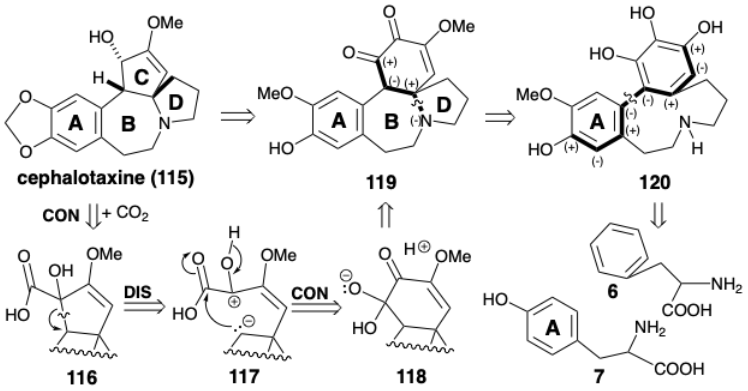
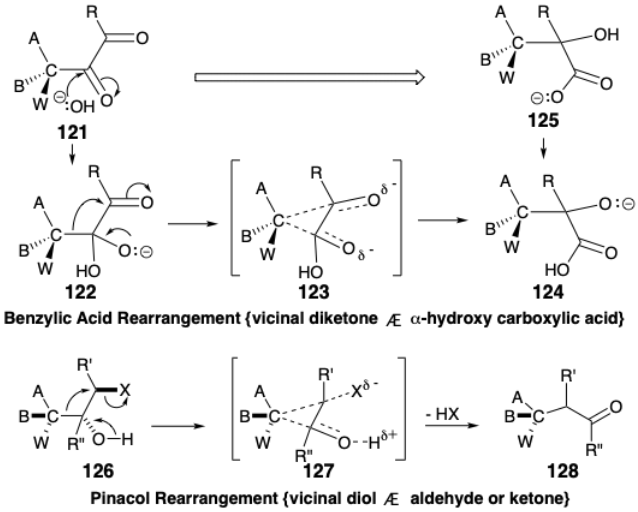
6.2: Cephalotaxine

The biosynthesis of cephalotaxine (**115**) involves a convergent strategy that assembles an intricate multicyclic skeleton from two aromatic amino acid precursors, phenylalanine (**6**) and tyrosine (**7**). As in the biosynthesis of colchicine (**8**), one aromatic ring is incorporated intact while the other is extensively modified. Thus in the biosynthesis of colchicine (**8**) the seven-membered C-ring is elaborated by a one- carbon expansion of a tyrosine-derived aromatic ring. In contrast, the biosynthetic strategy for cephalotaxine (**115**) exploits a one-carbon ring contraction to produce a five-membered C-ring from a phenylalanine-derived six-membered ring. The logic of the strategy is based on: (1) the ready availability of highly oxygenated cyclohexyl derivatives such as **119** by oxidative metabolism of aromatic precursors and (2) the possibility of extruding a carbon atom as carbon dioxide from an α-diketone by a benzylic acid rearrangement to an α-hydroxy acid. This suggests the α-hydroxy acid **116** as precursor to **115**.



Retrosynthetically, dislocation of a benzylic acid rearrangement product **116** to a precursor **119** corresponds to polar disconnection of the migrating carbon as nucleophile resulting in oxidation of the migration terminus. Subsequent connection of the nucleophilic migrating carbon in **117** results in reduction of the migration origin in the precursor **118**. Polar analysis of **119** suggests polar disconnection of nitrogen as nucleophile from an electrophilic carbon β to a carbonyl group. Polar analysis of the precursor **120** suggests that the aromatic rings of two precursors **6** and **7** might be joined by an oxidative coupling.

The connection-disconnection sequence of the benzylic acid rearrangement, generalized in the **121** to **125** conversion, is mechanistically analogous to the pinacol rearrangement discussed in chapter 4 (see section 3.4). The rearrangement of **122** into **124**, involved in the benzylic acid rearrangement, is **isoelectronic** with the **126** to **128** conversion of the pinacol rearrangement, i. e. the same electronic movements in identical arrays of atoms, bonds, and nonbonding electrons are involved. Nucleophilic addition of hydroxide to an α-diketone **121** initiates the benzylic acid rearrangement, that proceeds through a temporarily-bridged transition state **123**, and ultimately produces an α-hydroxy acid **125**. The pinacol rearrangement proceeds through a temporarily-bridged transition state **127**. In both the benzylic acid and pinacol rearrangements, the migrating group acts as an internal nucleofuge-nucleophile that adds to an electrophilic migration terminus. In both rearrangements the functionality level of the migration origin increases while the functionality level of the migration terminus decreases.



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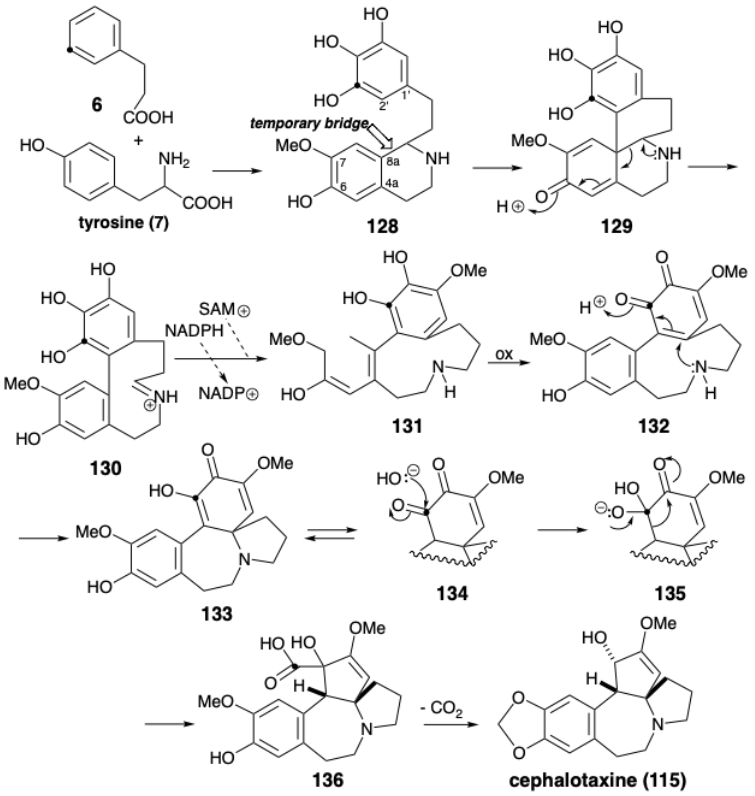
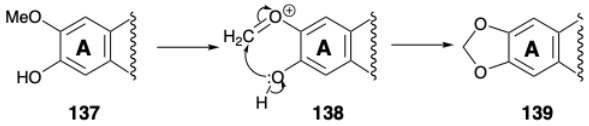
The biosynthesis of cephalotaxine (**115**) is believed to involve oxidative coupling of two electron rich aromatic rings in a phenethylisoquinoline[6] intermediate **128** delivering a tetracyclic δ-amino-α,β- unsaturated ketone **129**. The polar formation and subsequent polar cleavage of a temporary six-membered nitrogen heterocycle in **128**, facilitates the oxidative coupling by making it an entropically more favorable intramolecular cyclohexannelation rather than a cyclodecannelation that must generate **130** directly. It is reasonable to postulate the presence of a methoxyl group at position 7 in **128** since this could account for the regioselective oxidative coupling at position 8a which is *para* to the hydroxyl group presumed to be present at position 6. This regioselectivity contrasts with that observed in the oxidative coupling of autumnaline (**28**) at position 4a (see section 6.1). Thus, the O-methyl groups in **28** and **128** serve as regiocontrol elements in the oxidative couplings of these phenethylisoquino-lines. Reduction and regioselective methylation of **130** set the stage for regioselective electrophilic activation by oxidation of the *ortho* hydroquinone **131** to an *ortho* quinone **132**.

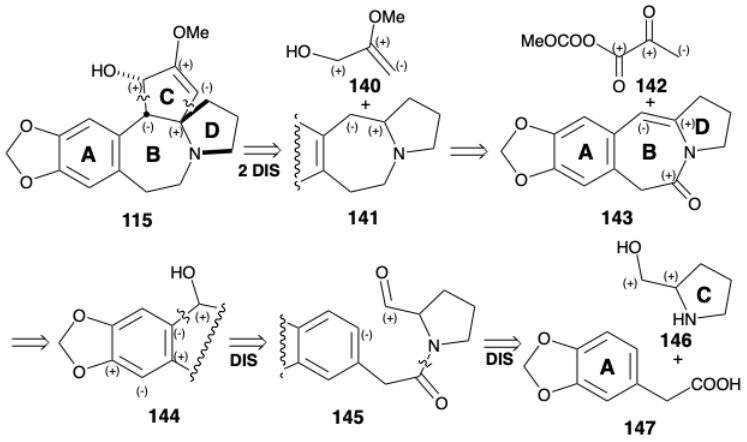


Nucleophilic Michael addition of the secondary amine then delivers **133** whose keto tautomer **134** is an α-diketone. Benzylic acid rearrangement initiated by conversion to **135** delivers α-hydroxy acid **136** in which the carboxyl carbon is derived from a *meta* carbon of the phenylalanine (**6**) starting material. Loss of this carbon as carbon dioxide then generates cephalotaxine (**115**) after conversion of the *ortho* methoxy-phenol array into a methylenedioxy group. This conversion, i.e. **137** to **139**, is common in Nature and presumably involves oxidative generation of an electrophile **138**.

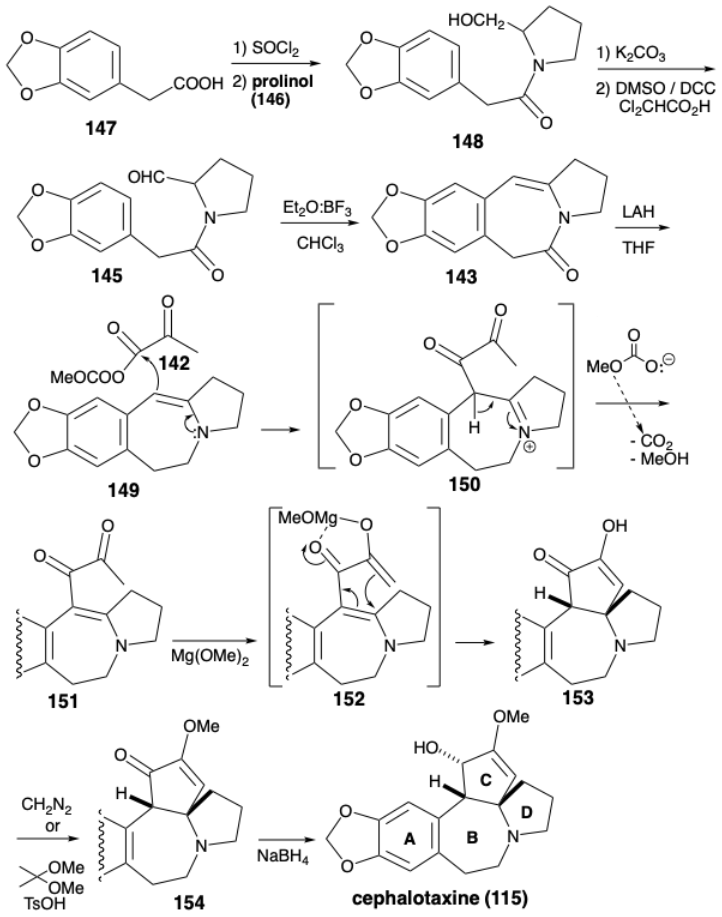


B Ring Annelation by Electrophilic Aromatic Substitution

As in the biosynthesis of cephalotaxine (**115**), the stability of aromatic derivatives recommends the utilization of an aromatic precursor for ring A. The Weinreb strategy for construction of the cephalotaxine skeleton7 recognizes the potential utility of the amino group and dissonant C-ring functionality for activating polar reactions that could append the C-ring onto an ABD-ring precursor. Synthetic equivalents **142** and **143** correspond to the polar synthons **140** and **141**. A carbonyl group in **143** is added to facilitate generation of a precursor **145**, the amide of prolinol (**146**) and the arylacetic acid **147**. The enamine in **143** could be produced by dehydration of a β-hydroxy amine precursor **144** that, in turn, should be available directly by polar union of an aromatic nucleophile and aldehyde electrophile in **145.**

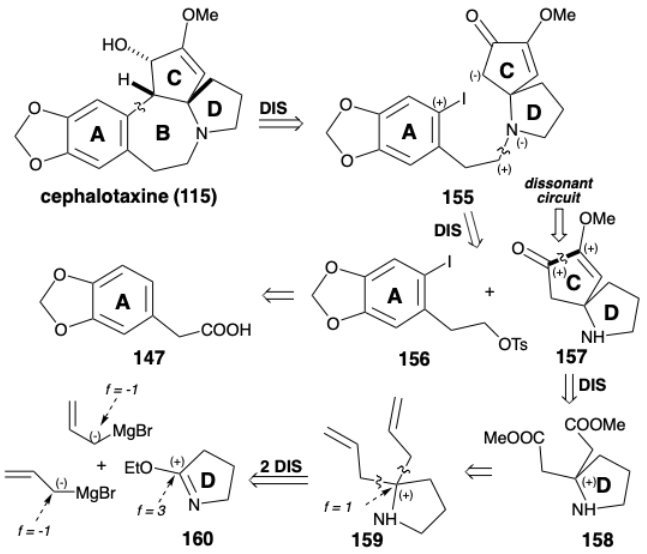


The enamine **143** was constructed by annelation of ring B between an aromatic ring A precursor **147** and a preformed ring D precursor **146**. Masking of the hydroxyl group in **146** is unnecessary since acylation occurs at the more nucleophilic nitrogen to give amide **148** rather than at the less nucleophilic oxygen to produce an ester. The final bond of ring B was formed by electrophilic aromatic substitution which occurred exclusively at the less congested aryl position in **145.** Having served its purpose, the amide carbonyl was reductively removed from **143** to deliver **149**. The polar activation afforded by the acyl group in **142** is first exploited to unite **142** and **149** to give **150**. Then the polar activation afforded by both carbonyl groups is exploited to complete the annelation of ring C. An intramolecular Michael addition of an enolate anion to the electrophilic β-carbon atom of an α,β-unsaturated carbonyl system leads to **153**. The required *cis*-ring fusion of ring C is undoubtedly the most stable. The methyl carbonate anion leaving group in **142** is especially noteworthy. Decarboxylation of this anion generates methoxide *in situ* that then deprotonates an intermediate iminium ion **150** to produce the Michael acceptor **151** under exceptionally mild conditions. Also noteworthy is the use of magnesium methoxide as base to generate the enolate **152** in the Weinreb synthesis of cephalotaxine. Magnesium can assist the cyclization by chelation that enforces a favorable cisoid conformation. Final adjustment of functionality involved enol etherification and hydride reduction. Delivery of hydride occurs from the less sterically congested convex face of **154** producing **115** with the correct relative configuration at the third asymmetric center in ring C. A regioisomeric enol ether was obtained together with **154**. This isomer could be recycled by acid catalyzed equilibration.

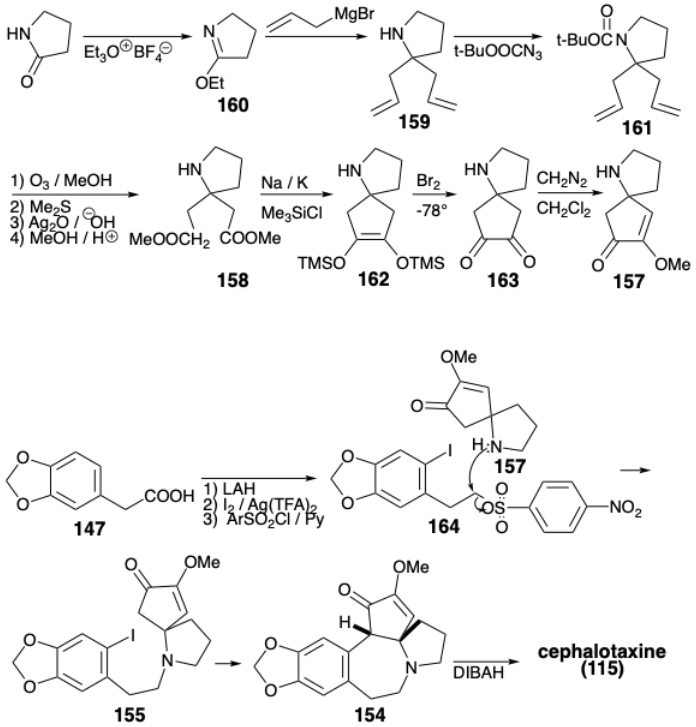


B Ring Annelation by Nucleophilic Aromatic Substitution

Whereas annelation of ring B in the Weinreb synthesis of cephalotaxine (**115**) was achieved by *electrophilic* aromatic alkylation, Semmelhack's synthesis creates the same connection by *nucleophilic* aromatic alkylation.[8] Semmelhack's strategy exploits a C-ring carbonyl to provide the requisite nucleophilicity in a final intermediate **155**. As in the biosynthesis and the Weinreb strategy, an aromatic precursor is exploited for ring A. N-alkylation of a CD-ring amine fragment **157** with the A-ring fragment **156** provides **155**. The same A-ring starting material **147** is used for both total syntheses. Ring C in **157** contains two oxygen functionalities that provide electrophilic activation at their respective carbon atoms. Thus, these functional groups cannot be exploited directly to create the bond between those carbon atoms by a polar reaction. In the Weinreb synthesis of cephalotaxine (**115**), ring C was constructed by polar reactions by using a starting material **142** that incorporates the dissonant circuit between the two oxygen functionalities in the C-ring. The Semmelhack strategy recognizes that this dissonant circuit in **157** can be formed by a nonpolar reaction, reductive coupling of the two electrophilic carbonyl carbons in a precursor **158**. Although **158** might be available directly by polar addition of two carbomethoxymethyl nucleophiles to an electrophilic D-ring precursor **160**, Semmelhack opted for the alternative strategy of adding two allyl nucleophiles to **160** followed by oxidative revelation of the latent carboxyl groups in an intermediate **159**.

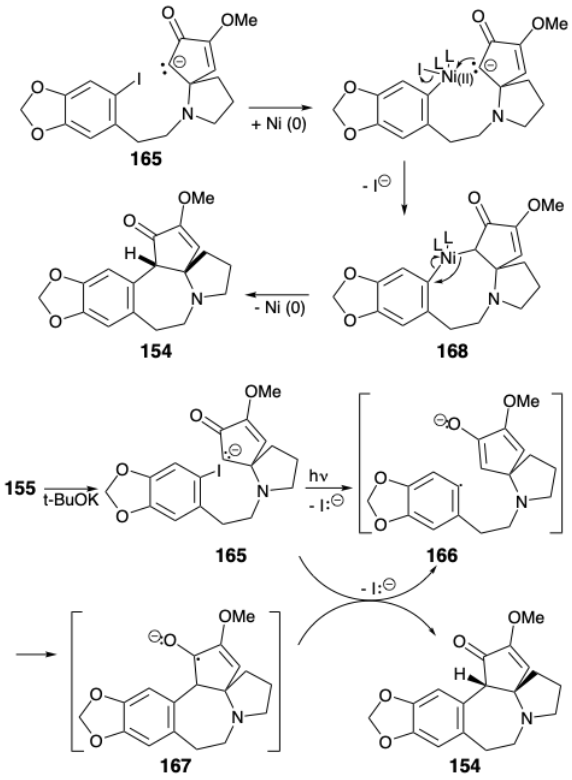


The CD-ring intermediate **157** was prepared from pyrrolidinone. The reaction of an imino ester **160** with an allyl nucleophile gave **159**. Masking of the amino group as an acid labile amide **161** was required prior to oxidative cleavage of the C-C π-bonds in **159** which ultimately provided the diester **158**. Intramolecular acyloin coupling of **158** in the presence of chlorotrimethyl silane (the Rühlmann modification) produced **162**, that was oxidized directly to **163** by a one-pot addition of bromine and elimination of TMSBr. Methylation of this symmetrical dione delivered **157**. Alkylation of this amine with the nitrosylate **164** provided **155**. Cyclization of **155**, *vide infra*, followed by reduction of the intermediate **154** delivered cephalotaxine (**115**). This synthetic strategy leads *directly to the correct enol ether* **154** *without formation of the regioisomeric enol ether that is a byproduct in the Weinreb synthesis.*



The key cyclization of **155** to **154** was achieved by a variety of reactions all involving nucleophilic aromatic substitution. Of course, direct nucleophilic attack on the electron rich A ring aryl iodide does not occur when an enolate nucleophile is generated from **155**. However, net nucleophilic substitution could be accomplished by photolysis of the enolate **165** or by treatment of **165** with Na/K or a nickel(0) catalyst. Best yields of the cyclization product **154** (94%) were obtained by a photostimulated $S_{RN}1$ reaction presumably involving the chain carrying anion radicals **166** and **167**. The $S_{RN}1$ reaction could also be achieved (45%) by

reaction of the enolate **165** with Na/K. A nickel(0)-catalyzed reaction of **165** provided **154** in 30% yield presumably by oxidative addition of the aryl halide to Ni(O) and nucleophilic substitution of iodide by a carbanion producing a σ-aryl-nickel(II) intermediate **168**, that undergoes reductive elimination of **154** to regenerate the Ni(0) catalyst.



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