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The Enchanting Alkaloids of Yuzuriha**

By Clayton H. Heathcock*

The oriental plant Yuzuriha (*Daphniphyllum macropodum*) elaborates a fascinating family of polycyclic, squalene-derived alkaloids that provide a test for state-of-the-art methods of organic synthesis. The intriguing structures of these natural products have inspired us to design and explore two rather different approaches for their laboratory synthesis. This article recounts and contrasts these two different syntheses. The first approach was based on a method of synthetic design that emphasizes efficient construction of the polycyclic skeleton of the molecule (Corey's "network analysis"). A strategic bond was identified and the synthesis planned around the late formation of this bond. The synthesis that was designed by this approach proceeded smoothly until the point where it was necessary to remove functional groups that had been incorporated solely for the purpose of forming the strategic bond. Although the problems were eventually overcome, the resulting synthesis was too long and did not control the configuration of one of the stereocenters. The second approach was based on a possible biosynthesis of one of the alkaloids and provided surprisingly easy access to the simpler members of the family. The success of this synthesis led to a concrete proposal about the biosynthesis of the alkaloids and to the discovery of the astonishing transformation depicted in Scheme 27. In this marvelous reaction, an acyclic squalene derivative is converted by successive treatment with ordinary commodity chemicals into a pentacyclic alkaloid. The transformation involves the formation of four carbon–carbon bonds, two carbon–nitrogen bonds, and one carbon–hydrogen bond!

1. Isolation and Structural Elucidation of the Alkaloids

In the Orient there grows a tree that the Japanese call "Yuzuriha," which, loosely translated, means to transfer leaves from hand to hand. The unusual name arose from the uncommon growth habit of Yuzuriha (*Daphniphyllum macropodum* Miquel), which develops an entire new set of leaves each spring before shedding the previous year's leaves later in the summer. Since antiquity, extracts of the bark and leaves of Yuzuriha have been used as a folk remedy for asthma. The first attempt to identify the active principles of the plant was made by the Japanese organic chemist Yagi, who reported in 1909 the isolation of an amorphous material, m.p. 75–84 °C, which he named daphnimacrine.[2] However, with the methods available at the time, no further progress could be made. It now appears that Yagi's daphnimacrine was a mixture of several alkaloids.

It was not until the 1960s that modern methods of structural analysis were equal to the task of deciphering the intricate structures of the alkaloids of Yuzuriha. As in many other cases, it was the group of Yoshimasa Hirata in Nagoya that finally succeeded in isolating two pure substances, daphniphylline (**1**)[3] and yuzurimine (**2**),[4] in 0.01% and 0.015%

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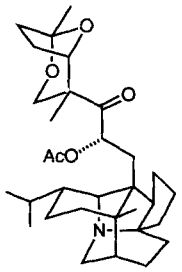
[**] This review article grew out of a series of lectures presented in Germany in July 1990, as the Merck-Schuchardt Lectureship. The full details of our work on the total synthesis of *Daphniphyllum* alkaloids are reported in a series of articles recently published in the *Journal of Organic Chemistry*: see ref. [1].

yields (based on dry weight of the plant material), respectively.[5] In the following decade, other *Daphniphyllum* alkaloids were identified, including daphmacrine (**3**),[6] macrodaphnine (**4**),[7] methyl homosecodaphniphyllate (**5**),[8] daphnilactone A (**6**),[9] daphnilactone B (**7**),[10] and yuzurine (**8**).[11]



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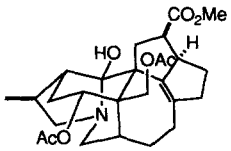

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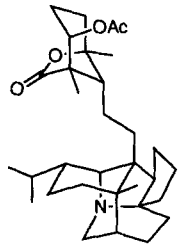

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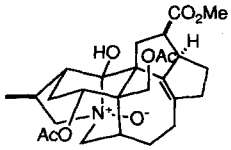

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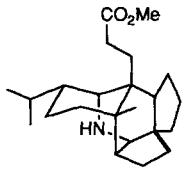

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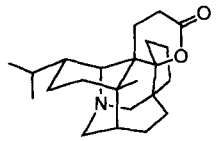

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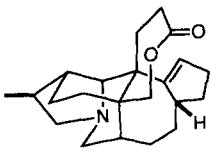

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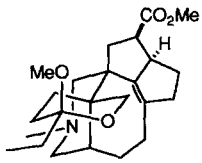

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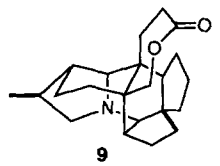

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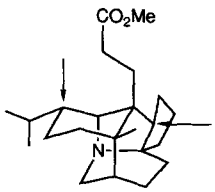
A total of 33 alkaloids from Yuzuriha have now been isolated and characterized. In addition, there was a report in 1990 of the isolation of a structurally related alkaloid, bukittinggine (**9**), obtained from the leaves and branches of *Sapium baccatum* collected near the town of Bukittinggi in West Sumatra, Indonesia.[12]

The 34 *Daphniphyllum* alkaloids, including bukittinggine, fall into seven skeletal classes: 1) daphnane (with 7 members), 2) secondaphnane (with 4), 3) daphnilactone A (with 1), 4) daphnilactone B (with 2), 5) yuzurimine (with 10), 6) daphnigracine (with 9), and 7) bukittinggine (with 1). Since the structures of compounds **1**–**9** have all been determined by single-crystal X-ray analysis, the structures, including absolute configuration, of all of the *Daphniphyllum* alkaloids are firmly established.

2. The First Synthetic Approach: Network Analysis

The seductive polycyclic structures of the *Daphniphyllum* alkaloids issue a siren call to the chemist interested in the de novo construction of complex organic molecules.When I first decided to answer this call about twelve years ago, the initial synthetic target that I selected was the C_{22} relative of daphniphylline, methyl homodaphniphyllate (**10**). There were two principal reasons for this choice. First, with only two functional groups and two independent stereocenters (indicated by arrows on its structure),[13] alkaloid **10** appears to be one of the simplest members of the group, its unusual pentacyclic structure notwithstanding. Second, the daphniphylline skeleton was thought to be archetypal of the family because daphniphylline is both wide-spread and abundant.



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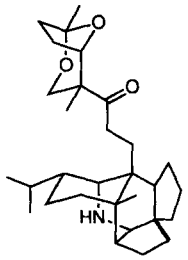

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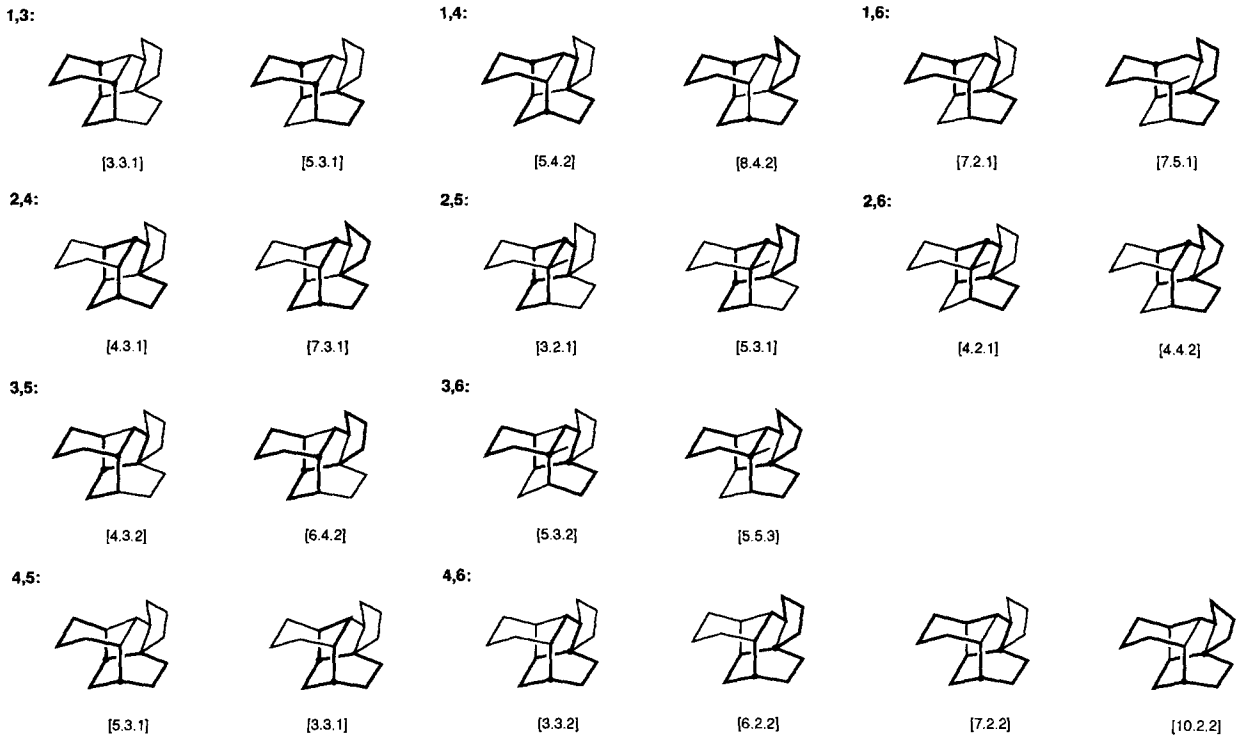
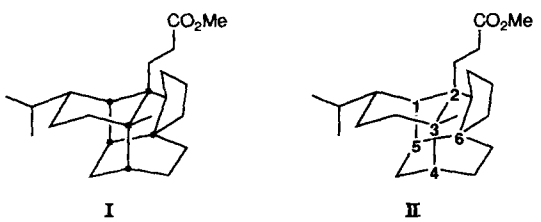
Clayton H. Heathcock was born in 1936 in San Antonio, Texas. After completing his secondary education in San Antonio and his undergraduate education at Abilene Christian College, he joined the Champion Paper and Fibre Company in Pasadena, Texas as Supervisor of the Chemical Tests Group in 1958. In 1960 he left this position and matriculated at the University of Colorado, where he did graduate work on steroidal nitrogen compounds with Alfred Hassner; he obtained his Ph.D. in 1963. He spent 1963–1964 in Gilbert Stork's laboratory at Columbia and joined the University of California at Berkeley as Assistant Professor in 1964. He has remained at Berkeley throughout his entire career and served as Chairman of the Department of Chemistry from 1986 through 1989. Professor Heathcock has also chaired the Organic Chemistry Divison of the American Chemical Society, the National Institutes of Health Medicinal Chemistry Study Section, and the Gordon Conference on Stereochemistry. He has served as Editor of Organic Syntheses and is currently Editor-in-Chief of the Journal of Organic Chemistry. His honors include the Ernest Guenther Award (1986), the American Chemical Society Award for Creative Work in Organic Synthesis (1990), the A. C. Cope Scholar Award (1990), and the Prelog Medal (1991). In 1978 he was a recipient of an Alexander von Humboldt United States Senior Scientist Award and was hosted in Germany by Professors Hans Bestmann and Paul Schleyer at Erlangen. In addition to his interest in natural product synthesis, Professor Heathcock has worked extensively in the area of stereocontrolled synthesis of acyclic compounds, and is particularly known for his work on the aldol and Michael addition reactions.



Scheme 1. For the numbering of the atoms see structure **II** (below).

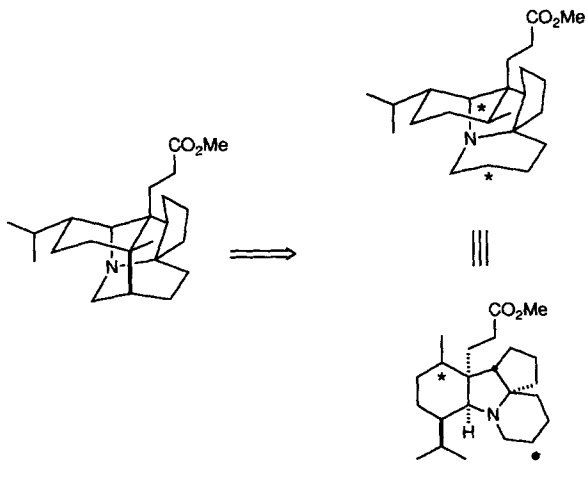
For example, one large-scale extraction of *D. macrododum* leaves yielded 100 g of daphniphylline and only 1.1 g of secodaphniphylline (**11**).[14] It will become clear in the sequel that this reasoning was fallacious and that our identification of **10** as an inaugural goal was unfortunate.

With the target identified, it was neccessary to develop a synthetic plan. Inspection of the structure of alkaloid **10** suggested that the primary obstacle to be overcome is assembly of the intricate pentacyclic skeleton. This is often the case in the synthesis of polycyclic compounds, and Corey has articulated a formal method of analyzing such problems. Corey's formalism, first used in connection with his synthesis of the sesquiterpene longifolene,[15] is called network analysis.[16] A polycyclic molecule will have embedded within its skeleton several bicyclic systems, some fused and some bridged. The basic premise of network analysis is that it is easier to synthesize fused-ring systems than bridged ones.



I **II**

The goal of the analysis is to identify the bond or bonds that are common to the most bridged bicyclic systems (the "maximally bridging" bonds), and to "retrosynthetically" remove these bonds, thereby achieving maximum structural simplification of the synthetic target. To locate the bridged-ring systems within the skeletal network of a polycyclic compound, one must first identify the atoms that can be bridgehead atoms in at least one bridged bicyclic system. The bridgehead atoms for methyl homodaphniphyllate are shown by the bold dots in structure **I**. The next step is to consider the bridgehead atoms in pairs and to identify all of the possible bridged bicyclic systems that exist. For the methyl homodaphniphyllate skeleton, the 22 bridged bicyclic systems shown in Scheme 1 are identified. Close examination of the 22 bridged bicyclic subsystems identified in Scheme 1 reveals that one skeletal bond is common to them all. Accordingly, this skeletal bond is identified as the strategic bond.[14] If this bond is retrosynthetically removed, the problem is simplified to the construction of the tetracyclic skeleton shown in Scheme 2. Although the skeleton of hypothetical target **A** is simpler than that of **10**, our stereochemical problem has become more complex, since **A** has five stereocenters. Nevertheless, the goal of network analysis is to

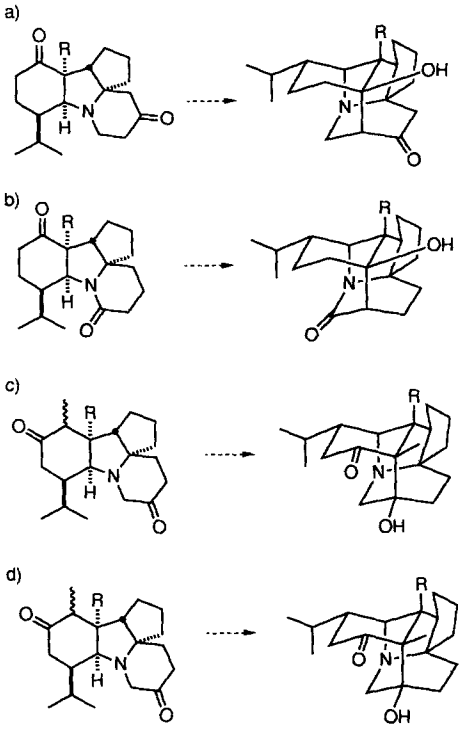


Scheme 2. **A**

identify possible synthetic precursors that have fewer bridged bicyclic systems, and skeleton **A** is clearly indicated as an appropriate target by this approach.

3. Functionality is Necessary to Create the Strategic Bond: "Consonant" and "Dissonant" Relationships

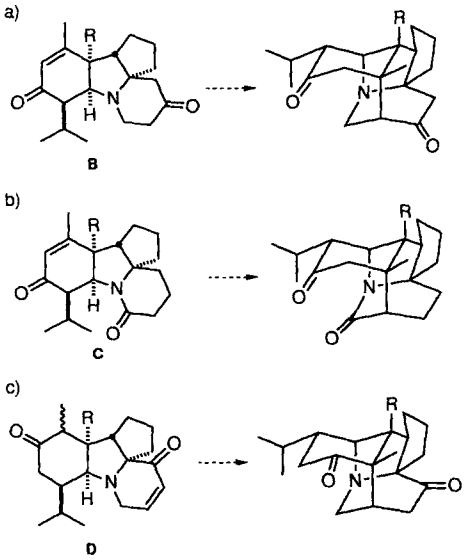
Network analysis only provides a target, not a method of synthesis. There remains the problem of devising a plan to synthesize the target and, equally important, a method of forming the strategic bond. For this purpose, we considered enol/enolate chemistry, namely, intramolecular aldol and intramolecular Michael reactions. For either of these reactions, we need functional groups either at or adjacent to the termini of the strategic bond. Four possible intramolecular aldol reactions are depicted in Scheme 3. A negative aspect



Scheme 3.

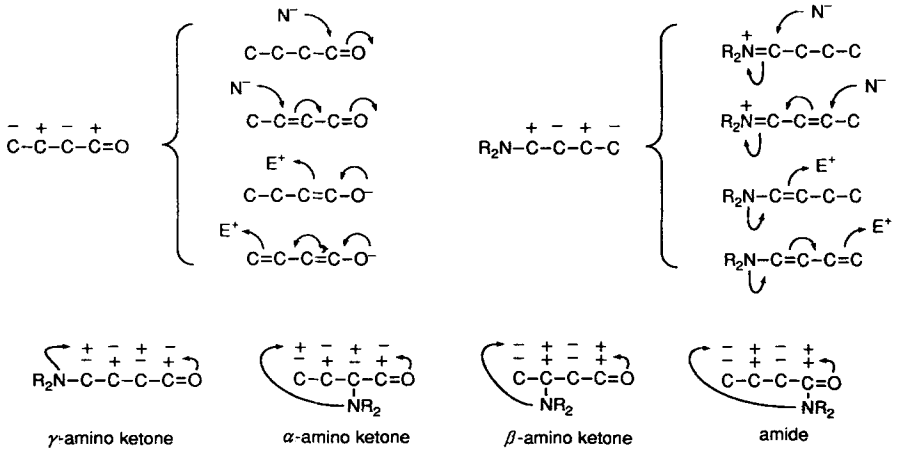
of possibilities a) and b) is the necessity of converting a bridgehead hydroxy group into a methyl group after the strategic bond has been formed. Although possibilities c) and d) are superior in this regard, they still would require a clumsy refunctionalization, replacement of a bridgehead hydroxy group by hydrogen, in addition to removal of the unwanted carbonyl group. Scheme 4 sketches three possible intramolecular Michael reactions that would provide the daphnane skeleton. These routes appear to be superior to the intramolecular aldol routes, because it would only be necessary to remove two carbonyl groups after the strategic bond is formed. Furthermore, there is ample precedent for the formation of six-membered rings by both base- and acid-catalyzed intramolecular Michael reactions.

However, the three possible Michael reaction substrates shown in Scheme 4 are not equally amenable to synthesis. In particular, the tetracyclic amino diketone **D** would be much more difficult to synthesize using standard methods than **B** or **C**. Compound **D** differs from **B** and **C** in its intrinsic functionality pattern. That is, in both **B** and **C** the amino



Scheme 4.

function is either β to a carbonyl group or attached directly to one. In **D**, however, the amino group is α and γ to the two carbonyl groups. The experienced synthetic chemist knows several methods to construct the array N–C–C–C=O (Mannich reaction, conjugate addition of an amino group to an α, β-unsaturated carbonyl function, acylation of an enamine, etc.) or N–C=O (amide formation), but few to construct the structural element N–C–C=O. The difference was recognized long ago by Lapworth, who formulated "the rule of alternating polarities,"[17] and formalized more recently by Evans in terms of "consonant" and "dissonant" bifunctional relationships.[18,19] The basic idea is that the presence of a heteroatom in a molecular skeleton can be viewed as imparting an intrinsic pattern of alternating electrophilicity and nucleophilicity to the atoms making up the skeleton. The situation is illustrated for a carbonyl group and an amino group in Scheme 5. Thus, the oxygen atom of a carbonyl group renders the carbonyl carbon atom itself and the β carbon atoms electrophilic, whereas the α and γ carbon atoms are intrinsically nucleophilic. The inherent difficulty in synthesizing α- and γ-amino ketones, relative to β-amino ketones and amides, is clearly seen from the diagrams at the bottom of Scheme 5. In the former case the two functional groups impart conflicting intrinsic polarities to the skeleton. Therefore, in the synthesis of α and γ-amino ketones it would be necessary to modify inherent polarity when constructing the skeleton. Of course, the reader will be aware that a considerable amount of research over the last two decades has been directed at reversing the innate electrophilicity or nucleophilicity of a given carbon atom through various contrivances. This strategy has been called "charge reversal" or "umpolung."[20] However, the use of



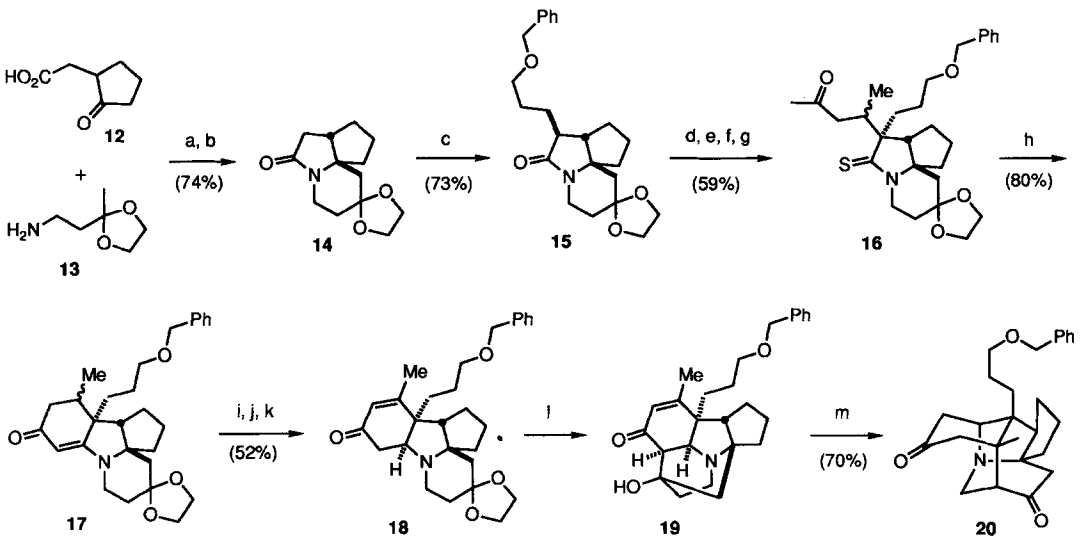
Scheme 5.

umpolung in a synthesis usually requires extra steps, expensive reagents, or esoteric reaction conditions. Since the goal of modern research should be to simplify synthetic routes, umpolung (and the use of protecting groups) must always be regarded as a compromise that is made when a given problem cannot be solved in a more direct manner. In the end, the best solution to a synthetic problem is a well-designed synthesis that takes maximum advantage of the natural functionality of the molecule to be synthesized.[21]

4. The First Synthesis of a *Daphniphyllum* Alkaloid: A Bittersweet Victory

The foregoing analysis directed our attention to the tetracyclic amino diketones **B** and **C** as potential synthetic intermediates for construction of the daphnane skeleton. Of these two possibilities, **B** appeared more attractive because of the great difference in acidity and ease of enolization of a ketone relative to a lactam carbonyl group. Accordingly, this compound became the focus of our attention. The synthesis of a tetracyclic amino diketone with the skeleton of **B** is summarized in Scheme 6. Keto acid **12**[22] and amino ketal **13**[23] were coupled using the mixed anhydride method to obtain a keto amide, which was cyclized by treatment with anhydrous acid. The cyclization reaction involves the reaction of a transient enol ether as the nucleophilic component in an intramolecular Mannich reaction with an acylalkylidenammonium (acylimmonium) ion, a reaction that was first observed by Wenkert et al.[24] The two-step conversion of **12** and **13** to the crystalline tricyclic ketal lactam **14** proceeded in excellent overall yield and was carried readily out on a multigram scale.

Treatment of the lithium enolate of lactam **14** with the benzyl ether of 3-bromopropanol[25] provided **15**, which was treated with the Lawesson reagent[26] to obtain the thiolactam. Surprisingly, thiation of the lactam carbonyl was accompanied by partial replacement of one of the dioxolane oxygen atoms, and it was necessary to remove and reinstall the protecting group before proceeding with the synthesis. In



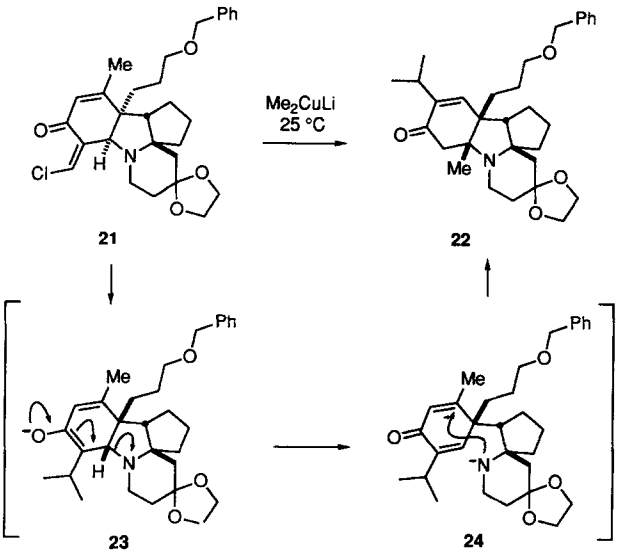
Scheme 6. a: i) **12**, Et_3N,$ClCO_2Et$; ii) **13**. b: *p*-toluenesulfonic acid, toluene, reflux. c: lithium diisopropylamide (LDA), $PhCH_2OCH_2CH_2CH_2Br$. d: Lawesson reagent. e: H_3O^+. f: $(CH_2OH)_2$, H^+. g: LDA, $CH_3COCH{=}CHCH_3$. h: i) $Et_3O^+BF_4^-$; ii) Et_3N. i: i) $Me_3O^+BF_4^-$; ii) $NaBH_4$; iii) H_3O^+. j: i) lithium-2,2,6,6-tetramethylpiperide (LTMP), THF, −78 °C; ii) PhSeCl. k: *m*-chloroperbenzoic acid. l: H_3O^+, acetone. m: MeONa, MeOH.

light of our philosophy with regard to protecting groups articulated at the end of the previous section, this unproductive maneuver constitutes a distinct flaw in the synthesis. However, as will soon be revealed, the entire approach turned out to be flawed for another reason, so there was little incentive to work out more appropriate thiation conditions. Treatment of the lithium enolate of the thiolactam with pent-3-en-2-one afforded **16** as a 6:1 mixture of diastereomers at the methyl-bearing stereocenter in about 80% yield.[27]

The fourth ring was closed by treatment of **16** successively with $Et_3O^+BF_4^-$ and triethylamine to give vinylogous amide **17**. Having reached our first goal of an intermediate with the skeleton of **B** (see Scheme 4), it was necessary to relocate the double bond and set the stage for formation of the strategic bond. This was accomplished by a three-step sequence wherein the double bond of **17** was reduced by successive treatment with $Me_3O^+BF_4^-$, $NaBH_4$, and aqueous acid to obtain a saturated amino ketone. The double bond was then reintroduced by deprotonation with LTMP in THF at $-78\,^\circ C$ and treatment of the resulting enolate with phenylselenyl chloride. Compound **18** was obtained in about 50% overall yield.

With **18** in hand, we could finally test the proposed intramolecular Michael addition and formation of the strategic bond of daphnane. To this end, compound **18** was subjected to aqueous acidic conditions in order to hydrolyze the ketal and thus obtain the enedione corresponding to structure **B** in Scheme 4. The infrared spectrum of the product revealed the presence of a saturated carbonyl group, not the desired α,β-unsaturated carbonyl function. Furthermore, the product clearly contained a hydroxy group. Unexpectedly (but predictably), the initial enedione had undergone an intramolecular aldol reaction under the acidic conditions. Fortunately, this unexpected cyclization was of no real concern, because the aldol cannot dehydrate for geometric reasons, and it is known that aldols are easily reversible under the basic conditions required for the intramolecular Michael reaction. Thus, treatment of aldol **19** with methanolic sodium methoxide smoothly furnished the amino diketone **20**, the first synthetic material having the pentacyclic daphnane skeleton.

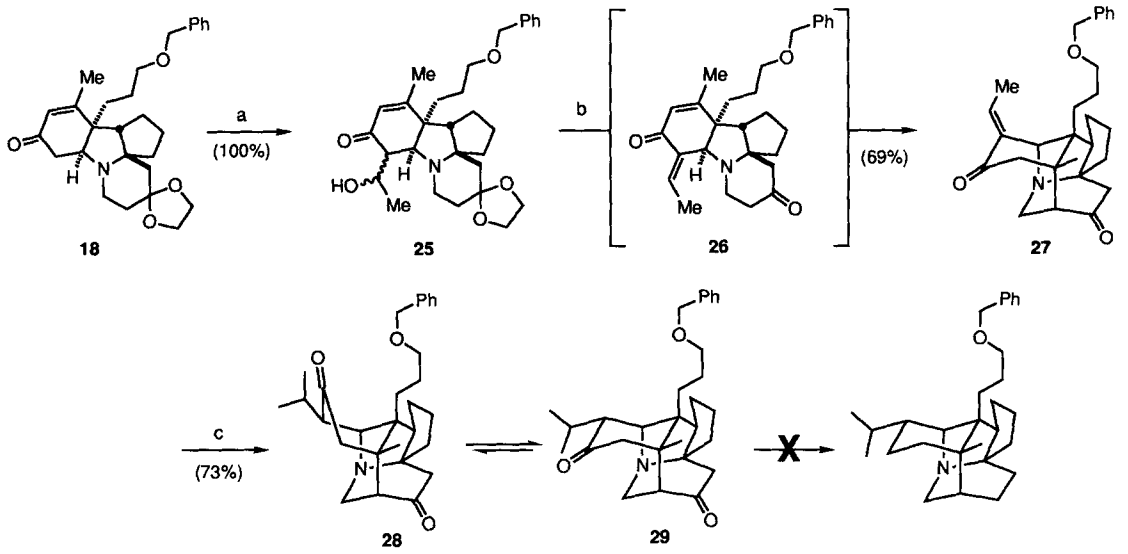
With the path to methyl homodaphniphyllate thus illuminated, three tasks remained before us. The first was installation of the final three carbon atoms, in the form of the isopropyl group. Second, there was the seemingly trivial task of removing the two carbonyl oxygens atoms which, having served their synthetic purpose, were now superfluous. Finally, it was necessary to correctly refunctionalize the three-carbon side chain. At this point, a brief detour was forced upon us. In an attempt to introduce the isopropyl group, compound **18** was formylated, and the resulting keto aldehyde was treated with oxalyl chloride to obtain the β-chloro enone **21**. When this material was treated with lithium dimethylcuprate in ether at room temperature, rearranged enone **22** was the only identifiable product (Scheme 7). At first glance, the transformation of **21** into **22** appears astonishing. Although the product is an enone, as expected, the isopropyl and methyl groups seem to have been miraculously relocated. However, the explanation is ordinary and, in fact, the reaction could have been anticipated. Enolate **23**, formed after reaction with the second equivalent of cuprate, simply undergoes β elimination to give a cyclohexadienone, **24**, which undergoes 1,4-addition at the methyl-bearing double bond. Ironically, the same intrinsic polarization that had made this skeleton easy to assemble also provided the seed of its destruction!



Scheme 7.

The retro-Michael problem was solved in a relatively straightforward fashion. As shown in Scheme 8, the lithium enolate of **18** reacted with acetaldehyde to provide aldol **25**, which was treated with sulfuric acid in aqueous acetone. Careful examination of the reaction intermediates disclosed that the aldol dehydrated rapidly and that the ethylene ketal hydrolyzed more slowly to **26**. This substance, now deprived of the possibility of β elimination or intramolecular aldol reaction by the presence of the ethylidene group, smoothly cyclized to the pentacyclic enedione **27**, which was obtained in about 70% yield.

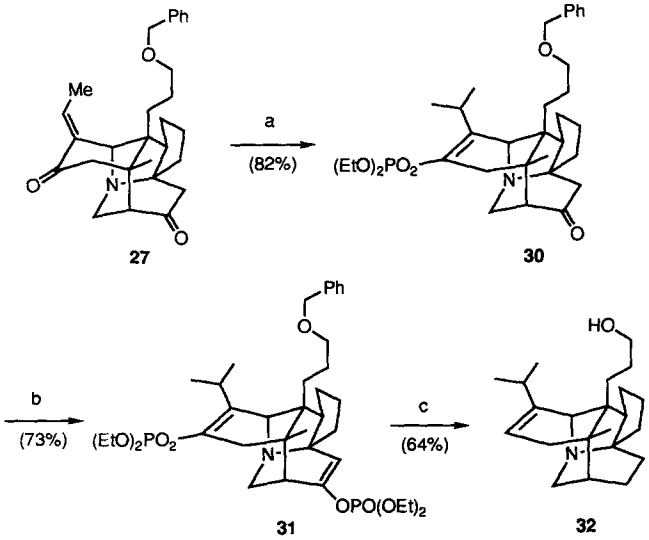
Efforts were next directed toward introduction of the final carbon atom of methyl homodaphniphyllate. We had planned to accomplish this task by conjugate addition of lithium dimethylcuprate to **27** an had anticipated no problems with the maneuver, since the isopropyl group in the natural product occupies an equatorial position. However, our estimation proved to be overly optimistic. Although **27** reacted smoothly with lithium dimethylcuprate, the product was a mixture of diones, epimeric at the isopropyl-bearing stereocenter, in a ratio of 4:1. This development presented us with three problems: First, the isomers equilibrated with great ease, even on attempted separation by column chromatography on silica gel. Second, although molecular modeling suggested that the desired isomer **29** would predominate in the equilibrium, the calculated strain energies of the two isomers were so close that we had no confidence that this isomer was, in fact, the major product. Finally, and most importantly, many attempts to remove the two carbonyl groups utterly failed. Although space does not permit a complete catalog of the methods that were evaluated for deoxygenation of **28** and **29**, it is sufficient to say that a great many reactions were tested, ranging from simple Wolff–Kishner



Scheme 8. a: LDA, CH_3CHO; b: H_2SO_4, acetone; c: Me_2CuLi, Et_2O.

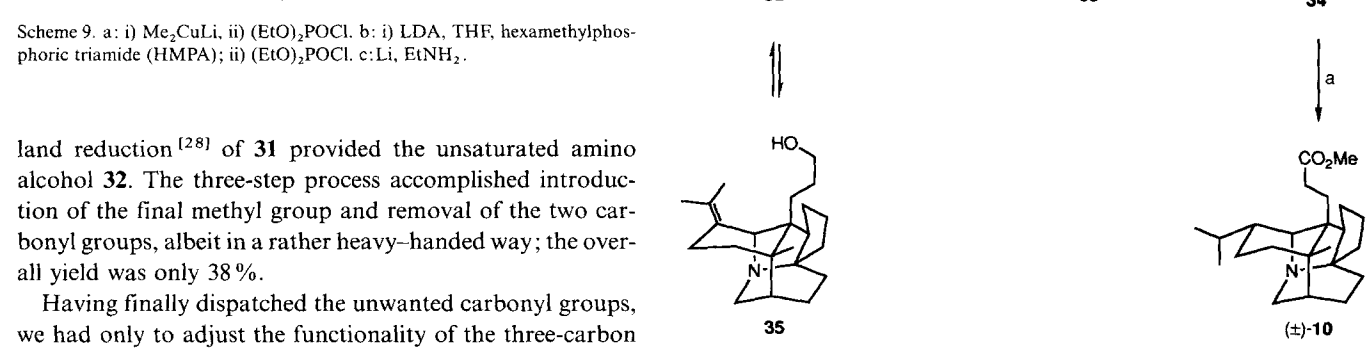
reduction to various strategies designed to proceed through free radical intermediates. The origin of the problem seemed to be the sterically hindered environment of the carbonyl next to the isopropyl-bearing center.

We eventually found a way around the impasse. As summarized in Scheme 9, the initial lithium enolate resulting from reaction of lithium dimethyl cuprate with **27** was phosphorylated to obtain **30**, which itself was deprotonated and phosphorylated to arrive at the bis(enol phosphate) **31**. Ireland reduction[28] of **31** provided the unsaturated amino alcohol **32**. The three-step process accomplished introduction of the final methyl group and removal of the two carbonyl groups, albeit in a rather heavy-handed way; the overall yield was only 38%.



Scheme 9. a: i) Me_2CuLi, ii) $(EtO)_2POCl$. b: i) LDA, THF, hexamethylphosphoric triamide (HMPA); ii) $(EtO)_2POCl$. c: Li, $EtNH_2$.

Having finally dispatched the unwanted carbonyl groups, we had only to adjust the functionality of the three-carbon side chain and reduce the double bond to complete the first synthesis of a *Daphiphyllum* alkaloid. We had not anticipated problems with saturation of the double bond, because molecular models of **32** showed that the same methylene group (indicated with an arrow in Scheme 10) that had impeded removal of the carbonyl oxygen atom now stood squarely in the path of any reagent seeking access to the "bottom face" of the cyclohexene double bond. For this reason, we were rather confident that hydrogenation would occur from the "top face", delivering the daphnane skeleton with the proper configuration at the isopropyl-bearing carbon. However, events proved otherwise. Initial hydrogenations over rhodium did give only one product, but the one having the wrong configuration at the new stereocenter! Subsequent investigations showed that the stereochemical outcome of the reduction was responsive to changes in catalyst and solvent, and we embarked on an extensive program of process development. However, even under the best conditions we could find (Scheme 10), we were able to achieve no better than a 1:1 mixture of the diastereomeric amino



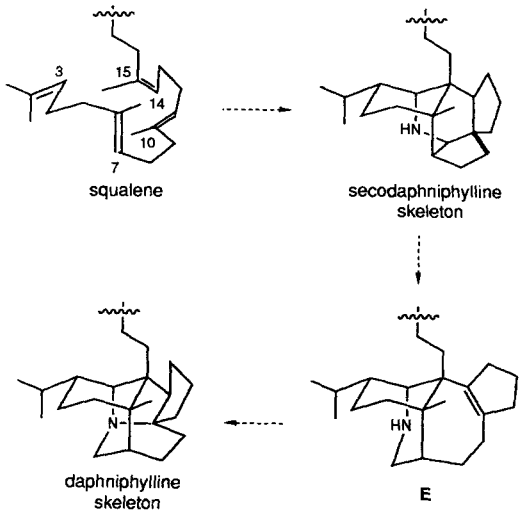
Scheme 10. a: i) Separation; ii) Jones oxidation; iii) 6 M HCl, MeOH.

alcohols **33** and **34** with the respective unnatural and natural configuration at the new stereocenter. Once again, nature had thwarted our simplistic plans. Because hydrogenation of the hindered double bond is slow, it is likely that isomerization occurs to give some isomer, perhaps **35**, in which the bottom face of the double bond is not as hindered as it appears to be in **32**. Nevertheless, amino alcohol diastereomers **33** and **34** were separable by chromatography, and the latter isomer was transformed by succesive oxidation and esterification into racemic methyl homodaphniphyllate, (±)-**10**.

By obtaining a few milligrams of (±)-**10**, we had achieved the first total synthesis of one of the alkaloids of Yuzuriha. However, the problem of finding a truly efficient route to these fascinating natural products had still not been solved. The synthesis just described was not especially long, given the state of synthetic art and the complexity of the target. Only 19 steps were required, starting with keto acid **12** and amino ketal **13**. Although the method of network analysis did identify a facile assembly for the pentacyclic skeleton, the concluding stages of the synthesis, which were occasioned by the need to remove the activating carbonyl groups, were awkward and failed to control one of only two independent stereocenters in the molecule. Thus, the very heuristic that had so simplified the synthetic design had also endowed the synthesis with its Achilles heel.

5. A Fresh Look at the Problem: Dissection of the Target Along Probable Biosynthetic Lines

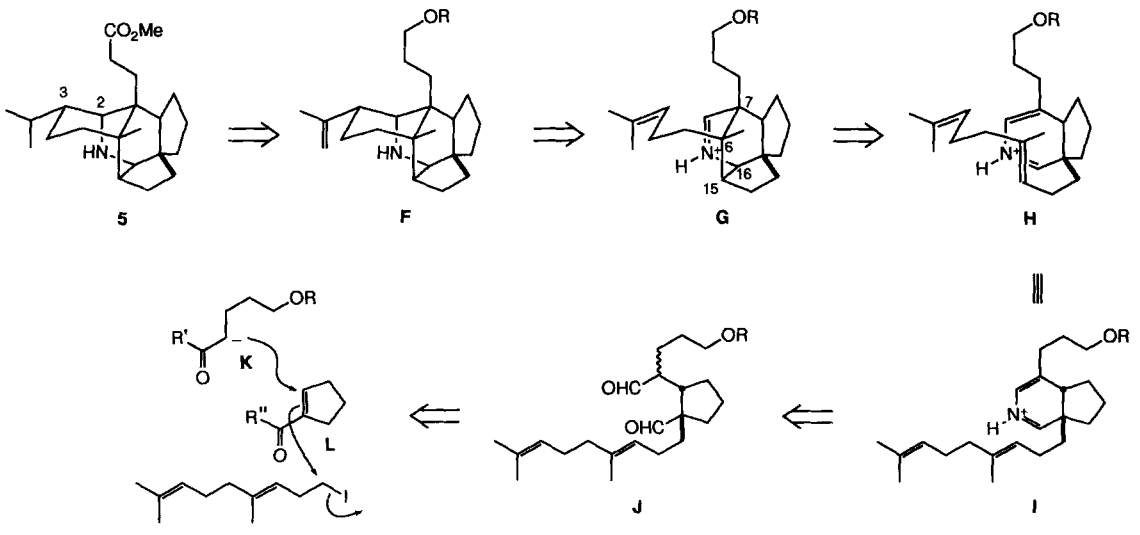
Even while we were struggling with removal of the two carbonyl oxygen atoms and stereocontrolled reduction of the double bond in **32**, we turned our minds back to the original design. Where had we gone wrong? In examining our assumptions, we reconsidered the reasons for selecting methyl homodaphniphyllate as our first target. Because it is widespread and abundant relative to the other *Daphniphyllum* alkaloids, we had made the mistake of bestowing it with singular importance and elected it as our original synthetic goal. However, an examination of the daphnane and seco-



Scheme 11.

daphnane carbon skeletons reveals an important difference. As shown in Scheme 11, the unbroken squalene molecule can be identified in the pentacyclic structural unit of secodaphniphylline but not in that of daphniphylline. That is, in order for squalene to be converted into secodaphniphylline, four C–C bonds must be created: C10 to C14; C6 to C15; C3 to the C15 methyl group; and C7 to the C10 methyl group. The nitrogen atom is inserted between the C10 and C15 methyl groups. In daphniphylline, on the other hand, the nitrogen atom has been inserted between C10 and its methyl group, which has also become bonded to C7. Although circumstantial, the evidence is strong that secodaphniphylline prededes daphniphylline biosynthetically. A reasonable biosynthetic link between secodaphniphylline and daphniphylline is an unsaturated amine with the partial structure **E**.[29]

The perception of this biosynthetic progression was significant, since it suggested the probability of some reasonable chemical path for the conversion of secodaphniphylline to daphniphylline by way of a ring-opened intermediate such as **E**. If we could discover the path, we could use it as a better route to **10**. A natural consequence of this line of thought was a redirection of our attention to the skeleton of seco-



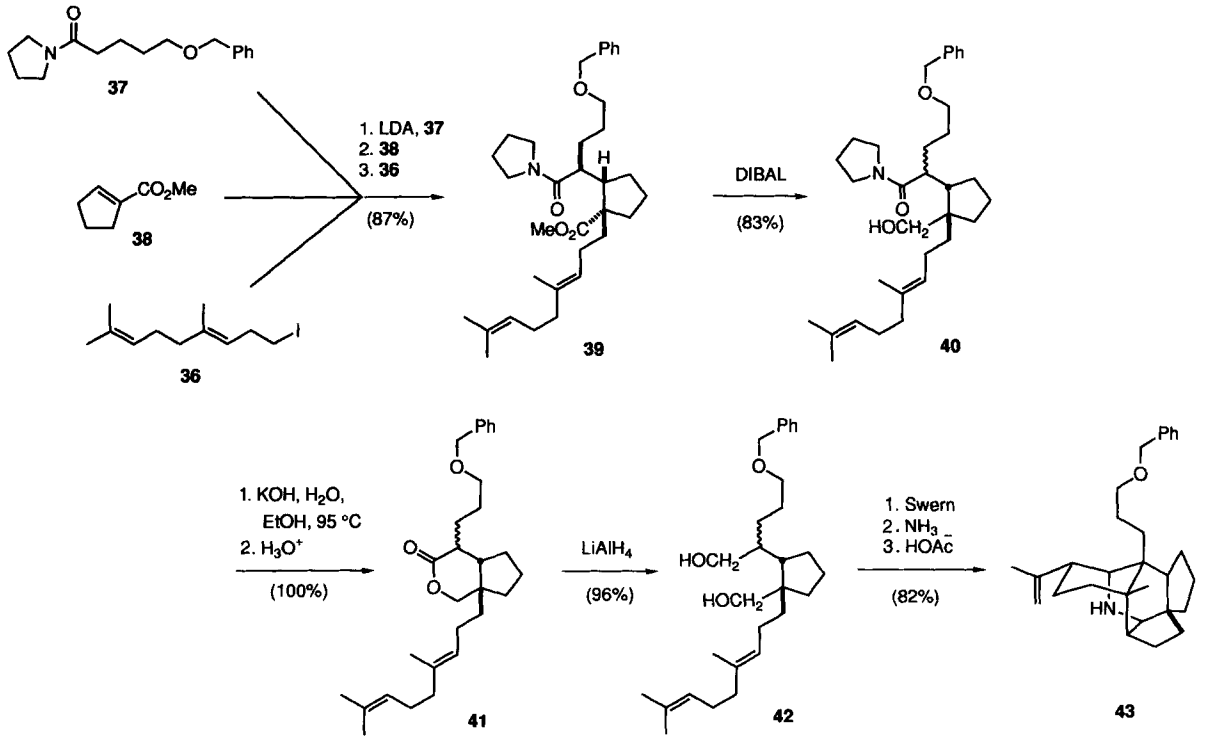
Scheme 12.

daphniphylline, as exemplified by its C_{22} congener, methyl homosecodaphniphyllate (**5**). Although a retrosynthetic analysis centered about the primacy of the pentacyclic network was again possible, we feared that the inevitable end of such a plan would be another struggle to remove necessary but unwanted functional groups. Thus, we abandoned the strategic bond approach in favor of synthetic plans by which the skeleton might be assembled without the wasteful use of auxiliary functional groups. How does nature forge the skeleton of secodaphniphylline from its triterpene raw material? The plan that emerged from these contemplations is summarized in Scheme 12. A key element was the dissection of the skeleton along probable biosynthetic lines. That is, in the retrosynthesis, bond disconnections were made so as to preserve the squalene chain for as long as possible until we recognized an obvious solution based on available materials and methods. This reasoning forced us to consider formation of the C2–C3 bond as the final carbon–carbon bond-forming operation in the formation of secodaphniphylline. Homoallylic amine **F** contains a reasonable retron for the desired transform,[30] which can be viewed as an ene or aza-Prins reaction. Once **G** had been identified as a possible synthetic intermediate, it was natural to take the next step and consider the possible formation of bonds between C6 and C7 and then between C15 and C16. It then became clear that a compound with the part structure of **I** might easily arise from reaction of a monocyclic dialdehyde **J** with ammonia. Up to this point, the plan being developed might even parallel the biosynthesis of the alkaloid. However, with the perception of dialdehyde **J** as an attractive intermediate, a decidedly nonbiosynthetic possibility occurred to us. Compound **J** might be obtained in one grand, triply convergent step by the assembly of an enolate **K**, some α,β-unsaturated carbonyl compound **L**, and homogeranyl iodide (**36**)!

6. Biomimetic Synthesis of Methyl Homosecodaphniphyllate: The Ruggeri Tetracyclization Reaction

The exciting plan was soon put into practice. Successive treatment of the lithium enolate of amide **37** with the α,β-unsaturated ester **38** and homogeranyl iodide (**36**)[31] provided a mixture of three diastereomeric adducts in a total yield of 99%. Compound **39**, the major isomer, was isolated in 87% yield. Two minor isomers were isolated as a 2:1 mixture in a combined yield of 12%. It is not insignificant that the entire carbon skeleton of alkaloid **5** is assembled in this one convergent step. The next task that stood before us was transformation of the ester and amide groups of **39** into aldehyde groups. A good deal of experimentation led to the three-stage protocol summarized in Scheme 13. Treatment of **39** with excess DIBAL gave hydroxy amide **40**, which was hydrolyzed by treatment with KOH in aqueous ethanol. Acidification of the saponification mixture furnished lactone **41** as a 1:1 mixture of diastereomers; epimerization of the benzyloxypropyl center had occurred under the harsh alkaline conditions. However, the configuration at this position is of no consequence because it is destined to have sp^2 hybridization at a later stage in the synthesis. Reduction of **41** with lithium aluminum hydride gave an equimolar mixture of epimeric diols **42** in nearly quantitative yield.

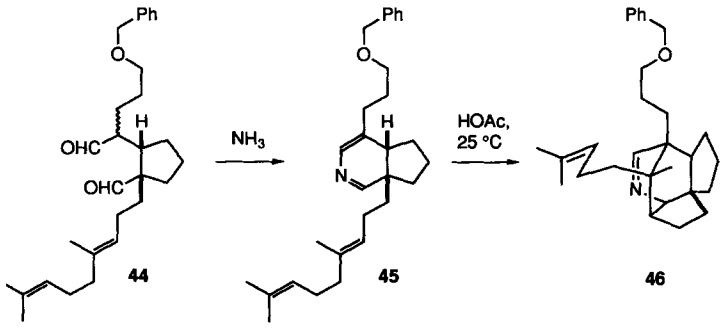
The way was now prepared for the most crucial stage of the plan. Oxidation of diols **42** by the Swern method[32] gave a dialdehyde that turned out to be rather vulnerable to a retro-Michael fragmentation. Consequently, a procedure was developed whereby the material was formed and used in situ. Thus, after the Swern oxidation was complete, gaseous ammonia was passed over the surface of the stirring methylene chloride solution. Concentration of the reaction



Scheme 13. DIBAL = diisobutylaluminum hydride.

solution gave a residue that was taken up in acetic acid containing NH_4OAc. This mixture was heated at 70 °C and worked up in the normal manner to obtain pentacyclic amine **43** in 82% yield. The structure of **43** was eventually proven by its conversion to (±)-methyl homosecodaphniphyllate.

Several intermediates in the conversion of diols **42** into pentacyclic amine **43** have been isolated (Scheme 14). As has already been discussed, the initial Swern oxidation provided the dialdehydes **44**. When the reaction was terminated after

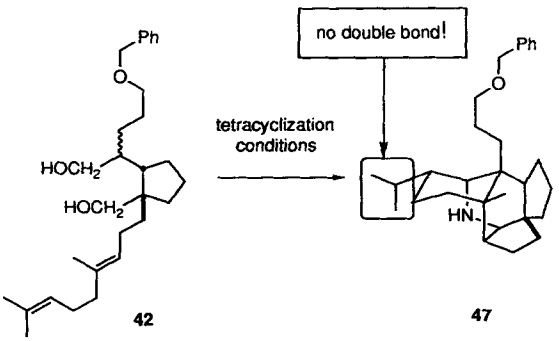


Scheme 14.

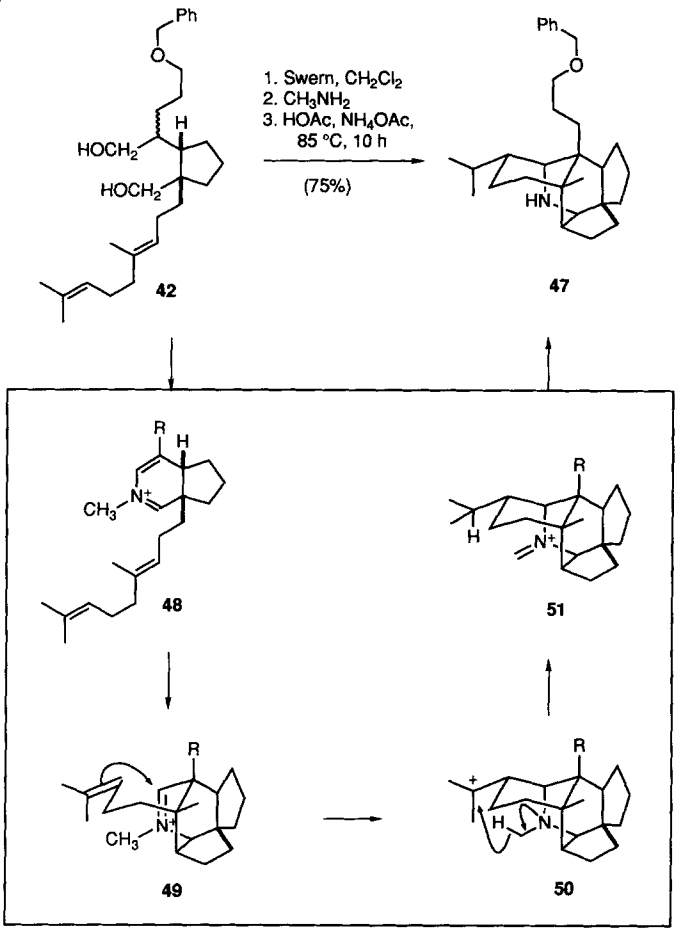
addition of ammonia and before treatment with acetic acid, azadiene **45** was isolated. This material was rapidly transformed into the tetracyclic imine **46** upon being dissolved in acetic acid. Analysis by thin-layer chromatography indicated that the Diels–Alder reaction was complete in less than five minutes. The Diels–Alder step is strongly catalyzed by acid, since the thermal conversion of **45** to **46** has a half-life of about 2 h in refluxing toluene.

7. Serendipity: The "Vollhardt Ammonia" Incident

At this point, a remarkable bit of serendipity will be described. One day, after repeating the tetracyclization process with the goal of obtaining a quantity of pentacyclic amine **43**, one of my co-workers brought me the seemingly impossible news that he had followed the standard protocol that had been developed over a period of about two years and, inexplicably, had obtained the saturated pentacyclic amine **47** instead of the normal product. After having been slandered with various aspersions ranging from amnesia to mixing up his NMR tubes, the co-worker repeated the remarkable



transformation and finally succeeded in convincing me that the product of the reaction was, indeed, **47**. Where had the double bond gone? A careful inventory of the materials used revealed one important clue. During the preceding week, our lecture bottle of ammonia had been exhausted and my coworkers had borrowed a new bottle from my colleague, Professor Vollhardt. Mass spectral examination of the "Vollhardt ammonia" revealed it to be methylamine, its label notwithstanding. Initially, this realization brought us no great comfort. The problem was now even more mysterious. Not only were we faced with the quandary of a disappearing double bond, but now we also had to deal with a disappearing methyl group! The explanation was eventually provided by another of my colleagues, Professor Pedersen, who suggested the mechanism shown in Scheme 15. Reaction of di-

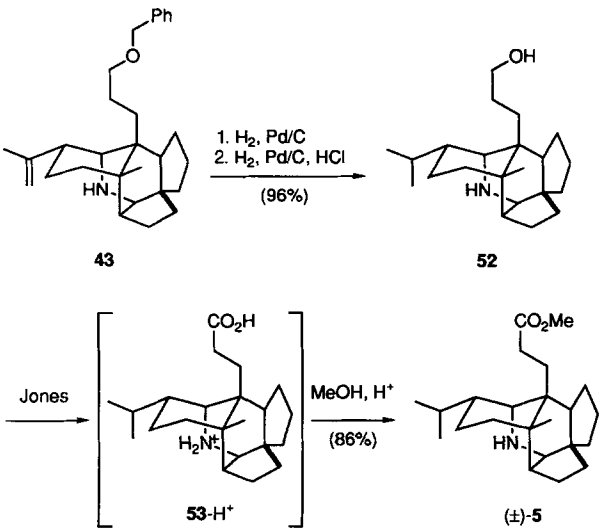


Scheme 15.

aldehyde **44** with the primary amine is postulated to lead to **48**, which reacts with acetic acid at room temperature to give the tetracyclic immonium salt **49**. In fact, an impure intermediate with NMR spectral features consistent with structure **49** has been isolated from the reaction mixture. Further cyclization of **49** is postulated to provide the amino cation **50**, a substance ideally constructed to undergo intramolecular hydride transfer to give **51**,[33] which is hydrolyzed on workup to afford **47**.

After achieving an efficient synthesis of amine **43**, we only had to modify the functionality of the three-carbon side

chain to complete the synthesis of methyl homosecodaphniphyllate. The alkene was readily hydrogenated with Pd/C as catalyst (Scheme 16). Analysis of the reaction mixture by ^{1}H NMR showed that amine **47** was rapidly produced, along with a small amount of amino alcohol **52**. Addition of a



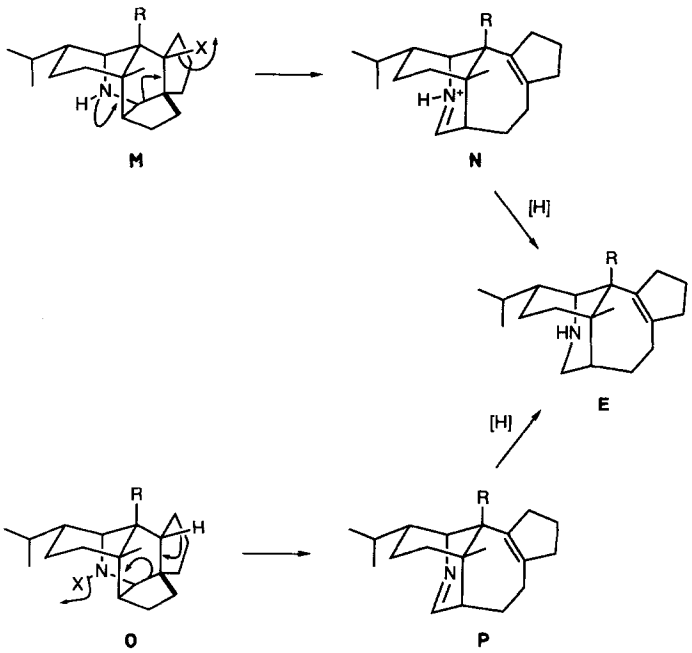
Scheme 16.

small amount of hydrochloric acid increased the rate of hydrogenolysis considerably and permitted complete conversion into **52**, which was isolated as the hydrochloride salt in 96% yield. This material was directly converted to amino acid **53** by oxidation with excess Jones reagent.[34] Finally, compound **53** was converted into racemic methyl homosecodaphniphyllate, (±)-**5**, by Fischer esterification. Comparision of the ^{1}H NMR spectra and R_f values showed the synthetic material to be identical to an authentic sample of the natural alkaloid.[35]

The total synthesis of (±)-methyl homosecodaphniphyllate requires only nine steps and proceeds in 48% overall yield from the simple starting materials **36**, **37**, and **38**. Amide **37** and ester **38** are each made in two steps from commercially available materials. The synthesis of iodide **36** is more complicated, requiring four steps form geraniol. The longest linear sequence requires thirteen steps from geraniol and proceeds in 18% overall yield. The key steps in the synthesis are the tandem Michael addition–alkylation reactions, which assemble all of the carbon atoms necessary for the skeleton, and the tetracyclization reaction, which provides the complete pentacyclic skeleton in one operation. The only disappointing sequence is the conversion of amide **39** to diol **42**; three steps are expended for what would appear to be straightforward functional group manipulations. However, this was the only workable method that we could find for this conversion, and the overall yield for the three steps is quite respectable. All of the steps in the sequence have been carried out on gram scale, and we have used the route to synthesize more than 3.5 g of (±)-methyl homosecodaphniphyllate, several times as much of the alkaloid as has ever been isolated from natural sources. Finally, the synthesis is wholly stereospecific, in contrast to our initial synthesis of methyl homodaphniphyllate.

8. Stealing Another Page from Mother Nature: Conversion of the Secodaphnane Skeleton to the Daphnane Skeleton

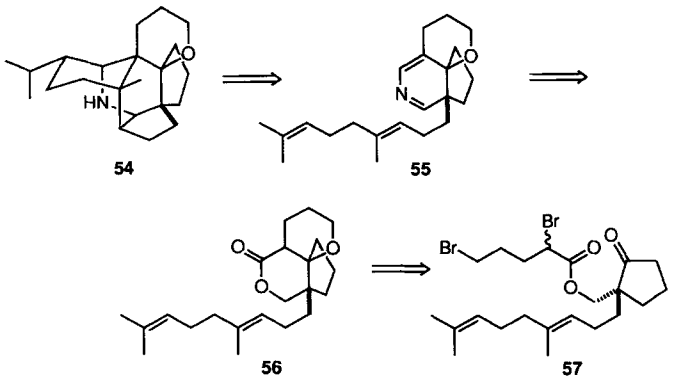
In spite of this success, the original problem that we had set before ourselves was only partially solved; we still had to discover a method to rearrange the secodaphnane skeleton to the daphnane skeleton. It has already been pointed out that the desired rearrangement might be realized in two stages by fragmentation of a secodaphnane to an unsaturated amine with structure **E**, which could undergo transannular addition to the double bond. Two possible fragmentation modes of the secodaphnane skeleton are summarized in Scheme 17. Both of these hypothetical transformations are



Scheme 17.

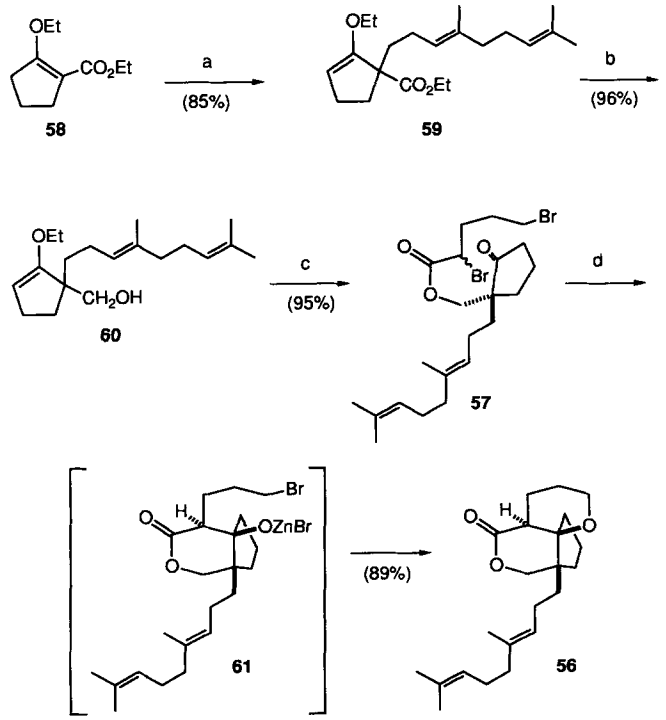
Eschenmoser–Grob fragmentation reactions.[36] The first is more conventional and would convert an angulary functionalized secodaphnane **M** into an immonium ion **N**. The second possibility is less well known and involves movement of electrons in the opposite direction, converting an *N*-functionalized secodaphnane **O** into the imine **P**. In either case, we would have to reduce the carbon–nitrogen double bond of the initial fragmentation intermediate to obtain **E**.

Both of the possibilities in Scheme 17 have been investigated. However, because of the constraints of space, I will only discuss the results of the more traditional fragmentation. Since X must be a heteroatom, and since the three-carbon side chain terminated in a heteroatom, it occurred to us that it would be economical to arrange for the same heteroatom to serve both functions. The substrate for the fragmentation would, therefore, be hexacyclic amino ether **54** (Scheme 18). The necessary cyclization substrate would then be the azadiene **55**. If we followed the same route that was already discussed for the synthesis of methyl homosecodaphniphyllate, we would need tricyclic lactone **56**, which might be available by an intramolecular Reformatsky reaction of **57**, followed by cyclization of the resulting bromo alcohol.



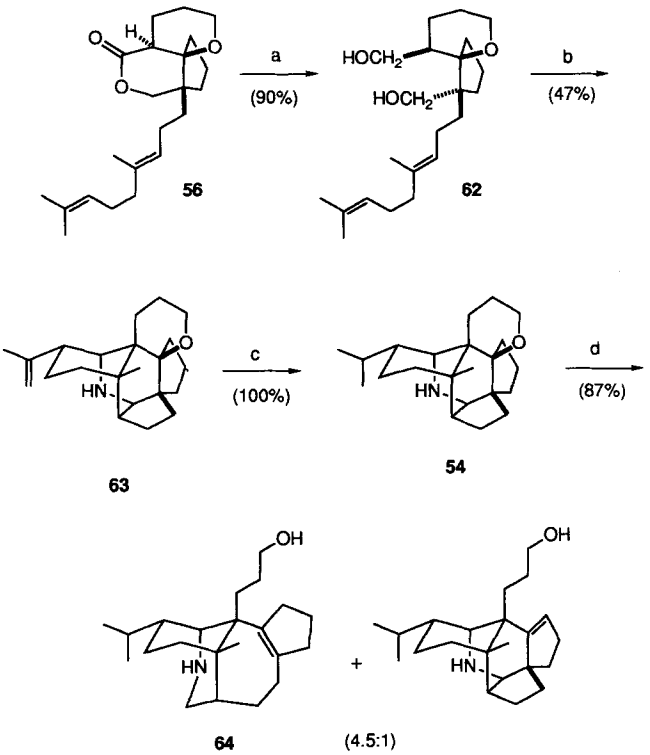
Scheme 18.

To prepare a suitable substrate for the proposed Reformatsky double annulation process, we started with enol ether **58**, which was conveniently prepared from the corresponding β-keto ester. Alkylation of the lithium enolate of **58** with homogeranyl iodide (**36**) provided **59**, which was reduced with lithium aluminum hydride to alcohol **60** (Scheme 19). Esterification with 2,3-dibromopentanoyl bromide[37] provided keto ester **57** after acidic hydrolysis of the enol ether. This material was treated with activated zinc, prepared by treatment of $ZnCl_2$ with sodium naphthalenide in THF,[38] to obtain the tricyclic lactone ether **56**. Although the Reformatsky reaction was rapid, the ensuing cyclization of the zinc alkoxide **61** was slow in pure THF. For this reason, HMPA was added immediately after addition of **57** to the activated zinc suspension. The relative configuration of **56** was assigned on the basis of a single-crystal X-ray structure analysis of a related compound having a methyl group in place of the homogeranyl group.



Scheme 19. a: i) LDA; ii) **36**. b: $LiAlH_4$. c: i) $BrCH_2CH_2CH_2CH_2BrCOBr$; ii) H_3O^+. d: Zn, THF, HMPA.

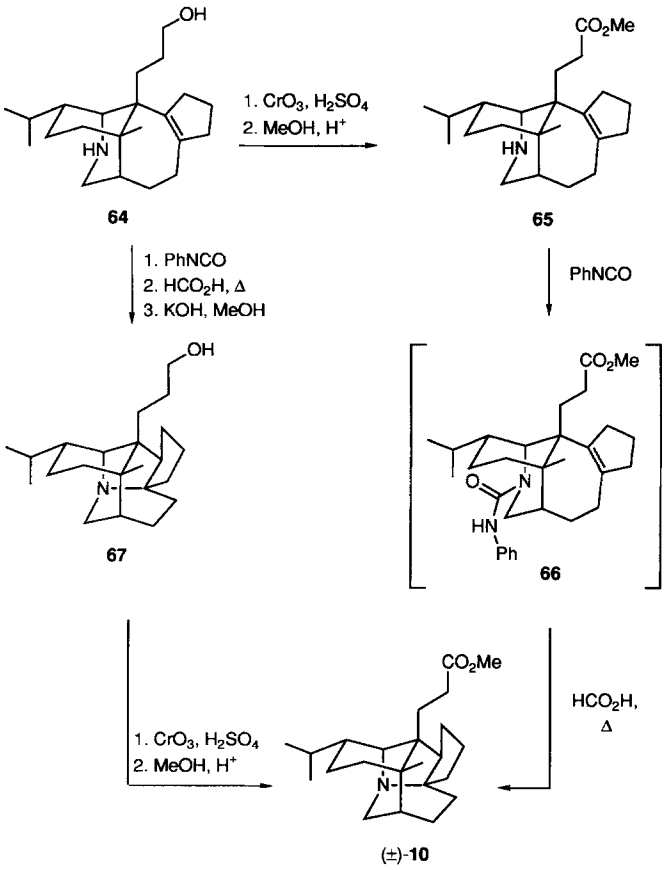
As shown in Scheme 20, reduction of lactone **56** provided diol **62** in high yield. Application of the tetracyclization protocol to this diol was successful, although the yield of the hexacyclic amino ether **63** was lower than that of the cyclization of diol **42**. However, given the fact that **62** has an ether linkage to a tertiary carbon atom that is allylic in some of the tetracyalization intermediates, we were more than pleased with the optimized yield of 47%. Hydrogenation of the double bond over Adams catalyst proceeded in quantitative yield to provide the saturated hexacyclic amino ether **54**. To



Scheme 20. a: $LiAlH_4$. b: i) Swern oxidation; ii) NH_3; iii) HOAc, 55 °C. c: H_2, PtO_2. d: DIBAL, toluene, reflux 36 h.

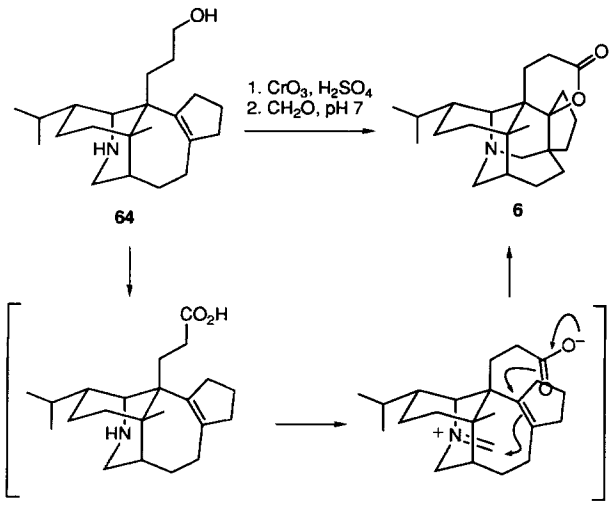
bring about the fragmentation suggested in Scheme 17 we needed a Lewis acid to activate the alkoxy leaving group and a reducing agent to reduce the immonium ion expected to result. We thought that a dialkylaluminium hydride might fulfill both functions and perhaps also activate the nucleofugal group by deprotonation of the secondary amine. To this end, **54** was treated with excess DIBAL in refluxing toluene for 72 hours to obtain the desired unsaturated amino alcohol **64** (71% yield), accompanied by some of the simple elimination product **65** (16% yield).

With unsaturated amino alcohol **64** in hand, we were poised for the second stage of the proposed secodaphnane → daphnane isomerization. To this end, **64** was subjected to Jones oxidation and the resulting amino acid treated with sulfuric acid in refluxing methanol of afford unsaturated amino ester **65** (Scheme 21). We were not surprised when **65** was recovered unchanged from other acidic media (e.g., refluxing formic acid, *p*-toluenesulfonic acid in refluxing benzene). Under these acidic conditions the amine is presumably firmly protonated and therefore not nucleophilic even if the double bond also happens to become protonated.



Scheme 21.

However, the *N*-phenylurea derivative **66**, formed by the reaction of **65** with phenyl isocyanate, cyclized smoothly in refluxing formic acid to provide (±)-methyl homodaphniphyllate (**10**) in 63% overall yield. In an alternative sequence of steps, unsaturated amino alcohol **64** was treated sequentially with phenyl isocyanate, refluxing formic acid, and methanolic potassium hydroxide to furnish (±)-homodaphniphyllol (**67**). Jones oxidation of this material and Fischer esterification of the resulting amino acid provided (±)-**10** in an overall yield of about 70%. These successful cyclizations therefore permitted us finally to solve the problem of a stereocontrolled synthesis of methyl homodaphniphyllate. The synthesis of (±)-**10** by this route required a total of 13 steps from homogeranyl iodide and proceeded in 11% overall yield.

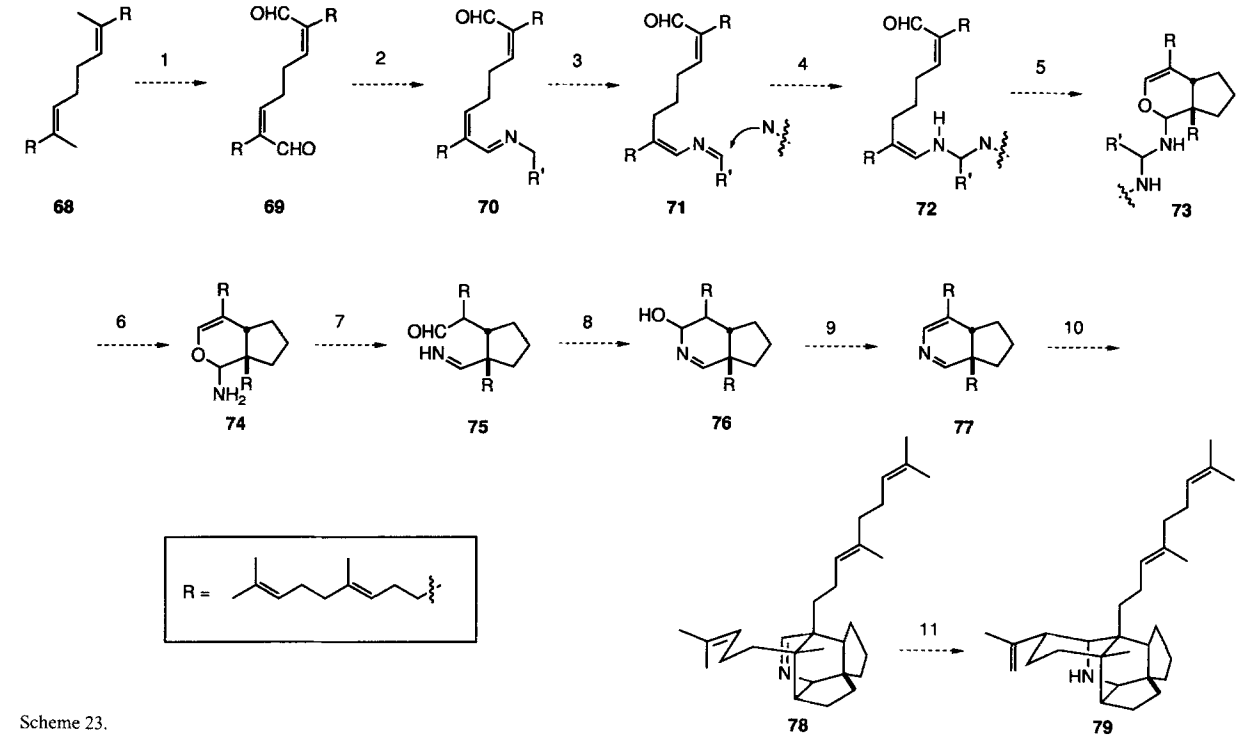


Scheme 22.

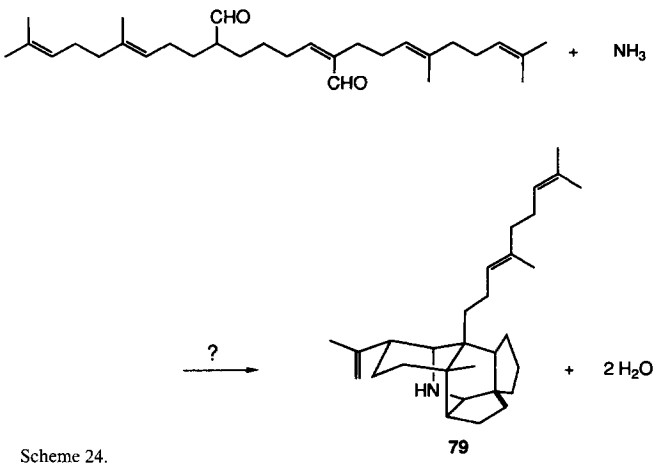
Compound **64** was also converted into racemic daphnilactone A, (±)-**6**, as shown in Scheme 22. Oxidation of **64** delivered the corresponding amino acid, which was treated directly with aqueous formaldehyde at pH 7 to obtain (±)-**6**, whose ^{1}H NMR spectrum and R_f value are identical to those of an authentic sample provided by Professor Yamamura. The complete synthesis of daphnilactone A required 11 steps from homogeranyl iodide and proceeded in 8% overall yield.

9. Transformation of a Squalene Derivative into a Pentacyclic Alkaloid in a Simple One-Pot Transformation

The goal of this project was purely synthetic—we were challenged as molecular architects and engineers by the fascinating structural complexity of the alkaloids of Yuzuriha. Although we applied in our second retrosynthetic analysis a biosynthetic philosophy in performing disconnections that preserved the squalene chain to the extent possible, the resulting synthesis was not truly biomimetic in the sense that it paralleled a known biosynthetic pathway. However, the analysis led us to discover the exceptionally facile tetracyclization process. Could it be that the process actually is biomimetic? A credible biosynthesis is put forth in Scheme 23. The rough outlines of this proposal are as follows: Step 1 is an oxidative transformation of squalene (**68**) into a dialdehyde, **69**.[39] In step 2 it is proposed that some primary amine, perhaps pyridoxamine[40] or an amino acid, condenses with one of the carbonyl groups of **69**, giving imine **70**. Step 3 is the prototopic rearrangement of a 1-azadiene to a 2-azadiene, a process that is well-precedented for the imines formed from α,β-unsaturated carbonyl compounds and benzylamine.[41] Although potassium *tert*-butoxide was used for the prototopic rearrangement of benzylimines, one can imagine that an imine derived from pyridoxamine or an amino acid would rearrange under much milder conditions. Because the 2-azadiene that would result from the foregoing rearrangement is an enimine, its double bond is not especially nucleophilic. However, if some nucleophilic species adds to the imine double bond, as in step 4, the product **72** is a nucleophilic enamine. The subsequent cyclization to give **73** has an exact precedent in vitro in the work of Schreiber, Meyers, and Wiberg.[42] In steps 6–9 the resulting bicyclic dihydropyran derivative **74** is transformed into a dihydropyridine derivative **77** similar to the intermediate in the in vitro conversion of **42** into **43**. Other possible scenarios can be envisioned for the metamorphosis of **74** into **77**. According to our supposition of the biosynthesis **77** would then be converted into **78** by a catalyzed Diels–Alder reaction and the final ring would result from an ene-like cyclization, giving **79**, the putative primordial *Daphniphyllum* alkaloid. Because of the likelihood that **79** is the first pentacyclic substance to occur in the biosynthesis of the al-



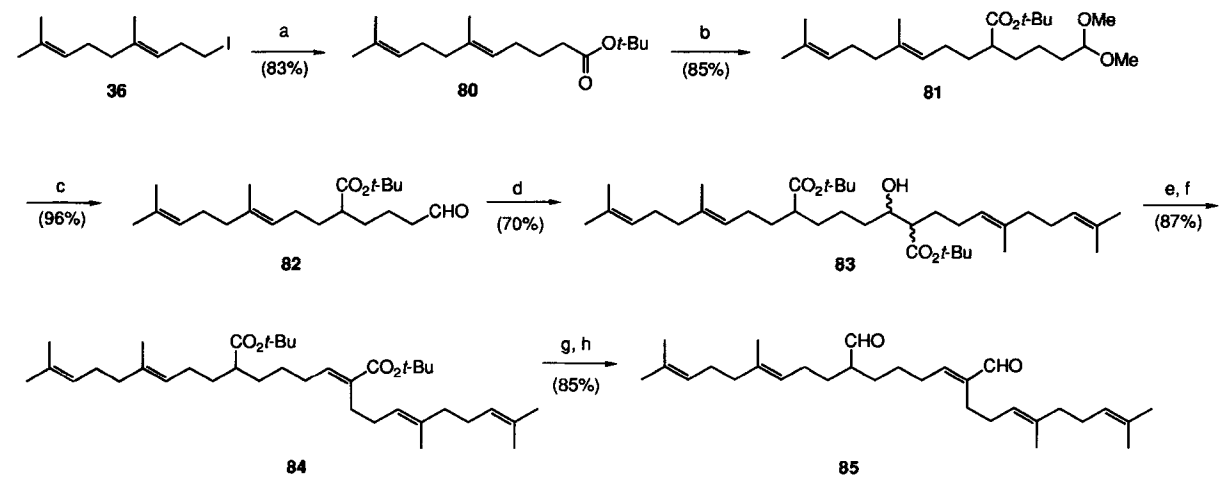
Scheme 23.



Scheme 24.

kaloids of Yuzuriha, we have named it protodaphniphylline.[43]

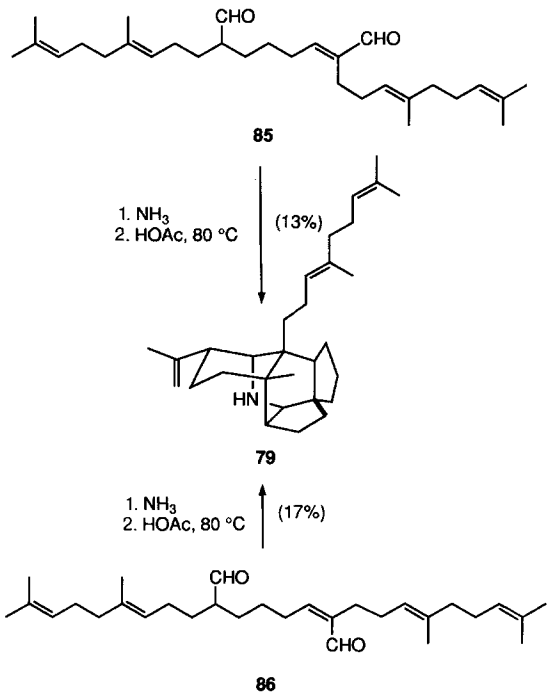
How much of this proposed biosynthesis might we be able to imitate in the laboratory? We thought it possible that we could intercept the proposed scheme at the stage of intermediate **72** or the corresponding dialdehyde (Scheme 24). We therefore set about the relatively simple task of preparing a suitable squalene derivative to put this proposition to the test. The route adopted is summarized in Scheme 25. Alkylation of the lithium enolate of *tert*-butyl acetate with homogeranyl iodide (**36**) afforded ester **80**, which was alkylated with the dimethyl acetal of 4-bromobutanal [44] to provide **81**. Hydrolysis of the acetal gave aldehyde **82**, which was condensed with the lithium enolate of **80** to obtain β-hydroxy esters **83** as a mixture of diastereomers. Elimination



Scheme 25. a: Li enolate of *tert*-butyl acetate. b: i) LDA; ii) $BrCH_2CH_2CH_2CH(OMe)_2$. c: H_3O^+. d: Li enolate of **80**. e: CH_3SO_2Cl, Et_3N. f: 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, Δ. g: DIBAL. h: Swern oxidation.

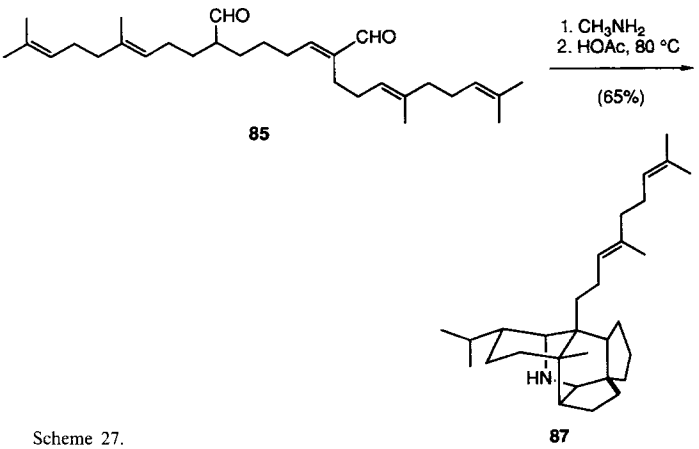
was accomplished by treatment of the methanesulfonate of **83** with DBU in toluene at 80 °C. Diester **84** was obtained in excellent yield, accompanied by approximately 10% of the *Z* isomer. After chromatographic separation to the stereoisomeric diesters, **84** was converted into the *E* dialdehyde **85** as shown in Scheme 25. The pure *Z* isomer **86** was prepared by a slightly different route wherein the C10–C11 double bond was formed by Peterson olefination.

The pentacyclization process was first investigated under the conditions that had served for the teracyclization of **42** to **43** (Scheme 26). Thus, a solution of either **85** or **86** in CH_2Cl_2 was treated with ammonia and triethylamine hydrochloride at room temperature for 16 hours, after which time TLC showed that starting material had been consumed. At this point the solvent was evaporated under vacuum and the resulting residue taken up in acetic acid and heated at 80 °C for 2 hours. Workup gave protodaphniphylline (**79**) in 15 ± 2% yield. Although the yield in this biomimetic synthesis is not high, it must be acknowledged that a profound structural change has occurred—five rings and six σ bonds have been created through the action of the most common of chemical reagents, ammonia and acetic acid.



Scheme 26.

A considerable amount of process development eventually resulted in a somewhat more complicated two-pot protocol wherein **85** or **86** was treated sequentially with KOH under phase-transfer conditions, ammonia in DMSO, and acetic acid, to obtain **79** in obout 50% overall yield. However, it was our unexpected experience with the "Vollhardt ammonia" (methylamine) that eventually provided the best solution to the pentacyclization problem. Because the low yield in the pentacyclization of **85** and **86** with ammonia was presumably due to poor selectivity in the formation of the first carbon–carbon bond, we reasoned that the more nucleophilic *N*-methylenamine derived from methylamine might improve upon the 15% yield observed with ammonia. Indeed, when dialdehyde **85** was treated with methylamine and the crude reaction product heated in acetic acid at 80 °C for 11 hours, dihydro-protodaphniphylline **87** was obtained in 65% yield (Scheme 27).



Scheme 27.

10. Epilogue and Editorial

If progress in important fields such as medicine, biochemistry, and materials science is to continue, it is essential that we be able to synthesize literally any structure that the imagination can conceive. The goal of research in organic synthesis is to reach a level of sophistication where this ability can be taken for granted. Yet, there is abroad an insidious notion that organic chemists have already become so adept at synthesis that further academic exercises such as that described here are no longer necessary, that there is no longer any need for research in multistep synthesis. I believe that, in part, this difficulty stems from a confusion of the adjectives effective ("adequate to accomplish a purpose" [45]) and efficient ("performing or functioning in the best possible and least wasteful manner" [45]). In fact, although chemists *have* over the last half-century become rather adept at constructing small amounts of very complicated molecules, we generally cannot prepare most desired organic compounds in an efficient, practical, and truly cost-effective manner. We *can* synthesize almost any given molecule and demonstrate that we have done it. However, this is due more to the development of high-powered separation and analytical tools (HPLC, capillary GC, TLC, FT-NMR spectroscopy) than to some discontinuous change in our ability to solve synthesis problems. That is, because we can carry out separations and establish structure with minute amounts of material, it is possible to do synthesis on very small scale. Thus, we can carry out multistep synthesis in a much shorter period of time than was possible ten or twenty years ago, since more time can be devoted to the development of new chemistry and less to the time-consuming "bringing up of material". This maturity should be considered a normal step in the development of a productive science, not a sign that all of the problems have been solved and that the field no longer merits investigation. Problems of synthesis still abound, as is known by anyone who practices the art. Our textbooks are

filled with hundreds of synthetic methods, all of which have limitations that will never be discovered unless the methods are tested in the challenging arena of the synthesis of multifunctional compounds. Although our approaches to problems have matured, we need even more mature strategies of synthesis. There is no reason that organic chemists should not be able to surpass nature's virtuosity in the synthesis of complex organic structures. In fact, we are still very far from this goal in most cases.

The cascade of reactions depicted in Scheme 27 represents a significant advance in our ability to orchestrate molecular reorganization. In this magnificent process an acyclic dialdehyde is transformed by ordinary commodity chemicals into a pentacyclic product by the formation of four carbon–carbon bonds, two carbon–nitrogen bonds, and one carbon–hydrogen bond. Furthermore, the process occurs with very high stereoselectivity and in excellent yield. However, it should not be misunderstood that even this highly efficient synthesis is perfect, because compromises have still been made. For example, the synthesis outlined in Scheme 25 still required the use of a protecting group (the dimethyl acetal) and involved the use of ester functions as surrogates for aldehyde groups. The inability to deal more directly with these issues demonstrates that there are still frailties in the science of synthesis, infirmities that will, no doubt, one day be cured through further research in multistep synthesis.

I am indebted to the talented and enthusiastic group of coworkers who performed the difficult experiments upon which this review article is based. The original methyl homodaphniphyllate synthesis was carried out by graduate student Mark Sanner and postdoctoral associates Sander Mills and Steven Davidsen. The tetracyclization reaction was discovered and perfected by graduate student Roger Ruggeri, who also applied it to the total synthesis of daphnilactone A and methyl homodaphniphyllate. Graduate student Marvin Hansen applied the Ruggeri cyclization to the synthesis of methyl homosecodaphniphyllate. The felicitous discovery of the methylamine cyclization was made by graduate student John Kath, who has also completed a total synthesis of the C_{30} alkaloid, (−)-codaphniphylline. The pentacyclization process and synthesis of protodaphniphylline were accomplished by postdoctoral associate Serge Piettre, who also carried out important mechanistic experiments that are described in detail in ref. [1c]. *The marvelous transformation of dihydrosqualene dialdehyde* ***85*** *into dihydroprotodaphniphylline was carried out by postdoctoral associate John Ragan. Not discussed here for lack of space are total syntheses of the C_{30} alkaloid (−)-secodaphniphylline (**11**, ref.* [1d]*) and (±)-bukittinggine (7, ref.* [1e]*), which were carried out by postdoctoral colleague Jeff Stafford. Also not covered here is unpublished research by graduate student Daisy Joe, who has explored the alternative mode of fragmention suggested in Scheme 17 and uncovered some fascinating rearrangements of the secodaphnane skeleton. I am also pleased to acknowledge the financial support of the National Science Foundation for a research grant.*

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