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Dearomative Access to (−)-Thebaine and Derivatives

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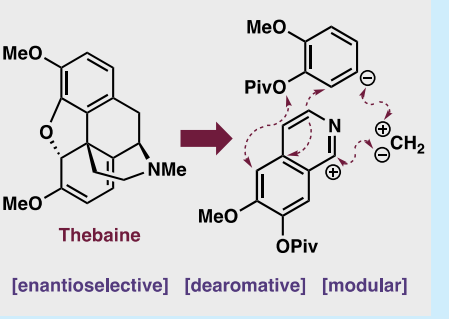
ABSTRACT: A synthesis of the natural product thebaine is reported in eight steps from commercially available starting materials, hinging on the dearomatization and coupling of simple aromatic starting materials. This provides divergent access to two unnatural opioid derivatives and is aimed at the long-term development of synthetic opioid analogs of the "wonderdrug" Naloxone. Additionally, a formal enantioselective synthesis of all reported targets is disclosed that leverages a catalytic asymmetric dearomatization via anion-pairing catalysis.



In the United States, the opioid crisis has been responsible for an increasing number of drug overdose deaths in the past two decades. In 2021 alone, over 80,000 deaths involved the abuse of at least one opioid, thus claiming, on average, approximately 220 American lives per day.[1] This number would likely have been much higher if not for the interventive treatment Naloxone (**1**) which serves as an opioid receptor antagonist capable of overdose reversal soon after intranasal administration (Figure 1).[2] While Naloxone (**1**) has been efficacious since the 1970s, its main drawback has been its rapid metabolism to the corresponding glucuronide (**4**) which occurs with a half-life of merely 30−80 min.[3,4] These disadvantageous pharmacokinetics hamper its ability to counteract emerging illicit agonists with increased activity such as carfentanil, an elephant tranquilizer that boasts a potency 10,000 times that of morphine.[5,6] In response to this crisis, the National Institutes of Health commenced the HEAL initiative to address these issues, with increased attention given to the development of antagonists with improved bioavailability relative to **1**.[7]

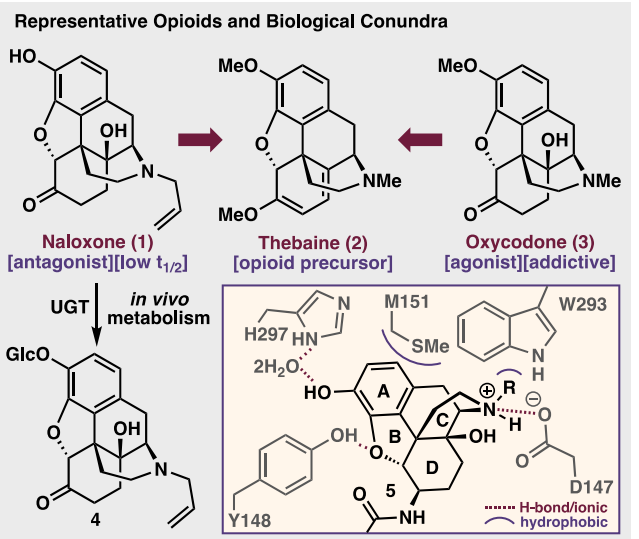


Figure 1.

One issue regarding the metabolism of **1** concerns the phenolic moiety that undergoes glycosylation by the action of uridine 5′-diphospho-glucuronosyltransferase (UGT).[8] Indeed, Kobilka and Granier annotated this phenol as crucial to the binding of morphinan-based opioid antagonists, establishing an important H-bond network to H297 in the mu-opioid receptor (see **5**, Figure 1, inset).[9] Previous research has established that this network, among other ionic (D147) and hydrophobic (M151, W293) binding interactions, is responsible for Naloxone's remarkable bioactivity. This provides a conundrum regarding the benzenoid substitution, putatively requiring effective Naloxone derivatives to both have a hydrogen-bonding capability at the phenolic position while obviating facile metabolism.

Intrigued by this structural paradox that plagues, in part, the efficacy of Naloxone (**1**), we hypothesized whether a modular synthesis of thebaine (**2**) could serve as a platform for divergent access to both novel derivatives of **1** as well as opioid agonists such as oxycodone (**3**). And, while there are many known synthetic approaches to the morphinan molecular

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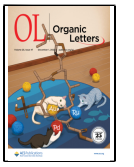


framework,[10−32] we were particularly inspired by past approaches that employed aromatic building blocks as platforms for synthetic assembly (see Figure 2). For example,

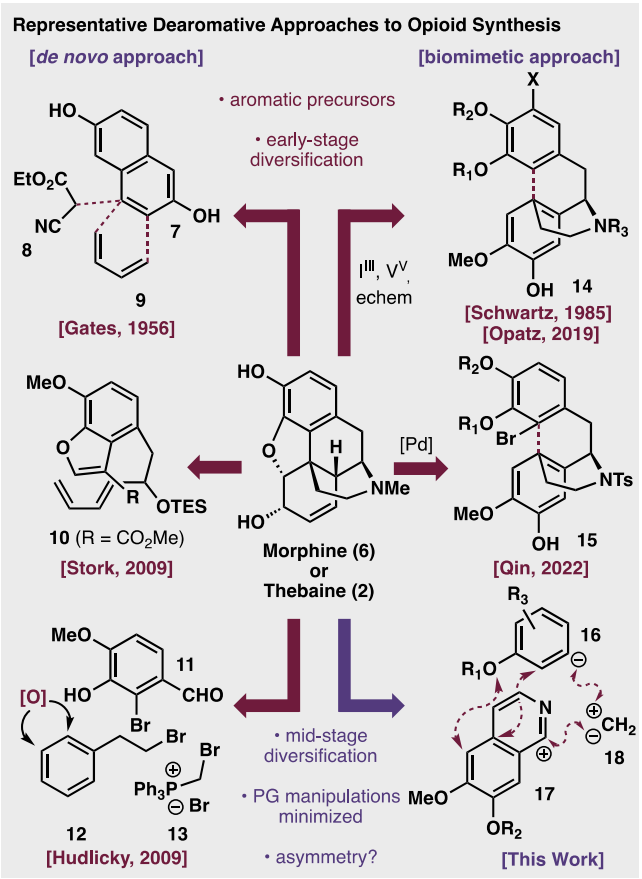


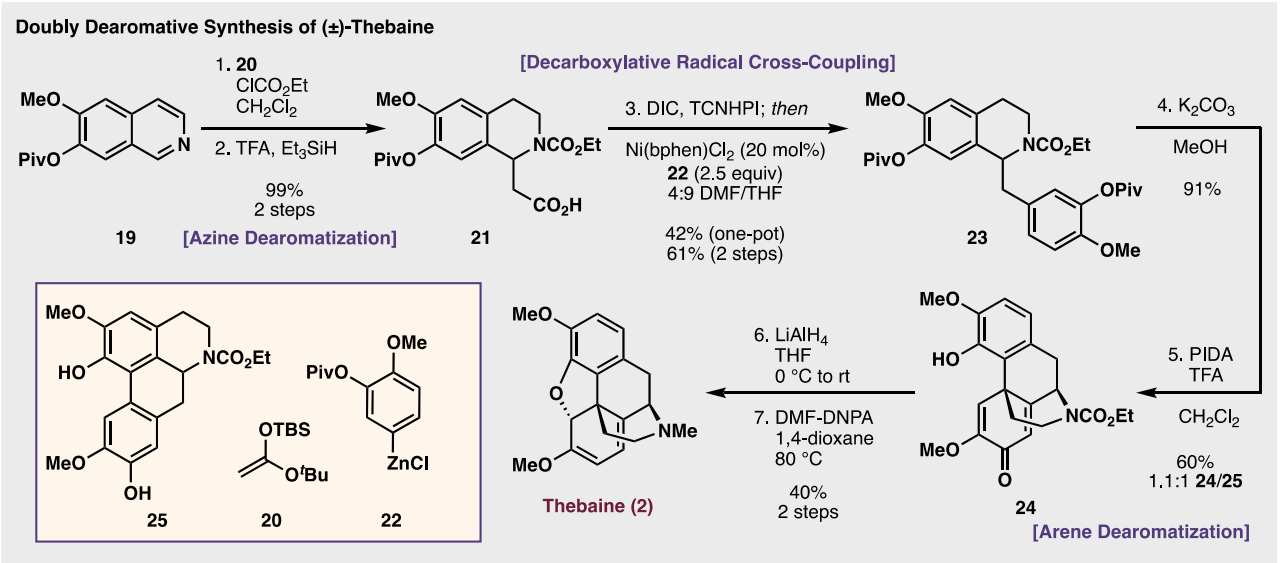
Figure 2.

Gates' inaugural synthesis of morphine (**6**) started from naphthol **7** and employed oxidative dearomatization to enable anionic addition of nitrile **8** and [4 + 2] cycloaddition of butadiene (**9**) to the bicyclic core.[26,27] Alternatively, Stork employed a dearomative intramolecular Diels−Alder reaction of benzofuran **10** enroute to both **2** and **6**.[13] In the late 1990s, Hudlicky's enzymatic dihydroxylation of aryl bromide **12** enabled the downstream coupling of **11** and **13** to construct the core of these targets.[33] The biosynthesis of these alkaloids also includes dearomatization that has been biomimetically leveraged in their preparation. Schwartz was one of the first to investigate this biomimetic oxidative cyclization utilizing both high-valent vanadium and/or hypervalent iodine(III) to cyclize substrates of structure **14** (X = H, OH).[34] This strategy was later modified by Opatz and Waldwogel in recent years, leveraging electrochemical coupling to build the tricyclic core of **2** and **6**.[21] Very recently, Qin and co-workers utilized a Pd-catalyzed coupling of **15** to construct the same bond and quaternary center.[35] While these synthetic approaches are remarkable achievements in their own right, they do have limitations with regard to step-economy and modularity potentially hampering their broad applicability toward rapidly exploring the aforementioned structure−activity relationships.[36]

Alternatively, we employed an approach to address this issue while still employing readily available aromatic starting materials. In practice, we reduced our retrosynthetic analysis to an arene of varied substitution (**16**), an appropriately oxidized isoquinoline (**17**), and an ambiphilic methylene unit (**18**). Importantly, we hypothesized that an acetate surrogate for **18** would be ideal as a means of capably effecting nucleophilic dearomatization of **17** (via enolate addition) while enabling subsequent decarboxylative radical cross-coupling (RCC) with various arenes (**16**).[37,38] While this RCC strategy would putatively provide for downstream synthetic variegation, another outstanding question surrounded the possibility of a catalytic and highly asymmetric dearomatization of isoquinoline **17**, an intriguing but challenging prospective transformation. Initially, we embarked on the racemic synthesis of thebaine (**2**), with the intentions of diversification and asymmetric construction as secondary and tertiary goals.

The total synthesis of (±)-thebaine (**2**) (Scheme 1) began from isoquinoline **19**, which can be accessed in one step from a

Scheme 1



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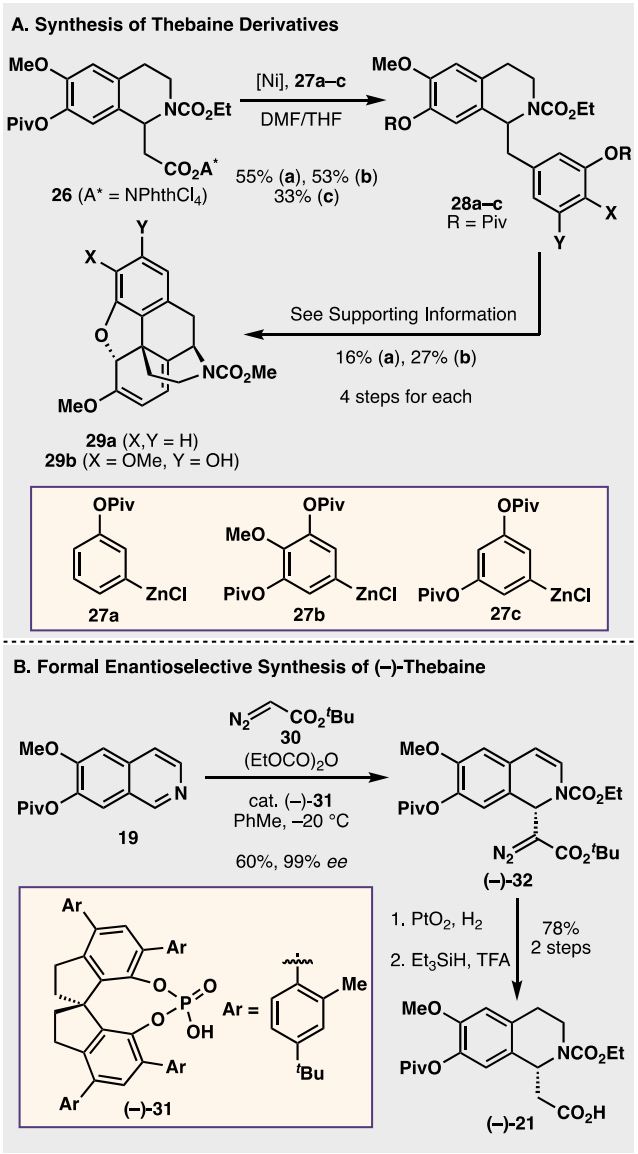
commercial material. If expensive to the practitioner, this isoquinoline can also be prepared on a multigram scale starting from isovanillin (See Supporting Information). Treatment of **19** with ethyl chloroformate and silyl ketene acetal **20** afforded an intermediate dihydroisoquinoline (not shown) that was reduced and protodealkylated with TFA and Et_3SiH to give acid **21** in a nearly quantitative yield over two steps. Next, decarboxylative cross-coupling between **21** and **22** was effected first by activation with TCNHPI to form an intermediate redox active ester (RAE), and then promoted by catalytic Ni(bphen)Cl_2 in the presence of $ZnBr_2$ to generate **23**.[39] Utilization of this additive and preformed catalyst was essential for mitigating the reformation of **21** and optimizing the yield of **23**, whether capitulated in a one-pot fashion (42% yield) or two steps (61% yield) with isolation of the intermediate RAE (**26**, See Supporting Information). Cleavage of the pivaloyl groups in **23** was promoted by K_2CO_3 in methanol to generate an intermediate bis(phenol), the substrate for intramolecular oxidative coupling. When treated with PIDA and TFA, the intermediate bis(phenol) underwent dearomative coupling to afford the salutaridine derivative **24** and isoboldine derivative **25** in a 60% yield and a 1.1:1 ratio.[40] As mentioned earlier, this biomimetic oxidative coupling has been the subject of much investigation with tactical implementation utilizing traditional oxidants, high-valent transition metals,[41−43] and electrochemical methods.[21,23] Despite the modest yield of **24**, this particular tactic was sufficient for our immediate goals, given the caveat that this coupling can be highly substrate dependent (*vide infra*). The synthetic endgame first started with a $LiAlH_4$ reduction that afforded an unstable bis(allylic) alcohol in tandem with the establishment of the methylated piperidine. This intermediate alcohol was not purified, but instead treated with dimethylformamide-dineopentylacetal (DMF-DNPA) to afford (±)-thebaine (**2**) in 40% yield over two steps.[29] This culminated in a racemic, eight-step synthesis of thebaine from commercial materials that employed both nucleophilic and oxidative dearomative events enjoined with decarboxylative radical cross-coupling as key transformations.

As the original impetus for this work was establishing a synthetic platform for accessing unnatural opioid antagonists, the synthesis of unnatural congeners of thebaine became of interest (Scheme 2A). Starting from RAE **26**, Ni-catalyzed couplings of organozinc reagents **27a**, **27b**, and **27c** (see Supporting Information for preparation) were accomplished in 55%, 53%, and 33% yields, respectively, to give adducts **28a−c**. Two of these coupling products were then elaborated toward differentiated derivatives of **2**. Cleavage of the pivaloyl groups on both aromatic rings of compounds **28a** and **28b** quantitatively afforded the corresponding phenol. Oxidative coupling, reduction, and cyclization delivered the desired derivatives, **29a** and **29b**, in 16% and 27% yields, respectively, over four steps. Of note, the least oxygenated congener (**28a**) underwent PIDA-mediated oxidative coupling while the trioxygenated (**28b**) variant required Kozlowski's V(V) catalyst to afford the corresponding tricyclic dienone.[43] Importantly, this established a platform for accessing unnatural benzenoid substituted morphinans, a crucial aspect toward the intended future construction of novel opioid agonists and antagonists.

Beyond the access that this synthesis establishes for the development of unnatural derivatives, rendering the approach asymmetric also stood as an outstanding need. To this end, we were ultimately inspired by Peng and co-workers to evaluate chiral Brønsted acids as a means of promoting asymmetric

Scheme 2



addition of nucleophiles like **30** to promote an enantioselective isoquinoline dearomatization.[44] At first, the utilization of silyl ketene acetals like **20** with chiral anion-pairing did not produce more than 10% *ee* (see Supporting Information), which was perhaps surprising given the success of these additions under anion-binding catalysis as reported by Jacobsen[45] and Mancheño.[46] After many attempts, treatment of **19** with diethylpyrocarbonate, diazoacetate **30**, and novel catalyst **31** in toluene at −20 °C gave the dearomatized isoquinoline (−)-**32** in 60% yield and in 99% *ee*. Elaboration of this product via Pt-catalyzed diazo cleavage and acid-mediated reduction and protodealkylation of the ester gave (−)-**21** in a 68% yield over two steps. This intercepted the known intermediate from our established route (Scheme 1), completing a formal enantioselective synthesis of (−)-thebaine (**2**) and derivatives **29a−b**.

In conclusion, we have developed a concise and malleable synthetic platform for the synthesis of novel morphinan derivatives that enables access to underexplored benzenoid substitution patterns. Importantly, the conciseness and modularity of the route is enabled by its employment of simple and accessible aromatic starting materials, to which the

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conjunction of dearomative and radical retrosynthesis[37] played a central role. Future work will involve the elaboration and generation of a library of unnatural opioid ligands to evaluate for their agonism, antagonism, and pharmacokinetic properties. Additionally, it is anticipated that expansion of the described catalytic platform will be the subject of increased study for intended implementation in other target-oriented endeavors with strategically designed azine dearomatization.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c03270.

Experimental Procedures and Compound Characterization (PDF)

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Notes

The authors declare no competing financial interest.

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