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Total Synthesis of (−)-Oxycodone via Anodic Aryl−Aryl Coupling

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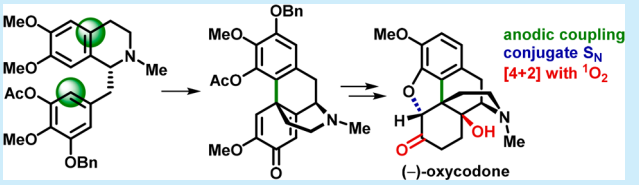
Supporting Information

ABSTRACT: A fully regio- and diastereoselective electrochemical 4a−2′-coupling of a 3′,4′,5′-trioxygenated laudanosine derivative enables the synthesis of the corresponding morphinandienone. This key intermediate is further transformed into (−)-oxycodone through conjugate nucleophilic substitution for E-ring closure and [4 + 2] cycloaddition with photogenerated singlet oxygen to accomplish diastereoselective hydroxylation at C-14. The anodic transformation provides high yields and can be performed under constant current conditions both in a simple undivided cell or in continuous flow.



Oxycodone is a semisynthetic opioid derived from naturally occurring thebaine and is commercially produced on a multiton scale.[1] It is prescribed as a strong analgesic, e.g., for pain management in cancer patients and has a significantly higher oral bioavailability than morphine.[2] Due to their outstanding medicinal relevance in combination with an attractive molecular structure, the morphinan alkaloids are appealing synthetic targets, and many approaches toward morphine and its congeners have been devised.[3] However, in view of recent developments within the United States, it must also be mentioned that severe problems can arise from opiate addiction and abuse.[4]

The biosynthesis of morphine proceeds through the intramolecular oxidative coupling of (*R*)-reticuline to salutaridine.[3b] The imitation of this enzyme-mediated coupling is hampered by the fact that it can form four different regioisomers, of which only the 4a−2′-coupled product can be further converted into morphine alkaloids (Scheme 1A). In the past decades, many approaches toward mimicking this challenging coupling using conventional oxidants such as $VOCl_3$, $K_3Fe(CN)_6$, MnO_2−silica, Ag_2CO_3−Celite, or $Tl(CO_2CF_3)_3$ were undertaken.[5] However, these attempts suffered from relatively low yields or undesired regioselectivity. Electrochemistry provides a versatile tool box for organic synthesis and offers an appealing alternative to the use of stoichiometric quantities of chemical oxidants.[6] The anodic coupling of laudanosine (*O*-methoxylated reticuline) is fully selective for the 4a position, thereby granting access to the desired morphinandienone skeleton.[7] However, for steric and electronic reasons, it is also inherently 6′-selective. As the obtained isosalutaridine-type products (4a−6′-coupled) do not have an oxygen substituent *ortho* to the newly formed bond, they cannot be converted into morphine alkaloids via E-ring closure. All attempts to overcome the troublesome 6′-selectivity failed, and a 4a−2′-coupling which would provide elegant biomimetic access to morphine alkaloids remained elusive.[7d−f,8] In a joint effort with Schäfer, our groups spent several years working on this electrosynthetic challenge.[7f,9] We recently discovered that the desired 4a−2′-coupled morphinandienones can be obtained from laudanosine derivatives bearing a 3′,4′,5′-trioxygenated[10] benzylic moiety with orthogonal O-protecting groups that create a sufficient electronic differentiation within the aromatic ring (Scheme 1B).[11] Herein, we report the optimization of this anodic coupling and its application to the asymmetric synthesis of non-natural opioids. (−)-Oxycodone was chosen as exemplary target because of its challenging structure and its outstanding medicinal relevance.

First, an optimization of the anodic coupling with respect to electrode material and solvent was undertaken (Table 1).

The best results were obtained using a boron-doped diamond (BDD) anode in combination with a platinum cathode in MeCN containing a small amount of aqueous HBF_4 as acidic electrolyte to prevent amine oxidation. In fact, BDD is often a superior choice for dehydrogenative couplings and has emerged as powerful electrode material for numerous transformations.[12] In contrast, the molybdenum anode,[13] which was recently shown to be a suitable material for the dehydrogenative coupling of oxygenated arenes, did not afford the desired product. Rapid passivation of the electrode surface was observed instead, and 81% of starting material could be recovered. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP), a frequently used solvent in organic electrochemistry, e.g., for dehydrogenative couplings,[14] proved to be unsuitable for the coupling of laudanosine derivatives. Complex mixtures containing neither starting material nor product were obtained. An extensive screening of reaction parameters comprising temperature, current density, reactant concentration, and stoichiometry of acidic additive was performed both in batch electrolysis and in continuous flow mode (see the Supporting Information). Under optimized conditions, morphinandienone

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Scheme 1. Selective Synthesis of a 4a-2′-Coupled Morphinandienone through a Combination of Electrochemistry and Substrate Design: Application to the Total Synthesis of (−)-Oxycodone

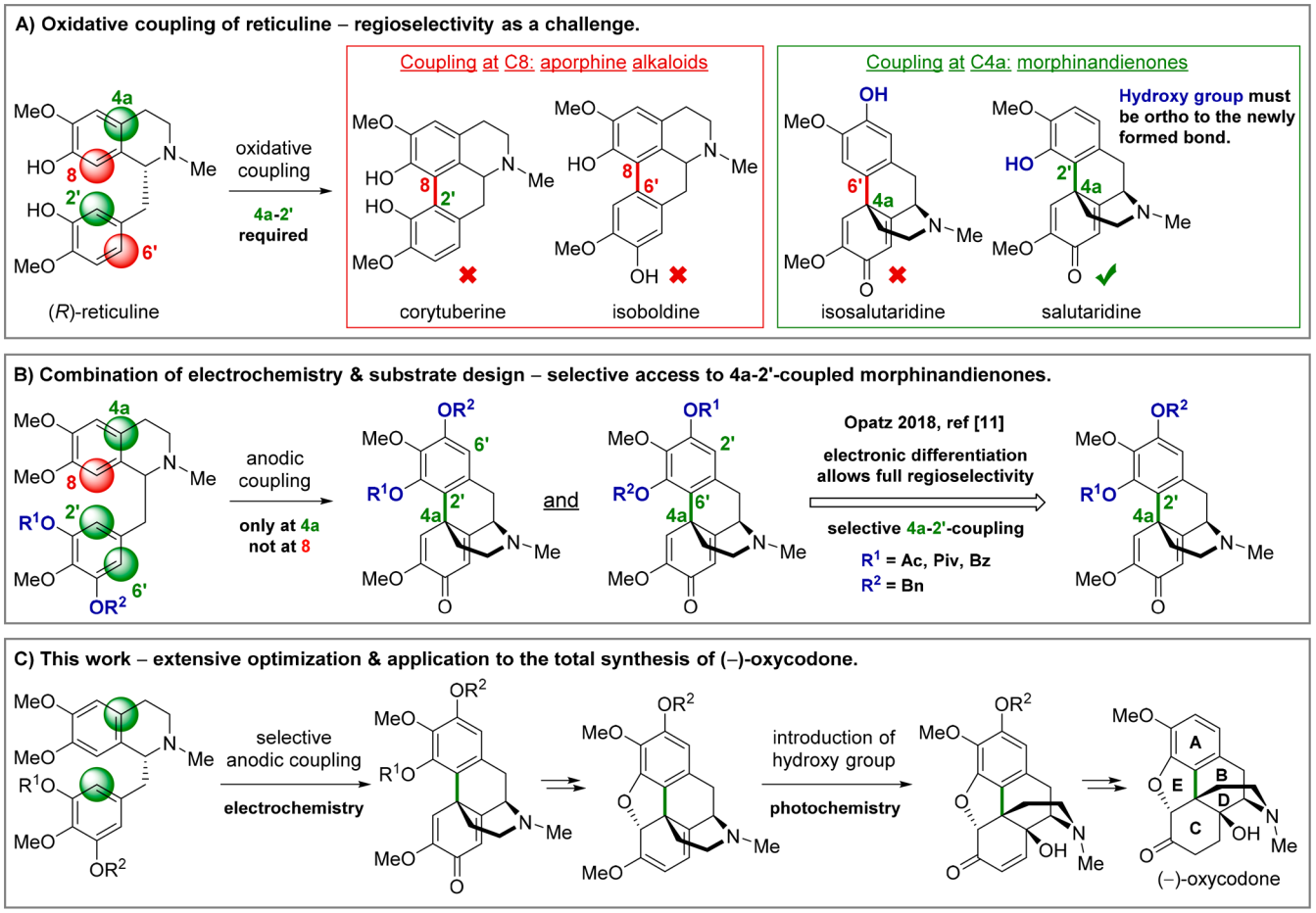
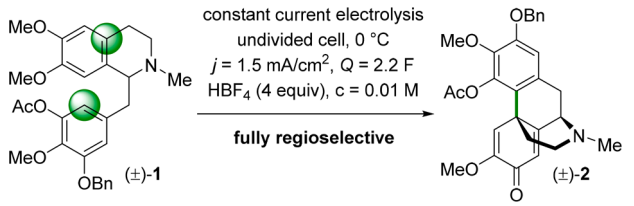


Table 1. Screening of Electrode Material and Solvent[a]



no.	anode	cathode	solvent	yield[b] (%)
1	graphite	Pt	MeCN	60
2	glassy carbon	Pt	MeCN	59
3	Pt	Pt	MeCN	59
4	Mo	Pt	MeCN	0[c]
5	BDD	Pt	MeCN	67
6	BDD	Ni	MeCN	58
7	BDD	steel[d]	MeCN	51
8	BDD	Pt	MeCN/DCM (2:1)	56
9	BDD	Pt	HFIP	e
10	graphite	Pt	HFIP	e
11	Mo	Pt	HFIP	e

[a]Reactions performed according to the general procedure given in the Supporting Information (for Table S1) using (±)-**1** (0.75 mmol, 1.0 equiv), HBF_4 (48% aq, 4.0 equiv), and 75 mL of solvent in an undivided cell; [b]Yields after chromatographic purification, full conversion. [c]81% of (±)-**1** recovered. [d]Stainless steel. [e]Complex mixtures, product not detectable.

(±)-**2** can be obtained under constant current conditions in an undivided cell (beaker-type, up to 69% yield) or in continuous flow[15] (up to 57% yield).

Considering the complexity of the transformation, this regio- and diastereoselective anodic oxidation affords appreciable yields. Furthermore, it is operationally simple and does not require a redox mediator or any supporting electrolytes other than aqueous HBF_4. The C−C bond formation demands an overlap of both π systems involved, and the resulting parallel positioning of the two aromatic rings leads to the observed diastereoselectivity. The regioselectivity (favoring coupling between positions 4a and 2′) is presumably induced by electronic differentiation within both aromatic moieties.[11]

Following a procedure previously reported by our group,[11,16] 1-benzyl-1,2,3,4-tetrahydroisoquinoline (*R*)-**1** was prepared from naturally occurring and inexpensive starting materials (methyl gallate and vanillin via homoveratrylamine) using a Noyori asymmetric transfer hydrogenation.[17] Thus, being based on natural feedstocks, the devised synthesis of (−)-oxycodone adds to the emerging field of xylochemistry.[18] Laudanosine derivative (*R*)-**1** was converted into the corresponding morphinandienone (+)-**2** using the optimized anodic coupling (Scheme 2). E-Ring closure was accomplished via selective 1,2-reduction of the carbonyl group under Luche conditions, deacetylation, and subsequent conjugate nucleophilic substitution enabled by activation of the intermediate allylic alcohol with *N*,*N*-dimethylformamide dineopentyl

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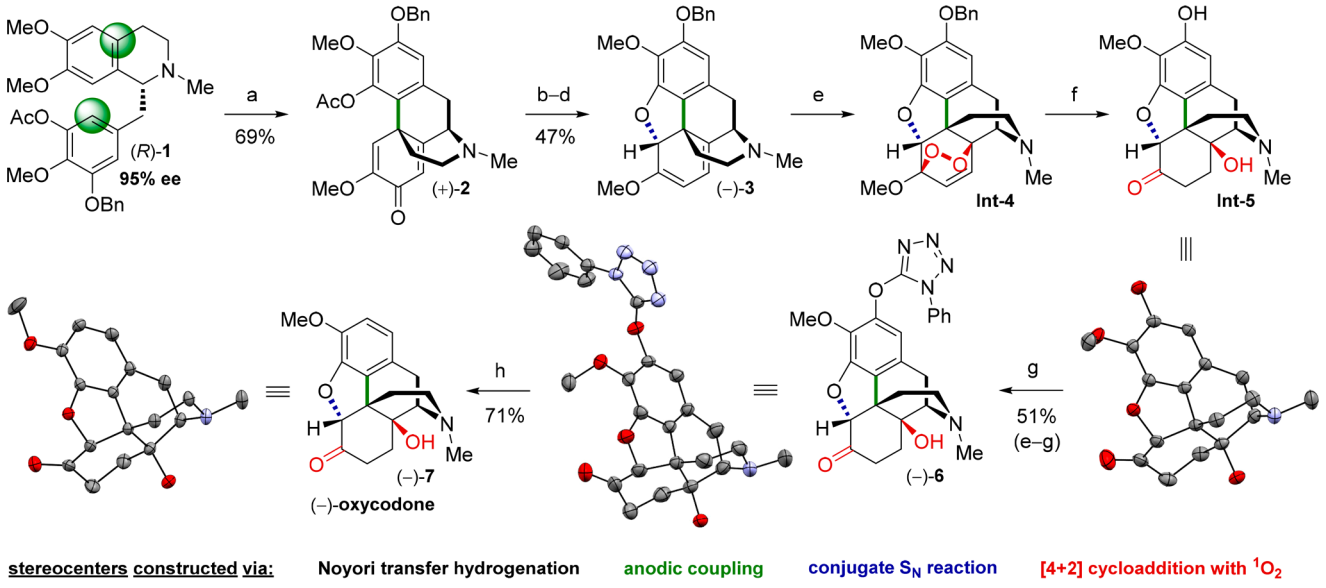
Scheme 2. Total Synthesis of (−)-Oxycodone[a]



[a]Procedures: (a) constant current electrolysis, undivided cell, BDD anode, Pt cathode, j = 1.5 mA/cm^2, Q = 2.2 F, MeCN, HBF_4, 0 °C; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C; (c) K_2CO_3, MeOH, rt; (d) *N*,*N*-dimethylformamide dineopentyl acetal, dioxane, 60 °C; (e) TPP, O_2, TFA, CH_2Cl_2, blue LED, rt; (f) Pd/C, H_2 (1 atm), CH_2Cl_2, rt; (g) 5-chloro-1-phenyl-1*H*-tetrazole, K_2CO_3, DMF, 70 °C; (h) Pd/C, H_2 (30 bar), CH_2Cl_2/EtOH, rt; tetrahydroisoquinoline (*R*)-**1** was prepared following a procedure previously described by our group (ref 11); X-ray molecular structures (ORTEP, ellipsoids displayed with 50% probability) were obtained for the racemic samples (±)-**5** (CCDC 1894339), (±)-**6** (CCDC 1894340), and (±)-7 (CCDC 1894341).

acetal.[3i] The required additional hydroxy group could be introduced using a one-pot sequence including diastereoselective [4 + 2] cycloaddition of singlet oxygen to the dienol ether's double bonds and subsequent reduction of the initially formed endoperoxide **Int-4**.[3s,19] In-situ generation of singlet oxygen was accomplished under visible-light irradiation (blue LED) via energy transfer from photoexcited tetraphenylporphyrin (TPP).

Hydrogenation on Pd/C led to rapid O−O-bond cleavage in **Int-4** with concomitant hydrogenation of the C═C-double bond and O-debenzylation. Intermediate **Int-5** was converted into (−)-oxycodone via another Pd-catalyzed hydrogenation of the preformed tetrazolyl ether (−)-**6**.[10,20]

In summary, a total synthesis of (−)-oxycodone was devised that relies on the regio- and diastereoselective formation of a 4a−2′-coupled morphinandienone through a combination of electrochemistry and substrate design. The remarkably selective anodic coupling is operationally simple, almost reagent-free, and can be performed in batch or in continuous flow. E-Ring closure via conjugate nucleophilic substitution and introduction of the required 14-hydroxy group via [4 + 2] cycloaddition with photogenerated singlet oxygen also proceeded with complete diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00419.

Detailed optimization studies, X-ray molecular structures of important intermediates, experimental procedures, HPLC chromatograms for determination of enantiomeric excess, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1894339−1894341 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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