Synthesis of Strychnine

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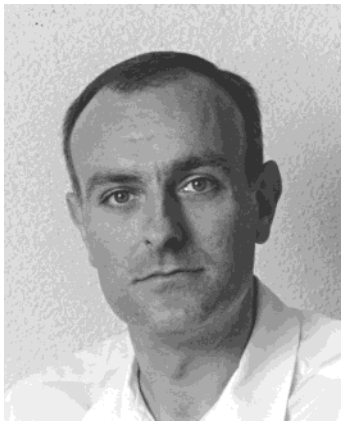
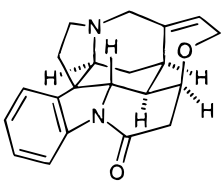


Daniel Solé Arjó was born in 1965 in Vielha, Spain. He studied Pharmacy at the University of Barcelona, where he received his Ph.D. in 1992. After postdoctoral studies at the Spanish research council (CSIC) with Prof. Josep M^{a}Moretó, he returned to the Faculty of Pharmacy at the University of Barcelona, where he became Associate Professor in Organic Chemistry in 1997. His research is centered on the use of transition metals in the synthesis of complex organic molecules.

I. Introduction

The historic total synthesis of strychnine by Woodward[1] in 1954 represented a milestone in the field of organic synthesis.[2] Strychnine ($C_{21}H_{22}N_2O_2$) ranks as one of the most complex natural products of its size, inasmuch as it incorporates six contigous asymmetric centers (five of which are in the core cyclohexane ring) and contains a mere 24 skeletal atoms compactly arranged in seven rings. Given its intricate architecture, coupled with its pharmacological and extremely toxic properties,[3] strychnine has always fascinated organic chemists.[4] It is a notorious poison



Strychnine

(~50 mg is lethal for an adult human), which blocks postsynaptic inhibition in the spinal cord where it antagonizes the transmitter glycine.[5] This property has made strychnine very useful as a tool in experimental pharmacology.

Strychnine was first isolated as far back as 1818 from the seeds and bark of *Strychnos nux vomica* by

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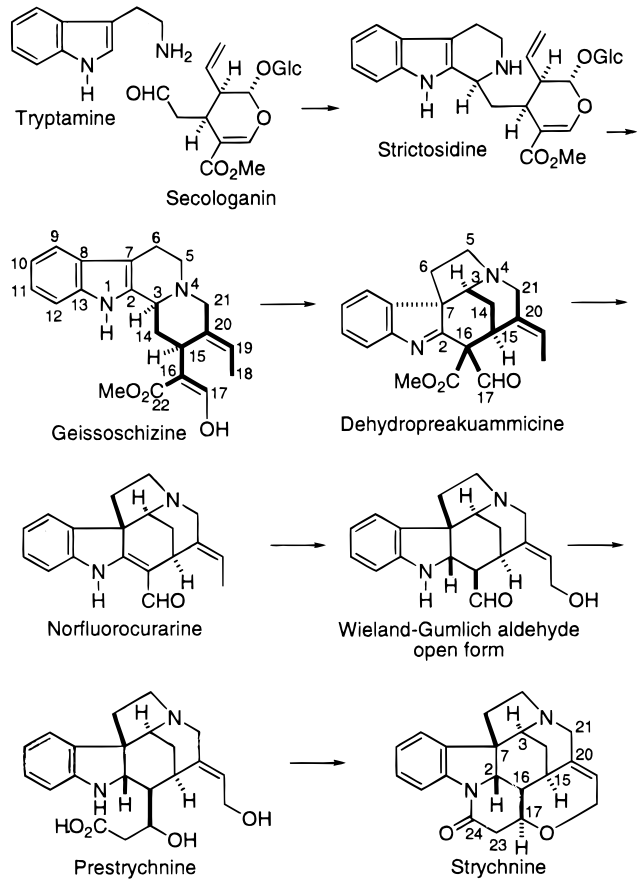
Scheme 1. Biosynthesis of Strychnine



Pelletier and Caventou[6] and its elemental composition was established some 20 years later by Regnault.[7] Strychnine was the subject of a very large number of degradative studies before the advent of modern spectroscopic techniques, and the elucidation of its constitutional structure represented one of the major achievements of classical organic chemistry. Degradative work started in the 1880s, and the finishing touches were published in 1948 by Woodward and Brehm,[8] the major contributions being made by Leuchs and his school and by Robinson and his collaborators.[9] An exhaustive and excellent review covering a century and a half of historical accounts of the work on the chemistry of strychnine was written in 1964 by Smith.[10] The relative configuration of strychnine was provided via two independent X-ray crystal analyses done by Robertson and Bevers, and Bijvoet.[11] The absolute stereochemistry of strychnine was established by Peerdeman[12] with X-ray crystallography and was later confirmed by Schmid and his collaborators[13] using a chemical method. The extensive NMR data available for strychnine[14] have been used for collecting information on conformational and configurational assignment of this and other related alkaloids or precursors.

Strychnine is the flagship compound of the family of *Strychnos* alkaloids,[15] one of the most populous classes of indole alkaloids. Its biogenetic pathway involves, in the initial steps, the enzymatically catalyzed Pictet−Spengler condensation of tryptamine with secologanin to provide strictosidine. Next to be formed is geissoschizine, the common biogenetic intermediate for all monoterpenoid indole alkaloids

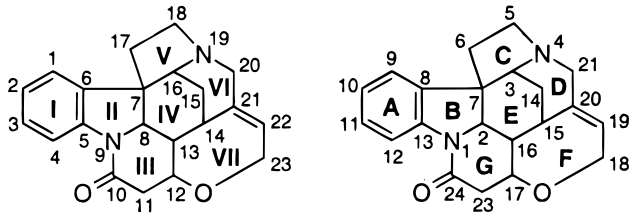


Figure 1. On the left, strychnine structure with numbering and ring labeling proposed by Woodward and used in *Chemical Abstracts*. On the right, strychnine showing the biogenetic numbering and ring labeling used in this review.

(Scheme 1). After an oxidative cyclization involving C-16, followed by a skeletal rearrangement, the characteristic framework of *Strychnos* alkaloids appears with dehydropreakuammicine. The unrearranged monoterpenoid unit characteristic of the *Corynanthe* skeleton (depicted in boldface in geissoschizine, Scheme 1), originally attached to the indole α-carbon (C-2), is now bonded to the *β*-position (C-7), and a new bonding between the rearrangable unit (C-16/C-17/C-22) and C-2 is in place.[16] The next step involves the loss of the methoxycarbonyl group from dehydropreakuammicine to give norfluorocurarine, which, upon hydroxylation and reduction, could lead to the Wieland−Gumlich aldehyde, a biogenetic precursor of the heptacyclic base strychnine, as shown by Heimberger and Scott[17] in 1973. To complete the strychnidine backbone,[18] two additional carbons are required. Robinson's suggestion that they come from acetate was proven by Schlatter in 1969,[19] and probably occurs through prestrychnine, formed by an aldol condensation involving acetyl-CoA.

The numbering system and ring labeling used throughout this review is based on the biogenetic interrelationship of indole alkaloids, as proposed by Le Men and Taylor.[20] To avoid confusion, it is worth mentioning that this numbering differs from Woodward's system,[8] which is used in some papers in the strychnine field as well as in the strychnidine stereoparent nomenclature of *Chemical Abstracts* (Figure 1).

II. An Overview of the Synthetic Strategies

Woodward's strychnine synthesis[1] remained the sole approach for a long time despite the monumental work in indole alkaloid synthesis developed in the second half of the twentieth century. After a dormant period of more than 30 years, interest in the chemistry of strychnine revived, and in the 1990s several groups succeeded in synthesizing this fascinating molecule.[21−28] Three syntheses[22,25,27] culminated in the enantioselective total synthesis of the natural enantiomer, (−)-strychnine,[29] Overman's route also leading to the dextro isomer, *ent*-strychnine.[22b]

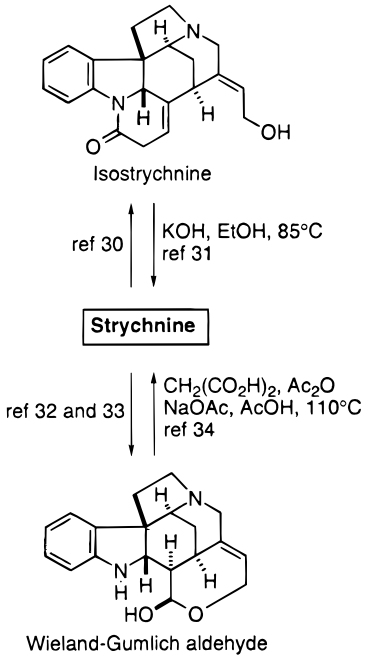
In an overview of strychnine syntheses, as outlined in Table 1, the first noteworthy feature is that all approaches are directed to isostrychnine or the Wieland−Gumlich aldehyde, whose synthetic conversion to strychnine was reported while Woodward's first total synthesis of strychnine was in progress (Scheme 2). Isostrychnine, which is the product of a base- or acid-induced retro-Michael addition with double-bond migration obtained from strychnine,[30]

Table 1. Main Features of Strychnine Syntheses

Main Author	Year	Form/Chirality Source	Spirocenter Generation[a]	Bridged Framework Formation[b]	Hydroxyethylidene Elaboration
			Sequence Followed in the Assembling of Rings		
Woodward	1954	(-)/relay compd	Pictet-Spengler	Nitrogen Addition to a Carbonyl	Allylic Rearrangement
	ref 1		A → AB ⇩ ABC → ABCG → ABCEG ⇩ ABCDEG ⇩ Isostrychnine		
Magnus	1992	(-)/relay compd	Transannular Oxidative Cyclization		Wittig Olefination
	ref 21		AB → ABD ⇩ ABCDE ⇩ Wieland-Gumlich aldehyde		
Overman	1993	(-) and (+)[c]/enzymatic[d]	Tandem Aza-Cope Rearrangement/Mannich cyclization		*syn* β-Elimination Reaction
	ref 22		A → AD ⇩ ACDE → ABCDE → Wieland-Gumlich aldehyde		
Kuehne	1993	(±)/none	Tandem Mannich Condensation/	Intramolecular Electrophilic	Wittig Olefination
	1998	(-)/L-tryptophan	[3,3]-Sigmatropic Rearrangement	Alkylation	
	ref 24		AB ⇩ ABCE ⇩ ABCDE → ABCDEG ⇩ Isostrychnine		
	ref 25		→ ABCDEF ⇩ Wieland-Gumlich aldehyde		
Stork	1992	(±)/none	Skeletal Rearrangement of a 3-Chloroindolenine	Intramolecular Conjugate Addition of a Vinyl Organometallic	
	ref 23		AB ⇩ ABCE ⇩ ABCDE → Wieland-Gumlich aldehyde		
Rawal	1994	(±)/none	Intramolecular Diels-Alder	Intramolecular Heck	
	ref 26		A → AC ⇩ ABCE → ABCEG ⇩ Isostrychnine		
Bonjoch/Bosch	1999	(-)/(*S*)-phenylethylamine	Claisen Rearrangement	Intramolecular Reductive Heck	
	ref 27		A → AE ⇩ ACE ⇩ ACDE → ABCDE → Wieland-Gumlich aldehyde		
Martin	[e]	(±)/none	Skeletal Rearrangement of a 3-Chloroindolenine		*anti* β-Elimination Reaction
	ref 28		AB → ABD ⇩ ABCDE ⋯→ Wieland-Gumlich aldehyde		

[a] See Chart 1. [b] See Scheme 3. [c] The synthesis of (+)-strychnine was published in 1995. [d] Desymmetrization of *cis*-3,5-diacetoxycyclopentene. [e] Personal communication (1999).

Scheme 2



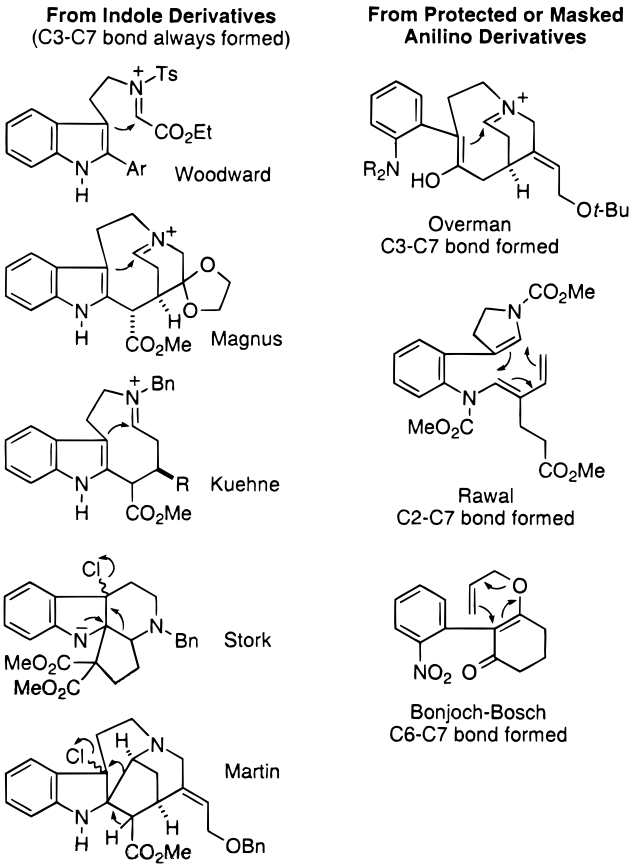
was converted back to strychnine in 20% yield when treated with alcoholic potassium hydroxide.[31] The Wieland-Gumlich aldehyde is another degradation product isolated in the course of strychnine chemical investigations.[32,33] Its conversion back to strychnine was achieved in 68% yield when treated with a mixture of malonic acid, sodium acetate, and acetic anhydride in acetic acid.[34,35]

After strychnine had been chemically correlated with isostrychnine and the Wieland-Gumlich aldehyde, both compounds were identified as *Strychnos* alkaloids, the former in 1973,[17] when it was isolated from a natural source, and the latter when it was found to be the same as the already known caracurine VII.[36]

The synthetic strategies developed to reach strychnine deserve a brief general comment. The major stumbling blocks in the synthesis of the target alkaloid are the following: (i) the generation of the spirocenter at C-7; (ii) the assembling of the bridged framework of the alkaloid (CDE core ring); (iii) the elaboration of the hydroxyethylidene substituent.

The crucial spirocenter at C-7 has been constructed by either taking advantage of the indole reactivity or elaborating this quaternary center without the use of indole derivatives (Table 1 and Chart 1). Woodward, Magnus, and Kuehne all use the electrophilic attack of an iminium ion upon a 2,3-disubstituted indole to generate the C-7 spirocenter, but they undertake this crucial step at different stages of the synthesis. Thus, Woodward constructs the quaternary center early on in the synthesis (ABC ring fragment), while Magnus and Kuehne elaborate the C-7 spirocenter at more advanced stages of the process: the former to assemble the pentacyclic curan skeleton (ABCDE rings) and the latter to construct the pyrrolo[2,3-*d*]carbazole fragment (ABCE rings). On the other hand, both Stork and Martin generate a 3-chloroindolenine to promote the formation of the key quaternary center by means of a skeletal rear-

Chart 1. Generation of C-7 Spirocenter of Strychnine



rangement that leads to a pyrrolo[2,3-*d*]carbazole intermediate (ABCE rings) and to a pentacyclic curan derivative (ABCDE rings), respectively.

In contrast, Overman, Rawal, and our team worked with intermediates incorporating a functionalized phenyl ring that does not participate in the elaboration of the spirocenter. Overman used a tandem aza-Cope/Mannich rearrangement, Rawal an intramolecular Diels−Alder reaction, and our team a classical Claisen rearrangement to build up the quaternary C-7 center. While the formation of the quaternary center in the Rawal synthesis also involves the closure of the indoline ring, in Overman's and our approach the substituted phenyl ring remains as a latent form of the indole nucleus until an advanced stage of the synthesis.

The second key step in the synthetic approaches to strychnine is the assembling of the bridged CDE ring fragment. The synthetic strategies adopted for its construction are outlined in Scheme 3. In the majority of the synthetic approaches the bridge framework is assembled once the quaternary C-7 center has already been constructed. In all of these cases the closure of the piperidine D ring, either by formation of the N4−C21 bond (Woodward; Kuehne) or by formation of the C15−C20 bond (Rawal; Stork; Bonjoch and Bosch), is used at this crucial step. In the former syntheses, the process involves a reaction of a nitrogen atom upon an oxygenated carbon (carbonyl, epoxide, or tosylate), whereas in the latter, the ring closure is accomplished by the addition of a vinyl organometallic species to a double bond.

In the other approaches, in which the piperidine ring has already been constructed, the bridged ring fragment and the C-7 spirocenter are assembled simultaneously, either by the transannular cyclization of a stemmadenine-type compound (Magnus, forming C3−C7 bond) or by multistep sequence processes, such as the cationic aza-Cope rearrangement/Mannich cyclization (Overman, C5−C6 and C3−C7 bonds formed) or the skeletal rearrangement of a 3-chloroindolenine (Martin, C3−C7 and C2−C16 bonds formed).

The last key operation in the synthetic routes to strychnine is the elaboration of the hydroxyethylidene side chain at C-20. Woodward, Magnus, and Kuehne took advantage of a ketone carbonyl at C-20 to introduce the hydroxyethylidene substituent in the last steps of the synthesis by either an allylic rearrangement (Woodward) or a Wittig olefination process (Magnus and Kuehne). On the other hand, both Overman and Martin constructed the hydroxyethylidene-bearing piperidine ring early on by means of β-elimination reactions that stereoselectively introduce the *E*-configured double bond. Finally, in the other approaches (Rawal; Stork; Bonjoch and Bosch) the stereoselective incorporation of the (*E*)-hydroxyethylidene double bond is accomplished during the closure of the piperidine D ring by means of intramolecular coupling reactions of vinyl halides with alkenes.

III. Total Syntheses

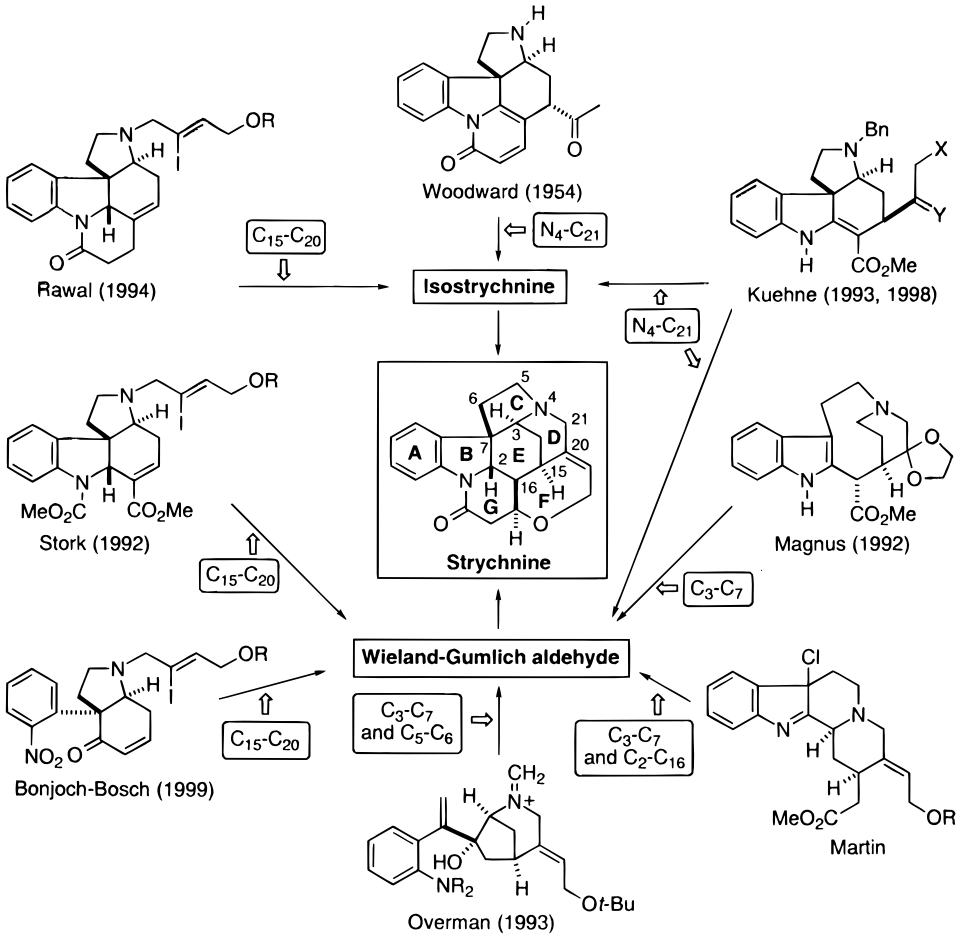
A. Woodward's Synthesis

The total synthesis of strychnine achieved by Woodward in 1954, only 6 years after the elucidation of its structure, is a historical landmark in organic synthesis. Considering the complexity of the strychnine molecule it is admirable that Woodward was able to undertake, let alone satisfactorily complete, its total synthesis with the resources at his disposal.

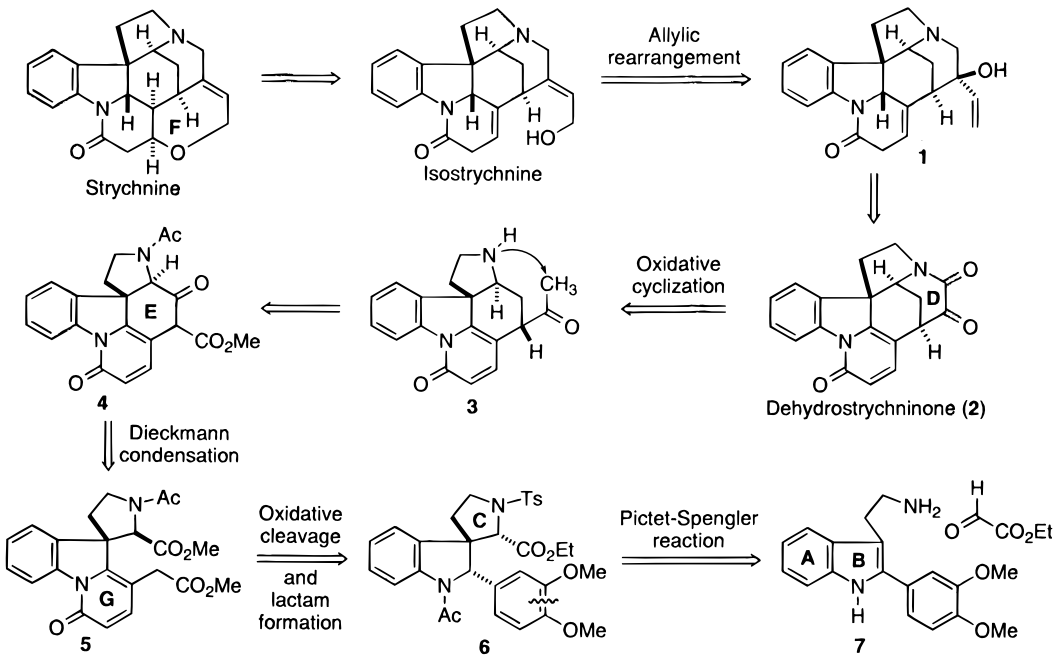
It is noteworthy that, when he devised a way to synthesize strychnine, Woodward was strongly influenced by contemporary ideas about the biogenesis of the indole alkaloids and especially by his own hypothesis about the biogenesis of strychnine itself,[37] which although finally shown to be not essentially correct, proved to be very fruitful. Woodward took advantage of two of his own biogenetic proposals in his synthetic work: (a) the nucleophilic character of the β-position of the indole nucleus and (b) the oxidative cleavage of an aromatic ring and the subsequent recombination of the fragments to build up the skeleton of the alkaloid.

The general features of the synthesis are shown, in retrosynthetic form, in Scheme 4. At the end of the 1940s, it was known that isostrychnine could be converted to strychnine by the action of a base.[31] Therefore, it is not surprising that Woodward chose this process for the last step (closure of ring F) when planning the synthesis of strychnine. Dehydrostrychninone (**2**) was envisioned as a suitable precursor of isostrychnine. Two crucial transformations needed to be done from **2**: (i) the introduction of the hydroxyethylidene side chain, which could be easily elabo-

Scheme 3. Construction of the Bridged Framework of Strychnine

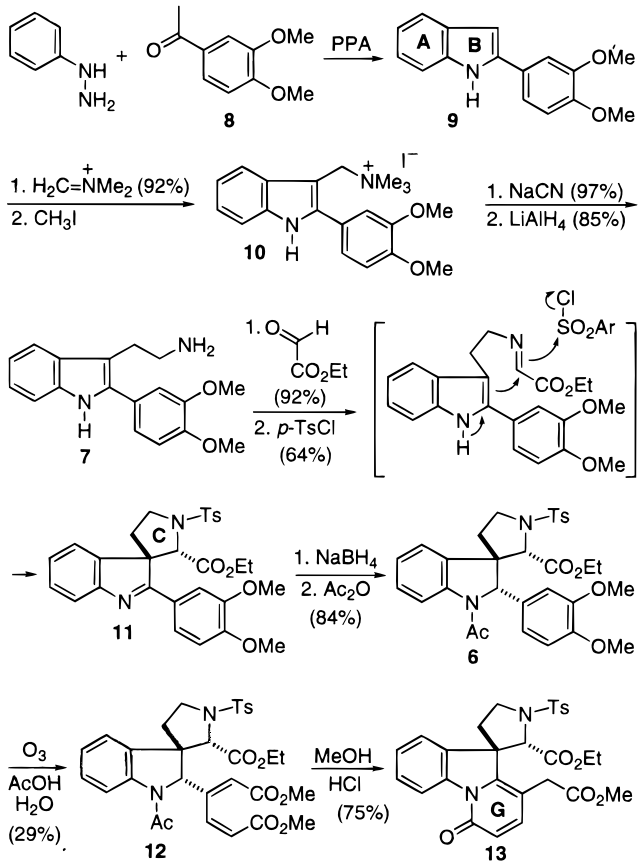


Scheme 4. Woodward's Retrosynthetic Analysis of Strychnine

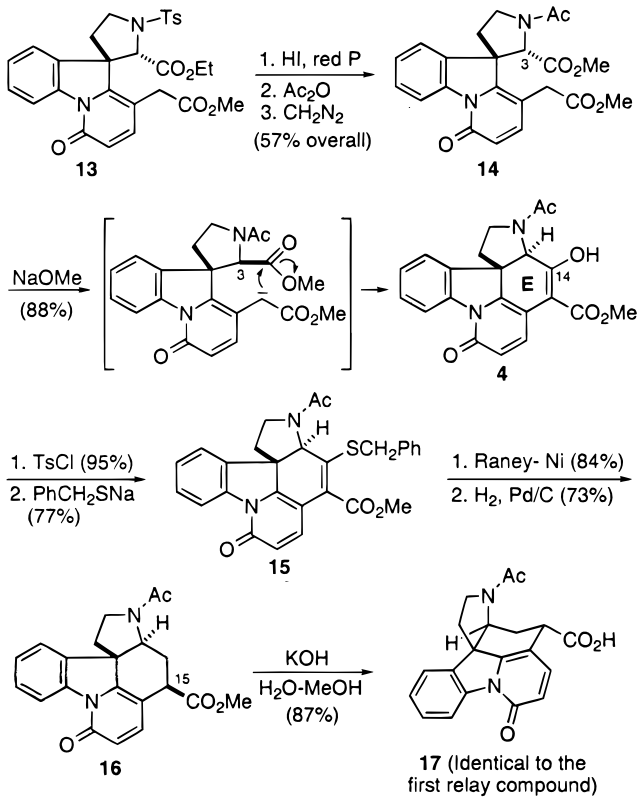


rated from the corresponding carbinol through an allylic rearrangement reaction, and (ii) the reduction of the aromatic α-pyridone ring to the dihydro level. The closure of the piperidine ring (ring D) was planned by oxidative cyclization of methyl ketone **3**, a compound that should be readily available from β-keto ester **4**. The disassembly of ring E at **4** by a retro-Dieckmann condensation would led to diester **5**, which, in turn, could be derived from **6** by selective cleavage of the veratryl protecting group and recombination of some of the carbon atoms to build up ring G. Finally, disassembly of intermediate **6** by a retro-

Scheme 5. Closure of Rings C and G: Synthesis of Intermediate 13



Scheme 6. Closure of Ring E: Synthesis of Intermediate 17



Pictet−Spengler reaction (ring C formation) would lead to 2-veratryltryptamine (**7**) and ethyl glyoxylate.

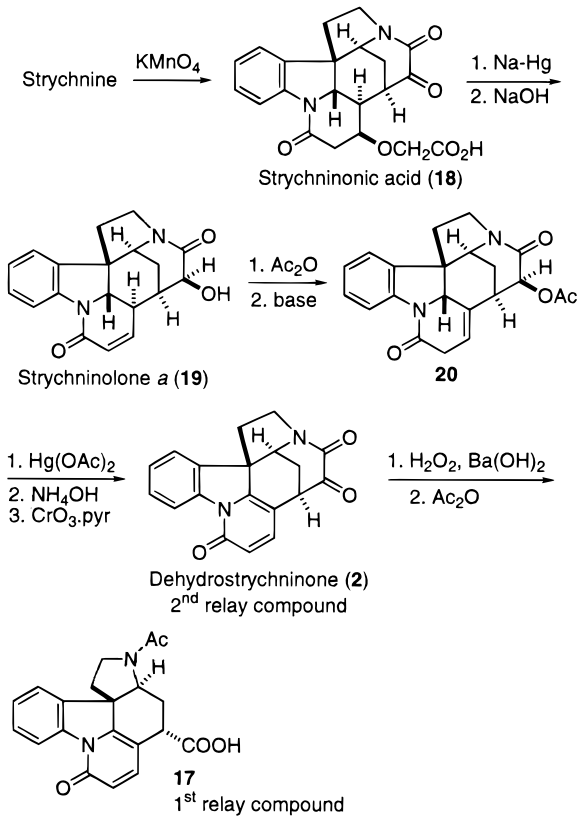
The starting material for the synthesis was the 2-veratrylindole (**9**), which was readily prepared by Fischer indole synthesis from acetoveratrone (**8**) (Scheme 5). The first steps in the synthesis involved the introduction of the 2-aminoethyl chain at the β-position of 2-veratrylindole (**9**). Thus, reaction of **9** with the iminium salt derived from formaldehyde and dimethylamine afforded a gramine derivative, which by treatment with methyl iodide was converted to the ammonium salt **10**. Reaction of the latter with sodium cyanide followed by reduction of the resulting nitrile with lithium aluminum hydride gave tryptamine **7**.

Having obtained 2-veratryltryptamine (**7**), Woodward undertook the first key step of the synthesis, the elaboration of the C-7 quaternary center, which was accomplished by the construction of a spiro ABC derivative. Although condensation of **7** with ethyl glyoxylate afforded the corresponding Schiff base, all attempts to promote the desired cyclization of this intermediate by means of acid catalysts resulted in failure. To drive forward the desired process, it was necessary both to increase the electrophilic character of the iminium moiety and to stabilize the cyclization product. In fact, when the Schiff base was treated with tosyl chloride in pyridine the indolenine **11** was obtained as the sole product.[38] Reduction of indolenine **11** with $NaBH_4$ occurred with complete stereoselection since an attack by the borohydride ion occurs from the more accessible β-face to give an indoline, which on subsequent treatment with acetic anhydride provided the *N*-acetyl derivative **6**.

Once the veratryl group had been used to block the α-carbon of the indole nucleus and direct the attack of the electrophilic species to the β position, Woodward wondered whether this protecting group could be used for the elaboration of the other rings of strychnine. When **6** was treated with ozone in aqueous acetic acid the veratryl group was selectively cleaved at the bond between the two methoxy groups to give muconic ester **12**, which on heating in methanolic hydrogen chloride directly afforded pyridone **13**. This transformation, which leads to the formation of ring G of strychnine, brought about the cleavage of the *N*-acetyl group, formation of the six-membered lactam, and isomerization of the exocyclic double bond to the stable aromatic α-pyridone.

Diester **13** contains all of the carbon atoms and the functionality necessary to undertake the construction of ring E by means of a Dieckmann condensation. Nevertheless, when **13** was treated with a base, the leaving group behavior of the tosyl group changed the expected course of the process, and consequently had to be removed prior to the condensation reaction. This removal was accomplished by treating **13** with hot hydriodic acid in the presence of red phosphorus (Scheme 6). These reagents also cleaved the two ethyl ester groups of the starting material to give an amino diacid intermediate, which on sequential *N*-acetylation and esterification with diazomethane afforded the dimethyl ester **14**. Treatment of **14** with sodium methoxide in methanol resulted in the epimerization of the stereogenic center at C-3 and the subsequent Dieckmann cyclization to give **4**.

Scheme 7. Preparation of Relay Compounds 2 and 17 by Degradation of Strychnine

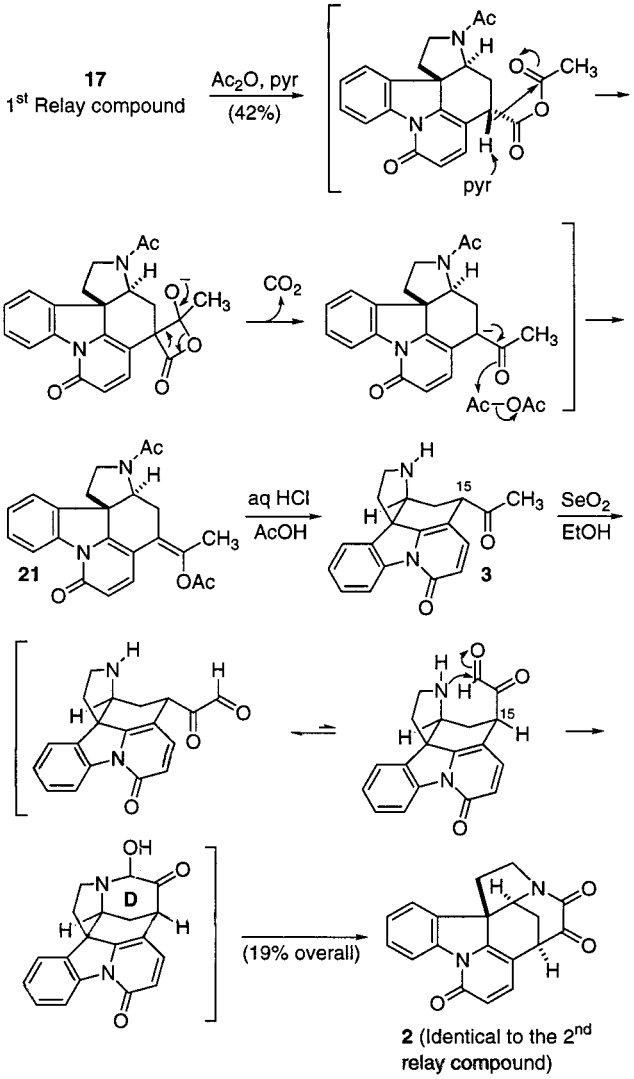


The β-keto ester **4** exists as a stable enol, thus preventing classical methods for carbonyl group reduction from being used to remove the oxygen atom at C-14. Fortunately, this oxygen atom could be removed by indirect methodology. Thus, reaction of **4** with tosyl chloride in pyridine afforded the corresponding *O*-tosyl derivative, which on treatment with sodium benzylmercaptide, gave sulfide **15** in an addition−elimination process. Desulfuration of **15** using deactivated Raney nickel, followed by hydrogenation of the resulting unsaturated ester furnished cis saturated ester **16**, together with a small amount of the trans isomer. The obtention of cis saturated ester **16** as the major isomer in the hydrogenation reaction is the result of the addition of hydrogen from the less-hindered α-face of the unsaturated precursor.

After epimerization at C-15, alkaline hydrolysis of ester **16** gave carboxylic acid **17**, with the more stable equatorial orientation for the carboxy group. Having obtained **17**, Woodward reached a point of intersection with a substance of the same structure which he was able to prepare by degradation of strychnine itself. So, at this stage it was possible not only to verify that the synthesis had followed its envisaged course but also to gain access to sufficient quantities of the relay compound to complete the work.

To degrade strychnine into the relay compound **17**, Woodward proceeded essentially along known lines,[39] although some reactions were significantly modified (Scheme 7). Thus, strychnine was oxidized by potassium permanganate to strychninonic acid (**18**), which was converted by successive sodium amalgam reduction of the ketone carbonyl and base promoted

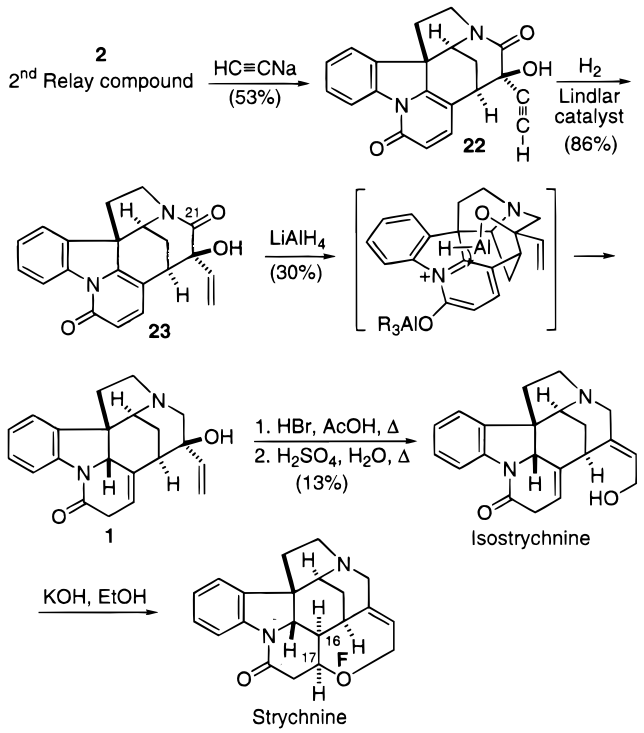
Scheme 8. Closure of Ring D: Synthesis of Intermediate 2



β-elimination to strychninolone *a* (**19**). Reaction of **19** with acetic anhydride in pyridine afforded the corresponding *O*-acetyl derivative, which on treatment with base isomerized to ester **20**. Dehydrogenation of **20** with mercuric acetate in acetic acid followed by hydrolysis of the acetyl group and oxidation of the resulting alcohol intermediate afforded dehydrostrychninone (**2**), a compound that would be used as a second relay compound (vide infra) in the last phase of the synthesis of strychnine. Finally, dehydrostrychninone (**2**) was oxidized with hydrogen peroxide and barium hydroxide, and the resulting amino acid was converted into **17** by acetic anhydride in pyridine.

The construction of the bridge framework of the alkaloid by closure of the piperidine D ring from **17** required two preliminary operations: (i) the attachment of an extra carbon atom and (ii) the inversion of the stereogenic center at C-15. Carboxylic acid **17** was converted into enol acetate **21** by treatment with acetic anhydride and pyridine (Scheme 8). This reaction involves the initial formation of a mixed anhydride, which undergoes conversion to a methyl ketone under the reaction conditions,[40] the evolution of carbon dioxide being the driving force of the

Scheme 9. Introduction of the Hydroxyethylidene Side Chain: Woodward's Synthesis of Strychnine



process.[41] Finally, in situ acetylation of the ketone enolate would give **21**. Hydrolysis of enol acetate **21** afforded amino ketone **3**, with the more stable equatorial orientation for the acetyl group. Oxidation of methyl ketone **3** with selenium dioxide in ethanol directly gave dehydrostrychninone (**2**, the second relay compound). Woodward suggested that the initial oxidation of the methyl group leads to an α-keto aldehyde, which would be expected to be in an equilibrium with the less stable cis epimer. However, once formed, the cis epimer can undergo cyclization to give an amino acetal intermediate. The well-known tendency of 1,2-dicarbonyl compounds to achieve a tetrahedral geometry shifts an otherwise unfavorable epimerization process to the formation of the cyclized compound. Subsequent oxidation of this α-hydroxy ketone intermediate under the reaction conditions gives dehydrostrychninone (**2**).

Dehydrostrychninone (**2**) possesses six of the seven rings of the target alkaloid and functionality adequate for the elaboration of its seventh and final ring. Reaction of **2** with sodium acetylide gave **22**, the nucleophilic addition to the ketone carbonyl taking place selectively from the more accessible β face (Scheme 9). Carbinol **22** was reduced to allylic alcohol **23** by hydrogenation in the presence of Lindlar catalyst. Treatment of **23** with lithium aluminum hydride not only removed the amide carbonyl group present at C-21 but also reduced the α-pyridone ring to the desired dihydro level, affording hexacyclic derivative **1** in only one step. Woodward proposed the intramolecular delivery of hydride ion within an aluminum alkoxide intermediate to account for the stereoselectivity exhibited in this reduction, which implies the attack of hydride from the more crowded side of the molecule.

Although **1**, the allylic isomer of isostrychnine, resisted mild acid conditions which suffice for the isomerization of simple tertiary allylic carbinols, it could be rearranged to isostrychnine by heating with hydrogen bromide in acetic acid followed by hydrolysis of the resulting halo compounds with boiling aqueous sulfuric acid. However, the elaboration of the hydroxyethylidene substituent, which proceeds in only 13% overall yield, was far from optimal, no doubt because the presence of a positive charge at the N atom in acidic media suppresses reactions which proceed through cationic intermediates. Finally, following the previously reported procedure,[31] isostrychnine was converted to strychnine by treatment with potassium hydroxide in ethanol.

In summary, Woodward developed a superb synthetic approach to strychnine, the most noteworthy retrosynthetic concept probably being the use of the veratryl group as a source of carbon atoms for the elaboration of the G, E, and D rings. Moreover, he reached the target despite having only a limited number of reagents available to carry out nontrivial structural transformations at a time which is now recognized as the beginning of the golden age of organic synthesis.

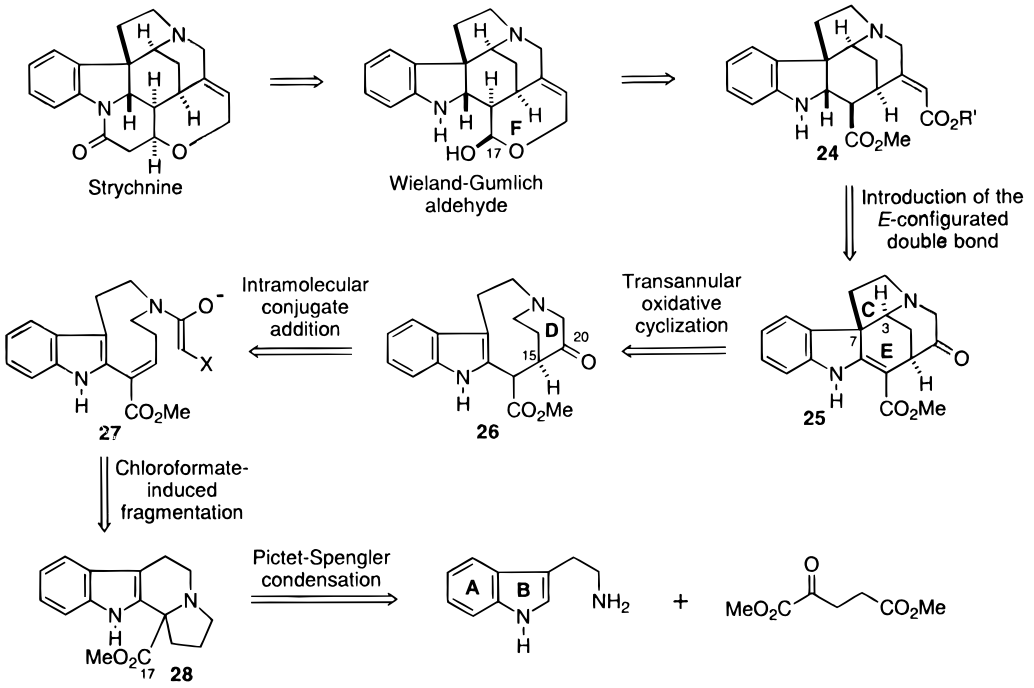
B. Magnus' Synthesis by Transannular Cyclization of a Stemmadenine-type Derivative

Although a number of novel approaches to *Strychnos* alkaloids (see Section IV) and hence to the strychnine core were developed after the first total synthesis by Woodward, strychnine itself remained unrevisited for almost 40 years. Finally, in 1992 Magnus reported the successful conclusion of the second total synthesis of this alkaloid.[21,42]

The last step in Woodward's synthesis involved the base-promoted conversion of isostrychnine into strychnine, a transformation that the author recognized as being exceptionally difficult. To avoid this inefficient process, Magnus undertook an alternative biomimetic route and directed his synthesis toward the Wieland-Gumlich aldehyde, whose straightforward conversion into strychnine had been demonstrated by Anet and Robinson many years before.[34]

The retrosynthetic analysis of strychnine by Magnus is shown in Scheme 10. Disconnection of the hemiacetal ring (ring F) in the Wieland-Gumlich aldehyde led to the pentacyclic diester **24**. Magnus postponed the construction of the *E*-configured double bond of this compound to an advanced stage of the synthesis by means of a stereoselective Wadsworth−Emmons reaction. The pentacyclic ketone precursor **25** was then sequentially disassembled in three well-differentiated phases: (i) disconnection of the key C_3-C_7 bond by a retro transannular oxidative cyclization (simultaneous formation of rings C and E) led to the nine-membered ring intermediate **26**, (ii) the closure of the piperidine ring (ring D) by formation of $C_{15}-C_{20}$ bond could be done by intramolecular conjugate addition of the heteroatom-stabilized amide enolate anion **27**, and (iii) the construction of the required nine-membered ring system was envisaged by chloroformate-induced fragmentation of tetracyclic amine **28**. It is interesting to note that the methoxy-

Scheme 10. Magnus' Retrosynthetic Analysis of Strychnine

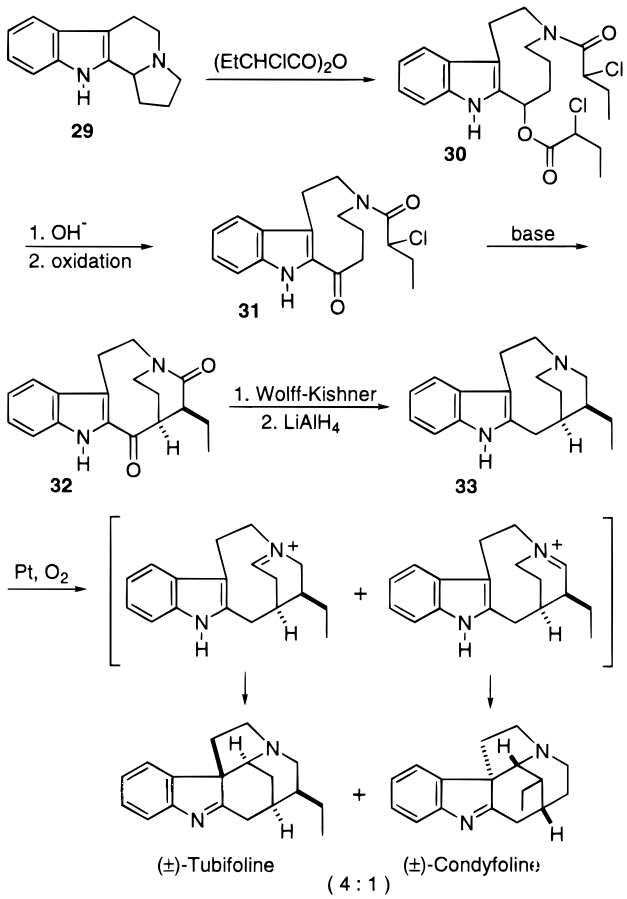


carbonyl group in **28** is maintained throughout the retrosynthetic sequence to become eventually the C-17 carbon in the Wieland-Gumlich aldehyde. Finally, amine **28** was simply disassembled by a retro-Pictet−Spengler condensation to tryptamine and dimethyl 2-ketoglutarate.

The above retrosynthetic analysis follows the strategy successfully developed by Harley-Mason in the 1960s and 1970s for the synthesis of *Strychnos* alkaloids.[43] In fact, in the synthesis of (±)-tubifoline,[44] represented in Scheme 11, which constituted the first total synthesis of a pentacyclic *Strychnos* alkaloid, Harley-Mason made use of the same sequence in the assembling of the skeleton. The cleavage of the N−C benzylic bond in the tetracyclic amine **29** by action of an acid anhydride led to the azonino[5,4-*b*]indole intermediate **30**, which, after successive hydrolysis, oxidation, and base-catalyzed cyclization, afforded the stemmadenine-type intermediate **32**. Reduction of the two carbonyl groups gave tetracyclic amine **33**, which on catalytic air oxidation over platinum,[45] underwent transannular cyclization to provide a 4:1 mixture of (±)-tubifoline and (±)-condyfoline.

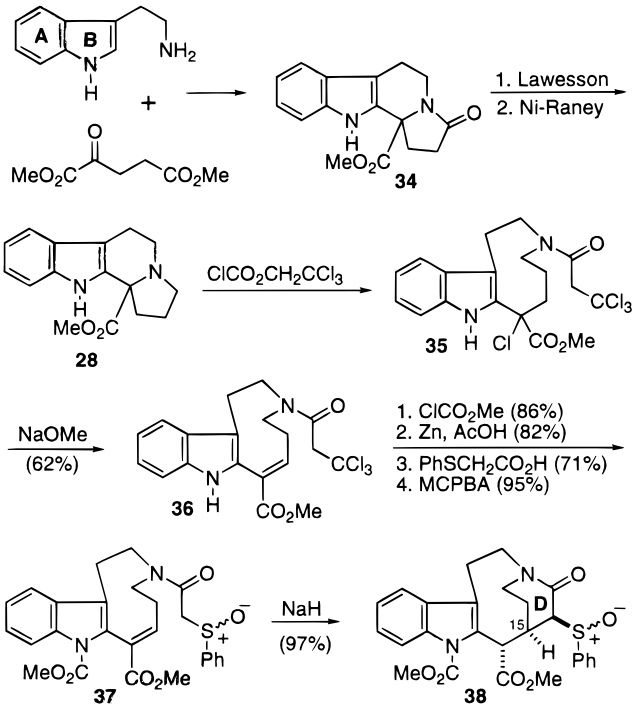
The strychnine synthesis started from the tetracyclic amine **28**, a compound Magnus had previously used in his total synthesis of vinblastine (Scheme 12).[46] Amine **28** was available in large quantities by Pictet−Spengler condensation of tryptamine with dimethyl 2-ketoglutarate to give lactam **34**, which, in turn, was reduced through its corresponding thiolactam. Cleavage of tetracyclic amine **28** to the desired expanded nine-membered ring system was induced by treatment with β,β,β-trichloroethyl chloroformate.[47] A mixture of α-chloro ester **35** and α,β-unsaturated ester **36** was obtained in this reaction, the former being quantitatively converted into **36** by treatment with sodium methoxide. Protection of the indole nitrogen atom with an electron-withdrawing group, followed by removal of the trichloroethyl

Scheme 11. The Harley−Mason Synthesis of *Strychnos* Alkaloids

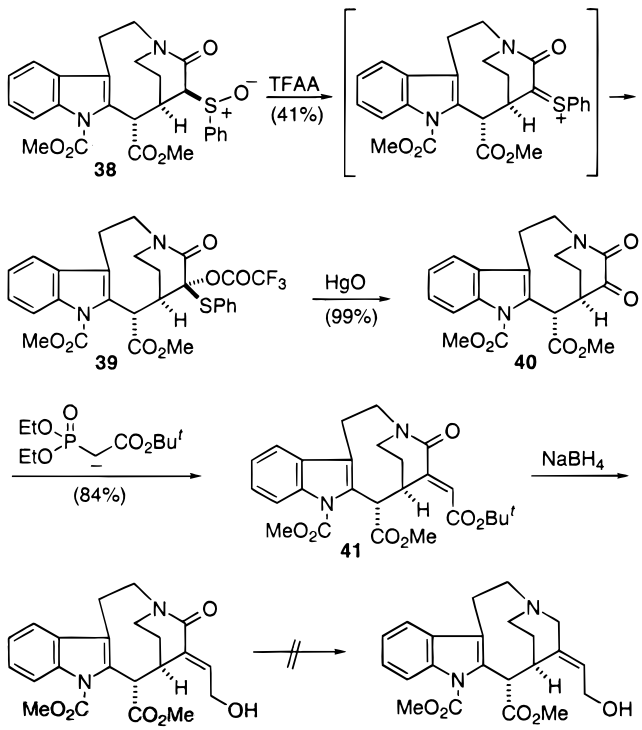


carbamate group, and acylation of the resulting secondary amine with (phenylthio)acetic acid provided an α-phenylthio amide, which, upon oxidation with *m*-CPBA, gave racemic sulfoxide **37**. The closure of the piperidine D ring was accomplished by treatment of sulfoxide **37** with sodium hydride in THF to

Scheme 12. Synthesis of Stemmadenine Intermediate 38



Scheme 13. Initial Attempts to Stereoselectively Elaborate the Hydroxyethylidene Substituent



give diastereomeric sulfoxides **38** in excellent yield. It is worth noting that although enantiopure **37** could be obtained by acylation of the secondary amine intermediate with (+)-(*R*)-*p*-toluenesulfinylacetic acid, its cyclization showed negligible stereoselection.

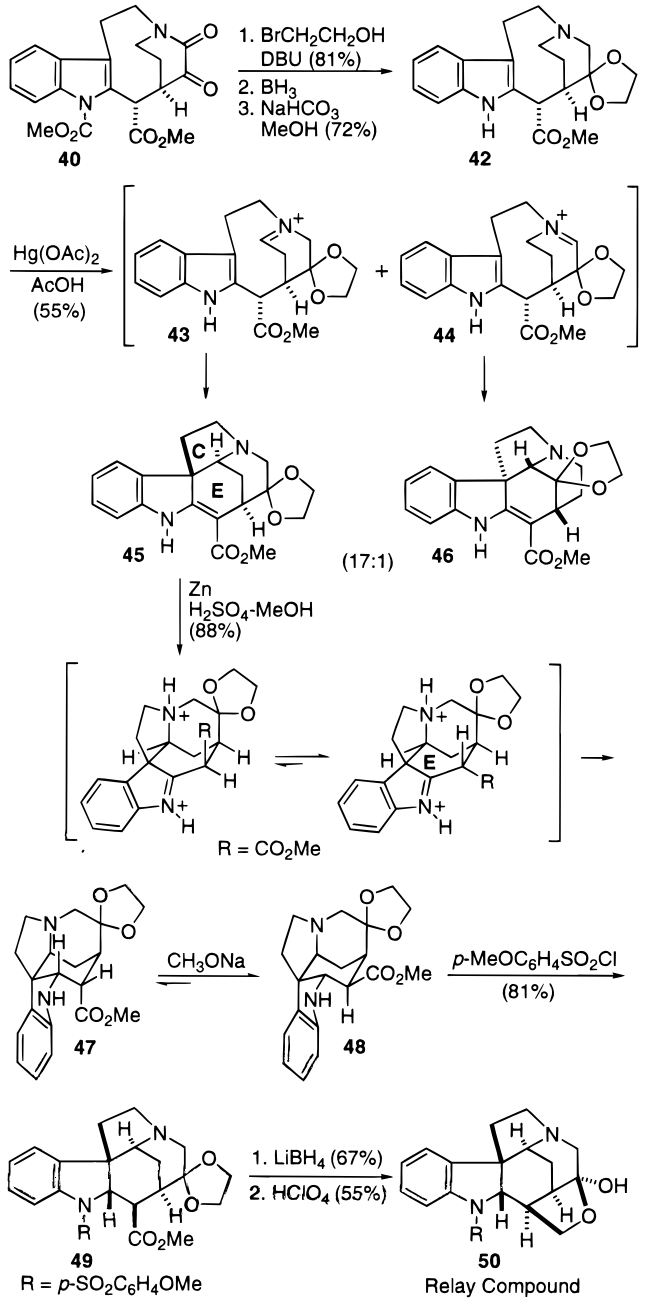
Once the stemmadenine-type system was built up,[48] Magnus faced for the first time what he considered to be the main problem in his synthesis of strychnine: the stereospecific elaboration of the hydroxyethylidene substituent. Sulfoxides **38** underwent Pummerer rearrangement[49] to give the α-phenylthio trifluoroacetate **39**, which, upon mercuric ion assisted hydrolysis, gave α-keto lactam **40** (Scheme 13). Wadsworth−Emmons olefination of ketone **40** stereoselectively afforded ester **41**, which has the natural configuration at the double bond. While ester **41** could be easily reduced to the hydroxyethylidene functionality, all attempts to reduce the amide carbonyl without simultaneous 1,4-reduction were unsuccessful. Consequently, although this route solved the stereoselective construction of the hydroxyethylidene substituent, it could not be incorporated to the synthesis of strychnine.

At this point, Magnus focused on the other critical step of the synthesis, the oxidative transannular cyclization of the stemmadenine system to close rings C and E, which involves the simultaneous construction of the C7 quaternaty center of the target alkaloid (Scheme 14). α-Keto lactam **40** was converted into **42** by successive ketalization, amide carbonyl reduction, and removal of the *N*-protecting group. Transannular cyclization of **42** was conducted with mercuric acetate in acetic acid.[50] The process was highly regioselective, and a 17:1 mixture of regioisomeric pentacyclic amines **45** and **46**, arising from cyclization of the regioisomeric iminium salts **43** and **44**, was obtained in 55% yield.[51] The *β*-anilino acrylate moiety of **45** was reduced with zinc dust in methanolic sulfuric acid to give the dihydroderivative **47**, which on treatment with sodium methoxide in methanol was readily epimerized to **48**. The stereochemical outcome of the reduction−epimerization sequence of the vinylogous carbamate functionality had been well established for related pentacyclic systems in the context of degradative studies of *Strychnos* alkaloids.[52] Thus, the initial protonation of **45** took place from the *β*-face so the methoxycarbonyl group could take the more stable pseudoequatorial orientation, ring E being in the boat conformation. Reduction of the resulting iminium ion from the *β*-face then generated **47**, in which ring E adopts a chair conformation and the methoxycarbonyl group is forced into an axial orientation. Epimerization of **47** with sodium methoxide in methanol afforded the more stable equatorial *β*-ester **48**.

Ester **48** was converted into hemiacetal **50** by sulfonylation, reduction with lithium borohydride, and acid hydrolysis. Compound **50** could also be obtained more readily and in larger amounts from strychnine, as outlined in Scheme 15. The first step in the sequence involved the conversion of strychnine into the Wieland-Gumlich aldehyde,[32,33] which, on protection of the indoline nitrogen atom followed by dihydroxylation, was converted into **51**. Finally, reduction with lithium borohydride and oxidative cleavage of the vicinal triol side chain afforded the relay hemiacetal **50**.

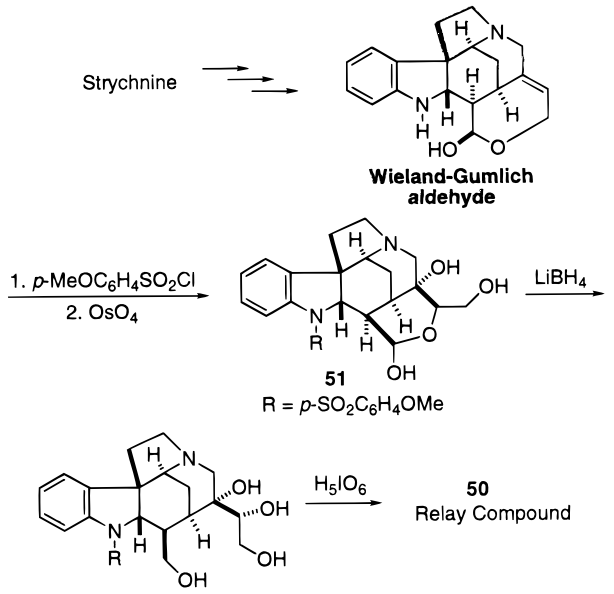
To complete the synthesis of the Wieland-Gumlich aldehyde from hemiacetal **50** only the elaboration of the hydroxyethylidene substituent and some adjustments of the oxidation level of the system remained to be done (Scheme 16). The open carbonyl form of hemiketal **50** was irreversibly trapped when it re-

Scheme 14. Simultaneous Formation of Rings C and E: Synthesis of Intermediate 50

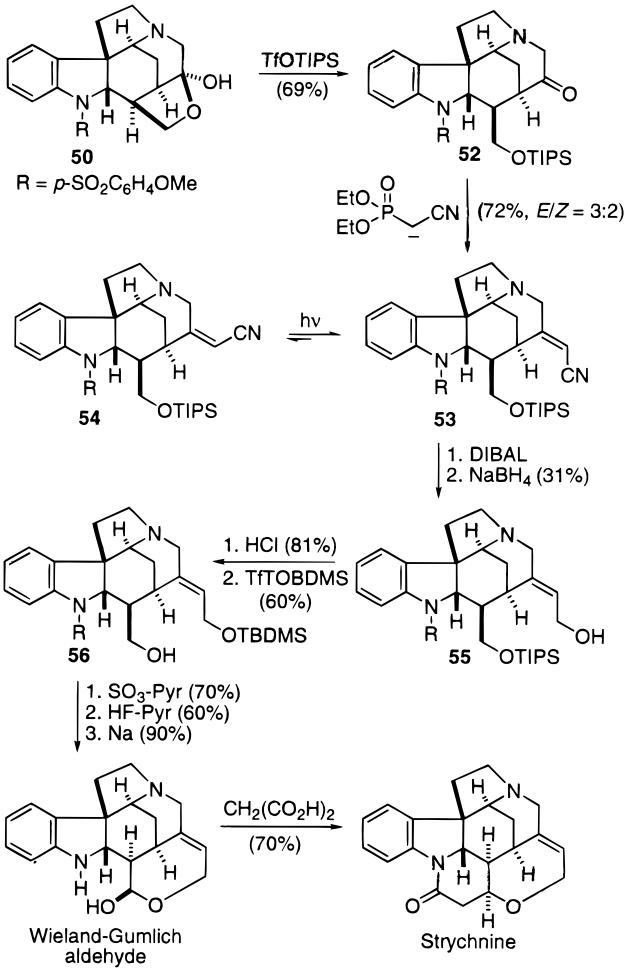


acted with the bulky silylating agent triisopropylsilyl triflate to give **52**. Although Wittig−Horner olefination of **52** led to a 3:2 mixture of *E*/*Z* α,β-unsaturated cyanides **53** and **54**, the *Z* isomer **54** could be recycled by photochemical isomerization, raising the yield of **53** to 52%. Reduction of nitrile **53** with diisobutylaluminum hydride and then with sodium borohydride gave allylic alcohol **55**, which on treatment with hydrochloric acid and subsequent selective silylation with *tert*-butyldimethylsilyl triflate afforded **56**. The synthesis of the Wieland-Gumlich aldehyde was completed by oxidation, desilylation, and removal of the sulfonyl protecting group. Finally, treatment of the Wieland-Gumlich aldehyde with malonic acid under the reported conditions[34] furnished strychnine in 70% yield.

Scheme 15. Preparation of Relay Compound 50 by Degradation of Strychnine

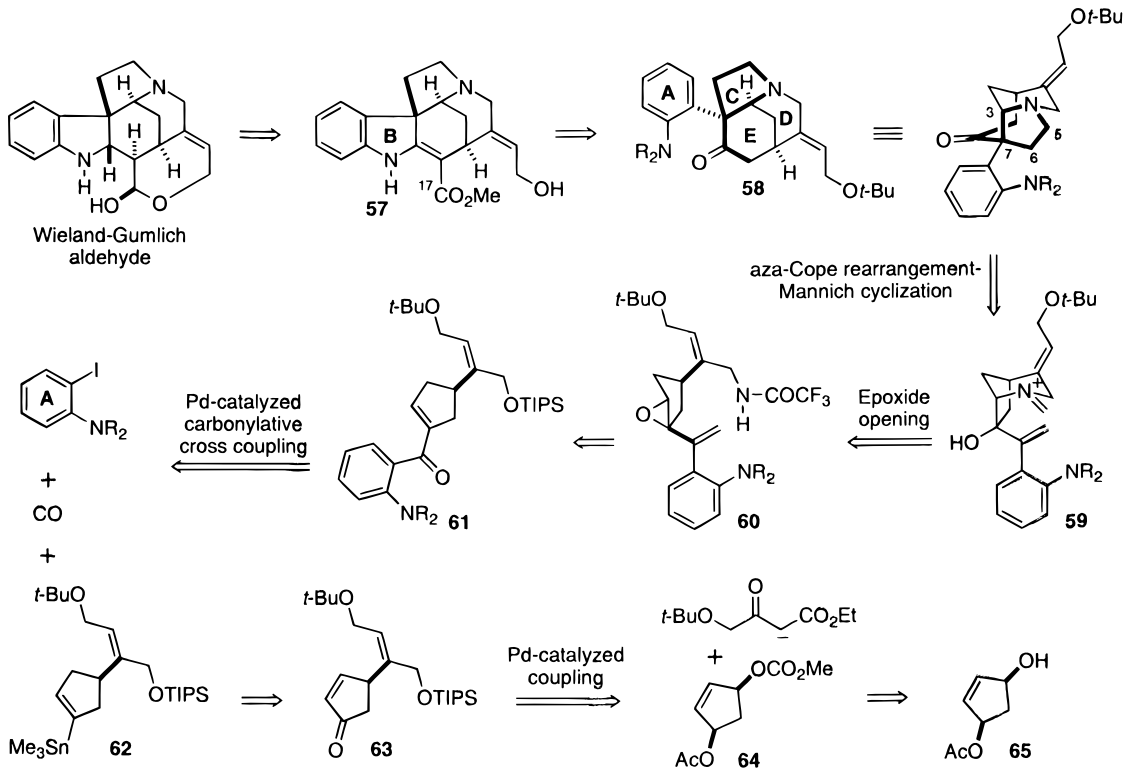


Scheme 16. Magnus' Syntheses of the Wieland−Gumlich Aldehyde and Strychnine



In summary, Magnus achieved the first total synthesis of the Wieland-Gumlich aldehyde and hence a new synthesis of strychnine (27 steps from the tetracyclic amine **28**, 0.03% overall yield). The strategy relies on the transannular oxidative cycliza-

Scheme 17. Overman's Retrosynthetic Analysis of Strychnine



tion of a stemmadenine-type derivative to construct the pentacyclic curan ring and the further stereoselective elaboration of the hydroxyethylidene side chain.

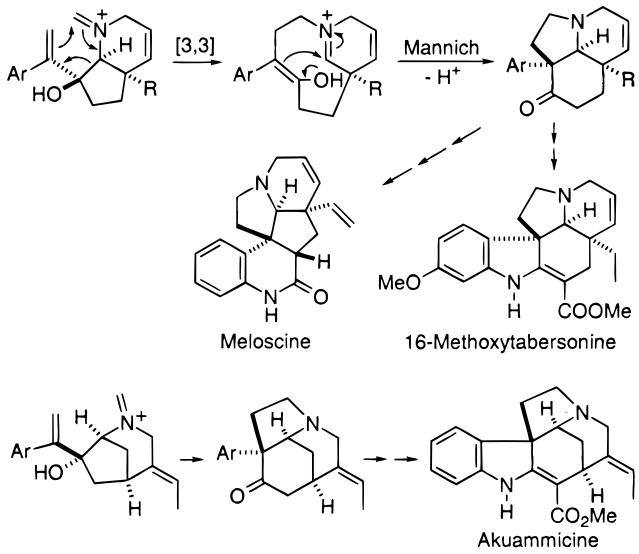
C. Overman's Synthesis through the Tandem Cationic Aza-Cope Rearrangement–Mannich Cyclization Reaction

Overman published the first enantioselective total synthesis of natural (−)-strychnine in 1993,[22] and 2 years later, the only synthesis of the unnatural (+)-strychnine to appear so far.[22b]

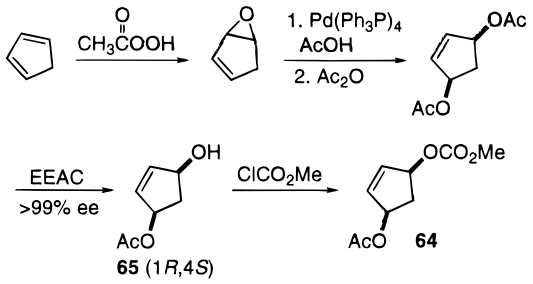
The disconnective analysis is outlined in Scheme 17. Overman directed his synthesis toward the Wieland-Gumlich aldehyde, which he simply disassembled to the pentacyclic intermediate **57**. Overman's synthetic plan for this pentacyclic compound was based on a synthesis of the *Strychnos* alkaloid akuammicine he had previously described.[53] Thus, retrosynthetic simplification of ester **57** led to the azatricyclic ketone **58**, which contains the ACDE ring fragment of the target alkaloid and allows the introduction of carbon C-17 and the closure of ring B. The key step in the retrosynthetic analysis is the disassembly of the 3-acylpyrrolidine substructure of **58** (shown in boldface in Scheme 17) by a retro-aza-Cope rearrangement−Mannich cyclization process,[54] which led to the iminium salt **59**. In the forward sense, this impressive tandem reaction would lead to the simultaneous closure of rings C and E by the stepwise formation of the C5−C6 and C3−C7 bonds. The piperidine D ring at **59** was then disconnected by cleavage at the β-amino alcohol moiety leading to oxirane **60**. In the synthetic direction, the intramolecular S_N2 opening of the epoxide should ensure the trans relationship between the nitrogen and the tertiary hydroxyl group, which is required to bring the alkene and iminium ion termini within bonding distance.[55] Functional group simplification of **60** led to the retrosynthetic precursor **61**, a compound with the appropriate functionality to allow the chemo- and stereoselective epoxidation of the conjugated double bond. Enone **61** was then disassembled by a retro-palladium-catalyzed carbonylative cross coupling reaction[56] giving a protected 2-iodoaniline and the key vinylstannane **62**. Finally, functional group simplification of **62** led to intermediate **63**,[57] which could itself be disconnected by a retro palladium-catalyzed coupling reaction[58] to the allylic carbonate **64** and a β-ketoester enolate. It is noteworthy that for the synthesis of **61** from **64** Pd-catalyzed reactions[59] were envisaged for all the C−C bond-forming steps. Since enantiomerically pure **64** can be prepared easily from the known enantiopure **65**, the above synthetic pathway allows an asymmetric synthesis of the target alkaloid.

The key strategic element in the above retrosynthetic sequence is the tandem cationic aza-Cope−Mannich cyclization reaction. This sequential reorganization constitutes a powerful method for preparing nitrogen heterocycles, which has been extensively developed by Overman and successfully applied to the synthesis of a number of structurally related complex alkaloids, such as *Aspidosperma*,[60] *Melodinus*,[61] and *Strychnos*[53] alkaloids. The 3-acylpyrrolidine unit is the basic structure constructed by the aza-Cope rearrangement−Mannich cyclization (Scheme 18). The high efficiency and the extremely mild conditions of this tandem reaction are the result of

Scheme 18. The Cationic Aza-Cope Rearrangement/Mannich Cyclization Reaction



Scheme 19. Synthesis of Enantiopure Allylic Carbonate 64

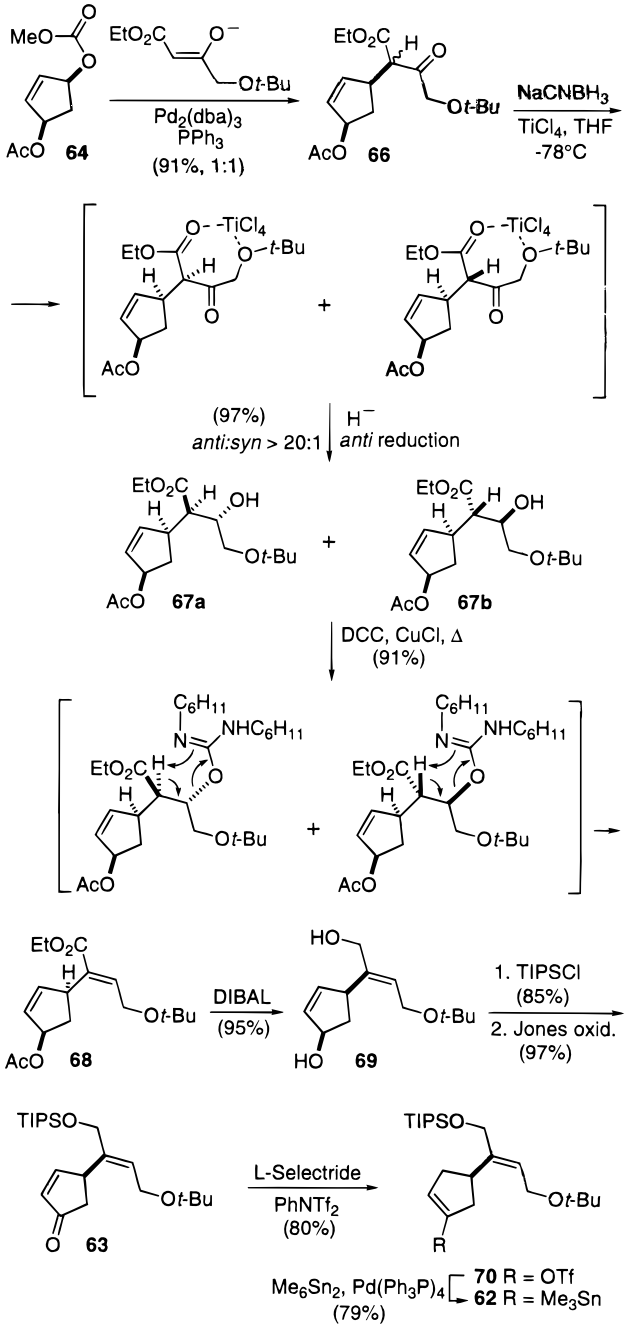


two factors: (i) the [3,3] sigmatropic rearrangement is highly favored, because of the presence of a charged atom in the molecular array involved in the process, and (ii) after the aza-Cope rearrangement, the resulting iminium ion is trapped by the proximate enol to give the 3-acylpyrrolidine system, shifting the otherwise reversible process.[54]

The synthesis commences with the preparation of allylic carbonate **64** by reaction of the known enantiopure allylic alcohol **65**[62] with methyl chloroformate (Scheme 19). Following a previously documented procedure,[62] this allylic alcohol could be obtained on a large scale with high enantiomeric purity by enantioselective hydrolysis of *cis*-3,5-diacetoxycyclopentene catalyzed by electric eel acetylcholinesterase (EEAC). *cis*-3,5-Diacetoxycyclopentene could be prepared easily from cyclopentadiene through a sequence involving monoepoxidation, palladium-catalyzed syn-1,4-addition of acetic acid to cyclopentadiene monoepoxide, and finally acetylation of the resulting alcohol intermediate.

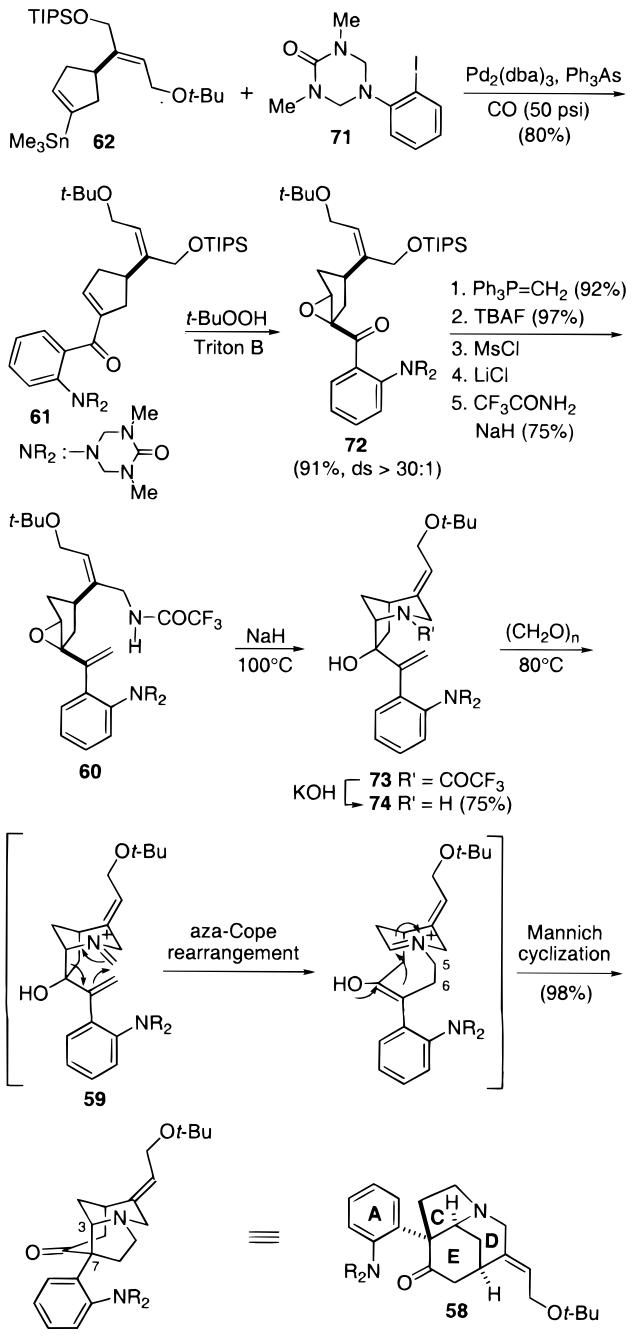
Palladium-catalyzed coupling of allylic carbonate **64** with the sodium salt of 4-*tert*-butoxy-3-oxobutenoate gave the cis adduct **66** as a 1:1 mixture of diastereomers (Scheme 20). Reduction of this mixture with sodium cyanoborohydride in the presence of $TiCl_4$ afforded the corresponding anti hydroxy esters **67a,b** with high stereoselectivity (anti:syn > 20:1). The high selectivity of this reaction was explained by the formation of a seven-membered chelate, which

Scheme 20. Synthesis of Vinyl Stannane 62



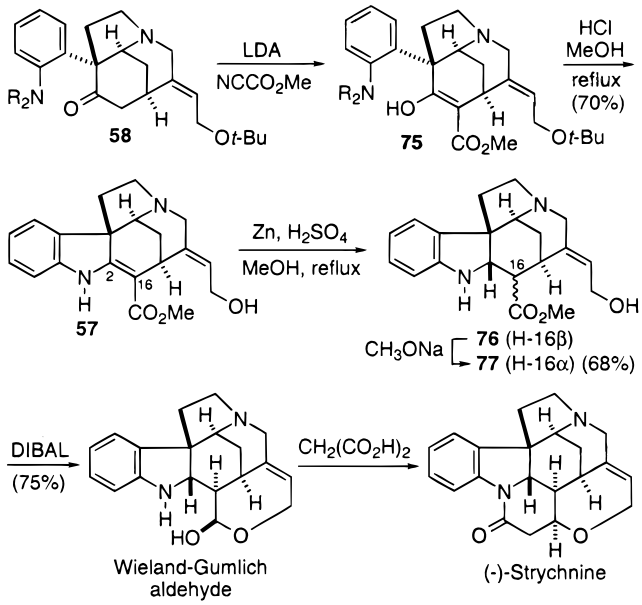
would be strongly biased toward the anti reduction. Stereospecific syn elimination[63] of the mixture of anti hydroxy esters **67a,b** with DCC and CuCl afforded the *E* ester **68**. It is noteworthy that by means of this simple sequence of anti reduction−syn elimination, the stereoselective construction of the *E*-configured double bond[64] of strychnine was solved early in the synthesis and with high diastereoselection (>20:1). Treatment of **68** with excess of DIBAL gave diol **69**. Selective protection of the primary alcohol at **69** as the triisopropylsilyl ether[65] and subsequent Jones oxidation afforded enone **63**, which by reduction with L-Selectride and trapping of the resulting enolate with *N*-phenyltriflamide provided the enol triflate **70**. Finally, palladium-catalyzed stannylation of **70** gave the key vinyl stannane **62**.

Scheme 21. Central Steps: Synthesis of Azatricyclic Ketone 58



The next crucial transformation in the synthetic pathway was the palladium-catalyzed carbonylative cross-coupling of vinyl stannane **62** with the triazone-protected[66,67] 2-iodoaniline **71** to provide enone **61** (Scheme 21), a compound containing an appropriately substituted aromatic ring to allow the further elaboration of the dihydroindole nucleus of the target alkaloid. Nucleophilic epoxidation of **61** with *tert*-butyl hydroperoxide proceeded with complete facial selectivity to provide the anti epoxide **72**. Through a straightforward multistep sequence of functional group modifications, involving Wittig methylenation, removal of the TIPS protecting group, and conversion of the allylic alcohol to the corresponding trifluoroacetamide, epoxide **72** was converted into **60**. At this point, Overman faced the construction of the bridged

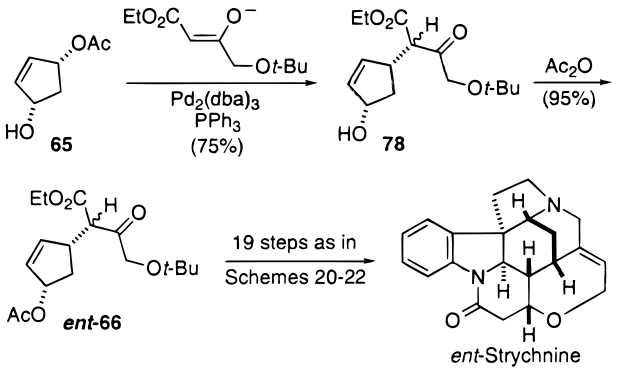
Scheme 22. Overman's Syntheses of the Wieland−Gumlich Aldehyde and (−)-Strychnine



azatricyclic framework (CDE rings) of strychnine. The first step in the assembling of rings was the closure of the piperidine D ring that was accomplished by intramolecular S_N2 opening of the oxirane ring in **60**. Thus, treatment of **60** with sodium hydride at 100 °C provided the 2-azabicyclo[3.2.1]-octane **73**, which has the required cis relationship between the styrene functionality and the nitrogen atom. Removal of the trifluoroacetyl group of **73** with KOH provided secondary amine **74**, from which the central aza-Cope rearrangement−Mannich cyclization process was undertaken. Thus, heating **74** in acetonitrile with excess of paraformaldehyde afforded the iminium salt **59**, which underwent [3,3]-sigmatropic rearrangement (bond formed C5−C6) under the reaction conditions, followed by internal Mannich reaction (simultaneous closure of C and E rings and formation of the quaternary C7 center) to give azatricyclic ketone **58** in nearly quantitative yield. Interestingly, this key cascade reaction took place in the absence of added acid under essentially neutral conditions. It should be mentioned that in the assembling of the bridged framework (CDE rings) of the alkaloid, the cyclopentane ring of epoxide **60** acts as a latent form of the cyclohexane E ring.

From ketone **58**, a compound incorporating ACDE rings of the alkaloid and ring B in a latent form, the synthesis of strychnine was straightforward (Scheme 22). Methoxycarbonylation of **58** with methyl cyanoformate[68] afforded *β*-keto ester **75**. Treatment of the latter with refluxing methanolic HCl resulted in the removal of both the *tert*-butyl and triazone protecting groups and in the formation of the *β*-anilino acrylate moiety to provide the pentacyclic intermediate **57**. Reduction of the 2,16-double bond in **57** with zinc dust in methanolic sulfuric acid gave a 9:1 mixture of epimeric esters **76** and **77**. This mixture was equilibrated to pure **77** by treatment with sodium methoxide, giving the natural and most stable stereochemistry at C-16. Finally, further adjustment of the oxidation level by partial reduction of ester **77**

Scheme 23. Overman's Synthesis of *ent*-Strychnine



with DIBAL at −100 °C afforded the Wieland-Gumlich aldehyde, which on treatment with malonic acid under the reported condensation conditions,[34] furnished (−)-strychnine.

Following the chemistry developed in the natural series and starting from ***ent*-66**, Overman also accomplished the first total synthesis of *ent*-strychnine (Scheme 23). Cyclopentene ***ent*-66** could be prepared easily from hydroxy acetate **65** by palladium-catalyzed coupling with the sodium salt of 4-*tert*-butoxy-3-oxobutenoate followed by acetylation of the resulting alcohol **78**.

In summary, Overman accomplished the first enantioselective total synthesis of strychnine, the pivotal reaction being the powerful tandem cationic aza-Cope rearrangement−Mannich cyclization process, which allows a highly efficient synthesis of the alkaloid's bridged ring fragment, which incorporates the functionality needed to achieve the target. Despite having a similar length to that of the previous syntheses (24 steps from the chiral acetate **65**), there is an impressive improvement in the overall yield (3%).

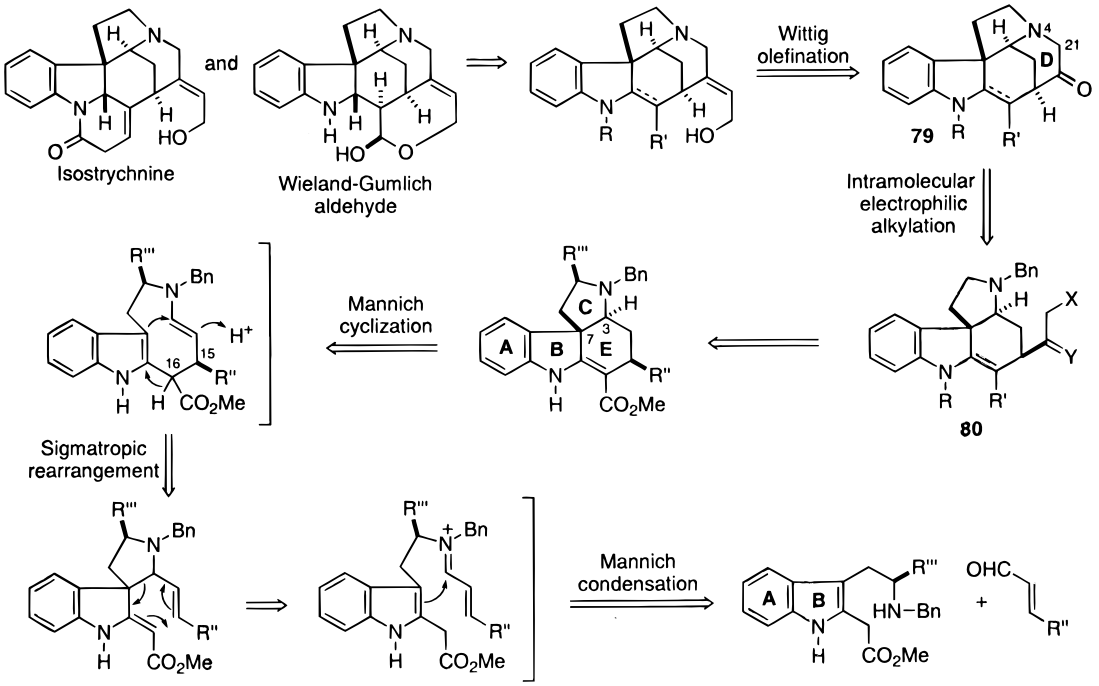
D. Kuehne's Syntheses Using a Tandem Sequence To Form Pyrrolo[2,3-*d*]carbazole Intermediates

During the past decade, the *Strychnos* alkaloids have been the subject of intensive synthetic investigation by Kuehne,[69] who has developed general and versatile strategies for the synthesis of both Aspidospermatan[70−72] and Strychnan[73−76] skeletal-types, based on the use of pyrrolocarbazole derivatives as synthetic intermediates. These studies have culminated in two total syntheses of strychnine: the first one was published in 1993[24] and the second in 1998, where Kuehne[25] revisited the alkaloid by means of a new enantioselective total synthesis.

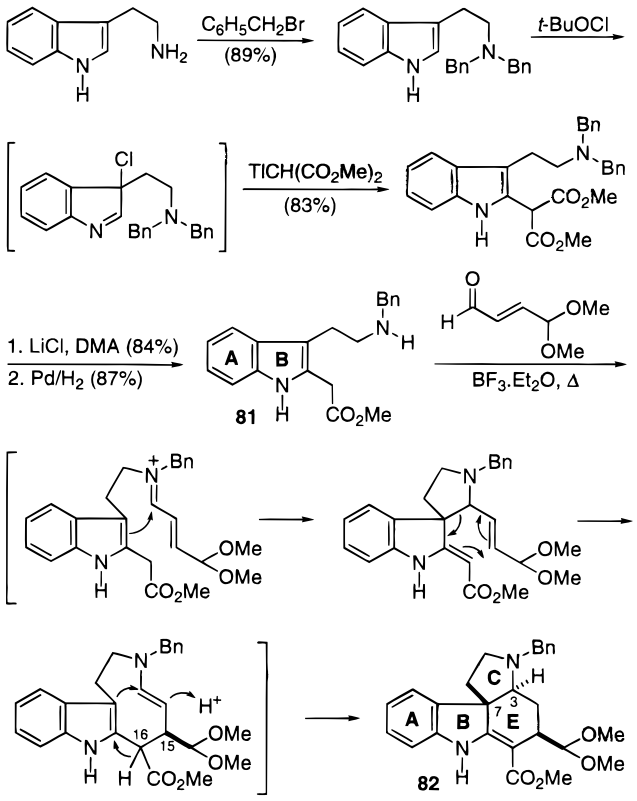
In the first approach, the isostrychnine to strychnine cyclization was used as the last synthetic step. This transformation suffered from an unfavorable equilibration ratio of the two compounds and was considered to be the least efficient step of the synthesis. To avoid this troublesome cyclization, the second approach was directed to the Wieland-Gumlich aldehyde. Apart from the change in the last synthetic intermediate, the two syntheses essentially follow the same retrosynthetic analysis shown in Scheme 24.

Kuehne undertook the elaboration of the *E*-configured hydroxyethylidene side chain required for the synthesis of strychnine at a late stage in the synthesis by means of a Wittig olefination reaction, as occurs in the Magnus synthesis. The pentacyclic precursor ketone **79** was disconnected at the N4−C21 bond leading to the hexahydropyrrolo[2,3-*d*]-carbazole intermediate **80**. In the synthetic direction the closure of the piperidine D ring could be done by intramolecular electrophilic alkylation of the pyrrolidine N atom. To assemble the ABCE tetracyclic core Kuehne took advantage of a new and very efficient synthetic pathway he had previously reported,[77]

Scheme 24. Kuehne's Retrosynthetic Analysis of Strychnine



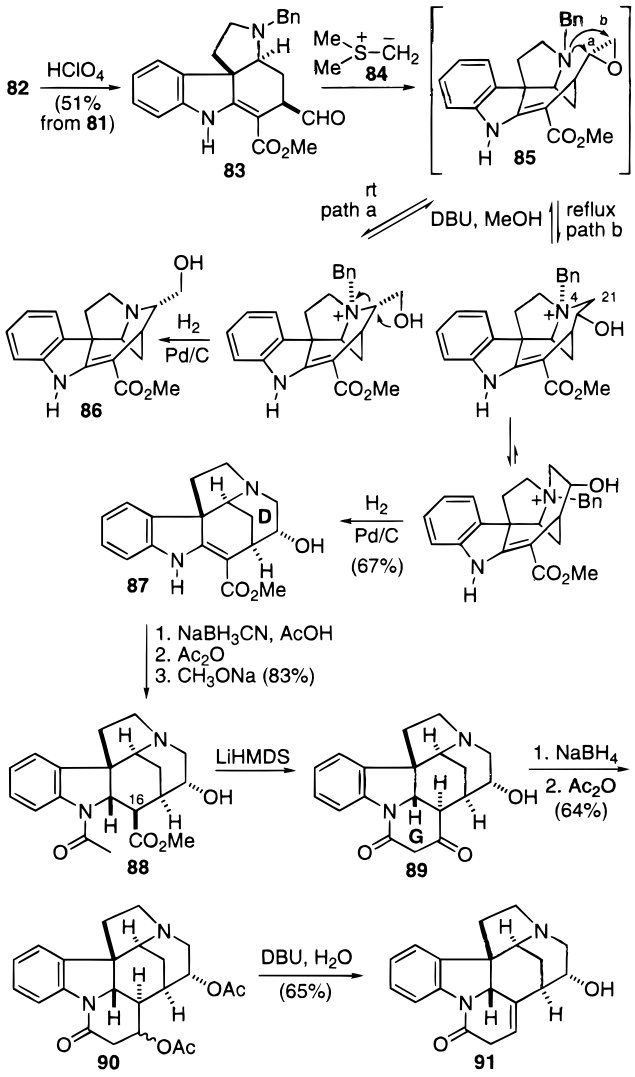
Scheme 25. Synthesis of Pyrrolo[2,3-*d*]carbazole Intermediate 82



based on a new condensation−sigmatropic rearrangement tandem process between a tryptamine ester derivative and an α,*β*-unsaturated aldehyde. In the forward sense, this multistep process involves the simultaneous closure of C and E rings by sequential formation of the C15−C16 and C3−C7 bonds. Using an L-tryptophan derivative in the above process would lead to the crucial hexahydropyrrolo[2,3-*d*]-carbazole[78] system in enantiomerically pure form, allowing the enantioselective synthesis of strychnine.

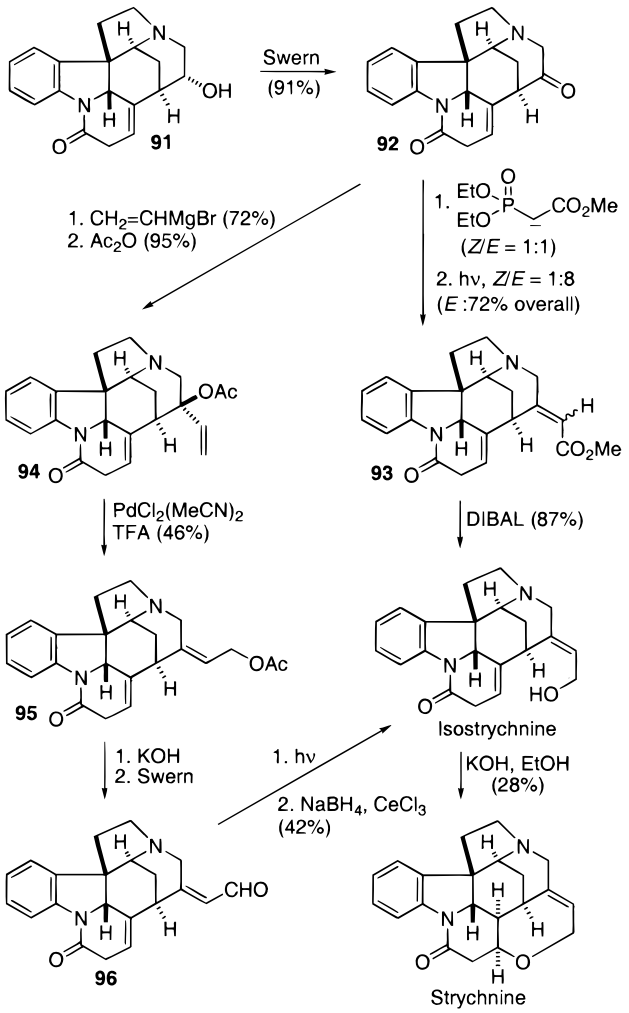
The starting material for the first synthesis was the tryptamine acetic ester **81**, a compound that could be readily obtained from N^b,N^b-dibenzyltryptamine by chlorination and reaction of the resulting chloro indolenine with thallium dimethyl malonate, followed by monodecarbomethoxylation and monodebenzylation.[77] From this key building block, which preforms rings A and B, the construction of the hexahydropyrrolo[2,3-*d*]carbazole core of the alkaloid was accomplished in only one synthetic operation by means of a tandem process. Thus, condensation of tryptamine derivative **81** with 4,4-dimethoxy-2-butenal in the presence of a calatylic amount of boron trifluoride etherate provided the tetracyclic acetal **82** as a single diastereomer. Although alternative pathways can be considered, this multistep process presumably follows the reaction sequence shown in Scheme 25: an initial Mannich condensation would lead to a spirocyclic derivative, which could undergo a [3,3]-sigmatropic rearrangement (bond formed C15−C16) to give an enamine. Finally, an acid-catalyzed Mannich-type cyclization of the latter would lead to the tetracyclic system by simultaneous closure of C and E rings, the C7 quaternary center being formed.

Scheme 26. Closure of Rings D and G: Synthesis of Intermediate 91



From tetracyclic intermediate **82** the closure of the piperidine ring by the formation of the N4−C21 bond was accomplished by intramolecular nucleophilic opening of an intermediate epoxide (Scheme 26).[79] Thus, the acetal group of **82** was first hydrolyzed by treatment with aqueous perchloric acid to give aldehyde **83**, which on treatment with the sulfur ylide **84** afforded the epoxide **85**. When the intramolecular opening of the epoxide was induced by treatment of **85** with DBU in MeOH at room temperature a five-membered ring was obtained mainly. Indeed, hydrogenolytic debenzylation of the resulting quaternary salt afforded the primary alcohol **86**, together with small amounts of the desired pentacyclic secondary alcohol **87**. However, when the cyclization mixture was heated at reflux and the resulting ammonium salt was hydrogenolyzed, only the six-membered ring D alcohol **87** was obtained. The formation of the latter is the result of the equilibration under the reaction conditions of the cyclization products to the more stable six-membered ring compound in which ring D adopts a chair conformation with the hydroxy group in an axial orientation, not well situated for the ring opening−epoxide reformation process.

Scheme 27. Kuehne's Synthesis of Strychnine



Having accomplished the construction of the bridged framework of the alkaloid by closure of the piperidine ring, the closure of ring G of strychnine was undertaken. Reduction of the anilino acrylate double bond[80] in **87** with $NaCNBH_3$ in acetic acid provided the dihydro product as an epimeric mixture at C-16, which on acetylation with acetic anhydride, followed by treatment with sodium methoxide, was converted to the most stable β-ester **88**. Treatment of the amide ester **88** with LiHMDS gave β-keto lactam **89**. Ketone reduction of **89** with $NaBH_4$ and acetylation of the resulting diol afforded a mixture of epimeric acetates **90**, which on heating with aqueous DBU, gave the olefinic alcohol **91**.[81]

At this point, to complete the syntheses of isostrychnine and hence strychnine itself, only the critical construction of the *E*-configured hydroxyethylidene side chain remained (Scheme 27). Swern oxidation of alcohol **91** furnished ketone **92**, from which two alternative procedures were explored for the elaboration of the hydroxyethylidene substituent. In the first one, a Wittig−Horner condensation of ketone **92** with methyl 2-(diethylphosphono)acetate led to a 1:1 mixture of *Z*/*E* acrylates **93**, which, on photochemical equilibration, provided a more favorable 1:8 *Z*/*E* ratio. Finally, reduction of the major *E* isomer with DIBALH afforded isostrychnine. The alternative procedure for the elaboration of the hydroxyethylidene side chain followed the same pathway used by Woodward. Thus, addition of vinylmagnesium bromide to ketone **92** followed by acetylation of the resulting alcohol gave allylic acetate **94**. Allylic rearrangement of the latter by treatment with $PdCl_2(CH_3CN)_2$ in the presence of trifluoroacetic acid proceeded in satisfactory yield but afforded acetate **95** with the undesired *Z* configuration. Hydrolysis of the acetate **95** followed by Swern oxidation gave aldehyde **96**, which was transformed to isostrychnine by photochemical equilibration and reduction with $NaBH_4$.

The synthesis was completed with the treatment of isostrychnine with KOH under the previously described conditions,[31] affording strychnine in 28% yield.

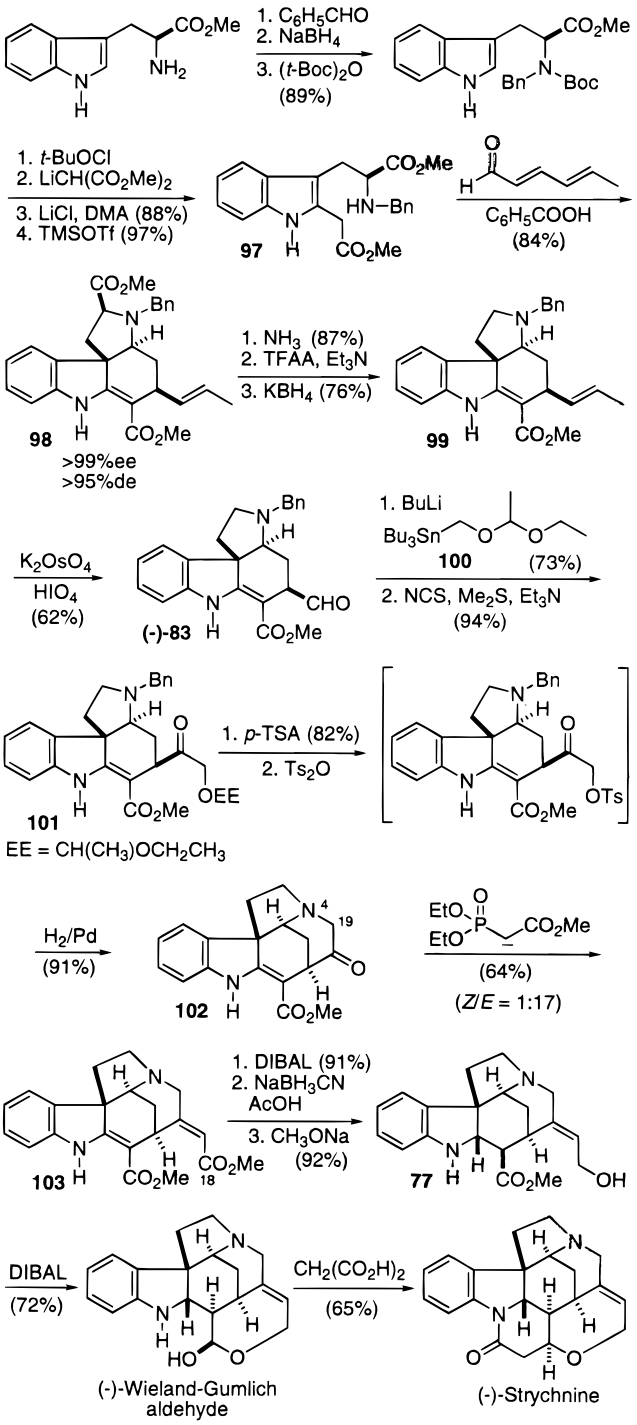
In 1998 Kuehne published an enantioselective synthesis of (−)-strychnine in which he avoided the isostrychnine to strychnine cyclization and directed his efforts toward the Wieland-Gumlich aldehyde.

The synthesis commences with the preparation of the amino ester derivative **97** starting from L-tryptophan and following in essentials the sequence of reactions previously used for the synthesis of **81** (Scheme 28). Reaction of aminoester **97** with 2,4-hexadienal afforded by means of the condensation−sigmatropic rearrangement tandem process the tetracyclic diester **98** with complete stereoselectivity.

Removal of the tryptophanyl ester group in **98** was readily achieved by its conversion to an amide, followed by dehydration to a nitrile, and subsequent reduction of the α-aminonitrile with potassium borohydride,[82] to give the tetracyclic intermediate **99**. Finally, cleavage of the exocyclic double bond with potassium osmate and periodate afforded enantiopure **(−)-83**.

From the pyrrolocarbazole **(−)-83**, Kuehne undertook the elaboration of the piperidine ring. For closure of the N_4-C_{19} bond he used the intramolecular alkylation of the N_b atom with a proximate sulfonate ester instead of the intramolecular epoxide ring opening used in the first synthesis. Thus, condensation of aldehyde **(−)-83** with the tin derivative **100** and butyllithium[83] furnished an epimeric mixture of alcohols, which was converted into ketone **101** by oxidation with chloro(dimethyl)sulfonium chloride. Cleavage of the acetal group of **101**, followed by reaction of the resulting α-hydroxy ketone with *p*-toluenesulfonic anhydride afforded a transient sulfonate ester intermediate, which under the reaction conditions underwent the intramolecular cyclization. Subsequent hydrogenolysis of the resulting quaternary salt yielded the pentacyclic ketone **102**. Wittig−Horner condensation of ketone **102** with methyl 2-(diethylphosphono)acetate provided pentacyclic ester **103** with high stereoselectivity (*Z*/*E* ratio 1:17), improving the elaboration of the *E*-configured double bond. Sequential chemoselective reductions of the methoxycarbonyl group at C-17 with DIBALH to the corresponding allylic alcohol and the anilinoacrylate moiety with $NaCNBH_3$ in acetic acid, followed by epimerization of the resulting saturated ester with sodium methoxide gave the pentacycle **77**, a compound that was also an intermediate in Overman's

Scheme 28. Kuehne's Syntheses of the Wieland−Gumlich Aldehyde and (−)-Strychnine



synthesis. The final reduction of **77** with DIBALH afforded the Wieland-Gumlich aldehyde, which on condensation with malonic acid was converted into (−)-strychnine.

In summary, Kuehne developed two synthetic routes to strychnine. The first, is in the racemic series via isostrychnine, while the second approach, directed to the Wieland-Gumlich aldehyde, constitutes a short and efficient enantioselective total synthesis of the alkaloid (14 steps from the tryptophan derivative **97**, 5% overall yield). Both syntheses adopted a tandem [3,3]-sigmatropic rearrangement−electrophilic cyclization sequence to obtain functionalized pyrrolocarbazoles, from which the pentacyclic backbone was constructed and then the side chain at C-20 elaborated.

E. Stork's Synthesis via Intramolecular Conjugate Addition of a Vinyllithium Intermediate

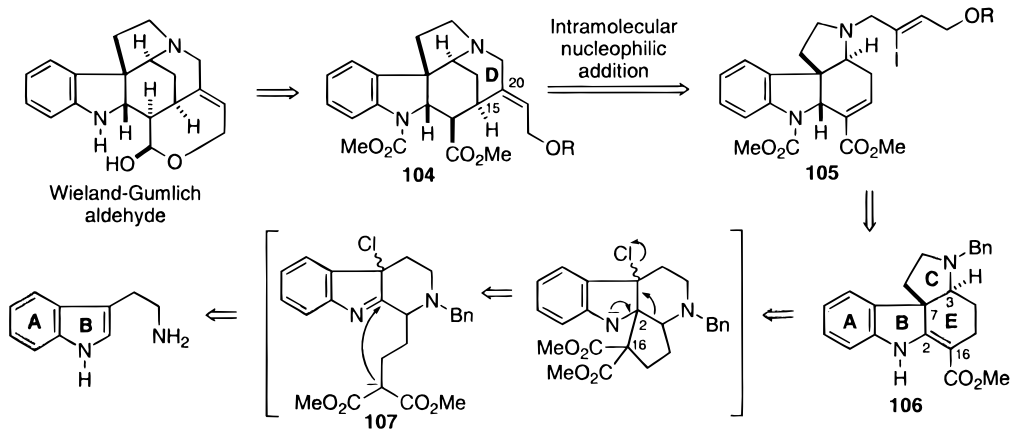
In 1992 Stork[23] contributed a new synthesis of strychnine through the Wieland-Gumlich aldehyde. Although related to the Kuehne approach by the use of pyrrolo[2,3-*d*]carbazoles as synthetic intermediates, the new synthesis differs from the former in the closure of the piperidine ring (ring D), which was accomplished by formation of the C15−C20 bond.

The retrosynthetic pathway is outlined in Scheme 29 and starts with the simplification of the Wieland-Gumlich aldehyde to the pentacyclic intermediate **104**. Disconnection of the latter at the C15−C20 bond by a retrointramolecular nucleophilic addition led to the α,β-unsaturated ester **105**, which was disassembled to pyrrolo[2,3-*d*]carbazole **106**. This tetracyclic compound, which incorporates the ABCE ring system of the target alkaloid, could be prepared easily from tryptamine through chloroindolenine **107** by means of previously developed methodology[84,85] that involves the simultaneous closure of C and E rings by the stepwise formation of C2−C16 and C3−C7 bonds.

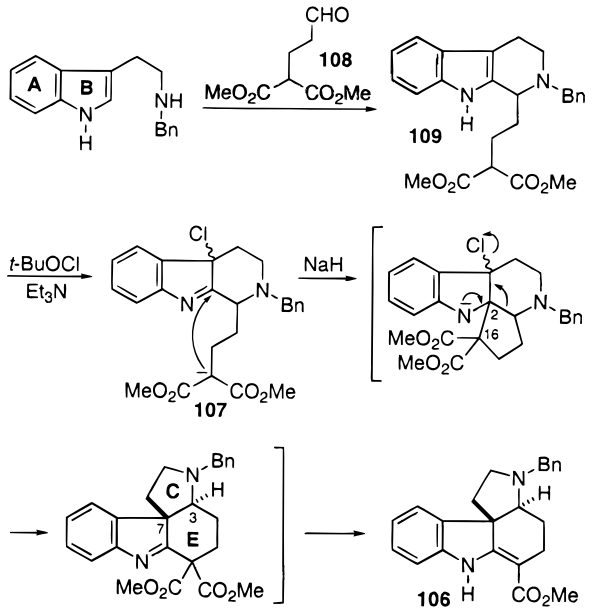
Stork's synthesis starts with the easy preparation of the hexahydropyrrolo[2,3-*d*]carbazole **106** from N_b-benzyltryptamine following the sequence shown in Scheme 30. Thus, Pictet−Spengler condensation of N_b-benzyltryptamine with aldehyde **108** afforded tetrahydro-β-carboline **109**, which was converted to chloroindolenine **107** on treatment with *t*-BuOCl. A subsequent treatment with sodium hydride directly gave pyrrolo[2,3-*d*]carbazole **106** through a process in which the initially formed malonate anion intramolecularly attacks the α-position of the indole nucleus (bond formed C2−C16) to afford a tetracyclic intermediate.[86] Skeletal rearrangement of the latter with simultaneous expulsion of chloride (bond formed C3−C7), followed by a Krapcho-like decarbalkoxylation[87] under extremely mild reaction conditions, afforded pyrrolo[2,3-*d*]carbazole **106**.

The closure of the piperidine D ring from the tetracyclic intermediate **106** required the generation of an α,β-unsaturated ester moiety[88] and the introduction of a vinyl iodide chain onto the pyrrolidine nitrogen atom (Scheme 31). Saturation of the vinylogous carbamate in **106** was accomplished either by reduction with sodium cyanoborohydride or by treatment with zinc dust in acidic methanol. The methoxycarbonylation of the resulting aniline followed by removal of the N_b-benzyl protecting group afforded the tetracyclic intermediate **110**. Generation of the C15−C16 double bond via an α-phenylselanyl ester and alkylation of the N_b atom with tosylate **111** led to α,β-unsaturated ester **105**. Closure of the piperidine ring from the latter was accomplished by an intramolecular conjugated nucleophilic addition to the α,β-unsaturated ester moiety. Thus, when **105** was treated with *tert*-BuLi followed by the addition of $MnCl_2$ and $CuCl_2$ to the reaction mixture, the pentacyclic compound **104** was obtained. This step,

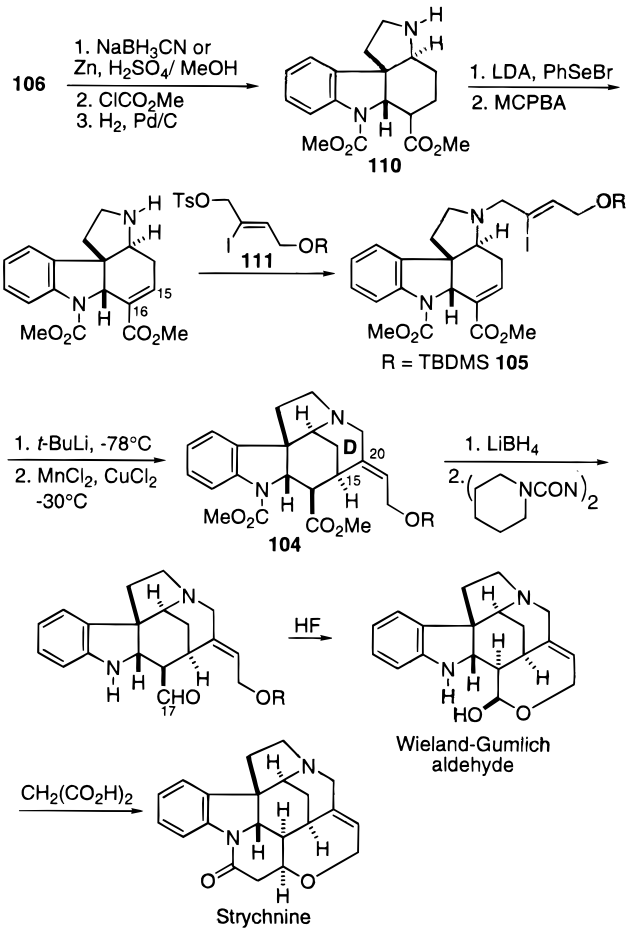
Scheme 29. Stork's Retrosynthetic Analysis of Strychnine



Scheme 30. Synthesis of Pyrrolocarbazole Intermediate 106



Scheme 31. Stork's Synthesis of Strychnine



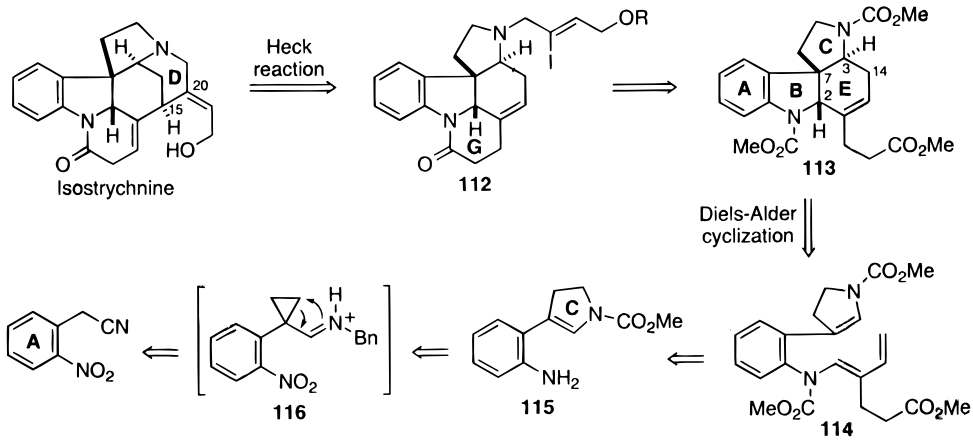
which solved the closure of the piperidine ring with the simultaneous stereoselective incorporation of the hydroxyethylidene side chain, proceeded in poor yields (~35%) and appeared to be the most troublesome part of the synthesis. Adjustment of the oxidation level at C-17 by reduction of **104** to the alcohol and subsequent oxidation to the aldehyde, and then the removal of the protecting group on the oxygen atom directly afforded the Wieland-Gumlich aldehyde, which was converted to strychnine by reaction with malonic acid under the previously described conditions.[34]

In summary, Stork's synthesis started with the construction of the ABCE ring intermediate and capitalized on an intramolecular conjugate addition of a vinyl organometallic species upon an α,β-unsaturated ester to construct ring D. Having achieved a curan intermediate, the final part of the synthesis is directed to the Wieland-Gumlich aldehyde.

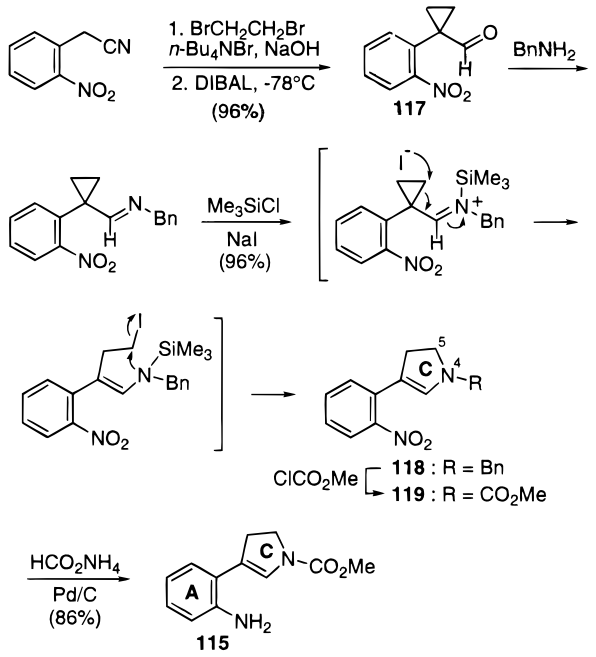
F. Rawal's Synthesis through Intramolecular Diels–Alder and Heck Reactions

Rawal's strychnine synthesis, published in 1994, chose isostrychnine as the final synthetic precursor.[26] The retrosynthetic analysis is outlined in Scheme 32. The synthesis is based on the strategy Rawal had previously developed to assemble the pentacyclic strychnan skeleton, in which he took advantage of intramolecular versions of both the Diels–Alder and Heck reactions.[89] The first key retrosynthetic disconnection was the cleavage of ring D at the C15–C20 bond, which led to the pentacyclic intermediate **112**. In the synthetic direction, it was decided to form this strategic bond by an intramolecular Heck reaction,[90,91] a process that would generate the *E*-configured double bond of the target alkaloid in a completely stereoselective way.[92,93] Retrosynthetic simplification of **112** led to the pyrrolo[2,3-*d*]carba-

Scheme 32. Rawal's Retrosynthetic Analysis of Strychnine



Scheme 33. Synthesis of Pyrroline Intermediate 115



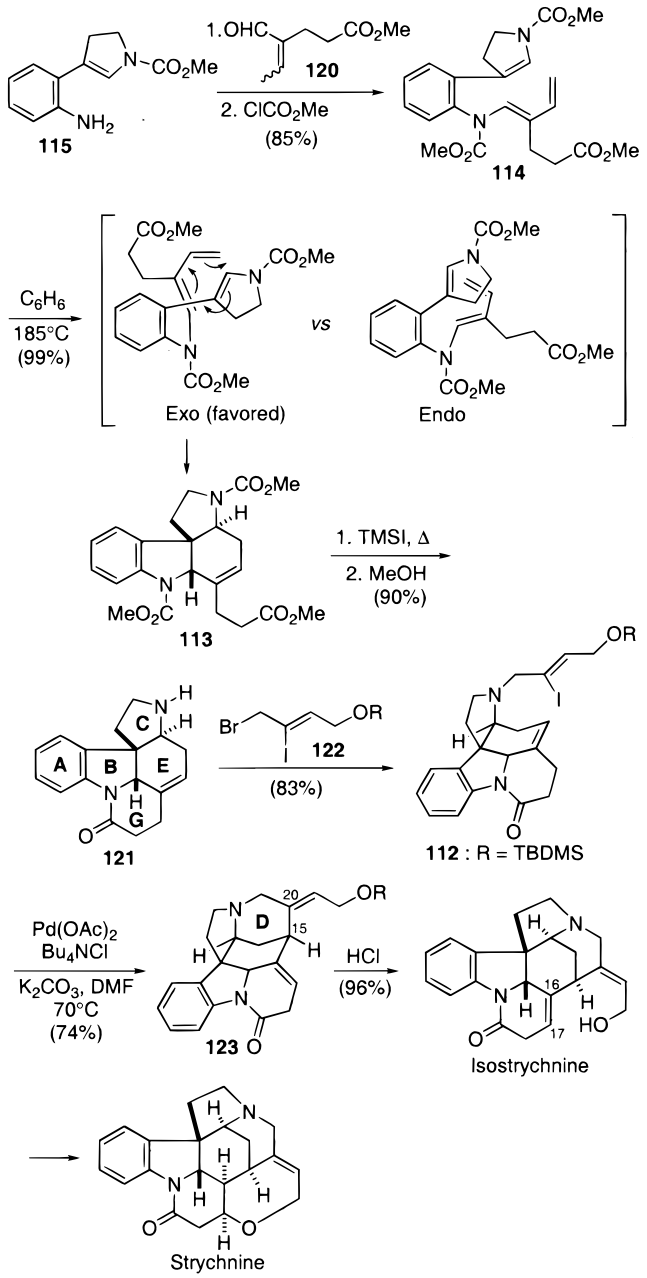
zole intermediate **113**, a compound containing rings A, B, C, and E of the alkaloid, and ring G in a latent form. Disconnection of the cyclohexene ring of **113** at the C2−C7 and C3−C14 bonds by a retro Diels−Alder reaction afforded pyrroline **114**. Finally, simplification of the latter led to pyrroline **115**, which could be easily obtained from *o*-nitrophenylacetonitrile by means of the rearrangement of cyclopropyliminium salt intermediate **116**.[94]

The synthesis commences with the preparation of pyrroline **115**, a compound containing rings A and C of the target alkaloid (Scheme 33). Reaction of commercially available *o*-nitrophenylacetonitrile with 1,2-dibromoethane and base under phase-transfer conditions followed by selective reduction of the nitrile group using DIBALH afforded cyclopropyl aldehyde **117**. Condensation of the latter with benzylamine gave an imine, which, on treatment with trimethylsilyl chloride and sodium iodide, underwent the cyclopropyliminium ion rearrangement to give pyrroline **118** (closure of ring C by formation of N4−C5 bond). Enamine **118** was converted to enecarbamate **119** by reaction with methyl chloroformate. Finally, reduction of the nitro group by catalytic hydrogenation afforded aniline **115**.

From pyrroline **115** Rawal undertook the construction of the framework of the target alkaloid using a sequence in which four rings are assembled in only five synthetic steps (Scheme 34). Thus, condensation of aniline **115** with the α,β-unsaturated aldehyde **120** afforded an imine, which was trapped with methyl chloroformate to give diene **114**. This compound, in which both the diene and the dienophile are electron-rich, underwent a smooth intramolecular Diels−Alder reaction[95] upon heating in benzene in a sealed tube at 185 °C to give pyrrolo[2,3-*d*]carbazole **113** in excellent yield with complete stereocontrol; the diastereomer obtained arising from the exo transition state in which the nonbonding interactions are minimized. Heating tetracyclic intermediate **113** with an excess of iodotrimethylsilane and then with methanol afforded pentacyclic lactam **121**, a compound containing five (ABCEG) of the seven rings of the alkaloid. Alkylation of secondary amine **121** with allylic bromide **122** gave the key intermediate **112**. The critical closure of the bridged piperidine D ring by formation of the C15−C20 bond was accomplished by an intramolecular Heck reaction, a process which was expected to be facilitated by the axially oriented pyrrolidine nitrogen. In fact, treatment of vinylic iodide **112** with $Pd(OAc)_2$ and n-Bu_4NCl[96] in DMF at 70 °C promoted the smooth intramolecular cyclization to afford the hexacyclic intermediate **123** in 74% yield.[97] This pivotal transformation not only allowed both the closure of the piperidine ring and the stereoselective incorporation of the *E*-hydroxyethylidene double bond but also introduced the C16−C17 double bond required for the synthesis of strychnine. Finally, removal of the silyl protecting group at **123** under acidic conditions afforded isostrychnine, which was then isomerized to strychnine under the reaction conditions previously described by Prelog.[31]

In summary, Rawal completed a concise synthesis of strychnine by a strategy that features an internal Diels−Alder cycloaddition to assemble the ABCE ring system and an intramolecular Heck reaction to achieve the closure of the bridged piperidine D ring with simultaneous stereoselective incorporation of the hydroxyethylidene side chain. The synthesis is

Scheme 34. Rawal's Synthesis of Strychnine



notable for the conciseness with which the framework is assembled and the high overall yield (15 steps, 10%).

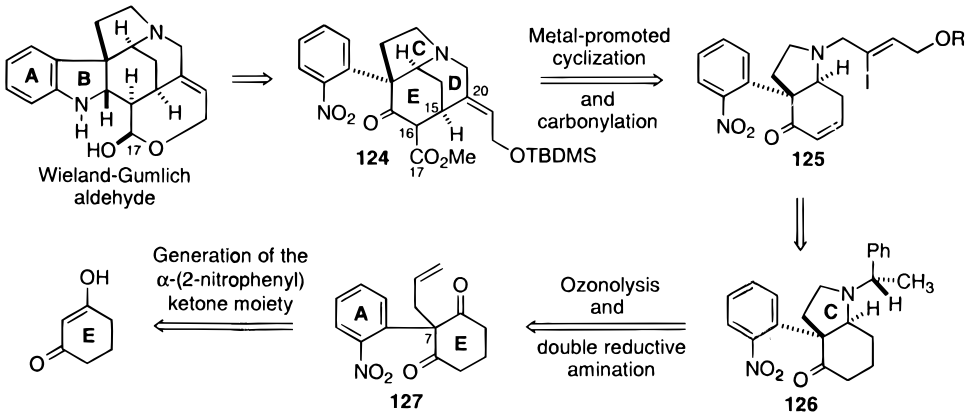
G. The Bonjoch–Bosch Synthesis Using a 3a-(2-Nitrophenyl)hexahydroindole as a Building Block

As the culmination of our studies on the synthesis of *Strychnos* alkaloids,[98] in 1999 we published a new enantioselective total synthesis of (−)-strychnine, which proceeds via the Wieland-Gumlich aldehyde.[27] The complete retrosynthetic analysis is shown in Scheme 35. As the ultimate precursor, we chose the nonindolic derivative **124**, in which the indoline nucleus (A and B rings) is present in a latent form (the nitrophenyl ketone moiety),[99,100] and the bridged tricyclic framework (C, D, and E rings), with the appropriate substituents at C-16 and C-20, has already been constructed. From this intermediate, the retrosynthetic analysis proceeded by disconnection of the CDE tricyclic core at the C15−C20 strategic bond to give the 3a-(2-nitrophenyl)hexahydroindolone **125**. In the synthetic direction, the use of a tandem metal-promoted cyclization−carbonylation process[101] would allow both the closure of the hydroxyethylidene-bearing piperidine ring and the introduction of the C-17 carbon atom. Retrosynthetic symplification of **125** led to octahydroindolone **126**, a compound that could be obtained in enantiopure form by an ozonolysis-double reductive amination sequence from the prochiral dione **127**. This intermediate, in which the crucial quaternary C-7 center has already been formed and a latent form of the indole ring has been incorporated, could be easily prepared from 1,3-cyclohexanedione, which preforms the core ring E of the alkaloid.

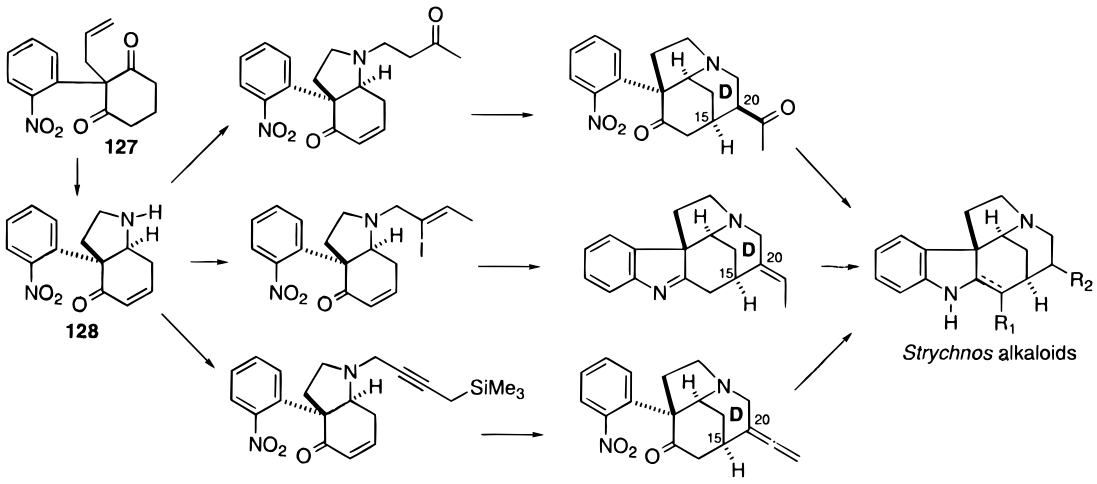
The above retrosynthetic analysis follows a strategy we have been developing during the past decade for the synthesis of *Strychnos* alkaloids and which has proved to be highly flexible for the synthesis of pentacyclic alkaloids of the curan type. The cornerstone of our synthesis is the use of 3a-(2-nitrophenyl)-hexahydroindol-4-one (**128**) as a common synthetic intermediate (Scheme 36). The versatility of this strategy lies in the fact that, depending on the functionality present in the substituent on the nitrogen, closure of the piperidine ring (bond formed C15−C20) can be effected by different methodologies to give azapolycyclic compounds bearing different piperidine substituents, which can be further elaborated into the variety of two-carbon substituents present at C-20 in *Strychnos* alkaloids of the curan type. In fact, we have employed three different procedures for the closure of the bridged piperidine D ring: (i) an intramolecular Michael-type conjugate addition,[102] (ii) a $Ni(COD)_2$-promoted biscyclization,[103] and (iii) an intramolecular cyclization of an enone-propargylic silane system.[104] Subsequent or concomitant reductive cyclization of the α-(2-nitrophenyl) ketone moiety completes the pentacyclic *Strychnos* system.

Our synthesis of (−)-strychnine started from the prochiral dione **127** available in multigram amounts.[105] This compound, having the crucial quaternary C-7 center of the alkaloid, was prepared from 1,3-cyclohexanedione through a three-step sequence involving direct arylation by a nucleophilic aromatic substitution reaction, *O*-allylation and, finally, Claisen rearrangement of the resulting allyl vinyl ether **129** (Scheme 37). The conversion of dione **127** into the perhydroindole system involved the elaboration of the pyrrolidine C ring by a double reductive amination process: the first, intermolecularly (bond formed N4−C5), upon the aldehyde group of the tricarbonyl derivative resulting from the ozonolysis of **127**, and the second, intramolecularly (bond formed N4−C3), on one of the two enantiotopic ketone carbonyl groups. The use of α-(*S*)-methylbenzylamine as the aminocyclization agent in this multistep sequence afforded octahydroindolone **126** (97:3 mixture of cis diastereomers) in 37% yield. Removal of the α-phenylethyl substituent via a carbamate followed by

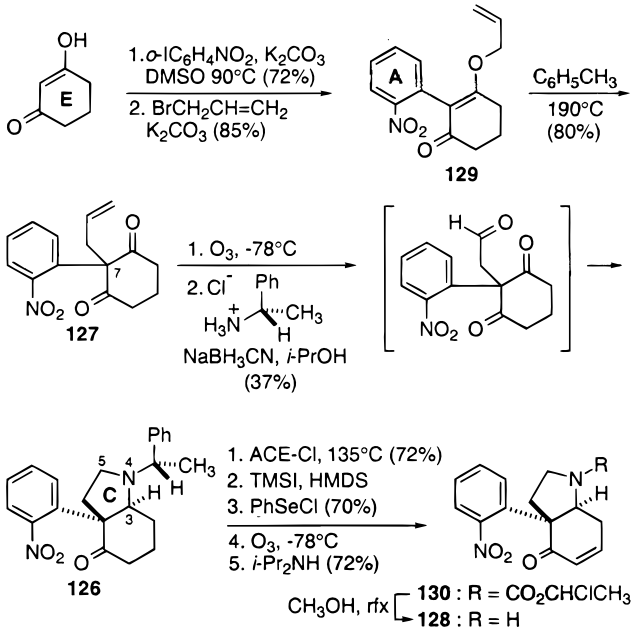
Scheme 35. The Bonjoch−Bosch Retrosynthetic Analysis of Strychnine



Scheme 36. Synthesis of *Strychnos* Alkaloids of the Curan Type via 3a-(2-Nitrophenyl)octahydroindol-4-ones



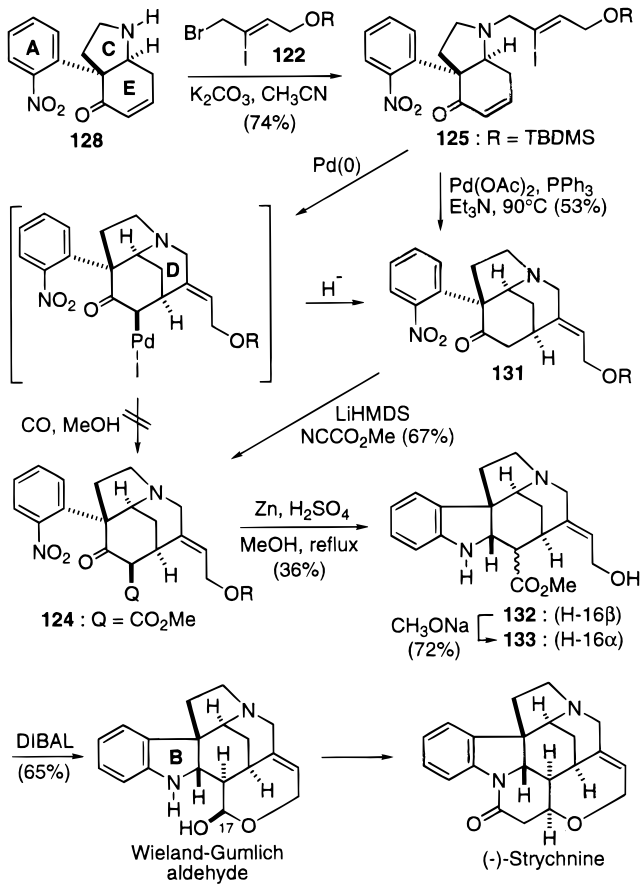
Scheme 37. Synthesis of the Key Hexahydroindolone 128



generation of the enone moiety through the α-phenylselanyl ketone intermediate afforded *N*-protected enone **130**, which on treatment with refluxing methanol was converted to the key enantiopure intermediate **128**.

Alkylation of secondary amine **128** with allylic bromide **122**[106] afforded hexahydroindolone **125** (Scheme 38), from which we undertook the elaboration of the piperidine ring. Our intention was to take advantage of a tandem Pd-promoted cyclization−capture process to simultaneously accomplish the closure of the ring with the *E*-configured hydroxyethylidene substituent and the introduction of an appropriate oxidized substituent at C-16. Thus, we expected that the transient alkylpalladium intermediate arising from the cyclization, with no hydrogen available for β-elimination, would be stable enough to be trapped with a suitable terminating agent. Disappointingly, however, all attempts to promote a tandem process failed,[107] and the only azatricyclic compound that could be obtained was ketone **131**, which is in fact the product of the reductive version of the Heck reaction.[108−110] At this point, we turned our attention to a less direct strategy, in which cyclization (formation of the C15−C20 bond) and introduction of the functionalized C-17 carbon atom would be achieved in two separate steps. In this context, the optimum conditions for the Pd-mediated reductive cyclization of **125** were found using $Pd(OAc)_2$ and PPh_3 as the catalyst in Et_3N at 90 °C. Under these conditions, the tricyclic ketone **131** was obtained in 53% yield. The subsequent methoxycarbonylation of **131** with LiHMDS and methyl cyanoformate provided β-keto ester **124**,[111] from which the

Scheme 38. The Bonjoch−Bosch Synthesis of (−)-Strychnine



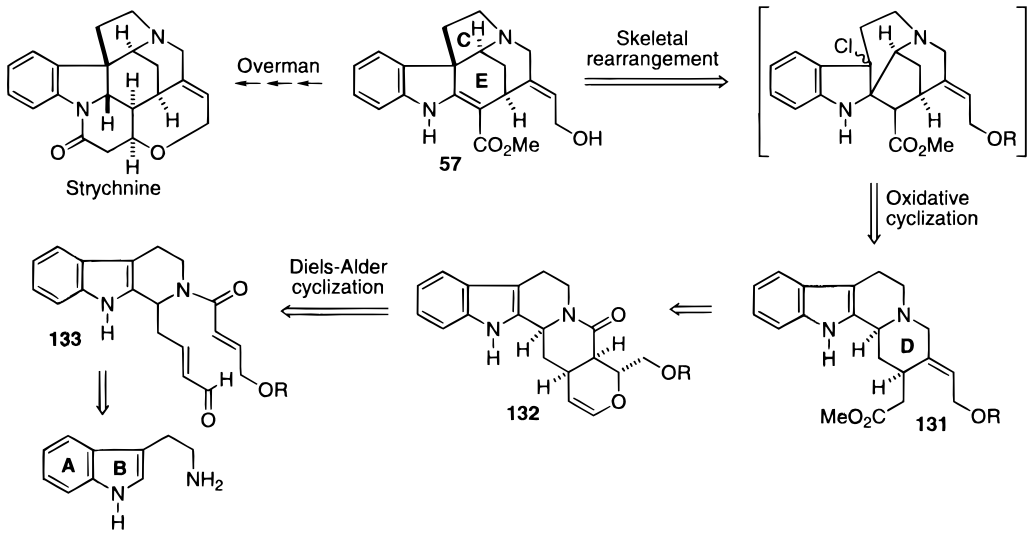
synthesis of the Wieland-Gumlich aldehyde only required closure of the indoline ring and the reduction of the ester functionality to an aldehyde. Treatment of **124** with zinc dust in methanolic sulfuric acid brought about both the removal of the TBDMS protecting group and the reductive cyclization of the α-(2-nitrophenyl) ketone moiety to afford an epimeric mixture of esters **132** and **133**. The mixture was equilibrated to pure **133**, which has the natural stereochemistry at C-16, by treatment with NaOMe in refluxing methanol. Pentacyclic ester **133**, which is also an intermediate in the synthesis by Overman, was converted to the Wieland-Gumlich aldehyde by partial reduction of the ester with DIBALH. Finally, the Wieland-Gumlich aldehyde was converted to (−)-strychnine following the known protocol.[34]

In summary, our team developed an extremely simple enantioselective route to strychnine by a series of stepwise annelations on a 1,3-cyclohexanedione to successively build the pyrrolidine, piperidine and indoline rings of the alkaloid (15 steps, 0.15% overall yield). The key step in the synthesis is the closure of the bridged piperidine ring from a 3a-(2-nitrophenyl)hexahydroindolone intermediate using a reductive Heck cyclization.

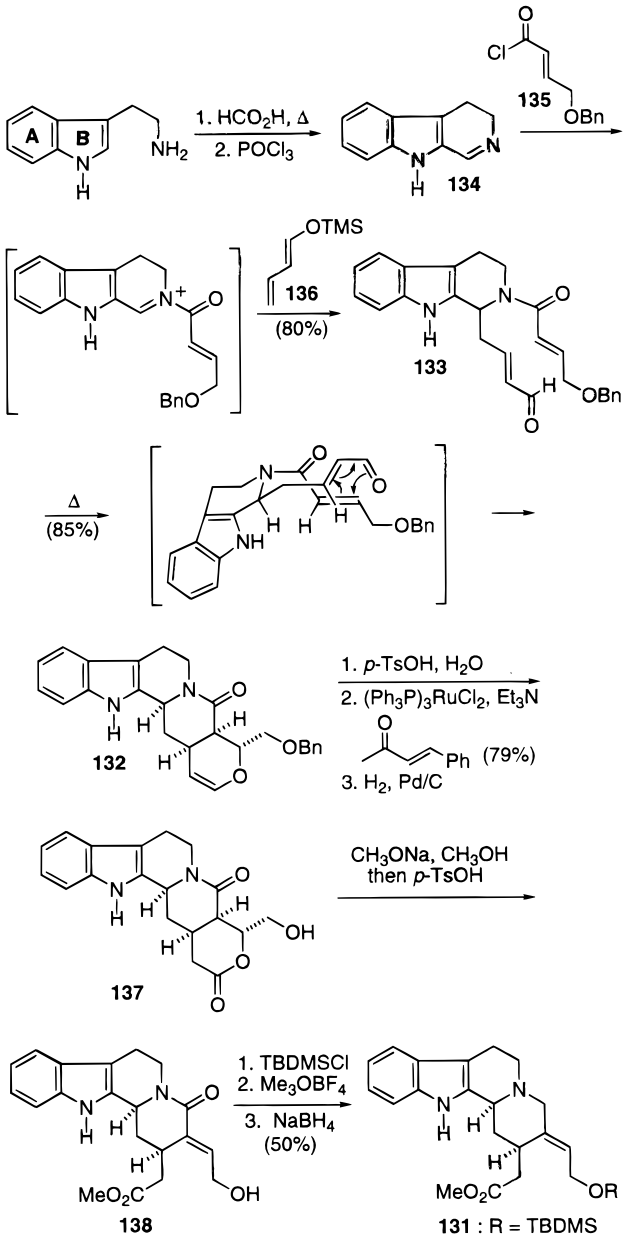
H. Martin's Formal Synthesis: A Biomimetic Approach

In 1996, Martin developed a fruitful new synthetic entry to the *Strychnos* alkaloids of the curan type, which has led to a formal synthesis of strychnine.[28] The retrosynthetic pathway is shown in Scheme 39. The critical element in the design of this synthetic plan was inspired by the proposed biogenetic conversion of the indole alkaloids possessing the corynantheoid skeleton (i.e., geissoschizine) into the alkaloids of the *Strychnos* family (see Scheme 1).[112] The synthetic objective was the pentacyclic intermediate **57**, which had previously been converted into strychnine by Overman.[22] The application of the biomimetic strategy to the synthesis of the anilino acrylate **57** led to the corynantheoid intermediate **131**, a compound in which the hydroxyethylidene-bearing piperidine D ring had already been elaborated. In the synthetic direction, the biomimetic reorganization, which involves the simultaneous closure of rings C and E, could be done by oxidative cyclization of tetracyclic intermediate **131**, followed by a skeletal rearrangement of the resulting chloroindolenine. The pentacyclic compound **132**, envisaged as the precursor of the key corynantheoid intermediate **131**, could be prepared by an intramolecular hetero-Diels−Alder reaction[113] from tetrahydro-β-carboline **133**, the latter being easily obtained from tryptamine.

Scheme 39. Martin's Retrosynthetic Analysis of Strychnine

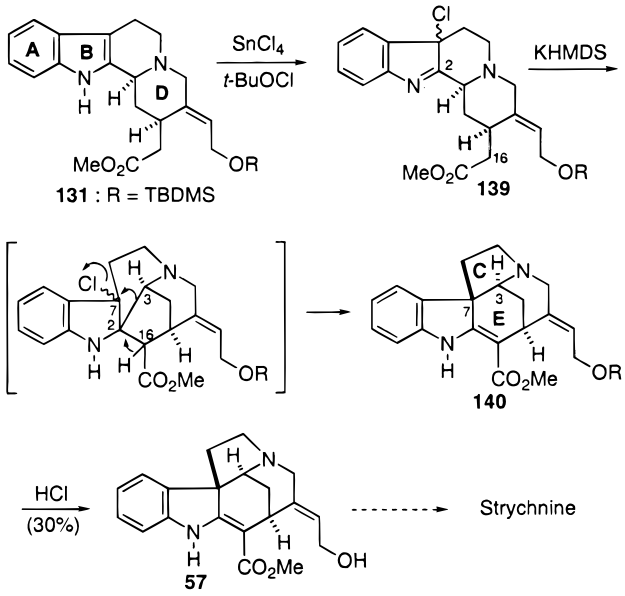


Scheme 40. Synthesis of the Corynantheoid Intermediate 131



Martin's formal synthesis started from dihydro-β-carboline **134**, which was prepared by condensation of tryptamine with formic acid followed by a Bischler−Napieralski reaction of the resulting *N*-formyltryptamine (Scheme 40). From **134**, the pentacyclic compound **132** was assembled using methodology Martin had developed in the context of the synthesis of heteroyohimboid and corynantheoid indole alkaloids, which involves a vinylogous Mannich reaction followed by an intramolecular hetero-Diels−Alder cyclization.[114] Thus, nucleophilic addition of trimethylsilyloxybutadiene **136** to the *N*-acyliminium salt generated by in situ reaction of carboline **134** with acyl chloride **135** provided α,β-unsaturated aldehyde **133**, which underwent smooth cyclization upon heating to give the pentacyclic adduct **132** as a sole diastereomer. Hydration of enol ether moiety of **132** followed by oxidation of the intermediate lactol and removal of the benzyl protecting group afforded

Scheme 41. Martin's Formal Synthesis of Strychnine



pentacyclic lactone **137**. A subsequent treatment with sodium methoxide resulted in a β-elimination reaction to give an acid intermediate that was esterified in situ to afford ester **138**. Finally, **138** was converted into the corynantheoid intermediate **131** by silylation of the hydroxy group and selective reduction of the amide moiety.

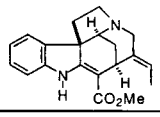
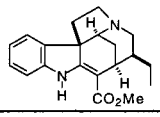
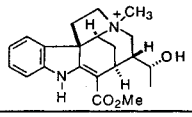
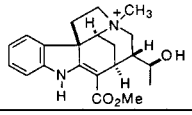
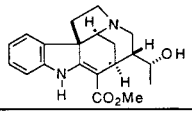
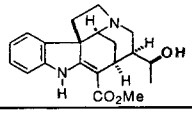
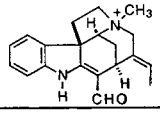
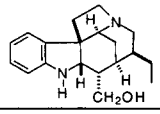
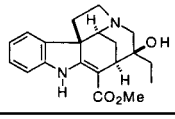
From this tetracyclic key intermediate, which incorporates rings A, B, and D, and the *E*-configured hydroxyethylidene substituent, the construction of the bridged framework of the target alkaloid was undertaken trying to mimic the biogenetic skeletal reorganization (Scheme 41). Treatment of **131** with *tert*-butylhypochlorite in the presence of $SnCl_4$ afforded a mixture of epimeric chloroindolenines **139**, which directly afforded the pentacyclic curan intermediate **140** on treatment with potassium hexamethyldisilazide.[115] The mechanism of this transformation has not been fully established, but probably involves the nucleophilic attack of the enolate on the imine carbon (bond formed C2−C16) to give a pentacyclic intermediate, which undergoes a skeletal rearrangement with concomitant expulsion of chloride (simultaneous closure of C and E rings with formation of the C_7 quaternary center) to afford anilino acrylate **140**.[116] Finally, removal of the silyl protecting group provided pentacyclic compound **57**, which had previously been converted into strychnine in four steps.[22]

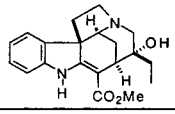
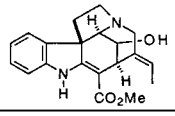
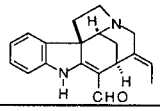
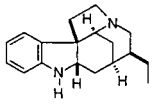
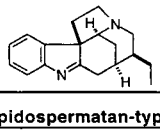
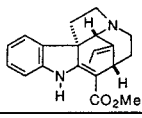
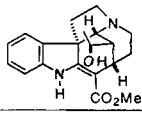
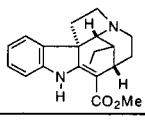
In summary, Martin developed a new route to strychnine, which involves a brilliant realization of the presumed corynantheoid-strychnan rearrangement that is the cornerstone of the biogenetic theory of *Strychnos* alkaloids.

IV. Concluding Remarks

In the past decade eight synthetic approaches to strychnine have been successful. Among these, three enantiospecific syntheses of (−)-strychnine have been described, starting from an enantiomerically pure

Table 2. Syntheses of Other *Strychnos* Alkaloids

Alkaloid	Form	Main Author	Year[a]	Ref[b]
Strychnan-type Alkaloids				
Akuammicine 	(±)	Overman	1993	53a
		Kuehne	1994	73
		Bonjoch/Bosch	1996	98
		Bonjoch/Bosch	1996	98
		Martin	1996	28b
19,20-Dihydroakuammicine 	(-)	Amat/Bosch	1997	126
	(±)	Bosch	1989	127
		Kuehne	1991	70
		Bonjoch/Bosch	1996	98
Alstogustine 	(±)	Kuehne	1994	73
19-*epi*-Alstogustine 	(±)	Kuehne	1994	73
N_b-Demethylalstogustine 	(±)	Kuehne	1994	72
Echitamidine 	(±)	Bonjoch/Bosch	1993	98
		Kuehne	1994	72
		Kuehne	1994	73
Fluorocurarine 	(±)	Harley-Mason	1971	128
Geissoschizoline 	(±)	Harley-Mason	1969	129
Lochneridine 	(-)	Kuehne	1998	76

Alkaloid	Form	Main Author	Year[a]	Ref[b]
Strychnan-type Alkaloids				
20-*epi*-Lochneridine 	(-)	Kuehne	1998	76
	(±)	Bonjoch/Bosch	1997	98
		Kuehne	1998	76
Mossambine 	(-)	Kuehne	1998	75
	(±)	Kuehne	1995	74
Norfluorocurarine 	(±)	Harley-Mason	1971	128
		Bonjoch/Bosch	1996	98
Tubifolidine 	(-)	Bonjoch/Bosch	1997	98
		Amat/Bosch	1997	126
		Shibasaki	1998	130
	(±)	Harley-Mason	1968	44
		Ban	1981	131
		Bosch	1988	127
		Bonjoch/Bosch	1993	98
		Bonjoch/Bosch	1996	98
Tubifoline 	(-)	Amat/Bosch	1996	132
	(±)	Harley-Mason	1968	44
		Ban	1981	131
		Bosch	1988	127
Aspidospermatan-type Alkaloids				
Condylocarpine 	(±)	Harley-Mason	1975	43
		Kuehne	1995	71
Lagunamine 	(±)	Vercauteren	1991	133
		Kuehne	1995	71
Tubotaiwine 	*ent*-	Massiot	1994	135
	(±)	Harley-Mason	1969	134
		Kuehne	1991	70
		Bonjoch/Bosch	1991	136

[a] Refers to date of first communication if exists. [b] Refers to full paper if published

compound, either prepared by an enzymatic desymmetrization[22] or derived from the chiral pool.[25,27] The new strychnine syntheses, which are the fruit and culmination of methodologies and strategies developed in the synthesis of other *Strychnos* alkaloids or even other types of monoterpenoid indole alkaloids, reflect the power of modern synthetic methods and demonstrate the usefulness of new procedures in assembling carbocyclic and nitrogen-containing rings.

The successful strychnine syntheses are only the tip of the iceberg of the synthetic work in this field, since there are numerous reports of partial studies or unsuccessful routes describing different approaches and ring constructs leading to advanced intermediates.[117−125] Last, but not least, it would be unfair not to remember the contributions of all of the chemists dedicated to studying the chemical and structural relationships of *Strychnos* alkaloids during the greater part of the last century.

V. Tabular Survey of Total Syntheses of Other Strychnos Alkaloids

In Table 2 are compiled all total syntheses of *Strychnos* alkaloids described to date, excluding those of strychnine and the Wieland-Gumlich aldehyde (see Table 1).

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VI. Note Added in Proof

Since this paper was written a new synthesis of (±)-strychnine has been reported by Vollhardt et al. (Eichberg, M. J.; Dorta, R. L.; Lamottke, K.; Vollhardt, K. P. C. *Org. Lett.* **2000**, *2*, 2479−2481). The synthesis is directed to (±)-isostrychnine, which was achieved either by a radical or a Heck reaction from an intermediate embodying ABCEG rings, prepared via a cobalt-mediated [2 + 2 + 2] cycloaddition along the lines described in ref 121.

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