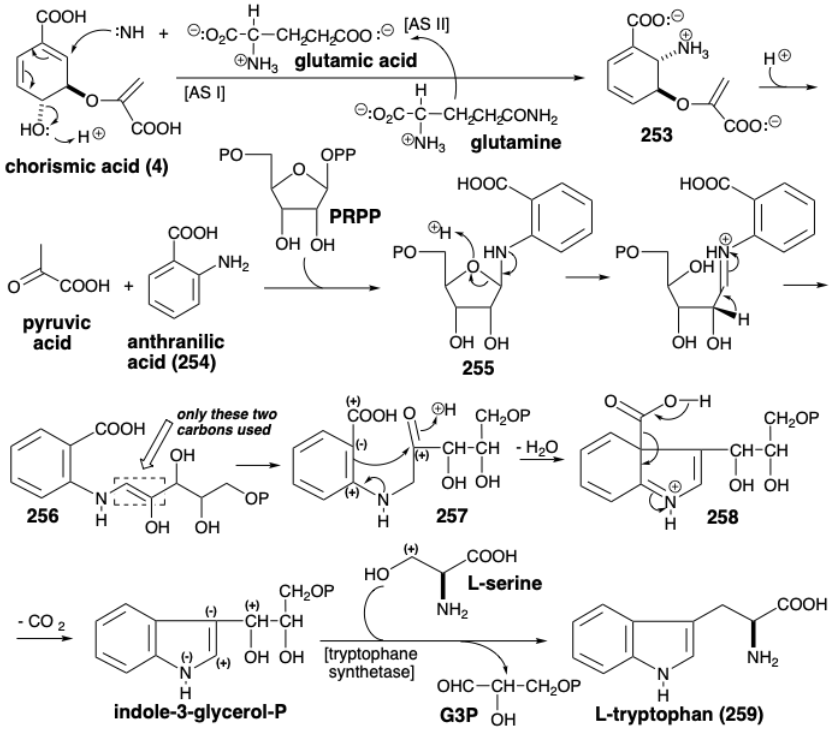
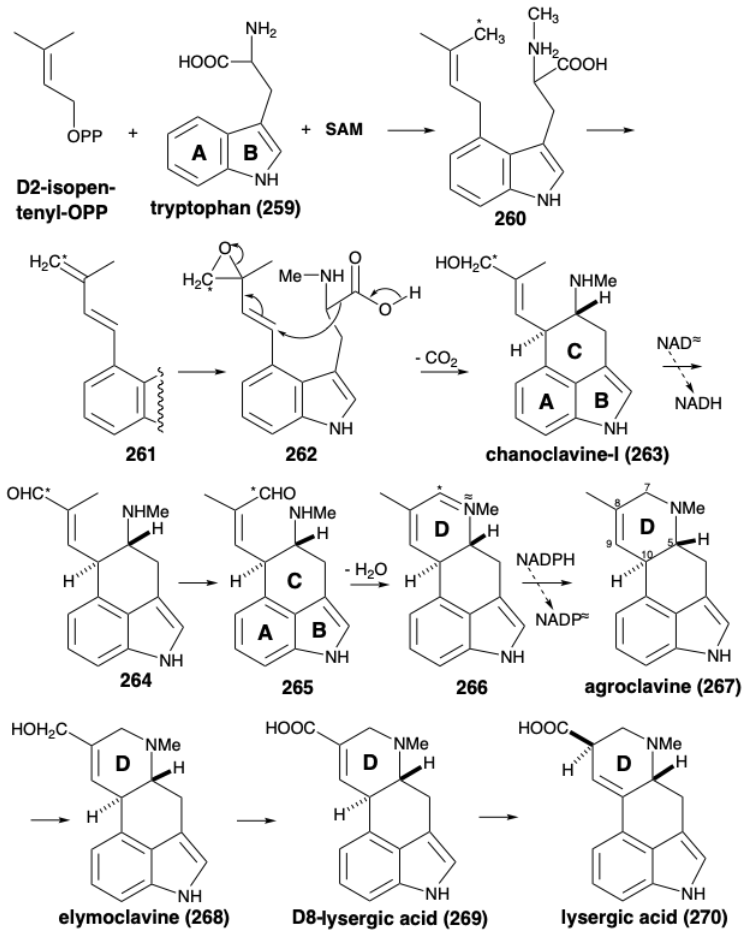
# 6.4: Lysergic Acid

## Biosynthesis of Tryptophan and Lysergic Acid

The carbon skeleton of anthranilic acid (**254**) is constructed in nature from two molecules of phosphoenol pyruvate and one of erythrose 4-phosphate via chorismic acid (see section 5.1). The two-component enzyme complex of *anthranilate synthetase* (AS) then promotes the transfer of $NH_3$ from glutamine to chorismic acid (**4**) affording amino acid **253** by conjugate displacement of a hydroxyl group. During the strategically intricate biosynthesis of tryptophan (**259**), the carboxyl carbon of **254** is ultimately lost. A five-carbon unit from ribose is appended to the amino group of **254**, but suprisingly all five carbons of phosphoribosyl pyrophosphate (PRPP) are not retained to complete the tryptophan skeleton (*vide infra*). Deprotonation of the imine derived from **255** delivers an enamine **256** that is also the enol tautomer of ketone **257**. Intramolecular Friedel-Crafts cyclization of the latter delivers a β-iminocarboxylic acid **258** that, being the nitrogen analogue of a β-keto acid, readily decarboxylates producing indole-3-glycerol phosphate. While the biosynthesis of tryptophan might be completed by simple functionality adjustments, Nature adopts a different, more convoluted, strategy. Thus, *tryptophan synthetase* catalyzes a remarkable Friedel-Crafts alkylation with L-serine coupled with a dealkylation that cleaves glyceraldehyde-3-phosphate (G3P) and delivers L-tryptophan (**259**).

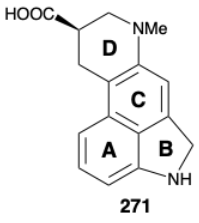



So far, we have seen that complex alkaloids may be assembled in Nature by a convergent strategy involving the union of two large fragments derived from aromatic amino acids. Alkaloids may also be constructed in Nature by the conjugation of amino acid-derived intermediates with terpenoid starting materials. Thus, as outlined below, lysergic acid (**270**) is forged from tryptophan (**259**) and $\Delta^2$-isopentenyl pyrophosphate. Later, we shall see how indole **259** is united in a variety of ways with secologanin, a terpene, to generate a vast array of structurally complex tryptophan-derived alkaloids. The carbons of these starting materials remain connected in the product, although the carboxyl carbon is lost. Thus, the biosynthetic strategy is simple.

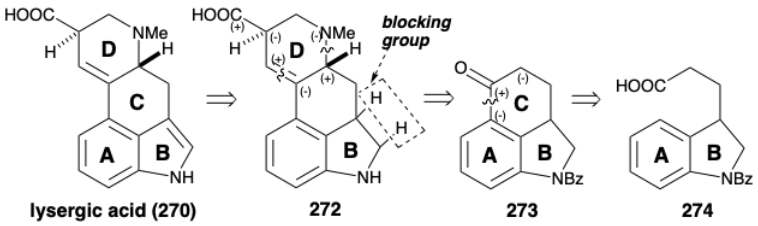



The biosynthesis of lysergic acid commences with the prenylation of tryptophan. Thus, $\Delta^2$-isopentenyl pyrophosphate is a potent electrophile that readily alkylates the nucleophilic benzene ring of tryptophan **259** to afford 4-prenyltryptophan (**260**). The cyclization of **260** to lysergic acid requires addition of functionality to the $\Delta^2$-isopentenyl (prenyl) group by oxidations. The process is accompanied by a remarkable odyssey of the allylic carbon marked with an asterisk in the intermediates **260** - **265**. Allylic hydroxylation and dehydration provide **261.** The diene **261** has free rotation, that allows interconversion of the E and Z-methyl carbons during the **260** to **263** conversion. Formation of the D-ring is believed to occur by a decarboxylative $S_N2'$ alkylation in the allylic epoxide **262**. Oxidation of the cyclization product, chanoclavine-I (**263**), to an E allylic aldehyde **264** is followed by *cis-trans* isomerization to the Z-isomer **265**. Condensation to the Schiff base **266** completes the lysergic acid skeleton. Final adjustment of functionality by reduction to agroclavine (**267**), allylic oxidation to elymoclavine (**268**), further oxidation to $\Delta^8$-lysergic acid (**269**), and isomerization gives lysergic acid (**270**).

## Dihydrogen as a Masking Group for an Alkene

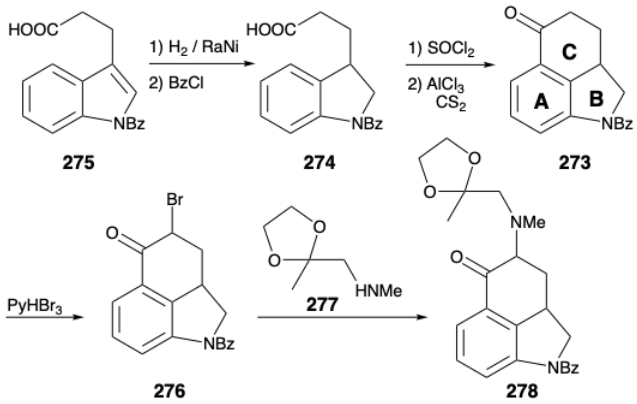



Lysergic acid is thermodynamically unstable. Acids, base, or noble metals readily catalyze the irreversible rearrangement of lysergic acid (**270**) into a naphthalene isomer **271** by migration of a D-ring and a B-ring C=C bond into the C ring. Therefore, the stability of aromatic derivatives, that may often be advantageously exploited in complex molecular synthesis, was seen by Woodward as a major obstacle for the synthesis of lysergic acid (**270**). A central tactic in the first successful synthetic strategy,[13] was the scrupulous avoidance of aromaticity in ring C. On the other hand, the crucial last step of the scheme, dehydrogenation of an indoline **272**, ingeniously exploits the aromaticity of the indole array in **270**. What is remarkable about this strategy is Woodward's recognition that, although it might seem unlikely that a way could be found to dehydrogenate **272** without also inducing isomerization of **270** to **271**, the search for a method to achieve such a selective reaction could provide an excellent solution to the central challenge of the synthesis, and, therefore, was well worth the effort.

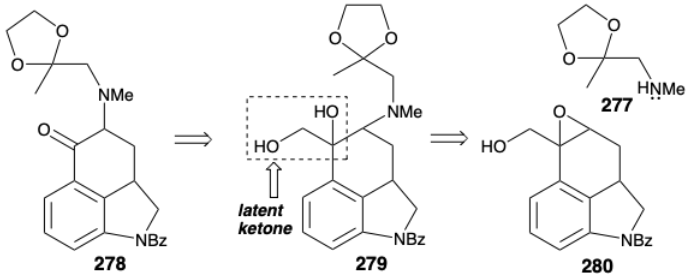



The Woodward strategy was channeled by the decision to use an intramolecular Friedel-Crafts acylation of the electron-rich A ring in **274** to generate the C ring in **273**. This approach is recommended by the ready availability of **274** as starting material, and by the potential utility of the carbonyl group in **273** to activate bond forming reactions required to add the D ring. However, construction of **272** from **273** can be achieved by polar reactions only if polar reactivity inversions are employed, because the polar reactivity patterns of **272** and **273** are opposed.

The ABC-ring intermediate **273** is readily available from **275** by selective catalytic hydrogenation followed by intramolecular Friedel-Crafts acylation of **274**. The carbonyl group in **273** provides activation at the adjacent methylene position that may be exploited for the attachment of the requisite nitrogen atom. However, an amino group is a nucleophile. To allow polar C-N bond formation, the potential nucleophilic reactivity of the methylene α to a ketone carbonyl must be inverted. This was achieved by bromination to afford **276** in excellent yield. An early attempt at alkylation of the amine **277** with **276** was unsuccessful. After exploring a very large number of alternative approaches for annelation of the D ring and developing an eleven stage sequence for preparing **278** from **273**, it was discovered that a nonpolar solvent was uniquely effective for the alkylation of **277** with **276**. Under these reaction conditions, the ketone ketal **278** was produced in excellent yield. This scenario is a poignant epitome of the vicissitudes of organic synthesis. It serves to underscore a caveat mentioned earlier (see section 1.2) that is worth repeating: *as the availability of starting materials or methods (new or more effective) for uniting and manipulating them vary, so will the relative merits of different pathways. A poor synthesis can become the method of choice if a way to improve a bad step can be discovered.*

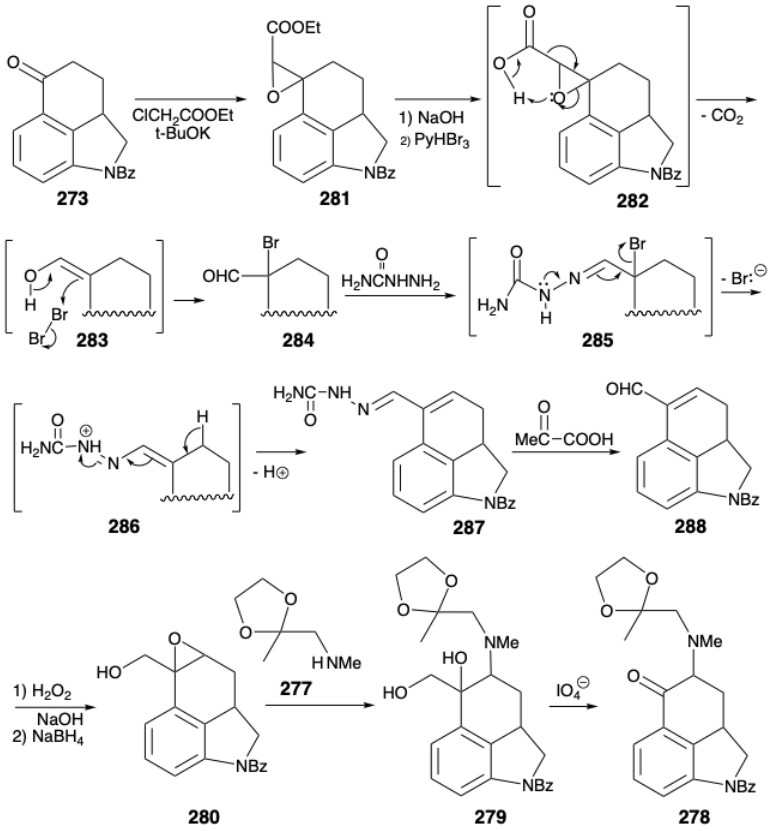



It is instructive to examine the alternative strategy for the synthesis of **278** from **273**, and to keep in mind that this alternative sequence was one of a great many that were painstakingly explored. The alternative route involves a strategy analogous to the **276** → **278** conversion, except that the carbonyl group of **276** and **278** is present in latent form as a vicinal diol in the corresponding key intermediates **280** and **279** respectively. Thus, the carbonyl is generated in the last step of the synthesis by oxidative cleavage.

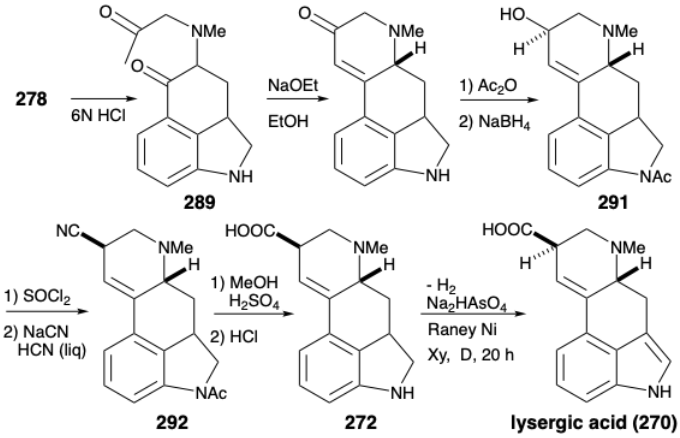



The synthesis of **279** involves a novel sequence in which the enol **283** from decarboxylation of the glycidic acid **282** is intercepted by bromine ($Br_2$ is in equilibrium with $Br_3^-$) delivering α-bromoaldehyde **284** from the Darzens condensation product **281**.

Dehydrohalogenation of the α-bromoaldehyde **284** was effected by the mild Mattox-Kendall procedure via semicarbazone **285** and unsaturated semicarbazone **287**, that afforded the unsaturated aldehyde **288** by transfer of the semicarbazide residue to pyruvic acid. Nucleophilic epoxidation delivered the key intermediate **280**. The latent carbonyl in **279** was deblocked by oxidative cleavage with periodate. This cumbersome route to **278** was abandoned when *conditions* for achieving the direct preparation of **278** from the bromoketone **276** were discovered.



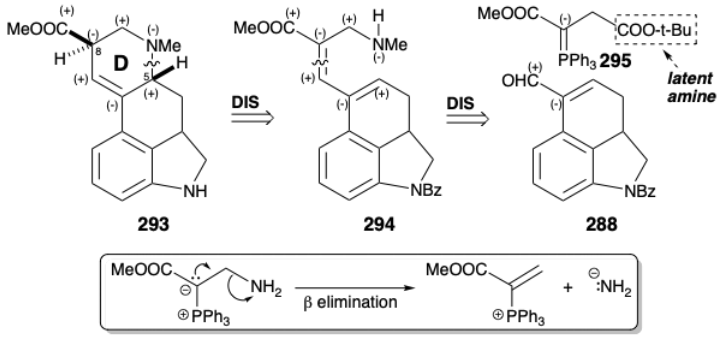

Completion of ring D was straightforward via intramolecular aldol condensation of the diketone **289**. The carbonyl group in the resulting enone **290** then provided reactive functionality in an alcohol **291** and the derived chloride for attachment of cyanide (a carboxy carbanion equivalent) as the final carbon atom of lysergic acid. After hydrolysis of **292** to **272**, the *two hydrogen atoms*, placed at the outset by design at C-5 and C-5a to *mask a rearrangement-prone C=C bond*, needed only to be removed to afford lysergic acid (**270**).



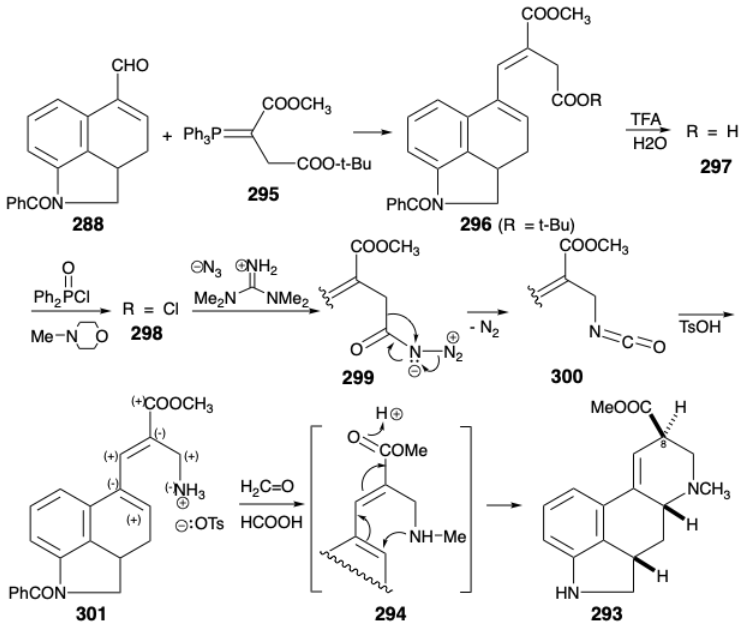

## A Polar D Ring Annelation Exploiting Target-related Functionality

The D-ring ester and amino functionality provide entirely consonant polar reactivity patterns in the derivative **293** of Woodward's carboxylic acid intermediate **272**. An alternative strategy[14] for annelation of the D-ring of lysergic acid exploits the polar activation

provided by these functional groups that suggests a dislocation to **294**. Dislocation of **294** to the aldehyde **288**, prepared previously by Woodward, suggests an ylide precursor **295** in which a t-butyl ester serves as a latent amine. A more direct approach using an α-amino ylide seemed inadvisable in view of a possible β-elimination.

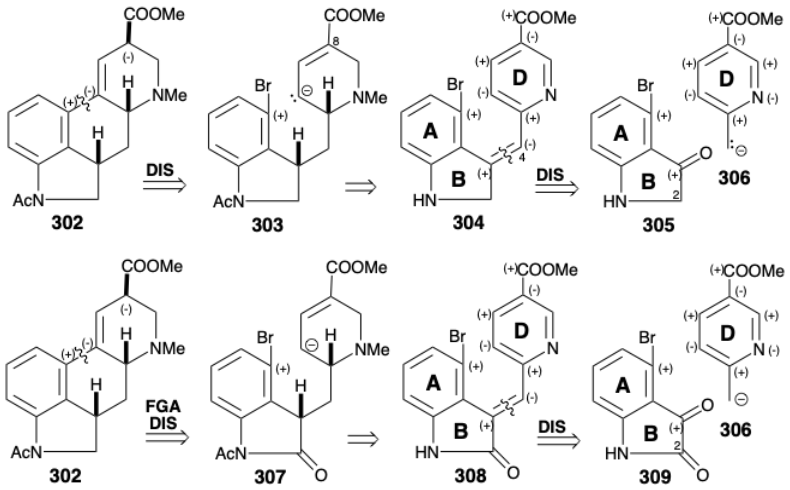



Introduction of the amino substituent was initiated by selective hydrolysis of the t-butyl ester in **296** under acidic conditions. The carboxylic acid **297** was then transformed into the corresponding chain shortened primary amine **301** in 80% yield by a Curtius degradation. Cyclization, i.e. of **294**, accompanied the reductive amination of formaldehyde with primary amine **301** to afford a 3:1 mixture of the desired ester **293** and its C-8 epimer.




## C-Ring Annulation by Nucleophilic Aromatic Substitution

Another synthesis of the key ester intermediate **302** involves annelation of ring C in a preformed ABD-ring precursor by intramolecular nucleophilic substitution with a carbanion **303** that is conjugated with the carboxyl functionality found at position 8 in the target.[15] The same carboxyl also provides nucleophilic activation at position 4. Thus, polar analysis of **304** suggests a polar dislocation to two aromatic starting materials that can be joined by an aldol condensation between ketone **305** and carbanion **306**. However, this strategy is fatally flawed owing to a preference for ketone **305** to exist as an enol. The addition of another carbonyl group at position 2, as in **309**, precludes enolization (blocking group), enhances the electrophilicity of the ketone carbonyl, in **309**, and activates the C=C bond in **308** toward dissolving metal reduction.




Actually, generation of an isomer of **309**, i.e. **310** with the bromo group para to nitrogen, is favored during a synthesis by electrophilic aromatic substitution owing to the powerful activating influence of the nitrogen substituent. However, this is not a flaw because a mecahanism exists for nucleophilic aromatic substitution with rearrangement. Thus, elimination of the nucleofuge leads to a benzyne intermediate **315** to which the nucleophile then adds regioselectively at the required position to give **316**. Having served its roles as a *reactivity* control element, the carbonyl group in **311** is then selectively removed by reduction with diborane. The pyridine ring of the product **312** is activated toward hydride reduction by N-methylation after acetylation of the indole nitrogen. Unfortunately, hydride reduction of the D-ring in **313** produces two epimers only one of which, i.e. **314**, cyclizes upon treatment with base delivering **302** in only 15% yield.