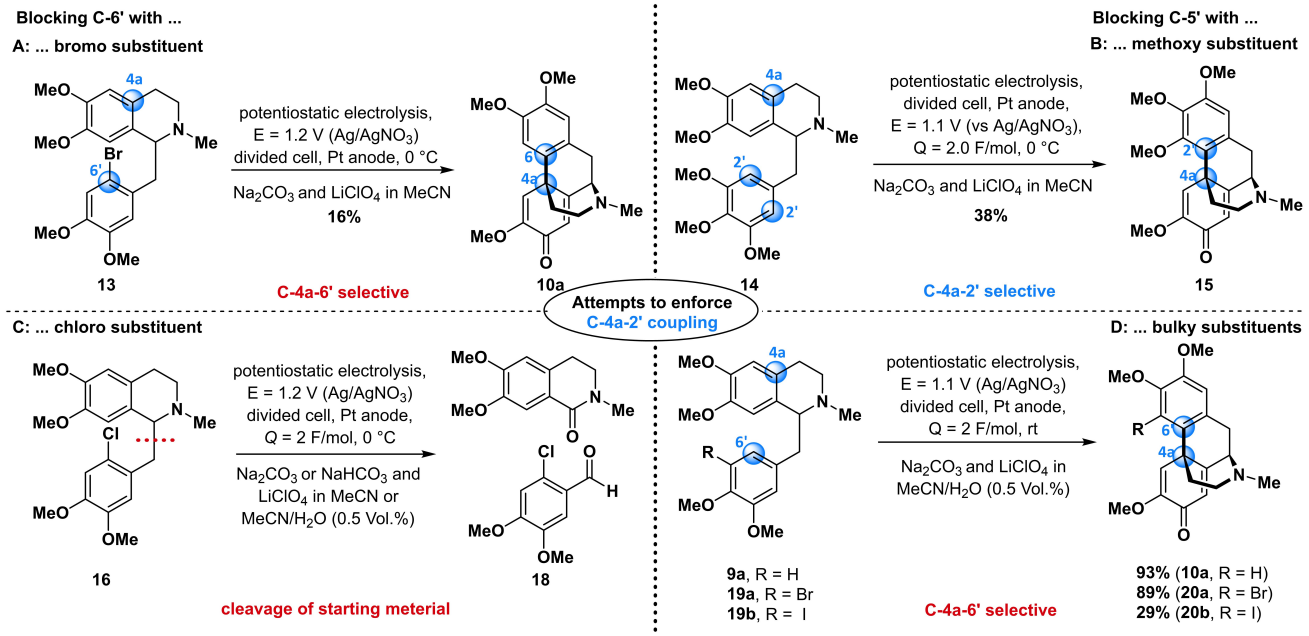
Five months later, Kotani und Tobinaga from the Showa College of Pharmaceutical Sciences in Tokyo showed that the

employment of tetrafluoroboric acid as a strongly acidic electrolyte and performing the reaction in an undivided cell led to even higher yields using similar starting materials.[35] Notably, the improved setup could also significantly reduce reaction times to 15 minutes. Under these conditions, the anodic oxidation of **9c** and **9d** furnished morphinandienones **10c** and **10d** in 86% and 74% yield, respectively (Scheme 2B). A related benzodioxole-containing benzylisoquinoline **11** also proved to be a suitable reactant as the corresponding natural product (±)-amurine (**12**) was obtained in 70% yield. Moreover, the authors successfully transformed the morphinandienones **10c** and **10d** into their naturally occurring analogues (±)-flavinantine and (±)-pallidine by acid-induced debenzylation.[35]

3. Further Improvements of the C-4a-6'-Coupling and Transition of Interest Towards C-4a-2' Selectivity (1973–2000)

Although this newly developed method for the formation of morphinandienones raised interest in the hotly contested area of the total synthesis of naturally occurring opium alkaloids and opioids, anodic oxidation of laudanosine derivatives suffered from an inevitable C-4a-6' selectivity. This shortcoming restricted the applicability of the method in organic synthesis: all products were lacking the oxygen-substituent adjacent to the newly formed C–C-bond in the B-ring, which would be crucial for the subsequent steps towards e. g. thebaine (**32**), codeine or morphine (**1a**).

In early 1974, Miller and Stermitz from the Colorado State University addressed this issue for the first time by trying to steer the reaction towards the desired 4a-2' coupling.[36] Efforts were made to block the more reactive 6'-position of laudanosine with a bromine substituent (**13**), but dehalogenation and the formation of *O*-methylflavinine (**10a**) were observed instead (Scheme 3A). The yield (16%)[36] was significantly lower than that found for laudanosine itself (52%).[31,33] With the 3',4',5'-trioxygenated laudanosine (**14**), a C-4a-6'- or C-4a-2'-coupling would lead to the same product, thereby circumventing the inherent regioselectivity problem. Unfortunately, the enhanced electron density of the trioxygenated aromatic moiety made the starting material susceptible to overoxidation, ultimately resulting in only a 38% yield of the coupled product (**15**) after optimization (Scheme 3B).[36] At this stage, the general setup and a lack of charge quantity control did not allow better results. Four years later, Miller also examined 6'-chlorolaudanosine (**16**), but due to the electron-withdrawing effect of chlorine, anodic oxidation led to cleavage of the starting materials generating fragmentation products **17** and **18** rather than oxidation and coupling of the aromatic core (Scheme 3C).[37,38] In the same work, another attempt aimed at blocking the 6'-position by installing various bulky substituents at C-5' (**19a** and **19b**),



Scheme 3. Overview of efforts made to steer regioselectivity towards C4a-2' coupling. A and C: Installing halogen substituents did not lead to success. B: Blocking the 5-position did not enhance the desired regioselectivity. D: Using a symmetrically trioxygenated laudanosine led to successful 4a-2' coupling but the product was not suitable for further elaboration.

but in all cases, 4a–6' coupling to **20a** and **20b** was still favored over C-4a-2' coupling (Scheme 3D).[37]

Meanwhile, improvements to the general coupling protocol, including optimization of the electrolyte composition,[37] arrangement of electrodes and strict control of the charge quantity[39] were made and finally resulted in greater yields, improved reproducibility and user-friendly setups.

Also, between 1976 and 1981, the Miller group published extensive cyclic voltammetry studies on several alkaloids, simple aliphatic amines and aromatic compounds leading to their proposed mechanism of anodic benzylisoquinoline coupling, which is still considered plausible within the electrochemistry community today.[40–42] In one set of cyclic voltammetry experiments applying electrolytes of different acidity, the previously postulated correlation between electrolyte composition and yield was proven: as the tertiary amine is predominantly protonated in acidic solution, it is effectively protected from oxidation and the oxidation of the ring with the highest electron density takes place instead. This which also enables the experimenter to perform the anodic oxidation at higher potentials and thus shorten the reaction time. For a more detailed discussion of the whole mechanism and for structural support, we refer the reader to the primary literature.[42]

4. Approaching C-4a-2' Selectivity (2000–2016)

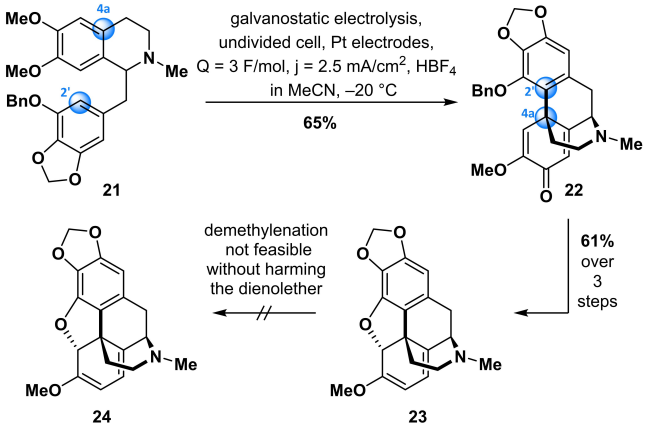
The hitherto most promising steps towards the desired 4a-2'-coupling were accomplished when 3',4',5'-trioxygenated laudanosine derivatives were first subjected to anodic oxidation. A critical lesson was learned from the experiments of the past three decades: As anodic oxidation of benzylisoquinoline derivatives is inherently 4a-selective and the trioxygenated precursor guarantees one oxygen substituent to be situated adjacent to the newly formed bond, the coupling products accessible have an appropriate substitution pattern for further transformation into the morphinan alkaloids. However, although Miller and Stermitz demonstrated in 1974 that 5′-methoxylaudanosine can be converted to the corresponding morphinandienone in the desired manner (Scheme 3B),[36] it was not until the turn of the millennium for this strategy to be re-evaluated. Presumably, the true value of the original findings remained hidden for almost 30 years because a) an improvement in yield beyond 38% could not be achieved even after its strong dependency on the total amount of passed current had been discovered,[36] and b) because the use of a methyl ether in this position does not hold obvious options for further elaboration into morphine alkaloids.

In 2003, Schäfer and Brockmeyer developed a very promising strategy based on an anodic transformation of a methylenedioxy-protected 3',4',5'-trioxygenated laudanosine derivative **21** into the 2'-4a-coupled product **22** with a suitable hydroxy substituent ortho to the newly formed bond.[43] After proving that selective debenzylation and subsequent E-ring formation could be carried out on this precursor, the further synthesis of **24** however failed due to the instability of the dienol ether moiety in **23** upon attempted acetal cleavage (Scheme 4).

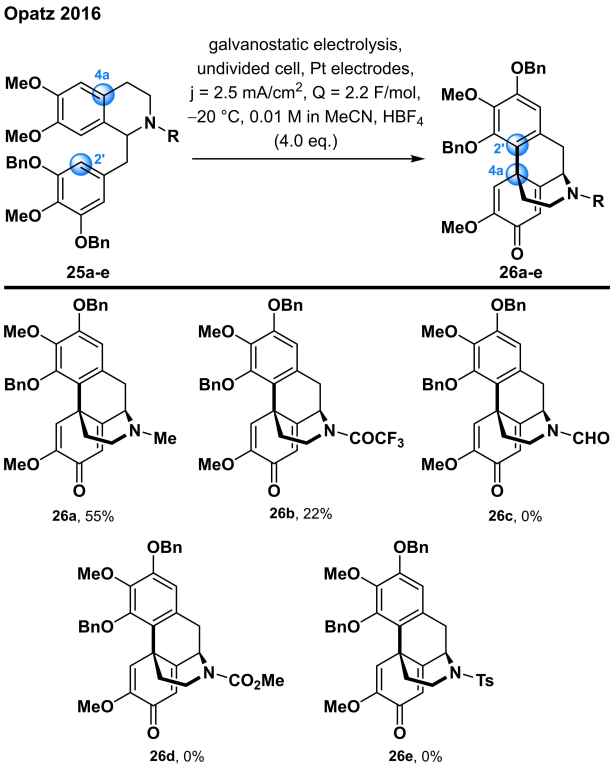
Based on this work, Geffe and Opatz performed detailed studies on symmetrically benzylated laudanosine derivatives with a focus on *N*-protecting groups in 2016.[44] They found that electron-withdrawing *N*-trifluoroacetyl (**25b**), *N*-formyl (**25c**), *N*-methoxycarbonyl (**25d**) or *N*-tosyl (**25e**) protecting groups only gave rise to products of benzylic C–C-cleavage under acidic conditions (Scheme 5). However, with an *N*-methyl group (**25a**), the reaction succeeded with 55% yield of the desired morphinandienone **26a** (38% yield when a symmetrical diallyl-substituted substrate was used). Unfortunately, the deprotection of the phenolic hydroxyl groups of **26a** lacked a sufficient chemoselectivity, thereby preventing the further transformation into thebaine (**32**). As was already the case in the work of Schäfer, the sensitivity of the C-ring was the cause of these problems.

5. Opatz Total Synthesis of (−)-Thebaine (32) and (−)-Oxycodone (34, 2016–2019)

The groups of Opatz and Waldvogel at the University of Mainz, Germany afterwards extended their research on symmetrically protected laudanosine derivatives by applying acyl- (**27a**), pivaloyl- (**27b**), triisopropyl- (**27c**) and benzyloxymethyl acetal- (**27d**) protected substrates, but none of them could be transformed into the corresponding



Scheme 4. Schäfers successful 2'-4a-coupling of a methylenedioxy-protected laudanosine derivative **21** and further transformation toward the opium alkaloids.



Scheme 5. Variation of the N-protecting group.

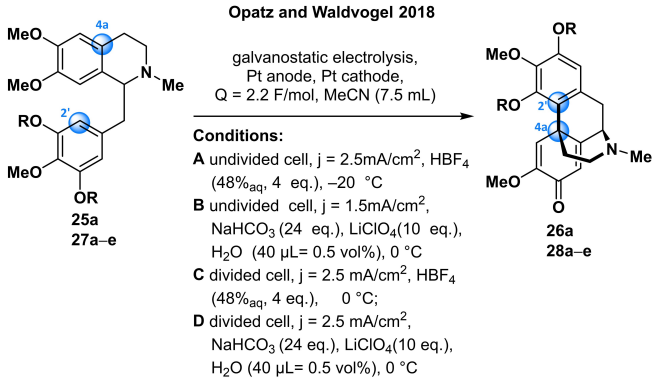
morphinandienones **28a–d** (Table 1, entries 2–5, Scheme 6). An attempt to use unprotected laudanosine derivative **27e** also did not produce the coupled product **28e** (Table 1, entry 6).[45] Under conditions A–D, only the symmetrical benzyl ether **25a** could be transformed to the desired morphinandienone **26a** (Table 1, entry 1), confirming the results of Geffe and Opatz of 2016 (Scheme 5).

Fortunately, the use of 3',4',5'-trioxygenated laudanosine derivatives **29a–c** bearing two orthogonal protecting groups,

Table 1. Yields of the anodic oxidation of symmetrically protected benzyliso-quinoline derivatives **25a** and **27a–e** shown above under different conditions.

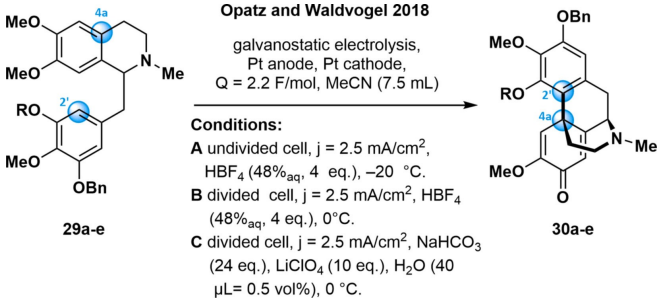
entry #	**R**, number	Yield[a] (%) under conditions A–D			
		A	**B**	**C**	**D**
1	**Bn (25a)**	**51**, 47[b]	**29**	–	**31**
2	Ac (**27a**)	nd	nd	nd	–
3	Piv (**27b**)	nd	nd	nd	–
4	TIPS (**27c**)	nd	nd	–	nd
5	BOM (**27d**)	nd	nd	–	–
6	H (**27e**)	nd	nd	–	–

[a] determined via ^{1}H NMR with 1,4-bis(trimethylsilyl)benzene as internal standard. [b] Isolated yield.



Scheme 6. Anodic oxidation of symmetrically protected benzylisoquinoline derivatives **25a** and **27a–e**.

one of which is electron-withdrawing (acetyl, pivaloyl, benzoyl), furnished the desired morphinandienones **30a–c** with the desired 4a–2' connectivity in 27–43% yield under various conditions (Table 2, entries 1–3, Scheme 7).[45] Applying a TIPS protecting group (**29d**) only gave low yields (Table 2, entry 4), while the unprotected compound **29e** did not result in any formation of morphinandienone **30e** (Table 2, entry 5). The authors speculated that the regioselectivity might result from a sufficiently strong electronic differentiation within the trioxygenated arene scaffold which directs the more electron-donating benzyl ether *para* to the newly formed bond. In this case, the combination of an electron rich benzyl ether and an electron-withdrawing acetyl group produced the best results with morphinandienone **30a** being isolated in 43–62% yield (Table 2, entry 1). The authors performed the electroorganic reaction under constant current conditions in an undivided cell with platinum electrodes and using tetrafluoroboric acid as the electrolyte. It is also important to note that the use of orthogonal protecting groups is advantageous since they permit the sequential liberation of the phenolic hydroxyl groups and thus a more promising synthetic approach towards morphinan-type natural products.



Scheme 7. Anodic oxidation of asymmetrically protected benzylisoquinoline derivatives **29a–e**.

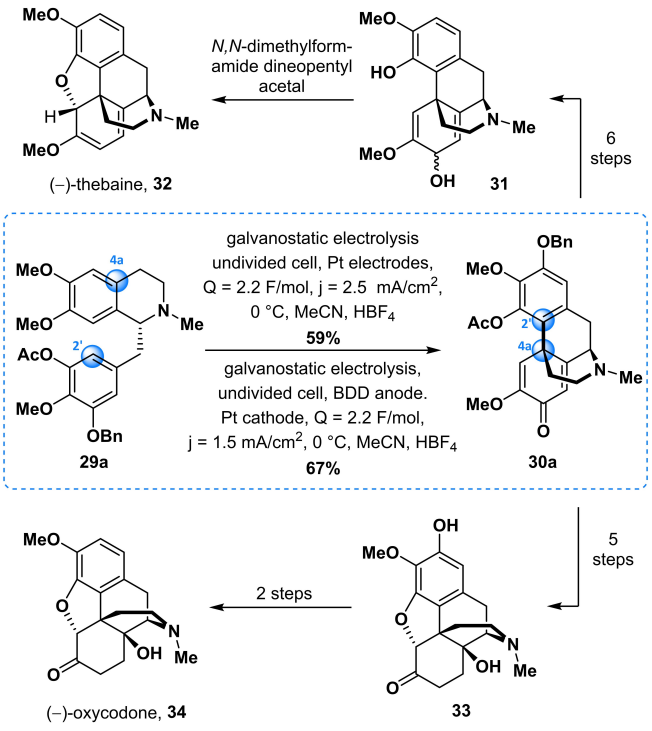
Table 2. Yields of the anodic oxidation of asymmetrically protected benzyliso-quinoline derivatives **29a–e** shown below under different conditions.

entry #	**R**, number	Isolated yield[a] (%) under conditions A–C		
		A	**B**	**C**
1	**Ac (29a)**	**43, 58–62**[b]	**36**	–
2	Piv (**29b**)	37	36	–
3	Bz (**29c**)	29	27	–
4	TIPS (**29d**)	6	nd	nd
5	H (**29e**)	nd	–	–

[a] Isolated yield after flash-chromatographic purification. [b] Optimized preparative conditions (0.75 mmol) at 1.5 mA/cm^2 and 0 °C.

Nearly 50 years after Miller's groundbreaking work, the first biomimetic electrochemical synthesis of (−)-thebaine (**32**) and (−)-oxycodone (**34**) was accomplished by Opatz, Schäfer, and Waldvogel (Scheme 8).[45,46] In the case of (−)-thebaine (**32**), selective debenzylation and reductive elimination of the phenolic hydroxyl group furnished compound **31**. Construction of the E-ring via conjugate nucleophilic addition then led to the formation of (−)-thebaine (**32**).[45] Morphinandienone **30a** could also be converted to (−)-oxycodone (**34**) via compound **33** by an additional introduction of the required 14-hydroxy group via [4+2] cycloaddition with photogenerated singlet oxygen. During this study, further optimization of the anodic oxidation regarding electrode material and current density led to an increased yield with a boron doped diamond (BDD) anode giving yields of up to 67 %.[46]

Based on these results, the Opatz group recently developed a route towards (−)-hydrocodone (**39**) devoid of any reprotection steps which further underlines the utility of the anodic coupling (Scheme 9).[47] The pivaloyl-protected benzyl bromide **35** was converted into the anodic coupling precursor **29b** through a deprotonation/alkylation/reduction sequence in combination with a Noyori-type asymmetric transfer hydrogenation[48] with α-aminonitrile **36**.[49] After optimization of the anodic oxidation, morphinanedienone **30b** was obtained in up to 61 % yield when a boron doped diamond anode (BDD) was applied. Simultaneous *O*-deprotection and reduction of the carbonyl group of **30b** with $LiAlH_4$ followed by conjugate nucleophilic substitution enabled by activation of the intermediate allylic alcohol with DMF-dineopentyl acetal furnished thebaine derivative **37**.[27] After diimine hydrogenation[50] and acidic hydrolysis of the enol ether, ketone **38** could be isolated in 42 % over four steps. This molecule already resembles opioid **39** and the final debenzylation/triflation/reductive detriflylation towards (−)-hydrocodone (**39**) is functional although optimization is required.

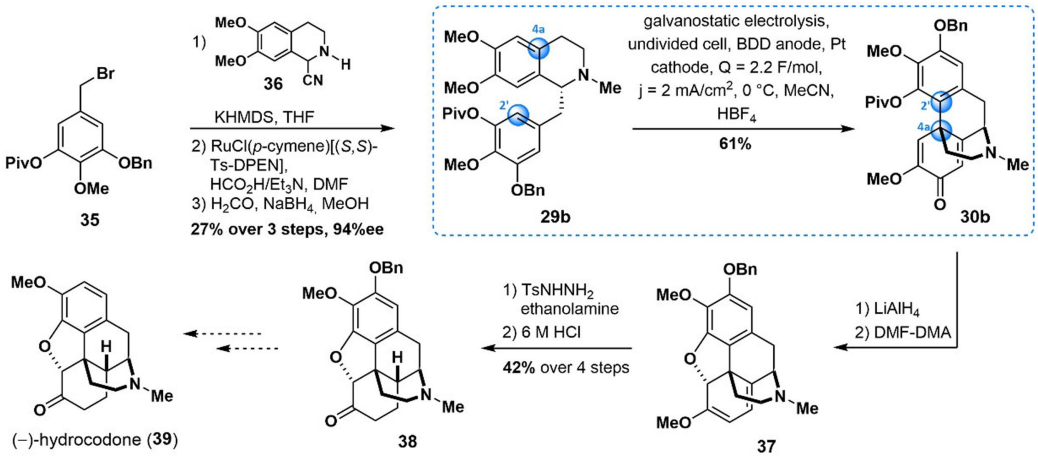


Scheme 8. First total syntheses of (−)-thebaine (**32**) and (−)-oxycodone (**34**) via anodic aryl-aryl coupling by Opatz and Waldvogel.

6. Conclusion

Since 1971, significant progress has been made in the field of electrochemical syntheses of morphinandienones from benzylisoquinolines. The historical developments, difficulties and proposed solutions are highlighted in this review. Initially, the focus was on developing more suitable reaction conditions to improve the yield of electrochemically generated morphinandienones, e.g. by using acidic electrolytes and controlling the charge quantity. Later, chemists transitioned into directing the regioselectivity of the anodic coupling toward the preferred 4a-2' selectivity found in nature. In this case, the application, combination and resulting chemoselectivity of different protecting groups were of particular importance and enabled biomimetic syntheses of the alkaloid (−)-thebaine (**32**) and the semisynthetic analgesic (−)-oxycodone (**34**).

Nevertheless, there are still further challenges and room for improvement in the field since nature constructs the morphinandienone skeleton selectively without the use of an additional phenolic hydroxyl groups or O-protection. As electrochemical transformations are gaining further momentum, more efficient solutions to the challenges of the electrochemical synthesis of morphinandienones through the invention of superior reaction conditions in combination with well-designed strategies, are likely to be developed in years to come.



Scheme 9. Unpublished results of a total synthesis of (−)-hydrocodone (**39**).

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