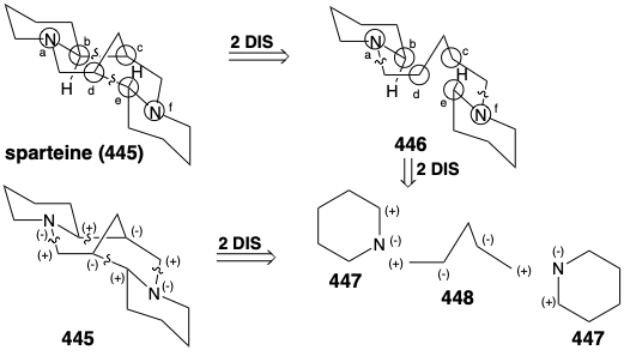
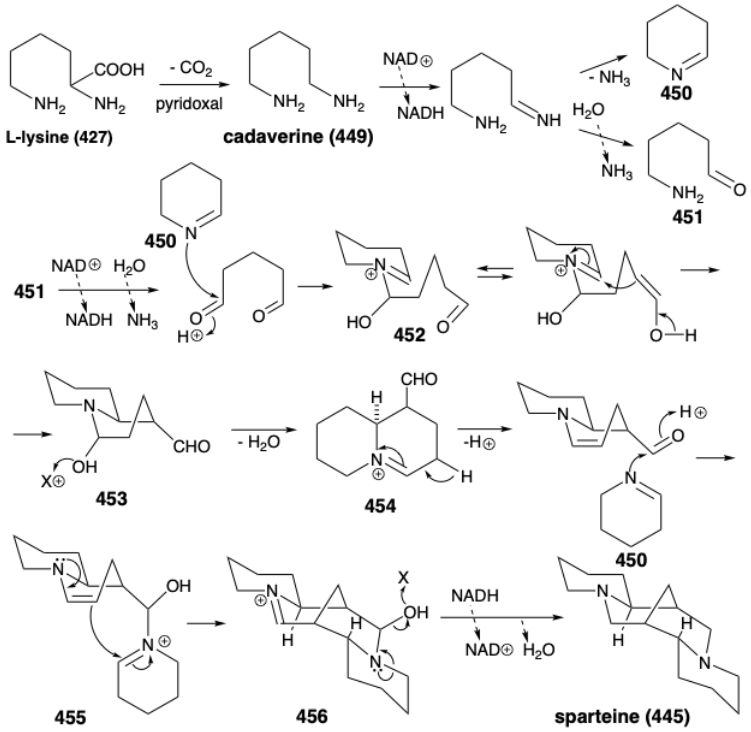
6.7: Lycopodine

Biosynthesis of Alkaloids from L-Lysine

A variety of topolgically complex saturated nitrogen heterocycles are constructed in nature from simple acyclic precursors. The incisive logic of these biosyntheses is especially striking when viewed either from a topological or a polar reactivity standpoint. For example, the *efficiency* with which the intricate multicyclic skeleton of sparteine (**445**) is assembled, exclusively from three molecules of a symmetrical synthon, is remarkable. Topological analysis of **445** reveals the presence of six common atoms a-f. Cleavage of two bonds between two pairs of common atoms, b-c and d-e, simplifies the topology to two piperidine rings joined by a straight chain in **446**. This intermediate is readily derived from two five carbon synthons **447** and **448**. Polar reactivity analysis of **445** reveals that polar reactions, activated by the amino groups in **445** should readily allow its construction from **447** and **448**.



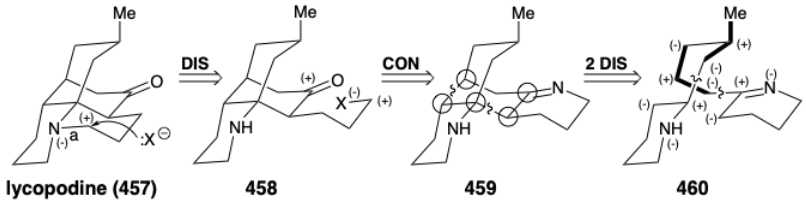
In fact, functionalized synthetic equivalents for both **447** and **448** are prepared in nature from L-lysine (**427**). Thus, pyridoxal catalyzed decarboxylation of **427** produces the symmetrical diamine **449**. Oxidation and hydrolysis of **449** via **451** afford pentanedial, which provides iminium derivative **452** by reaction with **450**. Intramolecular aldol condensation then affords **453**. The iminium derivative **454** from dehydration of **453** yields an iminium derivative **455** by reaction of the corresponding enamine with a second equivalent of the imine **450**. A second intramolecular aldol condensation affords **456**. Dehydration and reduction provides sparteine (**445**).



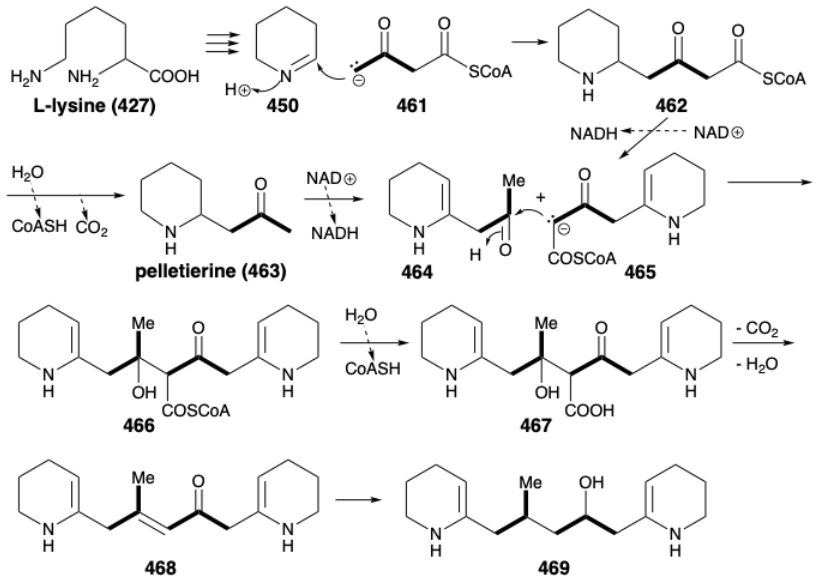
Biosynthesis of Lycopodine

We have seen that many natural products are formed from a single starting material, such as (a) many polyketides, fatty acids, or prostaglandins from acetyl CoA, (b) many alkaloids from shikimic acid, or (c) terpenes from mevalonic acid. However, some natural products are formed by ***mixed biosyntheses*** from combinations of these starting materials. Thus, lysergic acid (see section 6.4) arises from chorismic acid plus the mevalonic acid-derived isopentenyl pyrophosphate plus a sugar, D-ribose. Similarly, indole alkaloids (see section 6.5) arise from chorismic acid plus a mevalonic acid-derived terpene, secologanin, plus a sugar, D-ribose.

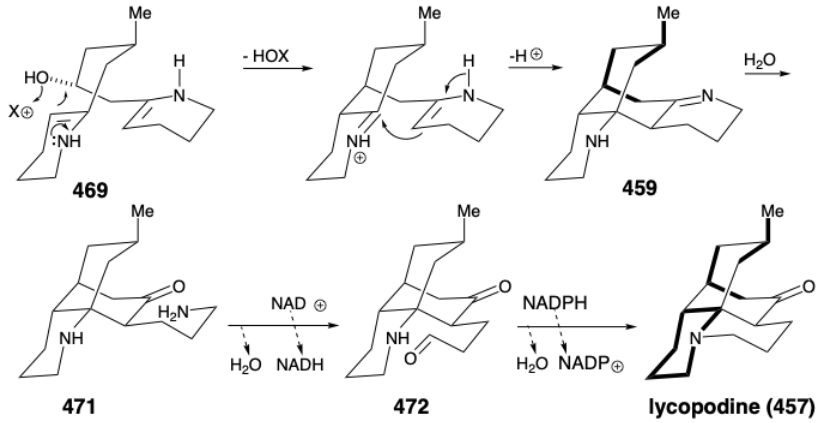
Now we shall see that the bridged multicyclic skeleton of the alkaloid lycopodine (**457**) arises from acetoacetyl CoA plus L-lysine (**427**). As for sparteine above, both topological and polar analysis of the biosynthetic strategy for **457** reveal its incisive logic. The carbonyl group in **457** is generated in nature by solvolytic cleavage of a temporary bridge. In the process, a propyl substituent with electrophilic activation at the end is generated, that is then used to construct the final ring of **457**. Retrosynthetically, this involves disconnection to **458**, followed by reconnection to **459**. A considerable simplification of this subtarget results from disconnection of two bonds between pairs of common atoms in **459** to afford **460**. Polar analysis of **460** reveals that reconnection of these bonds could be achieved by exploiting the polar activation provided by the nitrogen atoms in **460**. Furthermore, **460** could be assembled from two large fragments by a polar reaction forming any of the bonds in the carbon chain connecting the two nitrogen heterocycles.



In nature, the two piperidine rings in **460** are derived from L-lysine (**427**), and the connecting chain is assembled from two three carbon units derived from actetoacetyl CoA (**461**). Aldol condensation of **461** with **450** affords **462**. Note that alkylation of **461** occurs at the less acidic δ carbon. Perhaps this involves an enzyme-bound enamine derivative **470** (see below) of **461**. Oxidation and deprotonation of **462** provides **465**, while **462** also yields pelletierine (**463**) by hydrolysis and decarboxylation. Aldol condensation between **464** and **465** then provides **466**, that is hydrolyzed to **467**. Decarboxylative elimination gives **468**, that is reduced to provide **469**, a synthetic equivalent of the synthon **460** generated in the strategic analysis presented below.

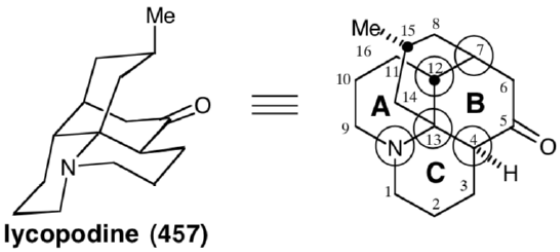


Cyclization of **469** by intramolecular enamine alkylation, followed by intramolecular aldol-like condensation, produces the intermediate **459** suggested in the strategic analysis. Hydrolysis of the imine in **459** generates the carbonyl group required for lycopodine. Oxidation of the resulting propyl amine **471** to an aldehyde **472** followed by intramolecular reductive alkylation then produces lycopodine (**457**) in which one lysine derived piperidine ring is clearly discernable while the two polyketide derived acetonyl units and a five carbon unit from a second molecule of lysine are intricately interwoven.

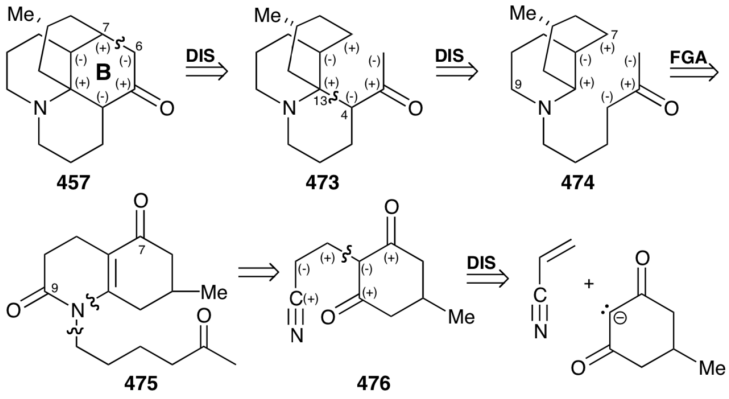


A Fatally Flawed Strategy for Lycopodine Synthesis

We have seen that both topological and polar analysis of the biosynthetic strategy for lycopodine (**457**) illuminate the logic of the process. The two functional groups in **457** can be exploited in a variety of strategies to facilitate construction of the skeletal network using polar reactions. There are five *common atoms* in **457**, four carbon atoms that are all in ring B, and the nitrogen. We will first consider a fatally flawed strategy that only generates an epimer rather than the natural product itself.

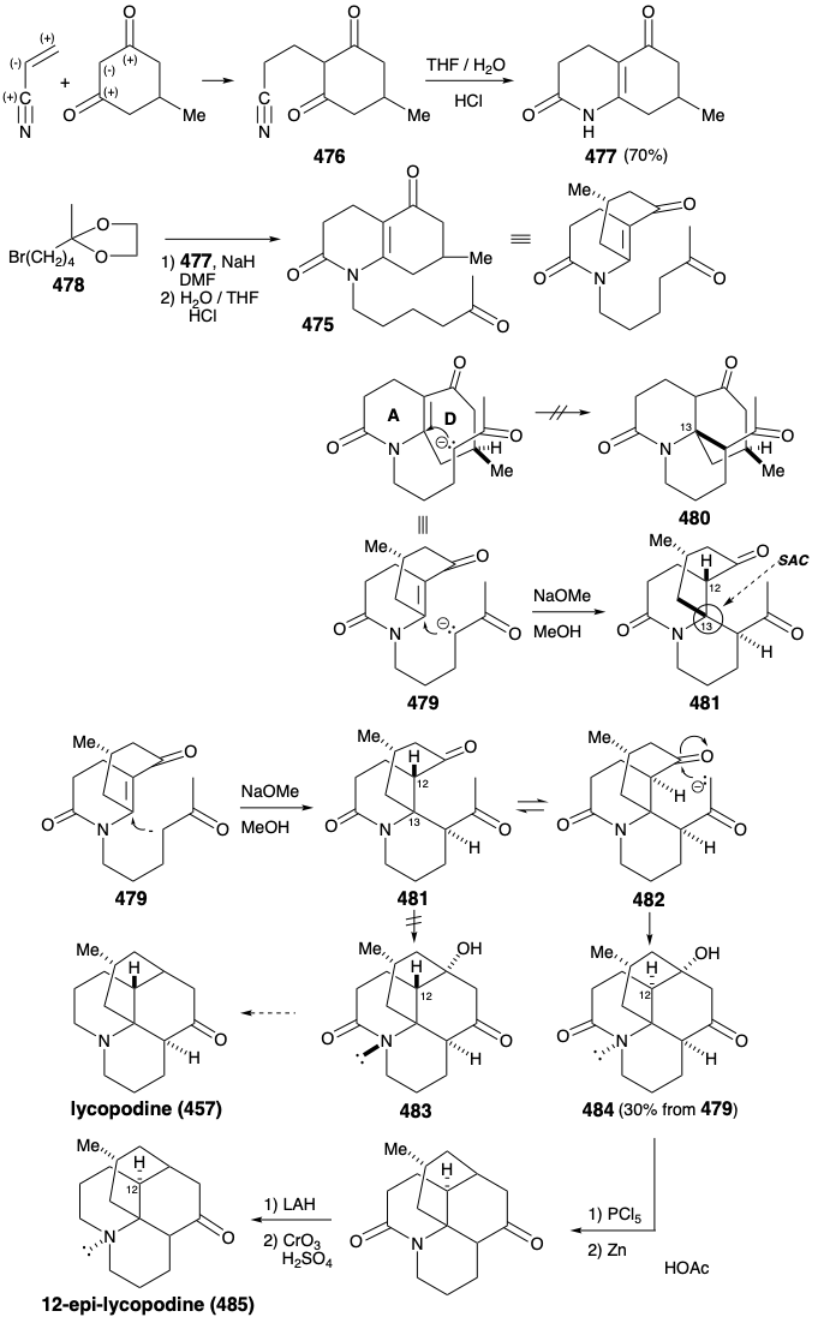


Polar analysis of ring B reveals that polar reactions, exploiting the polar activation afforded by the amino and carbonyl functionalities in **457**, could be used to construct any bond of this ring. In the Wiesner approach to lycopodine,19 the final skeletal bond formed is between common atom 7 and noncommon atom 6, corresponding to the dislocation of **457** to **473**. The penultimate bond formed is that between common atoms 4 and 13, corresponding to the dislocation of **473** to a bicyclic precursor **474**. The elegance of the strategy lies in the plan to accomplish cyclization of the bicyclic intermediate **474** to the tetracyclic skeleton of the target **457** in a single step. The synthetic equivalent **475** of **474** has additional carbonyl groups at the 7 and 9 positions. The former provides additional electrophilic activation at C-7, while the latter deactivates the nucleophilicity of the amino group. The bicyclic intermediate **475** might be available from a symmetrical monocyclic precursor **476**. The incipient amino group of **457**, the nitrile nitrogen in **476**, even provides polar activation for the construction of **476** from acrylonitrile and dihydroresocinal.



In fact, acid-catalyzed hydrolysis of **476** leads directly to the enamide **477** that afforded **475** by N- alkylation with the alkyl bromide **467** and subsequent hydrolytic removal of the masking ketal group. Base-catalyzed intramolecular Michael reaction of **475** could generate two stereoisomers at position 13 which result from addition of the carbanion to either face of the D-ring in **479**.

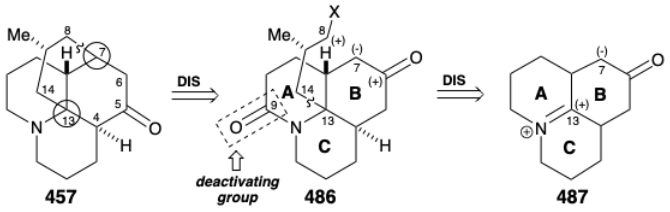
However, as expected, steric approach control fosters stereoselective addition on the side of the D-ring opposite the methyl substituent to afford an intermediate **481** rather than undesired stereoisomer **480**. Nevertheless, the synthesis is fatally flawed because the subsequent aldol reaction gave exclusively **484**, whose skeleton is epimeric with lycopodine at a C12. Thus, C-12 in the intermediate **481** is epimerizable, and the epimer **482** apparently cyclizes in complete preference to **481**. This produces **484** rather than **483**, that is required for the synthesis of lycopodine (**457**) . Reductive removal of the amide carbonyl and tertiary hydroxyl groups from **484** delivered 12-epi-lycopodine (**485**).



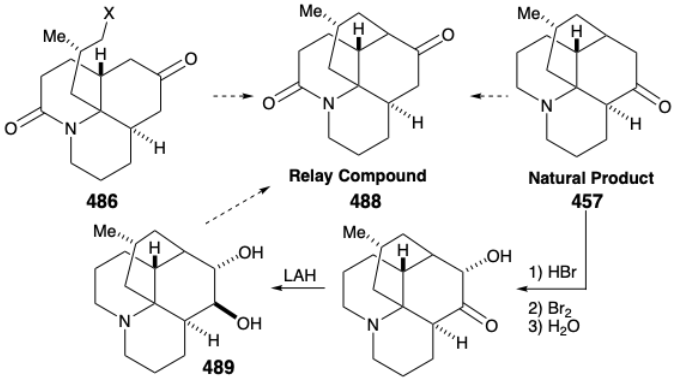
A Relay Strategy and a Symmetrical Precursor for Lycopodine

A second strategy for lycopodine synthesis generates ring D by cyclization of a tricyclic synthon **486** with preformed AB and C rings.[20] This strategy was channeled by the prospect of exploiting a symmetrical fused tricyclic ketone **487** as a starting material. Thus, topological analysis of **457** recommends disconnection of two bonds between a common (circled) and a noncommon atom, the 7-8 and 13-14 bonds, to entirely remove the D-ring. A concomitant transposition of the carbonyl group from C-5 in **457** to C-6 is required to generate a symmetrical precursor **487**. Furthermore, this transposition in **486** allows formation of the 7-8 C-C bond of

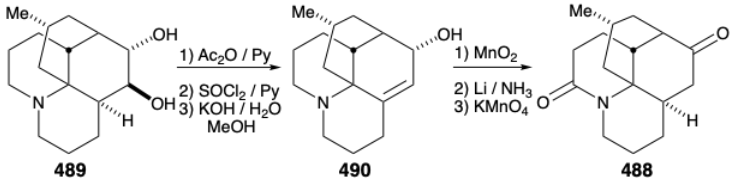
the lycopodine skeleton by an intramolecular alkylation that exploits the polar activation afforded by a carbonyl at position 6. Whereas, the nitrogen in **486** can provide electrophilic activation for C-C bond formation at position 13 in **487**. An amide carbonyl at C-9 in **486** is included as a **deactivating group** to decrease the nucleophilicity of the amino group disfavoring an undesired quaternization that might compete with alkylation of a carbanion nucleophile at C7.



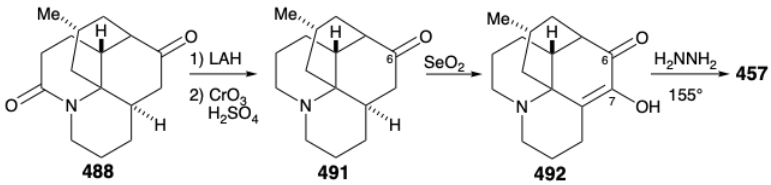
Intramolecular alkylation of the ketone 4**86** would yield **488**. It would be reassuring if the final steps in the synthesis could be worked out with a sample of **488** that might be readily prepared from the natural product **457**, perhaps via the diol **489**, that had already been prepared from **457** during structural studies on the lycopodium alkaloids. This sample of compound **488** could then be used, instead of the synthetic material, to work out the details of the conversion of **488** to **457**. This is another example of the strategem known as the *relay approach*, that we saw employed in syntheses of erythronolide B (see section 5.4) and quinine (see section 6.5). The advantage of this approach is that a valuable key intermediate can be obtained readily in quantity. The ***relay compound*** (e.g. **488**) becomes the target of the synthesis.



Let us first consider the *interconversion* of the relay compound **488** and **457** before examining the *total synthesis* of the relay compound. To differentiate the hydroxyls at positions 5 and 6, the diol **489** from natural lycopodine (**457**) was monoacetylated at the sterically most accessible C-6 hydroxyl. Dehydration followed by hydrolysis afforded **490**. Oxidation of the allylic hydroxyl followed by reduction of the resulting α,β-unsaturated ketone and permanganate oxidation α to the tertiary amine gave the proposed relay compound, amide **488**, in 13% overall yield from natural lycopodine (**457**).

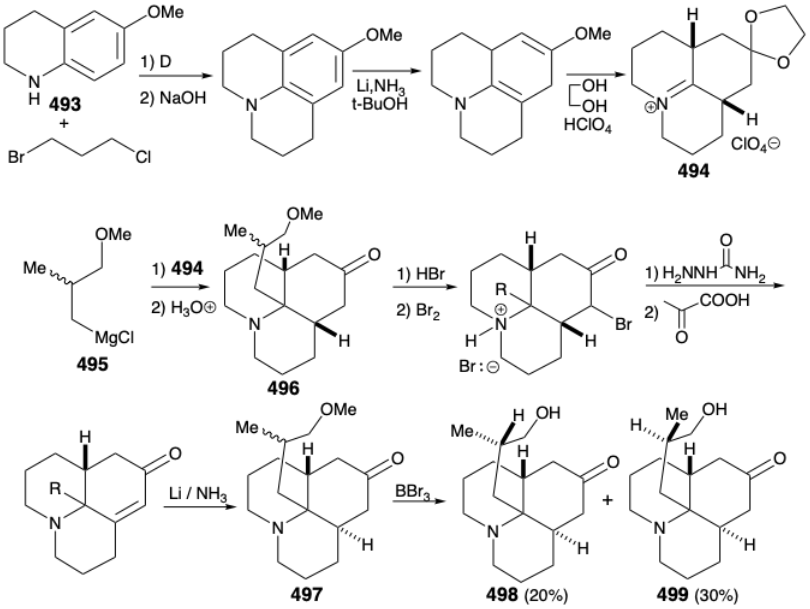


Reconversion of the relay compound **488** into lycopodine (**457**) was then achieved by removal of the amide carbonyl, by reduction with LAH, and oxidation of the resulting C-6 epimeric alcohols. The amino ketone **491** was then oxidized to the diosphenol **492**, that was reduced selectively by a Wolff-Kishner reaction with hydrazine hydrate to afford lycopodine (**457**).

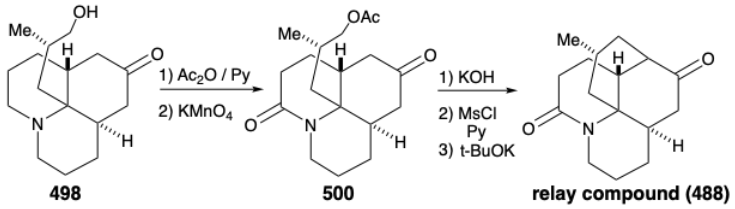


As noted above, a synthesis of **486**, and hence the relay compound **488**, *from a symmetrical starting material* was envisioned (see above). In particular, **486** might be prepared from **487** by reaction with a nucleophilic side chain synthon. With a provision for

masking the electrophilicity of the carbonyl group, this strategy proved viable. Thus, **494** was prepared from thalline (**493**) by alkylation with 1-bromo-3-chloropropane followed by dissolving metal reduction and ketalization. Reaction of **494** with the nucleophilic fragment **495** followed by hydrolysis gives the cis,cis-fused tricyclic amine **496**. Ring closure of this epimer is impossible. Epimerization to the trans,cis isomer **485** must precede ring closure. Therefore, epimerization was accomplished by exploiting the carbonyl functionality in **496** by bromination followed by Mattox-Kendall dehydrobromination and dissolving metal reduction. Demethylation of the product **497** then afforded a mixture of racemic diastereomeric ketones **498** and **499**. These were separated by chromatography on alumina. The *minor* isomer **498** possessed the natural relative configuration of the methyl substituent. Thus, the present synthesis is nonstereospecific, and a near fatal major loss of valuable material occurs owing to the formation of an unwanted stereoisomer **499**.

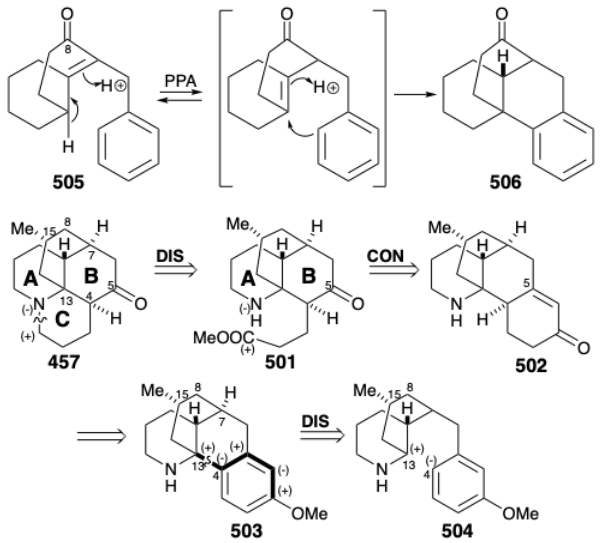


Before intramolecular alkylation of the tricyclic ketone could be accomplished, the nucleophilicity of the amino group had to be attenuated by conversion of the amino group in **498** into an amide **500** to avoid N-alkylation. Saponification, mesylation, and intramolecular alkylation then provided the relay compound **488** in racemic form. Since **476**, albeit homochiral, derived from natural lycopodine (**457**) had already been converted to **457** as discussed above, the total synthesis was complete.

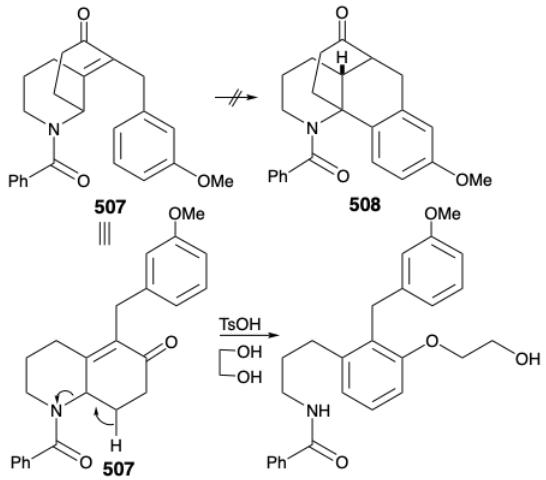


An Unintentionally Biomimetic Strategy

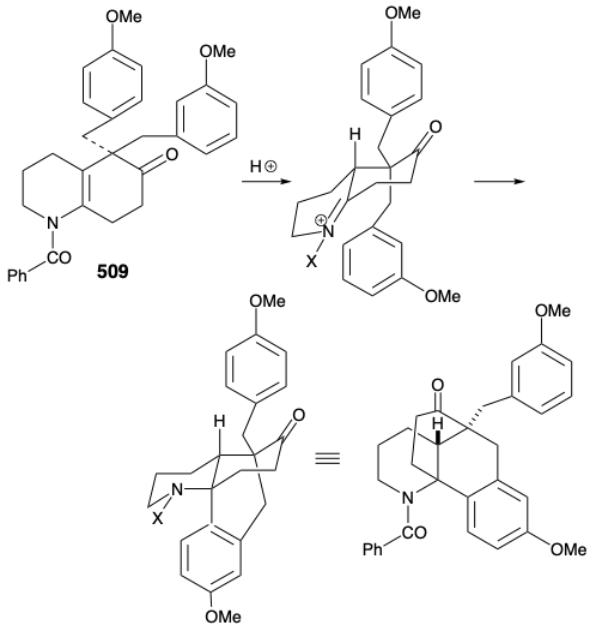
In the two strategies for lycopodine (**457**) discussed above, one generated ring B last and one generated ring D last. Now we shall consider a strategy that generates ring C last as found in the biosynthesis of **457**. Moreover, in further analogy with the biosynthetic strategy, the three carbon chain substituent on ring B of **501**, that is the used to complete ring C, is incorporated into a temporary ring in a precursor **502** by attachment at the (latent) carbonyl carbon at C-5. Finally, the consonant circuit between the amino and methoxy groups in the aromatic precursor **503** suggests a polar construction from **504** of the 4-13 C-C bond, again in analogy with the biosynthetic strategy, by attack of a C-13 electrophile on a nucleophilic center at the incipient C-4. However, this strategy was conceived before the biosynthesis of lycopodine had been elucidated. In the words of the author of the strategy, "although the particular synthetic plan followed for the construction of the tetracyclic system had no particular basis in biogenetic considerations, very recent work has suggested a biogenetic pathway in which the crucial cyclization step is strikingly similar to the one we devised."[21]



Before we consider the successful implementation of this plan, it is instructive to note that it was developed with the aid of lessons learned during attempts to achieve a synthesis using other, fatally flawed, strategies. One unsuccessful early plan for a transformation analogous to the generation of **503** from **504** was supported by successful model studies. Thus, a carbocyclic model **505** readily underwent an analogous cyclization to **506** on heating with polyphosphoric acid. It was anticipated that the methyl substituent at position 15 on the D-ring of **504** could be introduced subsequently by exploiting the nucleophilic activation afforded by a carbonyl group at position 8. Furthermore, the inclusion of this carbonyl group could enhance the general utility of the synthesis because oxygen substitution is found at position 8 in many lycopodium alkaloids. However, in contrast to the carbocyclic model **505**, cyclization of the heterocyclic analogue **507** to give **508** could not be achieved. Rather **507** was apparently prone toward elimination leading to aromatization.

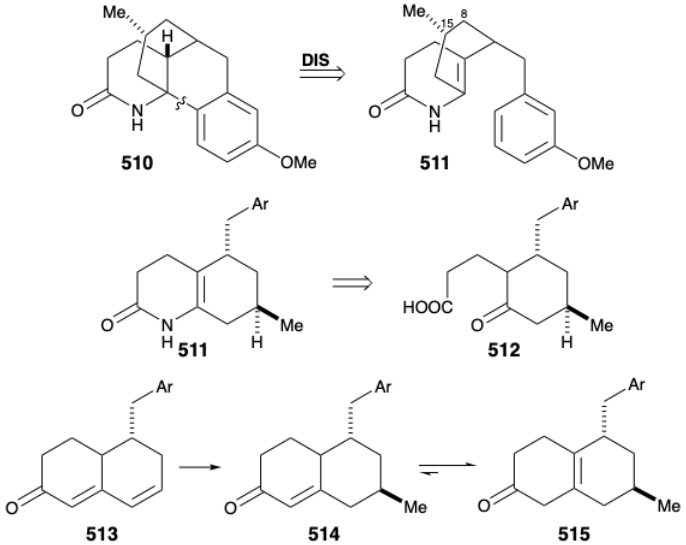


Nevertheless, an encouraging observation emerged from this model study. Thus, the dialkylated derivative **509**, a byproduct in the synthesis of **507**, underwent the desired type of cyclization. The success of this cyclization seemed attributable to two factors, an *axial orientation* of a benzyl substituent and *blocking of the elimination pathway*.

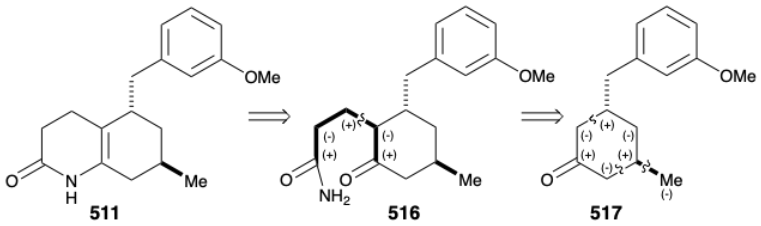


A modified strategy was then devised in which the methyl substituent required at position 15 was introduced prior to the annelation of ring B and the carbonyl group at position 8 was deleted. Moreover, the stereochemistry of this methyl substituent in lycopodine dictated a *trans* relationship of the methyl and m-methoxybenzyl groups in the new subtarget. The functionalized derivative chosen to embody these requirements was **511**. It was further recognized that the *trans* methyl subtituent in **511** should virtually eliminate the energy barrier to achieving the axial orientation of the benzyl substituent required for cyclization to **510**.

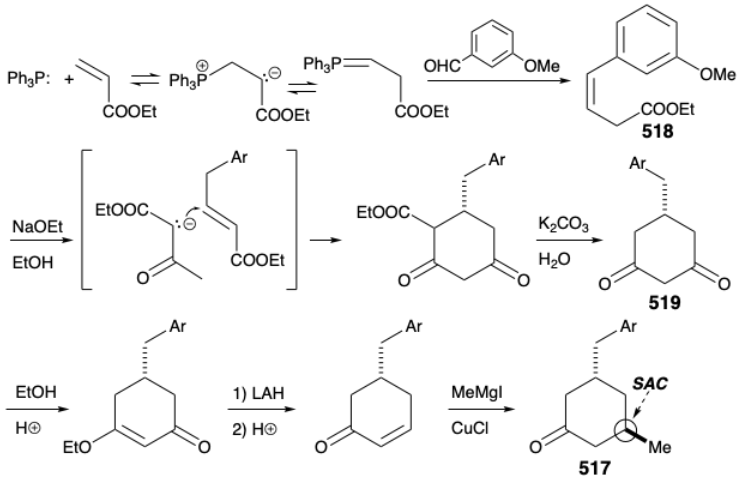
Several strategies were explored for synthesis of the subtarget **511**, that is obviously derivable from **512**. An approach to **512** via conjugate addition of a methyl nucleophile to **513** followed by oxidative cleavage of the cyclohexenone **514** was precluded by the proclivity of **514** to isomerize into the β,γ-unsaturated isomer **515**.



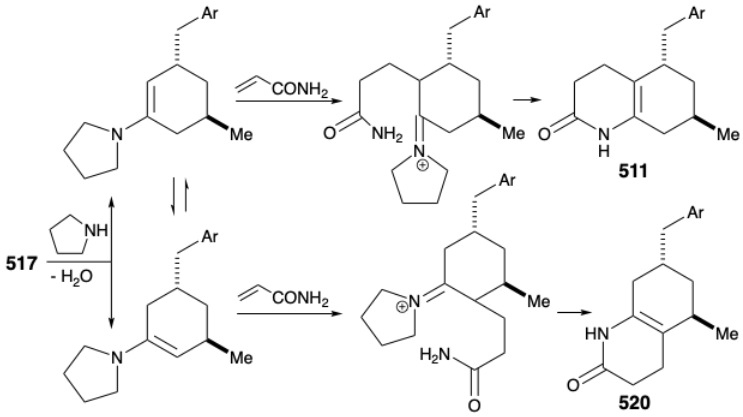
A second approach to **511** exploits the consonant circuit between the carbonyl carbon and enamide nitrogen in **511** or the related consonant circuit between the two carbonyl groups in keto amide **516**. Disconnection of the three carbon side chain suggests a cyclohexanone precursor **517** that can be generated by polar connections activated by the carbonyl group.



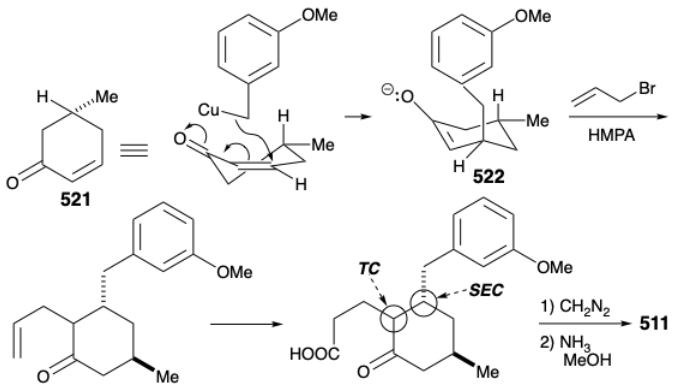
Cyclohexanone **517** was prepared by polar reactions between an acrylic ester and acetoacetic ester. Thus, a symmetrical dione **519** was generated from β,γ-unsaturated ester **518** by prototropic allylic rearrangement, followed by Michael addition of ethyl acetoacetate, Dieckmann cyclization, hydrolysis, and decarboxylation. Selective reduction of only one carbonyl group in **519** was facilitated by masking the second carbonyl of this dione as a vinylogous ester. Acid-catalyzed dehydration then provided a cyclohexenone that delivered **517** upon stereoselective 1,4-addition of a methyl nucleophile.



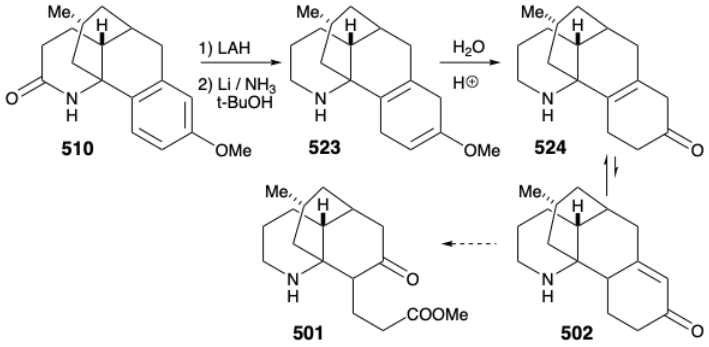
The original strategy for construction of key intermediate **511** from cyclohexanone **517** had one major shortcoming. Thus, conversion of **517** into **511** requires regioselective Michael alkylation. However, alkylation of **517** occurred nonregioselectively at both carbons α to the carbonyl producing a mixture of **511** and **520**.



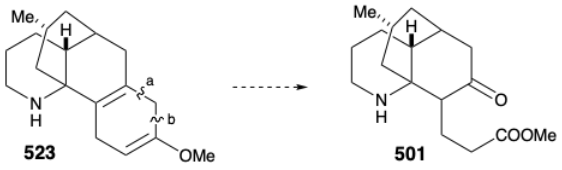
An improved, completely *structurally specific* synthesis of the subtarget **511** was finally devised that exploited regiospecific generation and electrophilic trapping of the enolate **522**. This was achieved by Michael addition of a benzyl nucleophile to the cyclohexenone **521**. The resulting regiospecific enolate was then alkylated with allyl bromide. The process is also highly stereoselective owing to a preference for axial attack in Michael additions of organocopper nucleophiles and a preference for an equatorial disposition of the methyl substituent in **521**. Furthermore, the required trans relationship between the allyl and benzyl substituents is assured by thermodynamic control owing to epimerizability α to the ketone carbonyl. Hydroboration and oxidation of the allyl side chain, esterification, and reaction of the resulting ketoester with ammonia afforded the key intermediate **511**.



Intramolecular electrophilic aromatic substitution gave mainly the desired *para* substituted cyclization product **510** (55%) together with some *ortho* substitution product (29%). The amide carbonyl was then removed by reduction with LAH, and the protective aromaticity of the aryl ring was removed by Birch reduction. A plan to effect ring cleavage by oxidation of an α,β-unsaturated cyclohexenone failed owing to a thermodynamic preference for the required enone **502** to exist as the corresponding β,γ-unsaturated tautomer **524**.



Once again, therefore, an alternative strategy had to be formulated. The original plan for generating **489** from **497** was fatally flawed. Indeed, while the each step in the original plan was well precedented, so was the likelihood that **502** would be in equilibrium with a substantial amount of **524**. Indeed, this same problem derailed an attempted synthesis of **512** from **514** (see above). As is so often the case, a shortcoming of well-known methodology for achieving an important synthetic goal, especially if it impedes the conclusion of an ambitious total synthesis, inspires the application of novel chemistry to provide a solution to the dillema. Necessity is the mother of invention! Thus, generation of **501** from **523** required oxidative cleavage of two bonds, "a" and "b", in the cyclohexadiene ring. The original plan called for cleavage of bond "a" first after an isomerization that placed a readily cleavable C=C bond in this position. In the alternative strategy, bond "b" is cleaved first after an isomerization that placed a readily cleavable C=C bond in this position.



Thus, the 1,4-cyclohexadiene **523** was isomerized to a conjugated 1,3-diene, and the amino group was masked to protect it from oxidation. Selective ozonolysis of the more electron rich C=C bond in **525** then afforded the aldehydo methyl ester **526**. An unusual Baeyer-Villager oxidation of **526** gave the enol formate **527** that afforded keto amide **528** after methanolysis of the enol ether, removal of the carbamate protecting group from the amino nitrogen, and lactamization. The amide carbonyl was then removed to provide lycopodine (**457**) by reduction with LAH followed by reoxidation of the C-5 hydroxyl to the required C-5 carbonyl group.