Synthetic philosophy: A study directed toward creation of an ideal synthetic method and its application for preventing global warming by combating desertification

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SYNTHETIC PHILOSOPHY: A STUDY DIRECTED TOWARD CREATION OF AN IDEAL SYNTHETIC METHOD AND ITS APPLICATION FOR PREVENTING GLOBAL WARMING BY COMBATING DESERTIFICATION

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Abstract – This review reports how the author has been realizing his synthetic philosophy and five dreams as his life work. The philosophy consists of such three elements as originality rate, intellectual property factor, and application potential factor. On the basis of these elements, an ideal and an efficient synthesis are defined. In the study for the total synthesis of ergot alkaloids, the first concrete example of an approximately ideal synthesis was demonstrated. Further examples are shown relying on the chemistry of 1-hydroxyindoles. A lot of intellectual properties created by the author are successfully condensed to provide promising lead compounds meeting for the respective dreams of developing five drugs 1) for making desert green and food increase in production, 2) for cardiovascular system disease, 3) for dementia, 4) for lifestyle-related disease (osteoporosis, etc.), and 5) for cancer and virus. With potent promoters of plant's root growth in hand, the first dream is going now successfully. Preliminary experiments combating desertification at Gobi desert in Inner Mongolia are reported in detail, aiming for preventing global warming.

1. Introduction

What kind of article content is judged to have high efficiency and high value in the field of organic synthesis? Is the originality evaluated highly if the quality of the research is judged to be high? Citation index and impact factor are usually used as means of the evaluation usefully. However, these numerical values are one index for relative evaluation and do not always accord with the originality of the author and article content, respectively.

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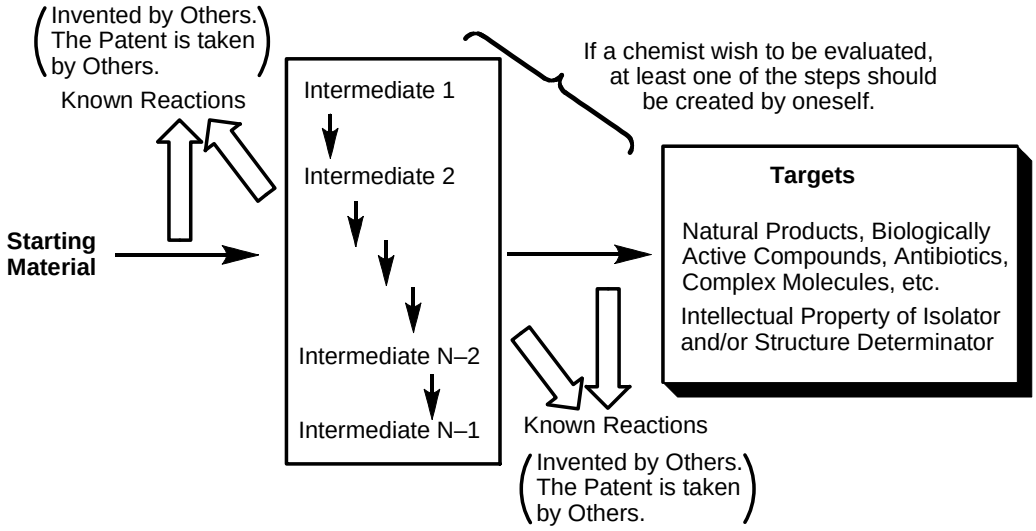
We believe the mission of the scientist is to create the intellectual property which transcend the fashion and popularity, and the best evaluation/value should be given to the creative power and the intellectual property (discovery, invention, and theory) which are brought about by the scientist.[1] However, nobody has so far proposed an index to measure the rate of originality and intellectual property involved in an article.

Let's evaluate a general long-step synthesis.[1] It is assumed that we achieved N-step synthesis as shown in Figure 1 directing toward drug development. In this synthesis the synthetic intermediates of N–1 unit are created besides a starting material and a target compound. If only the target compound is the lead for a new drug, there exist useless synthetic intermediates of N units involving the starting material. This is a typical inefficient synthesis with much waste. From this fact we can understand the way of thinking that "evaluation is high because the synthesis has many steps" is meaningless. Nobody doubts to judge the short-step synthesis to be superior to the long-step synthesis.

Figure 1. General N-Step Synthesis



What is the significance we can claim in achieving the synthesis of the target compound (for example, a biologically active natural product) as shown in Figure 1, costing much time, money, and labor, when the target compound is the intellectual property of the isolator and/or structural decider? Through the synthesis we can educate a beginner and/or a student. They can learn a lot of reaction and technology to use in future. But a synthetic chemist who passed the study times would not be satisfied with such synthesis. To get evaluation, the synthetic chemist must discover or invent as his intellectual property at least one step (a reaction or a reagent) among the N steps. The improvements of the reaction and/or

reagent created by other researcher are not one's intellectual properties.

2. Our Synthetic Philosophy

2-1. Originality Rate, Intellectual Property Factor, and Application Potential Factor[1]

We have thus far proposed our synthetic philosophy for evaluating the originality and efficiency of organic synthesis that consists of three measures such as the originality rate (**OR**),[2a-c] the intellectual property factor (**IPF**),[3] and the application potential factor (**APF**).[3] By comparing these numerical values, we can decide which research or article is excellent regardless of a nation and the times. The definitions[2] and formulas for calculating **OR, IPF**, and **APF** are shown in Figure 2.[4]

Figure 2. Definitions of **OR, IPF**, and **APF**

1. Originality Rate (**OR**)

$$\mathbf{OR} = 100 \times \frac{\text{The Number of Newly Developed Steps} + 1\ (\text{Novelty of the Synthetic Route})}{\text{Total Number of Synthetic Steps} + 1}$$

2. Intellectual Property Factor (**IPF**)

$$\mathbf{IPF} = 100 \times \frac{\left(\begin{array}{c}\text{The Number of Compound}\\ \text{Having Intellectual Property}\end{array}\right) + \left(\begin{array}{c}\text{The Number of Synthetic Steps}\\ \text{Having Intellectual Property}\end{array}\right)}{2 \times (\text{The Number of Synthetic Steps}) + 1}$$

3. Application Potential Factor (**APF**)

$$\mathbf{APF} = 100 \times \frac{\begin{array}{c}\text{The Number of Compound Having either}\\ \text{Biological Activity or Other Useful Functionality}\end{array}}{\text{The Number of Synthetic Steps} + 1}$$

OR is the ratio of the following numerator and the denominator. As the former is employed the number that added 1 to the total number of the step where a researcher applied a new reaction or a new chemical reagent that he created for the first time in the world. As the latter is used the number that added 1 to the number of the reaction steps needed for the synthesis. The numerical 1 in the numerator means the novelty of the synthetic route. When the synthetic route is known or belongs to other researcher, the numeral 1 disappears to zero, while it is left in the denominator. Since every synthetic chemist can develop his own synthetic route for the target, **OR** would be at least more than 1% and never become 0%. As evidenced by the definition, the **OR** shows the proportion of the originally developed steps to all of the synthetic steps.[2-4]

For the calculation of the **IPF**, the sum of compound and reaction step having intellectual property is

used as the numerator. While the number that added 1 to the double number of synthetic step is employed as the denominator. The **IPF** is the net rate of one's own intellectual properties involved in every reaction and every compound in the synthesis.[3,4]

APF is the sum of application potential of starting material, target compound, and all synthetic intermediates.[3,4] The numerator is the number of compound having either biological activity or other useful functions and the denominator is the number that added 1 to the number of synthetic steps.

2-2. What is an Efficient, Highly Original, and Highly Evaluated Synthesis? [1,2]

We define that an efficient, highly original, and highly evaluated synthesis is the one having high numerical value of three indexes: **OR**, **IPF**, and **APF**. In order to raise the **OR**, researchers are demanded necessary device and originality, not an accidental good luck. In this point, our concept is beyond the one called selendipity.[1,2] Reducing the use of known reaction, researchers should create the original reaction and chemical reagent for making the numerator bigger. On the other hand, to make the denominator smaller, researchers ought to shorten the synthetic step by creating new reactions, reducing the times of using protecting group, and so on.

OR demonstrates the number of the intellectual property called new discovery and/or knowledge beyond the chemical standard of each times that a researcher lived in. Therefore, it is the index that can compare the superiority or inferiority over the history. The responsibility as the creator is quite important. Through one's life, the creator can keep discovering new properties of matter, function, and pharmacological action of his compound.[1,2] Therefore, the creator should improve the numerical values of **IPF** and **APF.**

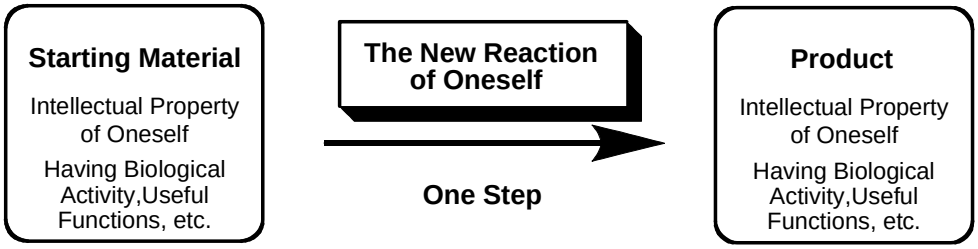
The most efficient and ultimate synthesis is the one-step synthesis as illustrated in Figure 3. In the case of a long-step synthesis, this ultimate synthesis would pile up. Therefore, the definition of waste free "ideal synthetic method" is the one: 1) the numerical values of **OR, IPF,** and **APF** are 100%, 2) every reaction employed for the synthesis is the intellectual property of the researcher, 3) every synthetic intermediate, including starting material and the target compound, has pharmacological activity or some kind of function. An efficient synthetic method is the one that has higher numerical values of **OR, IPF,** and **APF**.[1,2]

Original "synthetic philosophy" was newly born in this way. However, the severest criticism was the following: since anyone could propose only a theory, "show a concrete example". On the basis of the above philosophy, we had started challenging studies aiming at the realization of our "five dreams".

They are the development of drugs 1) for making desert green and food increase in production, 2) for cardiovascular system disease, 3) for dementia (senile dementia), 4) for lifestyle-related disease (diabetes, osteoporosis, etc.), and 5) for cancer and virus.

In order to create the concrete examples of approximately "ideal synthetic method" without waste with high **OR, IPF**, and **APF** values[1,3-5] and to achieve the above five dreams at the same time, 30 years (the time to the brink of the retirement) were necessary from the proposal of our synthetic philosophy.

Figure 3. The Ultimate Synthesis



1. Originality Rate (**OR**) = 100%
2. Intellectual Property Factor (**IPF**) = 100%
3. Application Potential Factor (**APF**) = 100%

3. A Study Aiming at Creating an Ideal Synthetic Method for Ergot Alkaloids as a Target

A lot of drugs and biologically active compounds are known among ergot alkaloids and their derivatives.[6] Therefore, we started the synthetic project for ergot alkaloids with an aim to create an example of synthetic method with high **OR** and, at the same time, to realize some of our dreams. The key point whether or not we could achieve the synthesis depends on whether we could develop new synthetic method of 4-substituted indoles which had been hardly accessible in indole chemistry.

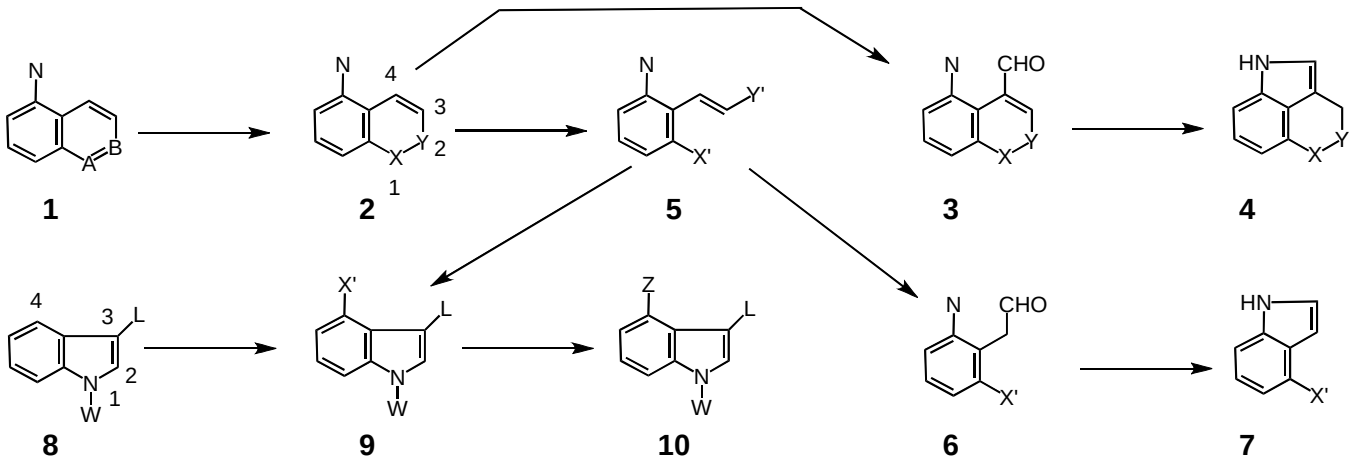
3-1. Strategy and Reality for Creating New Synthetic Methods of the 4-Substituted Indoles

Theoretical consideration suggests us three ways of strategy to create new synthetic methods for 4-substituted indoles (Scheme 1).[2a] The first strategy employs ring transformation. Utilizing the active *peri* position in the bicyclic aromatics, we can prepare the compound as shown in a general formula (**1**, N is an appropriate nitrogen containing functional group). Subsequent reduction transforms an A=B part to the X-Y group giving the dihydro-compound (**2**). For example, when Y is a nitrogen atom, an enamine structure is formed. So, the introduction of a formyl group onto the 4-position can be realized to give **3.** In the next stage, proper transformation of the N functional group would produce

3,4-disubstituted indoles (**4**).

The second strategy uses benzene derivatives. Suitably functionalized benzene derivatives (**5**) are produced initially. The compound (**5**) is provided alternatively from the intermediate (**2**) of the first strategy. Subsequent oxidation changes a styrene part into an acetaldehyde (**6**). The transformation of the N functional group into an amine equivalent spontaneously forms the pyrrole ring. As a result we can get 4-substituted indoles of type **7**. The third strategy employs the coordination chemistry of the metal. Using indoles of type **8** as a ligand in which suitable functional groups are arranged at the 1 and/or 3 positions, functionalization at the 4-position is made possible to give **9**. This compound can be provided from **5** of the second strategy. After fixing a functional group properly we can obtain 4-substituted indoles of type **10**. If we choose a suitable atom or a functional group to the respective N, A, B, X, Y, X', Y', L, and W in the general formula, and try a suitable combination in turn,[2a] we would be able to create various and a lot of new synthetic methods for the 4-substituted indoles.

Scheme 1. General Synthetic Plan for 4-Substituted Indoles



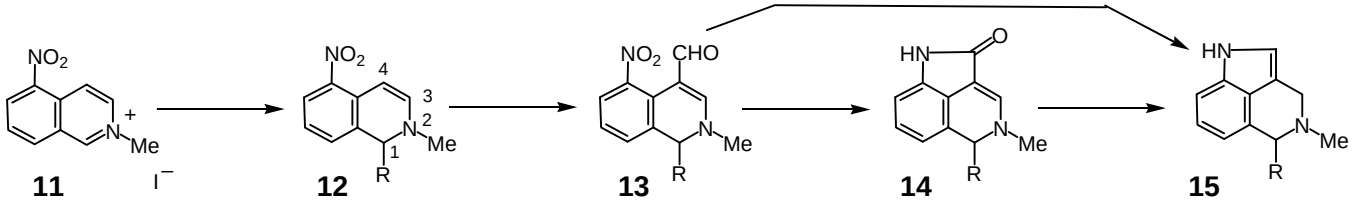
As the first concrete example, the compound (**2**) was examined where the combination of N=NO_2, X=CH_2, and Y=NMe is chosen. The initial heteroaromatic compound (**1**) is therefore 5-nitroisoquinoline. We employed 2-methyl-5-nitroisoquinolinium iodide (**11**) as a starting material (Scheme 2).

Reduction of **11** provided unstable 1,2-dihydro-compound (**12a**).[7] Application of the modified Vilsmeyer reaction successfully introduced formyl group into the 4-position, an active site of enamine part, affording a stable crystalline compound (**13a**). Subsequent treatment of **13a** with triethyl phosphite gave lactam (**14a**). It was too labile to purify and oxidized to tar during work-up. Therefore, crude lactam (**14a**) was reduced with diborane without purification culminating in the formation of **15a**. Alternatively,

high pressure catalytic hydrogenation was found to be successful for converting **13a** to **15a** in good yield.[2a]

Scheme 2. Synthesis of Pyrrolo[4,3,2-*de*]isoquinolines

a) R = H; **b**) R = CH_2COMe; **c**) R = CH_2-(2-methyl-1,3-dioxolan-2-yl)



The first strategy described in Scheme 1 worked well even in the case of the 1-substituted isoquinoline (X=CHR, Y=NMe).[7] Thus, the 1,2-dihydrocompound (**12b**) was obtained by the addition of acetone to the 1-position of **11**. Subsequent above-mentioned Vilsmeyer reaction led **12b** to **13b**. After protection of the ketone part of **13b** as a ketal group, treatment of **13c** with triethyl phosphite, followed by the reduction with diborane, produced 4-substituted indole (**15c**) through lactam (**14c**). High pressure catalytic hydrogenation of **13c** was also successful to provide 4-substituted indole (**15c**) in good yield.

As for X and Y in **2**, the respective combinations of NH, NH (1,2-dihydrocinnoline),[8] C=O, O (isocoumarin),[9] and CH_2, O (isochroman)[10] were examined culminating in the formations of 4-substituted indoles in good yields, respectively. Consequently, at one sweep as scheduled, we succeeded in creating many new synthetic methods for 4-substituted indoles as our intellectual properties. More informations including other methods are referred to our review.[2a,b]

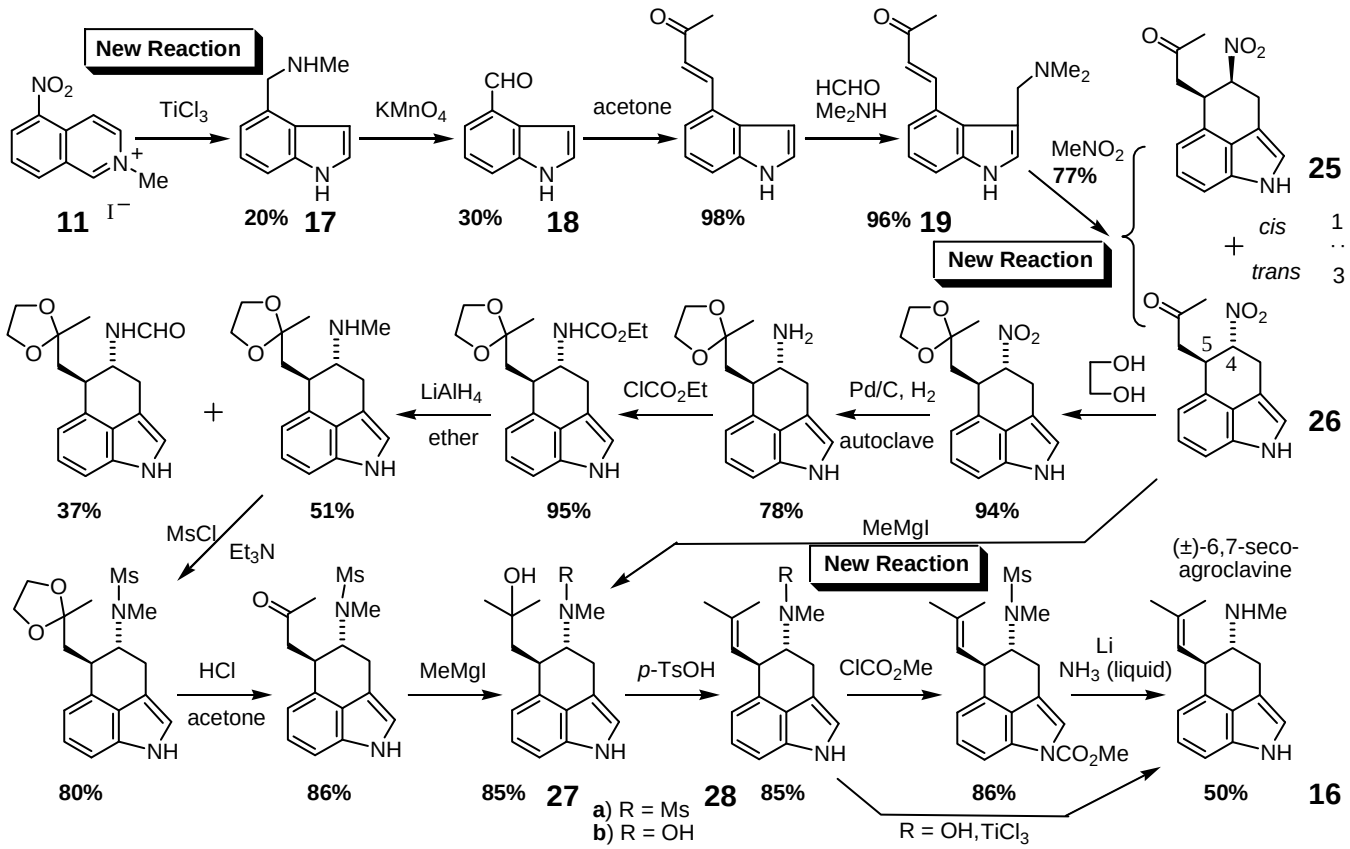
3-2. Our First Total Synthesis of 6,7-Secoagroclavine by Fifteen Steps

Ergot alkaloids' family consists of compounds having several different types of structure. For achieving total syntheses of all types of the alkaloids, we chose 6,7-secoagroclavine (**16**, Scheme 3) as a common synthetic intermediate. As the first step in the synthesis of **16**, we created a new reaction for the preparation of 4-methylaminomethylindole (**17**) from 2-methyl-5-nitroisoquinolinium iodide (**11**) by treating with titanium (III) chloride,[11] according to the first strategy shown in Scheme 1. In the second step, direct oxidation of **17** was carried out affording indole-4-carbaldehyde (**18**). Subsequent aldol reaction with acetone, followed by Mannich reaction led **18** to gramine derivative (**19**). The next step is the reaction of **19** with nitromethane.

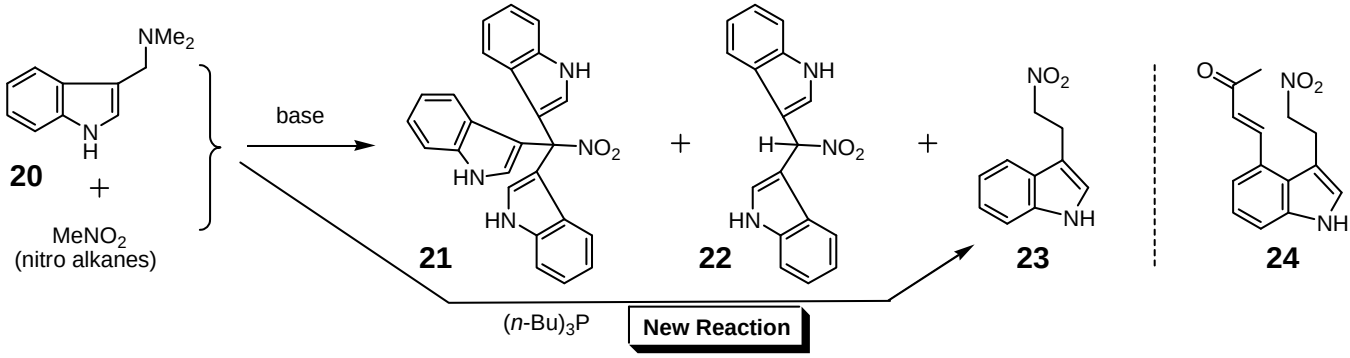
Generally speaking, the reaction of gramine (**20**) with nitroalkanes generated trimer (**21**) and dimer (**22**)

as shown in Scheme 4. No one achieved the selective production of monosubstituted nitroalkanes (**23**) in those days. We needed only gramine (**24**) corresponding to **23** and examined various attempts in search of the objective reaction. Finally we conceived the idea to utilize the coordination chemistry and the basicity of the phosphorus atom. As a result, we could create the new reaction with tri-*n*-butylphosphine as a catalyst to attain the predominant synthesis of **23**.[12] Later, this new reaction is used widely for the total synthesis of indolic natural product.

Scheme 3. Our Initial Synthesis of (±)-6,7-Secoagroclavine
15 Steps: **OR** = 3/16 = 19%



Scheme 4. Reaction of Gramine with Nitroalkanes



The above reaction was applied to the reaction of **19** with nitromethane. As expected, **19** generated **24**

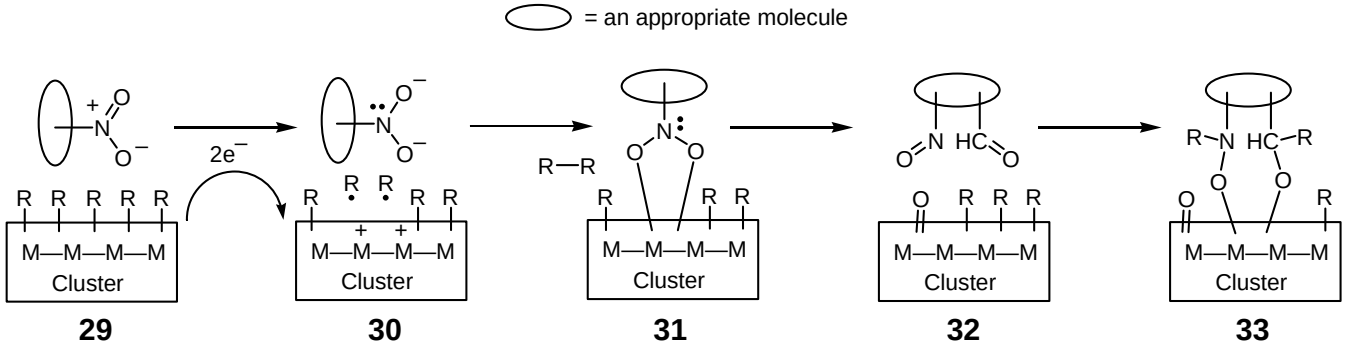
selectively as an intermediate and subsequent ring closure occurred simultaneously to give a 1:3 mixture of 4,5-*cis*- (**25**) and 4,5-*trans*-1,3,4,5-tetrahydrobenz[*cd*]indoles (**26**).[13] After application of a series of known reactions to **26**, we achieved our first total synthesis of (±)-6,7-secoagroclavine (**16**) through **27a** and **28a**.[12] This synthetic method requires 15 steps from **11** to **16** and includes two our reactions. Therefore, **OR** of this synthesis is calculated to be 100x(2+1)/(15+1)=19%.

3-3. Total Synthesis of 6,7-Secoagroclavine by Eight Steps

We were not able to be satisfied with the **OR** of the synthetic method shown in Scheme 3. In addition, from a standpoint as a critic we do not feel brilliance and creativity about the seven steps reaching **27a** from **26**. Moreover protection groups are used twice. Consequently protection and deprotection steps necessarily make the synthetic steps long. Six steps can be shortened at one sweep and **OR** rises high if we can create the short cut that can convert **26** into **27a** by one step.

On the basis of this idea, we transformed the target (**27a**) to the synthetic equivalent (**27b**). If we could imagine electron surplus organometalic cluster (**29**) in close vicinity of a nitro compound as shown in Scheme 5, the nitro group easily receives electrons and the substrate would be reduced to a nitroso compound (**32**) through **30** and **31**. In case where the substrate has both nitroso and carbonyl groups in a molecule at the same time, alkyl group of **29** could add to them resulting in the formation of the expected **33** (namely **27b**).

Scheme 5. Design for New Introduction of Alkyl Group to Nitroalkanes



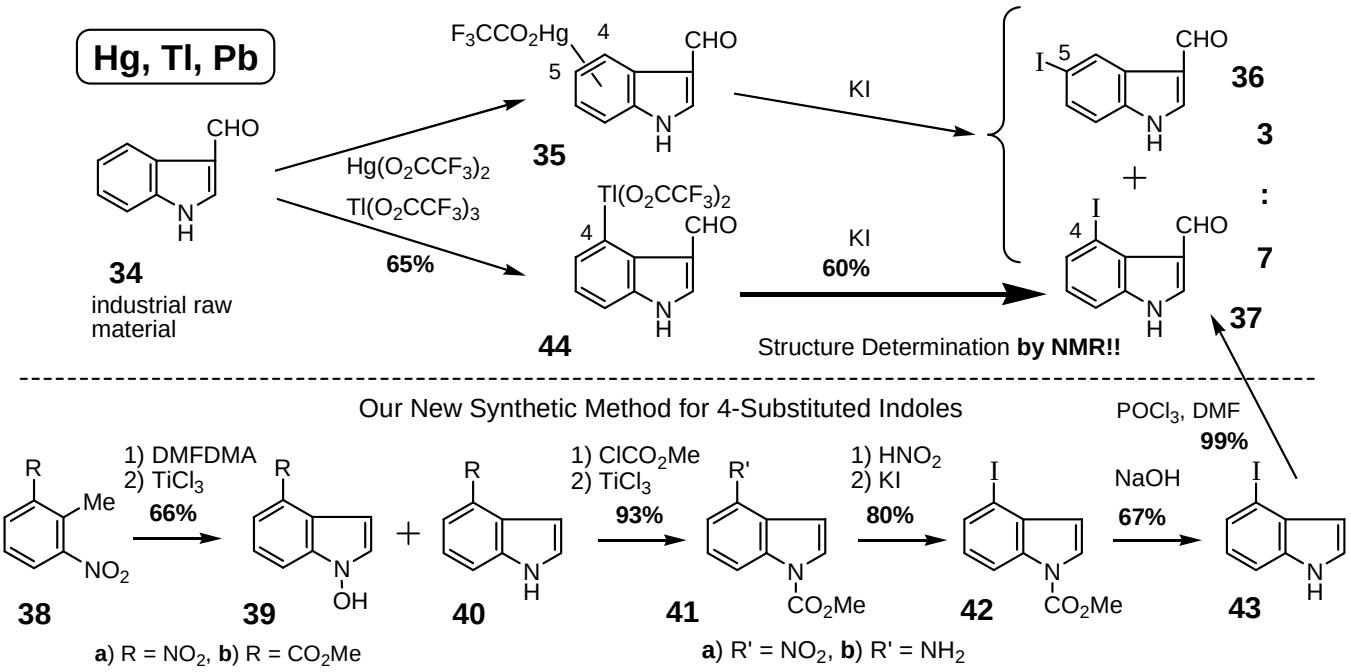
We chose Grignard reagent among various candidates of organometalic cluster (**29**), which is imagined to have both ability to generate methyl anion and to reduce the nitro group. After having repeated trials, we succeeded in discovering that 30－50 times of excess methylmagnesium iodide worked well as we expected, resulting in the formation of about 15% yield of **27b**.[14] Subsequent dehydration, followed by

the reduction of the resultant hydroxylamine (**28b**) with titanium (III) chloride provided **16**. Thus, an eight-step synthetic method was completed. Because an extra new reaction makes it possible to shorten the fifteen steps to eight steps, the **OR** of this synthetic method is 100x(3+1)/(8+1)=44%. In addition, **IPF** became 100x(4+3)/(2x8+1)=41% realizing a good level because **19**, **25** (and **26**), **27b**, **28b** were our compounds. However, **APF** was still low and this is the reason why we were not satisfied with this synthetic method either.

3-4. More Efficient Total Synthesis of 6,7-Secoagroclavine by Seven Steps

Creation of the new reaction suitable for meeting the purpose is necessary for making the synthetic step short. According to the third strategy (a metal coordination chemistry) in Scheme 1, we tried various reactions on the industrial raw material (**34**, Scheme 6) as one of the candidate of **8** and finally succeeded in discovering the desired reaction. Thus, the reaction of **34** with mercury (II) trifluoroacetate generated organomercuric compound (**35**). Without purification, the crude **35** was treated with olefins in the presence of Pd catalyst to give the corresponding 4- and 5-substituted indoles. When the crude **35** was treated with potassium iodide, a 3:7 mixture of 5-iodo- (**36**) and 4-iodoindole-3-carbaldehydes (**37**) were produced.[15]

Scheme 6. Synthesis of 4-Substituted Indoles by Metalation



We had to create authentic **37**, however, by a reliable alternative synthetic method to get the evidence

that **37** has the correct 4-substituted indole structure. According to the second strategy in Scheme 1, we selected 2,6-dinitrotoluene (**38a**) as a concrete candidate of **5**. Treatment of **38a** with dimethylformamide dimethyl acetal, followed by the reduction with 6 mol eq. of titanium (III) chloride, which is one electronic reducing agent, provided 4-nitroindole (**40**) in good yield.[16a,b] When 4 mol eq. of titanium (III) chloride was employed at the reduction step, we were able to get 1-hydroxy-4-nitroindole (**39a**) as main product.[16a] Similarly, **39b** and **40b** were produced when starting material was changed to **38b**.

By the way, nobody succeeded in the production of useful chemicals upon the reaction of 3-nonsubstituted aminoindoles with nitrous acid. Diazotization of them generated only tars so far and the attempt was believed to be a taboo in the indole chemistry. To overcome the problem, we tried to lower the electron density at the 3-position and to regulate the reactivity introducing electron withdrawing group into the 1-position (indole nitrogen). Thus, **40a** was converted to **41a** and then reduced to **41b**. By modifying the operation of the Sandmeyer reaction with potassium iodide, we succeeded in diazotization of 4-aminoindole (**41b**) to produce 1-substituted 4-iodoindole (**42**) in high yield.[16b] Afterwards this diazotization reaction is used often by synthetic chemists in the indole chemistry.

Alkaline hydrolysis of **42** afforded 4-iodoindole (**43**). Subsequent Vilsmeyer reaction produced the desired authentic sample of 4-iodoindole-3-carbaldehyde (**37**). This authentic sample was identical with **37** obtained by the reaction with mercury (II) trifluoroacetate.[16a,b]

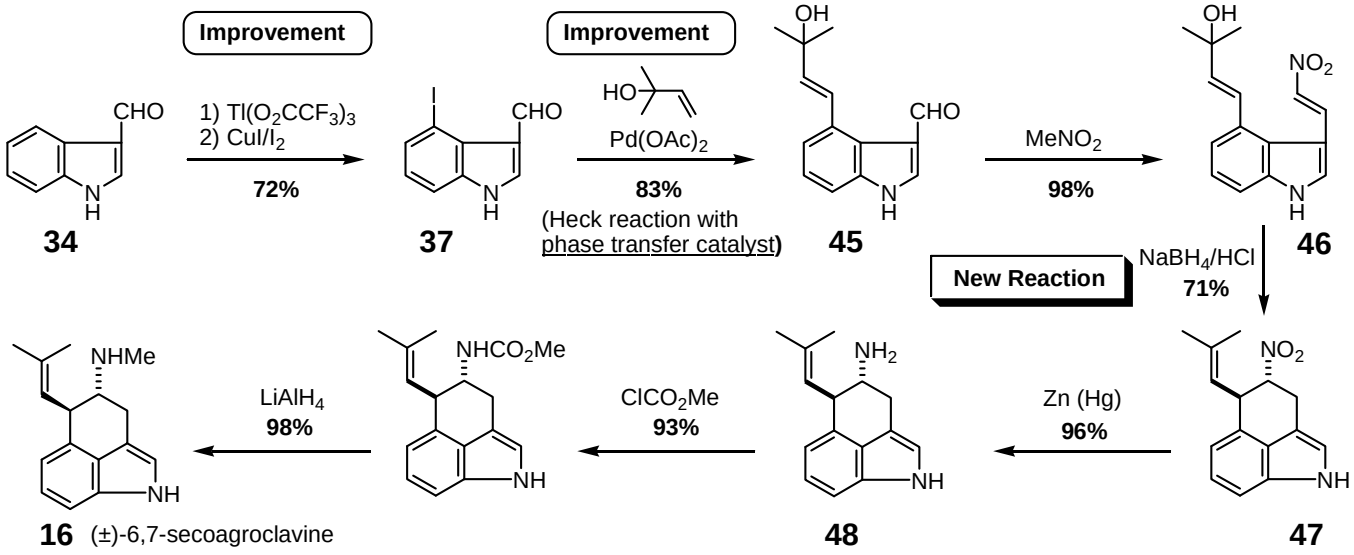
In inorganic chemistry, Hg, Tl, and Pb are well known to have similar properties. Since we found new synthetic method for 4-substituted indoles employing Hg chemistry, we next planned to examine Tl and Pb chemistry.

One day in a journal of the current issue, we found the report by Hollins' group that the compound (**37**) was regioselectively produced from **34** by the reaction of (3-formylindol-4-yl)thallium bis(trifluoroacetate) (**44**) with potassium iodide (KI) in an overall yield of 39%.[17] We were disappointed very much because we were not the first creator of **37**. To our surprise, however, their structure determination is merely based on the NMR spectral data. In those days, synthesis of 4-substituted indoles was difficult as stated thus far in this review. Therefore they could not identify by comparing their compound with the authentic sample, leaving a slight possibility to be a 7-substituted indole. We did a supplementary examination of their method. We then compared their product (**37**) with our authentic sample and could determine the structure, unequivocally. Furthermore, we found that when a combination of copper (I) iodide and iodine, instead of KI, was employed to the reaction of **44,** the iodination occurred quantitatively. Consequently we were able to improve Hollins' reaction and provide

37 in 72% overall yield from **34**.[18]

Applying the improved Hollins' reaction, we were able to establish a practical total synthetic method of 6,7-secoagroclavine (**16**) in seven steps as shown in Scheme 7. It is worthy to note that in this synthetic method, we do not use any protective group at all. This is the first example based on the concept called "total synthesis without using the protective group".[19] In addition, we improved Heck reaction employing a phase transfer catalyst[20] in the synthesis of **45** from **37**. Furthermore, a new ring closure reaction of **46** to **47** is invented by the addition of $NaBH_4$ into a MeOH solution of **46**, followed by the dripping of the resultant reaction mixture into an aqueous HCl. Consequently, **OR** of this synthetic method is 100x(1+1)/(7+1)=25%.

Scheme 7: Seven-Step Synthesis of (±)-6,7-Secoagroclavine
Overall Yield: 36%; **OR** = 2/8 = 25%



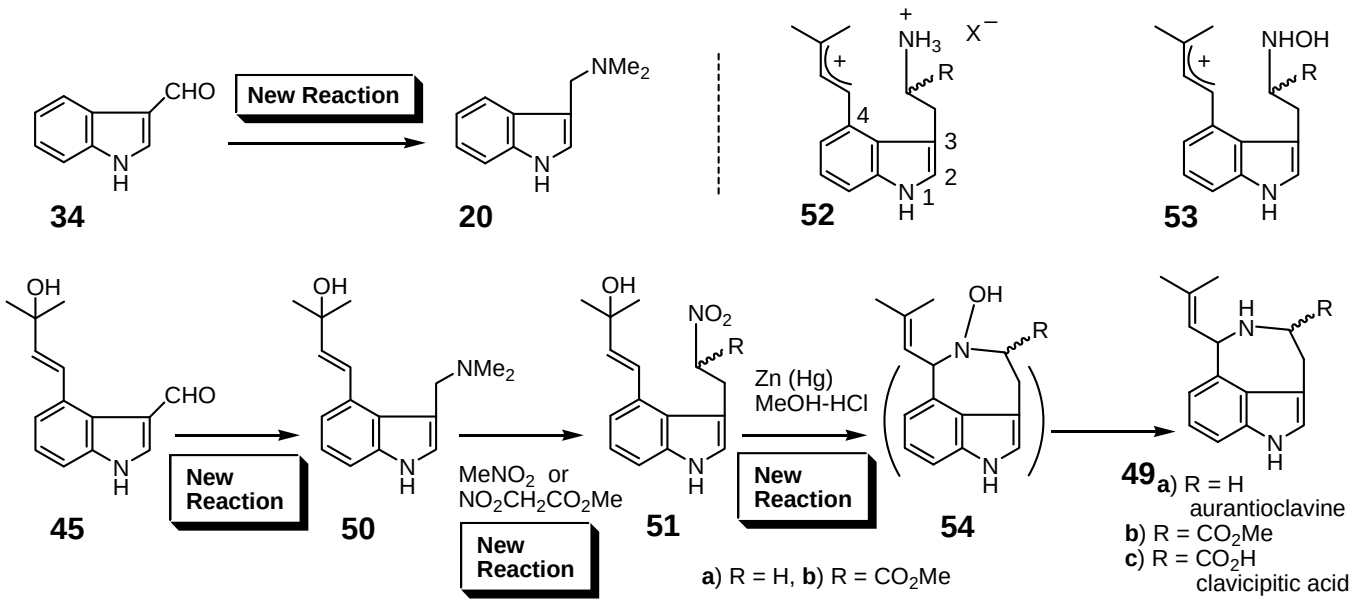
On the other hand, Kamuro brought us a report stating that the compound (**37**), originated from diazonium salt of **41b**, has strong plant growth stimulation effect.[19] Watanabe reported us that **48** and its *N*-alkyl derivatives are dopamine agonists.[19] Since we found that **37** and **48** have useful pharmacological activities, values of **APF** and **IPF** are 100x2/(7+1)=25% and 100x1/(2x7+1)=7%, respectively. As a result, we could demonstrate the substantial example of three indexes of our synthetic philosophy.

3-5. Total Synthesis of Aurantioclavine and Clavicipitic Acid Having Seven Membered Ring Structure

Total syntheses of aurantioclavine[20a,b] (**49a**) and clavicipitic acid[21] (**49c**), belonging to ergot alkaloids

having seven membered ring structure, were achieved by the following synthetic method with high **OR** as shown in Scheme 8. As the first step we created new reaction to change indole-3-carbaldehyde (**34**) into gramine (**20**) by one step.[22] Application of the reaction to the 3-formyl group of **45** afforded gramine (**50**). The second step is our reaction as well. Thus, treatment of **50** with nitromethane and methyl 2-nitroacetate in the presence of tri-*n*-butylphosphine catalyst provided **51a** and **51b** in good yields, respectively.

Scheme 8. Synthesis of Aurantioclavine and Clavicipitic Acid



Next we designed a new reaction to get the alkaloids (**49a,b**) having seven membered ring by generating a stable cation on the side chain at the 4-position of **51a** and **51b**, followed by simultaneous reduction of nitro group in an acidic condition. When the nitro group is reduced to the amine stage, rapid protonation is expected to occur giving **52** and the amine loses its nucleophilic character resulting in the failure of ring formation. If a reducing agent promise a long lifetime of the hydroxylamine stage, a desirable synthetic intermediate (**53**) generates, and the formation of seven membered ring is expected. Based on this idea, we tried reducing agents in various ways on **51**. As a result, we found that amalgamated zinc/HCl is a reagent of choice to produce **49a** and **49b** in good yields, respectively, through the respective unstable **54a** and **54b**. The conversion of **49b** to clavicipitic acid (**49c**) was already achieved by late Natsume group.[23]

3-6. New Synthetic Methods for the 4-Substituted Indoles Based on the Metal Exchange

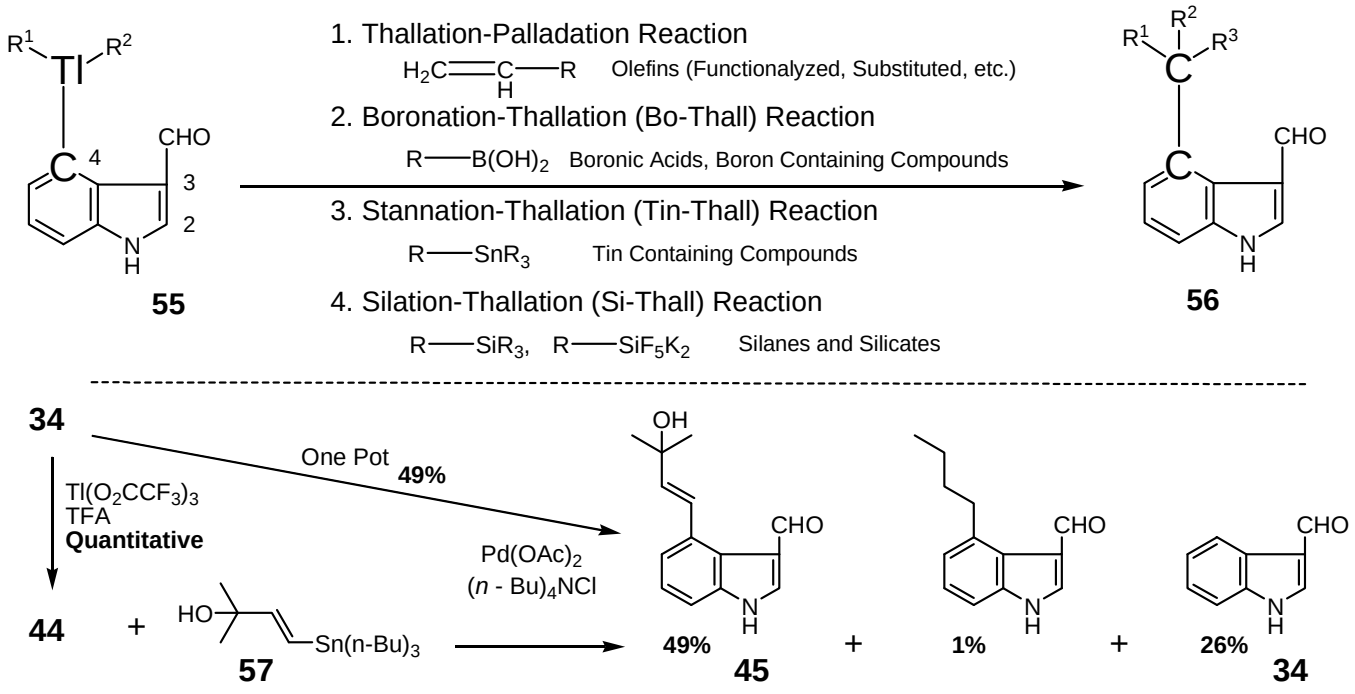
Mechanism[2b]

To raise the **OR**, we conceived the idea to get a product of **56** type by converting the C—Tl bond of the thallium compound (**55** type) into C—C bond directly (Scheme 9). Palladium catalyzed reaction such as Heck reaction, Stille reaction, etc. were reported and their reaction mechanisms were suggested in the literatures. We imagined a totally different mechanism in which metals in the carbon-metal bond could exchange freely among thallium, palladium, and other metals.

In fact, we could create the desired C—C bond forming reactions as imagined by reacting **55** with organometals in the presence of palladium catalyst as shown in Scheme 9.[24] We called the palladium catalyzed reaction of thallium compound (**55**) with olefins producing **56** "thallation-palladation reaction".[25] Similarly, we named the palladium catalyzed reaction of **55** with boron reagents, tin reagents, and silicon reagents boronation-thallation (bo-thall) reaction,[26] stannation-thallation (tin-thall reaction) ,[27] and silation-thallation (si-thall reaction),[28] respectively.

Scheme 9: New Methods for C—C Bond Formation

R, R^{1-3}: an appropriate substituent

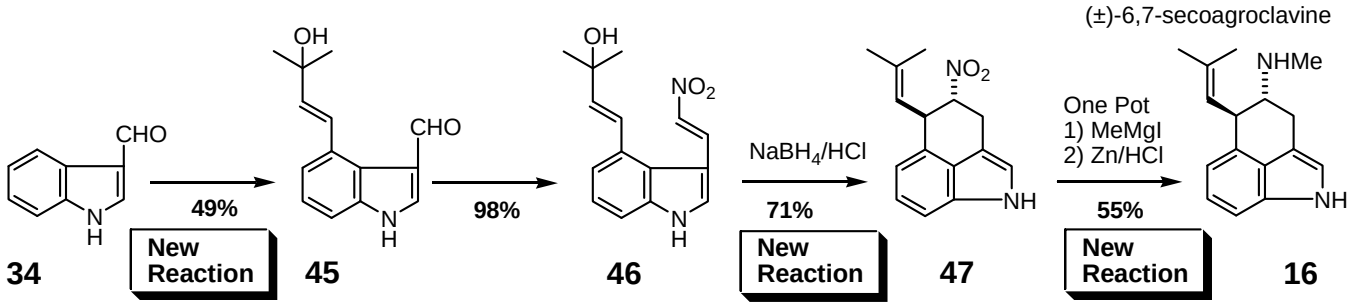


3-7. Four-Step and Approximately Ideal Synthetic Method of 6,7-Secoagroclavine: The Shortest Synthesis in the World

We could create various new synthetic methods for 4-substituted indoles based on the metal exchange mechanism as planned in the third strategy in Scheme 1. We decided to apply the tin-thall reaction as the

first step to the total synthesis of 6,7-secoagroclavine for establishing an efficient and highly original synthesis. When the compound (**44**) was reacted with tin reagent (**57**, Scheme 9) the successful production of **45** was observed in 49% yield. The isolation of **44** was not necessary. After evaporation of the solvent of the reaction mixture of **34** with thallium (III) trifluoroacetate, the resultant residue was reacted with **57**. This convenient one-pot tin-thall reaction worked well and the overall yield was 49% as well (Scheme 10).

Scheme 10. Four-Step Synthesis of (±)-6,7-Secoagroclavine
Overall Yield = 19%. **OR** = 4/5 = 80%



In the fourth step (Scheme 10), we applied new Grignard reaction to **47**, which was developed in the transformation of **26** → **27b** (Scheme 3). Without isolating the resultant methyl hydroxylamine derivative, the reaction mixture was treated immediately with Zn/HCl. This new one-pot reductive Grignard reaction produced the desired methylamine (**16**).[29] As a result, we succeeded in shortening the total synthesis of 6,7-secoagroclavine (**16**) to four steps from **34**. This means the birth of the shortest and efficient synthetic method of **16** approximately without waste.[29]

Among the four steps, our intellectual properties are accumulated in three steps. Therefore, **OR** is 100x(3+1)/(4+1)=80% which is close to an ideal. Since **16** became readily available, it is no more synthetic target. It is now a raw material of the derivative synthesis for the drug development. We therefore introduced various substituent into *N*(6) of **16**, and produced various derivatives for the structure-activity relationship study. Although biological activity of **16** was not reported, we have newly found that **16** and its derivatives are potent dopamine agonist.[30] Accordingly, **APF** is 100x1/(4+1)=20%, while **IPF** becomes 100x(3+1)/(2x4+1)=44%.

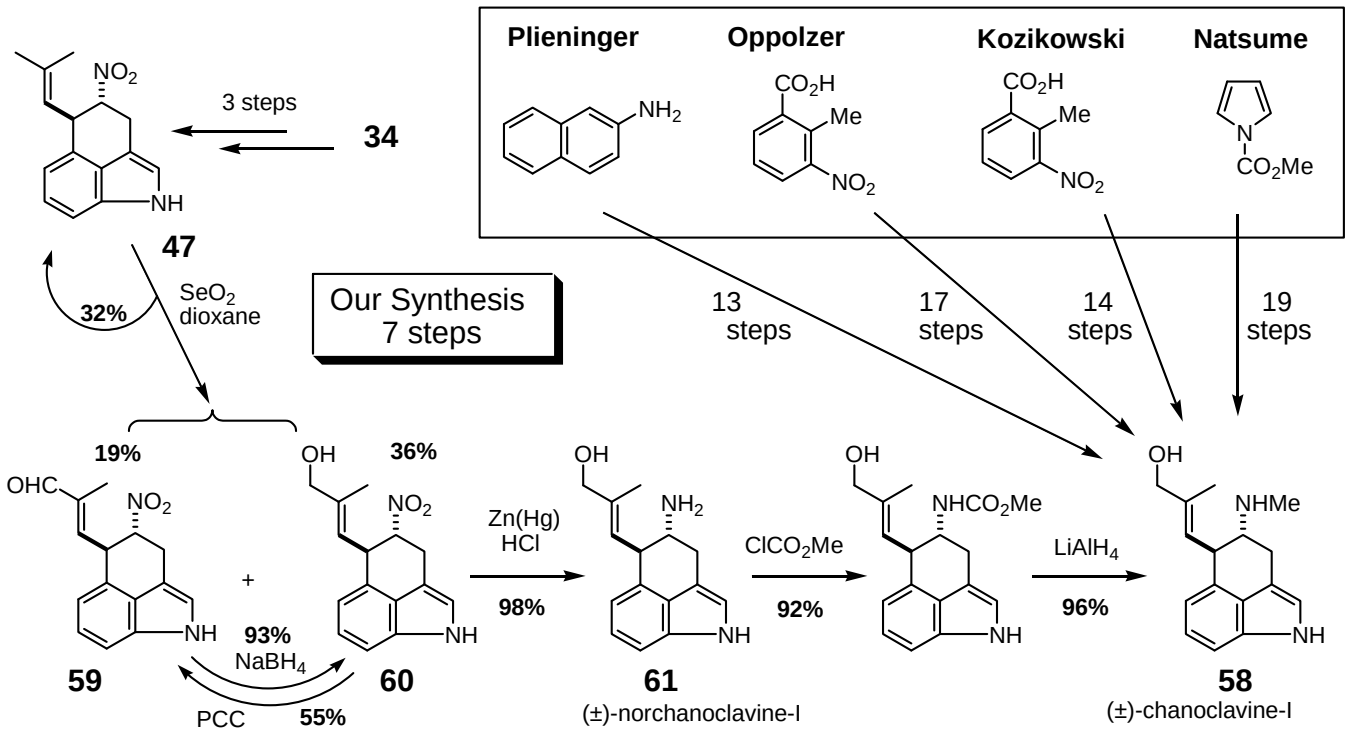
3-8. Highly Efficient Total Synthesis of Chanoclavine-I

Total synthesis of chanoclavine-I (**58**) had been reported untill the late 1980s by four groups as shown in

Scheme 11. Plieninger group[31] achieved its total synthesis by 13 steps from 2-aminonaphthalene. Oppolzer[32] and Kozikowski[33] groups utilized 2-methyl-3-nitrobenzoic acid as the starting material and they elaborated the total synthesis in 17 and 14 steps, respectively. In addition, late Natsume group[34] accomplished 19-step synthesis from 1-methoxycarbonylpyrrole.

With **47** in hand in 3 steps from bulk chemical (**34**), we tried the oxidation of isobutenyl side chain at the 4-position of **47** with selenium dioxide. The resultant aldehyde (**59**) and alcohol (**60**) were interconverted easily. Subsequent reduction of **60**, followed by the conventional two-step reaction, resulted in the total synthesis of chanoclavine-I (**58**) through norchanoclavine-I (**61**).[35] Thus, seven-step synthesis of **58** from **34** was established. The **OR** of the synthesis is 100x (2+1)/(7+1)=38%.

Scheme11. Comparison of Total Synthesis of Ergot Alkaloids, (±)-Chanoclavine-I

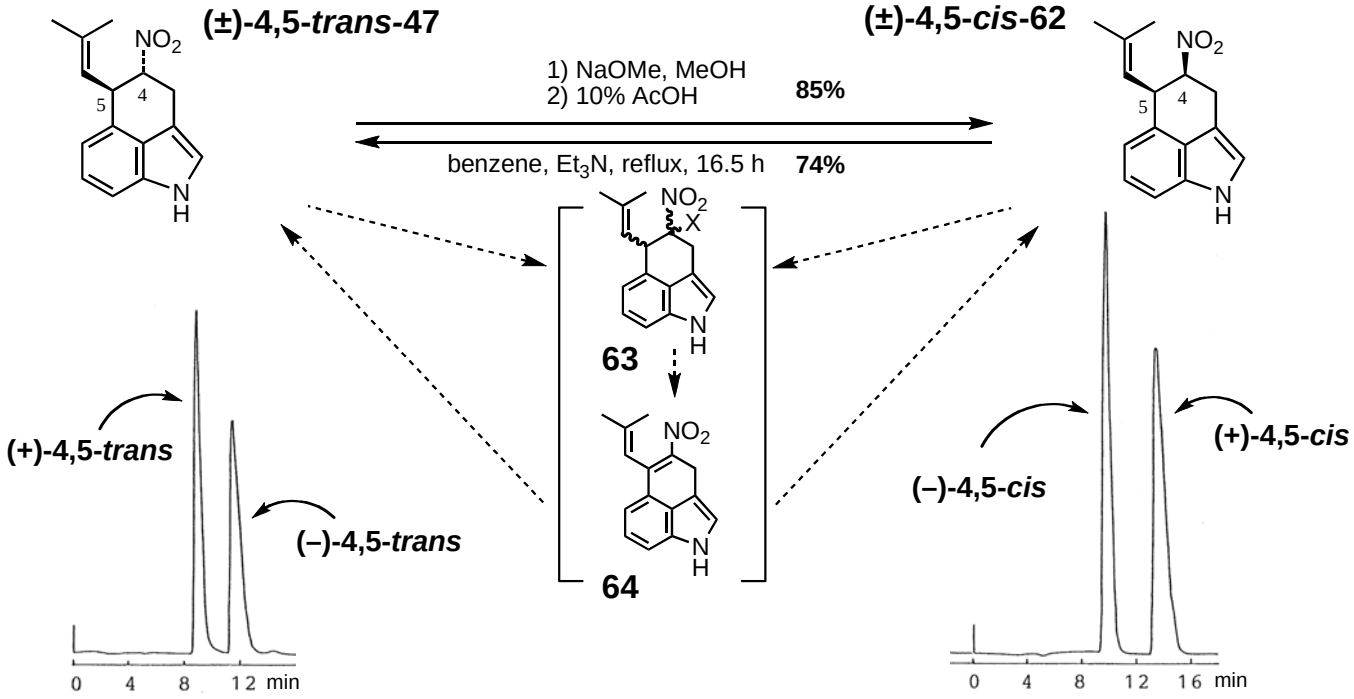


3-9. Development of an Efficient and Common Synthetic Method for All Types of Optically Active Ergot alkaloids

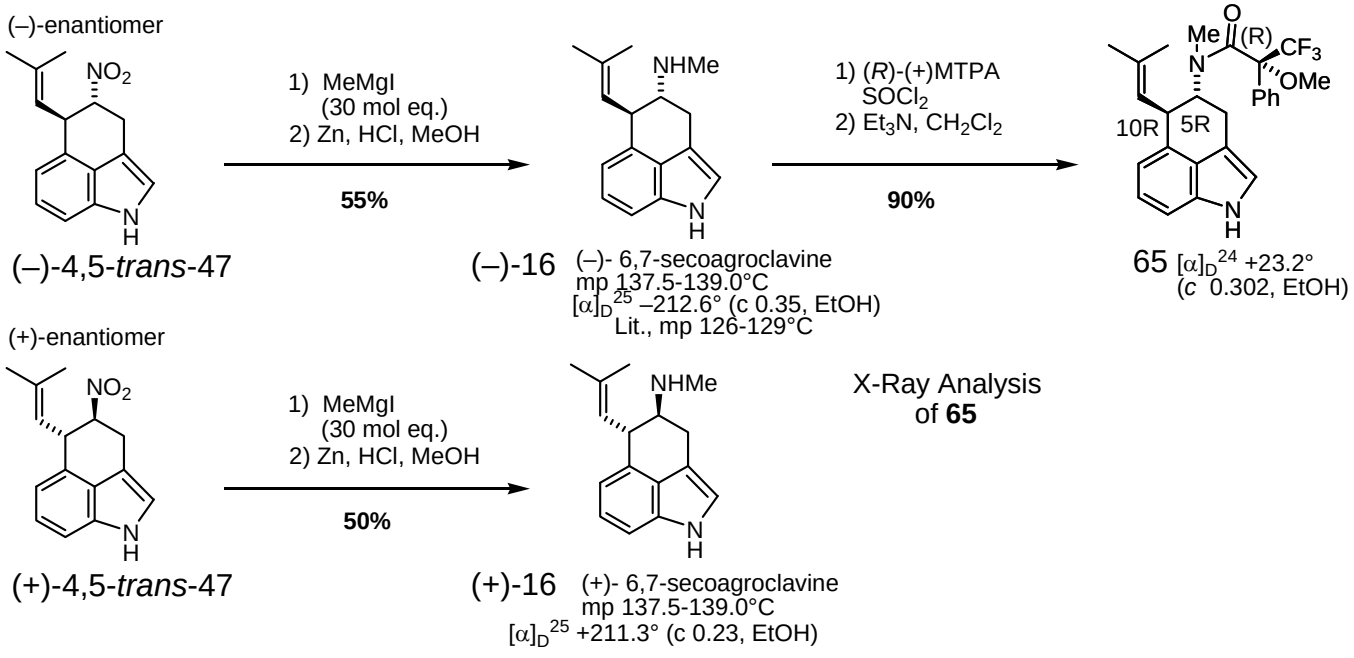
If we could employ optically active 4,5-*trans*- and 4,5-*cis*-compounds, **47** and **62**, respectively, as common synthetic intermediates (Scheme 12), we would be able to develop an efficient and common synthetic method for all types of optically active ergot alkaloids. Based on the idea, we first found the reaction conditions for the interconversion of (±)-4,5-*trans*-**47** and (±)-4,5-*cis*-**62**. Examination of the optical resolution of each compound was then carried out with a Chiralpak AS column of Daicel

Chemical Ind. Ltd. As the separation patterns are shown in Scheme 12, we could find the conditions to give base line resolution of optically active isomers for both (±)-4,5-*trans*-**47** and (±)-4,5-*cis*-**62**.

Scheme 12. Chemical Conversion and Optical Resolution of 5-(2-Methyl-1-propen-1-yl)-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indoles by HPLC (Chiralpak AS, Daicel)



Scheme 13. The First Total Syntheses of (–)- and (+)-6,7-Secoagroclavine and Its Absolute Configulation

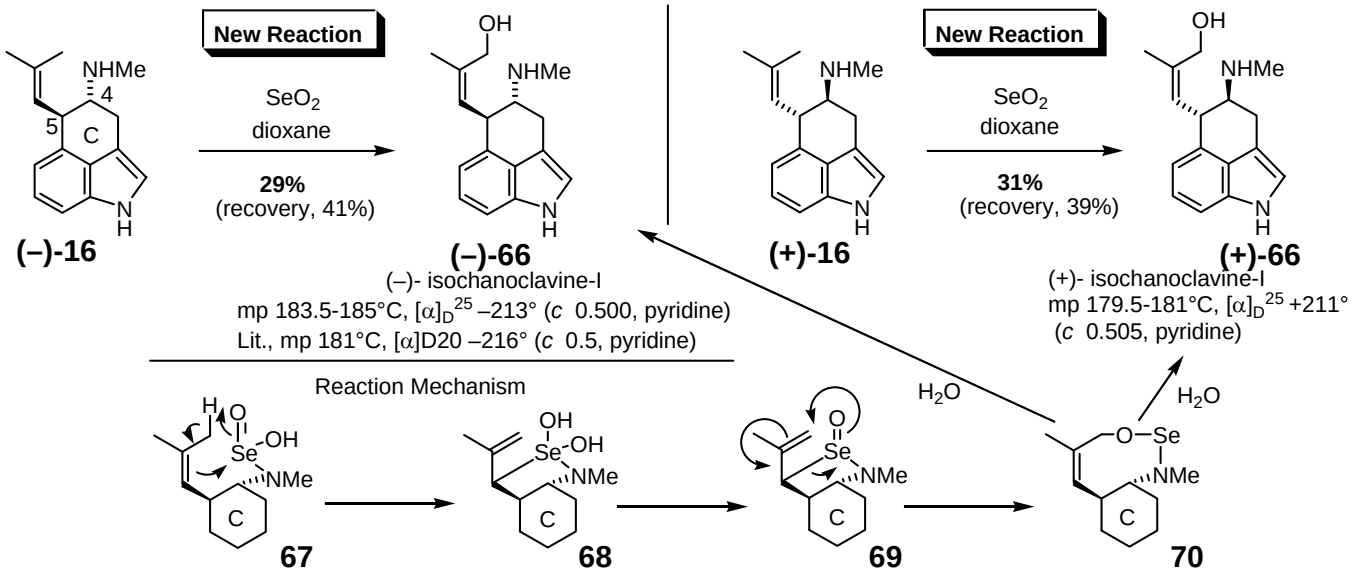


Furthermore, employing preparative chiral column chromatography, a large quantity of (–)-4,5-*trans*-**47**,

(+)-4,5-*trans*-**47**, (–)-4,5-*cis*-**62**, and (+)-4,5-*cis*-**62** were obtained.[36] In addition, we had a plan for making possible the interconversion among optically active isomers. Thus, once the compound (**63**) is produced from **47** and **62**, subsequent elimination of HX introduces double bond into the 4,5-positions to give **64**. Subsequent partial reduction or enantioselective reduction would return it to **47** and **62** or their optical isomers. However, at present, this plan is not examined because of my retirement.

We then determined the absolute structure of the natural product, (–)-6,7-secoagroclavine ((–)-**16**) as shown in Scheme 13. Thus, one-pot reductive Grignard reaction was applied to (–)-4,5-*trans*-**47** and (+)-4,5-*trans*-**47** to provide (–)- ((–)-**16**) and (+)-6,7-secoagroclavine ((+)-**16**), respectively. Subsequent reaction of (–)-**16** with (*R*)-(+)-MTPA yielded crystalline (+)-**65** which was suitable for the X-ray single crystal analysis and the results are shown in Scheme 13. The absolute configuration of (+)-MTPA is known to be *R*. Therefore, the absolute configurations thus far unknown at the 5 and 10 positions of natural product[37] are determined for the first time to be *R* configurations each.[36]

Scheme 14. The First Total Syntheses of (–)- and (+)-Isochanoclavine-I



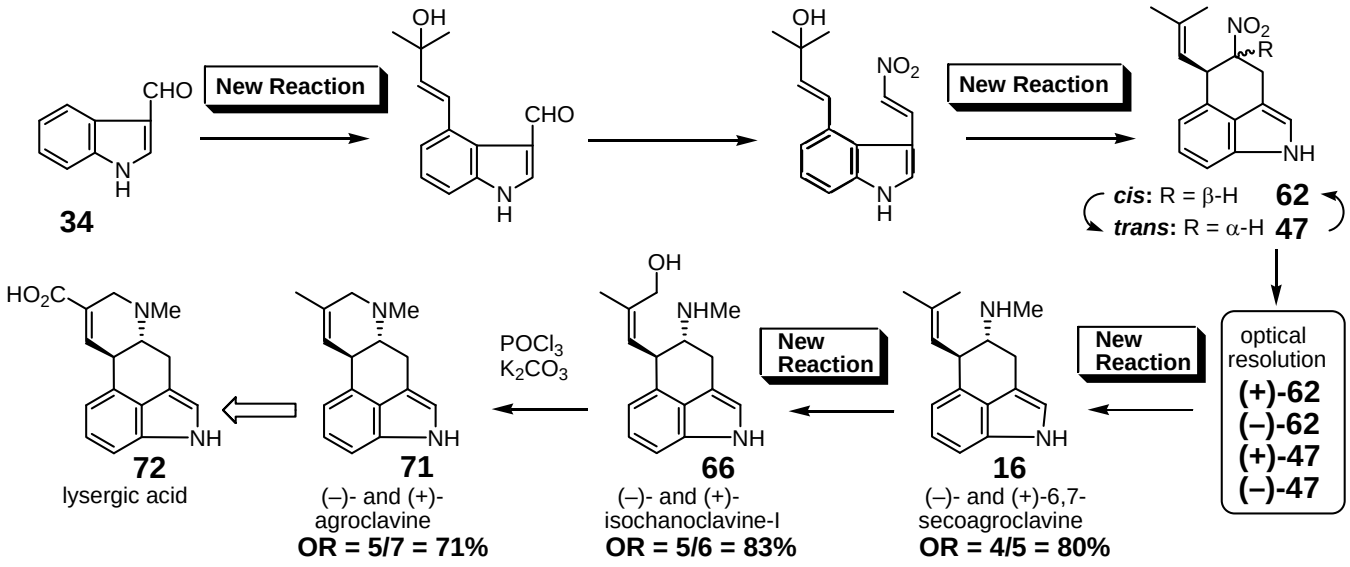
Total synthesis of (–)- ((–)-**66**) and (+)-isochanoclavine-I[38] ((+)-**66**) were achieved by merely reacting (–)-**16** and (+)-**16** with selenium dioxide, respectively (Scheme 14). This new reaction was designed to form an intermediate (**67**) relied upon the coordination effect of the 4-methylamino group of **16** to selenium dioxide. The reaction probably proceeds as planned by the reaction mechanism passing through intermediates, **68**, **69**, and **70** from **67.**

In the next step as shown in Scheme 15, (–)- ((–)-**66**) and (+)-isochanoclavine-I ((+)-**66**) were reacted

with phosphorus oxychloride in the presence of base. As a result, syntheses of both (–)- ((–)-**71**) and (+)-agroclavine ((+)-**71**) were achieved successfully.[39]

Above-mentioned various reactions were successfully applied to every corresponding 4,5-*cis*-compound: such as (±)-, (–)-, and (+)-4,5-*cis*-**62**. Accordingly, total syntheses of chanoclavine-II, isochanoclavine-II, and agroclavine-I, which are ergot alkaloids belonging to 4,5-*cis* family, were achieved as (±)-,[2b,40] (–)-, and (+)-isomers, at one's will.[39]

Scheme 15: The First and Simple Total Syntheses of Ergot Alkaloids, (–)-6,7-seco-agroclavine, (–)-Isochanoclavine-I and (–)-Agroclavine, and Their (+)-Enantiomers



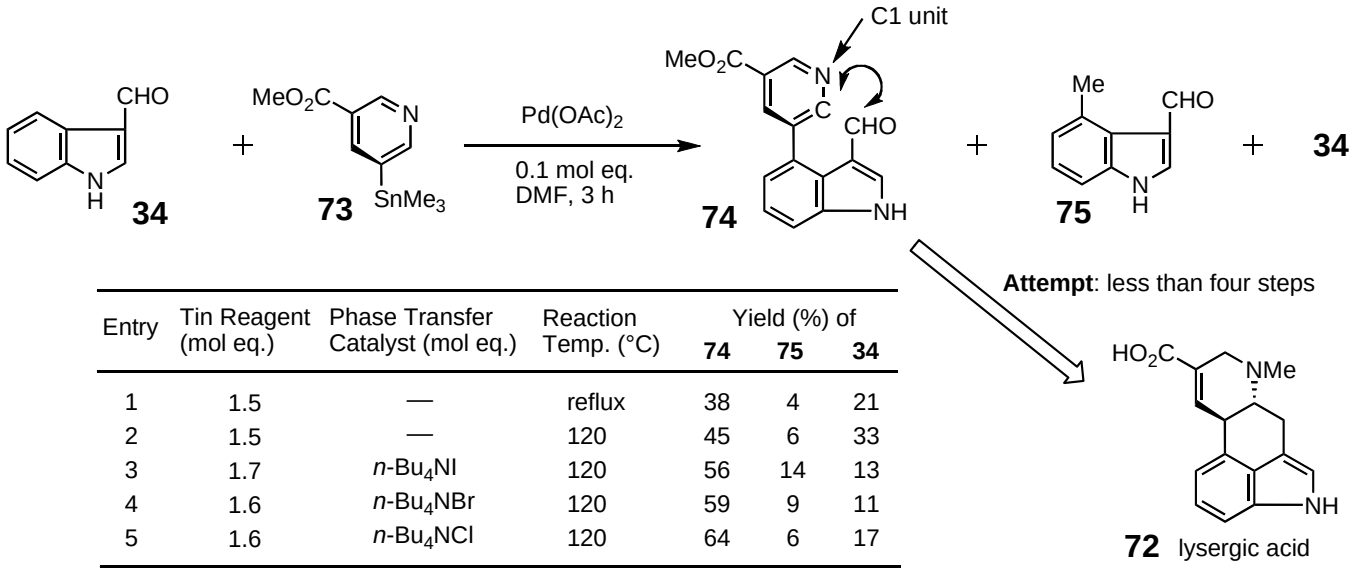
In this way we succeeded in establishment of the efficient and common total synthetic method for ergot alkaloids from **34** as summarized in Scheme 15. Large quantities of four kinds of optically active isomers of **47** and **62** are available by the preparative chiral chromatography. Then, using conventional reagents and employing common route without any protective groups, (–)- and (+)-isomers of **16**, **66**, and **71** and their corresponding 4,5-*cis*-family compounds are now available.[41] Regardless of *trans*, *cis*, and optically active isomers, **ORs** of **16**, **66**, and **71** are 80, 83, and 71%, respectively.

We could not be satisfied with this synthetic method because the synthesis of agroclavine (**71**), one of the tetracyclic ergot alkaloids, required still 7 steps from **34**. For lysergic acid (**72**) synthesis, extra 2 steps would be predicted. For starting a study for drug development with tetracyclic ergot alkaloid as a raw material, we must devise a new reaction to further shorten the synthetic steps.

In the tin-thall reaction of **34** as shown in Scheme 16, we employed **73** as a tin reagent which has a suitable pyridine nucleus.[42] After trials we found the reaction conditions to obtain the desired product

(**74**) from **34** in good yield accompanied by **75**.[39] It is interesting to note that when a phase transfer catalyst was employed as an additive, the yield of **74** was greatly improved as shown in the Table. This phenomenon is observed in the improved Heck reaction as mentioned before.[20] Compound (**74**) has all atoms needed to build the target (**72**) except one carbon atom. The problem left unfinished is the C—C bond formation between the 3-formyl group and the 2-position of pyridine nucleus, introducing one carbon onto the nitrogen of pyridine. Once the desired reaction is realized, tetracyclic ergot alkaloids would be available within 4 steps from **34** and we believe a lot of biologically active compounds will be waiting for us.

Scheme 16. Synthesis of Methyl 5-(3-Formylindol-4-yl)nicotinate



Entry	Tin Reagent (mol eq.)	Phase Transfer Catalyst (mol eq.)	Reaction Temp. (°C)	Yield (%) of **74**	**75**	**34**
1	1.5	—	reflux	38	4	21
2	1.5	—	120	45	6	33
3	1.7	*n*-Bu_4NI	120	56	14	13
4	1.6	*n*-Bu_4NBr	120	59	9	11
5	1.6	*n*-Bu_4NCl	120	64	6	17

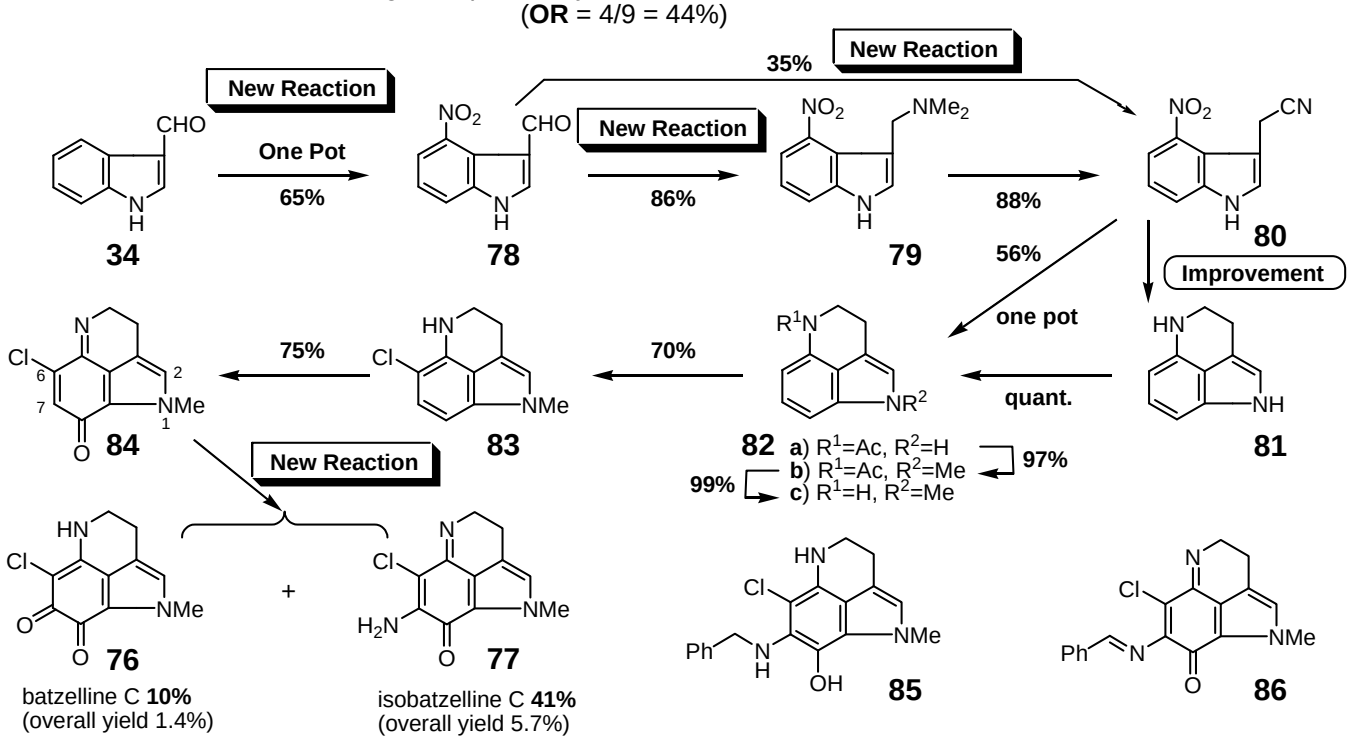
4. Total synthesis of Marine Alkaloid with High OR

With two purposes to realize our dream and to demonstrate more examples of the concept named originality rate (**OR**), we chose batzelline C[44] (**76**) and isobatzelline C[44] (**77**) (Scheme 17) as target compounds. These are members of biologically active marine alkaloid having 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline as a common skeleton.

At first we created a group of new reaction to convert the C—Tl bond at the 4-position of the thallium compound (**44**) into both a C—O and a C—N bond, at one's will.[45] Employing this new reaction, 4-nitroindole-3-carbaldehyde (**78**) was obtained from **34** in 65% yield in one-pot. Subsequently our new reaction,[22] converting indole-3-carbaldehyde into gramine, was applied to **78** resulting in the formation of 3-dimethylaminomethyl-4-nitroindole (**79**).

After leading **79** to 4-nitroindole-3-acetonitrile (**80**), we tried a catalytic reduction according to Hester's reaction conditions[46] in order to get 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**81**), but in our hand it was failure. By improving the reduction conditions to carry out under high pressure with heating, the desired **81** was obtained in good yield.[43] Subsequent treatment of **81** with acetic anhydride afforded **82a**. We challenged to develop new reaction for converting indole-3-carbaldehyde into indole-3-acetonitrile in one pot in order to shorten the reaction step, and succeeded in the creation of the desired reaction.[22] Application of the reaction to **78** produced **80**. Subsequent high pressure and high temperature catalytic hydrogenation in the presence of acetic anhydride provided **82a** in one pot. We consequently succeeded in shortening the reaction step by 2 steps.[47] Further applications of a series of known reactions to **82a** led to **84** through **82b**, **82c**, and **83**.

Scheme 17. Eight-Step Total Syntheses of Isobatzelline C and Batzelline C
(**OR** = 4/9 = 44%)



In order to introduce a nitrogen or an oxygen containing functional group into the 7-position of **84**, we thought of the application of the redox system of quinone-hydroquinone structure. If we employ benzylamine as a nucleophilic reagent for **84**, the resultant 7-benzylamine (**85**) would be oxidized simultaneously to 7-benzylideneamine (**86**). This new reaction was realized as expected and generated batzelline C (**76**) and isobatzelline C (**77**) in 10 and 41% yields, respectively. Unexpectedly, we proved that isobatzelline C, the natural product, is the protonated form of **77** instead of the free base.[47]

Yamamura group[48] achieved the total syntheses of **76** and **77** in 19 and 18 steps, respectively. Our synthesis requires only 8 steps[47] and its **OR** is 100x(3+1)/(8+1)=44%, because the reactions such as **34** →**78**, **78**→**79**, **78**→**80**, **84**→**76**+**77** are our intellectual properties.

5. Creation of the Waste Free and Approximately "Ideal Synthetic Method" Aiming at Our Five Dreams[1,4,5]

We have thus far studied aiming at realizing our five dreams by the creation of waste free "ideal synthetic method" fusing the following two thoughts: the one is our synthetic philosophy based on **OR**, **IPF**, and **APF** and the other is our synthetic principle we always have in facing synthetic work for drug developing. The principle consists of the following 9 elements. 1) Synthesis should be simple. 2) Starting material should be cheap possessing the possibility of mass production. 3) Target is recommended to have mother skeleton belonging to a living body required ingredient. 4) Conventional chemical reagents under normal conditions should be employed. 5) Molecular weight of the target is recommended to be less than 500 and if possible it should be around 300. 6) Reactions, synthetic intermediates, and target compounds should be one's own intellectual properties. 7) High yield of each synthetic step and high overall yield are required. 8) High selectivity of each reaction should be attained. 9) Target is desirable not to be a chiral compound. If a chiral compound is chosen, optically active and suitable starting material should be readily available.

We now succeeded in creating three satisfactory concrete examples of the approximately waste free "ideal synthetic method" as shown below in response to the demands that had been criticized for many years.

5-1. Creation of the First Concrete Example[1]

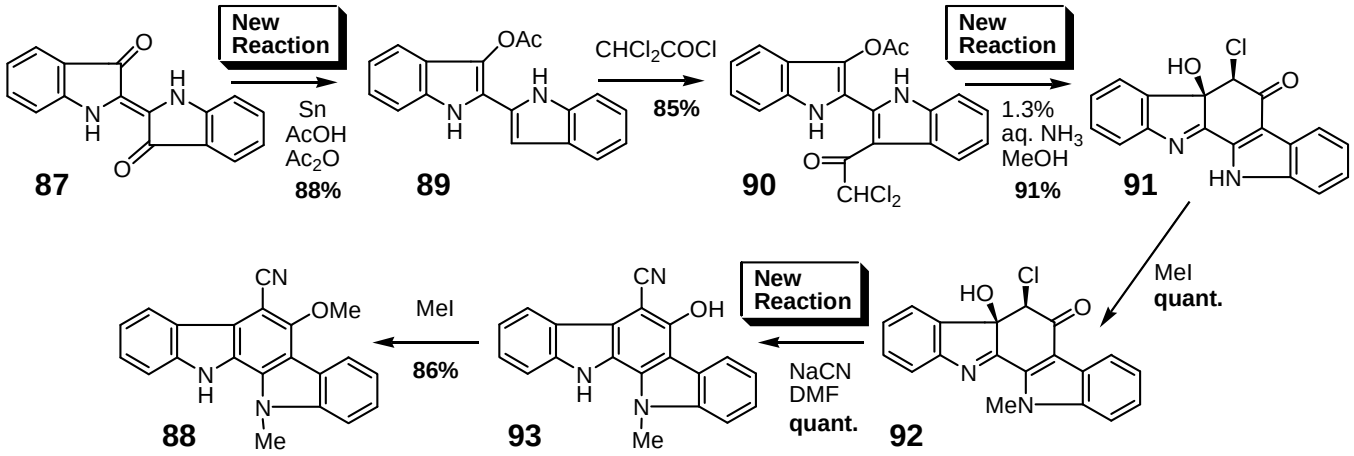
It took ten years to create the first concrete example. The project progressed by creating new reaction to reduce indigo (**87**) to 2-acetoxy-2,2'-bisindole (**89**) in high yield,[49] although no one succeeded in the reduction of **87** to a useful synthetic intermediate thus far (Scheme 18). Employing the reaction as the first step, we established[50] a 59% overall yield and 6-step synthetic method for the antibiotic, 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole (**88**) which was discovered by Knübel group.[51]

In this synthesis, the following reactions such as **87**→**89**, **90**→**91**, **92**→**93** and **90**, **91**, **92**, and **93** are our new reactions and compounds, respectively. The compound (**91**) is an α_2-blocker while **90**, **92**, and **93** are lead compounds as inhibitors of platelet aggregation. These intellectual properties are now under

patent application. Indigo has been known and used as the dye from the ancient times, and the compound (**89**) is an inhibitor of telomerase as reported by Sasaki group.[52]

Let's evaluate this synthesis. Every compound such as starting material, target compound, and synthetic intermediate has either pharmacological activity or a useful function, and all compounds have possibility of practical use and/or the commercialization. Therefore, **OR**, **APF**, and **IPF** of the synthetic method are 57, 54, and 100%, respectively. In this way, we succeeded in creating one concrete example of the approximately waste free and "ideal synthetic method".[1]

Scheme 18. An Almost Ideal Total Synthesis of 6-Cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole



However, both the target compound and the compound (**89**) are intellectual properties of Knübel and Sasaki, respectively. We were not satisfied with the fact based on our synthetic philosophy.

5-2. Creation of the Second Concrete Example[4]

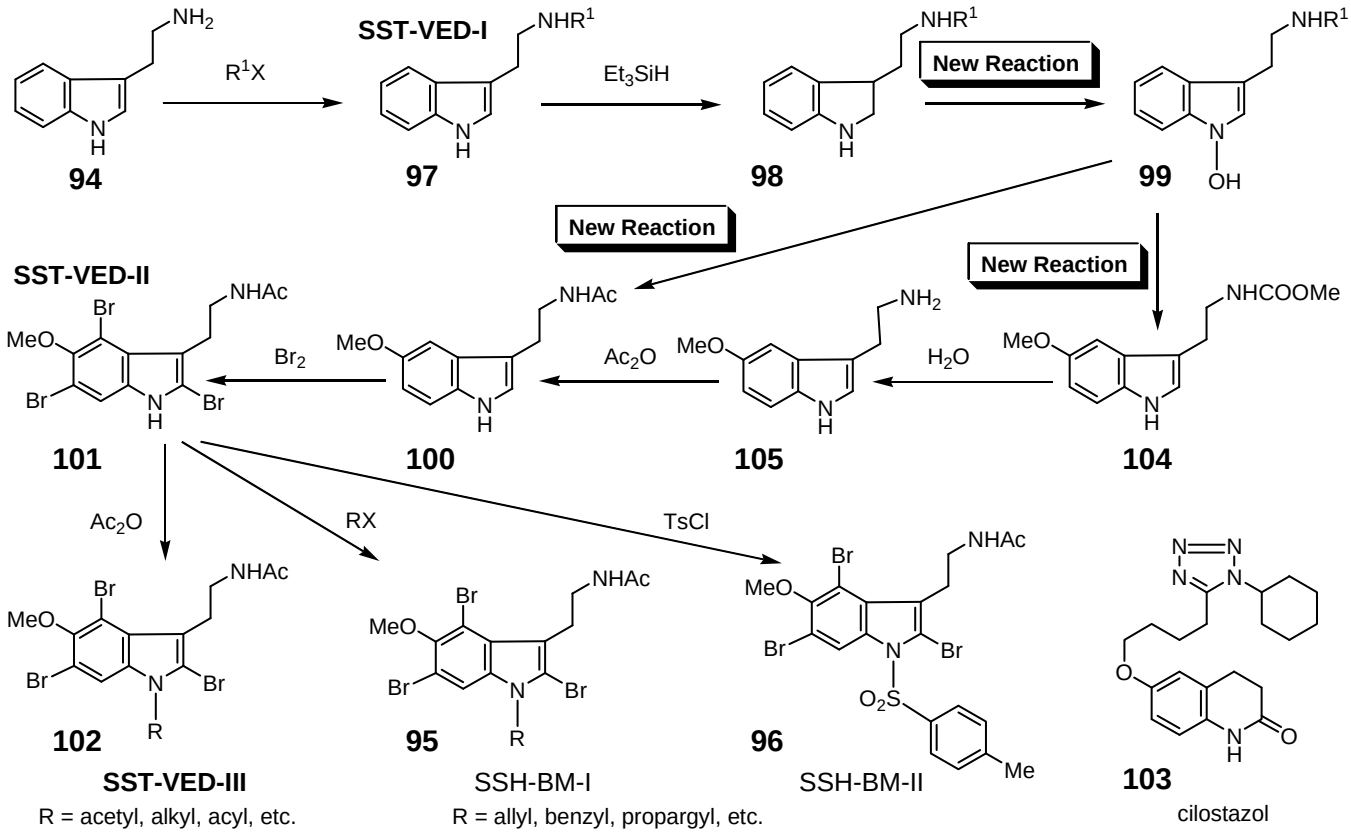
A target compound must be one's intellectual property again to get closer to the ideal. It took 25 years to create the chemistry of 1-hydroxytryptophan and 1-hydroxyindole which was a domain in the imagination.[53] After opening the door to the thus far unknown domain, we have discovered a lot of new reactions and new findings.[53] As a result, the obstacle that stood in the way to achieve the second concrete example disappeared at one sweep as shown in Scheme 19.

The second concrete example is an approximately waste free and "ideal synthetic method" of **95** and **96** from the bulk chemical, tryptamine (**94**), in 6 steps with an overall yield of 38—48%.[4] At first, 2,3-dihydrotryptamine (**98**) was prepared from tryptamine (**94**) through **97**. Subsequent application of our 1-hydroxyindole synthetic method to **98** provided the corresponding 1-hydroxytryptamine (**99**). In

indole chemistry only electrophilic substitution reactions were known thus far.[54] Nevertheless, we could establish nucleophilic substitution reactions against common sense.[55] Application of the new nucleophilic substitution reaction to **99** in MeOH produced *N*-acetyl-5-methoxytryptamine (**100**) in high yield. Next, we found selective tribromination of **100** under suitable brominating conditions to give tribromomelatonin (**101**).[55] Subsequent introduction of an appropriate appendage onto the 1-position of **101** afforded **95**, **96**, **102**, and so on.

Target compounds, **95** and **96**, are our intellectual properties. These are promising leads for the osteoporosis therapeutic drug. We referred them to **SSH-BM-I** and **-II** compound group, respectively.

Scheme 19. An Almost Ideal Synthesis Directed toward Our Lead, Anti-Osteoporosis Agent
R^1 = an appropriate substituent



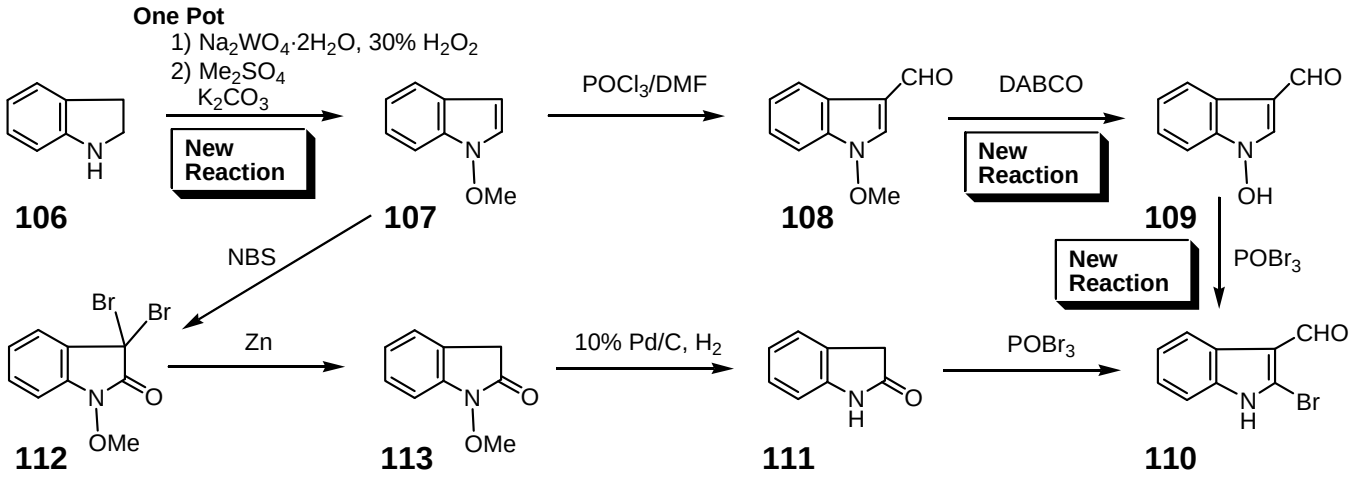
For the evaluation of them, we applied our original assay method with the scale of the goldfish, developed by the coworkers, Hattori and Suzuki.[4] In addition, compounds, **97**, **101**, and **102**, were discovered to be new α_2-blockers by the cooperation of Shigenobu and Tanaka.[4] The potency of these compounds is equal to yohimbine, and it became clear to be the leads for the erectile dysfunction therapeutic drug. We named these **SST-VED-I**, **-II**, and **-III** compound group. The synthetic

intermediate (**99**) is a new inhibitor of platelet aggregation that is stronger than cilostazol (**103**). Therefore, **99** is a group of lead compounds for the treatment of cerebral infarction and the myocardial infarction.[4] The compound (**100**) is melatonin and is multimodality having various biological activities. Synthetic intermediates, **104** and **105**, involved in the alternative route to **100** from **99**, have also pharmacological activity, respectively. In conclusion, every compound in the synthesis, including starting material, intermediates, and target compound is biologically active. The reactions such as **98**→ **99**, **99**→**100**, and **99**→**104** are our original new reactions. Therefore, **OR**, **APF**, and **IPF** of the synthetic method are 43, 54, and 100%, respectively.[1,4]

5-3. Creation of the Third Concrete Example[5]

The third concrete example has **OR**, **APF**, and **IPF** value of 80, 55, and 40%, respectively as shown in Scheme 20. Based on our 1-hydroxyindole chemistry,[53] indoline (**106**), one of industrial raw materials, was converted to 1-methoxyindole (**107**), which was further converted to 1-methoxyindole-3-carbaldehyde (**108**) by Vilsmeyer reaction. Then, we faced to create a mild ether bond cleavage reaction of **108**. Fortunately, we discovered the desired reaction treating **108** with 1,4-diazabicyclo[2,2,2]octane resulting in the formation of 1-hydroxyindole-3-carbaldehyde (**109**).

Scheme 20. An Almost Ideal Synthesis of 2-Bromoindole-3-carbaldehyde



In the next step, we needed to eliminate the 1-hydroxy group and the simultaneous introduction of bromide into the 2-position of **109**. This thus far unknown nucleophilic substitution reaction was discovered by treating **109** with $POBr_3$ culminating in the formation of 2-bromoindole-3-carbaldehyde (**110**). Thus, **110** is now available in 4 steps from **106**.[5] We had already succeeded in finding the special reaction conditions with tips for converting 2-oxindole (**111**) directly into **110**.[5] However, **111** is

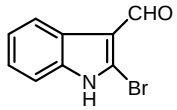
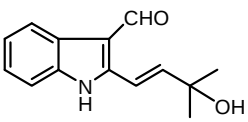
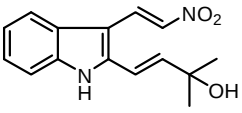
comparatively expensive. Therefore, we developed a novel 3-step synthetic method of **111** from **107** through **112** and **113**.[5]

On the basis of more than 20 years' structure-activity relationship study on the halogen containing indole-3-acetic acids (IAA), indole-3-acetonitriles, and their derivatives,[5] we have chosen **108**—**113** and related compounds as "the medicine for the earth" which have the possibility to make desert full of plant.[5] We named these intellectual properties **SOMRE** compounds.

As expected, **SOMRE** compounds extended the root of both rice and cucumber. The former is a representative of monocotyledonous plant and the latter is a representative of dicotyledonous plants (Table 1). Thus, the 3 ppm aqueous solution of **SOMRE–1** (**110**) lengthened the roots of rice 1.68 times in comparison with the control. As for the 50 ppm aqueous solution of **SOMRE–16** (**114**), the rice roots became 1.46 times longer. As for the roots of cucumber, the 3 ppm aqueous solution of **SOMRE–14** (**115**) lengthened 1.9 times compared with the control.[5]

The **SOMRE** compounds can be applied to various plants, vegetables, and a fruit tree. For example, a root of komatsuna, a kind of Chinese cabbage, was extended to 3 times compared with the contrast when the 1 ppm aqueous solution of **SOMRE–1** (**110**) was applied. We would like to apply them to all the plants whose roots are needed to be longer, fatter, and stronger.

Table 1. Average Root Length of Rice and Cucumber

Plant and Root Length of the Control / Sample	Rice Control: 46.8 mm (100%)				Cucumber Control: 12.1 mm (100%)			
	Concentration of the Sample (ppm)				Concentration of the Sample (ppm)			
	50	12.5	3	0.8	50	12.5	3	0.8
 **110 (SOMRE–1)**	14	140	**168**	130	100	105	**113**	98
 **114 (SOMRE–16)**	**146**	136	120	100	100	100	**118**	101
 **115 (SOMRE–14)**	**168**	133	113	109	120	180	**190**	114

6. Our Intellectual Properties Meeting "Our Five Dreams"

As we mentioned above, we were able to create intellectual properties with the possibility that could achieve our five dreams.[57] For the first dream to develop the medicine for making desert green and food increase in production, we now have both **SOMRE** compounds[58] and **SST-VED** compounds.[59,60] For the second dream to develop drugs for cardiovascular system disease, 1-hydroxyindoles[61,62] are prepared. **SST-VED** compounds can be applied to the third dream for production of dementia therapeutic drugs.[59,60] The fourth dream to get medicine of lifestyle-related disease (diabetes, osteoporosis) would be realized by **SSH-BM** compounds.[63,64,65] For the fifth dream to develop medicines for cancer and virus diseases, 1-hydroxyindoles[61,62] and **SST-VED** compounds[59,60] are prepared.[58]

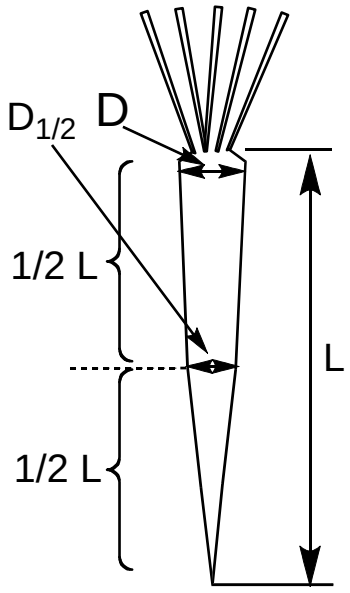
Here we wish to mention in detail only about the first dream, making desert full of plants.[66] In recent years Gobi desert in Inner Mongolia in China is spreading rapidly. It is crying necessity for all life living on earth to stop global warming and to prevent the outbreak of the yellow sand from this area, which pours into any place not only Japan but also all nations on the earth. The best way to cure the global warming is to make the desert and sterile land green with full of plants which absorb carbon dioxide.

Our philosophy combating desertification is quite different from the way of other groups working on desert in the following six points.[66] 1) We do not destroy natural vegetation. We do not use the plant which did not grow wild at the spot from old days. The success in introduction of plants growing in other countries means the destruction of the original environment of the native land. 2) We plant trees in wet season and get water under natural conditions. We revive the desert slowly to the old green environment. We do not take the method to pump up subsurface water and to irrigate. It promotes desertification because water level under the ground gradually lower or hastens the drying up of the subsurface water. We know from the past many failures that watering too much caused salt accumulation resulting in the formation of the sterile earth. 3) We do not use a polymer as water absorbent. The polymer is at great risk of being disintegrated by soil bacteria to generate acrylic acid, acetic acid, etc. which are harmful to man and beast, and they form acidic land where plants can not grow. 4) We don't play with local soil. When we use ameliorant, such ingredient as an organic and an inorganic substance changes the ingredient ratio of the local soil. As a result, local microbe environment changes and the original environment is lost for ever. In addition, yellow sand absorbed the above chemicals, ingredients, and newly born microbes would pour into many places of the world. 5) We create a non-toxic root extension agent drawing the growth ability that plants originally possess. 6) We create a breeding medicine for goats and at the same time achieve the increasing in the cashmere-growth. The goat is the income source

of the nomad. However, the goat is known to eat plants completely and promotes desertification. If we could promote the goat to breed a lot for meat production and to raise the volume of cashmere-wool per a goat while eating the same quantity of plants, we could reduce the head count of the goat guaranteeing the life of the nomad.

With our intellectual properties and ample fundamental data in hand, we performed six times of preliminary experiments from July 2005 to May 2007 at Gobi desert in Inner Mongolia with the cooperation of an NPO group and the local government.[66] We applied **SOMRE** compounds to the seeds of wild plant *Calligonum alaschanicum* (a kind of sand jujube) at Gobi desert and tested repeatedly. In the typical trial, seeds were divided into 5 groups and each group was dipped for 30 min into the 1, 3, 10 ppm aqueous solution of **SOMRE–1**, a 2 ppm aqueous solution of IAA (the reference), and H_2O (the control), respectively. Experiment farmland was divided into 5 parts as well. Seeds of each group were separately sprinkled to the divided farmlands on ditches of 5 cm depth and they were covered with sand.

Table 2. Plant Growth for 73 Days at Gobi Desert in Inner Mongolia



Planting: August 2, 2005. Digging: October 14, 2005

Sample / Root	**H_2O**	**IAA** 2 ppm	**SOMRE–1** 10 ppm	**SOMRE–1** 3 ppm	**SOMRE–1** 1 ppm
Length (**L** cm)	18.0	21.0	22.5	36.0	42.5
Width (**D** mm)	1.5	1.2	1.5	2.0	6.0
$D_{1/2}$ (mm)	1.0	1.0	0.8	2.0	4.0
Weight (mg)	620	310	360	1,390	4,980

They were brought up for 73 days (from August 2 to October 14, 2005) under natural environment of the desert except for watering every one-week. We then dug grown young plants and compared the average root length. The results are summarized in Table 2, which clearly shows that **SOMRE–1** has a remarkable effect on the plant's root growth. Especially, the 1 ppm aqueous solution encouraged the plant's root about 2 times longer and 8—15 times heavier than those of the reference and the control.

With these successful results in hand, we continued preliminary field experiment to make Gobi desert green. Our compounds (**SOMRE–1**, **–4**, related compounds) make the wild plant's roots longer enough to reach to the moisture part in the depth of around 30—40 cm from the earth surface of the desert. It is well known at Gobi desert that the plants grown from the seeds during wet season must experience hot summer and severe cold winter. Usually wild plants freeze to death in winter because of the shortage of root length. In between May 2006 and April 2007, we confirmed that the plants grown from the seeds treated with **SOMRE–1** had sufficient length of the root, three times of longer root (53.2 cm) than the control (19.1 cm), and survived without freezing to death through cold winter. They gave bud in spring and proved to be able to survive through a year! The ability of the extension agent, which make roots reach to a moisture part of the underground, decides the success or failure in the combating desertification.

In April 2007, we dipped young plant's roots of 2,700 sand jujubes into the 1 ppm aqueous solution of **SOMRE–1** for 30 min and planted them at about 2 hectares of Gobi desert. Under natural environment without artificial watering we observed their growth. Two months later, their survival rate is 87.6%, much better than 78.3% of the control group.[69] It is however impossible to dig holes and plant trees in each of them in global size.

The first trial in the world was carried out throwing seeds on the dune surface of Gobi desert while walking in the end of May 2007. The seeds were soaked in the 1 ppm aqueous solution of **SOMRE–1** in advance.[69] After having left them under natural conditions for two months, an impressive result was obtained at the beginning of August. Their germinating rate is not 0%, instead surprisingly more than 0.1%. This experiment means that we succeeded in the preliminary experiment to sow seeds from airplane to Gobi desert, and then to the deserts in the world.

On the other hand, we bought in total eight male goats and carried out feeding experiments[67] in two farms that located distantly from each other. At the one farm 6 goats (age 0.5) were divided into two groups. The one group is taking 1 mg of **SST-VED-1** every day, while the other is the non-taking control group. At the other farm, 2 goats (age 2.0) were divided into two groups. The one is taking 1 mg of **SST-VED-1** every day, while the other is the non-taking control. After one-year cultivation the weight of cashmere was examined and the results are summarized in Table 3. It is evident that **SST-VED-1** increased the growth of cashmere. Besides, the cashmere shines like silk and the quality is high.[68] Furthermore, the goats taking **SST-VED-1** became bigger than the control group. The fecundity of the taking goats became excellent. They made a lot of children, as desired.[69]

Table 3. Comparison of the Growth of Cashmere
At Gobi Desert in Inner Mongolia, China

Farm I 2006.7(Age 0.5, Male) ~ 2007.5

Goat	Weight of Cashmere (g)	
	Goat taking SST-VED–1	Control Group
No. 1	320	300
No. 2	300	200
No. 3	205	170
Average	275 (123%)	223.3 (100%)

Farm II 2006.5 (Age 2, Male ~ 2007.5

Goat	Weight of Cashmere (g)	
	Goat taking SST-VED–1	Control Group
No. 1	375 (167%)	225 (100%)

We hope **SST-VED** and **SOMRE** compounds would change Gobi desert again to the area with full of plants as it was 300 years ago. They would be useful for preventing disastrous global warming and for production of more food as a new technology. In addition the **SOMRE** compounds would be useful new probe for understanding the growth of plants. We believe **SOMRE** compounds become “the medicine for the earth.”

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