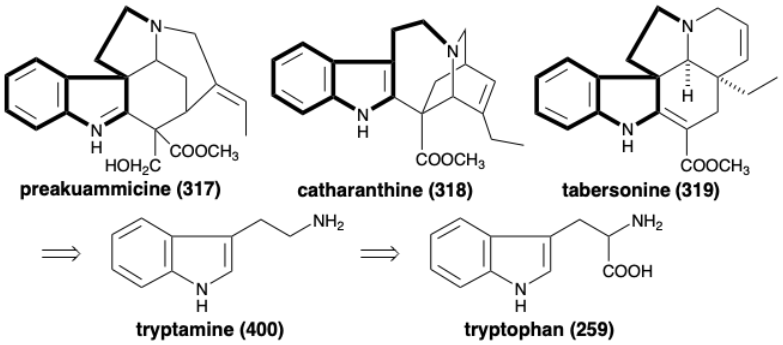
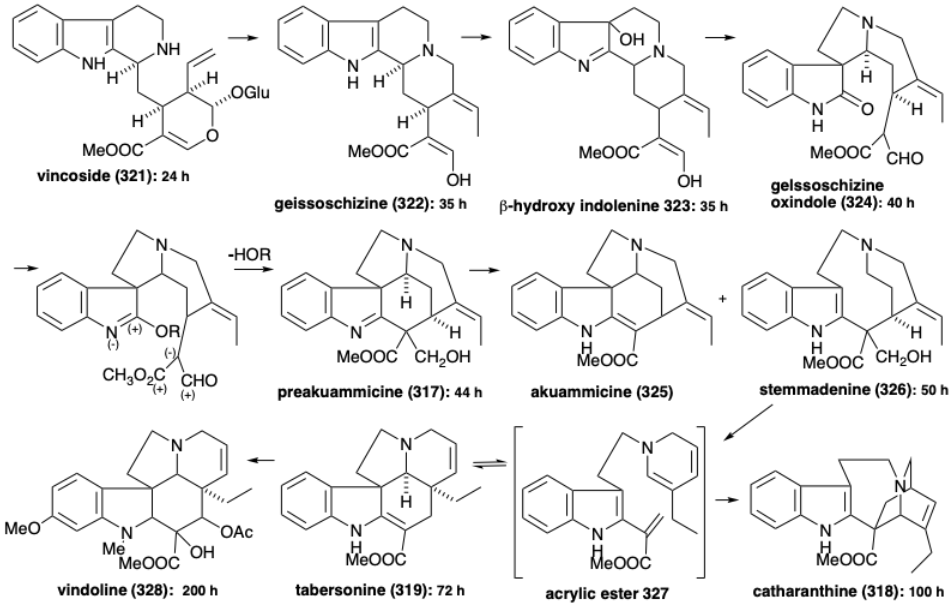
# 6.5: Quinine

## Biosynthesis of Alkaloids from Secologanin

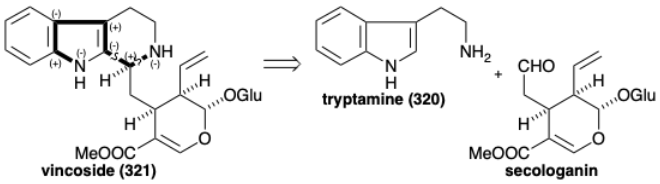
A comparison of the structures of polycyclic alkaloids with a variety of topologically different skeletons, such as preakuammicine (**317**), catharanthine (**318**), and tabersonine (**319**), suggests a biosynthetic strategy which assembles these heteromulticycles by the union of an aminoethyl indole starting material **400** with ten additional skeletal carbons. The aminoethyl indole, tryptamine (**400**), is reasonably derived from decarboxylation of the amino acid L-tryptophan (**259**) by a process analogous to the decarboxylation of tyrosine (**7**) discussed in section 6.4.



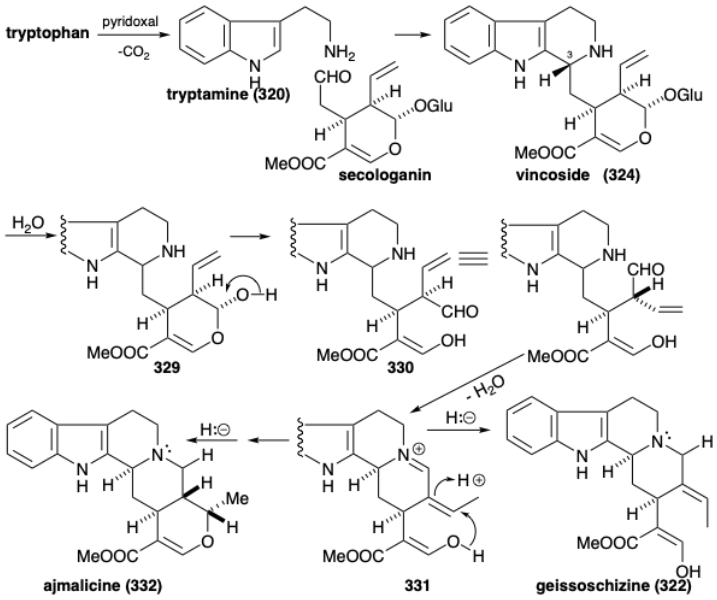

The origin of the remaining ten skeletal carbons is less obvious. The remarkable fact that these remaining carbons have a *common* origin is nicely illustrated by studies on the time evolution of alkaloid production in germinating seedlings of Vinca Rosea.[16] Thus, the alkaloids **317** - **326**, and **328** are all isolable from this plant while **327** is a putative common intermediate for the generation of **318** and **319** by two different $2\pi + 4\pi$ cycloadditions.



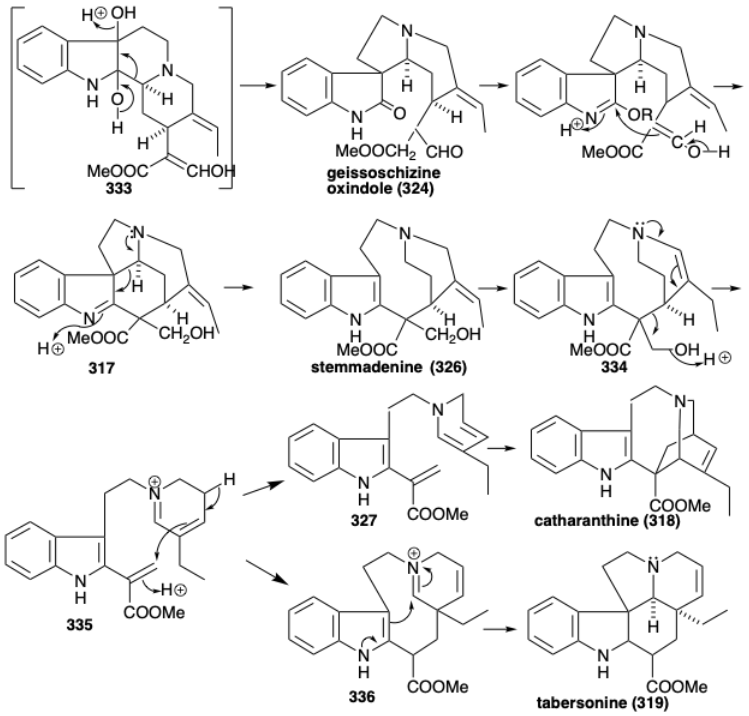

In the early intermediate vincoside (**321**), there is a consonant circuit that connects the two nitrogens. Two polar disconnections in this circuit reveal an aldehyde precursor that bears little resemblence to a monoterpene besides its ten skeletal carbon atoms. Nevertheless, this aldehyde is secologanin whose terpenoid origin was discussed in chapter 4 (see section 4.4).



The biosynthesis of over 1,000 **indole alkaloids** from tryptophan (**259**) begins with a Mannich reaction between tryptamine (**320**) and secologanin to produce vincoside (**321**). Hydrolysis of the glucoside **321** and deketalization of the resulting hemiketal **329** affords amino-aldehyde **330**. Cyclization of the latter gives an iminium derivative **331**. Intramolecular Michael addition of an oxygen nucleophile followed by reduction affords another isolable product, ajmalicine (**332**). Alternatively, reduction of **331** affords **322**.

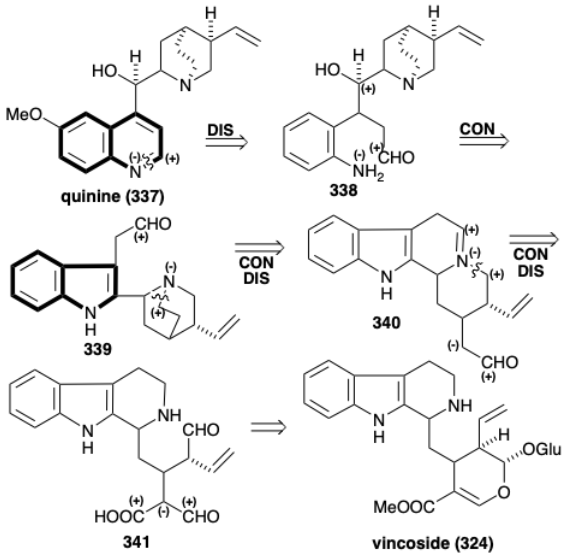



Generation of the other skeletal types from **322** involves rearrangements that are enabled by oxidative introduction of a vicinal diol array to produce **333**. This vicinal hydroxylation is accomplished by a stepwise process through the hydration of an isolable intermediate, the β-hydroxyindolenine **323**. A pinacol rearrangement of **333** produces **324**. Conversion to an imino ester would endow **324** with the reactivity required to form preakuammicine (**317**) by cyclization and reduction. Retero-aldol-like fragmentation of **317** followed by the reduction of the resulting immine affords stemmadenine (**326**). A second fragmentation of the enamine isomer **334** of **326** apparently produces an acrylic ester intermediate **335**. The dienamine tautomer **327** of **335** provides the iboga alkaloid skeleton of catharanthine (**318**) by an intramolecular Diels-Alder reaction (not necessarily concerted). Alternatively, the aspidosperma alkaloid skeleton of tabersonine (**319**) arises from the acrylic ester **335** via polyene cyclization to **336** and subsequent aldol-like cyclization of the latter followed by proton loss to afford tabersonine **(319)**.

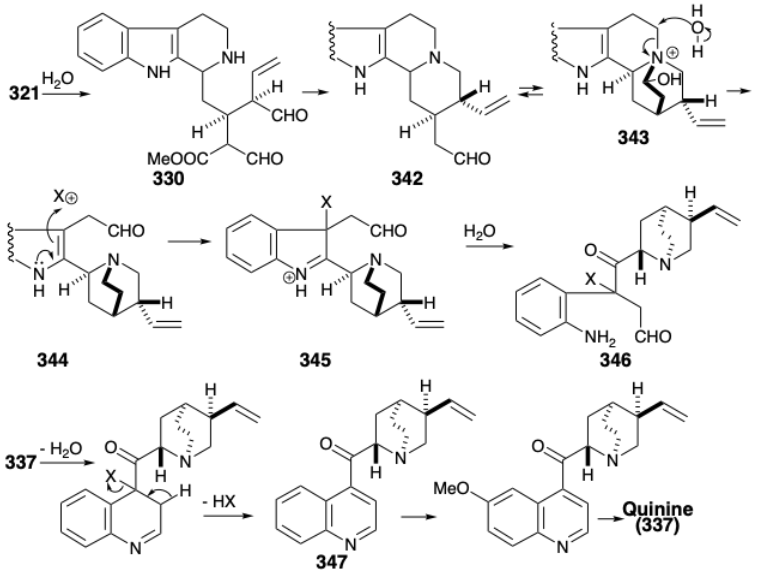



## Biosynthesis of Quinine

Even more cryptic is the biosynthesis of several alkaloids containing the quinoline heterocyclic ring system such as quinine (**337**). The surprising fact that the carbon skeletons of these alkaloids are also derived from tryptophan and secologanin further illustrates the lengths to which Nature must go to achieve the biosynthesis of some natural products owing to a limited inventory of available starting materials. It is an instructive exercise to infer the biosynthetic pathway by retrosynthetic analysis. Given the boundary condition of an indole precursor, the pyridine ring of the quinoline ring system in **337** must be generated. This might be accomplished by dehydrogenation of the imine produced from an amino aldehyde precursor **338**. The alcohol functionality in **338** could be the residue of electrophilic activating functionality in a precursor that was involved in a connection with the nucleophilic amino group in a pyrrole ring, as in the tryptophan **339**. Referring to the boundary condition of tryptophan as the biosynthetic starting material, the aldehyde in the precursor **339** could be generated by hydrolytic cleavage of an imine derivative **340** of the ethylamine sidechain of tryptamine. A concomitant disconnection of one bond to the tertiary amino group in **339** is required to make room for the connection. Referring to the boundary condition of vincoside as starting material, **340** could arise from acarboxy dialdehyde **341** by polar decarboxylation and heterocyclization.

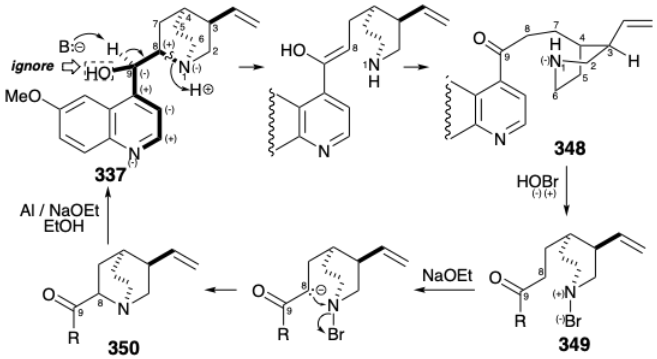


The biosynthesis of the quinuclidine portion of quinine (**337**) from the secologanin portion of vincoside (**321**) involves hydrolysis of the glucoside to give a dialdehyde **330**, followed by intramolecular reductive alkylation and decarbomethyoxylation to give **342**, that is in equilibirum with a hemiaminal **343**. Hydrolytic fragmentation of the latter accompanied by oxidation of a primary alcohol to an aldehyde and reduction of the hemiaminal to an amine affords **344**. The rearrangement of the indole portion of **344** to a quinoline skeleton is initiated by an oxidation to **345** followed by ring cleaving hydrolysis and recyclization of the resulting amino aldehyde **346**. Arene oxidation, methylation, and then reduction of the resulting quinoline derivative **347** delivers quinine (**337**).




## A Relay Synthesis of Quinine

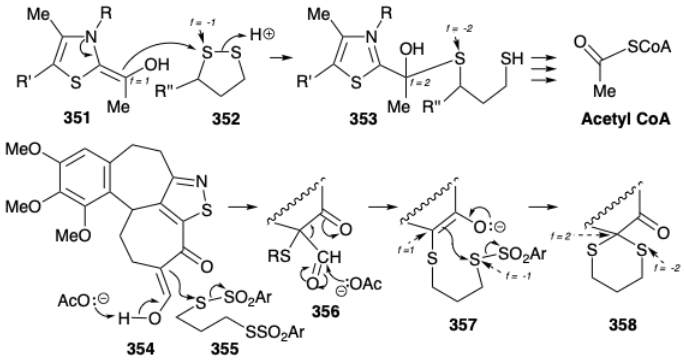
A major topological simplification of the quinine skeleton arises by disconnection of a bond between atoms 1 and 8. Atom 1 is a common atom of the multicyclic quinuclidine portion of **337**. Though atom 8 is a noncommon atom, its role as a link between the two major portions of **337** recommends removal of skeletal connections to this atom. This disconnection was actually achieved by Rabe during degradative studies on the structure of **337**.[17] The fragmentation of **337** to **348** depends upon the polar activation provided by the quinoline and quinuclidine amino groups (ignoring the activation provided by the C-8 hydroxyl).




## Polar Redox Reactions

Rabe also demonstrated that the reverse process, a synthesis of **331** from **347**, can be achieved by exploiting the polar activation of C-8 in **347** (quinine numbering).[17] This approach requires a *nitrogen electrophile* and involves oxidation via polar intermediates. Thus, the nucleophilic secondary amino group in **348** is converted into an electrophile in **349** by appending a more electronegative atom, i.e. bromine. This constitutes oxidation of the amino group. Electrophilic attack on carbon in **349** to give **350** produces a bond between carbon and a more electronegative atom (i.e. nitrogen). This constitutes oxidation of carbon coupled with reduction of the amino group. We shall refer to such reactions as **polar redox reactions**. An example of this reaction type occurs in the biosynthesis of acetyl CoA (see section 2.3) during nucleophilic attack by hydroxyethylidene TPP (**351**) on the the disulfide **352**. Thus, the nucleophilic carbon is oxidized from *f* = 1 in **351** to *f* = 2 in **353** while a sulfur atom in **352** is reduced from *f* = -1 to f = -2

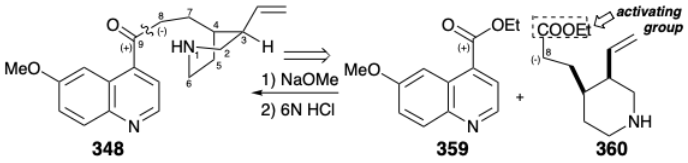
in **353**. This reaction is complex because another carbon in **351** is concurrently oxidized from *f* = 2 to *f* = 3 in **353** in conjunction with reduction of the second sulfur in **352** from *f* = -1 to *f* = -2 in **353**.



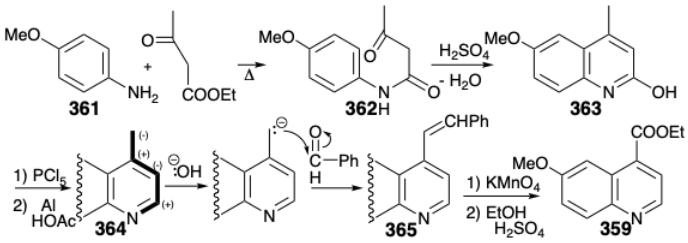
Another polar redox reaction, again with sulfur as electrophile, was encountered in the Woodward synthesis of colchicine (see section 6.1). In fact, the introduction of a dithioketal at the nucleophilic carbon α to a cabonyl group involves two successive oxidations of the α carbon, first of **354** to **356** then of the latter into **358**, coupled with two reductions of sulfur, first in the conversion of **355** to **356** then in the conversion of the latter, via **357**, into **358**. This reaction is also complex because another carbon in **354**, α to the enolic hydroxyl, is concurrently oxidized from *f* = 1 to *f* = 2 in **356** in conjunction with reduction of a second sulfur in **355**, and a second carbon is oxidized from *f* = -1 in **357** to *f* = -2 in **358** (the carbonyl carbon) in conjunction with reduction of a second sulfur.

## A Convergent Strategy for Key Intermediate 348

It should be noted that **350** (see above) is a mixture of epimers at C-8, and the reduction that produces **337** introduces another asymmetric center (at C-9). Fortunately, **337** was a major component of the isomeric mixture produced by this nonstereocontrolled conversion of **348** to **337**. This conversion makes quinotoxine (**348**) an attractive subtarget for the total synthesis of quinine (**337**). The subtarget **348** is further simplified by a dislocation, that breaks the molecule into two large fragments by severing one of the four bonds connecting the quinoline and piperidine rings. The dislocation chosen by Woodward and Doering for the first *total* synthesis of quinine (**337**) was dictated by the fact that the reverse process, synthesis of **348** from **359** and **360**, had excellent precedent. A dihydro derivative of **348** (with an ethyl instead of a vinyl group) was prepared by Rabe from **359** and a dihydro derivative of **360** which had been obtained from degradation of natural quinine (**337**).

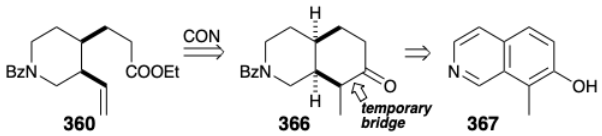


Total syntheses of the subtarget ethyl quininate (**359**) were also known when the total synthesis of **337** was undertaken. A particularly effective route introduces the carboxyl group in latent form as a benzylic methyl group, and constructs the nitrogen heterocycle on a preformed aromatic precursor **361** by polar reactions. Cyclodehydration of **362** affords **363**, that is reduced to **364**. Benzylic oxidation of **364** is achieved by oxidative cleavage of a latent carboxylic acid, a C=C bond in the precursor **365**, that is available by a polar condensation of **364** with benzaldehyde. The condensation exploits the nucleophilic activation of the benzylic methyl, that is provided by the nitrogen in **364**.

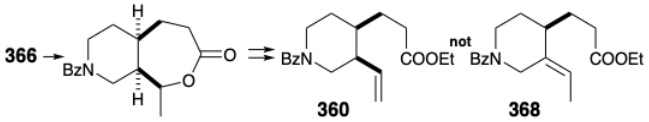


The only remaining synthetic objective was, thus, ethyl N-benzoylhomomeroquininate (**360**). The two side chains in **360** could be generated stereospecifically cis by oxidative cleavage of a temporary bridge in **366**. The cis ring fusion in **366** could be produced,

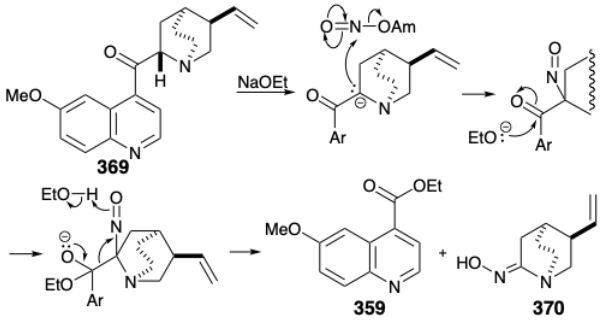
in turn, by catalytic hydrogenation of an aromatic isoquinoline precursor **367**.



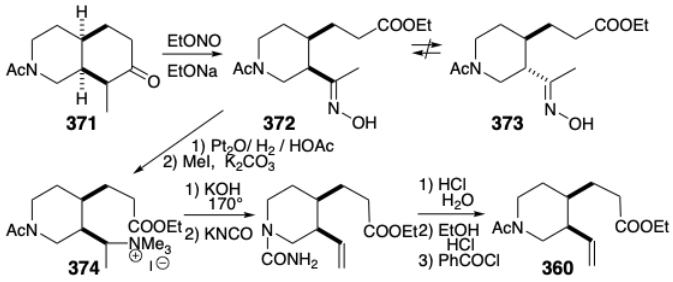

Several potential flaws must be avoided in designing a detailed scheme for the **366** to **360** conversion. For example, cleavage of the temporary bridge in **366** by a Baeyer-Villiger oxidation followed by an elimination to generate the vinyl group in **360** must avoid generating the alternative, thermodynamically favored, ethylidene derivative **368**.




Interestingly, the reaction chosen to achieve the ring cleavage was a reaction used earlier in degradation studies for determining the structure of quinine. Thus, Rabe effected cleavage of quininone (**369**) into ethylquininate (**359**) and an oximino compound **370** by treatment with amyl nitrate and sodium ethoxide. This cleavage is analogous to a retro-Claisen reaction, that occurs especially readily for nonenolizable β-keto esters.

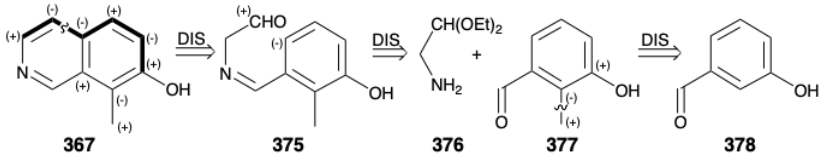



Application of this cleavage process to the N-acetyl analogue **371** of **366** generates oxime **372**. A potential flaw, epimerization of the cis-1,2-disubstituted product **372** into the thermodynamically more stable trans isomer **373**, was not a problem. In contrast to what would be expected for the corresponding acetyl derivative, the oxime **372** is not prone toward epimerization. Thus, the hydroxyl proton rather than an α-proton is preferentially abstracted upon treatment of oximes with base. Reduction and methylation of **372** readily affords a quaternary ammonium derivative **374**, that affords the requisite terminal vinyl group in **360** by base promoted Hofmann elimination involving regioselective abstraction of hydrogen from the less substituted β carbon.




As noted above, an aromatic precursor **367** was chosen for the synthesis of ethyl N- benzoylhomomeroquininate (**360**). A monocyclic aromatic precursor for **367** could be either a pyridine derivative or a benzene derivative. Choosing the latter allows exploitation of electrophilic aromatic substitution on an electron-rich precursor to accomplish annelation of the pyridine ring. This annelation requires carbon-carbon bonds meta and para to the hydroxyl group. Formation of the para bond by electrophilic aromatic substitution is favored over meta by the strong electron donating activating effect of the hydroxyl group. Formation of this para carbon-carbon bond in the last step of annelation suggests a phenolic precursor **375** with the four atoms of the incipient pyridine ring appended to the meta position. The bond between this meta substituent and the phenol ring can not be generated by electrophilic aromatic subsitution because ortho and para rather than meta substitution is favored. However, disconnection of this substituent by removal of the bond between nitrogen and the benzylic carbon suggests a dissonant carbonyl-masked amino acetaldehyde **376** and a benzaldehyde derivative **377**. The methyl substituent in **377** might also be introduced by electrophilic

aromatic substitution on the readily available m-hydroxy-benzaldehyde (**378**). However, achieving the requisite regiocontrol in such an alkylation might be difficult.




In fact, a different order of steps was adopted. Introduction of the ortho methyl substituent was postponed until after annelation of the pyridine ring was completed because introduction of a methyl group can be readily achieved regioselectively by electrophilic aromatic substitution on the β-hydroxy isoquinoline **379**. Thus, aminomethylation with piperidine and formaldehyde produced the benzylic amine **380** that was reduced to **367** upon heating in the presence of sodium methoxide. This unusual reduction involves hydride transfer from methoxide. Technical difficulties arose in the hydrogenation of **367** to **371**. Thus, because the amine poisoned the catalyst, the hydrogenation stopped after only the nitrogen containing ring had been reduced. The amine had to be blocked as an amide before reduction of the benzene ring could be achieved. The desired cis-stereospecificity in the reduction of **381** to **371** could not be achieved. Fortunately, however, this was not a fatal flaw because the required isomer could be isolated from the trans-fused hydrogenation reaction product **383**. Thus, catalytic hydrogenation is not entirely reliable for stereoselective delivery hydrogen to one face of an aromatic ring.