1.2 Milestones in Structure Elucidation

The vast majority of new chemical compounds isolated since the development of modern nuclear magnetic resonance and X-ray spectroscopic techniques in the 1950s and 1960s have yielded to complete structure assignment with relative ease. In the past, however, structure determination was an arduous task. The stories of many structure assignments are worth repeating, and we will relate a few of the more interesting ones here – those of glucose, morphine (whose structure eluded researchers for almost 100 years), aspidospermine, and patchouli alcohol.

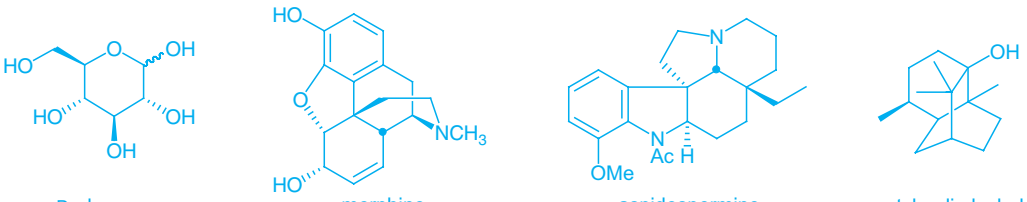

Figure 1.2-1 Milestones in structure determination.

1.2.1 Glucose*

The original proof of the structure of glucose by Emil Fischer [1], first disclosed in 1891, stands to this day as a great example of deductive reasoning. He was awarded his second Nobel Prize in chemistry, in 1902, for his research on sugars and purines. Little progress in the synthesis of carbohydrates would have been possible without his elegant work.

Aware of the basic topology of the carbohydrate framework, Fischer executed a series of reactions that elucidated the relative stereochemistry of D-glucose. Because the technology did not exist at that time to discern absolute stereochemistry, Fischer arbitrarily assigned a configuration [2], the one with the hydroxyl at C-5 to the right (in the Fischer projection, the horizontal bonds project toward the observer, the vertical ones away). Later, X-ray crystallographic techniques proved his assignment was correct [3].

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The Way of Synthesis. Tomáš Hudlický and Josephine W. Reed

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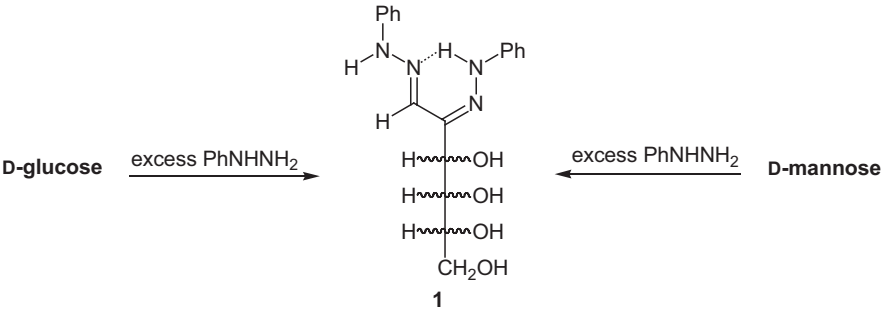


(a) When treated with excess phenylhydrazine (a reagent that Fischer discovered), both D-glucose and D-mannose form the same osazone, **1** [Note 1]; therefore, these two compounds must have identical stereochemistry at C-3, C-4, and C-5. Consequently, D-glucose and D-mannose must be either **2** and **3**, **4** and **5**, **6** and **7**, or **8** and **9**.

(b) Nitric acid oxidizes both D-glucose and D-mannose to optically active diacids. As oxidation of structures **2** and **8** would give meso diacids, these and their paired structures, **3** and **9,** are eliminated. Consequently D-glucose and D-mannose must be either **4** and **5** or **6** and **7** (Fig. 1.2-2).

(c) Kiliani–Fischer chain extension of D-arabinose gives a mixture of D-glucose and D-mannose. Therefore arabinose must have either the structure **11** or **13** (Fig. 1.2-3). (At the time, the structure of arabinose was not known.)

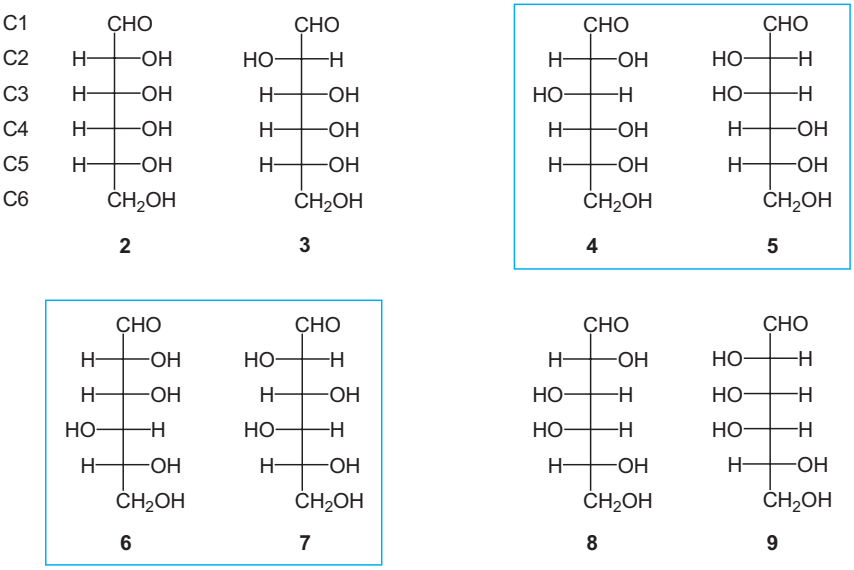


Figure 1.2-2 Part of Fischer's proof for the structure of glucose.*

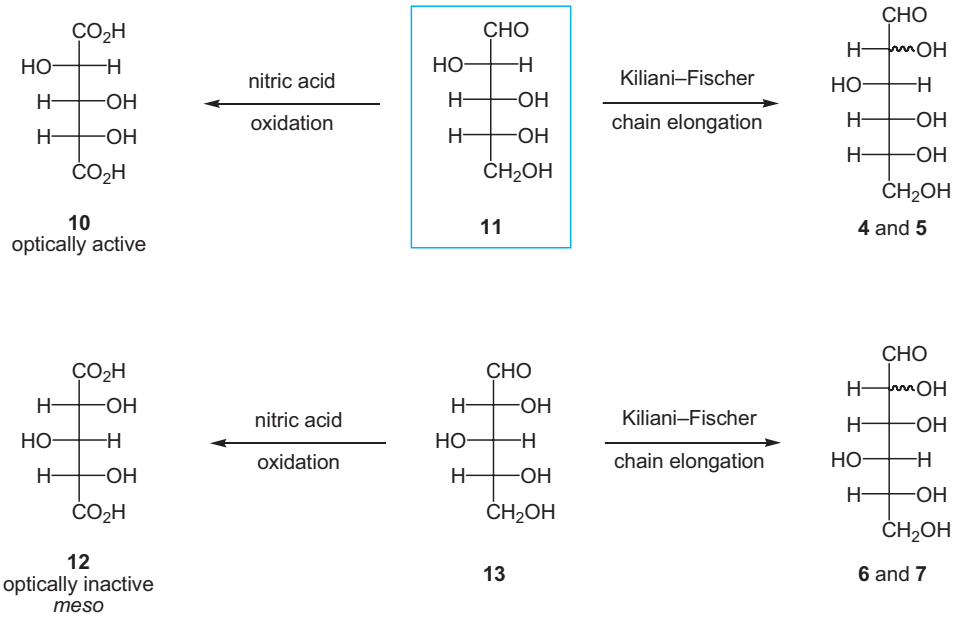


Figure 1.2-3 Fischer's deduction of the relative stereochemistry of arabinose.*

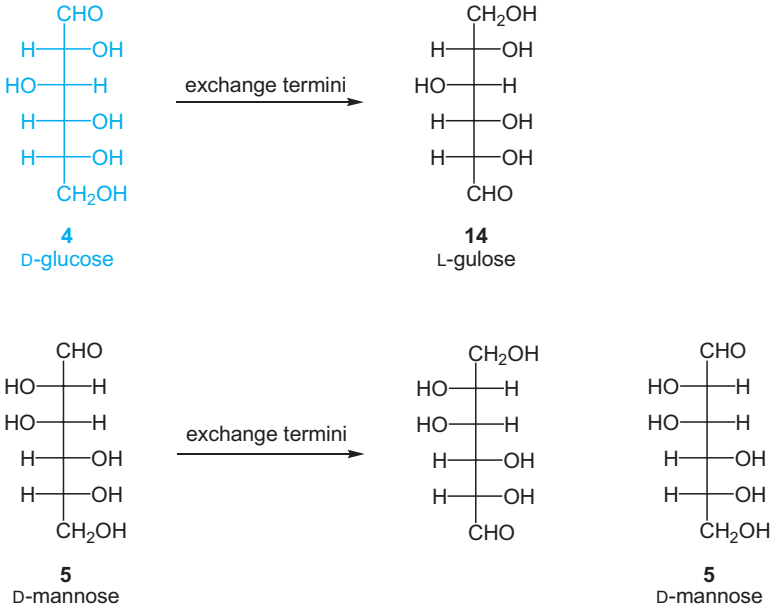


Figure 1.2-4 The final proof of the relative stereochemistry of glucose.*

(d) When arabinose is oxidized with nitric acid it produces an optically active diacid; therefore, it was assigned structure **11**. Structure **13** would give meso diacid **12**. This result, when combined with (b), means that D-glucose and D-mannose are **4** and **5,** in some order.

(e) Finally, to determine whether structure **4** or **5** was that of glucose, Fischer devised a series of reactions to exchange the aldehyde and primary alcohol termini. When D-glucose was subjected to those reactions, a new sugar was produced, which Fischer named L-gulose. When the termini of structure **4** are exchanged in this manner a new sugar **14** is formed; however, when the termini of structure **5** are exchanged, structure **5** is regenerated (Fig. 1.2-4). Therefore the structure of D-glucose corresponds to sugar **4**.

1.2.2 Morphine

Morphine stands out among chemical substances as one of wide societal impact. Many famous and creative people, from Coleridge to Janis Joplin, were intimately familiar with its source, opium, or its more potent derivative, heroin. Two excellent books, *Opium: A History* [4] and *Opium Poppy: Botany, Chemistry, and Pharmacology* [5], discuss cultural and pharmacological aspects of opiates and provide an interesting foundation for the study of their chemistry.

The scientific study of morphine began in 1805 when a German pharmacist named Sertürner, from Hannover, reported the isolation of the active component of one of the oldest of drugs, opium [6]. He named the substance after Morpheus, the god of dreams in Ovid's *Metamorphoses.* His work was not noticed until 1817 when it was republished in a more visible journal, *Gilbert's Annelen der Physik* [7]. After that time work on its structure began, but it defied elucidation for over 100 years. In 1998 we published a detailed account, based on the original literature, of this historical feat [8].

The isolation of morphine (**15**) from opium is complicated by the presence of codeine (**16**), the methyl ether of morphine. Grimaux [9] in 1881 and Hesse [10] in 1883 independently demonstrated the relationship between these two compounds, confirming the hypothesis voiced by Robiquet in 1833 [11]. Both Grimaux and Hesse prepared codeine by methylation of morphine, as did Rodionov in 1926 [12]; however, the reverse procedure is modern, suggested in 1977 by Rice [13], Fig. 1.2-5. Once the relationship between these two compounds had been established, most of the structural work was performed on codeine as morphine is subject to oxidative decomposition because of the presence of the free phenol.

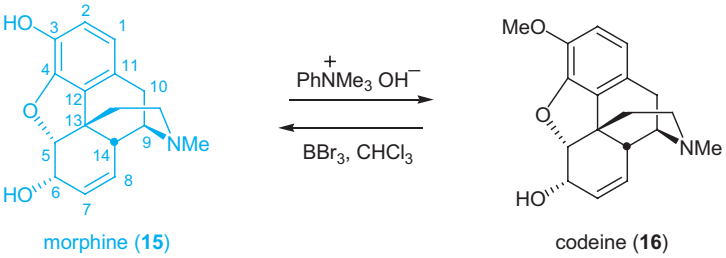


Figure 1.2-5 The relationship between morphine and codeine.

Acylation experiments by Wright in the 1870s [14] demonstrated the presence of an ether linkage and two alcohols. In 1881, von Gerichten established that morphine contained a phenanthrene (**17**) core when he isolated the hydrocarbon after pyrolysis of morphine with zinc dust [15].

He later confirmed the phenanthrene structure by isolating dihydroxyphenanthrene from the residue following Hofmann degradation of the methiodide (**18**) of diacetylmorphine (heroin) [16], Fig. 1.2-6.

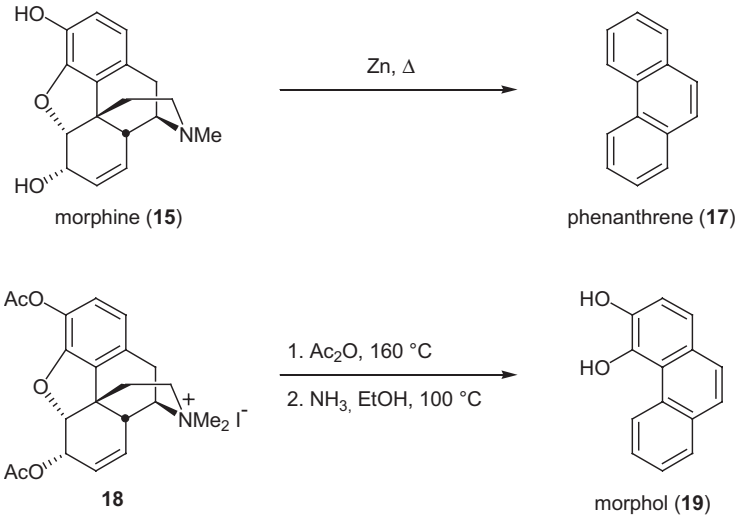


Figure 1.2-6 Proof of morphine's phenanthrene core.

The structure of dihydroxyphenanthrene (**19**), also called morphol, was later established by Pschorr's chemical synthesis [17], and by the brilliant deductive work in the late 1890s of von Gerichten, who assigned it as such based on a few facts in the literature and just two experiments [18]. There are 25 possible isomers of morphol; all but two were excluded on the basis of two degradation experiments. First, oxidation of morphol diacetate (**20**) produced *o*-quinone **21** with two acetates. Because the carbon number remained the same, neither C-9 nor C-10 could bear a hydroxyl. Second, isolation of *o*-phthalic acid (**22**) following further oxidation led to the conclusion that both hydroxyls were on the same ring, leaving only three possible isomers. Two of these were excluded on the basis of further experiments in which partial reduction of the Hofmann degradation product of codeine produced the bridged phenanthrene ether, methylmorphenol (**23**), Fig. 1.2-7 (page 28). All compounds were further reduced with zinc dust to phenanthrene. With the position of the catechol unit established, the placement of the hydroxyl at C-6 was elucidated by a series of additional degradations [Note 2].

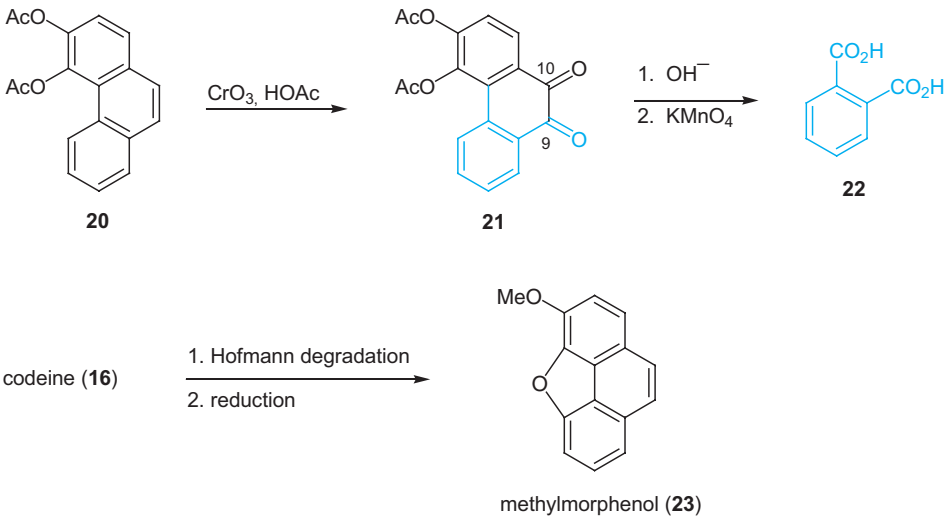


Figure 1.2-7 Proof of the position of the two hydroxyls of morphol.

The relationship of codeine to codeinone (**24**) was established and with it the identity of the C-6 alcohol, confirmed by the isolation of 4-methoxyphthalic acid (**26**) from the oxidative degradation of codeinone via **25**. These experiments confirmed the regiochemistry of all three of the oxygens present in morphine, Fig. 1.2-8.

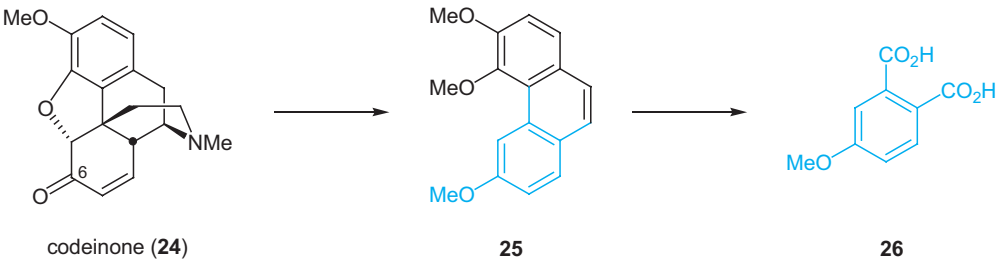


Figure 1.2-8 Proof of the position of the C-6 hydroxyl group.

The relationship of the C-6 alcohol and C-7/C-8 double bond followed from the synthesis and mutual transformation of chlorocodides, as shown in Fig. 1.2-9. Each of the four allylic chlorides formed on treatment of codeine with HCl was converted to the corresponding allylic alcohols; only two enones were obtained on further oxidation of the four allylic alcohols. One of these, codeinone (**24**), was reduced to codeine. These experiments thus confirmed the functional connectivity of C-6, C-7, and C-8 as that of an allylic alcohol.

The same experiments also excluded the attachment of the carbon terminus of the ethylamine bridge at either C-6, C-7, or C-8. That the nitrogen terminus of the bridge was attached to C-9 followed from careful analysis of Hofmann degradation experiments performed on oxycodeine (9-hydroxycodeine) (**27**). Under more controlled conditions oxycodeine gave ketone **28**; further degradation of **28** provided acetate **29**, which retained the original oxygen [19], Fig. 1.2-10.

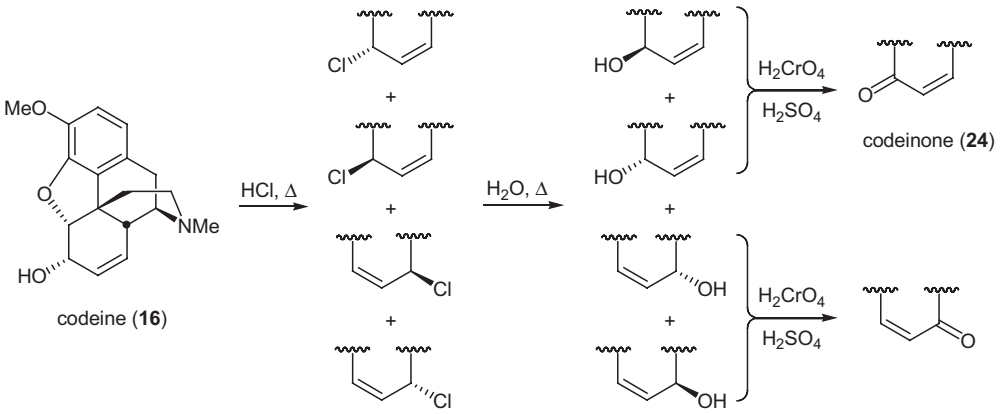


Figure 1.2-9 Proof of the relationship between the C-6 alcohol and the C-7/C-8 double bond.

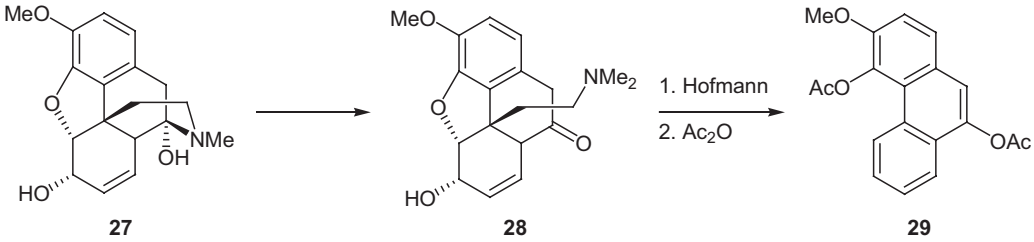
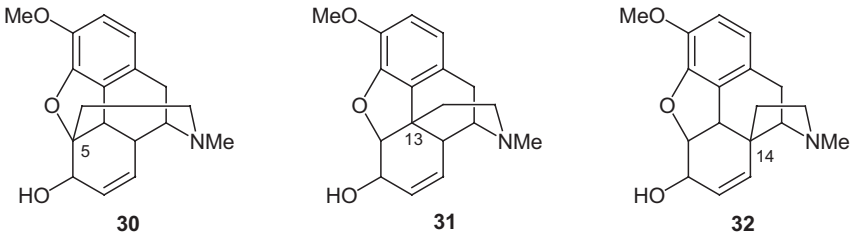


Figure 1.2-10 Proof of the position of the N-terminus of the ethylamine bridge.

The major challenge remaining was to discern the placement of the carbon terminus of the ethylamino bridge. Attachment at C-6, C-7, C-8, or C-10 had already been excluded on the basis of previous experiments, leaving three possibilities: attachment at C-5 (**30**), C-13 (**31**), or C-14 (**32**).



Structure **32** was excluded after further Hofmann experiments on codeine methiodide (**33**) yielded diene **34**, which was isomerized to **35**, Fig. 1.2-11. This conjugation with the original C-6/C-7 double bond would not be possible were C-14 a quaternary carbon. Knorr [20, 21], Pschorr [22], von Braun [23], von Gerichten [24], and Wieland [25] were responsible for this crucial elucidation.

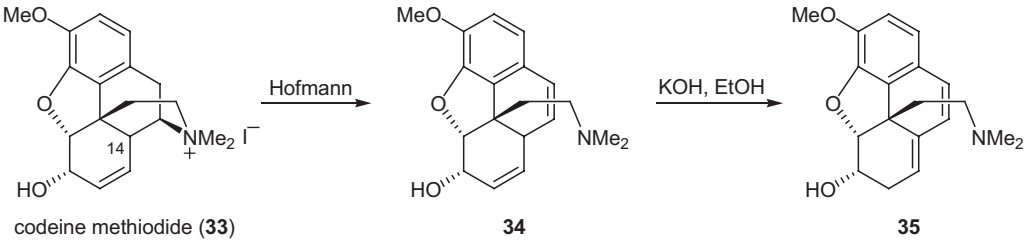


Figure 1.2-11 Proof that the C-terminus of the ethylamine bridge is not at C-14.

The final distinction (between **30** and **31**) was made on the basis of Schopf's [26] experiments involving the Beckmann rearrangement of the oxime derived from dihydrocodeinone (**36**). These experiments clearly yielded aldehyde nitrile **37** and *not* keto nitrile **38**, thus allowing the final assignments to be made, Fig. 1.2-12. The Gulland–Robinson proposals of 1923 and 1925 [27] were thus validated. To summarize, attachment at C-5 (**30**) was excluded because **37** (not **38**) was produced, and attachment at C-14 was excluded because the isolation of conjugated diene **35** precludes structure **32**. Structure **31** is therefore equivalent to that of codeine (**16**), and hence morphine must be **15**.

All that remained was confirmation of the structure by total synthesis, which was achieved by Gates in 1952 [28], and determination of the absolute stereochemistry, established by means of X-ray crystallography in 1955 by Mackay and Hodgkin [29].

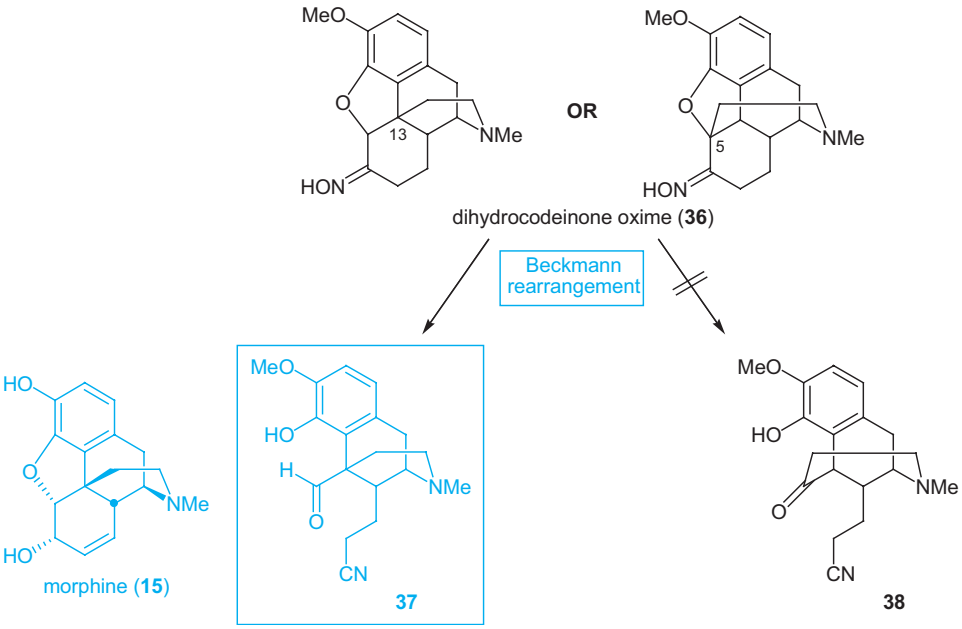
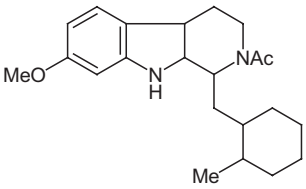


Figure 1.2-12 Proof that the ethylamine bridge C-terminus is at C-13, not C-5.

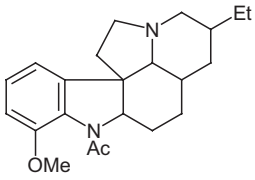
1.2.3 Aspidospermine

The pentacyclic indole alkaloid aspidospermine was first isolated in 1878 from the bark of the South American evergreen tree *Aspidosperma quebracho-blanco* Schlecht by Fraude [30], and it has since been found in other Apocynaceae species such as *Vallesia glabra* (= *V. dichotoma* Ruiz and Pav.) [31]. It eluded structure assignment for more than 50 years. Chemical degradation studies were begun with the work of Ewins in 1914 [32], who determined that the compound contained a methoxy group on an aromatic ring, an *N*-acetyl group, and possibly a reduced quinoline nucleus. Scholz [33a] was the first to suggest a structure, **39** (Fig. 1.2-13), based on the occurrence of aspidospermine with yohimbine, the structure of which he was working on at the time [34]. Structural studies were continued more intensively beginning in the late 1940s with the work of Openshaw and Smith [33b, 35] and that of Witkop [36].

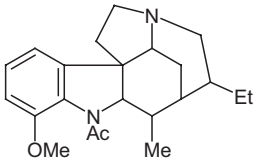
By the mid-1950s, these two groups had gathered the following information by means of degradations, colorimetric assays, and ultraviolet and infrared spectroscopy. (1) The tertiary nitrogen is not attached to the aromatic nucleus; it must be common to two rings as there is no *N*-alkyl group present [33b]. (2) The acetylated nitrogen is connected to the aromatic ring [33b]. (3) The compound contains a methoxylated dihydroindole nucleus [33b]. (4) The position of the methoxy group was established [35b, 36b].



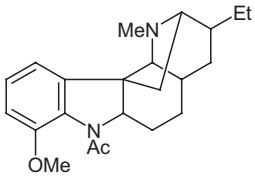
Scholz (1934)
39



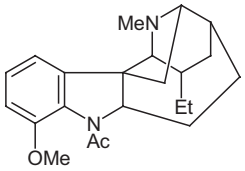
Witkop & Patrick (1954)
Chalmers, Openshaw, Smith (1955)
40



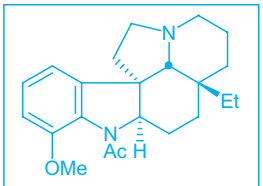
Witkop & Patrick (1954)
41



Conroy et al. (1957)
42



Conroy et al. (1957)
43



Mills & Nyburg (1959)
Conroy et al. (1959)
aspidospermine (**44**)

Figure 1.2-13 Structures proposed for aspidospermine.

When Witkop subjected aspidospermine to dehydrogenation with zinc dust, he isolated two fractions: one nonbasic, a mixture of skatole and 3-ethylindole, and one basic, containing 3,5-diethylpyridine [36b]. The identity of the last compound was in question as there were discrepancies in melting points of some of the derivatives of synthetic 3,5-diethylpyridine and those of the derivatives prepared from the degradation product. Witkop later speculated that this fraction actually consisted of a mixture of 3,5-diethylpyridine and 3-ethyl-5-methylpyridine [37]. Nevertheless, this information led to the proposal of the first reasonable structures for the alkaloid, **40** [35a, 36b] and

41 [36b], although both the Openshaw and Witkop groups acknowledged that **40** did not fit with Woodward's widely accepted biogenetic scheme for the related *Strychnos* alkaloids [38].

Several years later, after the correct structure had already been established, Smith and Wrobel [39] revisited the results of Witkop's zinc dehydrogenation. Curiously, they found that the picrate of 3-ethyl-5-methylpyridine does not depress the melting point of the picrate of 3,5-diethylpyridine. It is therefore not surprising that these structures would agree with the experimental findings. These authors proposed the fragmentation depicted in Fig. 1.2-14 to account for the isolation of the pyridines.

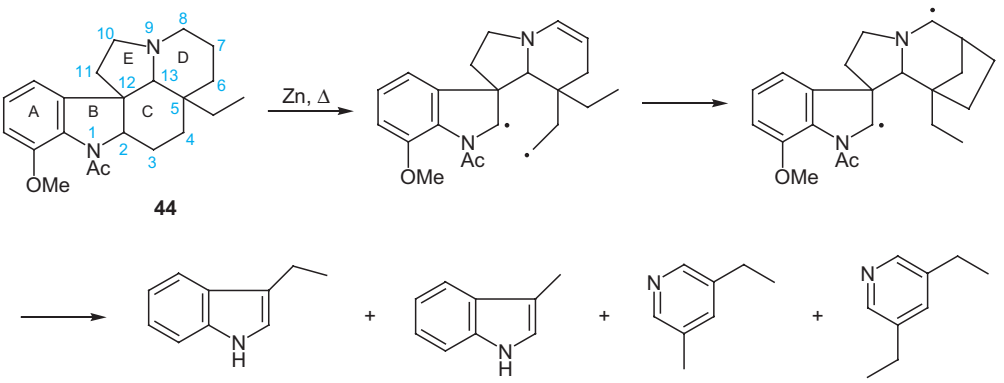


Figure 1.2-14 Suggested fragmentation of aspidospermine.

In 1957, Conroy and coworkers, who were among the first to use NMR as a tool for the structure elucidation of natural products, offered structures **42** and **43** [40], both of which have an *N*-methyl group. But within a year these were withdrawn [41] following Hofmann, Emde, and von Braun degradations and additional NMR experiments on aspidospermine and its degradation products. By this time the only structure still in serious contention was **40**. Finally in 1959 the correct structure (**44**) was announced simultaneously by the Conroy group [42], who based their conclusions on a combination of degradation and NMR experiments, and by Mills and Nyburg [43], who unequivocally established the structure by X-ray crystallography.

The Conroy paper [42] describes an intriguing proof of the attachment of the ethyl group to ring D based on a combination of chemical and spectral evidence. The chemical modifications of aspidospermine are shown in Fig. 1.2-15. The oxidation of the alkaloid with CrO_3 in pyridine gave a mixture of lactams **45**, **46**, and **47**. That lactam **47** was reduced to deacetylaspidopermine (**50**) verified that no skeletal rearrangement took place during the oxidation. The ^{1}H-NMR spectrum of **47** showed a clean AB quartet, and the spectrum of the acetate derived from **46** contained a singlet at δ 5.1 ppm. These observations coupled with the fact that **46** and **47** were also further oxidized to **45** indicate that ring E must contain the unit $–CH_2CH_2N(C–)_2$ attached to a quaternary center.

Oxidation of aspidospermine with mercuric acetate provided a mixture of enamines, including **48**, which could be reduced to aspidospermine with sodium borohydride. Further oxidation of **48** with silver oxide gave δ-lactam **49**, the reduction of which afforded deacetylaspidospermine **50**. These experiments confirmed that no skeletal rearrangements took place during these two oxidations. Enamine **48** reacted with *p*-nitrobenzenediazonium chloride to give an intensely red compound (**51**) that turned yellow (**52**) in acidic solution. This single experiment demonstrated that the enamine cannot be substituted at the 7-position.

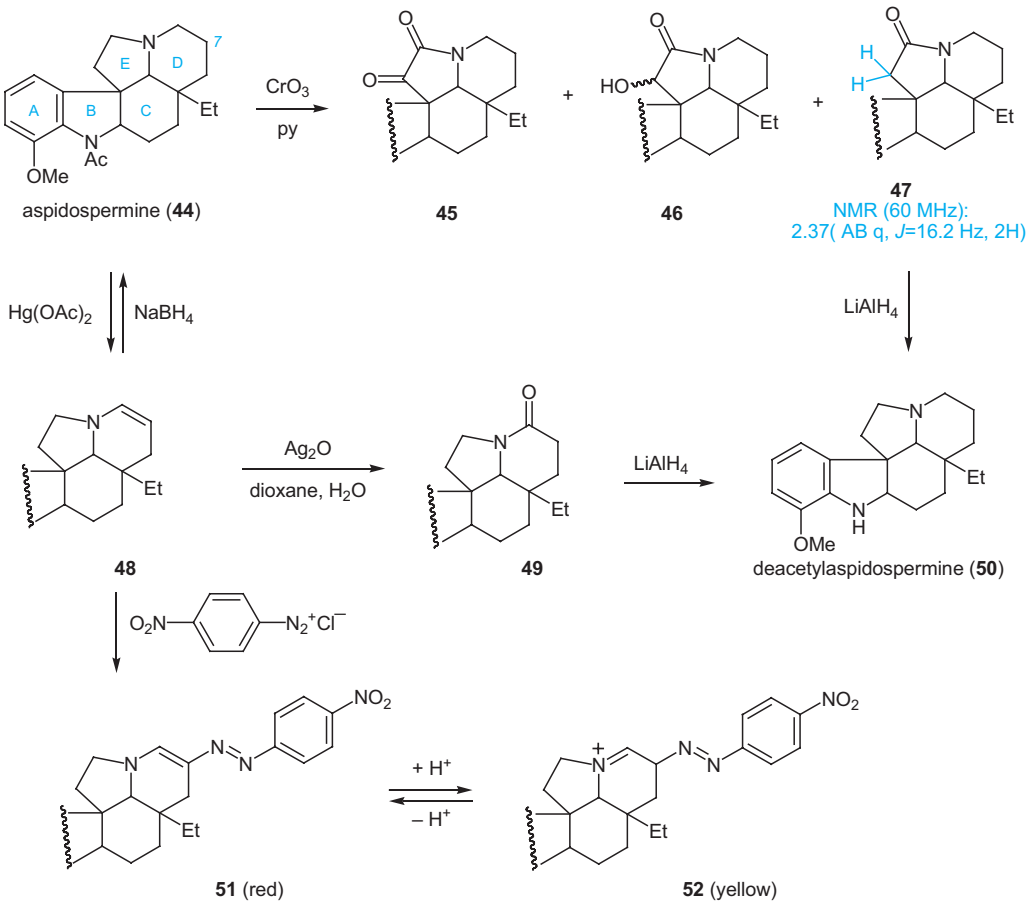


Figure 1.2-15 Degradation experiments to establish connectivity of aspidospermine's D and E rings.

To distinguish between enamine formation in either ring D or ring E, additional experiments were performed, as shown in Fig. 1.2-16. On Emde degradation [44], aspidospermine furnished the methylated amine **53**, which was subsequently subjected to Hofmann degradation. Only one product was obtained, either **54** or **55**. In the NMR spectrum of the product, the signal for vinyl proton H_c is a complex multiplet consistent with coupling to four other protons as in structure **54**. The signal for the analogous vinyl proton in structure **55**, where the vinyl group is attached to a quaternary center, would show coupling only to H_a and H_b. The presence of the methylene adjacent to the vinyl group was further proven by oxidative cleavage to aldehyde **56**; the NMR signal for the aldehydic proton was a triplet.

Isomerization of the olefin in **54** with acid gave **57**, which showed a trans olefin in its infrared spectrum and a vinylic methyl group in its NMR spectrum. The reader is reminded that this work was done in the very early days of NMR spectroscopy, at 60 MHz. Consequently infrared spectroscopy was used for determination of the olefin geometry (trans, 970 cm^{-1}). Compounds **54** and **57** were each hydrogenated to **58**, and the melting points of the perchlorate salts of each of the products were matched.

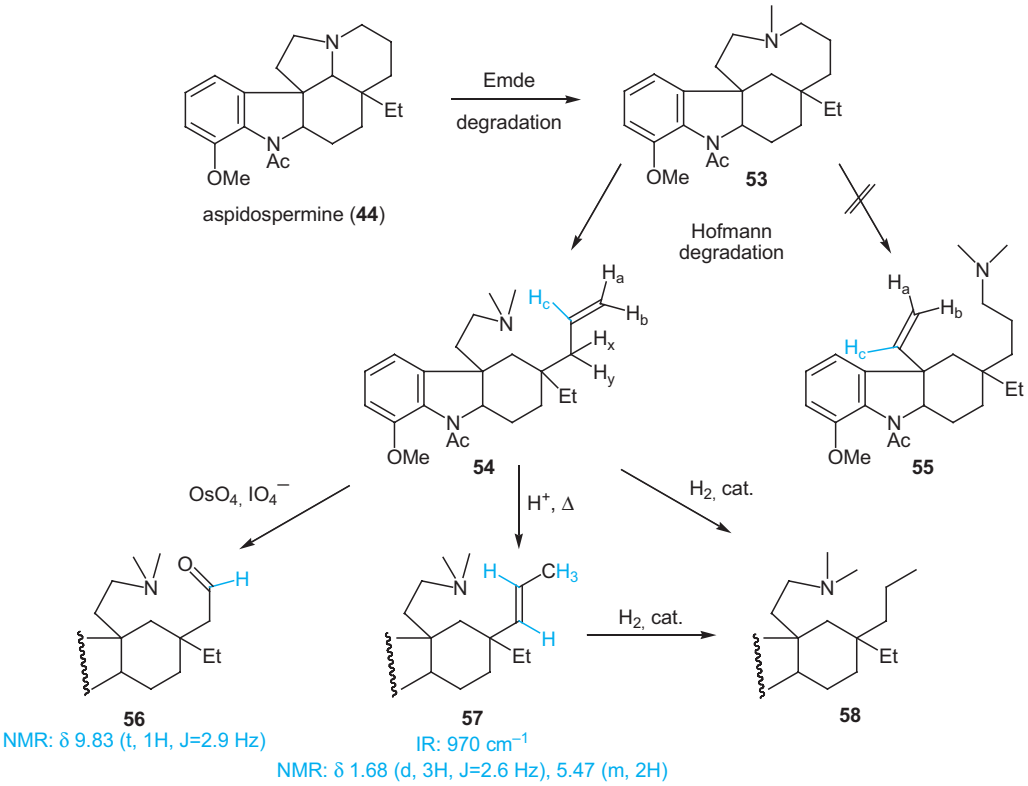
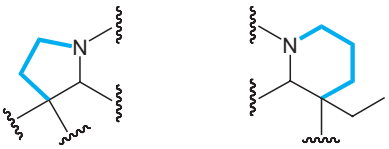


Figure 1.2-16 Chemical evidence for ring D versus ring E enamines.

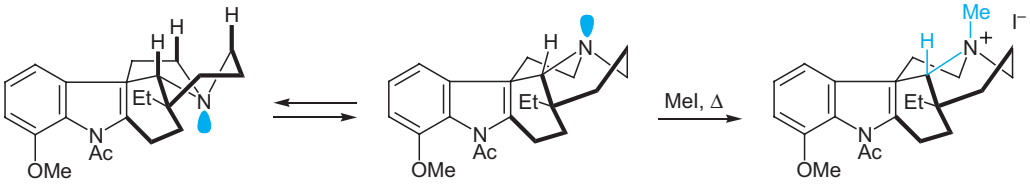
The conclusions drawn from these experiments can be summarized as follows. The formation of lactams **45**–**47** showed that ring E contains unit **59**. The oxidation to enamine **48** coupled with Hofmann degradation proved that the ethyl group is attached at the ring junction and that it is separated from the ring D nitrogen by three methylene units (**60**). It is noteworthy that this evidence coincided with the establishment of the correct structure by X-ray crystallography [43].



59 **60**

Mills and Nyburg's X-ray work [43] on the methiodide of aspidospermine established the relative stereochemistry of the alkaloid. The methiodide exists in a conformation in which the C ring is a chair and the D ring is a boat, with H-13 and the *N*-methyl group clearly maintaining a cis-relationship, as shown in **61**.

However, all aspidospermine derivatives with a tertiary nitrogen in the D ring show a well defined band of medium intensity between 2750 and 2800 cm^{-1} in the infrared spectrum. This is

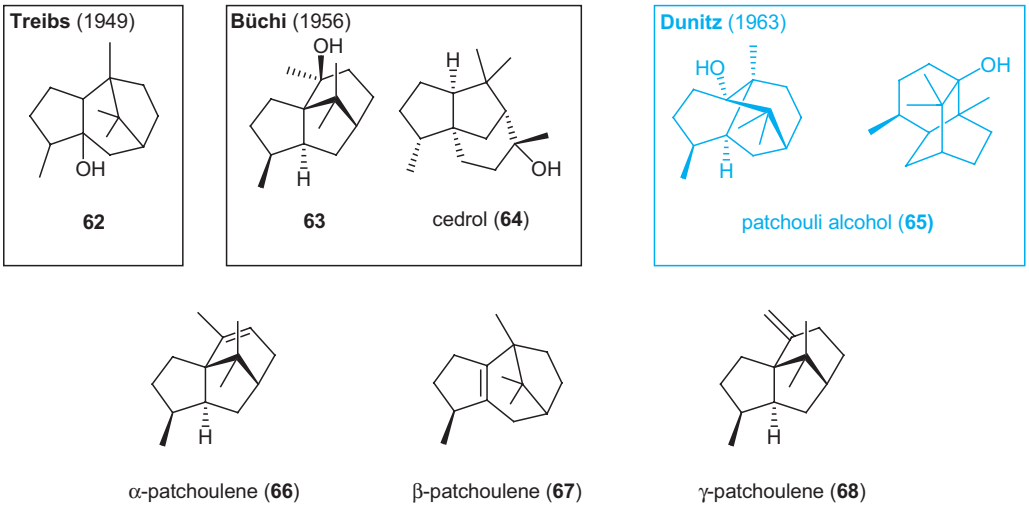


the so-called Wenkert–Bohlmann band [45], which is generally observed in systems that have more than two antiperiplanar relationships between a C–H bond and the nitrogen lone pair, and is also characteristic of compounds containing *N*-methyl groups [46]. This observation, coupled with the fact that the formation of the methiodide was sluggish, strongly suggested a conformational change from **44a**, where the lone pair is clearly hindered, to **44b** where it is more available. These brilliant and methodical deductions, made on the basis of simple observations, yielded important information about the stereochemistry of this alkaloid.

1.2.4 Patchouli Alcohol

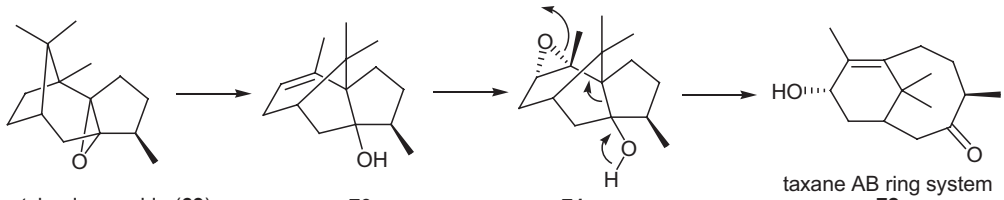
Patchouli alcohol, the major constituent of East Indian patchouli oil, has an intriguing history despite its relatively simple structure. Called patchouli-camphor in the oldest literature, it was first isolated in 1869 by Gal [47] from the fragrant plant *Pogostemon patchouli*. Treibs [48] (1949) offered the first representation (**62**) of a structure for patchouli alcohol, which he inferred from that of β-patchoulene (**67**), obtained along with the α and γ isomers (**66** and **68**, respectively) from the dehydration of patchouli alcohol under various conditions. (Treibs' structure for β-patchoulene was correct, but those that he proposed for the other two patchoulenes were not.)

In a 1956 communication [49] describing a series of degradation studies, Büchi proposed another structure, **63**, an interesting topological isomer of cedrol (**64**). His experiments and arguments



were elaborated in a full paper published in 1961 [50]. The proposed structure was seemingly confirmed by his total synthesis of the natural product, disclosed in 1962 [51]. Büchi's structure **63** was, however, not that of patchouli alcohol; the following year, Dunitz confirmed yet another structure (**65**) as the correct one during his X-ray investigation of chromium–oxygen–carbon bond angles in the patchouli alcohol diester of chromic acid [52]. There was no question of rearrangement during the formation of the chromate ester as the natural product was recovered on its hydrolysis.

In the full paper [53] (1964) on his total synthesis of patchouli alcohol, Büchi, now with the full knowledge of its correct structure, recounted the sequence of events and rearrangements that led to his originally proposed structure, detailing the "reverse rearrangement" of β-patchoulene oxide. It was amusing, Büchi admitted, that this was the same kind of rearrangement he had employed in the design for the synthesis of key intermediate α-patchoulene from β-patchoulene. Many years later, this rearrangement formed the cornerstone of Holton's design for his synthesis of the taxane skeleton (see Chapter 3.11) [54].



β-patchoulene oxide (**69**) **70** **71** taxane AB ring system **72**

In retrospect, the mystery of his erroneous structure assignments can be easily explained. Büchi's original structure assignment was based largely on the following observations. First, the dehydration of patchouli alcohol by treatment with one of several different acids gave only β-patchoulene (**67**). Second, the pyrolysis of patchouli alcohol acetate furnished a mixture of patchoulenes **66**, **67**, and **68** in a ratio of 52:4:46, respectively. Third, the dehydration of patchouli alcohol with $POCl_3$ and pyridine gave a mixture of **66**, **67**, and **68** in a ratio of 78:7:7. Last, a mixture of **66** and **68** provided **67** quantitatively upon treatment with acid. It was assumed that no rearrangement occurred during either pyrolysis or dehydration via its phosphate ester but that a Wagner–Meerwein shift was responsible for the formation of **67** from either **66** or **68**. Obviously both the acetate pyrolysis and the dehydration mechanisms must proceed with considerable cationic character to account for the ratios of the three olefins. (Perhaps the presence of acetic acid generated on pyrolysis is responsible for such a course.)

A key intermediate in Büchi's synthesis was α-patchoulene; he interpreted the sequence of reactions from that intermediate to the target as shown in Fig. 1.2-17, on the left side. The actual path (shown on the right side) involves a rearrangement proceeding in the reverse direction to that occurring during the pyrolysis of patchouli acetate (Fig. 1.2-18). This rearrangement may proceed with a significant cationic component, although a "concerted" pathway is possible as the carbonyl oxygen in the acetate in **78** is clearly sterically close to the α-hydrogen.

Büchi's synthesis of patchouli alcohol started with homocamphor (**79**), which was converted to β-patchoulene (**67**) and from there to α-patchoulene (**66**) (Fig. 1.2-19). The remarkable thing about this system is that the rearrangement of **67** to **66** via intermediates **69** and **70** was similar to what actually happens to the skeleton of patchouli alcohol upon the "forward" rearrangement. Thus any pathway to patchouli alcohol that intercepted α-patchoulene had to be, by definition, correct. Although Büchi could not have known it at the time, he did in fact make patchouli alcohol, and he may have intuitively "sensed" the correct route. Such has been his record in the field of Iboga alkaloids as well (see Chapter 4.8), attesting to the great gift he had for chemistry. (For a discussion of similar serendipity during his synthesis of ibogamine, see Section 4.8.3.)

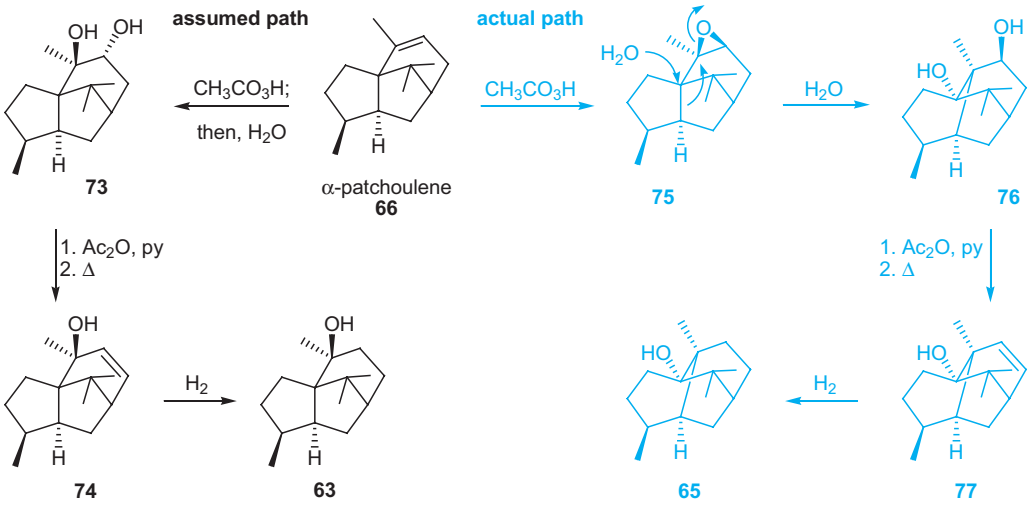


Figure 1.2-17 Assumed and actual pathways for the synthetic conversion of α-patchoulene to patchouli alcohol.

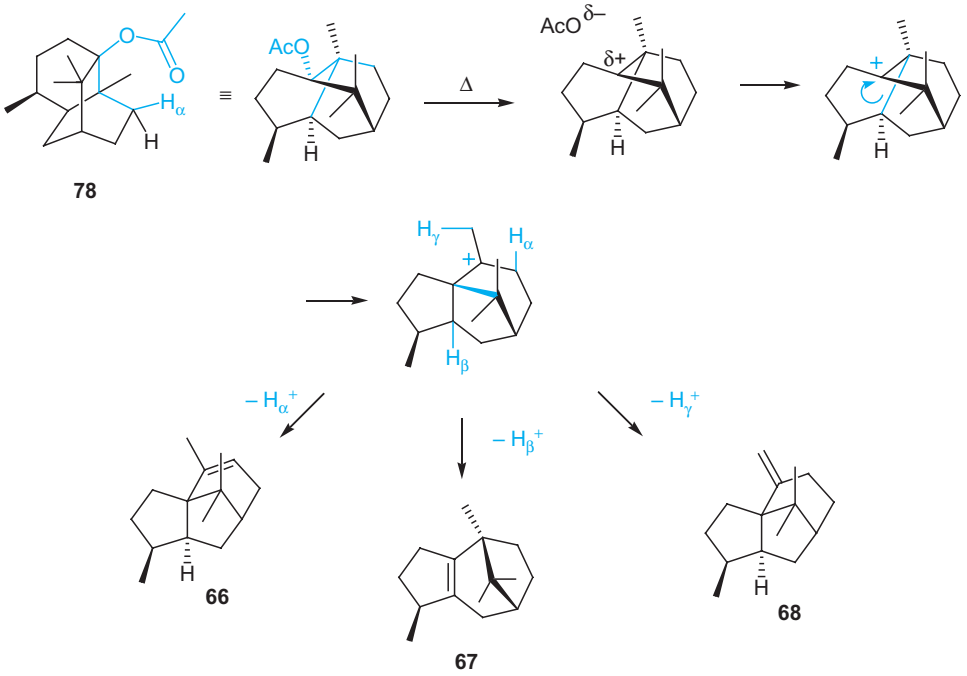


Figure 1.2-18 Pyrolysis of patchouli alcohol acetate (**67**).

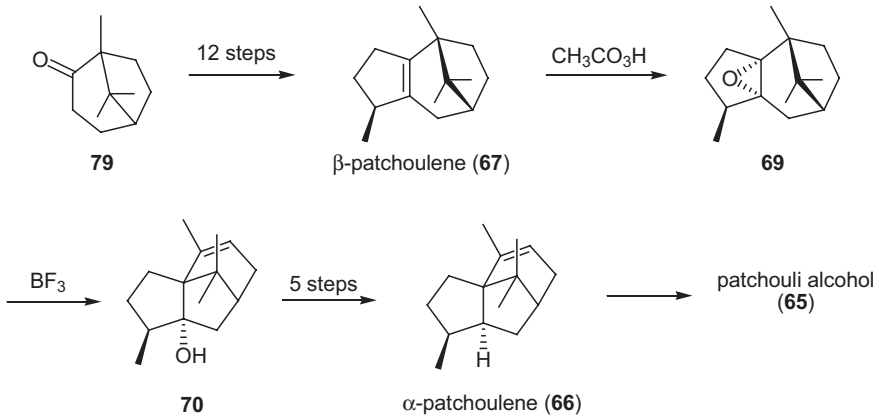


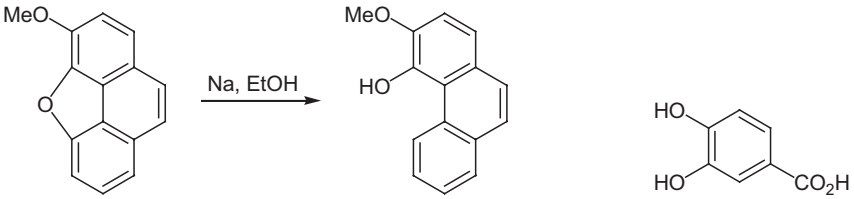
Figure 1.2-19 Büchi's synthesis of patchouli alcohol via α- and β-patchoulenes.

Descriptions of the elucidation of the structures of these four natural products make for fascinating stories, some of which (glucose and morphine) have achieved legendary status. The reader, especially one accustomed to the use of sophisticated NMR techniques, should appreciate the meticulous work and the logic required to establish chemical structures before the advent of modern analytical methods. The complete synthetic craftsman and artist of the 21st century should not discard the old and tried methods as they always provide useful hints. Sharp and alert thinking is still required to connect experimental observations with spectral and physical data in order to furnish deductions in a logical manner and thereby reach a concrete conclusion.

An enlightened experimentalist can learn many details of a reaction in progress by simple spray tests on thin-layer chromatograms or by IR monitoring long before work-up and the requisite "crude" NMR spectrum. Sadly, the qualitative approach to the structure determination of organic compounds used reflexively by old-school practitioners has been all but forgotten and replaced with 2-D NMR. Yet reaction monitoring and consequent changes in reaction parameters form the basis of all process optimizations in industry and are essential in providing optimum results. It is important that members of the synthetic community do not lose such skills.

Notes

1. In 1861 Butlerow reported that the reaction of formaldehyde with lime water (aqueous calcium hydroxide) resulted in a sweet-tasting syrup. In 1886 Loew repeated the experiment and named the product "formose." Fisher was able to identify components of formose by the use of phenylhydrazine.
2. The brilliance of von Gerichten can be truly appreciated when one examines the narrative of his reasoning. His conclusion that morphol is 3,4-dihydroxyphenanthrene was made on the basis of his memory of an old report in the literature concerning the isolation of 3,4-dihydroxybenzoic acid from the alkaline fusion of morphine. He excluded all but six of the 25 possible isomers of dihydroxyphenanthrene by two experiments. Of these only one structure could account for the observed reductive scission of methylmorphenol (**i**) to methylmorphol (**ii**).



i ii iii

This observation coupled with the structure of 3,4-dihydroxybenzoic acid (**iii**) led to the accurate assignment of hydroxyl groups in morphine's A ring. To put this deduction in perspective the reader should appreciate that today the structure of 3,4-dihydroxyphenanthrene could be assigned in a few minutes from a high field NMR spectrum.

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