Numerous alkaloids have been isolated over the years from the genus *Lycopodium*. Among these, Lycopodine first isolated in 1881, seems to be the most widely distributed. Structural work, ranging over a number of years, culminated in the structure and absolute stereochemistry shown in (I) for the alkaloid. The identical expression (II) can be written as in the two-dimensional representation (III).

We were attracted to the synthetic problem posed by this molecule because it not only presented a considerable stereochemical challenge, but more particularly because of its interesting feature of having a carbon atom (carbon 13) common to the four rings in the molecule. It is presumably these same synthetic complexities which incited a number of other groups to devise synthetic schemes for the construction of the Lycopodine molecule; and it is indeed remarkable that no two groups evolved identical approaches to the problem posed by the attachment of the various rings around C13. Because of the intrinsic interest of these approaches which illustrate the imaginative variety of possible solutions to the problem, as well as their
particular difficulties, we will outline the broad features of a number of these, before turning to a detailed consideration of our own synthetic efforts.

The first approach we consider, due to Wiesner, Valenta et al., involves starting with rings A and C onto which ring B is then attached by forming first the important bond at C13, then the bond to C7. In one variant of this scheme the goal was a structure of type (V) which appeared derivable by the introduction of an acetonyl group at the eventual C13 of what turns out to be a simple quinolone derivative illustrated by (VI).

![Chemical Structure](image)

The introduction of the acetonyl group was achieved in a particularly ingenious manner, via photochemical addition of allene to VII. Further transformation of one of the adducts (VIII) gave the crystalline intermediate IX in which the correct stereochemical relationship of the methyl group to the potential ring B has been established, but which (possibly because it may be IXb rather than IXa) cyclized to a ketol Xb which, after removal of the hydroxyl and attachment of ring C, eventually led to the C12 epimer XI of Lycopodine rather than to Lycopodine (II) itself.

An earlier version of this approach employed a Grignard addition (XII→XIII) to begin the construction of the potential ring B, again securing the proper stereochemical relationship to the methyl group. An internal Prins-type reaction (XIV→XV) served to complete the attachment, although the stereochemical result at C12 of this cyclization is unknown. The interesting hydride transfer reaction (XV→XVI), while confirming the methyl stereochermistry, led to problems which were circumvented in the aldol approach outlined previously.

In the next three approaches to be considered, the establishment of the quaternary centre at C13 is now made part of the construction of ring C. The first, and eventually successful, such approach by Ayer et al. introduces the methyl-bearing bridge via a Grignard addition to the julolidine derivative (XVII). The stereochemistry of the methyl group at C15 is in principle controllable via the use of the appropriate optically active Grignard reagent.

It is interesting that attachment of the newly introduced chain to C7 so as to complete ring C made necessary initial transformation of XVIII, which has
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(VII) → (VIII) → (IX)

(Xa) → (IXb)

(H) → (Xb) → (XI)

(II)

(11) → (Xb) → (XI)

(ClcLCH3) → OR

(R)

(OH)

(R)

(NR)

(R)

(NR)

(NR)

(R)

(OR)

(385)
conformation XVIIIa, into the C4 epimer XIX. The latter undergoes alkylation at C7, as desired, rather than at C5, apparently involving that enolate which is compatible with the presence of both cis and trans "decalin" systems. The ketolactam resulting from internal alkylation should be convertible to lycopodine by reduction of the amide function and transposition of the keto group from C6 to C5. These transformations were indeed effected by Ayer's group5 with the optically active, but otherwise identical, ketolactam obtained by degradation of lycopodine.

In another approach involving the establishment of the quaternary centre at C13 concurrently with the construction of ring C, Parker, Raphael and their collaborators6 also start with the attachment of the potential methyl-bearing bridge to C13, this time via the alkylation of a β-ketoester function. The C12 keto group of the latter serves the further role of activating C7 so as to allow the completion of ring C, and this in turn required devising an ingenious novel method for the attachment of ring A (cf. XX → XXI).

The two previous schemes involved attaching ring C by forming the bonds to C13 and C7 in that order. It is of course conceivable to reverse this, for instance by having an ABC system bearing a substituent at C7 which then might undergo internal addition to C13. Such an approach has been sketched by Bohlmann7 and, although a number of problems would have to be solved
to complete the elaboration of ring C, the elegant simplicity of the initial construction, which involves electrophilic olefin addition to an enamine and its subsequent acylation, makes it worth mentioning here.
We are now ready to consider our own approach in some detail. The goal was the keto ester XXII, the optically active form of which had previously been converted to lycopodine. An obvious possible precursor of XXII (e.g. via the enone XXIII) is the structure XXIV, the para-substituted anisole of which immediately opened up the possibility of forming the quaternary centre at C13 via an intramolecular alkylation of an anisole ring. This approach forms ring B via initial attachment at C7.

In order to lead to lycopodine the cation involved in the formation of the bond to C13 would have to be a species such as XXV. We initially considered the possibility of introducing the methyl group at C15 following the formation of the tetracyclic system, because we had shown many years ago that the carbocyclic analogue XXVII of the desired structure was readily produced on heating XXVI with phosphoric acid. The enolization of the bridged ketone (cf. XXVII) is only possible towards C15 thus allowing introduction of the necessary methyl group.

The stereochemistry of the methyl group could presumably be controlled because of the presence of the C16 carbonyl function which had the added attraction that many lycopodium alkaloids in fact have oxygen substitution at C16. On this basis, and leaving aside the stereochemical problems at this stage, the simple structure XXVIII became our initial goal.

The synthesis is illustrated below. Reduction of commercially available "thalline" (XXIX) with lithium–alcohol–ammonia, followed by treatment with benzoyl chloride in the presence of triethylamine, and oxalic acid hydrolysis gave, via the hexahydroquinoline XXX, m.p. 106°, the β,γ-unsaturated ketone XXXI, m.p. 112°. Alkylation with m-methoxybenzyl chloride (sodium hydride in dimethyl formamide–toluene) then led to the desired XXVIII, m.p. 127°.

Unfortunately, however, and in contrast to the carbocyclic "model" XXVI, cyclization to C13 via the β,γ-unsaturated isomer could not be
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achieved. Under some conditions (liquid hydrogen fluoride, p-toluene-sulphonic acid in hot benzene) cyclodehydration (to what appeared to be XXXII from its spectral properties) took place. Attempts to move the double bond of XXVIII to the β,γ-position via dioxolane formation gave an insight into the cause of some of the difficulties: the simple phenol derivative XXXIII, m.p. 160° was obtained upon heating with ethylene glycol and p-toluenesulphonic acid. The kinetically formed cross-conjugated enol derivatives from XXVIII need only eliminate the amide function to produce an aromatic ring, a contingency which does not arise with the carbocyclic “model”. Attempts to cyclize other relatives of the ketone XXVIII, such as the thioketal XXXIV or the cyanomethylene derivative XXXV similarly failed to achieve the desired result.

One important observation, however, emerged from this approach. The dialkylated derivative, A, obtained as a by-product in the formation of XXVIII, on standing at room temperature with a mixture of formic and phosphoric acid readily underwent the type of cyclization we had hoped for, leading to the tetracyclic system C, m.p. 163–164° in about 45 per cent yield. The easy cyclization is clearly the result of the axial orientation of one of the methoxybenzyl groups as shown in B, and it became apparent that the original scheme should be modified by removing the carbonyl group of XXVIII (cf. XXXVI). This would, of course, require having the methyl group which is to be at C15 in the final molecule already present in the starting material, in which (compare XXV) it would have to be trans to the m-methoxybenzyl group. This relationship, shown in XXXVII, incidentally produces the desirable result of essentially eliminating the energy barrier
to achieving the desirable axial orientation of the benzyl substituent. The molecule finally chosen to embody these requirements was XXXVIII. The route via XXXVIII indeed led eventually to the successful stereospecific synthesis of lycopodine, but the construction of this relatively simple molecule was not without its own particular problems.

Since the keto acid XXXIX would obviously be readily convertible to XXXVIII, we initially directed our efforts to the synthesis of XL as an obvious precursor. Reaction of m-methoxybenzylmagnesium bromide with the known ketone XLI, followed by treatment with dilute acid gave the conjugated dienone XLII, m.p. 85–86°, \( \lambda_{\text{max}}^\text{EIOH} \) 305 m\( \mu \), which on reduction with lithium–ammonia–tetrahydrofuran, and then isomerization of the unconjugated product with anhydrous hydrogen chloride in benzene led to the \( \alpha,\beta \)-unsaturated ketone XLIII \( \lambda_{\text{max}} \) 230 m\( \mu \), which could finally be converted into the dienone XLIV, m.p. 90–91°, \( \lambda_{\text{max}}^\text{EIOH} \) 282 m\( \mu \), by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene (room temperature; 3 h). It was anticipated that the desired axial introduction of the methyl group would result from conjugate addition of the methyl Grignard reagent (XLIV → XLV). Unfortunately, the product, after equilibration, appeared to be a mixture of \( \alpha,\beta \) and \( \beta,\gamma \)-unsaturated ketone XLVI from which we were unsuccessful in obtaining pure XL.
We had by that time evolved a simple synthesis for the parent quinolone system present in XXXVIII. This “aza-annelation” involved heating the pyrrolidine enamine of cyclohexanone with acrylamide in dioxane solution for 3 h, followed by refluxing 1 h after addition of water, a procedure which gave in 70 per cent yield the known$^{10}$ 3,4,5,6,7,8-hexahydro-2-quinolone (XLVII).

It therefore appeared that the desired substituted quinolone XXXVIII might result from the application of this aza-annelation to trans 3-m-methoxybenzyl-5-methylcyclohexanone (XLIX). The synthesis of this substance was performed via 5-m-methoxybenzyl-2-cyclohexenone (XLVIII) which was prepared by standard methods, starting with 3-m-methoxybenzyl-1,3-cyclohexanedione, m.p. 108.5–109.5°. Conjugate addition of methylmagnesium iodide to the cyclohexenone XLVIII proceeded best under relatively high dilution (1% solution in ether, 0°), in the presence of a catalytic amount of cupric chloride. Under these conditions, reproducible yields of 85–95 per cent of XLIX could be obtained as an apparently homogeneous substance showing a single methyl absorption as a doublet at $\delta$ 0.96 ($J = 6$ cps). The expected axial introduction of a methyl group in such a reaction is well-documented.$^{11}$

We were now ready for the construction of the pyridone ring via the enamine of XLIX. We realized, of course, that such a step would certainly result in the formation of two structurally isomeric quinolones since there is no particular reason to expect any selectivity in enamine formation from the asymmetric ketone XLIX. We decided to proceed nevertheless, because of the ready accessibility of the starting material, but we will shortly show how this lack of structural specificity may be circumvented. In agreement with expectations, addition of the pyridone ring proceeded normally and gave two isomeric quinolones which could be separated by initial chromatography on alumina, followed by crystallization from ether. The less soluble isomer, m.p. 132–133°, was readily obtained pure and fortunately proved to be the elusive XXXVIII. The other isomer, L, was not completely purified (m.p. 85–92°) but was essential in establishing that the structure of the 132° compound is indeed XXXVIII. This followed simply from the fact that, although i.r. and n.m.r. spectra could not distinguish between these two
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isomers, the mass spectra showed the ratio of the peak of the ion due to loss of \( m\)-methoxybenzyl (m/e 164) to that due to expulsion of methyl to be 37:1 for the higher melting isomer, only but 1:7:1 for the other. This is sufficient to assign structure XXXVIII to the 132\(^\circ\) compound.

\[
\begin{align*}
\text{XXXVIII}
\end{align*}
\]

Although we were thus able to prepare several grams of the proper quinolone by this method we were not satisfied with the lack of structural specificity. It is clear that the problem could be solved by finding a method for generating specifically the enolate, or enolate-like, structure LI. We have previously\(^{12}\) introduced a special solution to this type of problem, the addition of electrons to an \( \alpha,\beta\)-unsaturated ketone to form a specific enolate which can then be alkylated under suitable conditions (cf. LII → LI). It is clear that this concept can be extended to the addition of electrons associated with various nucleophilic species, provided the addition can be done in aprotic solvents. Such a requirement is met by the conjugate addition of Grignard reagents. It is evident that although the same 3,5-disubstituted cyclohexanone XLIX should (and does) result from the previously mentioned conjugate addition of methyl Grignard reagent to XLVIII, or from that of the \( m\)-methoxybenzyl Grignard reagent to LIV, the latter process should lead initially to a molecule LI in which \( X = \text{OMgX} \). We trapped the adduct (from addition at 0\(^\circ\) of an ether solution of 5-methyl-2-cyclohexenone to the solution obtained by adding a tetrahydrofuran solution of \( m\)-methoxybenzylmagnesium bromide to a catalytic amount of cuprous chloride) as its trimethylsilyl enol ether [LI, \( R = \text{OSi(CH\text{3})\text{3}} \)] and converted the latter to its lithium enolate (LI, \( X = \text{OLi} \)), using a procedure we recently developed\(^{13}\). The latter can then be alkylated, but we eventually found conditions which allow alkylation of the normally very unreactive magnesium enolates without losing structural specificity. This was done by the addition of allyl bromide, and enough hexamethylphosphoramide (HMP) to make ~ a 40 per cent solution. The maintenance of structural specificity is possible by this method.

\[
\begin{align*}
\text{XXXVIII}
\end{align*}
\]
integrity, even in the presence of the highly polar HMP, was expected on the basis of our previous spectral studies of magnesium enolates in various solvents. Conversion of the allylated ketone LV to the ketoacid XXXIX which had been the goal of a previous abortive sequence (described above, p. 391) was effected in routine fashion via hydroboration (preferably after ketalization) and oxidation. The homogeneous keto acid then gave (methanolic ammonia at 200° on methyl ester) the lactam XXXVIII in good yield.

We now can turn our attention to the crucial acid cyclization by which we expected to transform XXXVIII into XXIV. As is obvious from diagram LVI, the desired stereochemistry at C12 would naturally result from a concerted proton-initiated cyclization of XXXVIII. This deceptively simple possibility is almost certainly precluded by the fact that rapid, reversible protonation of the enamide double bond would be expected, with the slow, rate-determining, step being attacked by the anisole ring on the acylimonium cation. If that is so, either of the two protonated species represented by LVII and its C12 epimer could a priori be involved in the cyclization step, and only the former, another representation of which is as LVIIa, would lead to the necessary tetracyclic system XXIV. The two possible imonium ions are shown again as A(≡LVIIa) and its epimer B. It is clear that these have about the same energy, differing essentially in that a benzyl group is axial in the former and a methyl in the latter. It is also interesting that both possible cyclization products are strain-free, LIX corresponding in fact to the 12-epi-lycopodine.
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\[ \text{[Structural equations and diagrams]} \]
system synthesized by Wiesner, Valenta, et al. We nevertheless confidently expected the rate of cyclization of A to be much higher than that of B, since the former cation has the favourable axial benzyl orientation in an undistorted chair while B can achieve this feature only via a strained, boat-like configuration. In fact, treatment of the bicyclic lactam XXXVIII with a 10 per cent solution of 85 per cent phosphoric acid in formic acid for 20 h at room temperature gave an 85 per cent yield of cyclized products, separated by chromatography on silica gel. The first eluted substance, m.p. 213.5–215.5°C (55%), was followed by an isomer, m.p. 201–202°C (29%). These were easily recognized as the products of para- and ortho-substitution, respectively, by the typical n.m.r. patterns in the aromatic region. The important point is that, in agreement with the discussion above, only one product of cyclization para to the methoxy group was formed. We confidently assigned to it the structure and stereochemistry shown in LVIII in which four of the five asymmetric centres of lycopodine must be correctly established.
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It is worth noting that although the particular synthetic plan followed for the construction of the tetracyclic system had no particular basis in biogenetic considerations, very recent work\textsuperscript{14} has suggested a likely biogenetic pathway in which the crucial cyclization step is strikingly similar to the one we devised.

We had now reached the point at which all that remained was the apparently straightforward conversion of the anisole ring along the lines indicated earlier (cf. p. 388). As it happened, unexpected difficulties made this more of a challenge than we had anticipated.

The amine (cf. XXIV) from lithium aluminium hydride reduction of LVIII was very easily converted by Birch reduction to the usual dihydroanisole LX which, on acetylation, followed by dilute acid hydrolysis, was converted to the anticipated $\beta,\gamma$-unsaturated ketone (LXI, $X = \text{Ac}$), m.p. 122–125°. Under no circumstance of acid or base treatment could we convert it into the corresponding $\alpha,\beta$-unsaturated tautomer LXII. This remarkable fact finds a ready (ex post facto) explanation when one considers the equivalent three dimensional representations LXIa and LXIIa. The normally favoured $\alpha,\beta$-unsaturated ketone acquires two new CH$_2$/H repulsions instead of the smaller interaction when C$_4$ is trigonal. Additionally, the distance between C$_5$ and C$_{15}$ is now shortened.

The impossibility of obtaining the $\alpha,\beta$-unsaturated ketone necessitated using a different degradation sequence to the desired keto ester (cf. XXII). This was successfully done by taking advantage of the tendency of the double bond of the Birch reduction product LX to stay between rings B and C for the reasons already outlined. Conjugation of the enol ether (potassium t-butoxide–DMSO) therefore gave smoothly the homoannular diene LXIII, $X = \text{H}$, $\lambda_{\text{max}}^{\text{EIOH}}$ 273 m$\mu$ (3800), which could be acylated with either acetic
anhydride, or with trichloroethyl chlorocarbonate\textsuperscript{15} in the presence of 15 per cent aqueous sodium hydroxide. These enol ethers could then be ozonized selectively at $-80^\circ$ to the aldehydo esters LXIV, $X = \text{Ac-}$, m.p. 84–85° (44% overall from XXIV) and LXIV, $X = \text{Cl}_3\text{CCH}_2\text{CH}_2\text{OC-}$, m.p. 249 m\textdegree; $810.2\text{(s)}$. The latter was then changed first to the enol formate (selenium dioxide–anhydrous hydrogen peroxide in t-butanol) and hence to the keto ester LXVI (methanolic sodium methoxide), m.p. 141–141.5°. This series of transformations was quite efficient and LXVI was thus produced in about 30 per cent overall yield from the aromatic tetracyclic amine XXIV.

A few comments are in order with respect to the transformation LXIV $\rightarrow$ LXV. We had anticipated the formation of considerable carboxylic acid from the selenium dioxide–hydrogen peroxide reaction. Indeed, the yield of acrylic or methacrylic acid from the corresponding aldehydes is reported to be excellent\textsuperscript{16}. The high yield of enol formate may be related to the disubstituted nature of the $\beta$-carbon of the unsaturated aldehyde: we found that 2-methyl-$\Delta^1$-cyclohexene carboxaldehyde also gives a good yield of enol formate by this method. It seems likely that an intermediate of type $a$ is involved (as in the more usual peracid cleavage) and it is apparent that
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(LXIII) \[ \text{Product} \]

(LXIV) \[ \text{Reactant} \]

(LXV) \[ \text{Product} \]

(LXVI) \[ \text{Reactant} \]

(LXVII) \[ \text{Product} \]

(LXVIII) \[ \text{Reactant} \]
β-substitution should indeed facilitate the path leading to enol formate (a → c → d).

Simultaneous removal of the nitrogen protecting group¹⁶ and cyclization to the tetracyclic ketolactam LXVII, m.p. 143–144° resulted from heating with zinc dust in methanol at 150°.

Lithium aluminium hydride reduction of LXVII produced the tetracyclic aminoalcohol LXVIII, m.p. 185–187°, which did in fact turn out to be dl-complanatine (dl-dihydrolycopodine)¹⁷ as was demonstrated by the complete identity of the infrared spectra in different solvents, and by the identical t.l.c. behaviour of the synthetic dl-material and of the natural substance (cf. Figure 1). The oxidation of dihydrolycopodine to lycopodine had previously been described¹⁸ and the success of the synthesis confirms the structural and stereochemical arguments which we have made.

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