Total Synthesis

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Gram-Scale Enantioselective Formal Synthesis of Morphine through an *ortho–para* Oxidative Phenolic Coupling Strategy**

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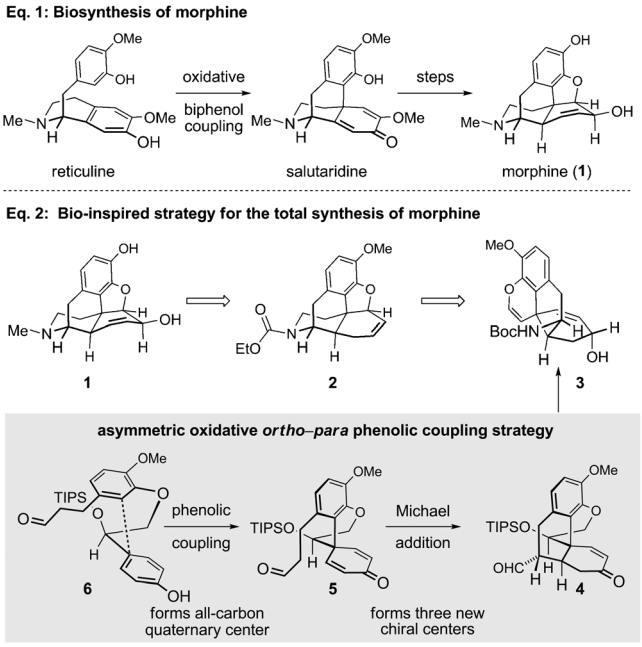
Dedicated to Professor Sir Alan Battersby on the occasion of his 90th birthday

Abstract: *A gram-scale catalytic enantioselective formal synthesis of morphine is described. The key steps of the synthesis involve an ortho–para oxidative phenolic coupling and a highly diastereoselective "desymmetrization" of the resulting cyclohexadienone that generates three of the four morphinan ring junction stereocenters in one step. The stereochemistry is controlled from a single carbinol center installed through catalytic enantioselective hydrogenation. These transformations enabled the preparation of large quantities of key intermediates and could support a practical and scalable synthesis of morphine and related derivatives.*

The medicinal properties of the morphinan alkaloids and their derivatives have ensured that studies toward their synthesis continue to be of significant interest to the chemical community.[1–3] However, a practical and scalable enantioselective synthesis of derivatives of these compact but densely functionalized natural products remains a challenge, despite the elegant advances made recently by the groups of Magnus[3ac] and Hudlicky[3ai] amongst others. A practical synthesis is an important goal from a medicinal chemistry viewpoint, as rapid access to significant amounts of related analogues could expedite the discovery of novel analgesics, which retain their painkilling properties without the drawbacks of addiction. Our interest in the morphinan alkaloids stems from their biosynthesis,[4] and in particular the *ortho–para* oxidative phenolic coupling that generates the core architecture of these complex molecules. Synthetic strategies that directly mimic the oxidative transformation of reticuline to salutaridine have been reported,[3d,f,j,m] but are generally low yielding, and despite the apparent simplicity of such a chemical dearomatization, a viable solution remains elusive. Here, we report a distinct synthetic strategy based on an *ortho–para* oxidative phenolic coupling and diastereoselective desymmetrization that can provide an enantioselective synthesis of morphine and codeine. Further notable aspects of our synthesis include a catalytic enantioselective ketone reduction to install a stereocenter that is able to control all of the remaining stereocenters in the target molecule, an acid-mediated cascade that rearranges this polycyclic framework into the morphine ring system, and a strategy that is amenable to a gram-scale synthesis of these alkaloids.

Oxidative phenolic coupling is a valuable strategy toward a variety of alkaloid scaffolds.[5] Many of the successful applications of this unique C–C bond forming step mimic the related biosynthetic pathway (Scheme 1, Eq. 1) and among the most noteworthy of these are the hypervalent iodine mediated oxidative phenolic couplings toward the galanthamine alkaloids.[6] In the context of the morphine alkaloids, the biomimetic *ortho–para* phenolic coupling was first reported by Barton et al.,[3d] although the efficiency of this process was extremely low. White and co-workers subsequently showed that brominated derivatives of the reticuline scaffold underwent a similar transformation, but again the yields were still moderate.[3j] Attracted by the simplicity of the oxidative phenolic coupling, but conscious of the previous



Scheme 1. Proposed biosynthesis of morphine and an outline of our "bioinspired" strategy.

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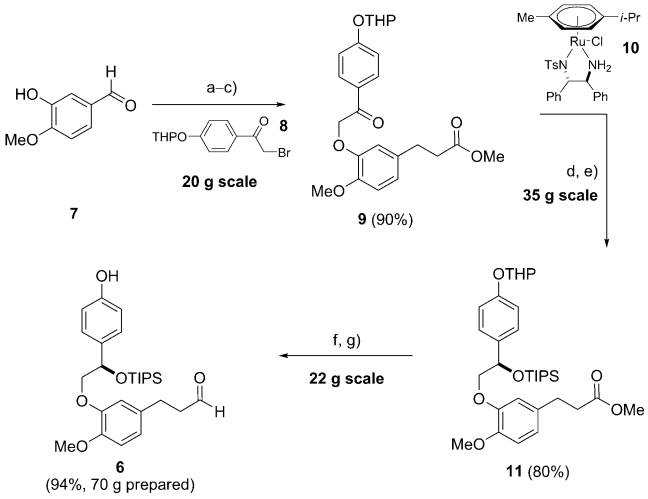
attempts at this coupling tactic, we reasoned that an alternative intramolecular arrangement of the two phenols may be better suited to a chemically induced version of this key C–C bond forming event. Therefore, we devised a strategy that would not only embed an *ortho–para* oxidative phenolic coupling at the heart of our synthetic approach to morphine but would also provide a means to generate a large proportion of the natural product architecture in a single process.

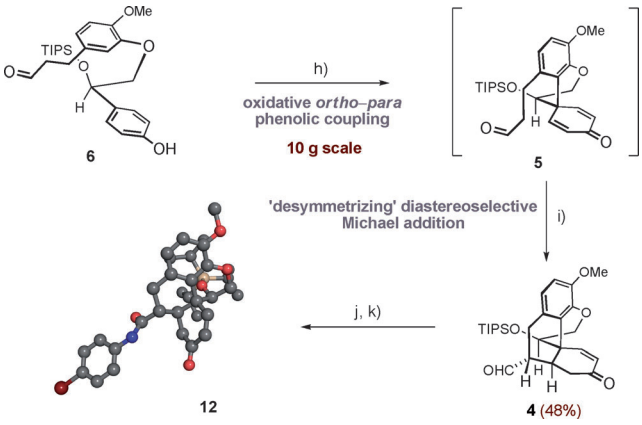
Retrosynthetically, our strategy began with the identification of key intermediate **2** that has been common to a number of strategies toward these molecules (Scheme 1 b).[3-x,ac] From here, we envisioned **2** would be accessible from a structural rearrangement of polycyclic intermediate **3**, in a manner that is related to Magnus's recent approach to the morphine skeleton.[3ac] In turn, **3** would be accessed from polycyclic aldehyde **4** by following a number of straightforward transformations. Deployment of our key strategic bond disconnection was proposed to transform phenol **6** into architecturally complex aldehyde **4** by a two-step process: first, by utilizing an oxidative phenolic coupling to generate the cyclohexadienone **5** that displays an all-carbon quaternary center; and second, a diasteroselective Michael addition that effectively desymmetrizes the cyclohexadienone subunit and sets three of the four morphinan ring junction stereocenters in a single step (two arising directly from the Michael addition and the third a consequence of the desymmetrizing nature of the transformation). We particularly aimed at developing a robust synthesis that was amenable to gram-scale production of these complex alkaloids.[7]

Our synthesis began with the assembly of the precursor to the key oxidative phenolic coupling (Scheme 2). Commercially available isovanillin **7** was advanced in 20 gram batches through a number of routine steps and union with **8** by phenol alkylation, enabling the preparation of large quantities of ketone **9**. A catalytic enantioselective ketone reduction by Noyori transfer hydrogenation[8] delivered the desired carbinol (not shown) with 93% *ee*. The robustness and efficiency of this asymmetric process provided decagram quantities of the enantioenriched alcohol without compromising the enantiomeric excess. This material was directly converted without purification to silyl ether **11** (80% yield over two steps, 35 g scale). DIBAL-mediated reduction of the ester motif in **11** to the corresponding aldehyde was followed by in situ cleavage of the THP protecting group and was conducted successfully on a 22 g scale, providing the key phenol **6** in 94% yield. Overall, a single batch of **7** could be converted into 16.6 g of aldehyde **6** through a reaction sequence that required only three chromatographic purifications; this optimized procedure has produced a total of 70 g of **6**.



Scheme 2. Large scale synthesis of **6**, precursor to the key oxidative phenolic coupling/Michael addition step. Reagents and conditions: a) Ph_3PCHCO_2Me (1.1 equiv), CH_2Cl_2, reflux, 18 h; b) H_2, Pd/C, MeOH, rt, 3 h; c) **8** (1.2 equiv), K_2CO_3 (1.5 equiv), nBu_4NBr (0.05 equiv), CH_2Cl_2/H_2O, 55 °C, 15 h, 89% over 3 steps; d) 1 mol% RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] (**10**), HCO_2H/Et_3N/DMF, 40 °C, 20 h; e) TIPSOTf (1.4 equiv), iPr_2NEt (3 equiv), CH_2Cl_2, 0 °C to rt, 2.5 h, 80% over 2 steps; f) DIBAL (1.1 equiv), CH_2Cl_2, −78 °C, 1 h; g) HCl (aqueous, 3 M), THF, rt, 2 h, 94% over 2 steps; DIBAL = diisobutylaluminum hydride, DMF = *N*,*N*′-dimethylaminoformamide, DPEN = diphenylethylenediamine, Tf = trifluoromethylsylfonyl, TIPS = triisopropylsilyl, Ts = tosyl.

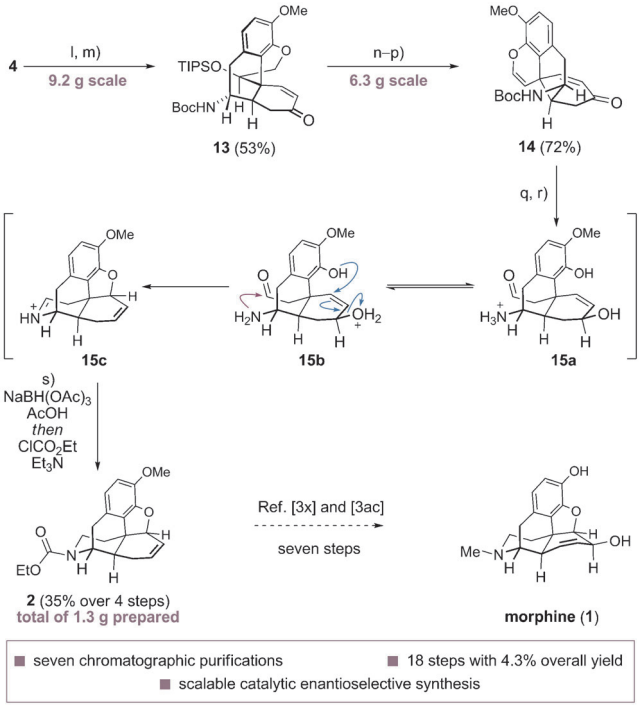
With decagram quantities of phenol **6** in hand we turned our attention to the key *ortho–para* oxidative phenolic coupling step (Scheme 3). After brief experimentation, we found that the optimal oxidation conditions required the treatment of phenol **6** with iodosobenzene diacetate to form the pivotal intramolecular coupling product **5**.[5e] Crucial to the success of this transformation was the use of trifluoroethanol as solvent.[9] Without purification, the cyclohexadienone was subjected to DBU-catalyzed Michael addition that delivered **4** as a single diastereomer in 48% yield from **6**. The overall two-step transformation could be conducted on a 10 g scale to afford significant quantities of **4**. We speculate that some substrate polymerization occurs during the dearomatization step; whilst no identifiable byproducts were observed, the yield of this step was always found to be moderate.



Scheme 3. Oxidative phenolic coupling followed by base-catalyzed Michael addition to obtain a single diastereomer of key intermediate **4**. Reagents and conditions: h) $PhI(OAc)_2$ (1 equiv), TFE, −40 °C, 2.5 h; i) DBU (0.1 equiv), CH_2Cl_2, rt, 24 h, 48% over 2 steps; j) $NaClO_2$ (4 equiv), NaH_2PO_4 (3 equiv) *t*BuOH/H_2O, 2-methyl-2-butene, 0 °C to rt, 1 h, 95%; k) 4-bromoaniline (1 equiv), EDCI·HCl (1.05 equiv), DMAP (1 equiv), CH_2Cl_2, rt, 18 h, 66%. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, TFE = 2,2,2-trifluoroethanol.

Notably, three new stereogenic centers are created in the second step. The desymmetrization of cyclohexadienones remains a topic of intense interest due to the generation of significant levels of molecular complexity from the planar aromatic starting material.[5a,10] With respect to morphine syntheses, Magnus and co-workers deployed a related disconnection that accessed a cyclohexadienone intermediate through an alkylative dearomatization tactic,[3ac] intercepting with a nitro-Michael addition at a later stage in the synthesis. However, they did not disclose an enantioselective protocol to perform this desymmetrization and the synthesis resulted in a racemate. In our case, the remote stereogenic center, installed through Noyori reduction of a ketone, controls the Michael addition of the aldehyde to the cyclohexadienone with remarkably selectivity; no diastereomeric compounds were observed. We propose that the origin of this selectivity derives from the bulky OTIPS group controlling the conformation of the tetrahydrobenzopyran ring such that the enolate of the aldehyde prefers to attack one side of the pseudosymmetric cyclohexadienone leading to a single product. Furthermore, **4** is produced as a single epimer at the carbon adjacent to the formyl group, most likely reflecting the thermodynamically favored product. Importantly, the structure of **4** displays all of the carbon atoms as well as a significant proportion of the architectural complexity required for the skeleton of morphine directly and can be readily derived from an acyclic precursor on multigram scale. Confirmation of the relative and absolute stereochemistry was obtained through conversion of **4** into an amide derivative **12** whose structure could be defined by X-ray diffraction of a single crystal (Scheme 3).

With a plentiful supply of aldehyde **4** now available to us, we advanced this intermediate through Pinnick oxidation to the corresponding acid followed by Curtius rearrangement, which we found worked best using diphenylphosphoryl azide[11] delivering the *N*-Boc protected amine **13** in 53% yield on a 9 g scale (Scheme 4). Apart from providing a handle to control the stereochemistry of the "desymmetrizing" Michael addition, the hydroxy function was also designed to serve as a means to cleave the arylether linkage and liberate the carbon chain required to form the piperidine ring of the morphinan architecture. A simple three-step sequence involving TBAF-mediated cleavage of the silyl ether, mesylation of the resulting hydroxy group, and E2 elimination with DBU gave the desired enol ether in 72% over the three steps (on a 6 g scale), requiring only one chromatographic purification. In preparation for the structurally rearranging cascade reaction, we found that Luche reduction of the enone (**14**) to the corresponding allylic alcohol was first necessary. Under acidic conditions, and assisted by microwave irradiation,[12] a cascade reaction was initiated and involved hydrolysis of the enol ether, addition of the resulting phenol to a putative allylic cation that resulted in the formation of tetrahydrobenzofuran ring, cleavage of the Boc group to release the amine, and subsequent intramolecular condensation with the pendant aldehyde (liberated on enol ether hydrolysis) possibly through a sequence involving intermediates **15a–c**. Immediate reduction with $NaBH(OAc)_3$ delivered the secondary amine, which was protected to form ethyl carbamate



Scheme 4. Completion of the formal total synthesis: acid-mediated rearrangement and conversion to the known intermediate **2**. Reagents and conditions: l) $NaClO_2$ (4 equiv), NaH_2PO_4 (3 equiv) *t*BuOH/H_2O, 2-methyl-2-butene, 0 °C to rt, 1 h, 95%; m) DPPA (1.1 equiv), NEt_3 (1.1 equiv), *t*BuOH, 65 °C to 85 °C, 48 h, 53% over 2 steps; n) TBAF (1.1 equiv), THF, rt, 0.5 h; o) MsCl (1.2 equiv), Et_3N (1.3 equiv), DMAP (0.12 equiv), CH_2Cl_2, 0 °C, 2 h; p) DBU (10 equiv), MeCN, 85 °C, 18 h, 72% over 3 steps; q) $NaBH_4$ (1.6 equiv), $CeCl_3.7H_2O$ (1.4 equiv), MeOH, −78 °C, 1 h; r) HCl (aqueous, 3 M), dioxane, 80 °C, μW, 2 h; s) $NaBH(OAc)_3$ (2.3 equiv), AcOH/DCE, rt, 1 h, then $ClCO_2Et$ (2.5 equiv), Et_3N (5 equiv), rt, 1 h, 35% over 4 steps; DCE = dichloroethene, DPPA = diphenylphosphoryl azide, MsCl = methanesulfonyl chloride, TBAF = tetra-*n*-butylammonium fluoride.

2. This four-step sequence to intermediate **2** represents a synthesis of an advanced compound, which is common to several other approaches to morphine, as well as being a potential precursor to derivatives of the morphinan class of alkaloids.

In summary, we have completed an operationally simple enantioselective synthesis of a key morphinan alkaloid derivative. The overall yield is 4.3% over 18 steps. We have demonstrated that our synthesis is scalable and capable of producing multigram quantities of these important molecules. The key feature of our synthesis is an *ortho–para* oxidative phenolic coupling that can be linked with an asymmetric Michael addition controlled from a remote stereocenter (installed using enantioselective catalysis). Our current efforts are geared toward a strategy that exploits a catalytic enantioselective dearomatization approach as a means to achieve a practical and scalable synthesis of this important class of molecules.[13]

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