

Recent Advances in Total Synthesis of Strychnine (2017-2022)

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Abstract. Known for the complexity of its structure, strychnine remains to be one of the challenging targets of total synthesis. Generations of chemists have contributed to the total synthesis of strychnine since Woodward's groundbreaking synthesis. Today, new strategies and tactics are still emerging for the optimization of the route of strychnine synthesis. In this review, I discuss the documents about strychnine synthesis in the past five years with the aim of demonstrating the trend of the strategy and tactics of total synthesis.

Key Words: Natural products, strychnine, synthesis strategy, total synthesis.

1. Introduction

1.1 The Discovery of Strychnine

The *Strychnos* species, whose seeds contain poisonous alkaloids called Strychnos alkaloids, are widely distributed in the Asian tropics[1]. Strychnine is one of the most celebrated members of the Strychnos alkaloids as well as famous organic molecules to chemists and the public. In 1818, Pelletier and Caventou first isolated pure Strychnine from *Strychnos ignatii* Bergius[2]. Over one century later, in 1946, Sir Robert Robinson and Herman Leuchs first accomplished the brilliant research on the elucidation of the structure of strychnine before modern spectroscopic techniques were developed[3][4]. In the 1950s, the gross structure of strychnine was confirmed by two independent X-ray crystallographic researches. Finally in 1956, Peerdeman successfully reported the absolute structure of strychnine[5].

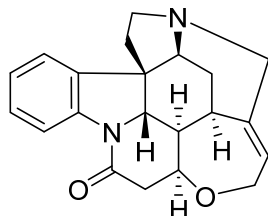


Figure 1. Strychnine

1.2 The Utility of Strychnine

In the 18th century the actual utility of strychnine remained uncertain[6]. Strychnine was said to have various advantages not only to increase appetite, enhance performance but also to tone skeletal musculature[7][8]. By now, strychnine has been proved to be a deadly neurotoxin whose mechanism of action has already been

fully studied. The alkaloid competitively binds to the glycine receptor chloride channel, eliminating glycinergic inhibition in the spinal cord[9]. That results in the overexcitation of nerves which may cause muscular convulsions, the inability to control respiration, and eventually asphyxiation[10]. Without direct cure for strychnine poisoning, the convulsions could merely be eased by anticonvulsants and muscle relaxants. As a result, strychnine has been used merely as a poison for rodents[8]. However, due to its extremely high toxicity that even a dose of 50 mg could be deadly to an adult human, its modern use is decreasing[11]. Furthermore, Significant contributions to understanding the chemistry of the nervous system have come from strychnine. Scientists were able to separate the first nicotinoid receptor from mammalian tissue because of strychnine's high-affinity binding to the glycine receptor[12].

1.3 Significance of Strychnine in Synthetic Chemistry

Strychnine stands out among traditional natural products since it was one of the first to be extracted and purified, but it was also one of the last to have its configuration determined. As a result, it has been crucial to the advancement of synthetic chemistry. After Robinson's elucidation of the configuration of strychnine, chemists sought to produce strychnine in the tube[3]. Only six years later in 1954, R.B. Woodward and colleagues accomplished their remarkable work of the total synthesis of strychnine[12]. It should be pointed out that at that time, strychnine was acknowledged as one of the most complicated molecules to access through chemical synthesis. Woodward's landmark synthesis of strychnine opened up a golden age of total synthesis and inspired generations of chemists who devoted themselves to total synthesis of natural products[11]. In the meanwhile,

strychnine remains today a popular target for total synthesis. Under constant efforts, chemists have successfully simplified the route of total synthesis of strychnine from Woodward's 29-step route to a concise 8 step route.

2. Analysis of the Structure

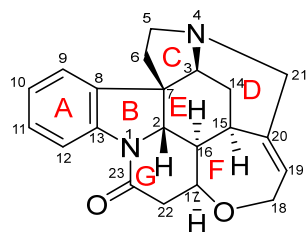


Figure 2. Numbering Figure for strychnine

As Robinson's remark about strychnine goes: "For its molecular size, it is the most complex substance known"[4]. Even with the development of modern synthetic strategies, significant challenges remain for synthetic chemists. One of those challenges is to construct the highly congested CDE tricyclic unit, containing five of six stereocenters of strychnine. In modern strategies, the F ring is to be constructed later in the route, which brings a secondary challenge of the stereocontrolled assembly of (E)-C19-C20 double bond[1].

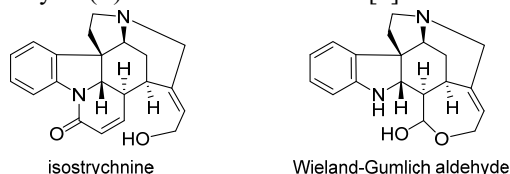


Figure 3. Two common targets

To date, all documented syntheses of strychnine have intercepted one of two common intermediates: isostrychnine or the Wieland-Gumlich aldehyde[1]. The maximum documented strychnine production from isostrychnine was about 28%, compared to 80% from the Wieland-Gumlich aldehyde. As a result, the Wieland-Gumlich aldehyde is regarded as the best strychnine precursor.

In light of numerous reported syntheses of strychnine, we have chosen the articles published during the past five years for discussion. Although the number of works related to total synthesis published in the past five years is small, the high quality of these works could not be denied. Inspired by the development of modern synthetic strategies, I tried to propose my own theoretical synthetic route of strychnine. And I hope to carry it out in the lab some day.

3. A selection of total synthesis of Strychnine during the past five years

3.1 Tang's Synthesis: A [4+2] Annulation Reaction (2017)

In 2017, Tang et al. envisaged a ligand-promoted catalytic [4+2] cycloaddition to quickly assemble the enantioselective ABC central skeleton of strychnos alkaloids (Figure 1). In their analysis, the D ring and F ring of strychnine was seen arising from a common-core scaffold of strychnos alkaloids 1 by an allylation with the substituted allyl bromide and an intramolecular radical or Heck cyclization reaction. By annulating PMB-protected tryptamine 3 with D-A cyclobutene 4 in the core stage of the synthesis, [4+2] annulation of the pyrrolidine ring 1 resulted in a cyclohexa-fused indoline motif 2.[13].

The central skeleton of strychnos alkaloids 2 was rapidly assembled from PMB-protected tryptamine 3 and D-A cyclobutene 4 which undergoes intramolecular [4+2] annulation to deliver a cyclohexa-fused indoline motif with three adjacent stereogenic centers and high diastereoselectivity [6]. Related [4+2] annulation reactions were performed on many alkynyl indole substrates. The cyclization product 6 was then produced from compound 2 in a 98% yield by first deprotecting it with TBAF and then performing an intramolecular Mitsunobu reaction. Exposure of compound 6 to LiCl solution under DMSO generated a decarboxylated product 7 in 92 % yield. However, Tang failed to convert 7 into the unsaturated ester directly under a PhSeBr/H₂O₂ condition. Hence, they changed the protecting group. Then compound 7 was treated with Na/naphthalene to produce the deprotection product, which was then transformed into the Boc-protected product 8. A two-step process comprising a PhSeBr/H₂O₂ oxidation sequence was then constructed to transform 8 into unsaturated ester 1[6]. The authors point out that a crucial step in the oxidation cascade was the protecting group's change..

Closing D F G rings was all that was needed to access strychnine from intermediate 1. (Figure 5). Through a two-step technique comprising allylation and deprotection, intermediate 1 was transformed into 9 with the substituted allyl bromide 10 in an overall yield of 71%. In three further stages, Wieland-Gumlich aldehyde was reached by substituted pyrrolocarbazole dienal 9. A reductive reaction of 9 provided pyrrolo[2,3-d]carbazole intermediate 11. To construct the C15-C20 bond with concomitant formation of the F ring hemiacetal, compound 11 was treated under Jeffery conditions[18] to undergo a intramolecular Heck reaction to give product 12. Trifluoroacetic acid and thiophenol were finally used to remove the PMB group, affording the Wieland-Gumlich aldehyde.

The versatile multifunctionalized cyclohexa-fused indolines are produced by Tang's ligand-promoted catalytic [4+2] annulation reaction of indole derivatives, which suggests that this novel synthetic technique could also be used as a general protocol for creating the common-core scaffold of strychnos alkaloids.[6]. This powerful transformation provides concise, facile and

alternative access to such natural alkaloids from basic commercially available starting materials.

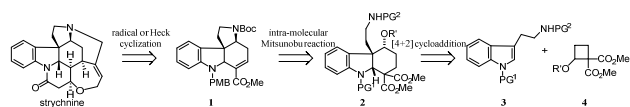


Figure 4. Retrosynthetic analysis of Tang's route to strychnine.

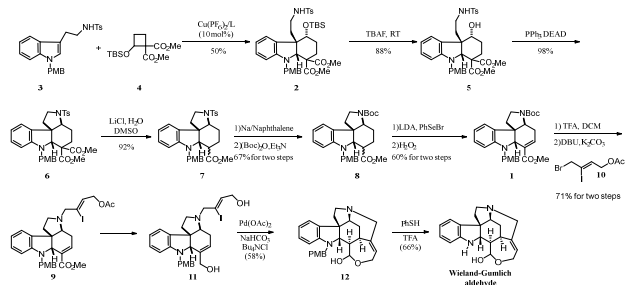


Figure 5. [4+2] annulation to form the ABE common-core scaffold of strychnos alkaloids 1.

3.2 Chen's synthesis: A most 'ideal' version

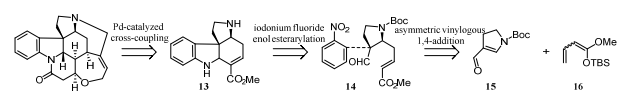


Figure 6. Chen's retrosynthetic analysis.

By collectively considering the monumental achievements of approximately twenty documented syntheses of strychnine, Chen et al. developed a most 'ideal' total synthesis of strychnine. In their approach, a sequential unification of building blocks was envisaged to forge BDE rings, through an asymmetric vinylogous 1,4-addition (B ring), an iodonium fluoride enol ether arylation (E ring), and a palladium-catalyzed cross-coupling reaction (D ring). Eventually, it was anticipated that the nitrogen-bearing C16 center would coordinate all of the remaining diastereoselective processes leading to strychnine. [14].

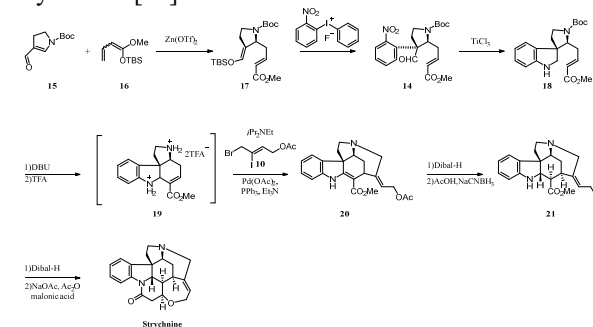


Figure 7. Chen's total synthesis of strychnine

In the first stage of Chen's synthesis (Figure 7), enol 15 and TBS silyl enol ether 16 reacted smoothly to produce TBS-enol ether 17 under the influence of $\text{Zn}(\text{OTf})_2$, which proved to be the most cost-effective choice of Lewis acid. This result was unexpected and, fortunately, gave rise to the right intermediate 17 in 77% yield. After the essential 1,4 addition, Chen failed several trails on installing the all-carbon quaternary C7 stereocenter.

Common strategies such as Pd-catalyzed arylation or Fischer-indolization largely afforded intractable mixtures. The most valuable clue came from the iodonium salt-based arylation chemistry developed by Koser and Rawal. The iodonium fluoride not only minimized desilylative protonation of **17** but also enhanced efficiency of the reaction, thus delivering nitroarene aldehyde **14** in the field of 63%. Next, under $\text{TiCl}_3\text{--NH}_4\text{OAc}$ reagent system, the nitro functionality of nitroarene aldehyde **14** was reduced to generate aniline which afforded imine **18** in 69% yield through intramolecular condensation with the proximal aldehyde. Then, imine **18** underwent an aza-Baylis-Hillman process to construct the E ring under the influence of DBU.

In three additional steps, the intermediate TFA salt was transformed into strychnine. (Figure 7) The prerequisite substrate for the constructing of the remaining DFG rings was N-alkylation of the intermediate TFA salt 19 with allylic bromide 10. This reaction proceeded smoothly under standard Heck conditions and afforded enamine 20 in 68% yield. Although several routes to strychnine containing intermediates closely related to 20 had already been documented, Chen decided to develop his route to bypass C13 epimerization. Under acidic quench and the introduction of NaCNBH₃ at -78°C, it was easy for the reductive removal of acetate group with DIBAL-H to be accomplished. They generated methyl ester 21 in 61% yield. After the further reduction through the reaction of DIBAL-H, ester 21 directly afforded Wieland–Gumlich aldehyde which was then treated under reported conditions to complete the total synthesis of strychnine. This 8-step synthetic sequence is the most concise entry to optically active strychnine to date. Moreover, under Chen's delicate design, the burden of experiment was minimized. 5 of the steps needed no aqueous work up while the remaining steps needed no chromatography purification, which was efficient for the production of strychnine. Meanwhile, through the further mechanistic understanding of the unprecedented vinylogous 1,4 addition reaction, it was also a successful implementation of asymmetric counter-anion-directed catalysis (ACDC) strategy[7].

3.3 Snaddon's synthesis: Enantioselective palladium-catalyzed allylic alkylation. (2020)

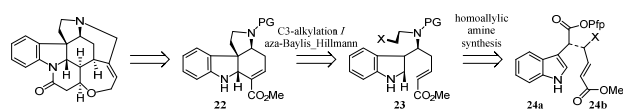


Figure 8. Snaddon's retrosynthetic analysis.

By intercepting a enantioenriched tetracyclic intermediate 22, Snaddon et al. accomplished a formal enantioselective synthesis of strychnine. According to their retrosynthesis, a functionalized electrophile 24b and a nucleophile 24a that contains an indole might go through their recently reported allylic alkylation/Hofmann rearrangement to directly access a homoallylic amine 23 that is properly decorated. Then, through a one-pot sequence, amine 23 underwent C3-indole alkylation followed by aza-Baylis-

Hillman annulation to deliver tetracyclic intermediate 22. Finally, they sought to integrate the documented works to complete the concise enantioselective synthesis of strychnine.

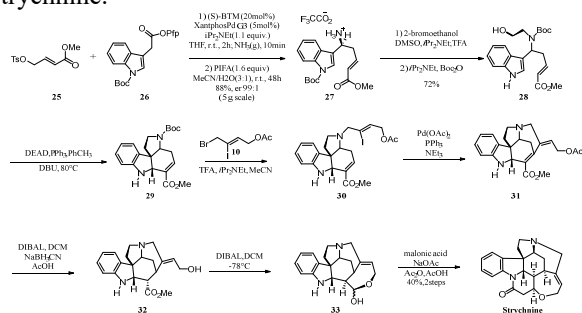


Figure 9. Snaddon's total synthesis of strychnine

Snaddon's strychnine synthesis began with the enantioselective (S)-BTM/Pd catalyzed allylic alkylation between γ -tosylate ester 25 and indole acetic acid 26, following an in situ ammonolysis of the Pfp ester[8]. To give the ammonium trifluoroacetate salt 27, the system was directly treated with PIFA in MeCN/H₂O. As expected, this procedure delivered ammonium trifluoroacetate salt 27 in high yield (88%) as well as good enantioselective control (99:1er) on a multigram scale (5 g). Next, 27 underwent a direct alkylation under a combination of 2-bromoethanol and Hünig's base in dry DMSO. The free indole was then liberated with TFA directly added to the solution. After concentration of the reaction mixture, compound 27 was treated with Boc₂O in Hünig's base so the second amine was protected to deliver t-butyl carbamate 28 in 72% yield. Thereafter, the primary alcohol in 28 was activated with PPh₃/DEAD the pyrrolidine ring in 29 could be directly formed through intramolecular indole C3-alkylation followed by Andrade's in situ DBU- catalyzed aza-Baylis-Hillman annulation strategy, giving the N-Boc-protected tetracyclic intermediate 29 in 59% yield. Nevertheless, Snaddon's group sought to design a most economical route to strychnine by streamlining of transformations into single-flask operations. The steps from indole acetic acid Pfp ester 27 to N-Boc-protected tetracyclic 29 could be carried out in merely three single-flask operations. In three additional routine steps, the N-Boc-protected tetracyclic 29 was transformed into strychnine[8].

3.4 Strychnine Biosynthesis

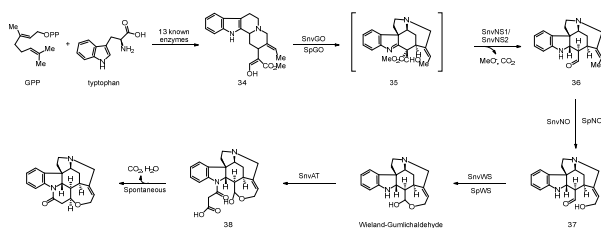


Figure 10. The complete biosynthetic pathway

In 2022, the O'Connor group successfully recapitulated strychnine biosynthesis in *Nicotiana benthamiana* from an upstream intermediate, which indicated that this class

compounds can now be harnessed through metabolic engineering approaches[9]. In their analysis, the Wieland–Gumlich aldehyde was seen arising from dehydropreakuammicine 35 due to their structural similarity. And dehydropreakuammicine 35 could be generated from an oxidative rearrangement of the indole ring of geissoschizine 34. Pictet–Spengler condensation between GPP and typtophan followed by a deglycosylation reaction generates geissoschizine 34.

After the oxidative arrangement of 34, 35 underwent a decarboxylation reaction to give norfl-urorurarine 36. Further oxidation of the terminal allylic position gave rise to 18-OH norflurorurarine 37. A subsequent reduction of the vinylogous formamide gave Wieland–Gumlich aldehyde. Different from a chemical synthesis, Strychnine's final G ring was constructed by condensation with acetic acid.

4. My route

Inspired by the development of organometallics, I am attempting to give my own theoretical route of the total synthesis of strychnine.

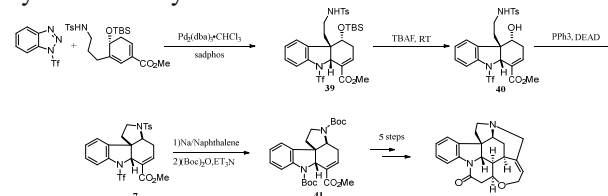


Figure 11. My theoretical route

In my synthesis, I was trying to take the asymmetric tandem denitrogenative Heck/ Tsuji–Trost reaction into consideration[10]. This reaction was developed by my research group. In the first step, a substituted cyclic 1,3-diene reacted with Tf-BFA under the catalysis of Pd to give intermediate 39. Due to the lack of experiments, the result of this step remains uncertain. Intermediate 39 has a similar structure to that of compound 2 occurred in Tang's synthesis. Compared to Tang's route, compound 39 needs no decarboxylation and oxidation to give intermediate 41, which could access strychnine in five additional steps.

5. Summary and Outlook

The documented total synthesis of Strychnine during the past five years presents a combination of unity and diversity.

All of the routes have intercepted Wieland–Gumlich aldehyde for its high yield of transformation to strychnine. Moreover, all group applied the late-stage bonding of C15–C20 to construct D ring. The number of steps required to produce strychnine stereoselectivity remains at a low level, with all of the synthetic routes discussed requiring 8 or fewer from several commercially available starting materials thanks to the development of modern synthetic techniques.

However, the focus of the synthesis work shifted to the general protocol for the concise construction of the

stereoselective common-core scaffold of alkaloids. Prominent among these is the intramolecular [4+2] cycloaddition reaction which allows facile construction of the same common-core scaffold of alkaloids bearing three contiguous stereogenic centers with excellent levels of diastereoselectivity.

Two centuries after strychnine's first isolation, it still represents a meaningful target for total synthesis. The complete synthesis of strychnine continues to present a number of challenges that are still guiding organic chemistry strategy and tactics.

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