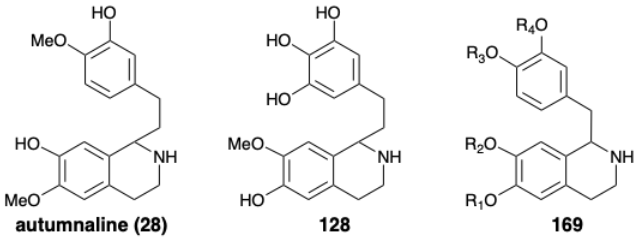
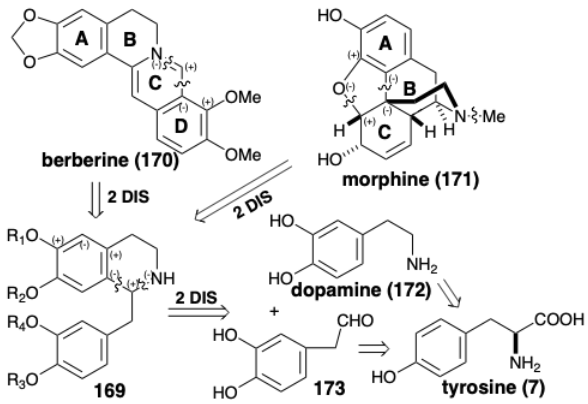
6.3: Morphine

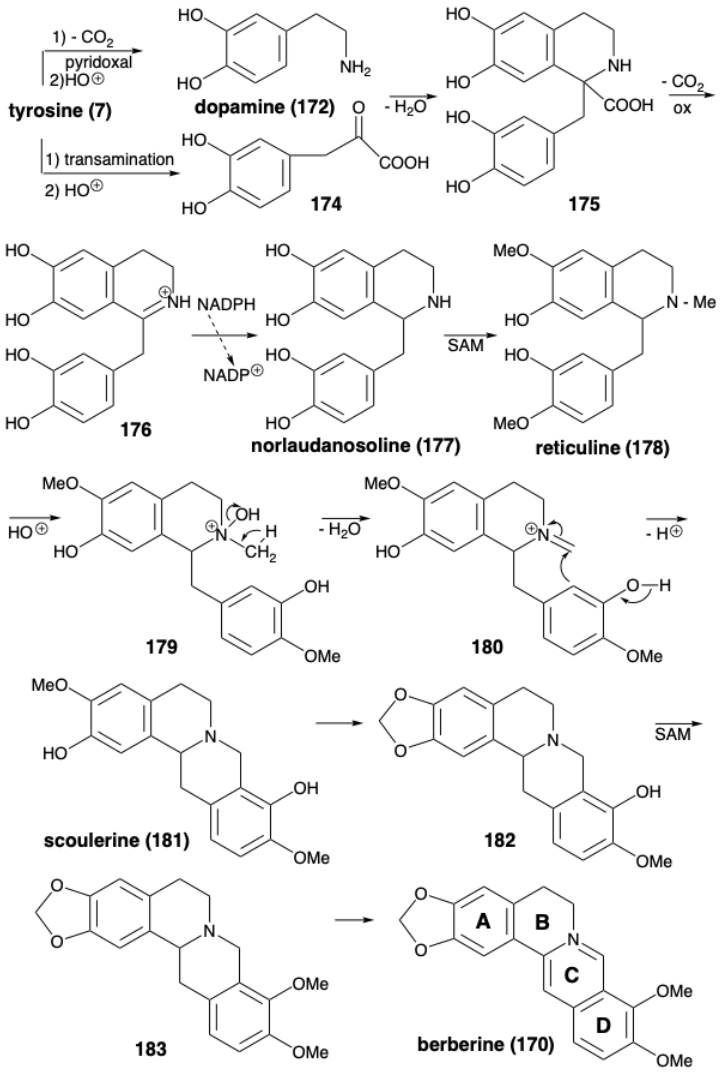
Biosynthesis of Benzylisoquinoline Derived Alkaloids

The biosyntheses of colchicine and cephalotaxine involve *phenylethyl*isoquinoline progenitors **28** and **128**. Many alkaloids, that are derived biologically from two molecules of tyrosine, share *benzyl*isoquinoline progenitors of general structure **169** (see below). In addition, both six membered rings derived from the aryl nuclei are often retained. Both may be aromatic as in berberine (**170**), or one may be nonaromatic as in morphine (**171**). The biogenetic strategy for berberine (**170**) involves a simple dislocation to a benzylisoquinoline precursor by disconnection of a one-carbon electrophile from the nucleophilic nitrogen and D-ring arene. An intact benzylisoquinoline structure is less evident in the convoluted multicyclic skeleton of morphine (**171**). If an electron rich aromatic precursor is presumed for the highly oxygenated C-ring, then polar disconection of a furan C-O bond suggests that oxidative coupling of aromatic A and C-rings of a benzylisoquinoline precursor can generate the B-ring of **171**. The key benzylisoquinoline intermediates **169** could be produced by Mannich reactions. These condensations might involve polar bond formation between a phenylacetaldehyde electrophile **173** and dopamine (**172**) as bisnucleophile.

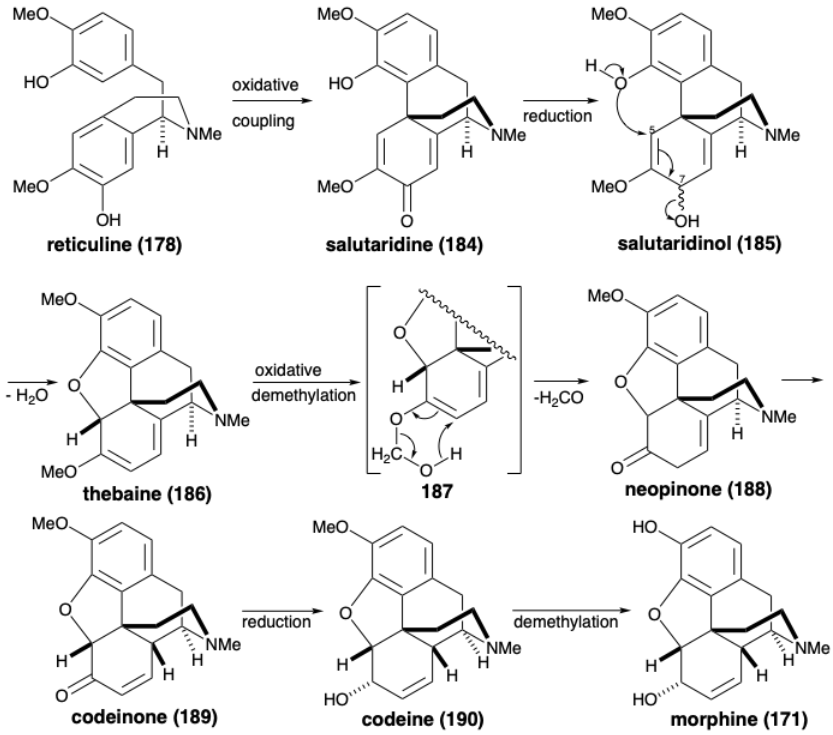




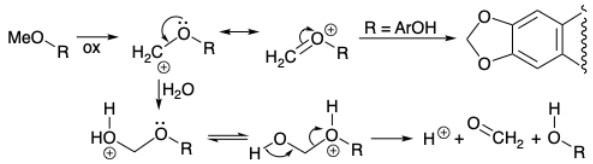
The biosynthesis of berberine (**170**) from two molecules of tyrosine (see below) commences with pyridoxal-catalyzed decarboxylation and electrophilic hydroxylation that produces dopamine (**172**). Replacement of the α-amino group of tyrosine with a carbonyl by transamination and electrophilic hydroxylation produces 3,4-dihydroxyphenylpyruvic acid (**174**). This highly reactive ketone, rather than a phenylacetaldehyde, serves as the electrophile in a Mannich reaction with dopamine (**172**). Polar condensation of the highly electrophilic carbonyl in **174** with **172** as bisnucleophile generates the benzylisoquinoline ring system in **175**. Oxidative decarboxylation of this α-amino acid followed by reduction of the intermediate **176** delivers norlaudanosoline (**177**) from which reticuline (**178**) is produced by O and N-methylation. The N-methyl group is incorporated into the berberine skeleton by a Mannich condensation of iminium derivative **180** produced by dehydration of an intermediate protonated N-oxide **179**. Conversion of an o-methoxyphenol array in the product **181** to a methylenedioxy group in **182**, methylation and aromatization of the product **183** delivers berberine (**170**).



The more topologically complex skeleton of the morphine alkaloids is also produced from reticuline (**178**). Thus, oxidative *ortho-para* coupling delivers salutaridine (**184**). Generation of the benzofuran ring of thebaine (**186**) occurs after adjustment of functionality level resulting in loss of functionality from position 7 of **185**. Interestingly, although simple hydroly-sis of enol ether **186** could produce ketone **188**, the oxygen of the methoxyl group is retained in **188**. Therefore, a different mechamism must be involved. Perhaps demethylation of **186** occurs through an oxidized intermediate **187** that undergoes retroene fragmentation. Allylic isomerization, reduction, and demethylation then deliver morphine (**171**).

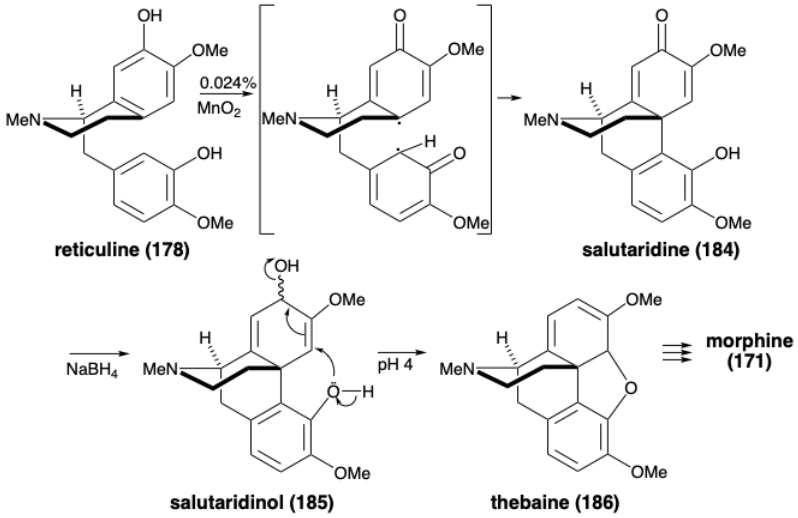


The demethylation of codeine (**190**) and of the enol ether **187**, as well as the conversion of ortho methoxy phenols **137** into methylenedioxy derivatives **139** (see section 6.2) may all be related mechanistically by the initial oxidative conversion of a methyl ether into an α-oxygen-stabilized carbocationic intermediate. Demethylation would occur upon nucleophilic capture by water and fragmentation of the resulting formaldehyde hemiacetal.

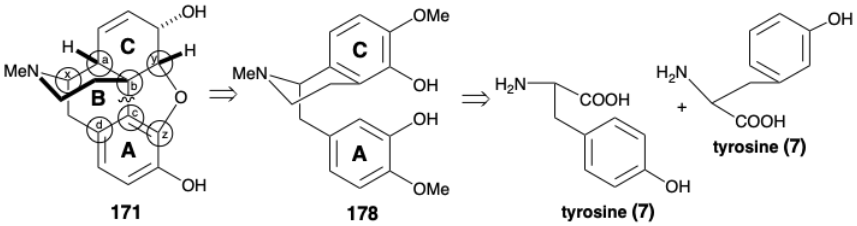


A Biomimetic Synthesis of Morphine

Morphine has been assembled in the laboratory by a biomimetic strategy involving oxidative coupling of reticuline (**178**).[9] Oxidative coupling of **178** was accomplished by treatment with manganese dioxide. Salutaridine (**184**) was obtained, albeit in miniscule yield. Hydride reduction provided the allylic alcohol **185**. With mild acid catalysis, **185** underwent intramolecular S_N2' displacement of the allylic hydroxyl by the phenolic hydroxyl to afford thebaine (**186**) from which morphine (**171**) can be produced (*vide infra*).

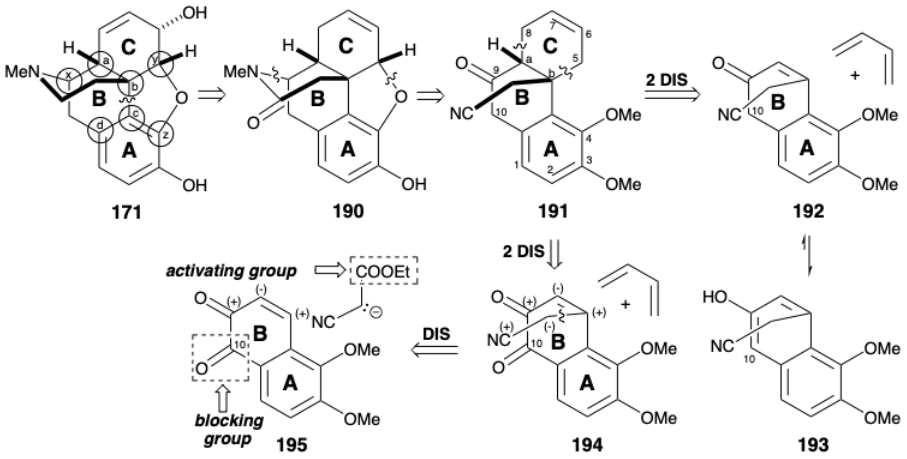


The bridged multicyclic skeleton of morphine has considerable topological complexity. A topological analysis (see section 4.4) may, therefore, be useful for synthetic planning. Considering only the *carbocyclic* skeleton of **171**, there are four common atoms, a-d, and three possible disconnections between them. Of these disconnections, only one, removal of the bond between common atoms b and c, leads to a structural simplification. If the *heterocyclic* skeleton is also considered, there are also three more common atoms, x, y, and z. Disconnection of bonds between these latter common atoms and a heteroatomic ring member are generally trivial because the heteroatoms are reactive functionality. Disconnection of the b-c bond (and the bond between common atom y and oxygen) suggests a precursor such as **178** (reticuline), the biosynthetic progenitor of morphine alkaloids. Interestingly, this is the only cleavage of a bond between a pair of common atoms that leads to simplification of the morphine carbon skeleton. Thus, cleavage of the bond between common atoms a and b leads to an intermediate with two fused ten membered rings, that would be a redoubtable synthetic challenge. Because it does not lead to reduction of molecular complexity, this dislocation is probably not useful. Cleavage of the π-bond between common atoms c and d disrupts an aromatic system and creates a ten membered ring. The stability of aromatic systems usually disfavors synthetic strategies involving annelation of aromatic rings in the final stages of a synthesis. Therefore, this dislocation is also probably not useful.

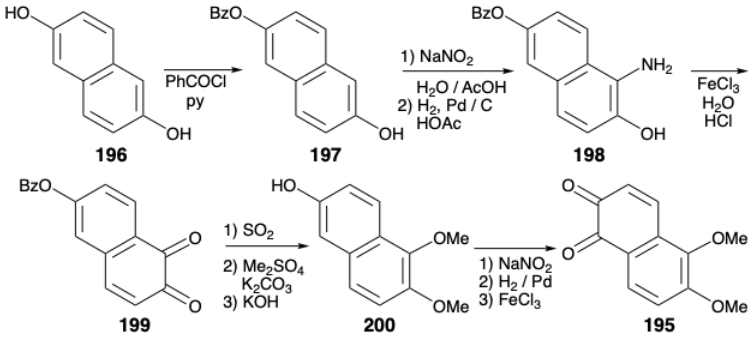


A Diels Alder Strategy for C Ring Annulation

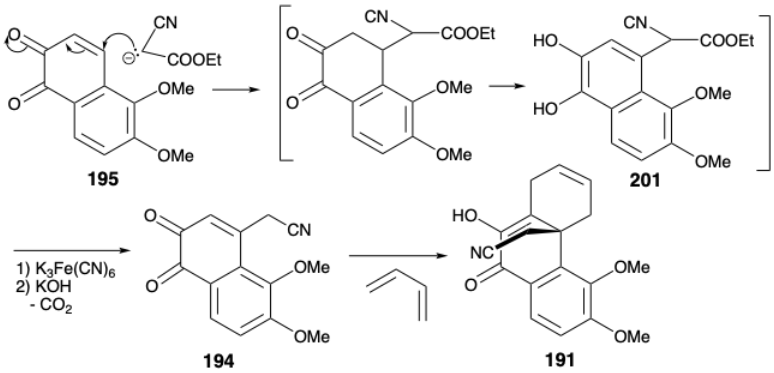
The presence of a cyclohexene array in the C ring of morphine (**171**) recommends consideration of a Diels-Alder reaction to generate two vicinal exendo bonds, each involving one common atom (i. e. a or b) and one noncommon atom. This topological simplification was exploited in the first total synthesis of morphine.[10] However, the C=C bond in the C ring of **171** is in the wrong location. Therefore, with the use of a Diels-Alder tactic as a boundary condition, dislocation of **171** to an amide **190** sets the stage for a retro Diels Alder dislocation. To allow the incorporation of a C=C bond for a dienophile, **190** is first dislocated to **191** by cleavage of carbon-heteroatom bonds to the common atoms x and y. The carbonyl at position 9 in **191** provides activation for a Diels-Alder construction of the C-ring from an AB-ring dienophile **192** and 1,3-butadiene, a relatively electron-rich diene. However, this strategy is fatally flawed because **192** is expected to exist almost exclusively in the aromatic enol form **193** that would not be a reactive dienophile. To block this undesirable enolization, a carbonyl group can be exploited at position 10 (morphine numbering) in a precursor **194.** The cyanomethyl sidechain can be appended by the polar union of a nitrile-stabilized nucleophile with the electrophilic β carbon of the α,β-unsaturated carbonyl array in **195**. The C-10 carbonyl in **195** also would facilitate this Michael addition of the sidechain nucleophile by preventing enolization of the enone in conjunction with aromatization.



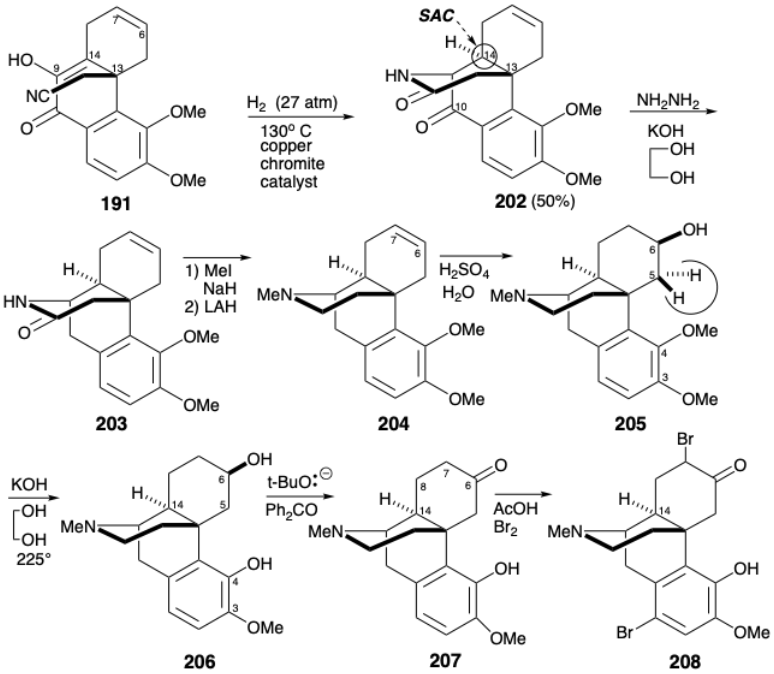
The scheme used for the synthesis of **195** exploits the symmetry of 2,6-dihydroxynaphthalene (**196**) that readily undergoes electrophilic substitution at the α-position. The electron withdrawing effect of the benzoyl group in the monobenzoate **197** diminishes the electron donating ability of the benzoylated hydroxyl. Therefore, nitrosation occurs regiospecifically at the α-position next to the free hydroxyl. Reduction of the nitroso group affords an amine **198**, that is oxidized to an ortho quinone **199.** Reduction, methylation, and saponification then delivers phenol **200** that affords **195** by regioselective nitrosation, reductive N-O cleavage and oxidation.



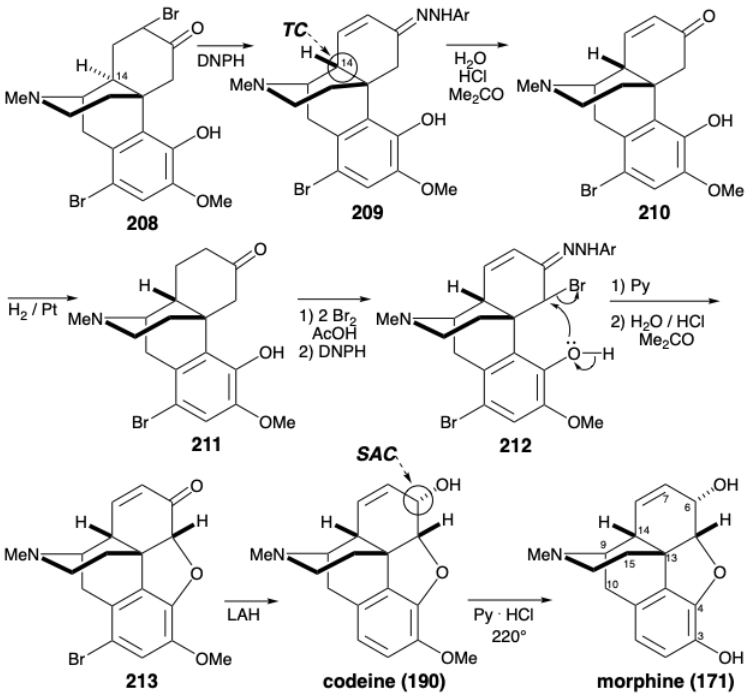
The carbon skeleton of the dienophile **194** is completed by Michael addition of ethyl cyanoacetate carbanion to **195**. After saponification, decarboxylation and aromatization, an intermediate hydroquinone **201** is oxidized to give the ortho quinone **194**. The carbocyclic skeleton of morphine is completed by a Diels-Alder cycloaddition that provided **191**. Elaboration of a piperidine ring began with a reduction that gave the lactam **202** directly. This lactam is epimeric with the morphine skeleton at position 14 presumably owing to steric approach control during delivery of hydrogen to the enolic 9-14 C=C bond in **191**.



The resulting alcohol presumably adds to the C≡N bond producing an iminoether intermediate that rearranges to the lactam **202**. Remarkably, the sterically far more congested 9-14-C=C bond is reduced while the 6,7-C=C bond remains unreduced under these conditions.



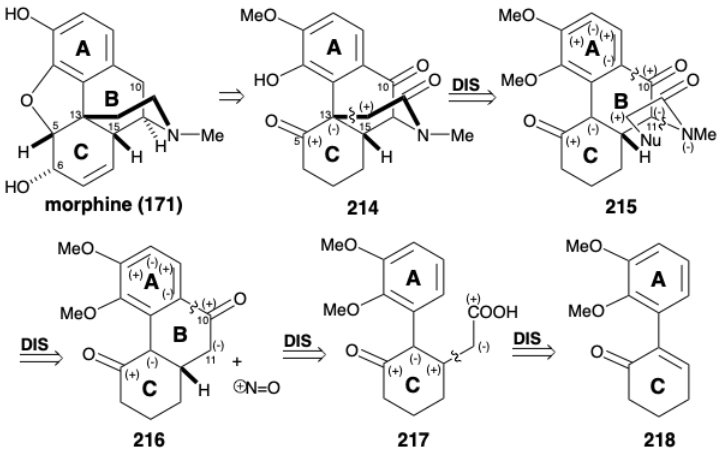
The C-10 carbonyl in **202**, having served its purpose was then removed by Wolff-Kishner reduction. After N-methylation of **203**, the amide carbonyl was removed by hydride reduction. Hydration of the isolated π-bond in **204** proceeded completely regio and stereoselectively to give **205** in "yields up to 28%". This fortunate selectivity is understandable in terms of a stereoelectronic preference for *anti* periplanar diaxial addition to the C=C bond with addition of the nucleophile preferentially *syn* to the protonated amino substituent. The original intention had been to demethylate both ether groups of **205** and to attempt a selective remethylation of the less sterically congested 3-hydroxyl. The action of pyridinium hydrochloride, however, not only cleaved both phenolic ether groups but also dehydrated the secondary alcohol. Fortunately some demethylation of the C-4 methyl ether had been observed during the **202** to **203** conversion. This discovery was exploited by developing conditions that afforded **206** in 54% yield upon heating with KOH in ethylene glycol. Presumably releif of steric congestion fosters demethylation of the 4-methoxy group by an S_N2 displacement of phenolate by hydroxide. Completion of the morphine skeleton by generating a furan ring required considerable adjustment of functionality and stereochemistry in **206**. A carbonyl at position 6 could be exploited both to allow activation of the 5-position toward intramolecular nucleophilic attack by the C-4 hydroxyl and to allow epimerization at the 14 position. Thus, oxidation of the C-6 hydroxyl in **206** by a variation of the Oppenauer reaction gave ketone **207**. To provide the conjugation with the C-6 carbonyl needed to allow epimerization at C-14, a C=C bond was introduced between carbons 7 and 8. Thus, bromination followed by Mattox-Kendall de-hydrobromination (see section 5.4) provided the epimerized tosylhydrazone **198**.



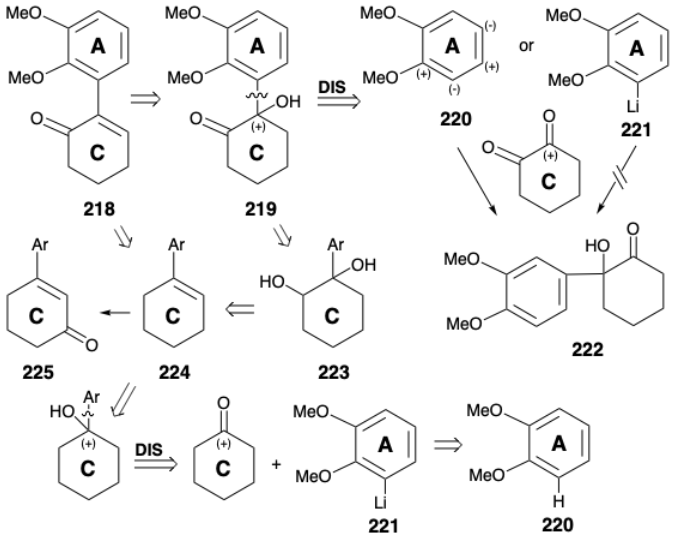
After hydrolysis to an enone **210** and reduction to a ketone **211**, activation at the 5-position was achieved by bromination with two equivalents of bromine. It is not clear why **207** could not be converted directly into **212** without the intermediacy of **210** and **211**. Subsequent monodehydrobromination of an intermediate α,α'-dibromo ketone with DNPH delivered **212**. This underwent cyclization in pyridine to yield benzofuran **213** after hydrolysis of the hydrazone. During the **207** to **208** conversion an adventitious bromo group was introduced into the A ring. This was conveniently removed during the reduction of the C-6 carbonyl with lithium aluminum hydride to give codeine (**190**), the monomethyl ether of morphine (**171**). Hydride delivery to **213** occurred stereoselectively from the more sterically accessible convex face. Demethylation of **190** was achieved by nucleophilic displacement by chloride of phenol from the protonated ether.

A Friedel-Crafts B Ring Annelation Strategy

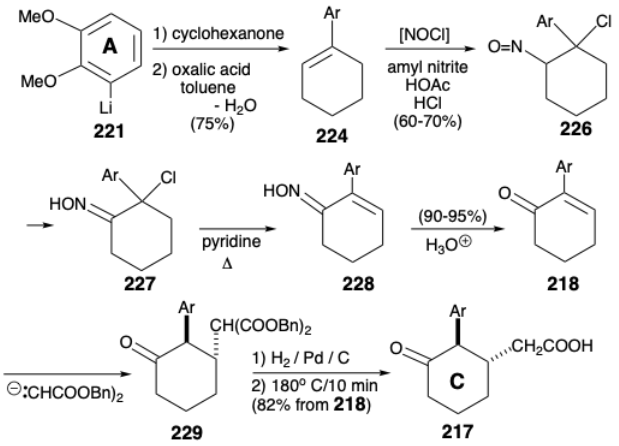
Another strategy for synthesis of morphine (**171**) is channeled by the decision to generate the B ring by electrophilic substitution of an electron-rich A ring nucleophile.[11] This tactic requires temporary carbonyl functionality at the incipient 10 position that would have to be removed in the final steps, e. g. by reduction of a precursor **214**. Target- related oxygen functionality at position 5 can be exploited to facilitate introduction of the remaining C-ring functionality and unsaturation and to facilitate generation of the nitrogen heterocycle by alkylation of a carbon nucleophile at position 13. This requires activation of the incipient carbon 15, i.e. α to the amide carbonyl in **214**, with a nucleofuge. Appendage of an amino *nucleophile* to position 11 in a precursor **216** for **215** cannot be achieved by a polar process since neither keto group in **216** can provide electrophilic activation at the 11 position. On the other hand, a nitrogen *electrophile* could be added to an intermediate that is nucleophilic at position 11 because of activation by the neighboring ketone carbonyl, e.g. by nitrosation of ketone **216**. The ABC-ring carbocyclic skeleton of morphine can be assembled by intramolecular Friedel-Crafts aromatic substitution of an electron rich AC-ring precursor **217**. Polar analysis of **217** recommends an a,b-unsaturated enone electrrophile **218** that would provide **217** by addition of a carboxy activated nucleophile.



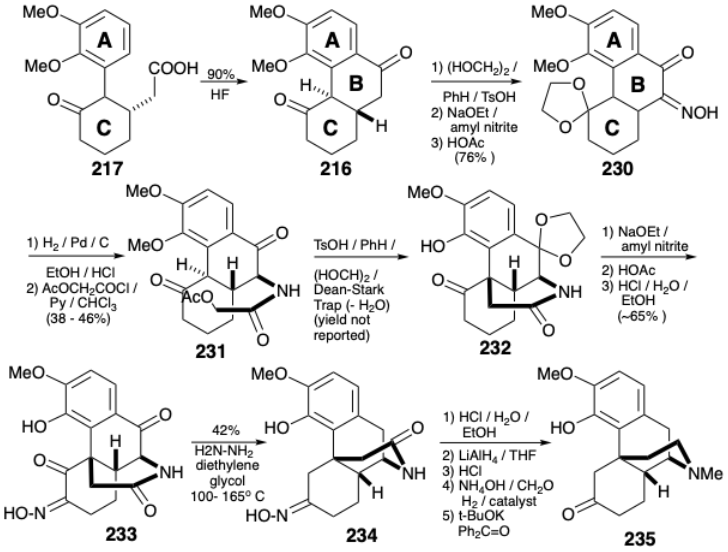
A precursor **219** of **218** might be generated by electrophilic aromatic substution of **220** by a carbonyl activated electrophile, 1,2-cyclohexanedione. However, steric congestion would favor the alternative regioisomeric product **222**. The use of an alternative nucleophile, the regioselectively ortho lithiated aromatic diether **221** as nucleophile, avoids this ambiguity. Alternative routes to **218** are recommended by the possibility of employing cyclohexanone as a more readily available C ring starting material. Thus, the arylcyclohexene **224** could be functionalized by a dihydroxylation-oxidation sequence to give **218** through **219** and **223**. The possibility of generating **218** directly from **224** by allylic oxidation suffers from the ambiguity of an alternative regiochemical course leading to **225**.



An arylcyclohexene **224** is readily available by ortho lithiation of veratrole (**220**) with butyllithium and reaction of the resulting aryllithium **221** with cyclohexanone followed by acid-catalyzed dehydration. Allylic bromination (with NBS) or chlorination (with t-butylhypochlorite) followed by hydrolysis and oxidation did deliver the requisite enone **218**. But this intermediate was more readily available (overall yields of 40 - 50%) by addition of nitrosyl chloride (from amyl nitrite, acetic acid, and 30% HCl), dehydrochlorination of the intermediate nitrosochloride **226** as the oxime tautomer **227** to the unsaturated oxime **228** and hydrolysis.



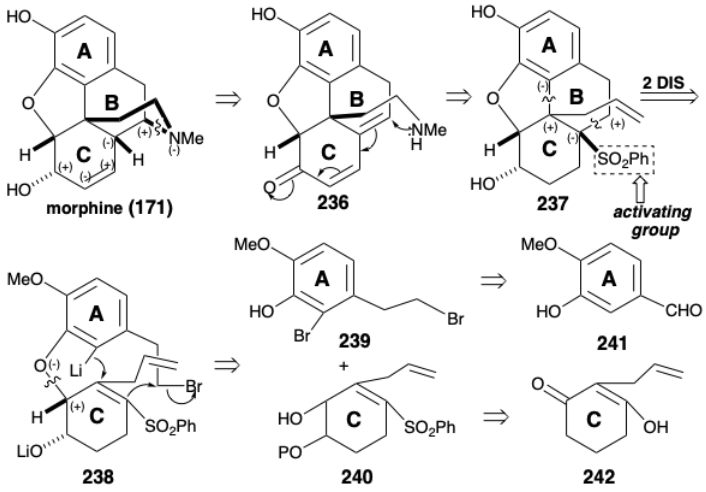
The two carbons required to complete the B-ring were appended by Michael addition of dibenzyl malonate carbanion to the enone **218**, hydrogenolysis of the resulting **229**, and decarboxylation. Friedel-Crafts cyclization of **217** provided the B-ring in **216**. Differentiation of the carbonyls in **216** could be accomplished by selective ketalization of the more electrophilic carbonyl. An amino substituent was introduced by nitrosation of an enolate. Reduction of the oxime **230** under acidic conditions was accompanied by deketalization. N-acylation delivered α-acetoxyacetamide **231**. Intramolecular alkylation and selective ketalization (now of the less sterically congested carbonyl) occurred upon treatment of **231** with acid. Transposition of the C-ring carbonyl was initiated by nitrosation of the enolate of **232**. Deketalization followed by Wolff-Kishner reduction of the intermediate diketo oxime **233** delivered oxime **234** removing two carbonyl groups but not the oxime-masked carbonyl. Hydrolysis of the oxime, reductive removal of the amide carbonyl, reductive methylation of the resulting amine, and oxidation of an intermediate secondary alcohol delivered the ketone **235**. Conversion of an analogous intermediate **208** to morphine (**171**) was described above.



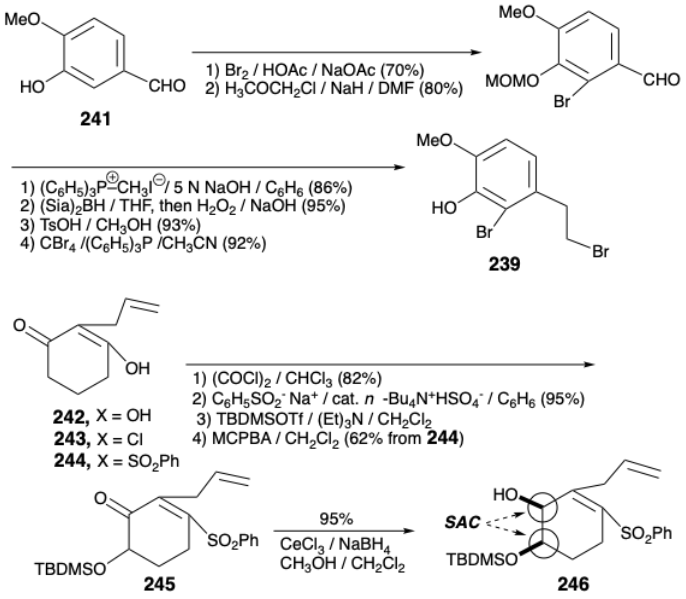
A Conjugate Addition-Alkylation Strategy for B Ring Annulation

Both of the foregoing syntheses of morphine involve: (1) extensive functional group manipulation after construction of the ABC and piperidine rings, (2) generation of the furan ring last, and (3) a dependence on carbonyl groups to activate or control reactivity. A completely different strategy was employed to achieve a more convergent synthesis of morphine.[12] This strategy involves: (1) generation of the piperidine ring last, (2) minimal functional group manipulation after completion of skeletal construction, and (3) exploitation of a sulfonyl group to provide polar activation. As for the biosynthesis and previous syntheses of morphine, the aromaticity of the A-ring recommends an aromatic starting material for this ring. A consonant circuit between C-ring oxygen and B-ring nitrogen substituents in morphine (**171**) suggests a construction of the piperidine ring, that exploits the polar reactivity provided by target-related functionality in an α,β,γ,δ-unsaturated ketone precursor **236**. A polar double disconnection of the B-ring, between a pair of common atoms and between a common and a noncommon atom, is made possible by a strategically placed phenylsulfonyl *activating group* in a precursor **238** of **237**. Polar disconnection of **238** suggests A and C-ring precursors **239** and

240 that should be available from isovanillin (**241**) and the symmetrical 2-allylcyclohexane-1,3-dione (**242**) by functional group additions and interconversions.



The key A-ring intermediate **239** is available on a large scale from isovanillin (**241**) in 40% overall yield as outlined below. Substitution of the enolic hydroxyl in 2-allylcyclohexane-1,3-dione (**242**) by a phenylsulfonyl group is accomplished through the vinylogous acyl chloride **243** to provide **244** by addition of phenylsulfinate and elimination chloride, respectively, in 74% yield overall. Oxidative functionalization of **244** was accomplished by a Rubottom reaction, i.e. treatment of the corresponding enol silyl ether with m-chloroperbenzoic acid. Neither the electron deficient α,β-unsaturated sulfone nor the terminal C=C bond are oxidized in competition with the more electron rich silyl enol ether. Steric approach control in a hydride reduction of **245** delivers the allylic alcohol **246** stereoselectively.



O-alkylation of **246** with **239** provides the key intermediate **247**, that undergoes a remarkable cyc- lization upon halogen-metal exchange. Intramolecular Michael addition of the intermediate aryllithium **238** leads *via* sulfone-stabilized carbanion **248** to **237**. Construction of the piperdine ring requires conversion of the allyl group in **237** into an ethylamino sidechain and conjugation of C-11 with the oxygen functionality at position 6 in **237**. Oxidation and enol etherification delivers **250** from **249**. Elimination of phenylsulfinate to give **251**, and hydrolysis to deliver **252** sets the stage for the completion of the morphine ring system by generation of the piperidine ring. Thus, neutralization of the ammonium salt **252** generates an amino group that undergoes spontaneous intramolecular 1,6-Michael addition to the dienone to deliver a mixture of neopinone (**188**) and codeinone (**189**) in 63% yield. Conversion of this mixture via codeine (**190**) to morphine (**171**) was accomplished as described previously by Rapoport. The required configuration of the hydroxyl at position 6 is established during a steric approach controlled delivery of

hydride to the carbonyl carbon in **189**. The correct configuration at the 15-position in **190** arises from equilibration through the common enol derivative of ketones **188** and **189**.