LITERATURE SURVEY ON SYNTHESIS OF STRYCHNINE

A DISSERTATION REPORT

SUBMITTED IN PARTIAL FULFILMENT OF THE DEGREE OF M.SC. (ORGANIC CHEMISTRY)

BY

KASIA CIFA DIAS

TO SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

APRIL 2022

LITERATURE SURVEY ON
SYNTHESIS
OF
STRYCHNINE

A DISSERTATION REPORT

SUBMITTED IN PARTIAL FULFILMENT OF THE DEGREE

OF

M.SC. (ORGANIC CHEMISTRY)

FROM,

KASIA CIFA DIAS

TO SCHOOL OF CHEMICAL SCIENCES

GOA UNIVERSITY

GOA 403206

APRIL 2022

STATEMENT

I herby declare that the matter presented in this dissertation entitled, 'SYNTHESIS OF STRYCHNINE' is based on the results of investigation carried out by me in the School of Chemical Sciences, Goa University, Goa under the supervision of Dr. Rupesh Kunkalkar and the same has not been submitted elsewhere for the award of a degree or diploma.

Kasia Cifa Dias

CERTIFICATE

This is to certify that the dissertation entitled 'SYNTHESIS OF STRYCHNINE' is bonafide work carried out by Ms. Kasia Cifa Dias under my supervision in partial fulfillment of the requirement for the award of the degree of Master of Science in Chemistry at the school of Chemical Sciences, Goa University.

Dr. Rupesh Kunkalkar
Guiding Teacher
Goa University

Kasia Cifa Dias
(M.Sc. Student)

ACKNOWLEDGEMENT

I would like to express my special thanks of gratitude to my teacher Dr. Rupesh Kunkalkar as well as our dean Dr. Vidhyadatta M. Shet Verenkar and vice dean Dr. Rajendra N.Shirsat who gave me the opportunity to this wonderful project on the topic" SYNTHESIS OF STRYCHNINE", which helped in doing a lot of research on the topic and its applications in chemistry, adding to my knowledge and better understanding of the subject. I am really thankful to them.

Contents

Strychnine

I. ABSTRACT

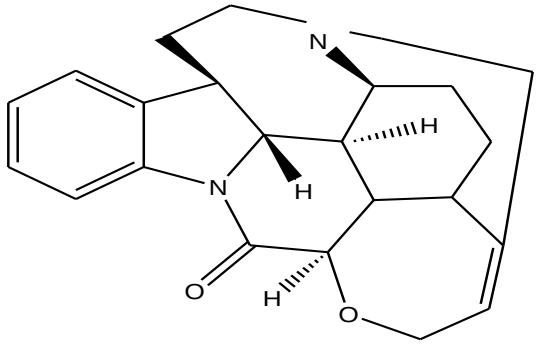
This literature survey highlights the importance of Alkaloid chemistry by focusing on the way to synthesis strychnine by using different methods. Which set the base for its uses to synthesis more complex structures, which will help in more advancements in different fields. In this survey it focuses more on obtaining of enantioselective pure compounds. Synthesis of strychnine in this survey focuses on i) the way to access optically active compounds i) the polycyclization strategy. It also puts some light on using of chiral artificial catalysis to obtain asymmetric catalysis to accomplish enantioselective synthesis of (-)- Strychnine.

II. INTRODUCTION

Strychnine is a poisonous monoterpenoid indole type alkaloid found in the plant genus of *Strychnos,* of the family of *Loganiacea.* A compound which is basic in nature, forming colorless or rhombic structured white crystals having a bitter taste.[1] Given its complex architecture coupled with pharmacological and extremely toxic properties, strychnine has intrigued organic chemists. It is a notorious poison (50 mg is lethal for an adult human , which blocks postsynaptic inhibition in the spinal cord where it antagonizes the transmitter glycin. This property has made the compound strychnine a very useful tool in experimental pharmacology.[1]

This compound found in the genus *Strychnos,* which contains around 196 various different species, contains the powerful posion in its seeds and barks. The species is spread through the warm tropical regions of Asia, Africa and America. Strychnine is commercially obtained from the seeds of the Saint Ignatius bean(*Strychnos ignatia)* and from the nux-vomica tree(Strychnos nux-vomica). The posion nut as it is also known, the S. nux vomica, is a deciduous tree native to India and south east Asia. Found in the open habitats. Its seeds contain approximately 1.5% strychnine and the dried blossoms contain 1.0%. The bark of it also contains other poisonous compounds. Strychnine was first discovered in the Saint Ignatius bean by French chemists Joseph- Bienaime Canoiu and Pierre Joseph Pelletier. The

plant of Strychnos also contains another poisonous derivative 9, 10 methoxy of strychnine



[2].

Figure 1:Structure of Strychnine

III. BACKGROUND

1) Chemistry and physiochemical properties

Strychnine has the molecular formula $C_{21}H_{22}N_2O_5$. It ranks as one of the most complex natural products of its size. Having a molecular weight (MW) of 334. The vast studies done by Robinson in determination on the structure of strychnine resulted in its structure determination in 1946. The numbering system and ring labeling of strychnine based on the biogenetic interrelationship of monoterpene indole alkaloids, as proposed by Le Men and Taylor is given down below. A year later Woodward proposed the same structure[3]. An x-ray crystallography study done in 1950 by Robertson and Bevers and Bijvoet, confirmed the relative configuration of strychnine. A study done by Perderman in 1956 of the x-ray crystallography of strychnine gave rise to its absolute stereochemistry which was also later confirmed by Schmid.[4]

It has only twenty-four skeletal atoms assembled in seven rings resulting in six contiguous stereogenic center (five of them in the core cyclohexane E ring). Therefore, strychnine is recognized as an important alkaloid of the family of strychnos alkaloids. It occurs as white crystals or powder that is odorless, with a melting point of 286 ℃. With a boiling point at 270℃ at 5mm Hg, density of 1.36g/cm^3, vapor density of 11.0(air=11), and vapor pressure 0 torr at 20℃. Strychinine is a stable compound and is compatible only with strong oxidising agent. Solubility of strychinine in water is very less about 160mg/L at 25°c and pH of the saturated solution is 9.5 Octanol/water partition coefficient (log K_{ow}) is 1.93. Strychnine has a mild solubility in the organic solvents like benzene ether, ethanol (6.7g/cm3), acetone. It is also highly soluble in chloroform and pyridine.[2]

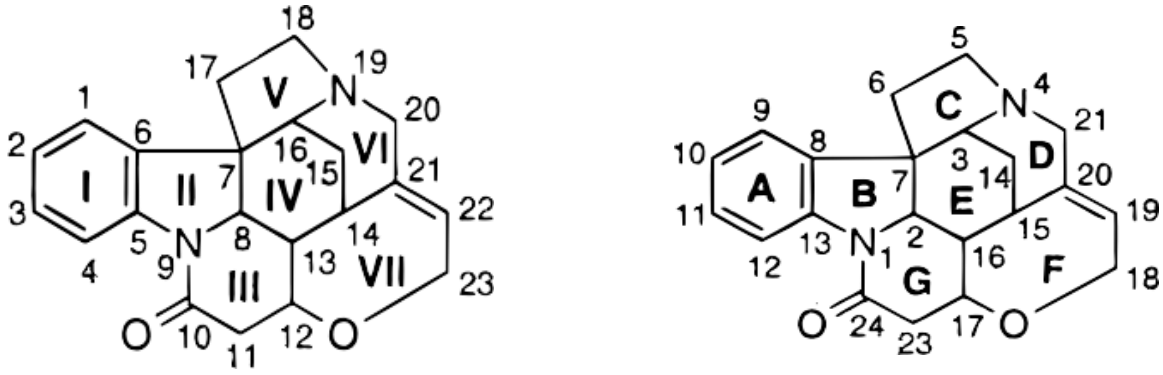


Figure 2:On the left, strychnine structure with numbering and ring labeling prposed by Woodwar. On the righ, strychnine showing the biogenetic numbering and ring labeling.

A. An overview of the earlier synthesis of strychnine (1954-1999)

Woodward in 1954 was the first person to synthesize strychinine. Later on eight more total synthesis of strychinine were achieved in 1990s. Out of which three were enantioselective synthesis of the natural enantiomers, (-) -strychnine. Below are given the synthesis of strychnine reported from 1954 to 1999. Which follow three main steps in achieving of the required structure 1) the sequence of ring construction; 2) the assembling of the CDE core ring including the C7 quaternary carbon center and 3) the way of access chiral intermediate. Studies started first from as early as 1880s had revealed that isostrychnine and Wieland -Gumlich aldehyde are degradation products of strychnine, and that they could be reconverted to strychnine in a single step by Prelog in 1948 and by Anet and Robinson in 1955 respectively. In the other case treatment of isostrychnine with alcoholic potassium hydroxide induces isomerization of the C-C double bond from the C17-C16 position to the C- 23 - C17 position to give a α - β unsaturated lactam having a stereocenter at C16.This conjugate addition gives rise to 20% strychine yield, with isostrychnine recovery. Treatment of W - G aldehyde with malonic acid sodium acetate and acetic anhydrid in acetic acid results in the direct formation of strychnine in 68% yield. Based on these findings, down below are given the different synthetic approaches that have been reported in the formation of the compound isostrychnine or W-G aldehyde.[4]

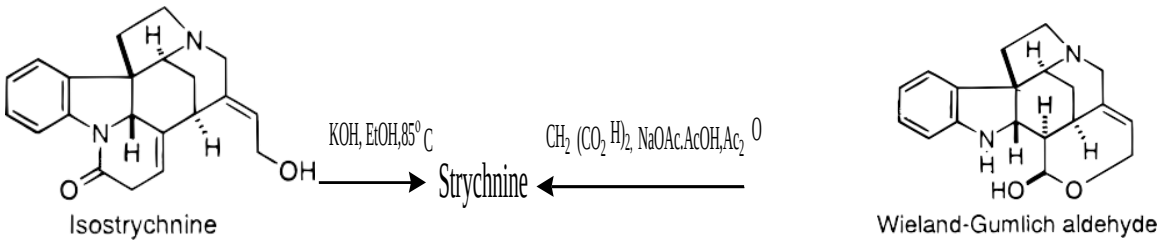


Figure 3:Two pathways to obtain strychnine

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/ [3,3]-Sigmatropic Rearrangement	Intramolecular Electrophilic Alkylation	Wittig Olefination
	1998	(-)/L-tryptophan			
	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		

Figure 4:Summary of synthesis of strychnine

B. Woodward's Relay Synthesis of (-)- Strychnine (1954)

[A→ AB →ABC → ABCEG → ABCDEG → Isostrychnine→ strychnine]

Woodward's strychnine synthesis began with a Fischer indole synthesis using phenylhydrazine and acetoveratrone [A→ AB] . In the later stages of the synthesis, the veratnyl group ($-CH_2-C_6H_3-3,4-(OMe)_2$) was used as parts of G, E and D rings. An introduction of an aminoethyl moiety at the (7 position actel – Spengler reaction of the corresponding 2- veratryl tryptamine with ethyl glyoxylate was induced by 4 – toluenosulfonyl chloride (TsCl) to give the Spiro annulated compound. [AB → ABC, which contains the C7 as the quaternary center].The highly electron – rich veratryl derived was cleared by ozone at the bond between the two methoxy groups, resulting six membered lactam formation. Before the formation of ring E the Ts group was changed to acetyl group in three step. Treatment with sodium methoxide induced epimerisation at C-3 position, with Dieckman cyclization enolester was formed [ABCG → ABCEG].Deoxygenation at C -14 , sulfide intermediate and the hydrogenation of C14 – C15 double bond, methyl ester (diostereomeric mixture of the C15 position Epimerisation at C15 under basic conditions gave a stable compound that is the carboxylic acid. The acetyl group at C-15 position along with oxidation of the resulting methyl ketone with SeO_2 gave the second relay compound [ABCEG → ABCDEG] . Diastereoselective addition of sodium acetylide to the ketone and the conversion to an allylic alcohol, also reduction of the amide carbonyl and by Li Al H_4 gave the core ring skeletal structure. Lastly rearrangement of the tertiary allylic alcohol to primary allylic alcohol resulted in isostrychnine formation which was then converted to strychnine by using the previously reported procedure.[3]

C. Magnus Relay Synthesis of (-)- Strychnine(1992)

(AB→AB→ $ABCDE$W→ $ABCDEF$. G Aldehyde → Strychnine

After about 40 years, Magnus accomplished yet another method in the synthesis of strychnine. In which a transannular oxidative cyclization is been done, at the same time the ring C and D are formed,it is a main step in this synthesis .Magnus strychnine synthesis started with the Pictet-Spengeler reaction of tryptamine with dimethyl 2-ketogularate to give lactam directly. [5]The lactam is the converted to a tertiary amine, with the treatment of β,β,β,-trichloroethyl chloroformate, which helped in the formation of a nine membered cyclic compound via cleavage formation. The ring D is formed by the intramolecular conjugate addition of an α-sulfinyl amide to give a characteristic tetracyclic lactam. [AB→ABD]. For the formation CDE,

the core ring Magnus employed the transannular oxidative cyclization. The dehydration of the tertiary amine functionality, gave rise to three iminium ions, on treatment with mercuric acetate in acetic acid formed the iminium ion, yielding the desired pentacyclic compound, [ABD→ABCDE, C7 quaternary center]. The β- amino acrylate was then converted to furanoside relay compound, the compound which is readily available on degradation of the W-G aldehyde. Optically pure was converted by using the Horner -Words worth -Emmons reaction. Giving a mixture of geometrical isomers in the ratio of 3:2(E:Z) respectively, the undesired Z isomer was converted by irradiation in benzene. The synthesis of W-G aldehyde was the achieved for the first time from the desired E isomer in seven steps. [ABCDE→ABCDEF]. Lastly by using Robinson's procedure, W-G aldehyde was converted to strychnine.[3]

D. Stork's Total Synthesis of Strychnine(1992)

[AB→ABCE→ABCDE→ABCDEF:W-G aldehyde→Strychnine]

In the Storke's synthesis of Strychnine, firstly the tetra hydro-β- carboline is converted to hexahydrpyrrol. The main starting material for the reaction was prepared by using the Pictet -Spengeler reaction in the conversion of N -benzyltryptamine by using an aldehyde. The tetra hydro-β- carboline was first chlorinated at the C-7 position by t-BuOCl and then treated with sodium hydride which resulted in the formation of a cleavage at the C2-C3 bond and led to the formation of a new bond at the C2-C3 bond, which led to form the another new compound hexahydropyrrolo carbazole. The use of alkenyl iodide gave the D and the F rings, allowing a E selective formation. Saturation of the C2-C16 double bond,and the generation of the C15-C16 double bond and the introduction of an E alkenyl iodide moiety gave the required skeletal structure. Using of t-Bu Li helped in the intramolecular conjugate addition and also the usage of manganese chloride and copper chloride gave the pentacyclic compound. [ABCE→ABCDE]. Finally, the total synthesis of strychnine was done in four steps via the W-G aldehyde.[6]

E. Overman's Total Synthesis of (-)- and (+) Strychnine(1993)

[A*→AD*→ACDE*→ABCDE*→ABCDEF : W-G aldehyde→ strychnine]

A optically pure compound of monoacetate was used to synthesis the enantioselective total synthesis of (-)- strychnine. The key reaction in this, is the synthesis of the cationic Cope - Mannich rearrangement, to assemble the CDE core ring system, which forms the bases for the skeletal ring structure. [7]After the conversion of the desired E isomer to the alkenyl stannane in [8], [9]five steps, the A ring portion was introduced by the Pd-catalyzed carbonylative Stille coupling reaction. Stereoselective epoxidation of the C2-C3 double bond, Wittig methylaenation of the ketone and introduction of the N4 source at the C21 position produced the trifluroacetamide derivative. The D ring formation was accompolished by heating NaH to give the intermediate after the removal of the trifluroacetyl group[A*→AD*][10]. The reaction involving the aza -Cope rearrangement and a Mannich reaction was done by heating with excess paraformaldehyde to provide the azatricyclic ketone. With the acidic treatement gave (-)- 18- hydroxyakuammicine [ACDE*→ABCDE*]. Finally, the pentacyclic alkaloid was transformed into the formation of the ultimate precusor (-)-strychnine via the W.G aldehyde, thereby achieving the first enantioselective total synthesis of (-)- strychnine. The efficiency and conscieness of this synthesis provided an important step to portray the power of the aza Cope rearrangement- Mannich reaction in solving the formidable problems in alkaloid construction.

F. Kuehne's Total Synthesis of Strychnine (1993)

[AB→ABCE→ABCDE→ABCDEG→Isostrychnine →Strychnine]

By using a condensation elctrocyclization reaction, in construction of the ring C and D, this step is used in the Kuehne's total synthesis. Starting from tryptamine, the C16-C17 unit was first introduced at the C2 position through chlorination by t-BuOCl and nucleophilic addition of malonate to give the diester. After conversion via two steps, Mannich type condensation was carried out with aldehyde with BF_3 and ethanol, it also underwent [3,3] sigmatropic rearrangement and an acid catalysed cyclization reaction to give a tetracyclic compound as a single diastereomer[11]. For the formation of ring D an intramolecular epoxide opening reaction was done. Then by refluxing it with MeOH and DBU gave a thermodynamically more stable six membered compound [ABCE→ABCDE]. The intermediate was converted to the N-acetyl compound, on heating it with LiHMDS, lead to the formation of ring G to give a β-keto lactam, which was later converted into $\beta, -$unsaturated lactam[ABCDE→ABCDEG]. As seen in the Magnus synthesis a side chain was introduced by a Horner -Wadsworth -Emmons reaction of Ketone, to give a mixture of geometrical isomers. Finally the E isomer was

converted to strychnine via isostrychnine. the use of readily obtained tetracyclic intermediate has allowed in its conversion of strychnine through five major stages of skeletal construction, with supporting adjustments of oxidation levels. The closing of ring G was done enantioselectivly, giving us the required product.[12]

G. Rawal's Total Synthesis of Strychnine(1994)

[A→AC→ABCE→ABCEG→ABCDEG→Isostrychnine→Strychnine]

In Rawal's strategy there is usage of Diels Alder reaction for the construction of the ABCE ring system. First, pyrroline was synthesized from 2-nitrophenulacetonitrile using the Stevens strategy, which involves cyclopropanation and cyclopropyl iminium rearrangement[A→AC]. Next the diene moiety was assembled by condensation with crotonaldehyde to give diene in four steps. Even when there was the presence of electron rich diene and dienophile, the desired Diels Alder reaction was carried out by heating (185-220℃), which gave us a single product [AC→ABCEE,CF quartenary center]. After lactam (G ring) formation by an intramolecular Heck reaction it resulted into alkenyl iodide. On comparison with Stork's conjugate addition, this process gave a much higher yield (74%). Finally, on the removal of the tert-butyldimethylsilyl(tbs) group under acidic conditions produced isostrychnin, which was then converted to strychnine using the conventional method.

H. Martin's Formal Synthesis of Strychnine (1996/2001)

[AB→ABD→ABCDEF:W-G aldehyde→Strychnine]

This synthesis is inspired by another reaction that is, the conversion of indole alkaloids. On this basis Martin synthesized strychnine. On changing the 18-hydroxyl- protecting group from benzyl to TBS. Martin,s synthesis is known for an intramolecular hetero Diels-Alder reaction. To obtain the first reactant, the dihydro -β-carboline was prepared from tryptaminein two steps, which was later converted to α,β-unsaturated aldehyde by Mannich reaction with silyl dienol ether in the the presence of the acyl chloride. Heating induced the intermolecular hetero Diels Alder reaction to give the pentacyclic adduct via transition state. Which on conversion gave a lactone and on basic treatement led to β-elimination to give the E configured α,β-unsaturated amide, which was transformed into the tetracyclic cotynantheoid derivative. To obtain the next skeletal structure the Massiot strategy was used. On chlorination and basic treatement of the

compound obtained gave rise to chloroindolelenine and also the C and E rings , to give a18-hydroxy akuammicine [ABD→ ABCDE→ ABCDE, C7 quartenary center] because Overman had tried obtaining the product in four steps, this process constitutes a formal process of strychnine.[13]

I.Kuehne's Total Synthesis of (-)- Strychnine (1998)

[AB* →ABCE* →ABCDEF: W-G aldehyde*(-)- Strychnine

Kuehne achieved racemic synthesis of strychnine as well as enantioselective synthesis of strychnine.To avoid the low yield conversion of isostrychnine to strychnine, the approach that was used to obtain the W-G aldehyde.gave a higher yield. Starting from L-tryptophan methyl ester, the cyclization precusor was prepared within seven steps like the before synthesis. The condensation-electrocyclization reaction with dienal, having quite high diastereoselective[AB*→ ABCDE].After conversion of the tetracyclic compound to tosylate, removal of the benzyl group gave the formation of the ring D.[ABCE* ABCDE]. Unlike the first synthesis, introduction of the hydroxyethylidiene side chain by Horner-Wadsworth-Emmons reaction of ketone proceeded with high stereoselectivity. Finally, the E isomer was converted to (-)- strychnine via the WG aldehyde.[14]

J. Bonjoch/Bosch's Total Synthesis of (-)- strychnine(1999)

[E →AE →ACE* →ABCDE*: W-G aldehyde (-)- s Strychnine

In 1990s, Bonjoch/Bosch prepared a strategy in the enantioselective total synthesis of (-) – strychnine. A strategy based on the diastereoselective, double reductive amination of a prochiral product for the construction of the CE ring system of strychnine. First the prochiral di ketone was prepared 1,3 cyclohexadione (sources of the core ring E) in tree steps, by introducing a ring moiety as well as Claisen rearrangement.[E EA , C7 quarternary centre]. Ozonolysis of the terminal alkene gave the prochiral diketo aldehyde and treatement with (S)-

1- phenylamine and NaBH_3 induced the double reductive animation, which involves (i) diastereoselective intermolecular reaction of the resulting chiral diketo amine, to afford the octahydroindolone {ACE* ACDE*]. In a similar way as Overman's synthesis, the tricyclicketone was converted to (-)- strychnine in five steps.[11], [12]

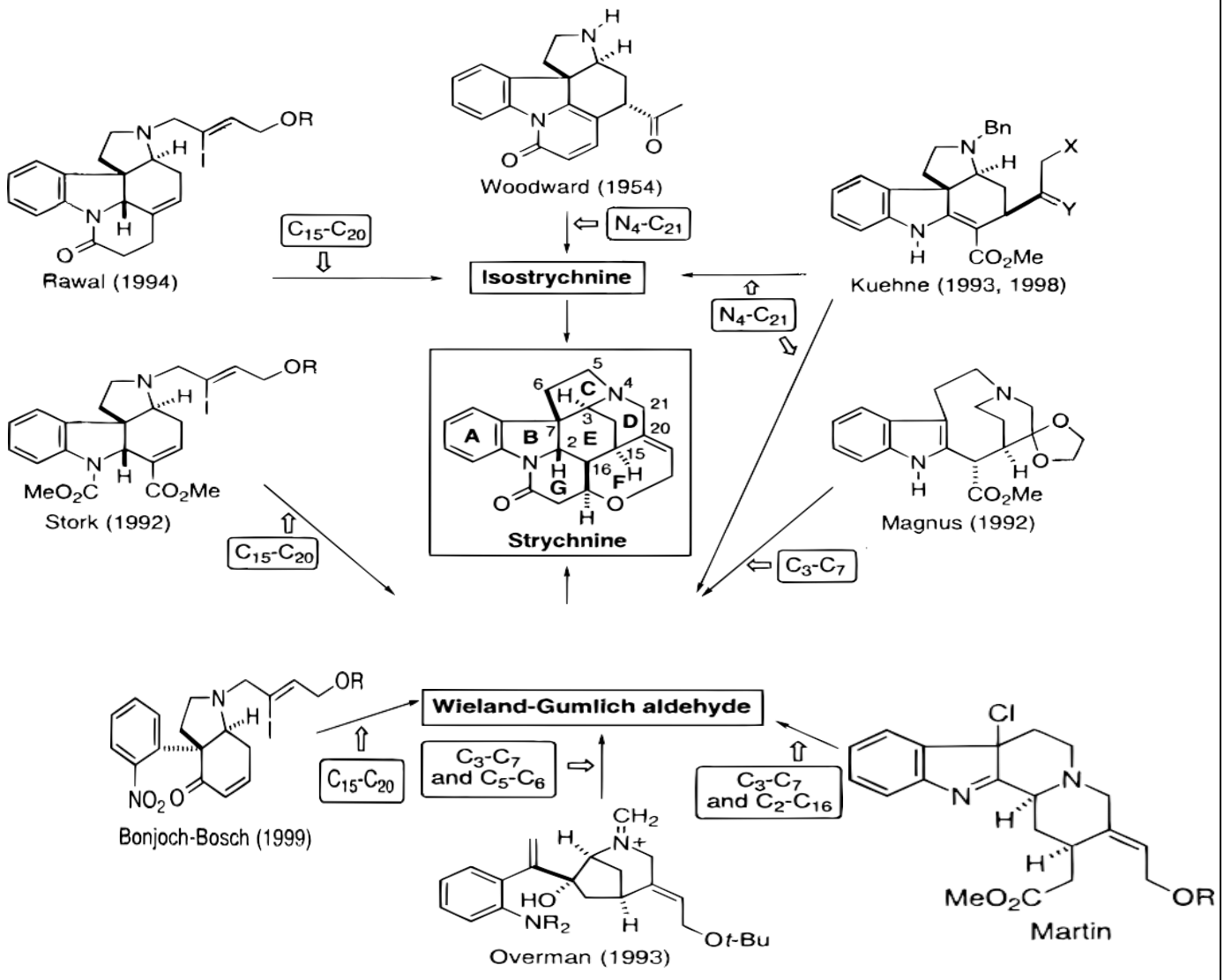


Figure 5:Construction of the bridged framework of strychnine

3. Recent Synthesis of Strychnine(2000-2006)

A GENERAL ASPECT

By 1999, nine synthesis of strychnine were discovered, it included few that involved both the enantiomers. Strychnine is one of the most used target molecule that can be used to study new strategies and reactions of alkoids , that can bring about more complexity in its molecular nature and more advancements.

B. Volhardt's Total Synthesis of Strychnine(2000)

[AB→ ABEG→ ABCEG→ ABCDEG →Isostrychnine→ Strychnine]

In this synthesis it is seen that strategic synthesis of strychnine using a cobalt mediated [2+2+2]cycloaddition gives a better yield and outcome.. This reaction was used for the closure of the E and G rings with the formation of the C7 quaternary center. Around five synthetic strategies were carried to obtain one successful one. Here tryptamine was converted to cronton aldehyde by coupling it with enynoyl chloride. The [2+2+2] cycloaddition was used to obtain a tetracyclic Co ccomplex as a single diastereomer.[AB→ ABEG] quarternary center. This reaction contains two important steps. i) two ligands of low valent CpCo.ii)oxidative coupling gives Co metallacyclopentadiene. iii)by performing a alkyne insertion or a Diels -Alder type cyclization gives a stable Co complex. In the next step the actamide functional group was hydrolysed using harsh conditions. The CpCo stabilized the amide bond in the C ring. Then the formation of [1,8] conjugate addition of the amine to give a unsaturated lactam system, giving a pentacyclic ring[ABEG→ ABCEG] for the formation of ring D,(i)metal-iodide exchange /conjugate addition,(ii)Pd mediated Heck/anion capture sequence (Rawal's synthesis) and (ii)radical mediated closure, these three methods were used, but gave a poor yield and unsatisfactory result. By reduction of the Heck product of silylated isostrychnine with lithium aluminium hydrid the desired product was obtained. Finally a successful method was obtained by using the radical cyclization with BuSnH and AIBN which generated a hexacyclic product[10]. This reaction gave a 50:50 mixture of geometrical isomers which were separated by HPLC chromatography. Thus, after the separation the desired isomer was used and converted to strychnine using Rawal's synthesis.[13]

C. Moris' Total synthesis of Strychnine (2001)

[E →AE*→ ABE*→ ABCEG*→ ABCDEG →Isostrychnine→ Strychnine]

In this synthesis of strychnine, cyclizations of Isostrychnine were carried out using Pd catalyzed reactions, including the first enantioselective allylic substitution[15]. The substrate was prepared using allylic alcohol, which is the source of ring, since the Pd catalyst has a chiral ligand the π- allyl palladium complex is formed, the nucleophilic attack. This palladium catalysis plays an important role in the total synthesis of the strychnine : rings A,B and E were constructed using palladium. This gave rise to the asymmetric allylic substitution of a cyclohexyl derivative followed by palladium catalyzed cyclization;20 ring C was formed by means of a palladium catalyzed allylic oxidation; 30 the synthesis of ring G and then ring F required palladium acetate salt. [16]

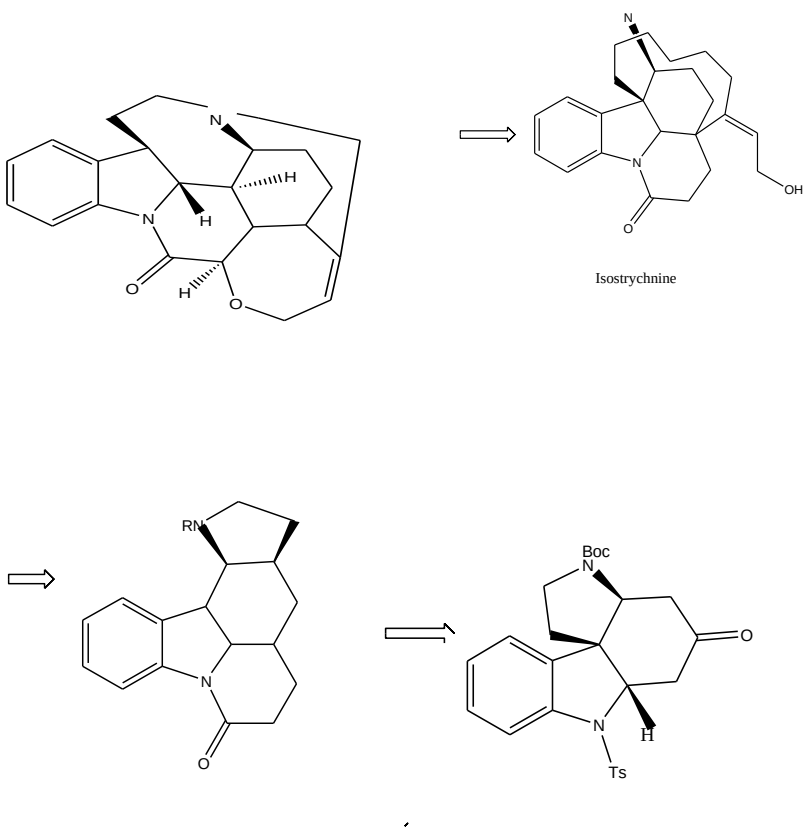


Figure 6:Retrosynthesis of Mori's synthesis of Strychnine

D. Bodwells's Formal Synthesis of Strychnine(2002)

[AB →ABCEG→ ABCDEG→ Isostrychnine →Strychnine]

In 2002, Bodwell reported the shortest synthesis of strychnine to date. The Diels-Alder reaction highlights some of the most important achievements in chemical synthesis as the primary method for constructing the functionalized stereo chemically complex 6-membered ring system. In the synthesis of strychnine, , an intramolecular Diels-Alder reaction was used to form bonds with C7-C2 and C3-C14 bonds . A feature of the Bodwell approach, is the use of t small cyclophane. It does not, in essence, serve as a substrate for the major reverse electron meridian deal as a target for natural product synthesis or as a major intermediate, Alder reaction (IEDDA) . Therefore, Bodwell hypothesized that the "double tether" arrangement of diene and dienophile of cyclophane facilitates the reaction as it can hold the two aromatic systems of 1 firmly in specific directions to each other. In fact, Bodwell had previously achieved a trans ring IEDDA of a double trimethylene bound cyclophane to produce a carbazole scaffold containing a pentacyclic compound. Bodwell's strychnine synthesis began with a tryptamine as its reactant . Methyl carbamate as an important substrate, and thus protects the resulting secondary amine of cyclophane. Strychnine was synthesized by Rawal in 4 steps, [1]completing a simple formal synthesis by Bodwell (12 steps from tryptamine).

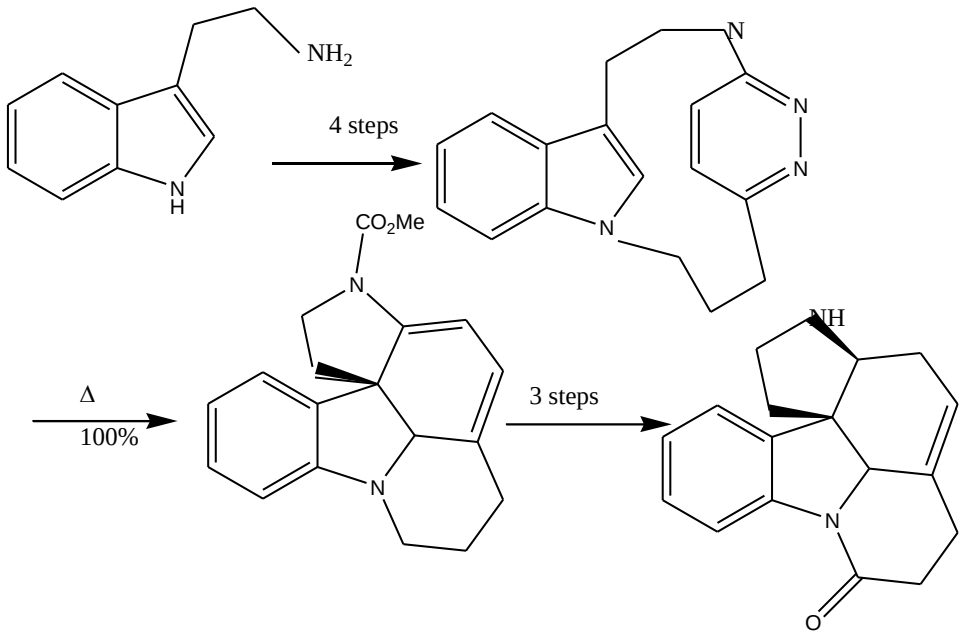


Figure 7:Retrosynthesis of Bodwell's synthesis of strychnine

E. Shibasaki's Total Synthesis of (-)- Strychnine(2002)

[E→ E*→ AE→* ABDE*→ ABCDEF :W-G aldehyde (-) -Strychnine]

In 2002, the entire emulsion of ()-strychnine employing a catalytic asymmetric Michael response and a completely unique domino cyclization that simultaneously constructed the B and D rings of strychnine was achieved. Previously, the largely practical, catalytic asymmetric Michael response supported themulti-functional catalyst was prepared (R) ALB complex, which was prepared from LiAlH4 and (R)-BINOL at a faster rate, which completed the Michael response of dimethyl malonate with cyclohexenone to go the enantiomerically pure Michael product on a lower than kilogram scale (91% yield,) . Using this Michael product as a starting material, we succeeded within the total emulsion of the Strychnos alkaloids ()-tubifolidine and . For the emulsion of strychnine, still, a special strategy was espoused as follows[9], [17] (i) the C17 unit was introduced before B ring conformation in consideration of F and G ring conformation, and (ii) domino cyclization was employed to assemble the ABED ring system more efficiently. Although ultimate of the contrary strategies for strychnine emulsion generated the C6 – C7 bond within the early stage of emulsion, so as to use the Michael product farther efficiently within the emulsion, the C ring at the C6 – C7 bond was assembled within the last stage. [18]

Starting from the enantiomerically pure product, prolusion of the spare two side chains to the core E ring was first conducted. The malonate half was converted to a b-keto ester through decarboxylation. By using modified Overman's conditions , the hydroxyethylidene substituent was constructed, using a E-isomer (EZ). It was converted to the triisopropylsilyl (TIPS) ether , regioselective silyl enol ether conformation was eased by the action of big lithium amide, and following a catalytic Saegusa – Ito response provided enone . Next, hydroxymethylation by the chemical response of an enol silyl ether in arid formamide , epimerization of the C16 stereocenter to the thermodynamically more stable-isomer, anda-iodination of the enone functionality gave alkenyl iodide . A Stille coupling response with 4-nitrophenylstannane 144 progressed fluently (E *-AE *), and also protection of the primary alcohol as a 2-(trimethylsilyl) ethoxymethyl (SEM) ether and dumping of the ideas group handed the pivotal intermediate . After prolusion of the amine half (N4 – C6) at the C21 position, treatment of the performing conflation with Zn dust handed the tet racyclic conflation in 77 yield (AE *-ABDE *). This domino cyclization may include the posterior three responses (i) reduction of the group to an amine by Zn dust; (ii) indole conformation (N1 – C2 bond conformation); and (iii)-addition of the N4 amine (N4 – C3 bond conformation). The C ring conformation by connecting the C6 – C7 bond was conducted using the intramolecular electrophilic attack of a thionium ion, which was previously employed for the emulsion of structurally simpler indole alkaloids by Bonjoch/ Bosch's group, to offer pentacyclic conflation in 86% yield (ABDE *-ABCDE *, C7 quaternary center). Also,the reduction of the imine half using the NaBH3CN – TiCl4 system was done. Although desulfurization using conventional styles constantly induced un asked responses, like migration of the exocyclic olefin to an endocyclic olefin andover-reduction, the response using Ni borite in an EtOH – MeOH mixed system swung the specified conflation with high chemo selectivity. Ultimately,it was converted into ()-strychnine in four way via W – G aldehyde.[1]

[19]

F. Fukuyama's Total Synthesis of (-)- Strychnine(2004)

[A →AB→ AB*→ ABCDE* →ABCDEF: W-G aldehyde (-)- strychnine]

In this synthesis of the (-)- strychnine, a total stereocontrolled reaction was done. Showing the unique nitrobenzenesulfonamide chemistry in construction of the medium cyclic amine. By removing the nosyl group under mild conditions we were able to construct a polycyclic core skeleton. This chemistry can be used to produce other alkaloids.fukiy[20]

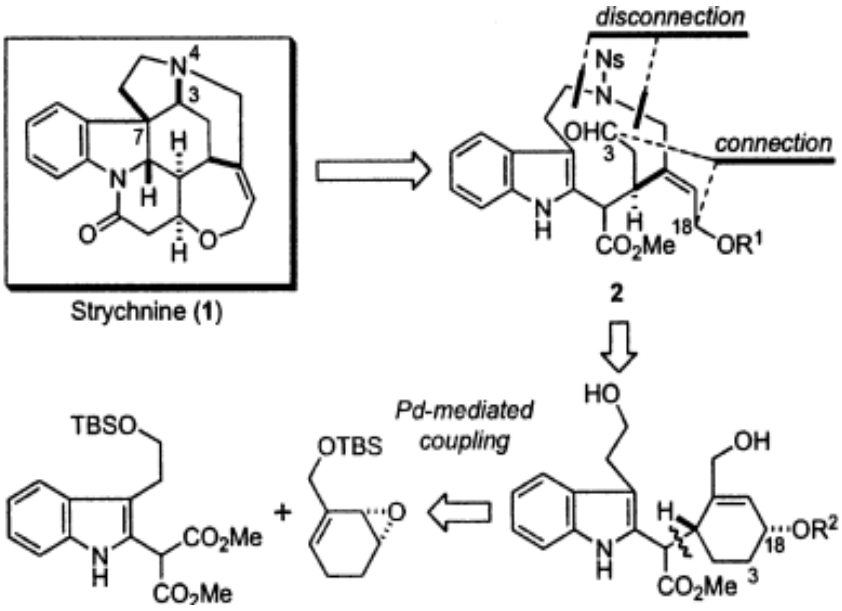


Figure 8: Fukiyuma's retrosysnthesis of Strychnine

G. Padwa's Total Synthesis of Strychnine(2007)

[AB→ ABCE→ ABCDE→ ABCDEF: WG aldehyde Strychnine]

Strychnine is a monoterpenoid indole alkaloid. The main step in this synthesis is done by the intramolecular [4+2] cycloaddition -rearrangement cascade of the indoly substituted amidofuran.In this synthesis the microwave irridation of the compound A in the presence of Magnesium chloride gave the compound B, via [4+2} cycloaddition. B has undergone a nitrogen assisited ring opening and subsequent elimination giving D. Palladium catalysed intramolecular coupling of vinyl iodide and (in situ generated) keto – enolate moieties afforded.[21]

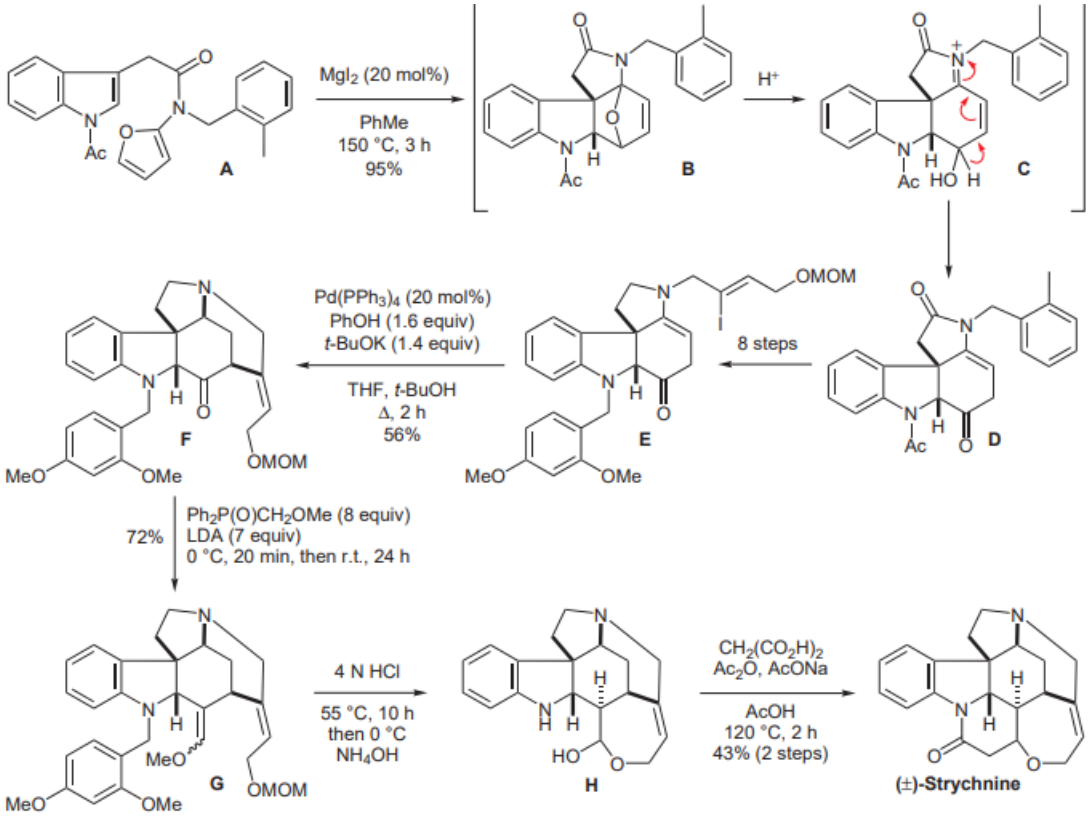


Figure 9: Padwa's synthesis of strychnine

IV. CONCLUSION

The chemistry used for the preparation of very useful indole alkaloids , sets the base for preparation of complex structures and molecules. This literature survey focuses on the 15 total synthesis of strychnine, which is based on i) the way to access optically active compounds ii) the polycyclization strategy. It also explains the need and the practical use of asymmetric synthesis to obtain enantiomerically pure compounds, which have a variety of uses in different fields.

V. BIBLIOGRAPHY

[1] J. Patocka, "Strychnine," in *Handbook of Toxicology of Chemical Warfare Agents*, Elsevier, 2020, pp. 239–247. doi: 10.1016/B978-0-12-819090-6.00016-7.

[2] J. Bonjoch and D. Solé, "Synthesis of strychnine," *Chemical Reviews*, vol. 100, no. 9, pp. 3455–3482, Sep. 2000, doi: 10.1021/cr9902547.

[3] "woodward1954".

[4] M. Shibasaki and T. Ohshima, "Chapter 3 Recent Studies on the Synthesis of Strychnine," *Alkaloids: Chemistry and Biology*, vol. 64, no. SUPPL.: COMPLETE. pp. 103–138, 2007. doi: 10.1016/S1099-4831(07)64003-6.

[5] P. Magnus *et al.*, "Synthesis of Strychnine and the Wieland-Gumlich Aldehyde," 1993.

[6] "126438b0".

[7] S. D. Knight, L. E. Overman, and G. Pairaudeauzb, "Asymmetric Total Syntheses of (-)-and (+)-Strychnine and the Wieland-Gumlich Aldehyde," 1995.

[8] P. J. Pelletier *et al.*, "For brief reviews of the am-Cope-Mannich reaction, see: Overman," American Chemical Society, 1993.

[9] M. J. Eichberg, R. L. Dorta, D. B. Grotjahn, K. Lamottke, M. Schmidt, and K. P. C. Vollhardt, "Approaches to the synthesis of (±)-strychnine via the cobalt-mediated [2 + 2 + 2] cycloaddition: Rapid assembly of a classic framework," *J Am Chem Soc*, vol. 123, no. 38, pp. 9324–9337, Sep. 2001, doi: 10.1021/ja016333t.

[10] J. S. Cannon and L. E. Overman, "Is there no end to the total syntheses of strychnine? Lessons learned in strategy and tactics in total synthesis," *Angewandte Chemie - International Edition*, vol. 51, no. 18. pp. 4288–4311, Apr. 27, 2012. doi: 10.1002/anie.201107385.

[11] M. E. Kuehne and F. Xu, "A Short, Stereocontrolled Synthesis of Strychnine'," Pergamon Press, 1994.

[12] M. E. Kuehne and F. Xu, "Syntheses of strychnan- and aspidospermatan-type alkaloids. 10. An enantioselective synthesis of (-)-strychnine through the Wieland-Gumlich aldehyde," *Journal of Organic Chemistry*, vol. 63, no. 25, pp. 9427–9433, Dec. 1998, doi: 10.1021/jo9813989.

[13] W. He, P. Wang, J. Chen, and W. Xie, "Recent progress in the total synthesis of: Strychnos alkaloids," *Organic and Biomolecular Chemistry*, vol. 18, no. 6. Royal Society of Chemistry, pp. 1046–1056, Feb. 14, 2020. doi: 10.1039/c9ob02627d.

[14] M. E. Kuehne, F. Xu, R. P. Parsons, J. D. Berk, and R. L. Parsons, "Total Synthesis of Strychnan and Scheme I," American Chemical Society, 1993.

[15] "Synthesis of (±)-Strychnine," *Synfacts*, vol. 2007, no. 06, pp. 0568–0568, May 2007, doi: 10.1055/s-2007-968519.

[16] M. Nakanishi and M. Mori, "Total Synthesis of (À)-Strychnine," 2002. [Online]. Available: http://www.angewandte.com

[17] W. He, P. Wang, J. Chen, and W. Xie, "Recent progress in the total synthesis of: Strychnos alkaloids," *Organic and Biomolecular Chemistry*, vol. 18, no. 6. Royal Society of Chemistry, pp. 1046–1056, Feb. 14, 2020. doi: 10.1039/c9ob02627d.

18] L. He *et al.*, “Asymmetric Total Synthesis of (+)-Strychnine,” *Organic Letters*, vol. 21, no. 1, pp. 252–255, Jan. 2019, doi: 10.1021/acs.orglett.8b03686.

[19] G. Aldehyde, E. Peidro, and J. Bosch, “Total Synthesis of (À)-Strychnine via the,” 1999.

[20] Y. Kaburagi, H. Tokuyama, and T. Fukuyama, “Total synthesis of (-)-strychnine,” *J Am Chem Soc*, vol. 126, no. 33, pp. 10246–10247, Aug. 2004, doi: 10.1021/ja046407b.

[21] “INFORMATION TO USERS.”