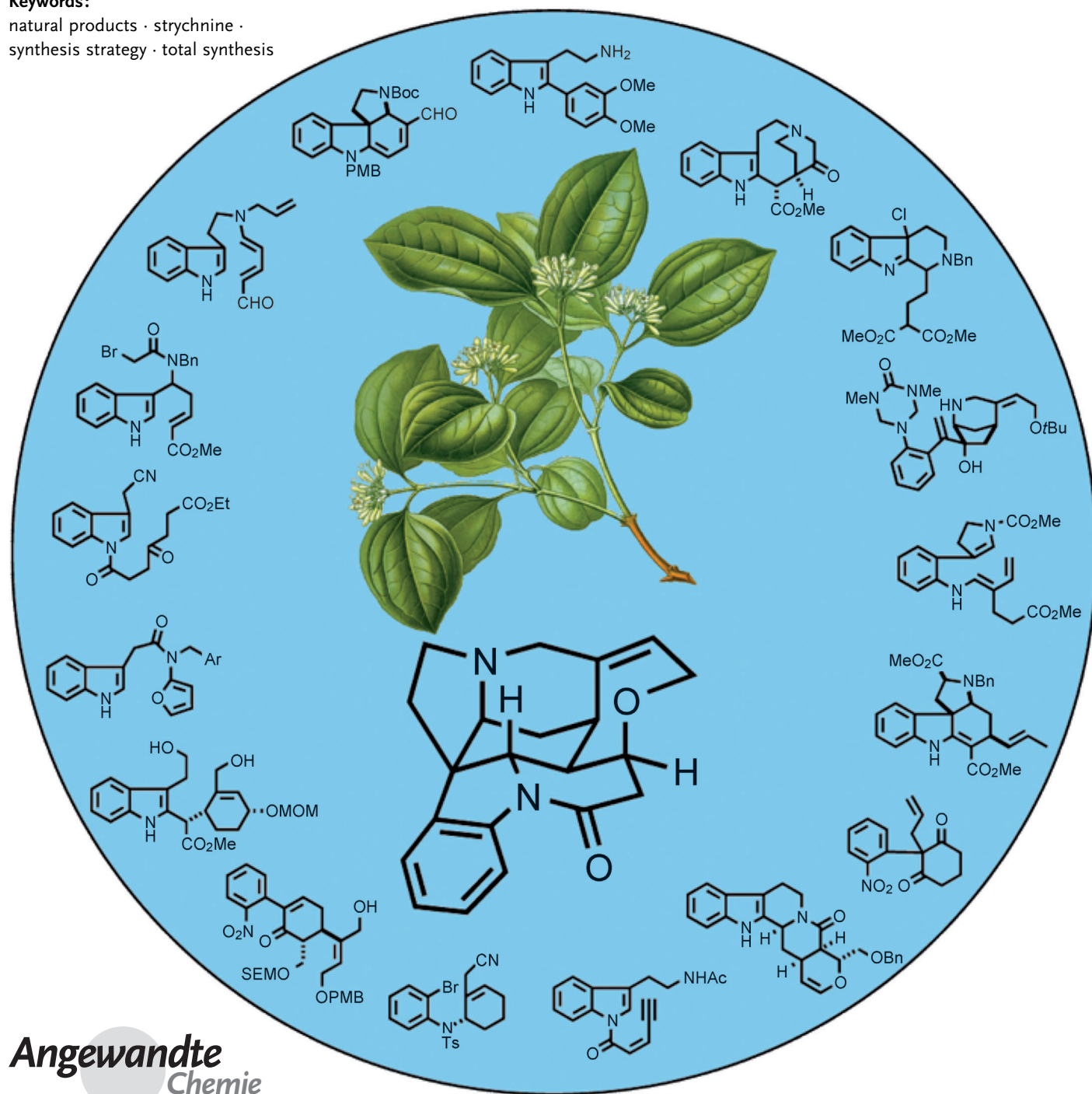Total Synthesis

# Is There No End to the Total Syntheses of Strychnine? Lessons Learned in Strategy and Tactics in Total Synthesis

*Jeffrey S. Cannon and Larry E. Overman**

*F*rom the 19th century to the present, the complex indole alkaloid strychnine has engaged the chemical community. In this Review, we examine why strychnine has been and remains today an important target for directed synthesis efforts. A selection of the diverse syntheses of strychnine is discussed with the aim of identifying their influence on the evolution of the strategy and tactics of organic synthesis.

## From the Contents

## 1. Introduction

Strychnine is one of the most famous chemical compounds, being known to chemists and the public alike. It is the major alkaloid isolated from the seeds of the trees *Strychnos nux-vomica* and *Strychnos ignatii* Bergius (Saint Ignatius bean), which are broadly distributed in the Asian tropics.[1] The powerful and dangerous physiological properties of powdered nuts of *Strychnos nux-vomica* have been known since the Middle Ages.[2] This preparation (nux vomica or vomiting nuts) was investigated haphazardly by doctors in Germany in the 16th and 17th centuries and more systematically by physicians in France and England during the 19th century.[3] Strychnine was first isolated in pure form from *Strychnos ignatii* Bergius by Pelletier and Caventou in 1818,[4] and subsequently purported to have various benefits including increasing appetite, toning skeletal musculature, increasing memory, and curing snakebites.[3,5] At one time, strychnine was even taken as a "performance-enhancing drug".[6] However, its only actual utility is as a poison. The ease of its isolation led to strychnine being a widely used pest control agent in the 18th century, with its use as a poison for rodents continuing today.[5,7] Thankfully, its modern use is dwindling as a dose as small as 50 mg can be fatal to an adult human and more effective rodenticides with lower human toxicities are now available. Regardless, the throes and seizures symptomatic of strychnine poisoning have made it irresistible to artists looking to portray dramatic deaths, including masters such as Alfred Hitchcock in the movie *Psycho* and Agatha Christie in her novel *The Mysterious Affair at Styles*.
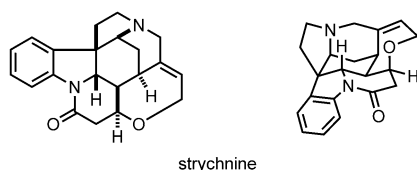


strychnine

Strychnine is a powerful neurotoxin whose mode of action is well characterized. The alkaloid competitively binds to the glycine receptor chloride channel (also named the strychnine-sensitive glycine receptor), eliminating glycinergic inhibition in the spinal cord.[8,9] The resulting overexcitation of nerves causes muscular convulsions, the inability to control respiration, and eventually asphyxiation. There is no direct antidote for strychnine poisoning, which is treated by administering anticonvulsants and muscle relaxants to ease the convulsions.[10] Strychnine has played an important role in elucidat-

ing the chemistry of the nervous system. As a result of its high-affinity binding to strychnine ($K_d$ in the nanomolar range), the glycine receptor was the first nicotinoid receptor isolated from mammalian tissue.[11] Strychnine's covalent attachment to the transmembrane $\alpha_1$ subunit upon UV irradiation helped identify the ligand binding site of the glycine receptor. In addition, autoradiographical mapping of [3*H*]strychnine made it possible to determine the location of glycine receptors in the central nervous system.[8,9]

### 1.1. Importance of Strychnine in Organic Chemistry

Strychnine stands out among classical natural products as one of the first to be isolated and purified, yet one of the last to have its structure established.[12] As such, it has played a central role in the development of several major movements in organic chemistry.

Extensive investigations towards characterizing the structure of strychnine were pursued throughout the early 20th century, led by Leuchs and Robinson et al. who published nearly 400 papers addressing strychnine's structure using degradative methods.[13] Finally, Woodward and Brehm proved the correct structure in 1948 from a combination of degradative evidence and a key use of UV spectroscopy.[14,15] The connectivity and absolute configuration of strychnine were soon confirmed by X-ray crystallography.[16] Strychnine was one of the last natural products whose structure was solved using largely classical methods, although Woodward's use of UV spectroscopy foreshadowed the preeminent role that spectroscopic techniques would play in structure elucidation.

With the structure of strychnine finally resolved, organic chemists hoped to produce strychnine in the flask. Remarkably, this daunting feat was accomplished merely six years later when Woodward et al. announced the first total synthesis of strychnine in 1954.[17] At the time, strychnine was by

[*] J. S. Cannon, Prof. Dr. L. E. Overman
    Department of Chemistry, University of California, Irvine
    Irvine, CA 92697-2025 (USA)
    E-mail: leoverma@uci.edu

far the most complex molecule to be produced by chemical synthesis. Woodward's monumental achievement is often considered the beginning of a golden age of total synthesis. It is certain that this synthesis inspired many of the organic chemists who contributed to the remarkable surge of natural product total syntheses in the 1970s and 1980s.
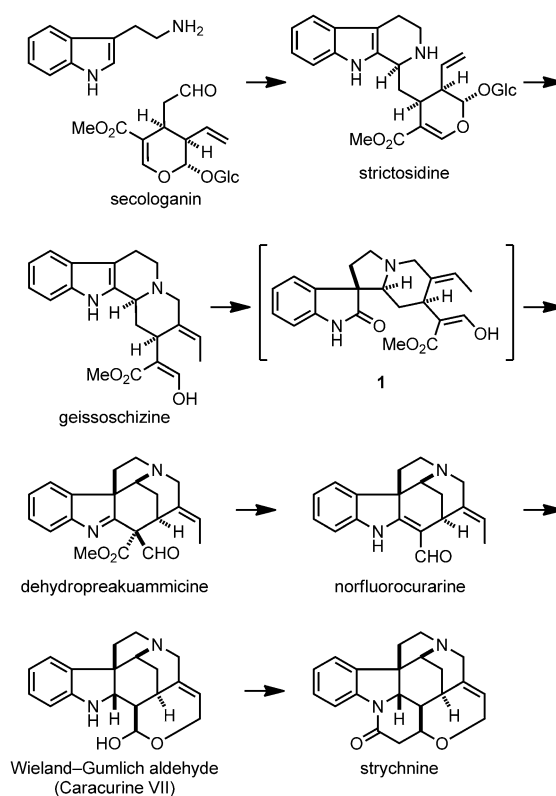
### 1.2. Strychnine Biosynthesis

Nearly 30 naturally occurring *Strychnos* alkaloids are now recognized.[1] As with all monoterpene indole alkaloids, their biosynthesis originates from the union of tryptamine and secologanin (Scheme 1).[18,19] Pictet–Spengler condensation of these precursors generates strictosidine, which further converts to geissoschizine after deglycosylation.

Geissoschizine is a major branching point in indole alkaloid biosynthesis. Elaboration of geissoschizine without rearrangement of the fused tetracyclic ring system generates the yohimbine, heteroyohimbine, and corynantheine subgroups of indole alkaloids. However, alkaloids of the *Strychnos* group derive from geissoschizine by a cascade sequence believed to originate by oxidative rearrangement of the indole ring to generate spiroxindole (**1**), which subsequently condenses with the pendant 1,3-dicarbonyl side chain to arrive at dehydropreakuammicine. Decarboxylation of dehydropreakuammicine generates norfluorocurarine. Further oxidation of the terminal allylic position and reduction of the vinylogous formamide give rise to the Wieland–Gumlich aldehyde, a natural product also known as caracurine VII. Confirming earlier postulates by Woodward[20] and Robinson,[21] the intermediacy of the Wieland–Gumlich aldehyde in the biosynthesis of strychnine was established by Heimberger and Scott in 1973.[22] Strychnine's final piperidone ring is installed by condensation with acetic acid.[23]

### 1.3. Natural Products and Total Synthesis: Bound Together in the History of Organic Chemistry and a Pertinent Union Today

Nature's molecules and organic chemical synthesis have been intimately linked since Wöhler's rational synthesis of urea in 1828.[24–27] For the next 150 years, chemical synthesis

**Scheme 1.** Biosynthesis of strychnine.

played an indispensible role in structure elucidation and verification. This function has been supplanted largely by analytical methods. Nonetheless, the crucial role that total synthesis stills plays in structure elucidation is seen in the large number of natural products whose structures have been revised recently as a result of total synthesis endeavors.[28]

Natural products continue to play a major role in human health, as both therapeutic agents and the inspiration for marketed drugs.[29] Although natural product drugs are rarely produced entirely by chemical total synthesis,[29c] for rare natural products isolated from sources other than plants or microorganisms, total synthesis can provide initial supplies for preclinical studies (Figure 1).[29b] For example, Novartis's evaluation of discodermolide, an antitumor agent that binds

*Jeff Cannon was born in Escondido (USA) in 1985. He studied at Occidental College in Los Angeles, CA, where he received his B.A. degree in chemistry in 2007. He is currently working on his PhD in the laboratory of Prof. Larry Overman at the University of California, Irvine. His current research interests focus on the asymmetric total synthesis of complex alkaloid natural products.*

*Larry Overman was born in Chicago (USA) in 1943. He obtained a B.A. degree from Earlham College in 1965 and completed his doctoral dissertation in 1969 under the guidance of Prof. Howard W. Whitlock, Jr. at the University of Wisconsin. After an NIH postdoctoral fellowship with Professor Ronald Breslow at Columbia University, he joined the faculty at the University of California, Irvine, in 1971 where he is now Distinguished Professor of Chemistry. His research interests center on the invention of new transformations and strategies in organic synthesis and the total synthesis of natural products and their congeners.*

to microtubules with higher affinity than paclitaxel, was enabled by Paterson's total synthesis.[30] Another example was the total synthesis of crambescidin 800 developed in our laboratories, which was employed by Pharma Mar to obtain preclinical supplies of this structurally novel antineoplastic marine natural product.[31]

Natural product total synthesis endeavors often provide intermediates and chemical tools that allow modification of the natural product's structure. Such changes can improve biological and physical properties, and make it possible to identify the natural product's molecular target. One salient example is Danishefsky's "diverted total synthesis" of migrastatin, a macrolide antibiotic that inhibits tumor metastasis by blocking human tumor cell migration. These efforts identified a number of migrastatin analogues having enhanced drug characteristics (Figure 2).[32] Another fine example is Wender's synthesis and biological evaluation of simplified analogues (bryologs) of the powerful antitumor agent bryostatin.[33] The crowning recent achievement in this arena was the launch of eribulin (Halaven) for the treatment of metastatic breast cancer in 2010. Kishi's remarkable total synthesis of halichondrin B[34] led to the identification of the macrocyclic fragment of this dauntingly complex natural product as the essential anticancer pharmacophore, and provided much of the chemistry that has allowed eribulin to be produced commercially by chemical synthesis.[35]

Thus far our discussion of the relationship of natural products and target-directed total synthesis has not touched on the vital role played by natural products in advancing the logic and tools of synthetic organic chemistry. For years natural products having unique structures have inspired the development of new chemical synthesis strategies and chemical transformations.[25,36] Illustrative examples of the latter include Barton's invention of the deoxygenation of secondary alcohols in connection with the synthesis of aminoglycoside antibiotics,[36] our invention of the aza-Cope/Mannich reaction during the synthesis of gephyrotoxin,[37] and Baran's recent invention of silver-catalyzed arylation of electron-deficient aromatics with boronic acids as an outgrowth of the synthesis of palau'amine.[38] Polyfunctional natural products moreover serve as an ideal platform for evaluating the selectivity, scope, and utility of synthetic methods, knowledge that is essential for effective synthesis planning and execution.

Our aim in this Review is to illustrate the fundamental role that natural products total synthesis plays in the
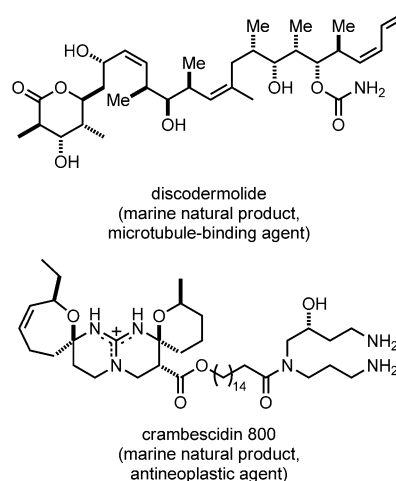


**Figure 1.** Representative natural products whose preclinical evaluation was enabled by total synthesis.
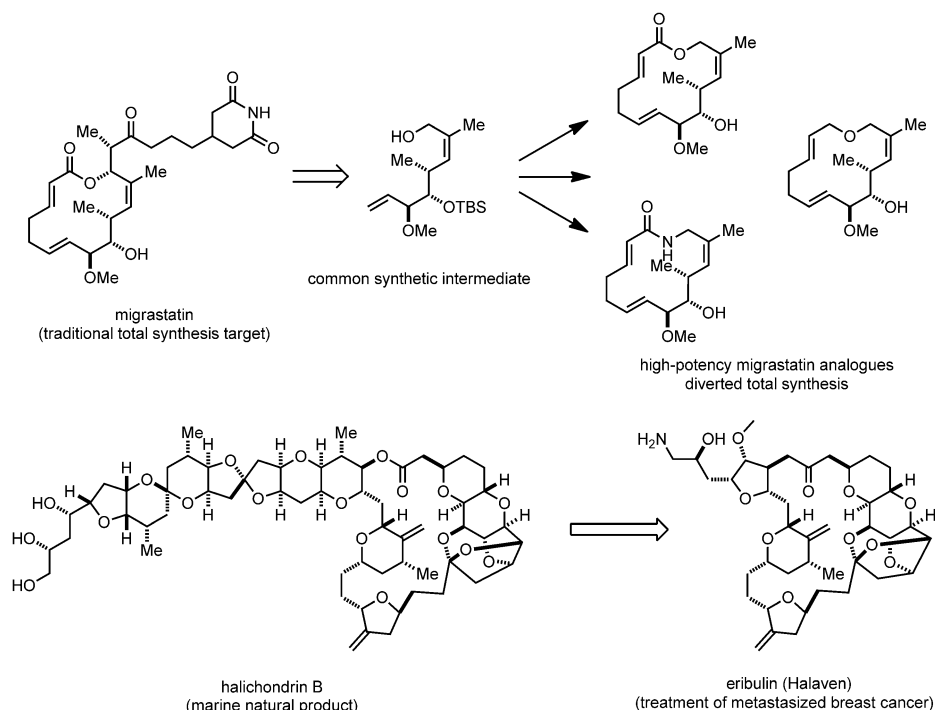


**Figure 2.** Examples of recent drugs and potential therapeutics developed as the result of total synthesis efforts.

continuing evolution of the science of chemical synthesis by considering a selection of past and very recent total syntheses of strychnine. Strychnine is an ideal focus for such an analysis. Its structure presents a serious challenge for total synthesis, while its seven distinctly different rings provide much latitude in synthesis strategy. Moreover strychnine's popularity as a synthesis target—stimulated in part by its historical significance to the field of organic chemistry—makes this molecule ideal for benchmarking the utility of new chemical transformations and new chemical synthesis strategies.

## 2. Overview of Strychnine as a Synthetic Target

At the time of its first synthesis, Robinson remarked about strychnine: "*For its molecular size, it is the most complex substance known*".[39] Even by modern standards, strychnine poses significant challenges for total synthesis. Foremost is construction of the umbrella-like CDE tricyclic unit (F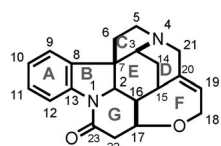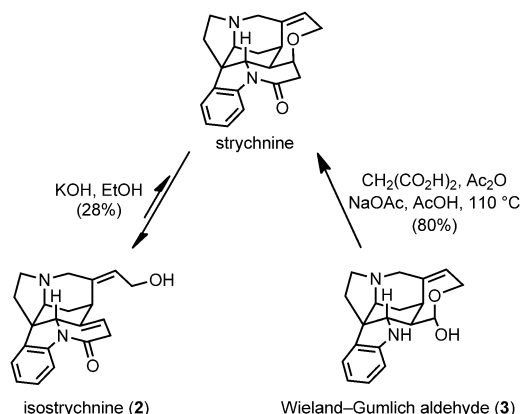igure 3). This fragment is highly congested, containing five of the six stereogenic carbons of strychnine and its sole quaternary carbon stereocenter. If the F ring is to be constructed late in a synthesis, a secondary challenge is the stereo-controlled assembly of the (*E*)-C19–C20 double bond.

To date, 17 total and formal syntheses of strychnine have been reported.[40] All syntheses of strychnine have intercepted one of two common intermediates: isostrychnine (**2**) or the Wieland–Gumlich aldehyde (**3**, Scheme 2). Both intermediates can be converted in one step to strychnine. As first demonstrated by
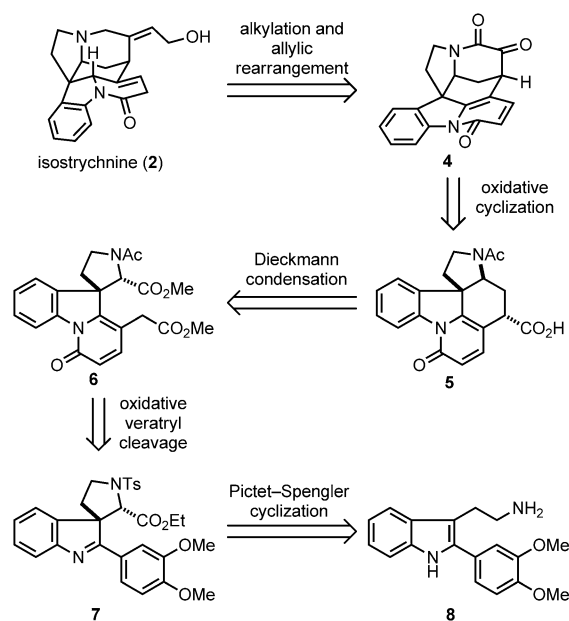
*Figure 3.* Numbering scheme for strychnine.

chemical synthesis strategy and/or tactics. When a general strategy has been utilized in several syntheses, we have chosen the ones that we feel best illustrate the advantages of the approach. We will consider the syntheses in chronological order, which will provide some insight into the progress of chemical synthesis over this period. Our selection is admittedly highly personal. The syntheses we do not discuss have all contributed substantially to the art of synthesis in this area and are discussed in previous comprehensive reviews.[40, 44]

## 3. A Selection of Total Syntheses of Strychnine and Lessons Learned

### 3.1. Woodward's Landmark Synthesis (1954)

The total synthesis of strychnine by Woodward et al. in 1954 was a milestone in chemical synthesis.[17] Woodward's approach was based on his proposal for strychnine's biosynthesis, a suggestion that was shown later to be incorrect.[45] Nonetheless, this hypothesis provided a roadmap for a successful total synthesis. Woodward targeted isostrychnine (**2**), which was seen arising from α-keto lactam **4** by partial reduction of the pyridone and elaboration at the ketone carbonyl group (Scheme 3). The piperidine D ring would derive from γ-amino acid **5**, with the E ring of this intermediate being formed by Dieckmann cyclization of diester **6**. Woodward envisioned a 3,4-dimethoxyphenyl (veratryl) ring serving as a latent precursor of the G ring during Pictet–Spengler-type cyclization of an iminium ion derived from glyoxal and 2-veratryltryptamine **8**. Early introduction of the veratryl group was a strategic decision to direct this cyclization to the β carbon of the indole to produce spiroindoline **7**.

Woodward's strychnine synthesis began with the preparation of 2-veratrylindole (**9**) from 3,4-dimethoxyphenyl methyl ketone and phenylhydrazine by Fischer indole syn-

*Scheme 2.* Conversion of isostrychnine and the Wieland–Gumlich aldehyde to strychnine.

Prelog et al., strychnine and isostrychnine (**2**) are equilibrated under basic conditions by fragmentation and reformation of the oxepene ring.[41] However, this equilibrium favors the ring-opened isomer in an approximate 3:1 ratio. As a result, the highest reported yield of strychnine from isostrychnine is 28%.[42] The Wieland–Gumlich aldehyde (**3**) can be converted to strychnine by condensation with malonic acid and decarboxylation, a transformation that takes place in high yield, typically on the order of 80%.[43] Thus, the Wieland–Gumlich aldehyde is the most advantageous strychnine precursor in terms of synthetic planning; however, isostrychnine can be a viable alternative, particularly if it is accessed in high efficiency.

In light of the large number of syntheses of strychnine reported, we have chosen only a subset for discussion. We consider syntheses that introduce new ways to construct the complex strychnine skeleton and teach general lessons about

*Scheme 3.* Retrosynthetic analysis of Woodward's route to strychnine.

thesis (Scheme 4). In four subsequent steps, the aminoethyl side chain of tryptamine intermediate **8** was incorporated. Closure of the C ring and formation of the quaternary carbon was achieved under neutral conditions by activation of the
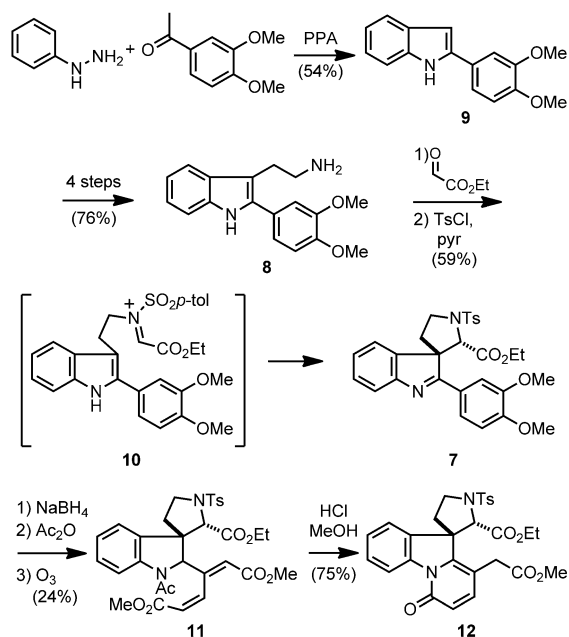


**Scheme 4.** Synthesis of a tetracyclic intermediate containing the ABCG rings.

imine formed by condensation of **8** with ethyl glyoxal by reaction with *p*-toluenesulfonyl chloride and pyridine. The resulting *N*-sulfonyliminium ion **10** cyclized to form spiroindole **7** with high stereoselectivity.[46] Stereoselection in this step undoubtedly arose from destabilizing steric interactions between the ethyl ester and the veratryl group. After reduction of the imine of **7** and acetylation of the indoline nitrogen, the veratryl group was cleaved selectively with ozone in aqueous acetic acid to yield diester **11**. Heating this product in methanolic HCl cleaved the acetate group and promoted lactonization and double-bond isomerization to give pyridone **12**. At this stage, four of the seven rings of strychnine were assembled and the stage was set for constructing the congested D and E rings.

From the outset, Woodward foresaw construction of the E ring by Dieckmann cyclization, which would necessitate prior epimerization at C3 of precursor **12** (Scheme 5). Exposure of **12** to NaOMe did result in enolization of the ethyl ester, but subsequent elimination of *p*-toluenesulfinic acid and eventually glycine ethyl ester led to the unexpected formation of carbazole **13**. Woodward attributed this reactivity to the leaving-group ability of the arylsulfonyl substituent on nitrogen of the α-amino ester. Removing this leaving group by converting sulfonamide **12** to acetamide **6** allowed, after epimerization of the aminoester, smooth Dieckmann condensation to form the E ring. The pentacyclic product (**14**) was reduced at C14 in four steps to provide carboxylic ester **15**. Epimerization of the β ester **15** during its hydrolysis with
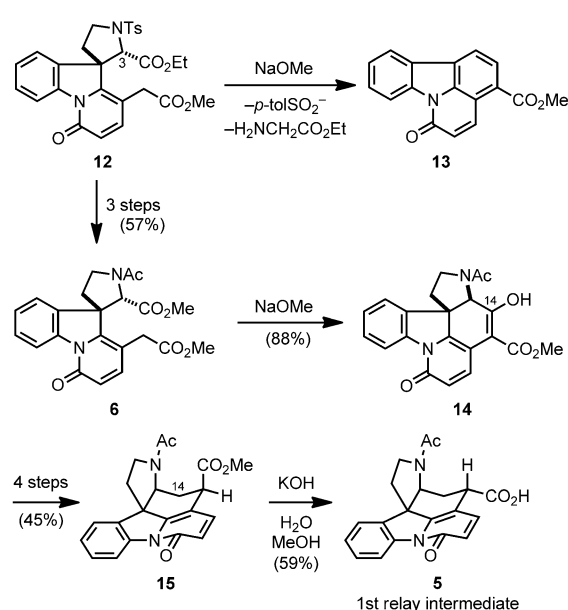


**Scheme 5.** Woodward's construction of the E ring.

KOH relieved the destabilizing quasi 1,3-diaxial interactions present in **15** to give equatorial carboxylic acid **5**. This intermediate was resolved with quinidine and served as the first relay point of the synthesis.

Woodward then approached the installation of the two-carbon bridge that would form the D ring (Scheme 6). Initial attempts to build this ring focused on the possibility of
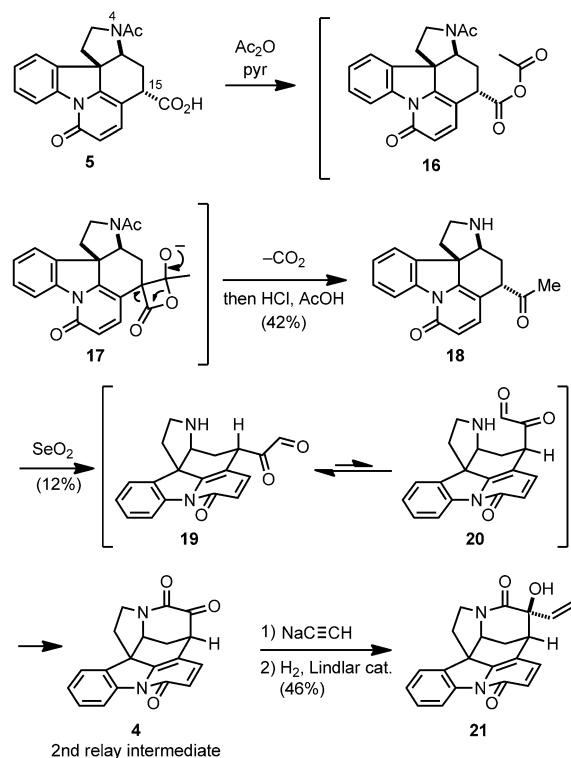


**Scheme 6.** Cyclization to form the D ring and installation of the final two carbon atoms.

appending a two-carbon dielectrophile between the potentially nucleophilic atoms 4 and 15 of acid **5**. However, this strategy was never fruitful and an alternate approach was devised.[47] Carboxylic acid **5** was converted to the methyl ketone by reaction with acetic anhydride, a classical transformation involving intramolecular attack in this case of a C15 enolate on the acetyl carbon of mixed-anhydride intermediate **16** with loss of carbon dioxide from the resulting β-lactone (**17**).[48] Subsequent hydrolysis of the acetamide under acidic conditions provided aminoketone **18**. Upon exposure to selenium dioxide, methyl ketone **18** was converted to hexacyclic α-keto lactam **4**. The equatorially disposed α-ketoaldehyde **19** produced initially in this oxidation was in equilibrium with its less-favored axial isomer **20**. Intramolecular capture of this transient intermediate by the pyrrolidine nitrogen generated a hemiaminal intermediate, which upon further oxidation with selenium dioxide gave lactam **4**. Addition of sodium acetylide to the ketone of intermediate **4**, followed by partial reduction of the triple bond using Lindlar's catalyst installed the final carbon atoms of the strychnine skeleton. Although achieved in only low yield (2%), the **5→21** conversion assembled the critical, sterically congested CDE fragment of strychnine.

After installation of all the required carbon atoms, isostrychnine (**2**) was accessed from hexacyclic intermediate **21** in three additional steps (Scheme 7). Reduction of the
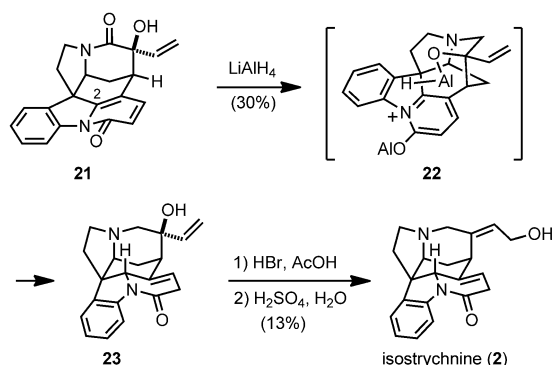


**Scheme 7.** Completion of the first total synthesis of strychnine.

pyridone ring of **21** by lithium aluminum hydride provided dihydro product **23**. The regio- and diastereoselectivity of this reduction was rationalized by initial reaction with the tertiary alcohol to generate aluminum alkoxide **22**. This intermediate would allow delivery of hydride selectively to C2 from the more sterically hindered concave face, providing the required stereoisomer **23**. Transformation of the tertiary allylic alcohol to a mixture of allylic bromides and subsequent hydrolysis of these intermediates in boiling aqueous sulfuric acid provided isostrychnine (**2**), with the yield of this sequence being compromised by the formation of the corresponding Z-allylic alcohol.

In this way, Woodward was able to synthesize what was the most complex natural product known in 1954, an event signaling that no natural structure was too complex to be synthesized. Woodward's success in forging this demanding

target is particularly impressive in light of the few selective C–C bond-forming reactions available at the time. Two themes still important in modern organic synthesis strategy are apparent in the Woodward synthesis: use of a masked precursor of a reactive unit—in Woodward's case an aromatic veratryl antecedent of a dienyl diester—and intramolecular delivery of a reagent. Perhaps most impressive is the fact that nearly forty years transpired before subsequent total syntheses of strychnine were recorded.[44a–c, 49]

### 3.2. Overman's Synthesis: A Cationic Rearrangement Cascade (1993)

In 1993, nearly 40 years after Woodward's accomplishment, our group reported the first enantioselective total synthesis of strychnine.[49] Our retrosynthetic analysis focused on the Wieland–Gumlich aldehyde (**3**) as the most efficient precursor of strychnine (Scheme 8). The Wieland–Gumlich
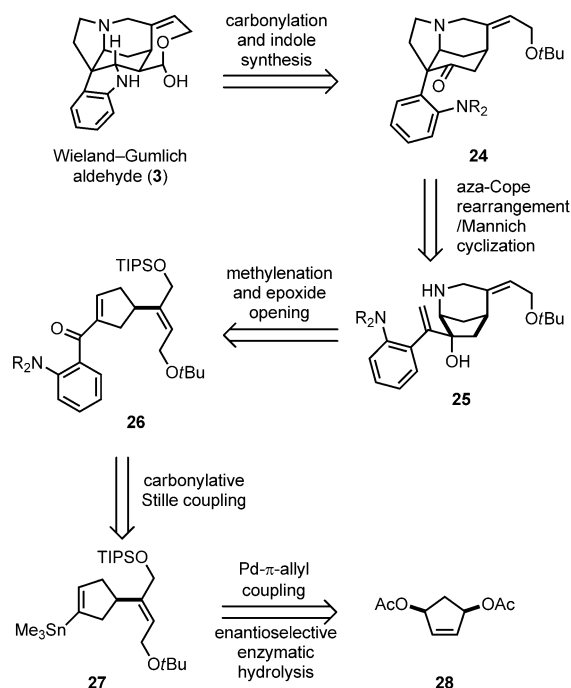


**Scheme 8.** Retrosynthetic analysis of Overman's route to strychnine.

aldehyde, upon disconnection of the B ring, simplifies to tetracyclic keto aniline **24** containing the critical CDE tricyclic unit. The aza-Cope rearrangement/Mannich cyclization cascade reaction developed in our laboratory was seen as delivering **24** from precursor **25**, an intermediate containing only two of the final rings of strychnine (A and D).[37] Disconnecting the two heteroatom bonds to the cyclopentane ring of **25** and simplifying the styrene fragment to an aryl ketone yields **26**. In the synthetic direction, formation of the piperidine ring and the proper relative configuration of the tertiary allylic alcohol would arise by intramolecular opening of a cyclopentyl epoxide derived from dienone **26**, a tactic that

had been developed during our earlier synthesis of the simpler *Strychnos* alkaloid akuammicine.[50] Intermediate **26** would in turn come from carbonylative Stille coupling of cyclopentene **27** and an aniline precursor. Stannane intermediate **27** was originally envisioned to arise from the 1,4-addition of a fully fashioned *Z*-butenyl organometallic to an enantioenriched cyclopentenyl electrophile. However, with this coupling never realized in a satisfactory manner, *meso* diacetate **28** became the starting material.

The Overman synthesis of (−)-strychnine began with desymmetrization of *cis*-1,4-diacetoxycyclopent-2-ene **28** using electric eel acetylcholinersterase, following a procedure documented in *Organic Syntheses* that delivered alcohol **29** in high yield and 99% *ee* (Scheme 9).[51] Stereospecific palladium-catalyzed coupling of this enantioenriched intermediate
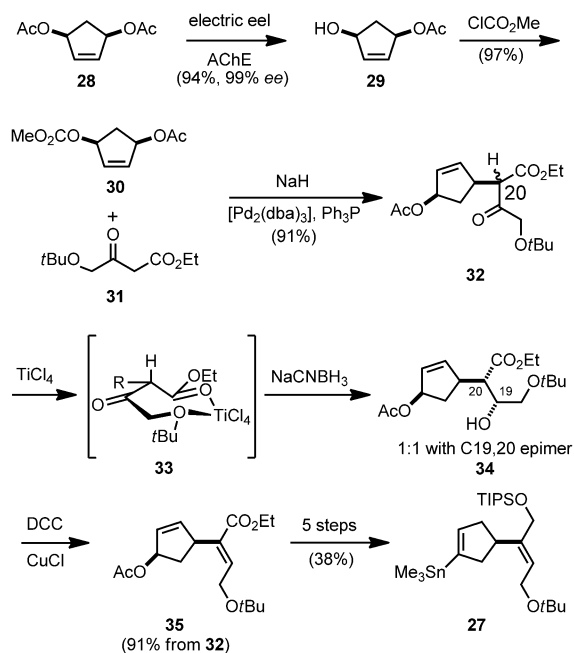
**Scheme 9.** Synthesis of vinyl stannane **27**.

with carbon nucleophiles had been described at the time.[52] To arrive at the natural enantiomer of strychnine, the carbonate derivative **30** was prepared and coupled with β-ketoester **31**. As expected, this palladium-catalyzed coupling took place with complete site and stereoselectivity to give **32**, a 1:1 mixture of ester epimers, with complete retention of enantiomeric purity.[53] In order to introduce an *E* double bond, the keto group of β-ketoester **32** needed to be reduced in a stereoselective manner. Although conventional reduction of these β-ketoester epimers to give *syn* β-hydroxyester products could not be accomplished,[54,55] addition of sodium cyanoborohydride to a solution of **32** premixed with titanium tetrachloride afforded the *anti* β-hydroxyester product of each ester epimer in high stereoselectivity. This unconventional outcome was proposed to result from chelation of titanium to both the ester and the *tert*-butyl ether to form intermediate **33**, with hydride addition from the less hindered axial face then providing the observed products. Stereospe-

cific *syn* elimination of intermediates **34** yielded exclusively the *E*-trisubstituted double bond.[56] Five standard transformations then converted diester **35** to the vinyl stannane **27**.

The aza-Cope/Mannich cyclization precursor was synthesized in eight steps from vinyl stannane **27** (Scheme 10). Carbonylative Stille coupling of cyclopentyl stannane **27** with
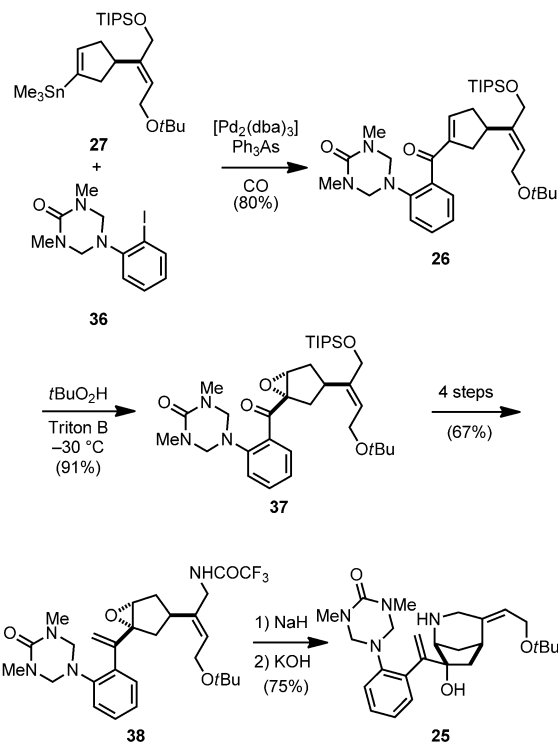
**Scheme 10.** Synthesis of aza-Cope rearrangement/Mannich cyclization precursor.

triazone-protected *o*-iodoaniline **36** provided ketone **26** in high yield.[57] Regioselective epoxidation of enone **26** with *t*BuO$_2$H and base took place with high stereoselectivity from the face opposite the butenyl side chain to give epoxide **37**. Wittig methylenation of the ketone and standard conversion of the silyl ether to a trifluoroacetamide then delivered epoxy amide **38**. Deprotonation of the trifluoroacetamide induced intramolecular epoxide opening to form the piperidine D ring and provide intermediate **25** after cleavage of the trifluoro-acetyl group with base.

Assembly of the pivotal CDE tricyclic core of strychnine was accomplished in a single step and nearly quantitative yield by exposure of amino alcohol **25** to paraformaldehyde at 80 °C (Scheme 11). This aza-Cope rearrangement/Mannich cyclization cascade proceeds by initial generation of iminium **39**, which undergoes [3,3]-sigmatropic rearrangement to construct the C5–C6 bond and generate iminium ion enol **40**. Formation of the C3–C7 bond by a transannular Mannich cyclization then terminates the cascade process. This process generated two new carbon–carbon bonds as well as a carbon–nitrogen bond while constructing the congested CDE tricyclic core of strychnine.
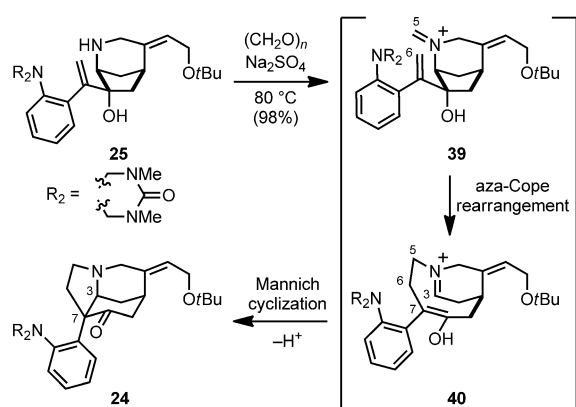
**Scheme 11.** Aza-Cope/Mannich reaction to form the C and E rings.

Tetracyclic intermediate **24** was advanced to the Wieland–Gumlich aldehyde in five steps (Scheme 12). Carbomethoxylation of the enolate derived from **24** and removal of the triazone protecting group with acid yielded hydroxyakuam-
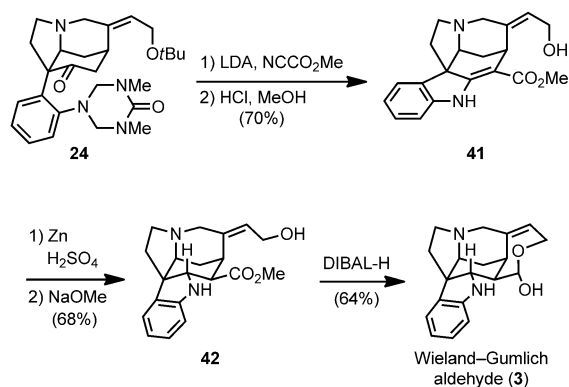


**Scheme 12.** Synthesis of the Wieland–Gumlich aldehyde.

micine (**41**).[58] Whereas attempted reduction of the enamine of **41** under neutral or weakly acidic conditions resulted in decomposition, treatment with zinc in sulfuric acid successfully saturated the C2–C16 double bond. Equilibration of the initially produced axial ester then delivered **42** in good yield (68 %). The configurational outcome of these steps had some precedent from related transformations of akuammicine.[59] Partial reduction of the ester of **42** with diisobutylaluminum hydride at −90 °C afforded the Wieland–Gumlich aldehyde (**3**), which was transformed to (−)-strychnine in high yield.

The Overman synthesis of (−)-strychnine from 1993 was both the first enantioselective and the first nonrelay total synthesis of strychnine. Although it was of similar length as the Woodward synthesis, it was several orders of magnitude more efficient. As we suggested in our full account,[49b] this substantial increase in efficiency resulted in large part from the progress in synthetic organic chemistry registered in the intervening 40 years, as no more than half of the reactions utilized in the Overman synthesis would have been available to Woodward in 1954. In particular, this synthesis highlighted

the utility of palladium-catalyzed reactions ($\eta^3$-allylpalladium alkylation and carbonylative cross-coupling) and the aza-Cope/Mannich reaction cascade for constructing critical C–C bonds. The use of enzymatic desymmetrization and exploitation of symmetry were illustrated also, the latter underscored by a minor modification of the sequence—employing hydroxy ester **29** in the early Tsuji–Trost coupling—that allowed *ent*-strychnine to be obtained for the first time.[60,61]

### 3.3. Rawal's Synthesis: Diels–Alder and Heck Cyclizations (1994)

Rawal and Iwasa envisioned a streamlined route for the synthesis of strychnine by way of isostrychnine (Scheme 13).[62] The plan was to employ an intramolecular Heck reaction to construct the piperidine D ring from
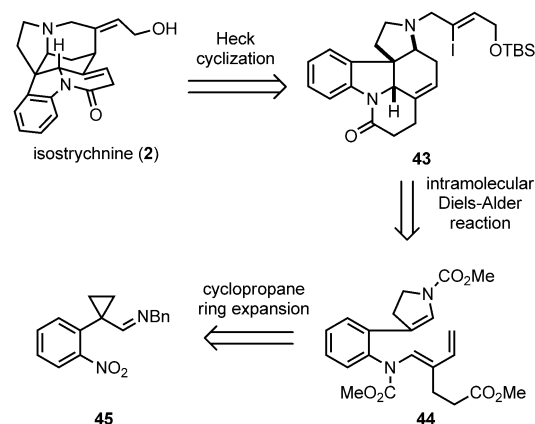


**Scheme 13.** Rawal's retrosynthetic analysis.

pyrrolo[2,3-*d*]carbazole vinyl iodide **43**,[63] itself arising from intramolecular Diels–Alder reaction of enecarbamate **44**. The pyrroline ring of **44** would stem from ring expansion of cyclopropyl imine **45**. This sequence was based on Rawal's earlier synthesis of structurally less elaborate *Strychnos* alkaloids.[64]

The Diels–Alder substrate **44** was assembled in seven steps from commercially available *o*-nitrobenzylnitrile (**46**; Scheme 14). Initially cyclopropyl imine **45** was synthesized in three standard steps from nitrile **46**, 1,2-dibromoethane, and benzylamine. Nucleophilic opening of the cyclopropane with TMSI generated intermediate **47**, which upon intramolecular alkylation provided dihydropyrrole **48**.[65] Reduction of the nitro group, followed by condensation of the product with methyl 4-formylhex-4-enoate and N-alkoxycarbonylation delivered diene carbamate **44**.

In five steps, the Diels–Alder substrate **44** was transformed into isostrychnine (Scheme 15). Heating **44** at 185 °C induced intramolecular cycloaddition by way of the less sterically hindered *exo* transition state to provide pyrrolocarbazole **49** in nearly quantitative yield. Dispatch of the carbamate groups of **49** upon reaction with TMSI was accompanied by formation of the G ring to provide lactam **50**, which upon alkylation with allyl bromide **51** gave rise to the Heck cyclization substrate **43**. In the second pivotal step

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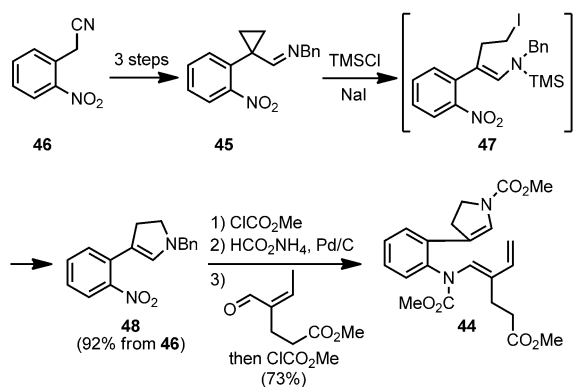
**Scheme 14.** Synthesis of the Diels–Alder precursor.
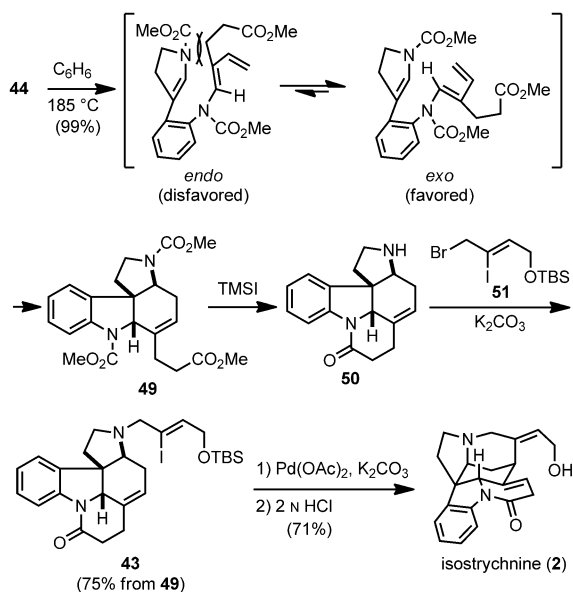


**Scheme 15.** Intramolecular Diels–Alder reaction and synthesis of iso-strychnine (**2**).

of the sequence, cyclization of **43** under Jeffery–Heck reaction conditions formed the final piperidine D ring.[66] Removal of the silyl protecting group then delivered isostrychnine (**2**).

Rawal's synthesis of strychnine was remarkable for both its low number of steps and high efficiency. Isostrychnine (**2**) was formed in 34% overall yield from **46**, corresponding to roughly 10% overall yield of racemic strychnine over 13 steps. This is the most efficient construction of racemic strychnine reported to date. Like the Overman synthesis, the Rawal synthesis illustrated the utility of transition-metal-catalyzed C–C bond-forming transformations, in this case the intramolecular Heck reaction to assemble the challenging piperidine D ring. The high strategic value of this tactic is apparent from its use in five subsequent strychnine syntheses. A crucial feature contributing to the efficiency of the Rawal synthesis was the incisive design whereby the intramolecular Diels–Alder reaction produced the six-membered carbocyclic E ring with the double bond in exactly the position required for the subsequent intramolecular Heck closure of the D ring.

### 3.4. Kuehne's Synthesis: A Cationic Rearrangement Cascade (1998)

Kuehne and Xu first described the total synthesis of racemic strychnine in 1993[42] and five years later the synthesis of (−)-strychnine by a related strategy.[67] As in Rawal's synthesis, a pyrrolo[2,3-*d*]carbazole was a central intermediate. In Kuehne's synthesis it was seen as the product of a cationic rearrangement cascade (Scheme 16). Targeting the Wieland–Gumlich aldehyde, the retrosynthetic analysis in the
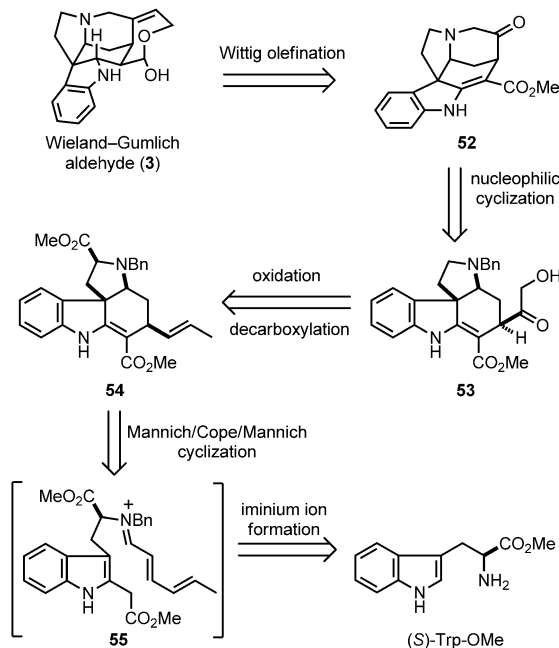


**Scheme 16.** Kuehne's retrosynthetic analysis.

1998 synthesis envisioned late-stage formation of the F ring and C19–C20 double bond from ketoester precursor **52**. Conventional disconnection of the D ring revealed hydroxy-ketone **53**, which would arise from precursor **54**. The C and E rings of pyrrolocarbazole **54** were disconnected by a cyclization/rearrangement cascade of iminium ion **55**, an approach that had been developed[68] as an alternative to the biomimetic secodine-like cyclizations Kuehne et al. had previously pioneered to prepare *Aspidosperma*[69] and some *Strychnos* alkaloids.[70] Iminium ion intermediate **55** would be generated from an appropriate aldehyde and a tryptophan derivative (**56**), which would ultimately derive from (*S*)-tryptophan methyl ester.

Starting with (*S*)-tryptophan methyl ester, tryptophan derivative **56** was synthesized in five conventional steps (Scheme 17). Acid-promoted condensation of amino ester **56** and 2,4-hexadienal in refluxing benzene proceeded with high diastereoselectivity to generate pyrrolo[2,3-*d*]carbazole **54** in 84% yield. This impressive transformation is believed to take place by intramolecular Mannich reaction of the initially generated iminium ion via conformer **55**-*Re* in which desta-bilizing steric interactions between the methyl ester and the indole are minimized. After tautomerization, 1,5-diene **57**
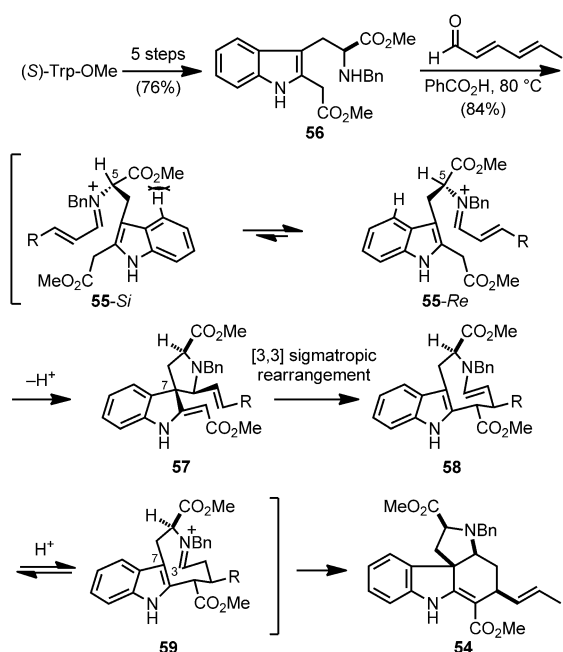
**Scheme 17.** Diastereoselective Mannich cyclization/Cope rearrangement/Mannich cyclization cascade (R = CH=CHCH₃).

undergoes Cope rearrangement by a favored chair geometry that places the propene and ester substituents in pseudo-equatorial positions (**58**). Intramolecular Mannich cyclization of iminium ion **59** then forms the C3–C7 bond, completing the construction of the C and D rings of strychnine with complete diastereoselectivity.[71]

The final three rings of strychnine were constructed from pyrrolocarbazole **54** as outlined in Scheme 18. Removal of the now unneeded methyl ester substituent—accomplished by way of the corresponding nitrile[72]—and oxidative elaboration of the propenyl side chain delivered hydroxyketone
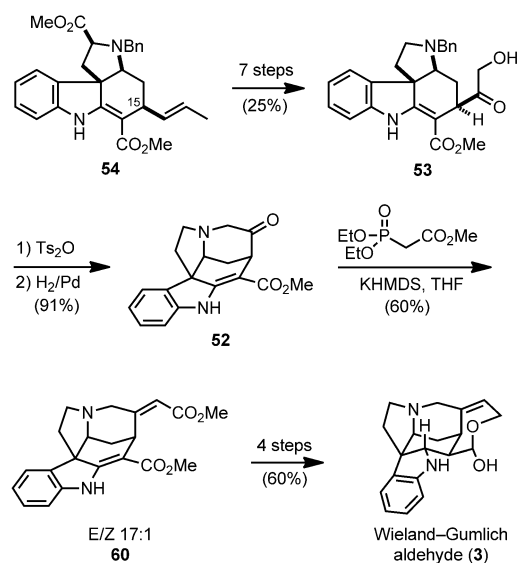


**Scheme 18.** Closure of the D ring and completion of the synthesis.

intermediate **53** in seven steps. After conversion of the primary alcohol to a tosylate, hydrogenolytic removal of the benzyl-protecting group took place with concomitant intra-molecular alkylation to generate piperidinone **52**. Horner–Wadsworth–Emmons olefination of this intermediate provided enoate **60** as nearly exclusively the *E* alkene stereoisomer. In Kuehne's earlier synthesis of racemic strychnine,[42] this olefination was carried out on an intermediate having the piperidone G ring already in place and occurred in a non-stereoselective fashion. Kuehne and Xu note that stereo-selection in the formation of **60** was critically dependent upon the experimental conditions, although no rational for the high selectivity obtained using the potassium salt in THF was advanced. A four-step sequence involving stepwise reduction of the ester and the vinylogous carbamate then yielded the Wieland–Gumlich aldehyde (**3**).

The power of iminium ion initiated cascade reaction sequences is nicely illustrated in the Kuehne synthesis, as the C and E rings of strychnine were fashioned in short order from (*S*)-tryptophan methyl ester. In this sequence the ultimately unneeded methyl ester played an important role in directing the enantioselective evolution of pyrrolo[2,3-*d*]carbazole intermediate **54**. Although several steps were required to elaborate this intermediate to (−)-strychnine, Kuehne's contribution remains one of the shorter enantio-selective syntheses of strychnine achieved to date.

### 3.5. Vollhardt's Synthesis: A [2+2+2] Cycloaddition (2000)

Vollhardt et al. envisaged a cobalt-mediated [2+2+2] cycloaddition to quickly assemble the ABEG tetracyclic core of (±)-strychnine (Scheme 19).[73] In this analysis, the D ring of isostrychnine (**2**) was seen arising from dienone vinyl iodide **61** by an intramolecular Heck or radical cyclization reaction. Disconnection of the pyrrolidine ring of **61** led to cobalt-bound triene **62**, which in the central step of the synthesis was seen resulting from [2+2+2] cycloaddition of acetylene and indolyl enyne **63**.

The tetracyclic core of (±)-strychnine was rapidly assembled from N_b-acetyltryptamine (**64**; Scheme 20). Amide formation between indole **64** and acid chloride **65** under
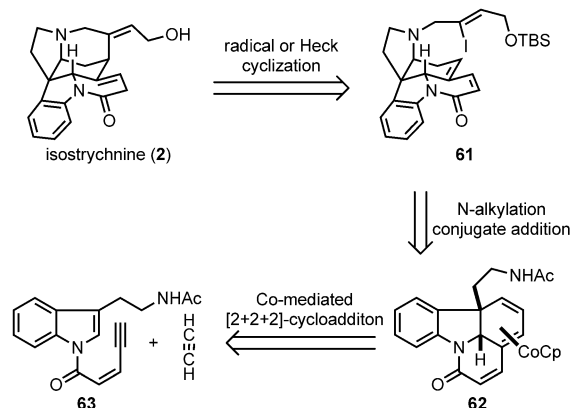


**Scheme 19.** Vollhardt's retrosynthetic analysis.
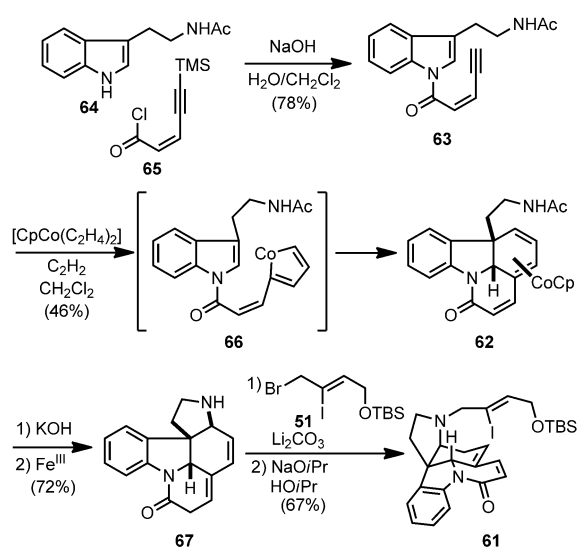
**Scheme 20.** [2+2+2] cycloaddition to form the ABEG tetracyclic intermediate **62**.

Schotten–Baumann conditions afforded indolyl amide **63**. Exposure of this intermediate to [CpCo(C$_2$H$_4$)$_2$] under an acetylene atmosphere generated a single stereoisomer of cobalt-bound triene **62** in 46% yield.[74] This transformation presumably occurs by initial formation of metallacyclic intermediate **66**, which undergoes intramolecular [4+2] cycloaddition and bond reorganization to deliver **62**.[75] Related [2+2+2] cycloaddition reactions were performed on a number of alkynyl indole substrates.[73,74a] Oxidative removal of the cobalt after cleavage of the acetyl group of **62** resulted in conjugate addition of the β-aminoethyl side chain to form the strychnine C ring (**67**). Alkylation of the resulting secondary amine with allyl bromide **51** provided intermediate **61**.

All that remained to access isostrychnine from intermediate **61** was closure of the piperidine D ring (Scheme 21). Reductive radical-chain cyclization of **61** proceeded in good yield to give a 1:1 mixture of TBS-protected isostrychnine **69** and double-bond isomer **68**, with the loss of configuration of
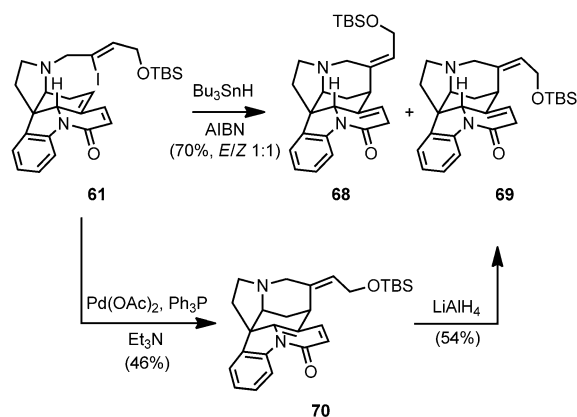
the C19–C20 double bond arising from rapid isomerization of the vinyl radical intermediate.[70c,76] Alternatively, Heck cyclization of **61** provided pyridone **70**, which could be reduced to isostrychnine derivative **69** using lithium aluminum hydride, but the overall yield of the two-step stereoselective process was lower than the yield of pure **69** obtained from radical cyclization. It is noteworthy that the LiAlH$_4$ reduction yielded the correct configuration at C2 without the presence of a directing group, remarkable selectivity the authors attributed to hydride attack from the less hindered *Si* face of the pyridone.[73] Acidic cleavage of the TBS group of **69** provided isostrychnine (**2**) in high yield.[62]

Vollhardt's concise total synthesis of (±)-strychnine illustrates the participation of the C2–C3 double bond of indole in cobalt-mediated [2+2+2] cycloadditions.[74] This powerful transformation allows a high degree of complexity to be introduced into an indole starting material in one synthetic step. The success of this step in Vollhardt's synthesis of (±)-isostrychnine depended critically upon the nature of the oxidant employed in the demetalation step, as Vollhardt et al. had reported earlier that oxidation of closely related complexes can lead to non-demetalative formation of propellane products.[77] This synthesis also evaluated the potential to generate the C15–C20 double bond using a radical cyclization; however, as likely expected, generation of the C20 vinyl radical resulted in loss of alkene configuration.

### 3.6. Martin's Synthesis: A Biomimetic Approach (2001)

In 2001 Martin et al. reported a biogenetically inspired synthesis of strychnine.[78] Hydroxyakuammicine (**41**) was selected as a late-stage intermediate, because its three-step elaboration to strychnine was known from the Overman synthesis (Scheme 22).[49] Martin planned to mimic the biogenesis of *Strychnos* alkaloids (Scheme 1) by forming hydroxyakuammicine from deformylgeissoschizine derivative **71** by an oxidative rearrangement cascade. Intermediate **71** was seen deriving from an intramolecular hetero-Diels–Alder reaction of aldehyde **72**, which in turn would arise by tandem acylation/vinylogous Mannich reaction of dihydro azacarbazole **73**.

The tetracyclic deformylgeissoschizine analogue **71** was assembled by a general strategy developed earlier by Martin et al. for the synthesis of heteroyohimboid and corynantheoid alkaloids (Scheme 23).[79] Azacarbazole **73**, available in two steps from tryptamine, was allowed to react with acryloyl chloride **74** to generate *N*-acyliminium intermediate **75**, which underwent subsequent vinylogous Mannich addition with 1-trimethylsilyloxy-1,3-butadiene. This one-pot sequence rapidly generated intermediate **72**, which contains all the carbon atoms of hydroxyakuammicine (**41**). Intramolecular hetero-Diels–Alder cyclization of enal **72** cleanly gave intermediate **76** having a heteroyohimboid ring system, which was elaborated in six additional steps to oxidative rearrangement precursor **71**.

Initial attempts to realize the pivotal biomimetic oxidative rearrangement were carried out with several structurally related precursors.[80] For example, oxidation of lactam **77**
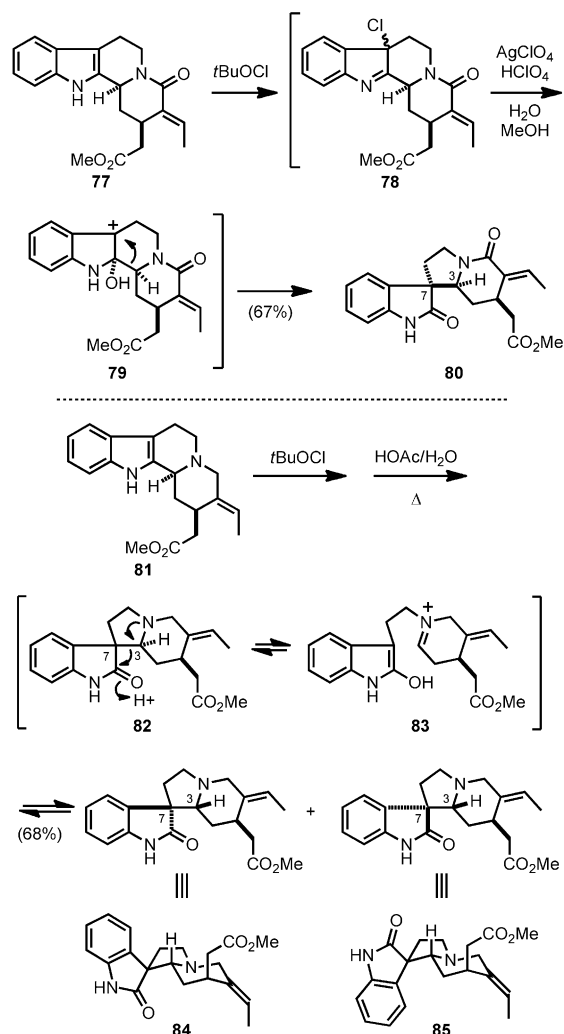


**Scheme 21.** Cyclization of the vinyl iodide side chain to form the D ring.
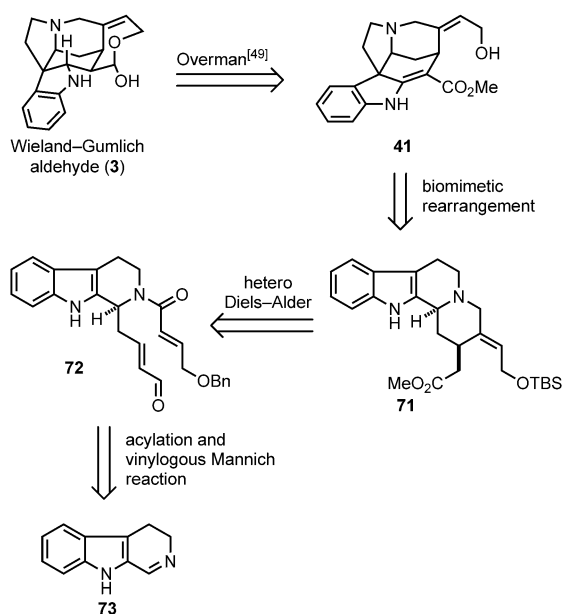
**Scheme 22.** Martin's retrosynthetic analysis.
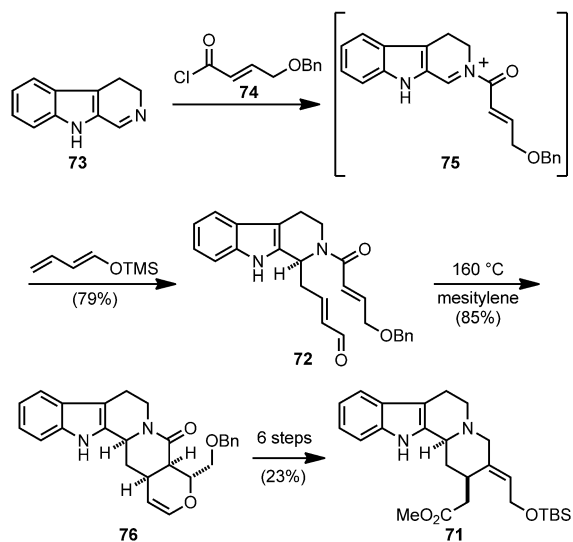


**Scheme 23.** Synthesis of deformylgeissoschizine-type precursor **71**.



**Scheme 24.** Initial attempts at oxidative rearrangement.

with *tert*-butylhypochlorite, followed by reaction with AgNO₃ and perchloric acid in aqueous methanol promoted the desired carbon–carbon bond migration of chloroindolenine intermediate **79** (Scheme 24).[78b] However, spiroxindole product **80**, in which the configuration at C7 is opposite to that found in *Strychnos* alkaloids, was formed. A related sequence starting with deformylgeissoschizine (**81**) provided two oxindole products **84** and **85**, both of which possessed the unwanted configuration at C3. In this case retro-Mannich fragmentation of the initially formed product(s) (**82→83**) leads to equilibration at both C3 and C7 to generate **84** and **85**. Of the four potential C3/C7 stereoisomers, these two are favored thermodynamically. This preference arises from the piperidine ring preferentially adopting a conformation having

the acetic ester side chain axial in order to avoid unfavorable A¹,³ interactions with the (*E*)-ethylidine group, thus favoring an axial orientation of the hydrogen at C3.[81]

To access hydroxyakuammicine (**41**), the biomimetic strategy was modified by elaborating the chloroindolenine intermediates under basic conditions (Scheme 25). Chlorination of indole **71** by sequential reaction with SnCl₄ and *tert*-butylhypochlorite is presumed to provide a mixture of epimeric chloroindolenines **86** and **87**. Treatment of this mixture with LHMDS generates the ester enolate, which in the β-epimer series (**86**) cyclizes to form **88**. The *anti* relationship of the chlorine and C2–C3 σ bond in **88** results in facile 1,2-migration to give **89**, which upon treatment with methanol/HCl afforded hydroxyakuammicine (**41**) in 22 % yield. It is hypothesized that the related adduct derived from the α-chloroindolenine **87** does not undergo 1,2-rearrangement because of the *syn* relationship of the chlorine and C2–C3 σ bond. Early investigation of this sequence with the analogue of **71** lacking the OTBS group had shown that pretreatment with SnCl₄ favored formation of the β-chloro-indolenine intermediate, which resulted in akuammicine being formed in 52 % yield.
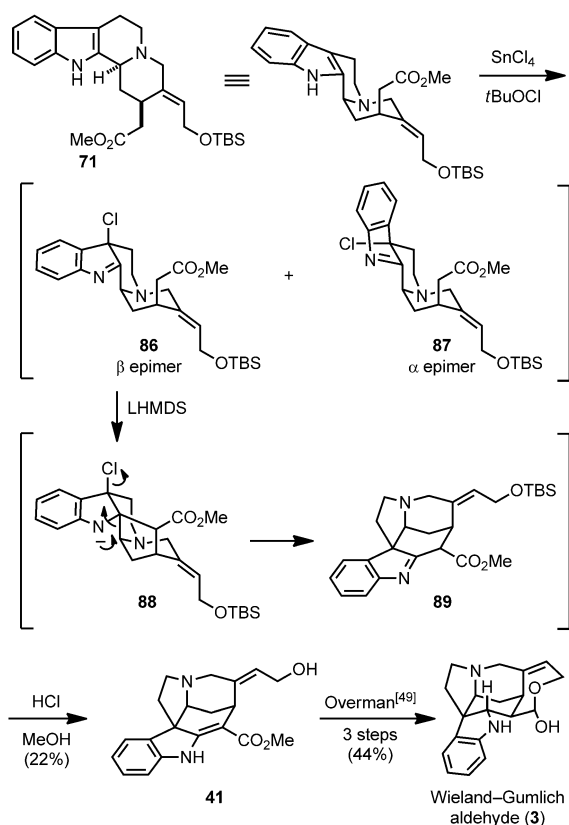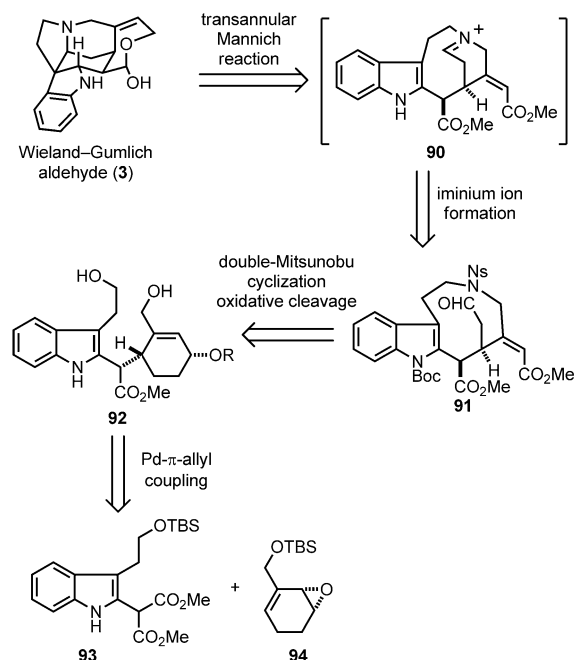
**Scheme 25.** Biomimetic rearrangement of deformlgeissoschizine derivative **71** to hydroxyakuammicine (**41**).

C3–N4 bonds to yield the tricyclic amino aldehyde **91** (Scheme 26). Further simplification by doubly disconnecting the nine-membered azacyclic ring of **91** to give diol **92** anticipates forming this challenging medium ring by dual



**Scheme 26.** Fukuyama's retrosynthetic analysis.

The Martin formal total synthesis of (±)-strychnine and total synthesis of (±)-akuammicine represent the first successful biomimetic constructions of *Strychnos* alkaloids. These syntheses demonstrate both the advantages and challenges of a biomimetic synthesis strategy. Although biomimetic rearrangement cascades can develop a great deal of complexity in a single step, laboratory methods for the stereoselective introduction of functionality to initiate such cascades can lack the selectivity and efficiency of the biological counterparts. In this case, the efficiency of the pivotal cascade rearrangement was likely undermined by low stereoselectivity of the oxidation of precursor **71** to generate chloroindolenine intermediate **86**. It merits note that the intramolecular capture of a chloroindolenine intermediate by a malonate nucleophile to initiate skeletal rearrangement was used by Stork to access a pyrrolo[2,3-*d*]carbazole intermediate in his unpublished synthesis of (±)-strychnine.[44c]

### 3.7. Fukuyama's Synthesis: A Transannular Pictet–Spengler Cyclization (2004)

Intramolecular additions to iminium ion intermediates played a central role in four of the syntheses that we have considered thus far. Nonetheless, Fukuyama et al. foresaw orchestrating this tactic in a unique manner.[82] In their retrosynthesis, the CDE fragment of the Wieland–Gumlich aldehyde was simultaneously disconnected at the C3–C7 and

Mitsunobu coupling with *o*-nitrophenyl sulfonamide (NsNH₂), an effective tactic introduced earlier by Fukuyama and Kan.[83] Additional simplification of indole intermediate **92** leads to indole malonate **93** and allylic epoxide **94**, which were anticipated to be joined stereoselectively by palladium-catalyzed Tsuji–Trost coupling.[84]

The Fukuyama synthesis begins by preparation of the partners for the palladium-catalyzed coupling reaction from inexpensive starting materials (Scheme 27). In three conventional steps,[85] benzoic acid was converted to bromohydrin **95**, which was resolved using lipase AYS and vinyl acetate to give enantiopure acetate **96**.[86] In three additional steps, this intermediate was elaborated to enantioenriched allylic epoxide **94**. The indole malonate nucleophile **93** was prepared in five steps from quinoline. Addition of water to the quinolinium salt generated by thioacylation of quinoline with thiophosgene (**97**) resulted in opening of the pyridine ring to provide the Z-enal isothiocyanate **98**, which was directly reduced to the Z-allylic alcohol **99** with sodium borohydride. The allylic alcohol was protected as the silyl ether, and dimethylmalonate was added to the isothiocyanate to provide thioamide **100**. In an indole construction developed earlier by Fukuyama et al.,[87] the α-amino radical, generated from the reaction of the thioamide with borane and tributyltin hydride, cyclized onto the pendant double bond to generate the indole malonate **93**.

The union of fragments **93** and **94** via the π-allylpalladium complex generated from **49** was accomplished with a palla-
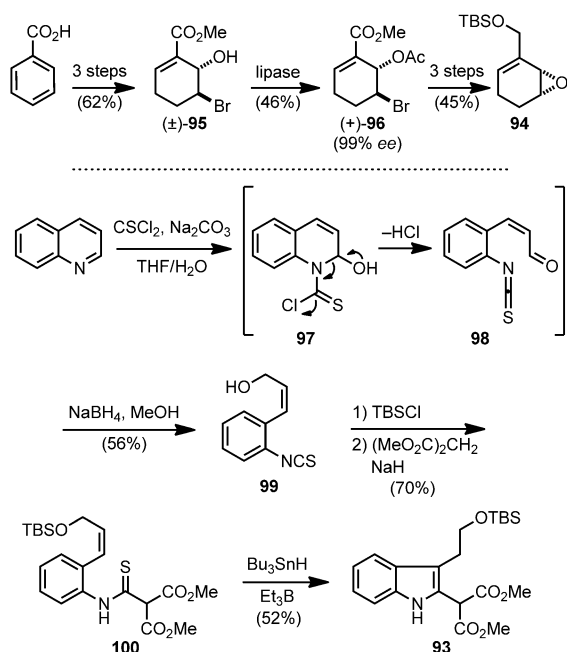
**Scheme 27.** Synthesis of coupling partners.



**Scheme 29.** Double-Mitsunobu reaction and aldehyde synthesis.

dium(0) trifurylphosphine catalyst (Scheme 28). As expected, this alkylation took place by double-inversion to produce cyclohexenyl indole malonate **101** in good yield.[84b] Protecting group manipulations and decarboxylation then provided macrocyclization substrate **102** in four additional steps.



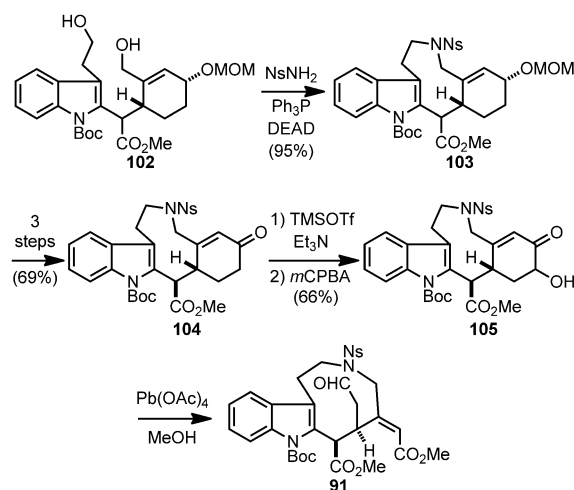**Scheme 28.** Tsuji–Trost coupling of **93** and **94** and elaboration to diol **102**.

Diol **102**, containing all of the carbon atoms of the Wieland–Gumlich aldehyde was advanced to the tricyclic intermediate **91** in seven steps (Scheme 29). Mitsunobu reaction of diol **102** with o-nitrobenzene sulfonamide gave the nine-membered ring intermediate **103** in 95% yield.[83,88] Epimerization at C16, followed by cleavage of the MOM ether and oxidation of the alcohol yielded enone **104**. Rubottom oxidation of the silyl enol ether derived from ketone **104** provided α-hydroxyketone **105**.[89] Subsequent

reaction with lead tetraacetate in methanol resulted in cleavage of the cyclohexenone ring to give tricyclic aldehyde **91**.

Intermediate **91** was properly functionalized to investigate the proposed transannular Mannich cyclization (Scheme 30). Simultaneous removal of the nosyl and Boc protecting groups
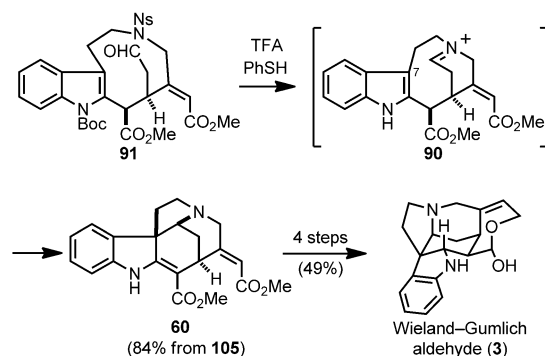


**Scheme 30.** Transannular Mannich cyclization.

upon reaction of **91** with thiophenol and TFA revealed the secondary amine, which condensed with the pendant aldehyde to generate iminium ion **90**. Intramolecular nucleophilic attack by the indole fashioned the C and E rings as well as the quaternary carbon stereocenter of strychnine, delivering **60** in 84% yield from precursor **105**. This transannular Mannich cyclization had precedent from the early Magnus synthesis of strychnine in which the iminium ion intermediate was generated by oxidation of a piperidine ring.[44a,b] Reduction of the vinylogous carbamate and ester functional groups of **60** provided the Wieland–Gumlich aldehyde (**3**) in four additional steps.[67]

Fukuyama's use of a Mitsunobu macrocyclization allowed for a strategically unique approach for the synthesis of strychnine. The congested CDE core ring system was constructed in a single step from a macrocyclic precursor

(**91**). The drawback of this approach was the rather lengthy sequence required to assemble this macrocyclic precursor. The utility of enzymatic resolution and palladium-catalyzed C−C bond formation were further illustrated in this route to (−)-strychnine, as was the Fukuyama indole synthesis.

### 3.8. Reissig's Synthesis: A Ketyl Radical Cyclization (2010)

By intercepting Rawal's pentacyclic intermediate **50**,[62] Reissig et al. completed a concise formal total synthesis of (±)-strychnine. In their strategy, the pyrrolidine ring of **50** was disconnected to arrive at the tetracyclic precursor **106** (Scheme 31). Retrosynthetic cleavage of the C2–C16 and C3–C7 bonds of this intermediate led to *N*-acylindole **107**, which was seen evolving to intermediate **106** in one step by a samarium-mediated ketyl-radical cyclization cascade developed earlier in the Reissig laboratories.[90,91]
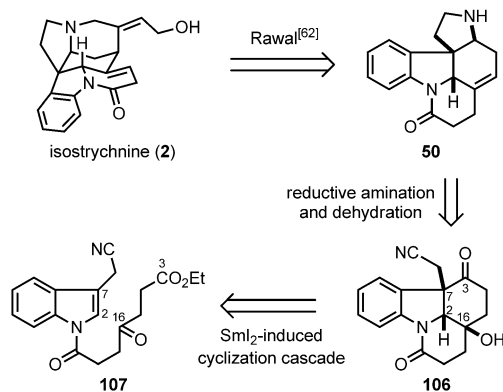


**Scheme 31.** Reissig's retrosynthetic analysis.

Tetracyclic intermediate **106** was assembled in a three-step sequence from commercially available diethyl 4-oxopimelate (**108**; Scheme 32). The synthesis began with lipase-catalyzed selective hydrolysis of diester **108** to provide the monoester of 4-oxoheptanedioic acid,[92] which was coupled with 3-indolylacetonitrile to provide amide **107**. Reaction of this intermediate at room temperature with excess samarium iodide and HMPA initiated a cascade sequence that gave tetracyclic intermediate **106** in 70–75 % yield.[93] In this effective sequence, 6-*exo*-trig cyclization of ketyl radical **109** generates benzyl radical **110**, which is further reduced to alkylsamarium intermediate **111**. Intramolecular acylation of this organosamarium species then delivers tetracyclic product **106**.

In three to five additional steps, tetracyclic intermediate **106** was transformed to Rawal's intermediate **43** (Scheme 33). In a crucial step in this sequence, the nitrile of **106** was reduced to the primary amine and intramolecular reductive amination was realized upon reaction of **106** for an extended period with Raney nickel under a hydrogen atmosphere. The high stereoselectivity observed in the reduction of the imine intermediate, which had some precedent,[94] was suggested to result from shielding of the β face by the angular hydroxy
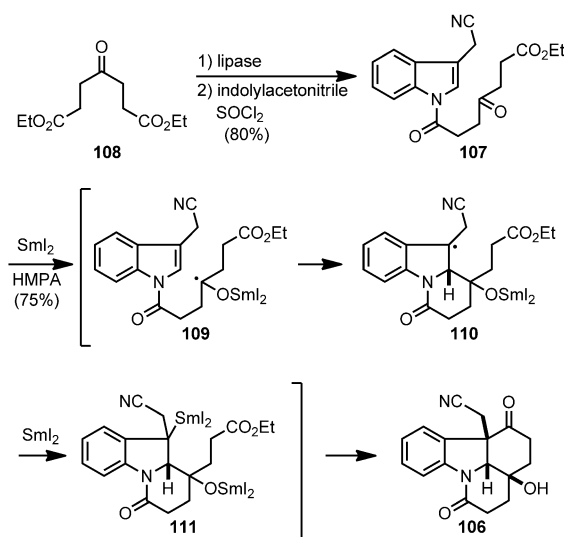


**Scheme 32.** SmI$_2$-induced cyclization cascade to form tetracyclic intermediate **106**.
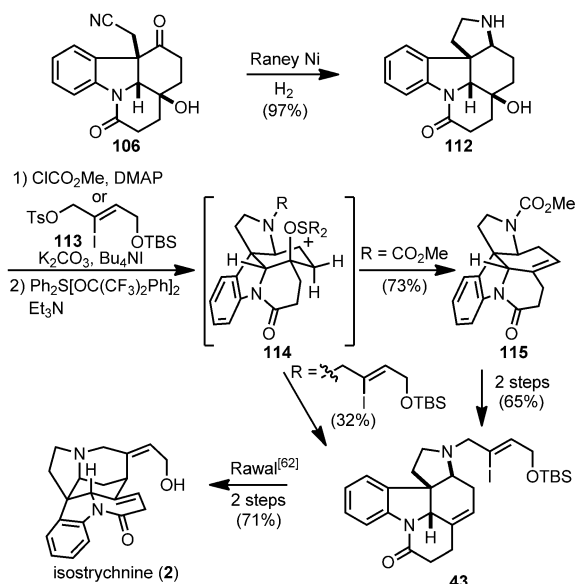


**Scheme 33.** Transformation to Rawal's intermediate.

group. The final step required to arrive at **115** was regioselective dehydration of the tertiary alcohol. Attempted dehydration of the methyl carbamate derivative (or methyl sulfonamide congener) with the Burgess reagent produced a 2:1:1 mixture of the three possible alkene products. Selectivity was enhanced when this dehydration was accomplished with Martin's sulfurane, giving isomerically pure **115** in 73 % yield over two steps. In two additional steps, this product was converted to Heck precursor **43**, completing a formal total synthesis of (±)-strychnine. Alternatively, the product of nitrogen alkylation with vinyl iodide **113** could be similarly dehydrated to directly afford **43**, albeit in lower yield as a result of reduced selectivity in the sulfurane-mediated elimination.[95]

In this approach to strychnine, construction of intermediate **106** containing the ABEG rings of strychnine in only three steps from commercial starting materials showcased the power of the reductive cascade processes developed in the Reissig laboratory. The opening step of the synthesis exemplified another use of enzyme catalysis, in Reissig's case to selectively desymmetrize a symmetrical achiral precursor. Reissig's elaboration of tetracyclic intermediate **106** in five additional steps to intercept Rawal's intermediates **43** and **50** completed a concise formal total synthesis of (±)-strychnine.

### 3.9. Vanderwal's Synthesis: Intramolecular Cycloaddition of a Zincke Aldehyde and Indole(2011)

The Vanderwal approach to strychnine envisaged a succinct series of disconnections.[96] Formation of the D ring by intramolecular addition of a butenyl organometallic side chain to an electron-deficient double bond would form the C15–C20 bond (Scheme 34). In contrast to the earlier uses of
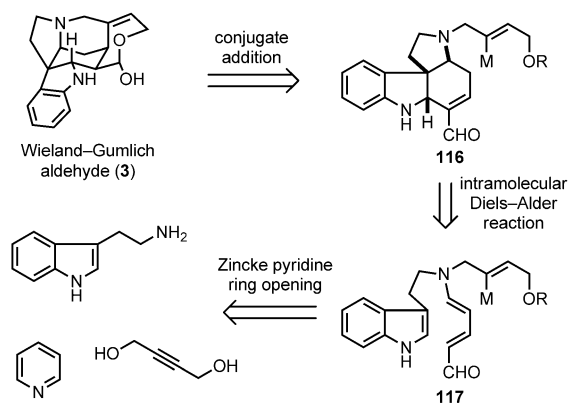


**Scheme 34.** Vanderwal's retrosynthetic analysis.

this bond construction, in this plan the conjugate addition would lead directly to the more efficient precursor of strychnine, the Wieland–Gumlich aldehyde (**3**). Pyrrolo[2,3-d]carbazole intermediate **116** was seen arising by intramolecular Diels–Alder reaction of indole dienal **117**. In a key simplification, this tryptamine dienal (**117**) would arise from tryptamine and pyridine by means of the venerable Zincke ring opening of pyridinium salts.[97]

The Vanderwal synthesis began with the construction of pyrrolocarbazole **122** in three steps from commercial reagents (Scheme 35). Reaction of $N_b$-allyltryptamine, available in one step from tryptophyl bromide, with 2,4-dinitrobenzenepyridinium chloride initiated the Zincke pyridine ring-opening to generate imine **120** by electrocyclic ring opening of dihydropyridine aminal **119**. Hydrolytic workup then yielded the tryptamine-derived Zincke aldehyde **121**.[98] Because of push-pull stabilization, Zincke aldehydes were known to be poor 4π components in intermolecular Diels–Alder reactions.[99] As a result, earlier attempts to realize intramolecular cycloaddition of intermediates similar to **121** under thermal or Lewis acid or protic acid catalyzed conditions met with
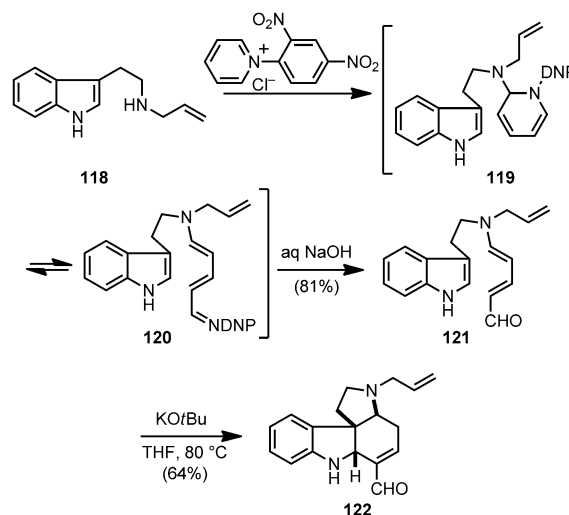


**Scheme 35.** Synthesis of a pyrrolo[2,3-d]carbazole intermediate from a Zincke aldehyde.

failure.[100] The enabling finding of Vanderwal's investigations was the discovery that the desired bond construction could be achieved under basic conditions by what is likely a stepwise anionic bicyclization. Thus, heating intermediate **121** at 80 °C in the presence of a slight excess of potassium *tert*-butoxide gave rise to pyrrolocarbazole **122** in 64% yield. An intramolecular Diels–Alder reaction of an indole, in this case with a tethered furan, played a central role in Padwa's synthesis of (±)-strychnine.[44h,i] The strategic advantage of the Vanderwal approach is that cycloaddition product **122** is generated appropriately functionalized for rapid conversion to the natural product.

In three additional steps, tetracyclic intermediate **122** was elaborated to racemic Wieland–Gumlich aldehyde (**3**) (Scheme 36). Removal of the allyl-protecting group from **122** proved to be challenging, as reductive, oxidative, and acidic conditions were not compatible with the reactive enal functionality. Ultimately it was found that palladium-catalyzed alkylative deallylation was successful when methyl Meldrum's acid was employed to trap the allyl fragment. This bulky nucleophile undergoes 1,4-addition or Knoevenagel condensation with the enal only slowly, thus minimizing these side reactions that had plagued more conventional deallylation procedures. Exploiting ruthenium-catalyzed *trans*-hydrosilylation,[101] the (Z)-2-butenyl fragment **125** was prepared succinctly in three steps from 2-butyne-1,4-diol by way of oxasilacycle **123**. Although intermediate **124** was relatively unstable—it contains both nucleophilic and electrophilic functionalities—the crude amino aldehyde generated by deallylation could be directly alkylated with allyl bromide **125** to yield the stable tertiary amine **126**. After extensive experimentation, it was found that generation of the alkoxide of **126** in the presence of cuprous bromide initiated a Brook rearrangement, with the resulting vinyl copper species (**116**) undergoing intramolecular conjugate addition to the enal. Unfortunately, the yield of this penultimate step in the Vanderwal total synthesis of (±)-strychnine was low (5–10%) under a variety of surveyed reaction conditions.
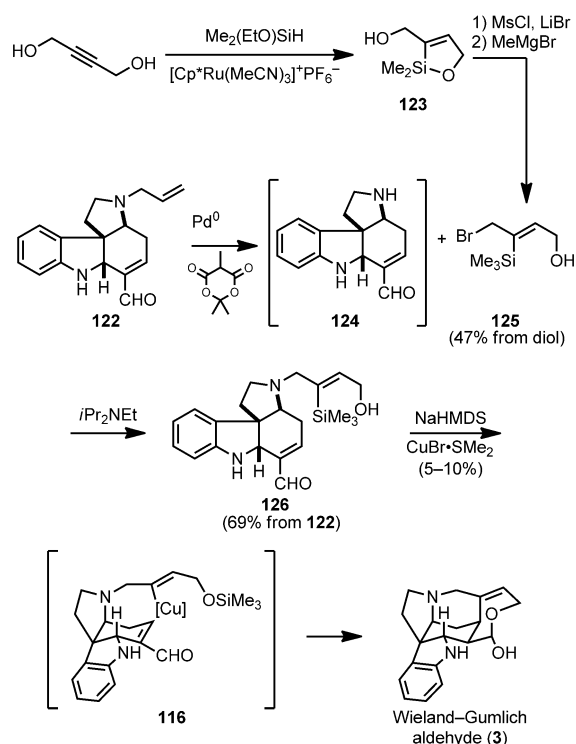
**Scheme 36.** Alkylation and conjugate addition to give the Wieland–Gumlich aldehyde.

The Vanderwal total synthesis of (±)-strychnine is the most direct reported to date, with the longest linear sequence being only six steps. Even though the final conjugate addition step was low yielding, the overall efficiency of this construction of racemic strychnine was a respectable 2–3 %. This synthesis beautifully illustrates the power of incisive synthetic strategy. Its conciseness arises because each key step delivers a product with exactly the functionality required for the next transformation; moreover, there is no need to adjust the oxidation state throughout the sequence.

### 3.10. MacMillan's Synthesis: An Organocatalytic Cascade (2011)

The Macmillan group envisioned a short enantioselective synthesis of (−)-strychnine as part of an indole alkaloid total synthesis endeavor in which a common enantiomerically enriched intermediate would serve as a precursor of several structurally distinct indole alkaloids.[102] In the context of (−)-strychnine, MacMillan's retrosynthetic analysis disconnects the C15–C20 bond to give pyrrolo[2,3-d]carbazole precursor **127**, which upon intramolecular Heck reaction would yield directly a protected form of the Wieland–Gumlich aldehyde (Scheme 37). Intermediate **127** was further simplified to pyrrolo[2,3-d]carbazole dienal **128**, which in turn was seen arising from 2-alkenyltryptamine **129** by an enantioselective organocatalytic Diels–Alder/amination cascade reaction.

In the first stage of MacMillan's synthesis of (−)-strychnine, an enantioselective organocatalytic cascade reaction was utilized to construct pyrrolo[2,3-d]carbazole inter-
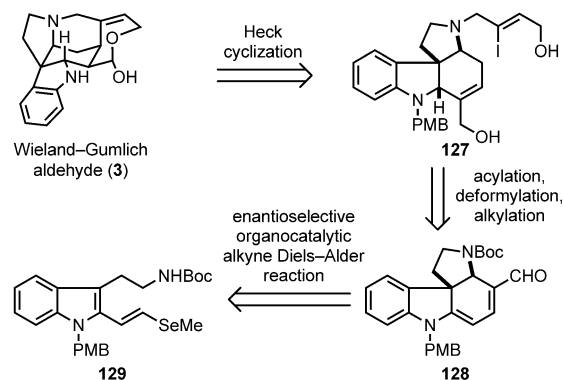


**Scheme 37.** MacMillan's retrosynthetic analysis.

mediate **128** rapidly (Scheme 38). Starting with readily available tetrahydro-β-carboline (**130**), indole vinylselenide **129** was assembled in three conventional steps. Reaction of 2-
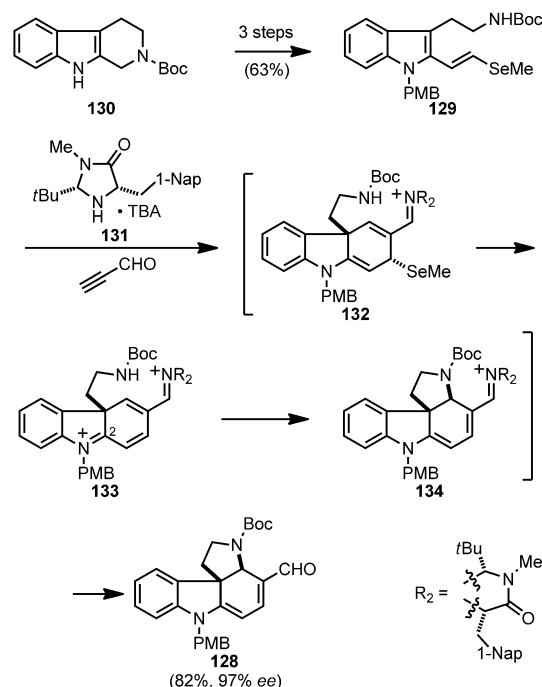


**Scheme 38.** Enantioselective organocatalytic cascade to form a pyrrolo-[2,3-d]carbazole intermediate.

alkenylindole **129** with propynal in the presence of enantiopure imidazolidinone catalyst **131** gave rise to pyrrolocarbazole **128** in 82 % yield and 97 % ee. This impressive transformation takes place by initial catalytic enantioselective formation of Diels–Alder adduct **132**, which rapidly loses methylselenide to give diiminium intermediate **133**. After intramolecular 1,4-addition of the carbamate nitrogen, hydrolysis of iminium ion **134** yields product **128** and regenerates the imidazolidinone catalyst. The regioselectivity of the intramolecular addition of the nitrogen was controlled by the leaving group ability of the selenide. In earlier studies, MacMillan et al. had observed that under similar conditions,

the methylthio analogue of **129** underwent C–N bond formation at C2 to give a pyrrolidinoindoline product that retained the thiomethyl substituent.[103,104]

In seven additional steps, pyrrolocarbazole dienal **128** was advanced to the Wieland–Gumlich aldehyde (Scheme 39). Refunctionalization of the cyclohexadiene ring was accom-
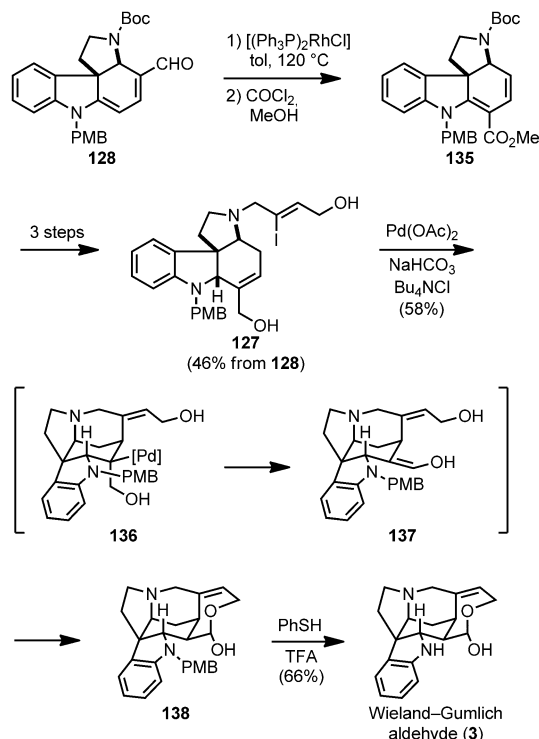


**Scheme 39.** Heck cyclization to form the Wieland–Gumlich aldehyde.

plished by deformylation of **128** in the presence of 1 equiv of Wilkinson's catalyst, and subsequent methoxycarbonylation of the dienamine product by sequential reaction with phosgene and methanol to form **135**.[105] The uncommon reactivity of the dienamine intermediate with phosgene at the internal, rather than terminal, position likely reflects steric shielding of the terminal vinylic carbon by the bulky NBoc substituent. Three additional routine steps gave pyrrolo[2,3-d]carbazole intermediate **127**. Intramolecular Heck reaction of **127** under Jeffery conditions[66] was found to be optimal for constructing the C15–C20 bond with concomitant formation of the F ring hemiacetal (**138**). The authors note that the presence of the *p*-methoxybenzyl substituent was critical in facilitating β-hydride elimination from carbopalladate **136** away from the angular methine hydrogen to form the critical enol precursor **137** of product **138**. Removal of the PMB group with trifluoroacetic acid and thiophenol provided the Wieland–Gumlich aldehyde (**3**).

In the MacMillan synthesis, an enantioselective organo-catalytic cascade was exploited to construct the pyrrolo[2,3-d]carbazole tetracyclic core of (−)-strychnine quickly. The significance of recent advances of enantioselective organo-catalysis,[106] in which the MacMillan laboratory has played a major role, are nicely highlighted in this synthesis which

achieves the shortest and most efficient route (12 steps and 6% overall yield) to (−)-strychnine to date.

## 4. Summary and Outlook

A number of trends become apparent when one compares the ten syntheses of strychnine discussed in this review (Table 1). In the nearly sixty years since Woodward's inaugural total synthesis in 1954, the efficiency with which chemists can construct a molecule of strychnine's complexity has advanced remarkably. Whereas Woodward's pioneering synthesis was realized in 0.0002% overall yield and required two relay intermediates, six of the syntheses we have considered proceed in 2% overall yield or greater, with Rawal's synthesis of (±)-strychnine proceeding in a remarkable 10% overall yield. In addition, the number of steps required to prepare (±)- and (−)-strychnine has dropped significantly, with five of the syntheses we considered requiring 15 or fewer linear steps from a commercially available starting material, and the shortest, from Vanderwal, only 6.

Remarkable also is the diversity of the chemistry and synthesis strategies that have been implemented to address the challenges strychnine poses for chemical synthesis. This variety is apparent in the syntheses discussed in this Review, and even more evident in the structures of key intermediates employed in all the strychnine syntheses reported to date (Figure 4).

Even with this diversity in approach, some disconnections have been recognized as particularly strategic. Most notably, late-stage construction of the C15–C20 bond, first demonstrated by Stork,[44c] is the most common method for construction of the D ring; ten of the 17 published syntheses rely on this bond formation. Another common feature is creating the C7 quaternary carbon by formation of the C3–C7 bond, a strategy employed in all but the Rawal synthesis. The Overman and Rawal syntheses were unique in not employing an indole precursor in the transformation that constructs the C7 quaternary carbon center.[107]

It is instructive to consider some of the important factors that have contributed to the recent remarkable increase in our ability to prepare a molecule of strychnine's complexity (Table 1). Prominent among these is the large number of selective C–C bond-forming transformations that have been introduced since the time of Woodward's groundbreaking synthesis. The well-appreciated central role of palladium-catalyzed C–C bond-forming processes in contemporary organic synthesis is apparent in the use of intramolecular Heck reactions, Tsuji–Trost cross-couplings, and carbonyla-tive cross-coupling in six of the ten syntheses that we considered.[108] This feature is notably highlighted in the Mori synthesis in which four bonds (three C–C and one C–N) were fashioned with palladium-catalyzed reactions.[44g] In addition, the important role that other catalytic reactions play in contemporary organic synthesis is evident in three of the enantioselective syntheses, where enzymatic desymmetriza-tion,[49] enzymatic resolution,[82] or enantioselective organo-catalysis[102] were utilized to access a chiral intermediate in high enantiomeric purity. Particularly apparent is the impact

***Table 1:*** Tabulated summary of highlighted syntheses of strychnine.
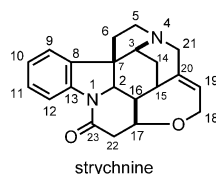


strychnine

| Main author | Year | Target strychnine precursor | C–C bonds formed[a] | Step count[b] | Overall yield [%][c] |
|---|---|---|---|---|---|
| Woodward[17] | 1954 | (−)-isostrychnine[d] | C7–C8, C7–C6, C7–C3, C15–C14, C20–C19 | 29 | 0.0002 |
| Overman[49] | 1993 | (−)-Wieland–Gumlich aldehyde | C15–C20, **C2–C7/C7–C8**, C7–C6, **C5–C6/C7–C3**, C16–C17 | 25 | 3 |
| Rawal[62] | 1994 | (±)-isostrychnine | C7–C6, **C2–C7/C14–C3**, C15–C20 | 12 | 10 |
| Kuehne[67] | 1998 | (−)-Wieland–Gumlich aldehyde | C2–C16, **C7–C3/C16–C15**, C20–C21, C20–C19 | 21 | 4 |
| Vollhardt[73] | 2000 | (±)-isostrychnine | C16–C17, **C2–C16/C7–C3/C15–C14**, C15–C20 | 14 | 0.7 |
| Martin[78] | 2001 | (±)-Wieland–Gumlich aldehyde | C3–C14, C15–C20, **C2–C16/C7–C3** | 16 | 1 |
| Fukuyama[82] | 2004 | (−)-Wieland–Gumlich aldehyde | C2–C7, C16–C15, C7–C3 | 25 | 1 |
| Reissig[90] | 2010 | (±)-isostrychnine | **C2–C16/C7–C3**, C15–C20 | 9 | 4 |
| Vanderwal[96] | 2011 | (±)-Wieland–Gumlich aldehyde | **C2–C16/C7–C3**, C15–C20 | 6 | 2–3 |
| MacMillan[102] | 2011 | (−)-Wieland–Gumlich aldehyde | C16-C15, **C7–C3/C15–C14**, C16–C17, C15–C20 | 12 | 7 |

[a] Bonds are listed in the order that they are formed in the synthesis. Bonds formed in a single transformation are joined by a slash and highlighted in bold. [b] The longest linear sequence from a readily available commercial precursor to strychnine. A step is counted when a product is isolated, though not necessarily purified. [c] Overall yield of strychnine was calculated as the combined reported yields of reactions in the longest linear sequence starting from a readily available commercial precursor. [d] Resolution of an intermediate was used to access the natural enantiomer.
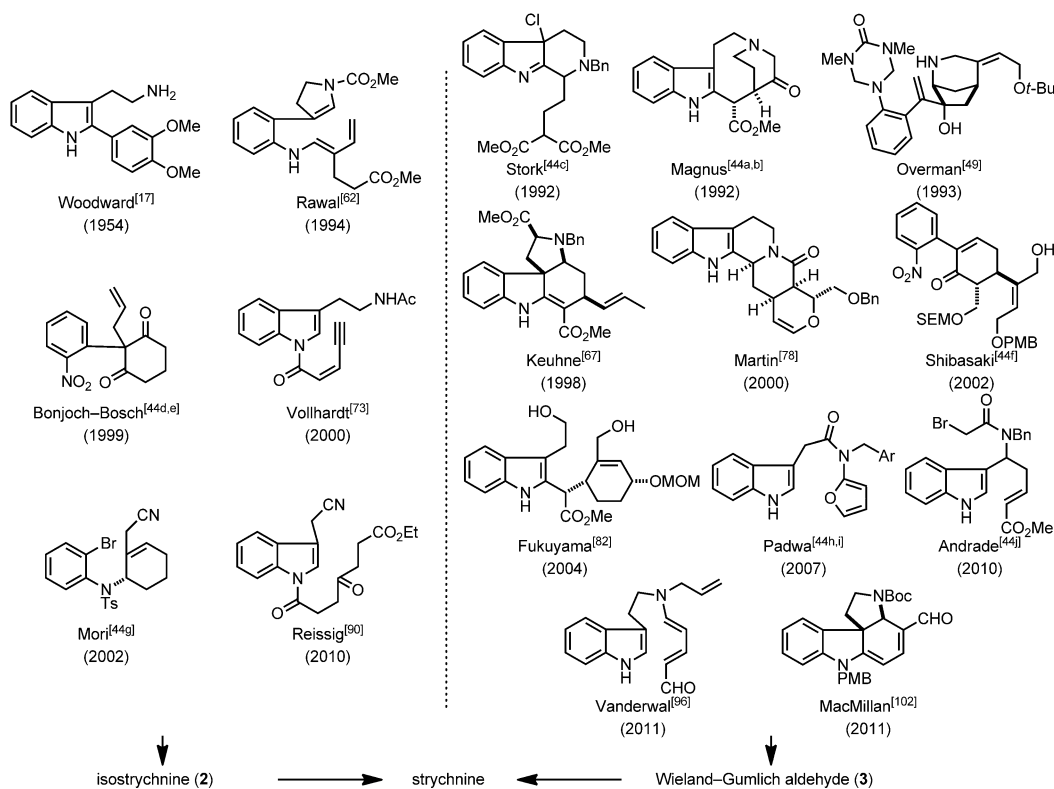


***Figure 4.*** Structural diversity of key intermediates employed in strychnine syntheses.

of transformations that form more than one C–C bond.[106c, 109] Although no reactions of this type were used in the Woodward synthesis, all but one of the subsequent strychnine syntheses that we have considered employed at least one, with three C–C σ bonds being forged in the central cobalt-promoted [2+2+2] cycloadditon step of the Vollhardt synthesis (Table 1).

An effective synthesis of a complex organic molecule requires both powerful bond-forming reactions and an insightful strategy. Although many of the factors that contribute to synthetic efficiency have been discussed and evaluated,[110] suffice it to say that minimizing steps that do not form bonds of the target structure is a hallmark of powerful synthesis strategy. The importance of minimizing

refunctionalization steps—oxidation, reduction, protection, deprotection—is well illustrated in the most concise strychnine syntheses; redox and protecting group refunctionalizations were minimized in the Rawal, Vollhardt, and Reissig syntheses of (±)-strychnine and absent in Vanderwal's concise construction.

An additional trend is apparent in the syntheses that we have considered. Until the most recent synthesis by MacMillan, enantioselective constructions of (−)-strychnine were substantially longer than total syntheses of the racemate. We speculate that this is not an isolated example, but a reflection of the fact that for many chiral structural motifs powerful enantioselective methods for the simultaneous formation of multiple bonds are not yet available though a topic of much current research.

Although it is difficult even in one's own research to recognize all the factors that contributed to important discoveries, we feel confident that a number of the advances in organic synthesis strategy and tactics that underpinned the strychnine total syntheses we have discussed were influenced early on by the structure and historical importance of strychnine. Does strychnine still represent a meaningful target for total synthesis? Yes indeed, with the proviso that consequential future contributions will be more effective than those recorded to date and most likely introduce new directions in organic synthesis strategy and tactics.

## 5. Abbreviations

| | |
|---|---|
| Ac | acetyl |
| AChE | acetylcholinesterase |
| AIBN | azobisisobutyronitrile |
| Ar | aryl |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadienyl |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexylcarbodiimide |
| DEAD | diethyl azodicarboxylate |
| DIBAL-H | diisobutylaluminum hydride |
| DMAP | *N,N*-dimethylaminopyridine |
| DNP | 2,4-dinitrophenyl |
| Glc | glycoside |
| HMDS | hexamethyldisilylamide |
| HMPA | hexamethylphosphoramide |
| LDA | lithium diisopropylamide |
| *m*CPBA | 3-chloroperoxybenzoic acid |
| MOM | methoxymethyl |
| Ms | methanesulfonyl |
| 1-Nap | 1-naphthyl |
| Ns | 4-nitrobenzenesulfonyl |
| PMB | 4-methoxybenzyl |
| PPA | polyphosphoric acid |
| *p*-tol | *p*-tolyl |
| pyr | pyridine |
| SEM | 2-(trimethylsilyl)ethoxymethyl |
| TBA | tribromoacetic acid |
| TBS | *tert*-butyldimethylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TMS | trimethylsilyl |
| Trp | tryptophan |
| Ts | *p*-toluenesulfonyl |

[1] W. A. Creasey in *Monoterpenoid Indole Alkaloids, Supplement to Vol. 25, Part 4* (Ed.: J. E. Saxton), Wiley, New York, **1994**, pp. 715–754.

[2] The first recorded mention of nuts having powerful medical properties is believed to be a treatise by Haly Abbas, the Bagdad physician to Calif Adud al-Dawlah, that became known in the West as *Liber regius* or the *Pantegni*.[3]

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[15] The correct structure of strychnine first appeared in publications from Robinson's laboratory. However, his group favored a different structure.[13]

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