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Total Synthesis of ± Lysergic Acid

A New Diels-Alder Pyridine Synthesis

A Dissertation

Presented to

The Faculty of the Graduate School of Arts and Sciences

Brandeis University

Department of Chemistry

Professor James B. Hendrickson, Advisor

In Partial Fulfillment
of the requirements for the Degree
Doctor of Philosophy

by

Jian Wang

February, 2002

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This dissertation, directed and approved by **Jian Wang**'s Committee, has been accepted and approved by the Faculty of Brandeis University in partial fulfillment of the requirements for the degree of:

DOCTOR OF PHILOSOPHY

Dean of Arts and Sciences

Dissertation Committee:

Chair, Professor James B. Hendrickson, Chemistry Dept.

Professor Thomas Pochapsky, Chemistry Dept.

Professor John Neumeyer, Harvard Medical School

For My Parents

And

My Wife and Daughter

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I am sincerely thankful to all those who made these studies possible. In particular, I would like to thank

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ABSTRACT

Total Synthesis of ± Lysergic Acid

A New Diels-Alder Pyridine Synthesis

A dissertation presented to the Faculty of the

Graduate School of Arts and Sciences

Brandeis University, Waltham, MA

By Jian Wang

Struck by the extent of redundancy in past syntheses of lysergic acid, we developed a non-redundant, efficient synthesis plan quite different from those. Our plan was based on the dissection of the target structure into two simple halves corresponding to indole and nicotinic acid, with only two skeletal bonds (a and b) to construct (Scheme 9).

Of the two orders for joining these units we examined (b+a) first by acylating indole with 6-chlorocarbonyl-nicotinic ester (Chapter 1) or their halogenated derivatives (Chapter 2). Our attempted cyclizations to close bond a with several

quite different reactions all failed, apparently because of severe crowding in the cyclizing transition state.

Turning to the other variation (b+a) we first created bond a via Suzuki coupling of 4-halo-indoles with 5-chloro-6-carboxy-nicotinic diester (Chapter 3). Conversion of the 6-carboxyl to aldehyde afforded successful cyclization of bond b. The synthesis was finished by N-methylation and pyridine ring reduction.

In conjunction with this synthesis we also developed a new synthesis of substituted pyridines by the Diels-Alder reaction of tosyl cyanide with various α-pyrones, catalyzed by $TiCl_4$ (Chapter 4). The reaction is driven by pyridine aromatization and extrusion of CO_2 and affords good yields. The α-tosyl substituent on the product pyridines may be replaced by common nucleophiles.

Table of Content

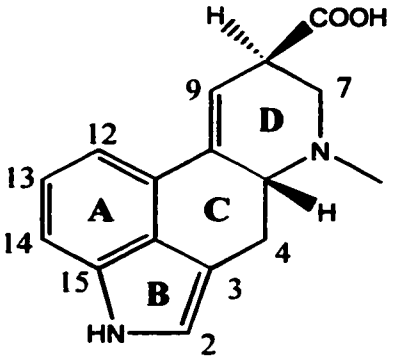
Introduction

1. Background

Lysergic acid, popularly known by its derivative lysergic acid diethylamide (LSD), is the parent member of the ergot alkaloids family. Ergot alkaloids are the metabolic products of various species of the parasitic fungus *Claviceps* (Clavicipitales). The historical interest in this class of compounds may be attributed to their toxic features. These naturally occurring products caused mass poisonings in both animals and man until the end of 19th century. One famous accident in the history was " St Anthony's fire" in Central Europe during the Middle Ages, when people ate bread made from rye flour which was contaminated with scleratia of *Claviceps purpurea* (Fries) Tulsane, which grows on rye grains.

However, in later years the broad range of pharmaceutical effects[1,2,3] of ergot was recognized, leading to extensive study on this class of products. Even now, natural and semi-synthetic ergots still find a wide range of use in medical practice. Ergonovine and methylergonoine are used for the treatment of postpartum hemorrhage, nocergolione for hypertension and poor blood circulation, methysergide for migraine attacks, and the common natural ergotamine for depression.

In addition to being important pharmaceutical agents themselves, ergot alkaloids play a key role in the development of other drugs by providing information about the generic structure features. The structure elucidation[4,5] of lysergic acid and related compounds led to the development of the pharmacology of the tetracyclic ring system. The medicinal importance stimulated synthetic efforts on this class of compounds. Several syntheses of lysergic acid are outlined in the next section.



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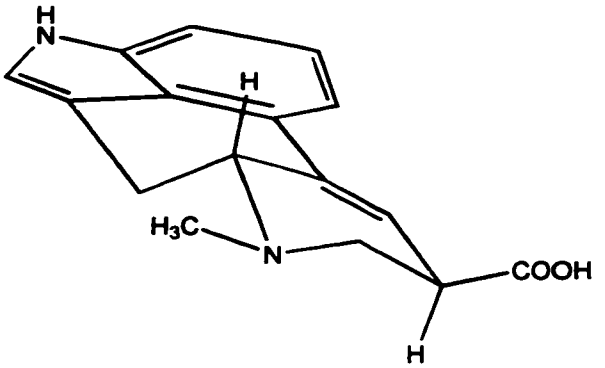


1

Scheme 1: The Structure of Lysergic Acid

2. Previous syntheses of lysergic acid

There are about seven syntheses of lysergic acid so far. Most of them share a common feature in the route design. They are summarized in the following sections.

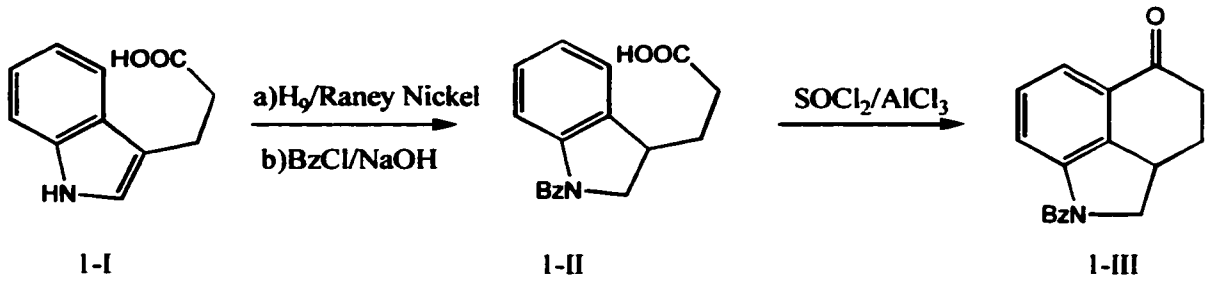
2.1. The Woodward synthesis (1955)

The first total synthesis of lysergic acid was finished by R. B. Woodward and E. C. Kornfeld in 1956[6]. Scheme 2 shows this 15-step synthetic route. The

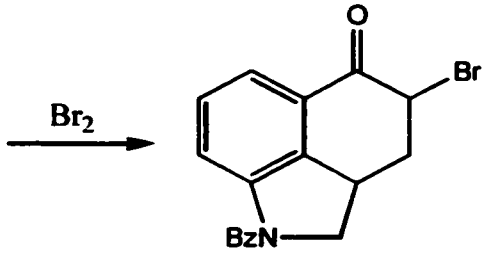
starting material, 3β-carboxyethylindole, was converted to the key intermediate, Ulhe's ketone 1-III, by a 3-step sequence. This ketone, containing three of the four rings present in lysergic acid, was α-brominated and substituted with the amine 1-VIII, then transformed into the tetracyclic compound 1-XI via an aldol condensation. Addition of the ester group via a nitrile and reoxidation of the indole ring serve to finish this first synthesis of lysergic acid.

This is an elegant synthesis. It was designed in a way that every functional group plays a role and was fully utilized. However, there is some redundancy, typical of most of the later syntheses as well, since the indole nitrogen was protected and deprotected twice, and the indole ring was reduced to an indoline at the beginning and only recovered at the end. This was necessitated because the indole together with olefin functionality of the ergot alkaloids was known to isomerize irreversibly to a naphthalene under acid conditions[7a,b] and so was only restored at the very end of the route by a mild oxidation.

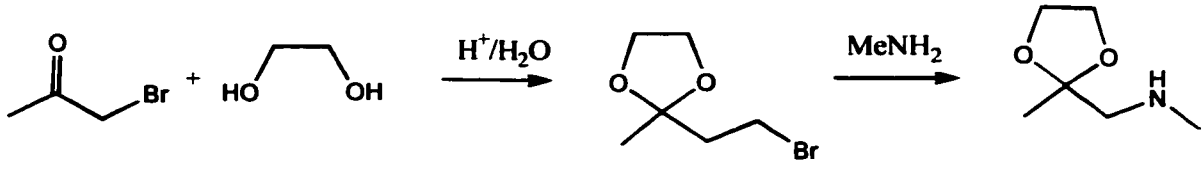
In the next four syntheses, the same strategy was used to avoid this isomerization. All four also started with Uhle's ketone (1-III) and then offered variations in the way the fourth ring was attached.



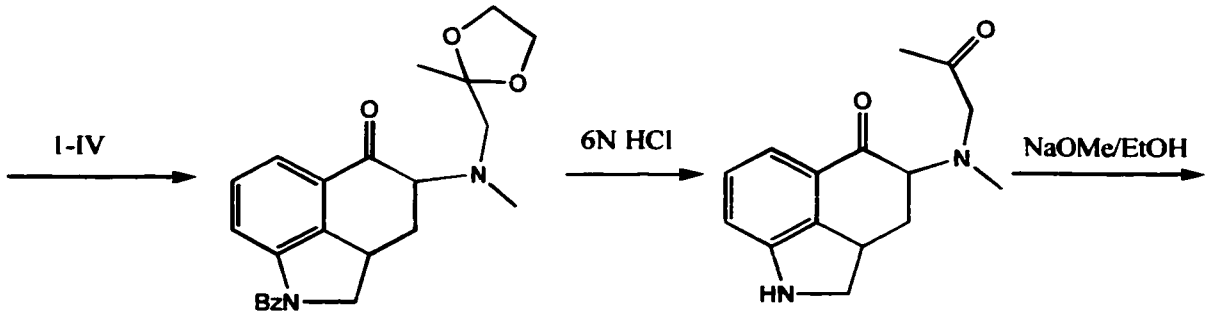
I-I I-II I-III



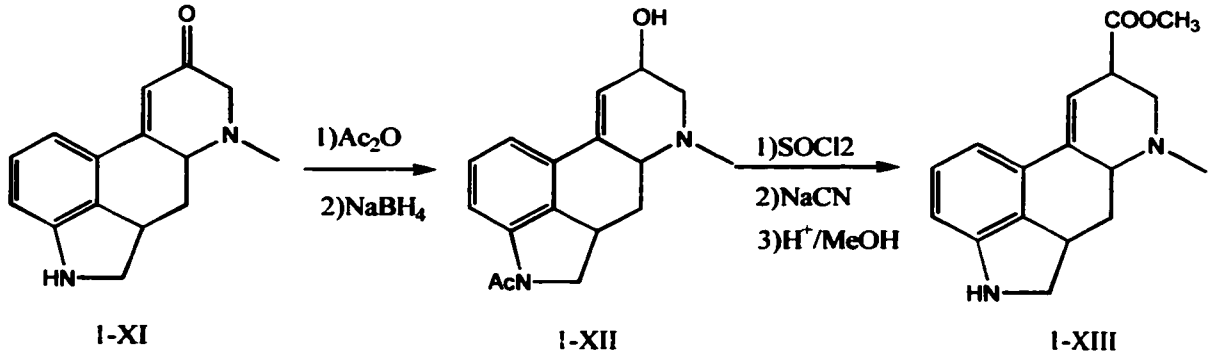
I-IV



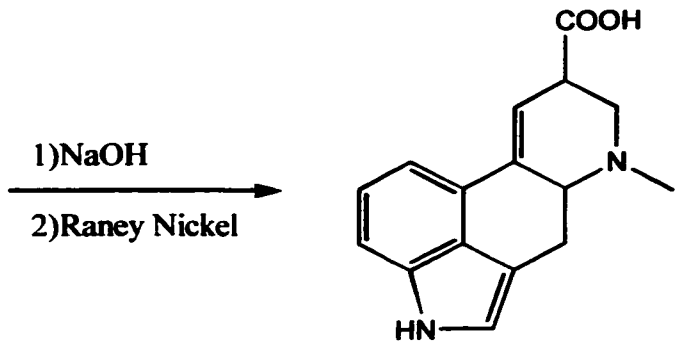
I-V I-VI I-VII I-VIII



I-IX I-X



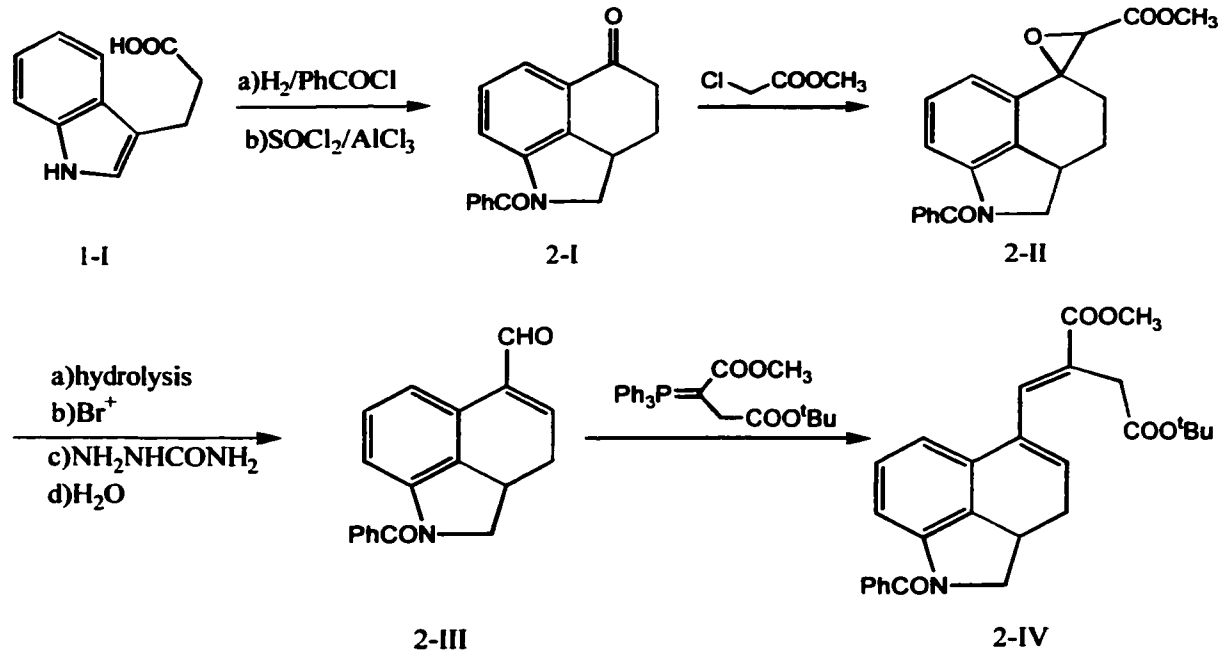
I-XI I-XII I-XIII

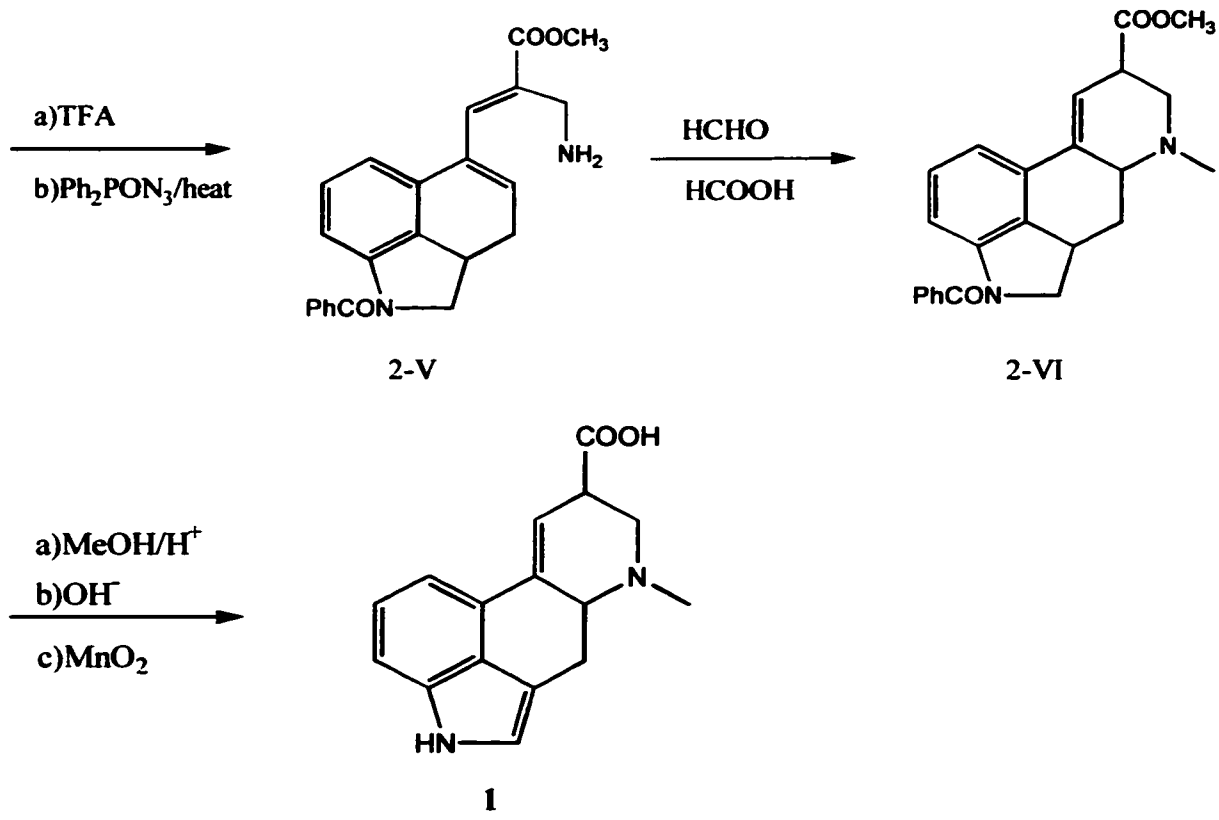


Scheme 2: Woodward's Synthesis

2.2. The Ramage synthesis (1981)

Ramage's synthesis of lysergic acid[8] differed only in building the fourth ring by a pericyclic ring closure variant suggested by Woodward earlier, and its key steps are summarized in Scheme 3.

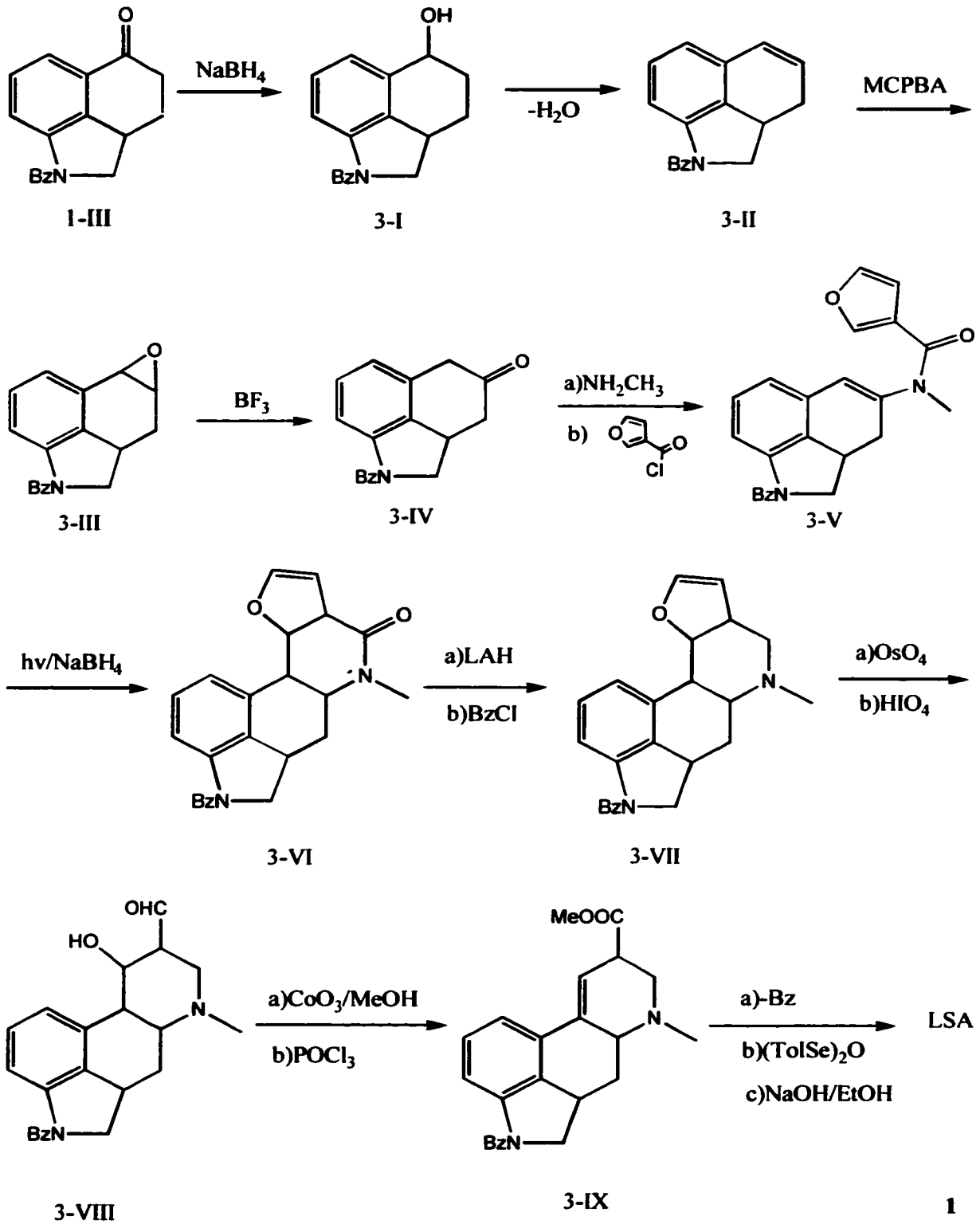




Scheme 3: Ramage's Synthesis

2.3. The Ninomyia synthesis (1985)

The same intermediate 1-III was also used in this synthesis[9], shown in Scheme 4, but the ketone was then transposed by a 4-step sequence to ketone 3-IV. Its methylimine was acylated by 3-furoyl chloride to 3-V and reductive photocyclization afforded 3-VI in which the characteristic tetracyclic ring system of lysergic acid was constructed. Removal of the amides followed by re-protection of the indole nitrogen afforded compound 3-VII. Oxidative cleavage of the dihydrofuran ring afforded 3-VIII with the desired tetracyclic skeleton. Aldehyde oxidation and dehydration of the alcohol gave a diastereomeric

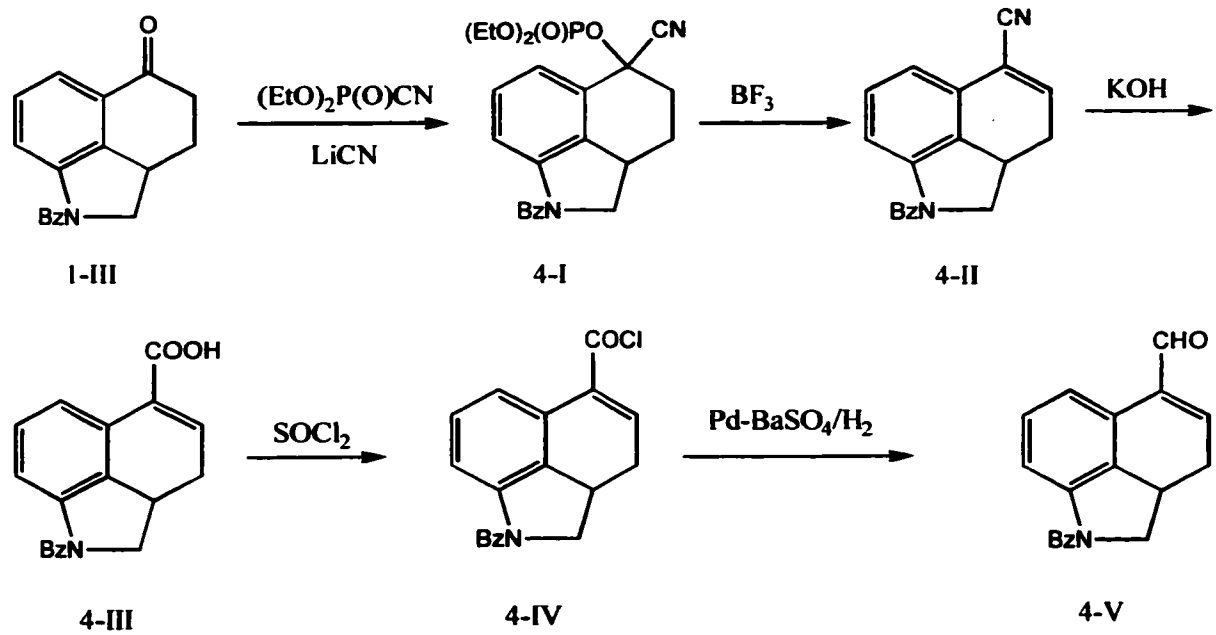


Scheme 4: Ninomyia's Synthesis

mixture of 3-IX isomers. The indole was formed in a different mild oxidation and isomerized to yield lysergic acid.

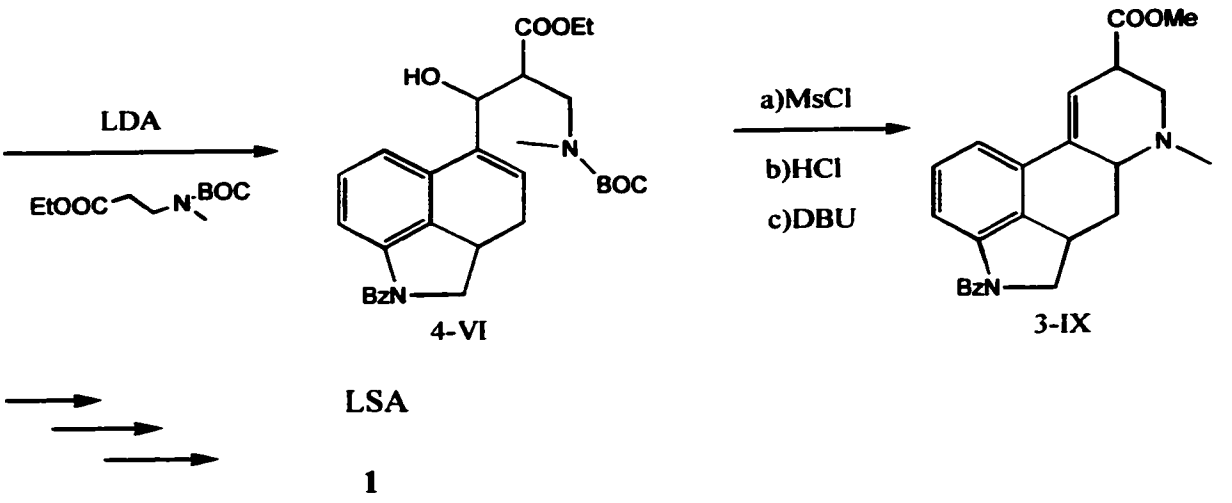
2.4. The Kurihara synthesis (1986)

In this synthesis[10, 11], the same starting material 1-III was used as in the previous syntheses. In Scheme 4 a 2-step sequence extended Uhle's ketone 1-III to an α,β-unsaturated nitrile 4-II. This was reduced to the aldehyde 4-V in a 3-step sequence. Aldol condensation of 4-V with 3-(N-t-butoxycarbonyl-N-methyl)aminopropionate gave the key intermediate 4-VI, which was refunctionalized and cyclized in an SN_2' reaction to 3-IX, the same final product as obtained by Ninomiya above.



1-III 4-I 4-II

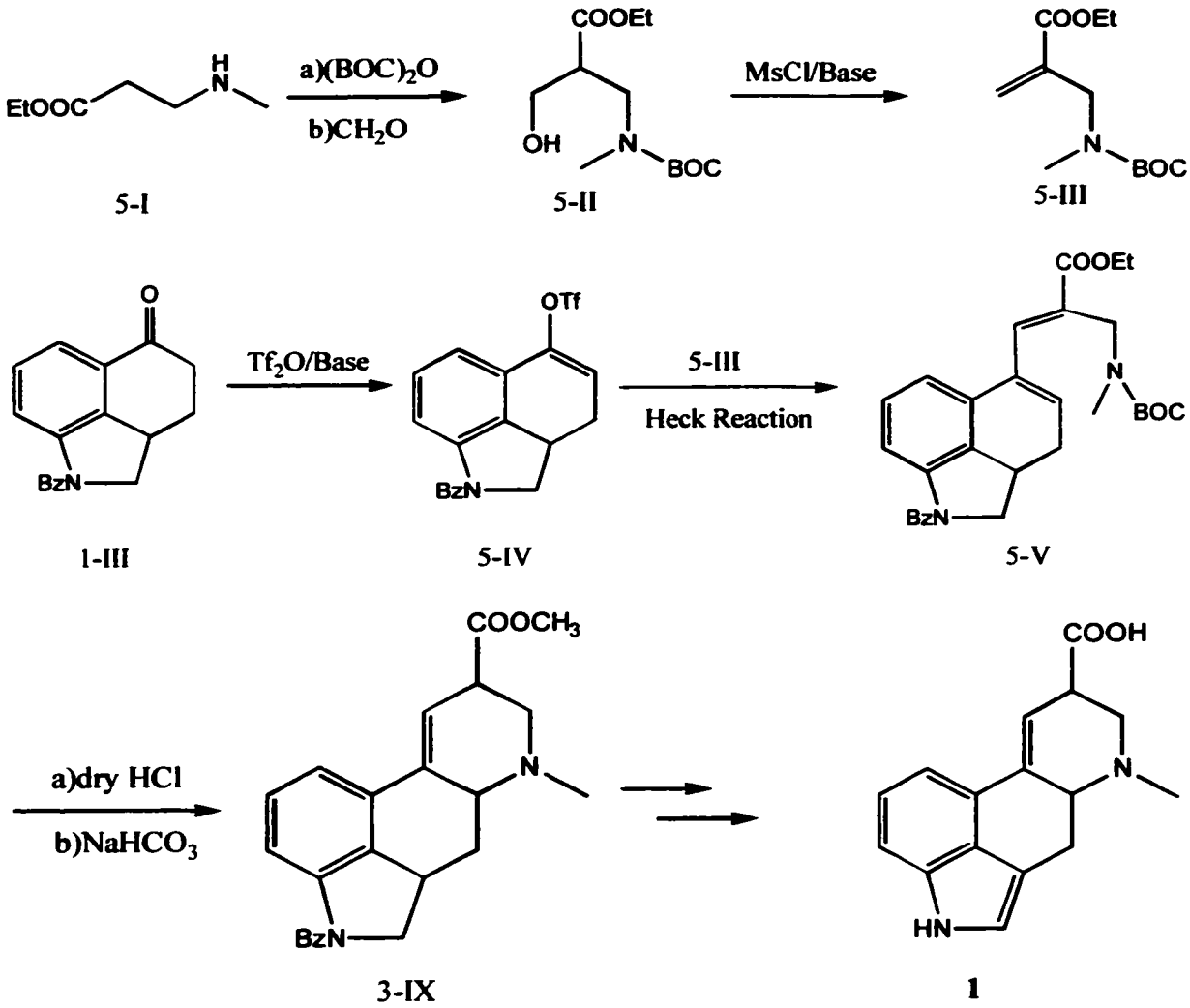
4-III 4-IV 4-V



Scheme 5: Kurihara's Synthesis

2.5. The Cacchi synthesis (1988)

In this synthesis[12], summarized in Scheme 6, Uhle's ketone 1-III was converted to the enol triflate 5-IV for linking to the preformed olefin 5-III by a Heck reaction. The product 5-V cyclized in a conjugate addition similar to that of Ramage and gave the same product 3-IX, which was converted to lysergic acid as in all the other syntheses. Overall, this synthesis of lysergic acid is a modified version of Ramage's. However, this is a much more efficient and shorter route, only 9 steps in all.

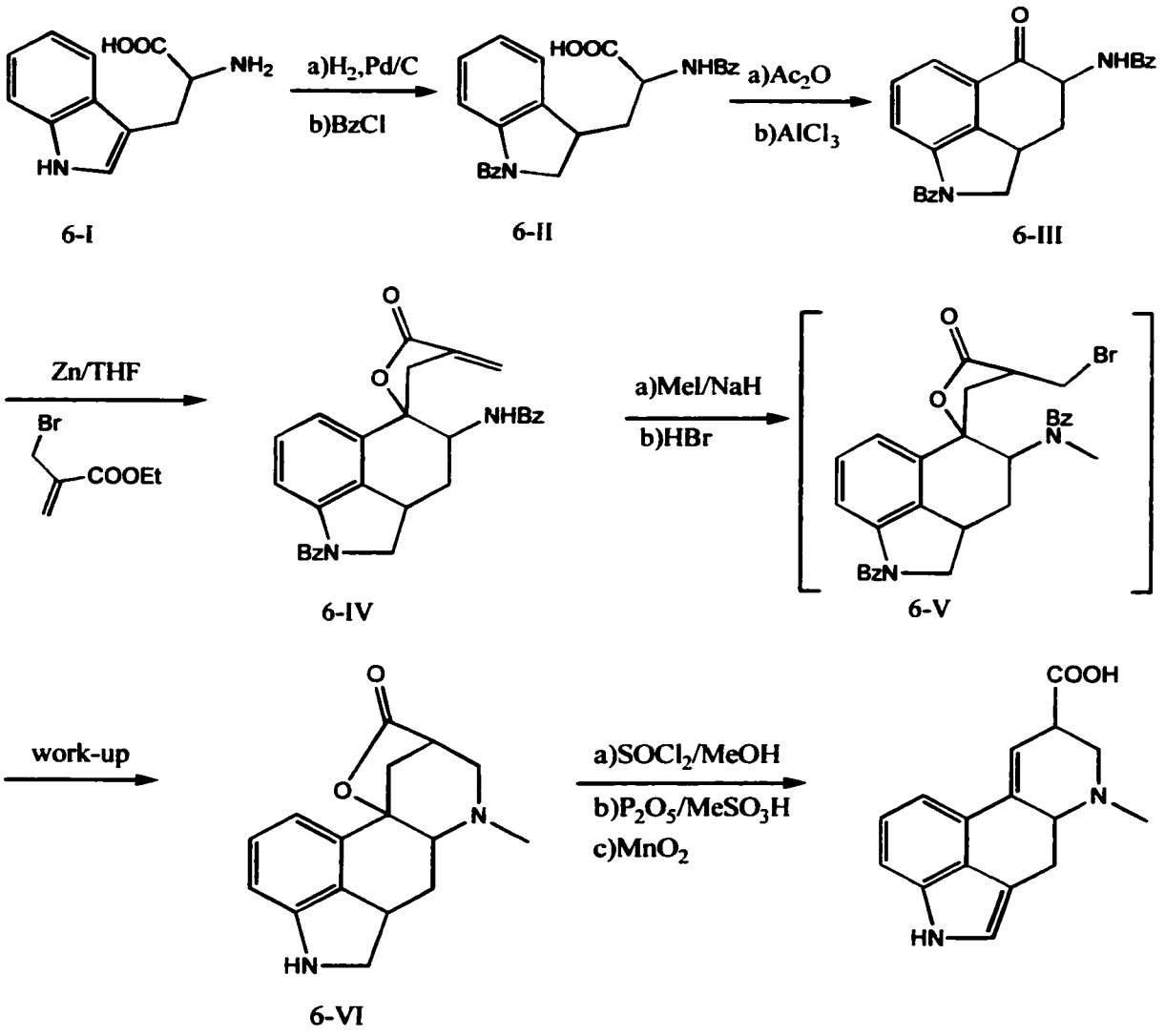


Scheme 6: Cacchi's Synthesis

2.6. The Rebek synthesis (1984)

This route[13], shown in Scheme 7, represented the first time that tryptophan was used as the starting material for lysergic acid synthesis, as it is in the natural biosynthesis. This was the first synthesis to afford a single enantiomer of lysergic acid instead of the racemate. Hydrogenation and double benzoyl protection led to 6-II, which underwent intramolecular Friedel-Crafts

acylation to a tricyclic ketone intermediate, 6-III. Reformatsky reaction with ethyl α-(bromomethyl) acrylate introduced the remaining four carbons and led to a spiro methylene lactone 6-IV. Alkylation of 6-IV with MeI/NaH followed by treatment with HBr afforded the intermediate 6-V, which cyclized spontaneously to the pentacyclic compound 6-VI during workup.



Scheme 7: Rebek's Synthesis

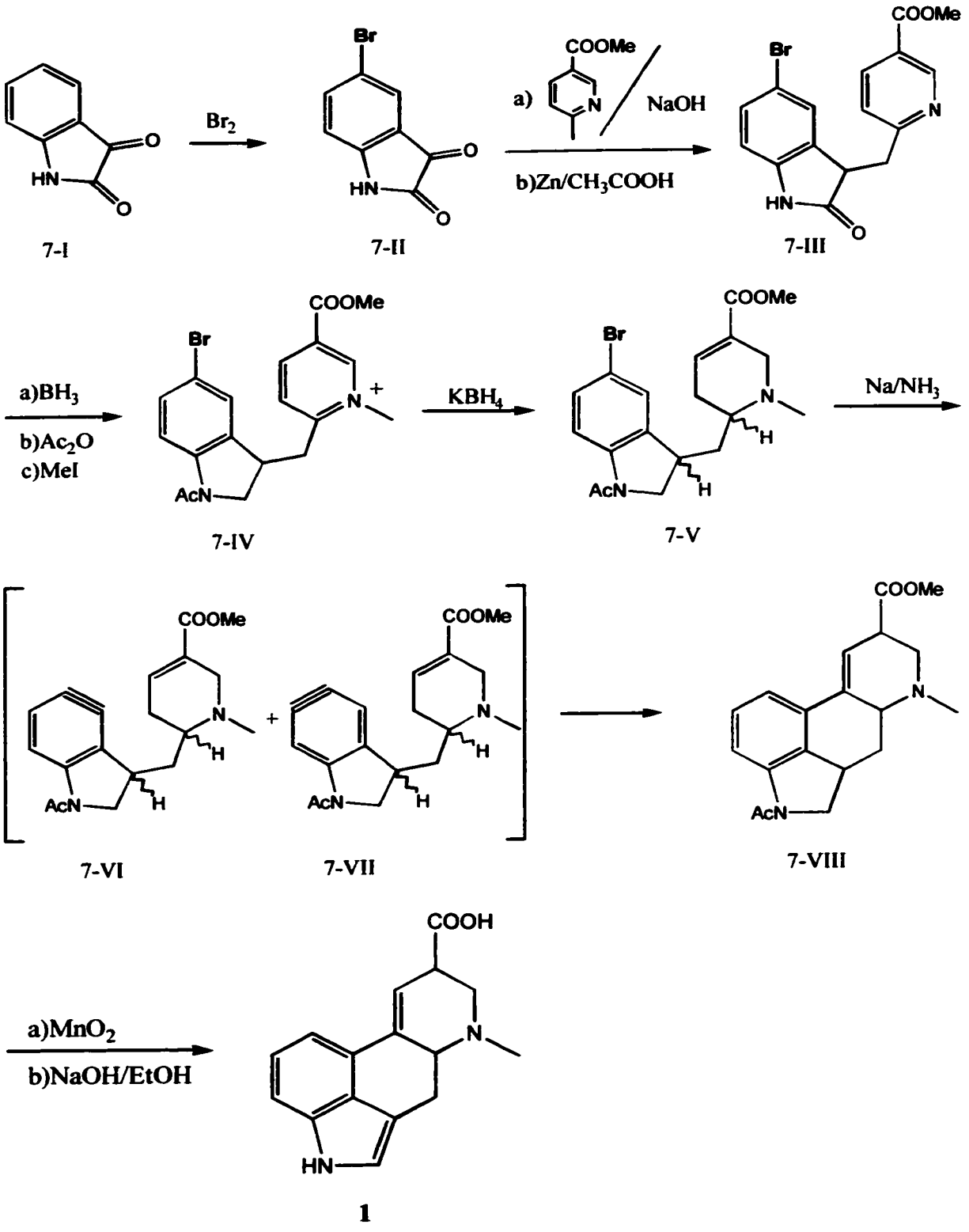
Treatment of 6-VI with thionyl chloride opened the lactone and the resulting hydroxyl derivative was dehydrated to the known compound 6-VII in the presence of P_2O_5. Oxidation of the indoline by MnO_2 followed by hydrolysis furnished methyl lysergate in an efficient, short synthesis (10 steps).

2.7. The Julia synthesis (1969)

Beginning with Woodward's synthesis, all syntheses discussed above go through the tricyclic intermediate 1-III (Ulhe's ketone), or its close analogue as 6-III in Rebek's synthesis. Julia's approach to lysergic acid[14] is very different from the other syntheses mentioned so far and is summarized in Figure 8. Rather than a focus on the construction of the D-ring, Julia's synthesis features C-ring construction.

This route requires that the starting materials should have indole and pyridine skeletons. For this reason, isatin (7-I) and the substituted pyridine derivative methyl 6-methyl-nicotinate were employed as the two building blocks. 5-Bromoisatin (7-II), the bromination product of isatin, condensed with methyl 6-methyl nicotinate, followed by reduction of the hydroxyl group with zinc, to afford compound 7-III. Methylation followed by borohydride reduction delivered a mixture of two diasteromers 7-V.

Only one of the two diastereomers could cyclize to yield the tetracyclic ring compound. This is a big drawback of this synthesis, because half of the material is wasted at this point. Treatment of 7-V with sodium metal in liquid ammonia presumably produced a pair of benzyne intermediates 7-VI and 7-VII.



Scheme 8: Julia's Synthesis

Again, half of the material will not be utilized because only one of these two intermediates could be cyclized to tetracyclic compound 7-VIII. Routine regeneration of indole from indoline and hydrolysis finally afforded lysergic acid in a very low yield, but the route is a short one (10 steps).

3. The Basis and Outline of Our Synthetic Route

3.1. Criteria for the Synthesis of Lysergic Acid

By examining the previous synthesis routes, one can conclude that many of them are showcases for a key step reaction. The indole rings are always masked as indoline derivatives and the indole nitrogen must be protected and later deprotected. These reduction and protection steps, and subsequent oxidation and deprotection steps, are wasted effort and make the syntheses longer than ideal.

Almost three decades ago, Professor Hendrickson started analyzing the logic of synthesis design, and pointed to several criteria for an efficient synthetic plan. These criteria are: 1) minimization of both skeletal constructions and functional group transformation steps, including protection steps; 2) selection of starting materials with a skeleton as large and cheap as possible; 3) formation of as many bonds as possible in one chemical operation to avoid exponential yield loss. All these factors ultimately derive from a fundamental criterion: performing the minimum number of chemical reactions[15a, b, c].

Based on these criteria, some computer software has been developed in Hendrickson's group since then. One of these is the SYNGEN program. The

SYNGEN program aims to provide the most efficient synthetic routes in terms of the number of steps and literature precedent to achieve the specific desired target. Using the program one can select the best route or modify the best ones to reduce the proposed route to practice.

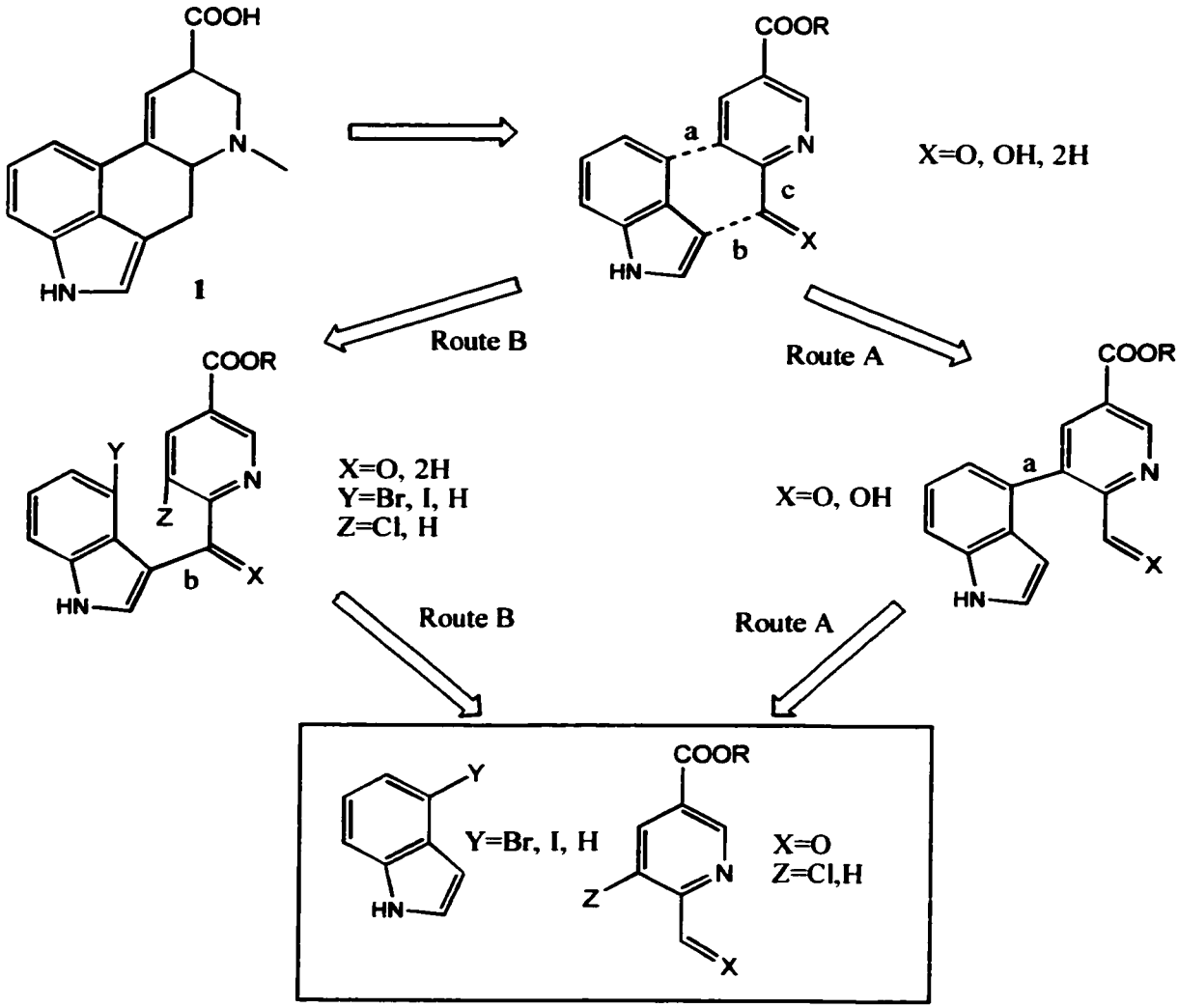
We examined the previous syntheses of lysergic acid with these criteria in mind and proposed that the most efficient synthetic route of lysergic acid would be one in which readily available pyridine and full indole derivatives are used as the starting materials, and the indole function would be retained throughout. Therefore, the C-ring is the only ring that needs to be constructed to furnish the tetracyclic skeleton. Based on this, only two bonds need to be made to close the C-ring and arrive at the lysergic acid skeleton. These are bonds **a** and **b**, which can be made in either order as outlined in Scheme 9.

3.2. Consequences of the Synthetic Choice

The two variants of this retrosynthetic analysis in Scheme 9 are labeled Route A and Route B. Both routes commence with a simple indole and a derivative of nicotinic acid as starting materials, both readily available. In this way to obtain the desired tetracyclic ring system, only two skeletal bonds, namely bond **a** and bond **b**, have to be constructed.

Theoretically, there is another possible choice, which is to construct bond **c** instead of bond **b**. However, since the indole β-position is nucleophilic, very reactive, and regiospecific, while the α-position of pyridines is less reactive and not as regiospecific, bond **b** was chosen to construct instead of bond **c**. In one

attempt to make ergot alkaloids, Doll[16] chose bond **c** instead of bond **b** to get the tetracyclic ring system, and he obtained the wrong regioisomer at the pyridine unit.



Scheme 9: Proposed retrosynthesis of lysergic acid

Of the two possible different routes in Scheme 9 we elected to examine Route B first. In this route, bond **b** is constructed first. This construction is facile and well precedented by indole acylation with an acid chloride. In our case this

requires pyridine-2,5-dicarboxylic acid, which is readily available as isocinchomeronic acid. To do so, the two acid groups must be differentiated so that indole acylation will proceed regioselectively at the pyridine 2-ester rather than the 5-ester; this problem will be discussed in detail in chapter 1.

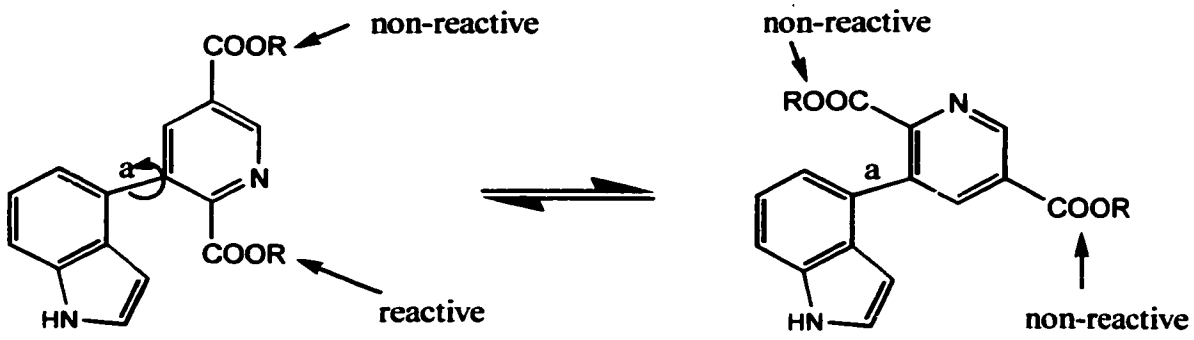
Once bond **b** is constructed, the next step is to construct bond **a** in an intramolecular fashion. Construction of bond **a** requires a reaction to couple two aromatic rings and commonly these will require prior substitution of directing groups on both of the aromatic sites to be joined, as X and Y in Scheme 8. This in turn leads to Suzuki and Ullmann reactions or other organometallic variants. However, the overall goal of economy of steps is compromised by the need to introduce both of these substituents in separate reactions before the coupling.

Alternatively, since the pyridine ring must finally be reduced for lysergic acid, this reduction might be done before the intramolecular coupling in order to facilitate that construction. This suggested a Heck reaction or radical cyclization with only one substituent, i.e., Y on the indole 4-position. We also considered a thermal pericyclization for this ring closure. These cyclizations are discussed in Chapter 1 and 2 below.

The other choice is Route A, to construct bond **a** before bond **b** is made. To do this, halogen substituents on the 4-position of the indole and the 3-position of the pyridine ring are required. Since we considered that construction of bond **a** might be more facile if it were done second, as a cyclization, we elected to explore Route B first and only came to Route A, discussed in Chapter 3, after that cyclization proved difficult.

Various diarylhalide couplings were investigated for initial construction of bond **a** as discussed in detail in Chapter 3. In Route A, after joining the two basic units at bond **a**, bond **b** would then be constructed second. There is a special advantage with this route since, to construct bond **b** first, one must differentiate the two carboxyl groups on the pyridine ring.

However, in Route A it is no longer necessary to differentiate the two carboxyl groups on the pyridine. This can be seen on Route A in Scheme 9. By rotating around bond **a**, there are two conformers for the Route A intermediate compound. Only one of the two conformers can react to form bond **b** intramolecularly, and so only one of the two carboxyl groups in this reactive conformer is eligible to acylate the 3-position of the indole, to form the desired tetracyclic ring system.



reactive conformer non-reactive conformer

Scheme 10: Two Conformers of Biaryl Precursor

Once the tetracyclic ring is constructed, methylation of the pyridine nitrogen and reduction of the pyridinium salt will result in the desired oxidation state and functionality pattern for lysergic acid.

Both plans seek to pass fairly directly from large, cheap starting materials with a minimum of two skeletal constructions and also without unnecessary functional group transformations, and so in principle to produce a much shorter synthesis than the previous routes.

Chapter 1

Approach via Route B

As described in the introduction chapter, we proposed that the tetracyclic ring system for lysergic acid be constructed from available pyridine and indole starting materials, and that this in turn required making bonds **a** and **b** in ring C, in either **ba** or **ab** order. For reasons discussed above we examine the **ba** order first, Route B in Scheme 8.

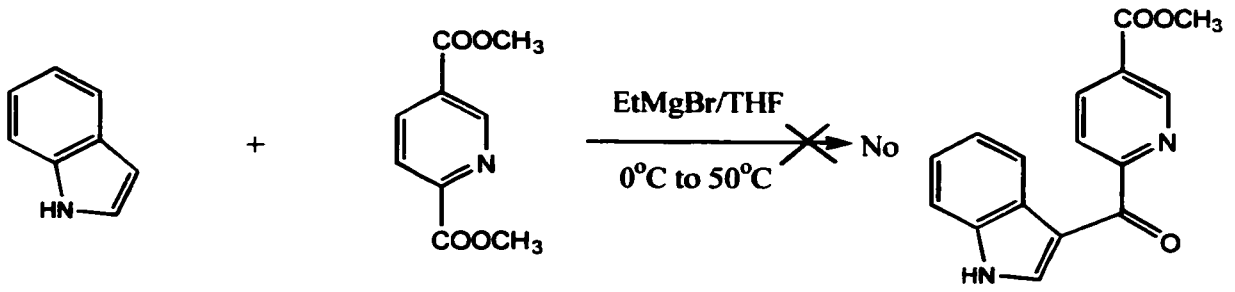
In this chapter, the study of indole 3-acylation and the subsequent attempts at construction of bond **a** to close the ring will be presented and discussed.

1. Indole Acylation on the 3-Position

1.1 Ester Condensation

The first thing to do is to pick the simplest available starting materials to prove the concept. So simple indole and isocinchomeronic methyl ester were chosen as the starting materials. It was reported[17a, b] that when magnesium was used as a soft counter ion, the reactive nucleophilic center of indole is 3-C rather than 1-

N. We also speculated that the lower ester (2-position) of isocinchomeronic methyl ester would be more reactive than the upper one because it is ortho to pyridine nitrogen and consequentially more electron deficient, and so selectivity between the two ester groups might be achieved. However, when indole was treated with isocinchomeronic methyl ester, no desired ester condensation adduct was obtained and only starting materials were recovered.



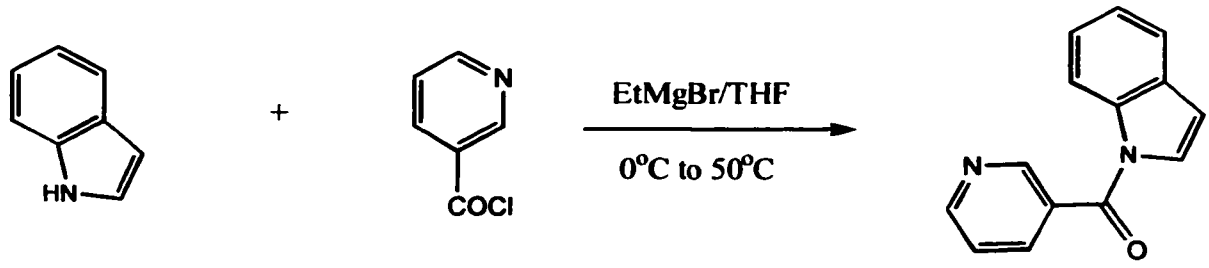
2 **3** **4**

Different reactions were also tried. When indole was treated with magnesium dimethoxide, a red-colored species was generated. When this species was treated with isocinchomeronic methyl ester in boiling methanol, no desired product was obtained and only starting materials were recovered as in the previous experiment. After these two experiments we concluded that the isocinchomeronic methyl ester is not reactive enough to form any ester condensation adduct with indole anions in basic conditions.

1.2 Acylation by Acid Chlorides - A Model Study

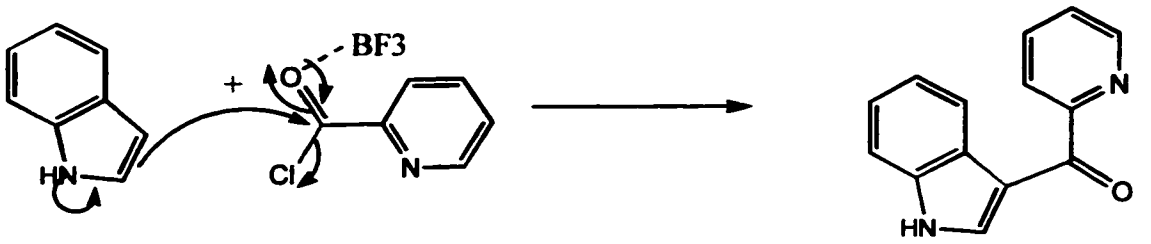
Since the ester group on pyridine is not reactive for indole 3-acylation, different conditions were investigated. A reasonable approach will be the one in

which the acid group is converted first into its acid chloride then reacted with indole, catalysed by Lewis acid. So nicotinic acid was treated with neat thionyl chloride to yield the corresponding acid chloride, then reacted with indole in the presence of boron trifluoride in ether. The reaction did go, but not in the desired way: the N-acylation product was isolated, instead of C-acylation at the indole 3-position. The proton NMR, which showed that the N-H disappeared and the distinguishable proton on the indole 3-position (about 6.3 ppm) was still present, supported this. So it was obvious that nitrogen in the indole is more nucleophilic than the 3-position in these conditions.

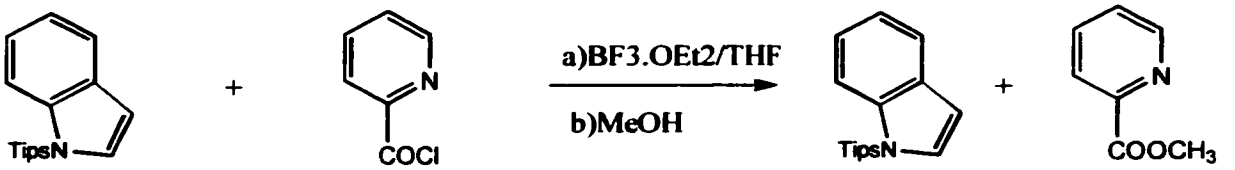


2 **5** **6**

One obvious alternative is to mask the nitrogen of indole. So indole was treated with BuLi in THF, then reacted with triisopropylsilyl chloride to give the silyl-protected indole, which in turn was allowed to react with nicotinic acid chloride in the presence of BF_3. The reaction was quenched with dry methanol. After work-up, the silyl-protected indole starting material and methyl nicotinate were the only two compounds isolated, and no desired product was obtained. From this, we concluded that the indole nitrogen has to be unprotected in order to activate the 3-position of indole as shown in the following scheme.



Scheme 11: Indole 3-acylation



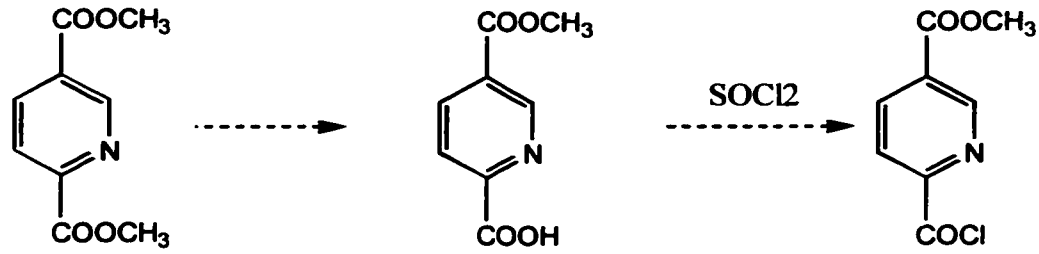
7 **8** **7** **9**

At this point, it was clear that unprotected indole must be selected as the acylation partner. For the other partner, isocinchomeronic di-acid chloride was selected. The reasons for doing this were twofold: one is to test the acylation between indole and our acid chloride in the presence of Lewis acid; another is to see the selectivity between two activated carboxyl groups during acylation. So isocinchomeronic acid was treated with neat thionyl chloride at elevated temperature to give the corresponding di-acid chloride, which in turn reacted with indole in the presence of BF_3 and was worked up with methanol. Two regioisomeric monoesters, in a 1:1 ratio, were obtained from this reaction in a 35% combined yield. 1H NMR showed that the characteristic indole 3-H (6.3

ppm) disappeared and two sets of indole and pyridine protons were observed. This tells us that there is no selectivity between the two carboxyl groups.

1.3. Differentiation of Ester Groups

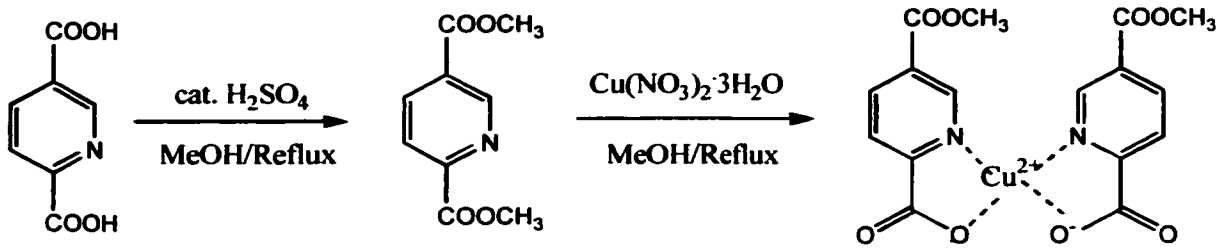
Only one of the two products from the above reaction could potentially lead to the lysergic acid skeleton, and the other one would have to be discarded. This is not acceptable in the early stage of the synthesis. One way to solve this problem is to differentiate the two carboxylate groups in isocinchomeronic methyl ester. If a monoacid could be made from isocinchomeronic methyl ester, then the corresponding acid chloride can also be made by treatment with thionyl chloride.



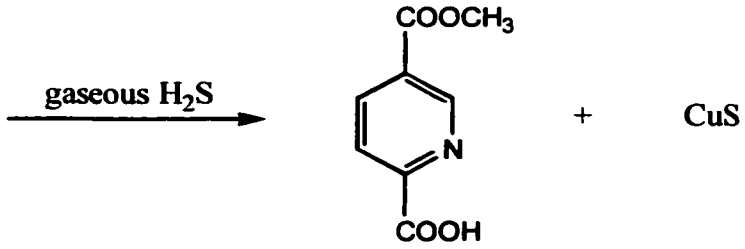
3 **10** **11**

We were fortunate to find a literature preparation of this mono-acid of isocinchomeronic methyl ester[18]. Commercial isocinchomeronic acid was converted into its dimethyl ester in refluxing methanol in the presence of catalytic sulfuric acid. Upon reaction with copper(II) nitrate hydrate in refluxing methanol, isocinchomeronic methyl ester was converted into a deep violet-blue crystalline mass. The original paper[18] did not explain the composition of this copper complex, but we believe that the real composition of this complex is the one

shown in the following scheme based on the stoichiometric amount of copper(II) sulfide collected as a precipitate. The mono-acid of isocinchomeronic methyl ester was formed as the desired product. 1H NMR showed the disappearance of one methyl ester group and the other features of the NMR pattern remained. The driving force of this reaction appears to be that the ester in the 2-position forms a stronger coordination bond with copper(II) than the other because of the adjacent nitrogen ligand and so is more rapidly hydrolyzed to the acid salt, coordinated as shown to the copper. The disappearance of one ester in the proton NMR indicated the formation of desired product. Therefore, the two ester groups were cleanly differentiated by this 2-step sequence.



12 **3** **13**



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The isocinchomeronic mono-ester acid was dissolved in neat thionyl chloride and refluxed for 2 hours. A white solid was obtained after removing the solvent with mp. 194.1-195.1°C. This white solid was dissolved in anhydrous

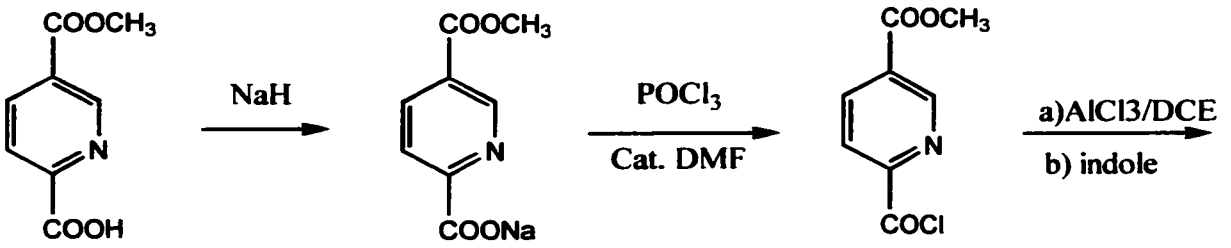
methylene chloride and reacted with methanol, which quantitatively converted it into isocinchomeronic diester and confirmed the identity of the white solid as the acid chloride. The diester showed two methyl ester peaks in the NMR spectrum, at 3.98 and 4.03 ppm, while the mono-acid and the acid chloride showed only one peak at 4.03 ppm. These two positions are characteristic of the two differently sited esters, 3.98 ppm for the adjacent 2-ester and 4.03 ppm for the remaining 5-ester. This was shown since after acylation (below) the same single ester methyl group showed also at 4.03 ppm. Similarly, the mixture of acylated mono-esters from indole and the bis-acid chloride above, and quenching with methanol, showed their methyl peaks at 3.98 and 4.03 ppm.

1.4 Optimization of Acylation Conditions

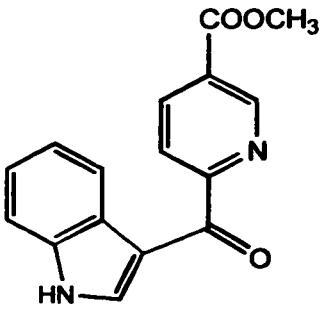
At this point, we knew that acylation worked between indole and acid chloride, but the yield was low: the combined yield for the reaction of the bis acid chloride was only 35%. Better conditions needed to be found to improve the yield. When we examined the literature more carefully, two sets of different conditions were found.

Following the first optimized condition, the monoacid was converted into its sodium salt by sodium hydride. This salt was then treated with $POCl_3$ in the presence of catalytic amount of DMF to give the corresponding acid chloride. When the reaction without the presence of DMF was quenched with methanol, no expected isocinchomeronic dimethyl ester was formed. It indicated that DMF is necessary in this acid chloride formation. When it was used, the acid chloride

was treated with aluminum chloride and reacted with indole, forming the desired product in about 65% yield.



10 **14** **11**



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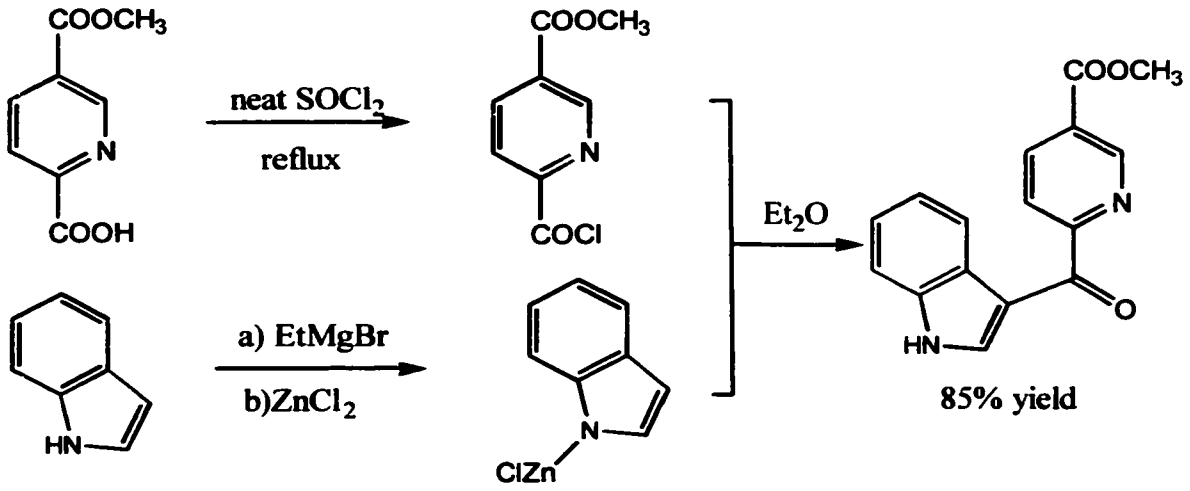
When the acid chloride was made from monoacid and neat thionyl chloride, it did not react with indole under the above acylation conditions. In another optimization trial, the monoacid was converted into its acid chloride by treating with neat boiling thionyl chloride. In this case, the acid chloride was obtained as a white solid and could be stored under nitrogen at 0°C over several weeks. Meanwhile, indole was treated with ethyl magnesium bromide to give indole anion. There was evidence[19] that the indole nitrogen is the acylation site if the counter ion of indole anion is hard, such as sodium or potassium, but when a soft ion such as zinc is used, the acylation site will be the 3-position of indole.

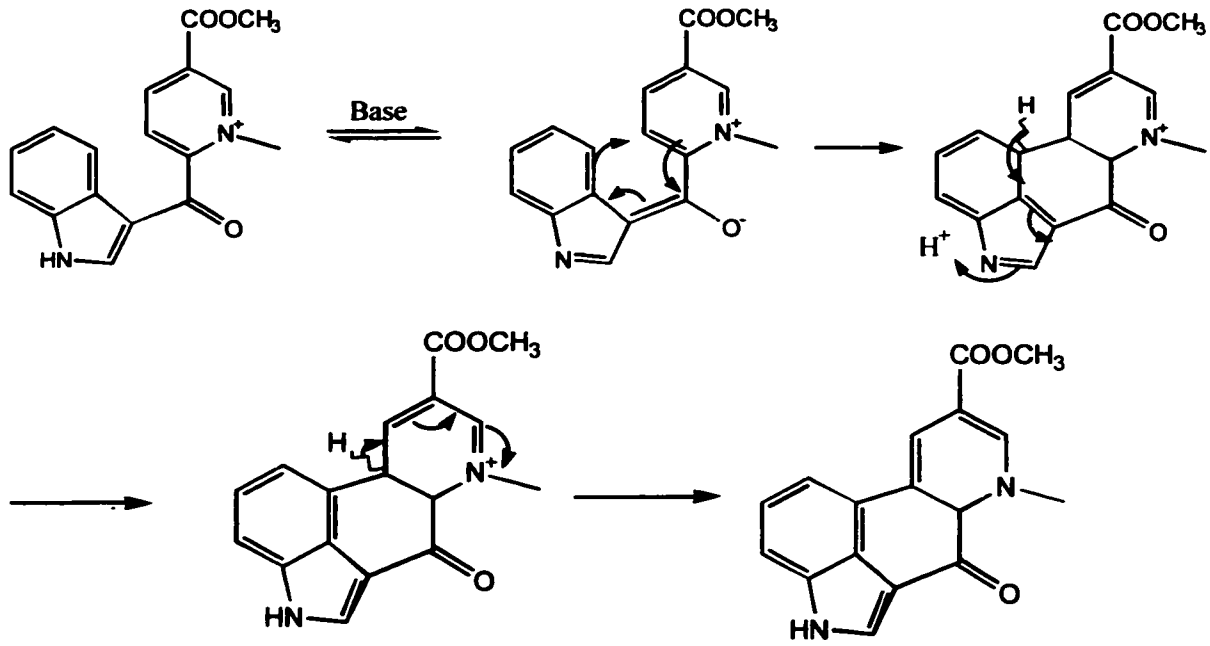
So after indole was treated with ethyl magnesium bromide, the resulting Grignard reagent was treated with an equal molar amount of zinc chloride in anhydrous ether. When this mixture reacted with the isolated acid chloride, the desired acylation product was obtained in 85% overall yield.

The product was isolated as an off-white solid with mp 215.7-216.8°C. Its proton NMR exhibited a characteristic pattern that we were to see in many of the following products. The aromatic peaks were well resolved and appeared as expected. The indole 2-position showed as a singlet at 7.80 ppm, and the protons on the benzene ring as: δ_4 = 8.25 (doublet); δ_5 = 7.23 (triplet); δ_6 = 7.23 (triplet); δ_7 = 7.25 (doublet), all with couplings of J = 8.0Hz. The pyridine protons were nicely separated with the α-proton as a singlet at δ = 8.27 and the other two as doublets at δ =8.45 and 8.60 (J = 5.5Hz). In accord with the findings above the ester methyl protons showed as a singlet at δ = 4.02.



2. Attempts of Construction of Bond a after Bond b

With the acylation product in hand, we began the investigation of the construction of bond a on this compound. We were attracted by the simplicity of the pericyclic ring closure outlined below in Scheme12. This corresponds to the parent example of the thermal cyclization of *cis*-stilbene, which is known to be difficult[20]. In our case in Scheme 12 the pericyclic transition state is more favored because of the charged nature of the atoms in the cycle. Whereas Scheme 12 shows the reaction occurring on the basic salt, one may write the equivalent change with protonation in an acid medium.

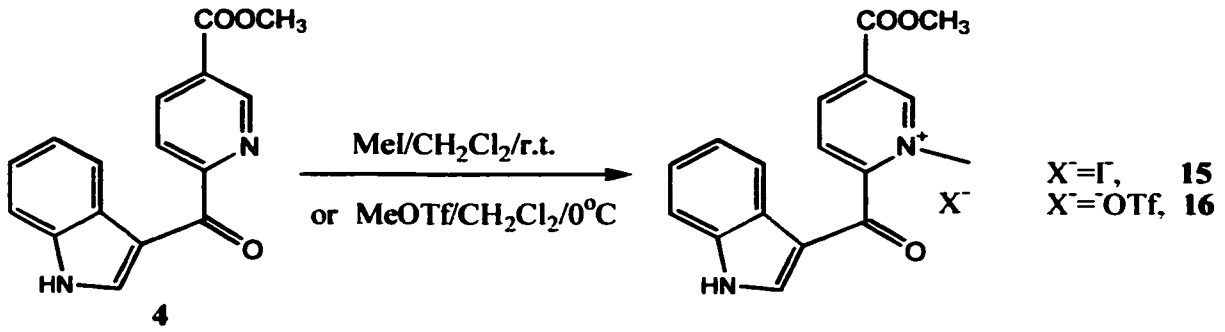


Scheme 12: Proposed Pericyclization

In any case the possibility of achieving this reaction will depend on the relative stability of the product compared to the starting compound since pericyclic reactions are always equilibria. On the positive side the base is neutralized, the charges are cancelled in the product, and a new σ-bond and ring are formed; on the other side is the loss of stability on de-aromatizing the pyridinium aromatic ring.

2.1 Methylation of Pyridines to Pyridinium salts

It is standard procedure to methylate pyridines at nitrogen to get the corresponding pyridinium salt. Usually, this methylation is done with iodomethane or methyl triflate. To get familiar with this reaction, we first tried methylation on the model, methyl nicotinate. The reaction went smoothly in methylene chloride in the presence of excess iodomethane. The corresponding pyridinium salt appeared as a solid which precipitates out from the solution within 1 hour. However, when this methylation was used on ketone, the complete reaction took much longer to finish, usually more than 3 days, when this methylation was used on the ketone, even in the presence of ten equivalents of iodomethane. The reason for this might be that the ketone group between indole and pyridine decreases the electron density on pyridine nitrogen.



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A more reactive methylation reagent, methyl triflate, was also tried. When the reaction was done at room temperature, starting material disappeared within thirty minutes, but the reaction was not as clean as that in which iodomethane was used and the product was an oil instead of a nice solid. When the reaction was done at 0°C, it was much cleaner and finished within 4 hours, yielding a nice solid (mp. 245.3-244.2°C) in 98.3% Yield. The NMR showed downshifted peaks for the pyridinium protons at 9.78, 9.29 and 8.61 ppm respectively, compared with the corresponding peaks in the parent pyridine at 9.20, 8.60 and 8.45 ppm.

2.2 Attempt of Electrocyclization on the Pyridinium Salt

As discussed at the beginning of this section, we believed that a electrocyclization could happen in principle. If the desired product is obtained, only two subsequent functional group manipulations are required, namely reduction of the ketone and reduction of the dihydropyridine to tetrahydropyridine, leading to methyl lysergate.

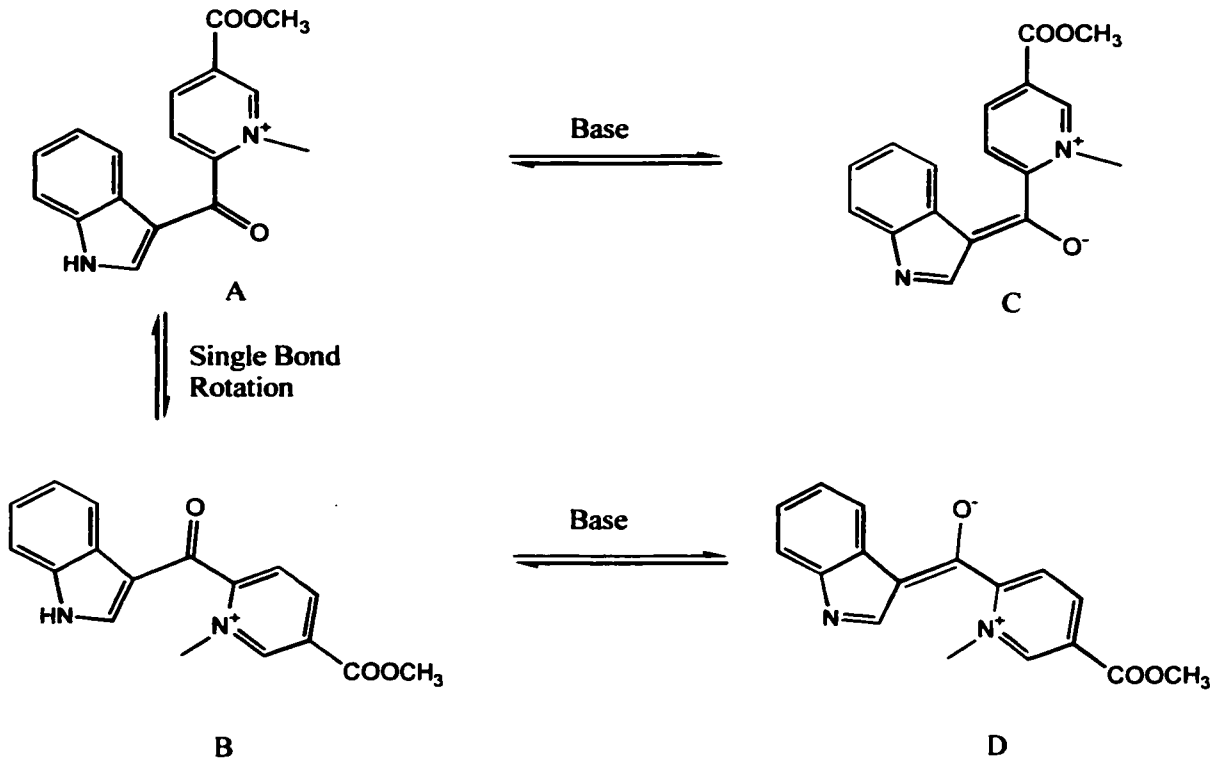
The ketone pyridinium salt was treated with sodium methoxide in methanol at refluxing temperature. The reason to choose methoxide as the base is that it would not introduce the complication of ester exchange. No reaction occurred during an overnight period. Higher temperature might be needed for this reaction so the ketone pyridinium salt was next dissolved in dry DMSO and sodium hydride (2.0 equiv.) was used as the base. After 12 hours at 150°C, no desired product was observed and the starting material was fully recovered.

Two reasons were proposed for this outcome. 1) The transition state of this electrocyclization involves a state in which two aromatic systems (indole and pyridine) have to be destroyed at the same time, which implicates a higher transition state energy, hence higher temperature needed to push the reaction. 2) The preferred conformation of the starting material might not be the one drawn in the proposed reaction mechanism in Scheme 12.

Before the base treatment, the single bond between indole and ketone can more or less freely rotate, giving two conformers, A and B, in equilibrium, with B probably the more stable conformer, as shown in Scheme 10. In fact there is considerable resonance between the indole and the ketone so that it is more profitably seen as a vinylogous amide and as such the bond has more double bond character restricting free rotation. Once base acts on this compound, however, the two enolates C and D will be obtained, with much more double bond character in the indole-ketone bond.

If a full mole of base is used then essentially only forms only hope of achieving this will be to use only a catalytic amount of base so as to provide the

full equilibrium in Scheme 12 between C and A, A and B, B and D, thus insuring enough of C that it can be drawn off of the equilibrium to the cyclized product. It will of course only be drawn off if the product is the most stable of the various structures in equilibrium.C and D will be present and if C is heavily favored there can be no pericyclization.



Scheme 13: Reactive conformer

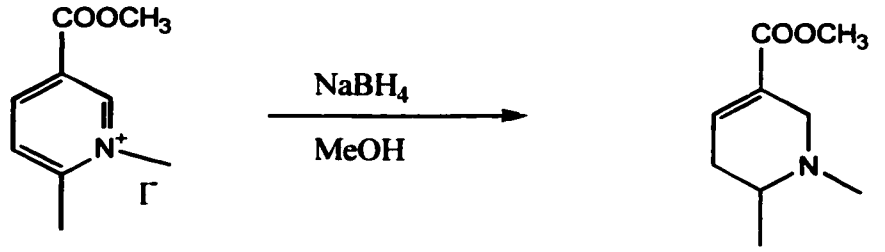
However, when a catalytic amount of base was used in the same reaction conditions, the desired product was not obtained either, and only the starting material was recovered completely.

2.3. Reduction of the Ketone Pyridinium salt

Based on these analyses, a more amenable electrocyclization candidate has to be used. We proposed that the pyridinium salt might be reduced to its tetrahydropyridine or dihydropyridine derivatives, and these reduced compounds used as the electrocyclization starting material. Then the transition state will not involve a state in which two aromatic systems have to be destroyed at the same time, and only the indole aromaticity needs to be temporarily disrupted.

The literature shows that pyridinium salts can be reduced to their tetrahydropyridine derivatives by sodium borohydride in methanol[21].

Methyl 6-methyl-nicotinate was chosen as a closer model to the ketone pyridinium salt since it has an alkyl substitution on the 6-position. Its pyridinium salt (iodide) was made in the manner described in section 2.1. The resulting salt was treated with sodium borohydride in methanol at room temperature and the desired product, arecoline, was obtained in 75% yield.



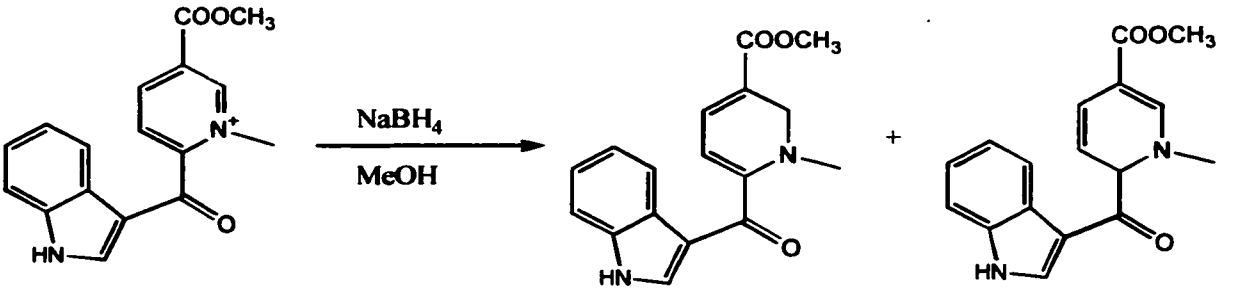
17 **(arecoline)18**

The reduction of the ketone pyridinium salt was carried out in the following way. The salt was only marginally soluble in methanol, and sodium borohydride was added into this suspension as a solid. The starting material disappeared in about 5 minutes. Two new neutral products were observed on the TLC plate. Attempts to separate these two products by chromatography

failed due to the instability of the product on silica gel. One of the decomposed products has the characteristic NMR peaks of the indole and another has the character of a reduced pyridinium salt besides some unrecognizable peaks in the NMR spectrum. The mass spectrum did not provide useful information to solve this decomposition.

A different way to harvest the products was tried for this ketone pyridinium salt reduction. After reduction was done in methanol by sodium borohydride as before, water was added into the reaction. A red precipitate came out of solution. This solid was determined to be a 4:1 mixture of two products by NMR. Mass spectrum was also in agreement with the proposed products.

It is worth noticing that the obtained mixture was not very stable in solution. The material dissolved in the NMR tube was observed to decompose after 2 hours, and was totally decomposed within two days. However, the solid material directly precipitated could be kept over a period of two weeks or so at 0°C.

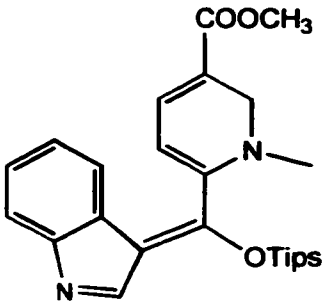


16 **19** **20**

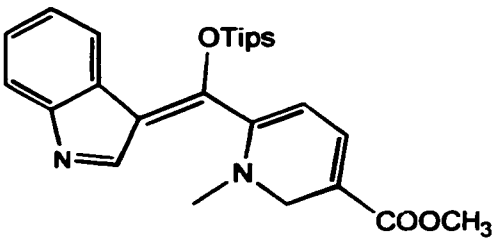
2.4 Electrocyclization on Partially Reduced Pyridinium Salts

As discussed in section 2.2, one of the reasons that electrocyclization failed on the ketone pyridinium salt might be that the transition state involves a stage in which two aromatic systems (indole and pyridine) have to be destroyed at the same time and this decreases the possibility of electrocyclization. Now we have an intermediate, which only has one aromatic system. This material has a better chance to electrocyclize than the previous ketone pyridinium salt.

The major product in that 4:1 mixture has the double bond in the tetrahydropyridine at the desired position to electrocyclize. Since it is the major component, the mixture could be used as it is.



bulky Tips group in open space,
favored conformation



bulky Tips group close to indole,
unfavored conformation

Scheme 13: Conformation Analysis

Another problem remaining in this approach is to create a double bond between indole and ketone, so that three double bonds are set for the electrocyclization. This might be solved by making the enol ether of this ketone compound as shown below. Triisopropylsilyl chloride was chosen as the

enolation reagent because the bulkiness of this reagent might keep the enol in the desired conformation.

So the mixture was dissolved in methylene chloride and sodium hydride was added as the base. Triisopropylsilyl chloride was added after that. TLC showed many products with no starting material left after 10 minutes. Separation of this reaction mixture resulted in no desired product. It was argued that this observation might be due to the instability of this tetrahydropyridine derivative.

3. Summary

The proposed Route B, discussed in this chapter, involves making two bonds, bond **b** and **a**, in that order. Bond **b** was successfully made by indole 3-acylation with an acid chloride in the presence of either $AlCl_3$ or a combination of EtMgBr and $ZnCl_2$. A lysergic acid precursor with every carbon in place was obtained after differentiation of two ester groups and methylation of pyridine. Various attempts to make bond **a** after bond **b** failed. The reasons for this failure appear to have been: 1) the transition state involves a species in which both indole and pyridine aromaticities have to be destroyed at the same time; 2) the electrocyclization candidate has a conformation which disfavors such a reaction; and 3) the more suitable reduced electrocyclization candidate is unstable.

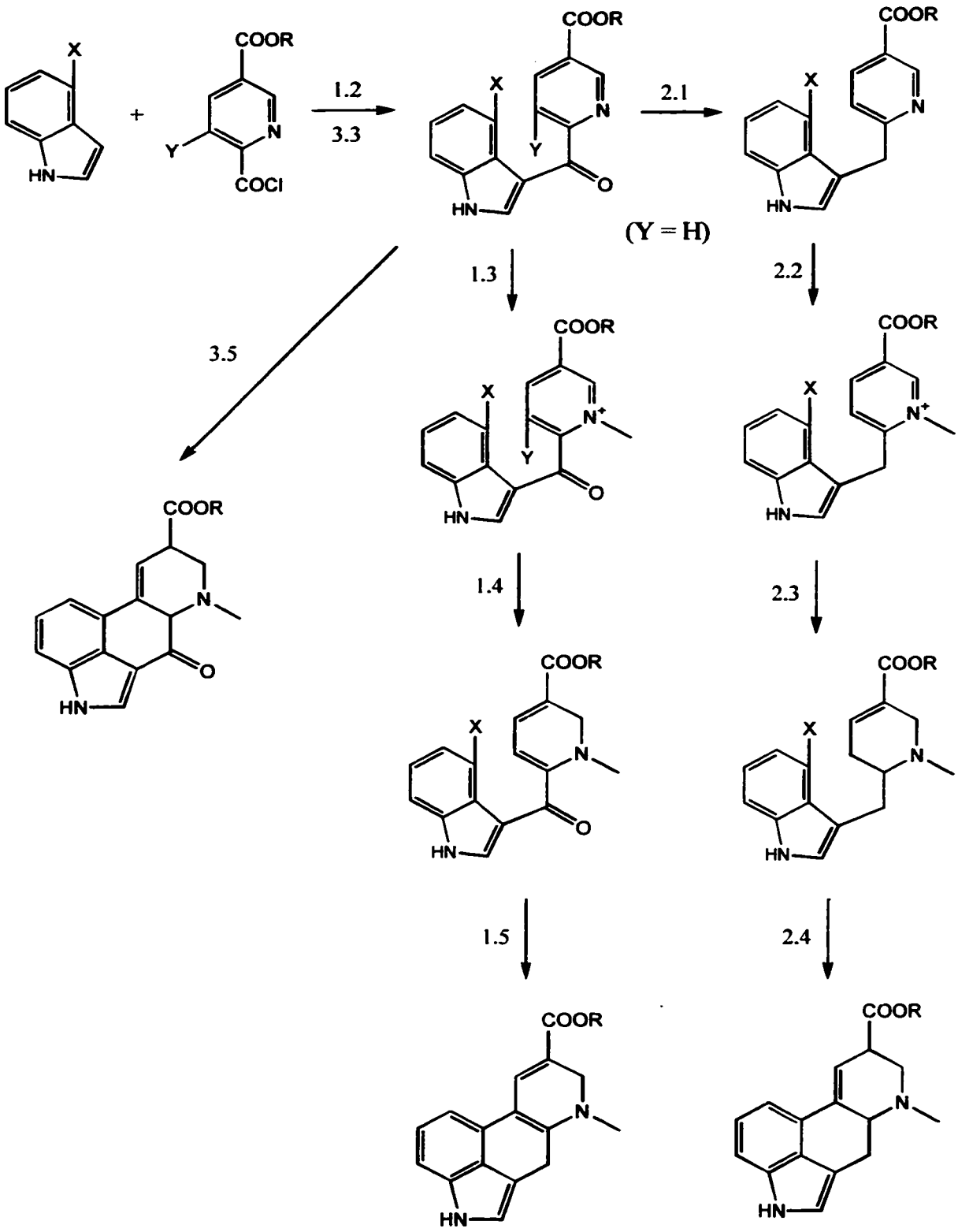
Installation of halogen(s) on indole and pyridine, and subsequent attempts at ring closure, will be discussed in chapter 2.

Chapter 2

Approach via Route B with Substituted Aromatics

In chapter 1, attempts were discussed for making bond **a** by electrocyclization after bond **b**. Reasons for the failure of this electrocyclization approach were also discussed. One of them is that the transition state of cyclization involves a stage in which the aromaticity of both the indole and the pyridine has to be destroyed. To avoid this loss of aromaticity in the transition state, one could instead install halogen(s) at the sites for joining bond **a** on the indole and/or pyridine ring. These can serve as handles to close the ring via various aryl halide and diaryl halide coupling reactions in the literature[22], which suggests that such a route might be feasible.

This approach begins with a facile joining of the two main fragments and explores the subsequent chemistry and attempts at cyclization of bond **a** from various halogenated derivatives containing all the skeletal atoms of lysergic acid. Chapter 2 describes these experiments, which are summarized as a guide in Scheme 14.



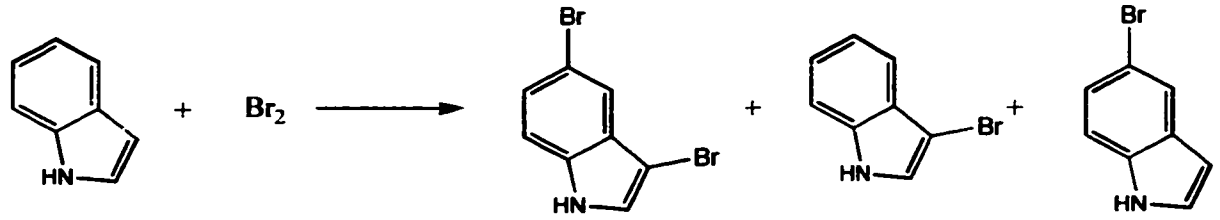
Scheme 14: Summary of Route B in Chapter 2

(chapter sections on arrows)

1.1 Preparation of the 4-Halo-indoles

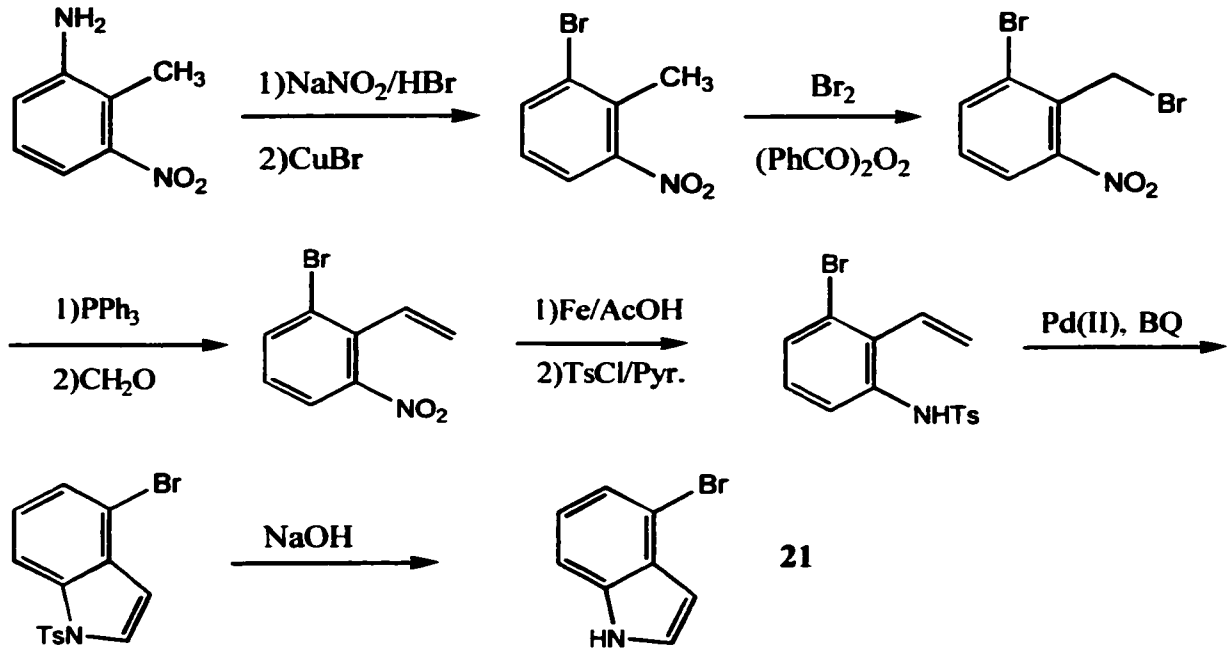
If the 4-position of indole can be halogenated, bond **a** could be constructed by using the aryl halogen as a handle. Various organometallic methods are available but the electrocyclization approach in Scheme 14 can still be fruitful because it is the most efficient way to construct bond **a** in one reaction. Intramolecular Heck reaction is also a choice if the pyridine is partially reduced. Intramolecular radical cyclization and cyclization via a benzyne intermediate as in Julia's synthesis are also choices which will be examined in this chapter.

It is not easy to introduce halogen onto the 4-position of indoles since the 3- and 5-positions are usually the most reactive sites towards halogenation. For example, when indole is treated with bromine, a mixture of products is obtained, with no regioselectivity.



Fortunately, there are several methods to introduce halogen at the 4-position of indole in the literature, starting either with a substituted benzene derivative or with indole itself. In fact 4-bromo-indole is an article of commerce but is very expensive. The following methods are the three most widely adopted ones.

Method A: A synthesis of 4-bromo-1-tosylindole based on the Pd (II)-catalysed cyclization of an o-vinylaniline p-toluenesulfonamide has been developed by Hegedus[23] for the synthesis of ergot alkaloids.

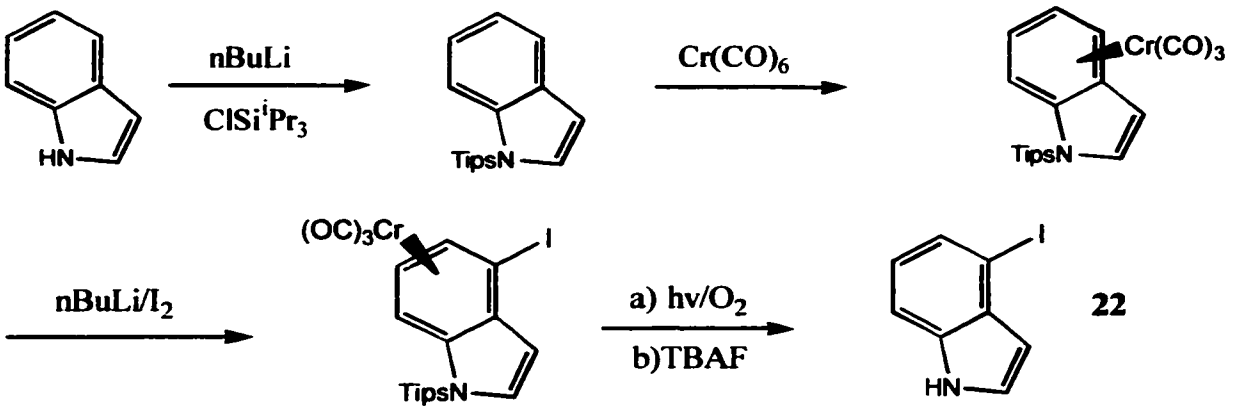


Scheme 15: Synthesis of 4-bromo-indole (method A)

In this method, 2-Amino-6-nitrotoluene, a commercially available compound, was converted by a Sandmeyer reaction to the 2-bromo compound[24]. Free radical monobromination produced α,2-dibromo-6-nitrotoluene. Phosphonium salt formation and Wittig reaction with formaldehyde provided the styrene derivative. Reduction with iron in acetic acid produced the requisite aniline, and tosylation gave the p-toluenesulfonamide. Pd (II)-catalysed oxidative addition converted the product to N-tosyl-indole. This compound was readily hydrolyzed to the free 4-bromo-indole by NaOH.

Overall, however, this is a 7-step sequence, relatively long to make a target molecule of this size and complexity even though the overall yield is about 30%.

Method B: It is known that arenes can be coordinated under mild conditions with tricarbonylchromium(0)[25a,b]. In 1988 Widdowson reported[26] that N-protected indole tricarbonylchromium(0) complexes could be substituted regioselectively at the 4-position of indole.

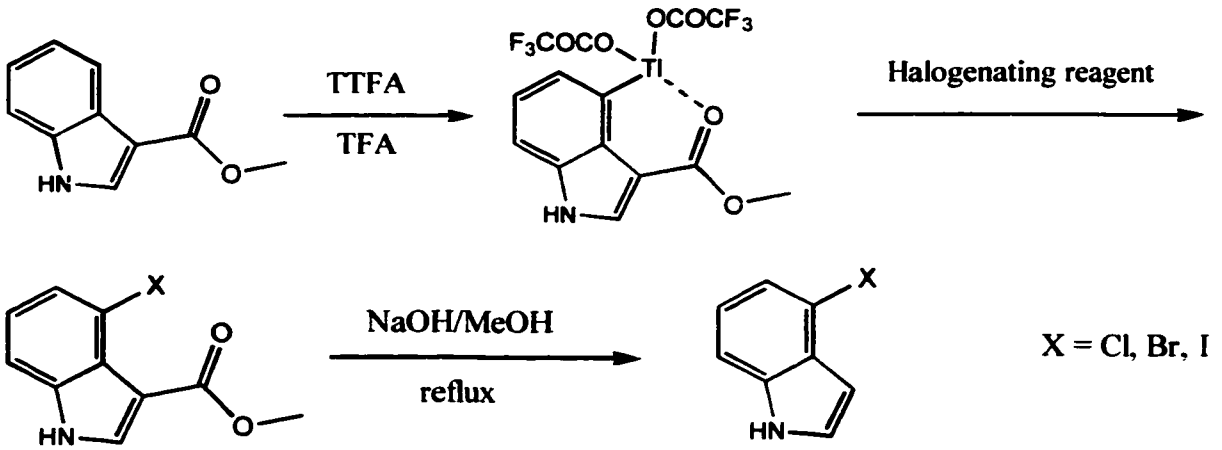


Scheme 16: Synthesis of 4-iodo-indole (method B)

N-Silylation of indole gave the protected indole in quantitative yield. Direct complexation of the N-protected indole with hexacarbonylchromium gave the chromium complex, which was lithiated with n-BuLi then quenched with iodine to give the 4-Iodo-indole complex. The bulky protecting group on the indole nitrogen provided adjacent hindrance to protect the 2- and 7- positions. The complexing chromium was irradiated with oxygen for decomplexation to the silylated 4-iodo-indole. Desilylation was carried out with tetrabutylammonium fluoride (TBAF) to afford the requisite 4-iodo indole.

Compared with method A, this route is much shorter and more efficient. But still, N-protection is needed and this generally adds two steps to the route, which we wished to avoid.

Method C: A simpler variation of this approach involves regioselective thallation to activate the indole at the 4-position[27]. When 3-methoxycarbonylindole was treated with thallium(III) trifluoroacetate (TFAA) in trifluoroacetic acid (TFA), 3-methoxycarbonyl-indole-4-thallium(III) bis-trifluoroacetate, was obtained. This intermediate was treated with various halogenating reagents to give 3-methoxycarbonyl- 4-halogeno-indole. Hydrolysis and decarboxylation affords the desired 4-halogeno-indole.



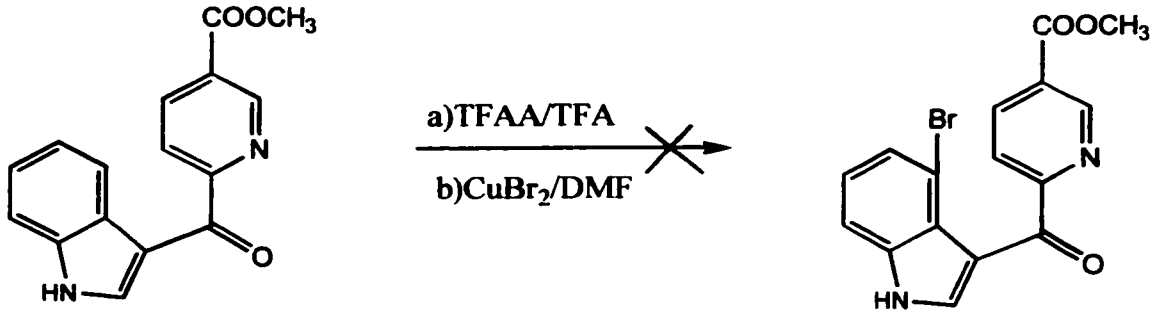
Scheme 17: Synthesis of 4-halo-indole (method C)

Compared with methods A and B, method C is much shorter. The first two steps are combined as a one-pot reaction, no purification needed for the thallium-containing intermediate. The overall yield is 41%.

It is also worth notice that the same protocol was successful on indole-3-carboxaldehyde, which implies that it is the carbonyl oxygen, common to the ester and the aldehyde, which directs the thallium (III) intramolecularly onto the 4-position of the indole.

We decided that method C is the best choice because it is the most efficient and shortest route, and more importantly, no N- protection is needed. Since the regiochemistry in the above examples is apparently dictated by a carbonyl group at the indole 3-position, method C was chosen to introduce the halogen onto the 4-position of the indole in our pyridine-indole ketone.

Unfortunately, when the indole 4-bromination method was applied to this ketone compound, no desired product was obtained, and only the starting material was recovered. We also tried the iodination on the ketone compound using the same method for the preparation of 4-iodo-indole. Again, no desired product was formed and only the starting was recovered.



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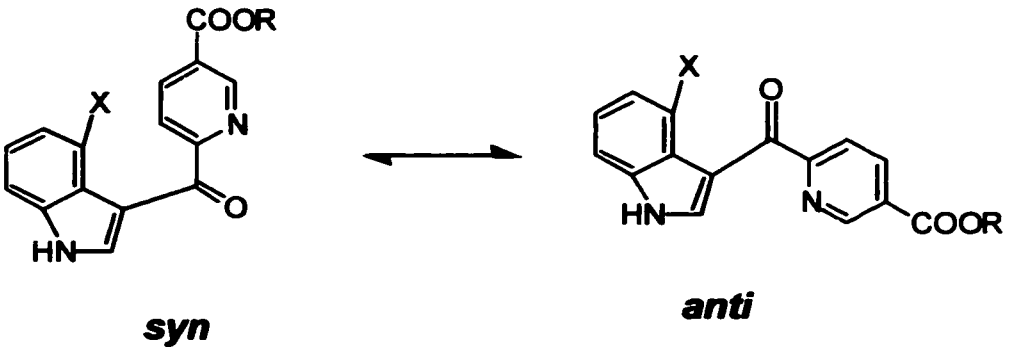
This result suggested that the directing carbonyl in the simple cases had a conformation *syn* to the entering thallium and coordinating with it, whereas in the present ketone that conformation was not available, the other being apparently more stable. Conceivably more vigorous thallation conditions, i.e., higher temperatures, might have succeeded but we did not try this, having a healthy respect for the poisonous nature of thallium compounds.

The alternative was to halogenate first and acylate afterwards, although this involves intermediate removal of the activating 3-ester before acylation; this



syn ***anti***

Scheme 18: Conformation Analysis for Halogenation

extra step would have been avoided in the direct halogenation of our 3-acyl-indole. The 3-methoxycarbonyl-indole at least was an available starting material.

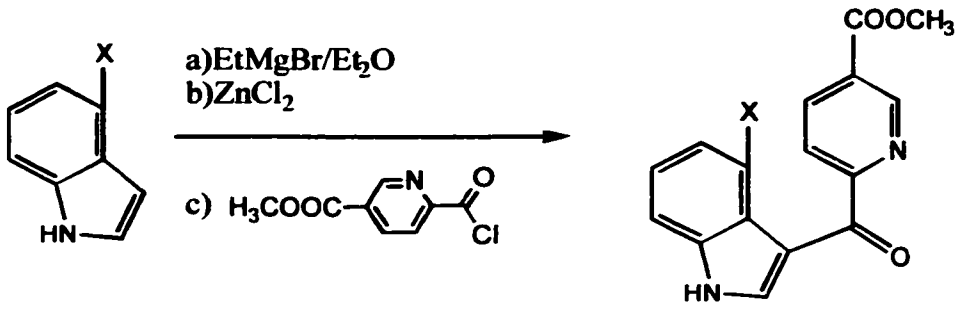
These halogenated indoles were prepared according to the procedure of Somei[27] by thallation of commercial 3-methoxycarbonyl-indole with thallium(III) trifluoroacetate in trifluoroacetic acid at room temperature followed without isolation by $CuBr_2$ in DMF for the bromo derivative, or KI for the iodo derivative. The corresponding halogenated esters were hydrolyzed in each case with NaOH

in aqueous methanol to the 4-halo-indoles themselves, identical with the authentic products described by Somei. The carbon-13 NMR showed the characteristic peak for halo-substituted aromatic carbons at 88-90 ppm.

1.2 Acylation of the 4-Halo-indoles

Following the acylation procedure in chapter 1, the two 4-halo-indoles were acylated with the acid chloride of isocinchomeronic acid mono-ester. The aluminum chloride acylation on the solid isolated mono-acid chloride again was unsuccessful, but the basic Grignard/$ZnCl_2$ procedure cleanly afforded the bromo- and iodo-derivatives in good yield as crystalline keto-esters, mp. 235° and 246°C, respectively.

The proton NMR of these compounds showed the characteristic pattern of the 4-substituted indoles with only two doublets and one triplet. This also showed that the halide on the 4-position survived the Grignard formation conditions with no halo-metal exchange occurring. The proton NMR also showed the disappearance of the distinguishable indole 3-proton at 6.3 ppm, which stands out from the rest of the aromatic peaks. NMR also showed the pyridine peaks encountered before. All of these supported the identity of the desired compounds.



X=Br 23

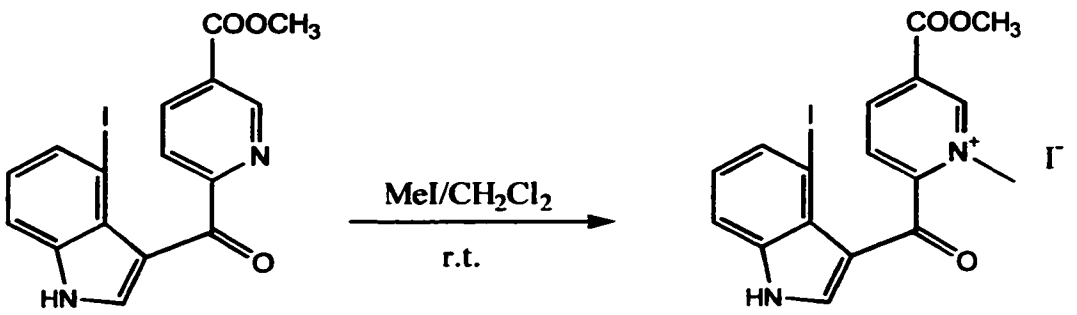
X=I 24

1.3 Methylation of the Keto-Pyridines

As discussed in chapter 1, it is very difficult to make bond **a** if two aromatic systems have to be destroyed at the same time. It was also known from chapter 1, that the dihydropyridine ketone derivatives decomposed too readily without undergoing the desired electrocyclization reaction. However, we considered that with halogen on the indole 4-position, the situation might be different. The halogen might facilitate the electrocyclization reaction by loss of HX, either on the full pyridinium salt or on its dihydro derivative. To proceed via such an approach, it was obvious that the pyridine nitrogen should be methylated and the subsequent pyridinium salt has to be partially reduced.

It was to be expected that the aromatic iodo-derivative would be more reactive than the bromo-compound, and so the iodo ketone was chosen as the candidate to move forward. Dissolved in methylene chloride with 5 equivalents of iodomethane, the iodo-ketone produced a precipitate of the methyl-pyridinium salt on standing overnight. This pale yellow solid was filtered and washed with cold methanol. The salt was obtained in good yield with mp. 256.9-257.8°C and the proton NMR in CD_3CN showed an additional methyl peak at 3.8 ppm and the

three typical pyridine protons shifted downfield to a singlet at 9.8 ppm and two doublets at 8.8 and 8.2 ppm (J = 7.8 Hz).



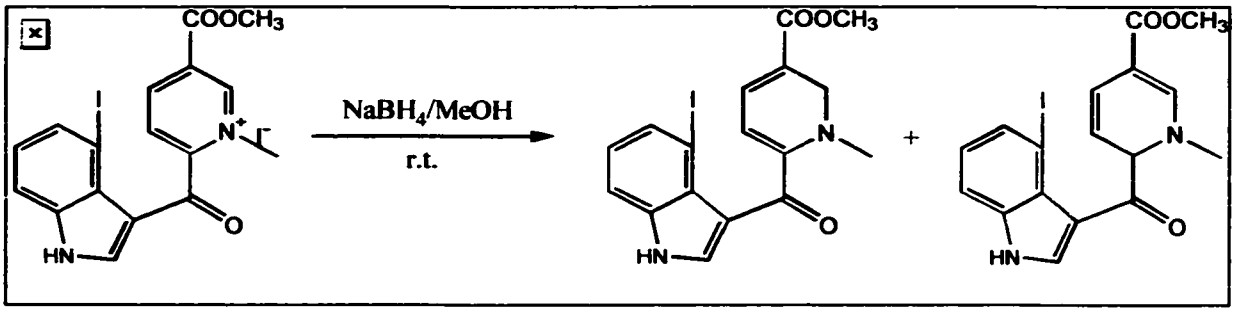
23 **24**

1.4 Reduction of the Keto-pyridinium Salt

The same reaction conditions were used as in chapter 1 to reduce this pyridinium salt. The salt was suspended in methanol and excess $NaBH_4$ was added. The reaction turned red and the solid disappeared within a couple of minutes. As before addition of water induced a red precipitation from the solution. This solid was collected and washed with a cold mixture of methanol and water. The red solid obtained had mp. 135.0-136.0°C (dec.) and its NMR in $CDCl_3$ indicated again that it was a 4:1 mixture of the same two dihydropyridine isomers as obtained without the iodine substitution, as shown in the following scheme.

Despite our concern that this mixture might not be stable enough to manipulate, we found that the precipitated solid itself can be kept under nitrogen over a period of two weeks at 0°C. However, it was also found that when the

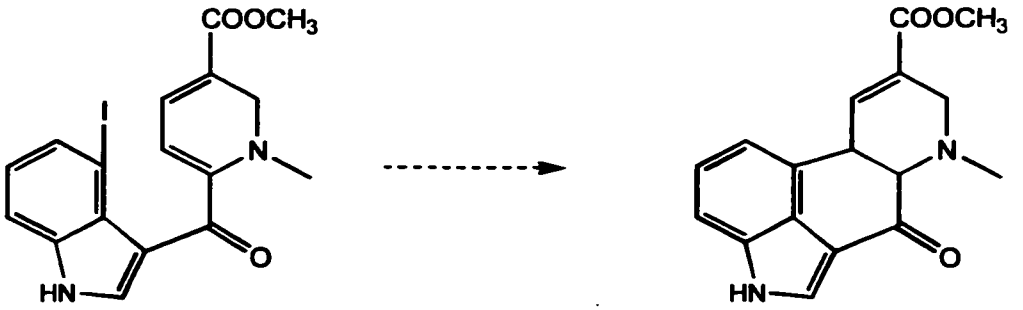
solid material was dissolved in NMR solvents, such as $CDCl_3$ and acetone-d6, the spectrum became very messy after about two hours, and no original compound peaks could be recognized in the spectrum after 6 hours. In this the mixture mirrored the behavior of the non-iodinated species in chapter 1.



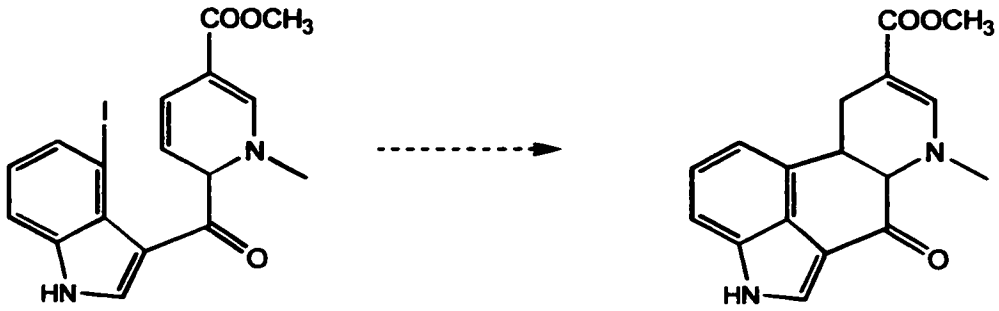
24 **25** **26**

1.5 Attempts at Cyclization

Although this partially reduced dihydropyridine derivative was not very stable, we tried various attempts at electrocyclization in the hope that the cyclization reaction might be faster than the decomposition we had seen in the spectra.



25 (major SM)



26 (minor SM)

Experiment	Reaction Conditions	Ref.	Results
1	Bu_3SnH/AIBN/Toluene	35	aromatic proton peaks broadening in NMR, indicating the polymerization of starting material, no SM left
2	Pyridine-d5/r.t.	36	Decomposition of SM, SM disappeared completely after 2 hours
3	a)t-BuLi (3 equiv)/ THF,-78°C to r.t. b)H_3O^+	37	Decomposition of SM, dehalogenation observed from proton NMR (2 doublets & 2 triplets from indole phenyl moiety)
4	SmI_2/TMG/THF/-18°C	38	many different spots on TLC, none of them major; isolation of the relative major products leads to no desired one.

Table 1: Attempted Cyclization on (25 + 26)

In the above table are summarized four different experiments trying to effect the cyclization. None of these was promising.

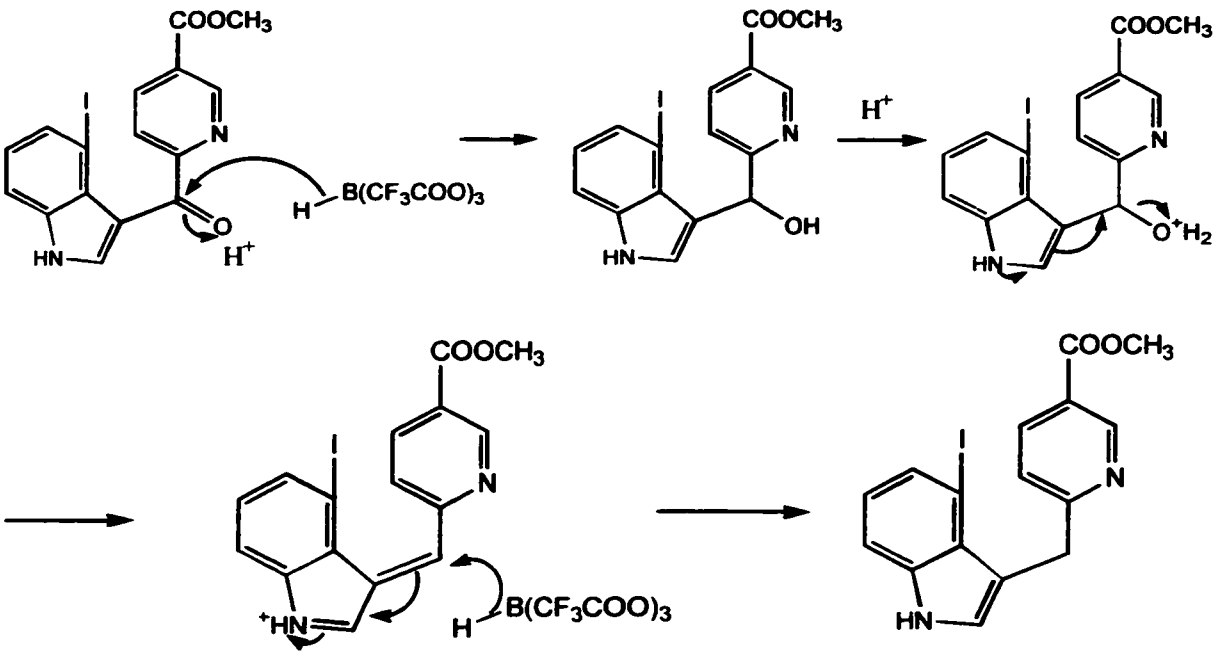
2.1 Reduction of the 3-Acylated Indoles

A number of plans for cyclization of bond **a** required the reduction of the ketone between the two aromatics, and in any case it must ultimately be reduced, so we explored ways to achieve this.

We first attempted to reduce the ketone by reduction of the tosylhydrazone. However, we were surprised to find that the ketone compound was inert to tosylhydrazine, even under forcing conditions. One plausible explanation to this is that this ketone is not a simple ketone, but more accurately is a vinylogous amide much stabilized by resonance with the indole N-H.

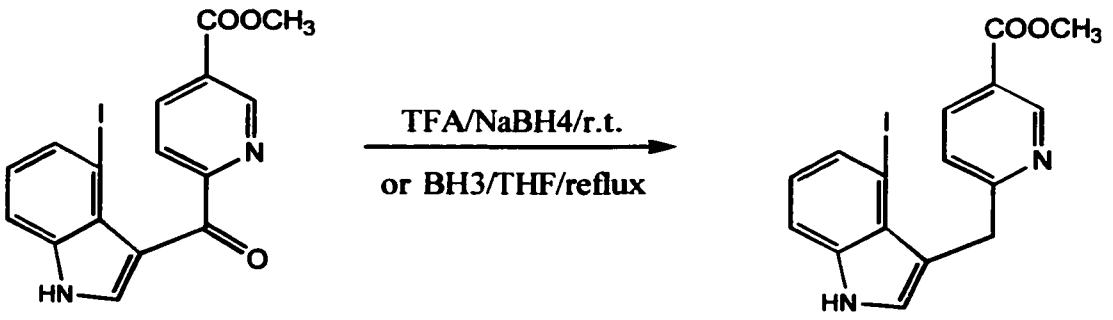
It was also known[28] that ketone functional groups on the 3-position of indole can be reduced by $NaBH_4$ in DMF/H_2O. When these conditions were tried on our ketone, however, only starting material was recovered.

However, two acidic reductions were found to effect this reaction. One of these is the reduction with $NaBH_4$ using TFA as both the solvent and one reagent[29, 30, 31]. $NaBH_4$ +TFA forms trifluoroacetoxyborohydride first as the more acidic reducing reagent[32]. The facile deoxygenation can be rationalized by invoking a resonance-stabilized carbocation (indolenium ion) formed in the deoxygenation sequence: 1) initial reduction of the ketone carbonyl by trifluoroacetoxyborohydride formed *in situ* to produce an indolyl carbinol; 2) acid-catalyzed protonation of the resultant alcohol and loss of water affording an indolenium ion and 3) conjugate addition of hydride to the indolenium species to re-establish the indole.



Scheme 19: Mechanism for Ketone Reduction

After aqueous workup and chromatographic purification the desired methylene product was obtained in 62% yield as a white solid (mp. 189.2-190.3°C). The proton NMR showed a new singlet of two protons at 4.6 ppm, which indicated the reduction of ketone to methylene. The aromatic protons retained their characteristic NMR pattern.



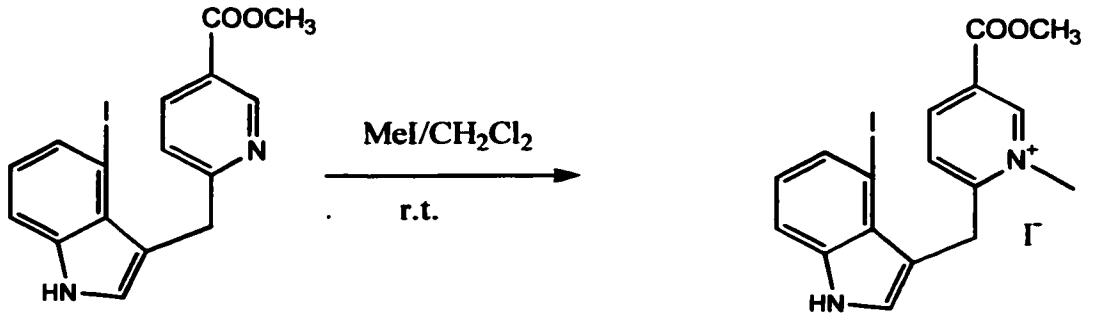
23 **27**

An alternative acidic reduction of this diaryl ketone to methylene was also successful by the action of BH_3 in refluxing THF, presumably by essentially the same three-step mechanism. The product prepared in this way was identical.

2.2 Methylation of the Reduced Keto-pyridines

Once the ketone has been reduced, it was methylated to the methyl-pyridinium salt. As discussed in chapter 1 (section 2.1), the ketone functional group decreases the electron density on the pyridine nitrogen, which in turn sharply reduces the rate of the methylation reaction. We presumed that with the ketone group removed, the methylation should go much faster and the more reactive methylating agents, such as methyl triflate, would not be necessary.

Iodomethane was used as the mild methylation reagent. After two hours, no neutral compound was detected on TLC, implying that the neutral starting material was completely converted into the pyridinium salt. A precipitate came out of solution during the reaction and the solid was collected and washed with cold ether. The pyridinium salt was obtained as a solid in quantitative yield (mp. 213.9-215.1°C).



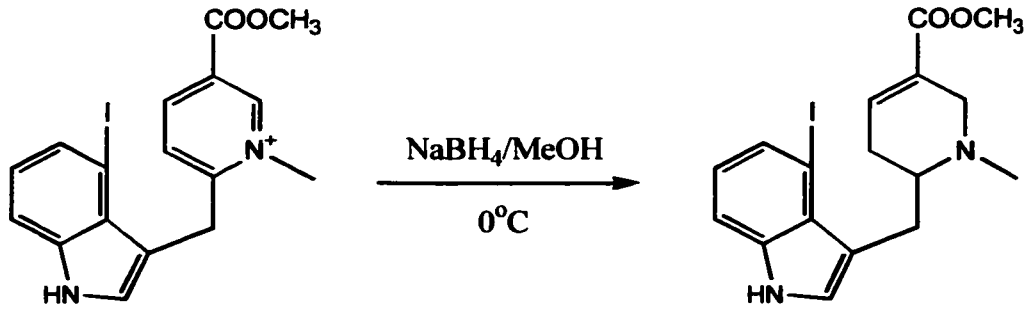
27 28

The proton NMR showed an additional methyl peak at 4.6 ppm and the same downfield shift of pyridine protons as before, without much effect on the indole protons.

2.3 Reduction of the Keto-pyridinium Salt

In chapter 1, section 2.3, it was shown that the pyridinium salt can be reduced to its tetrahydropyridine derivative by the action of $NaBH_4$ in methanol[21]. The same conditions were applied to the methylene pyridinium salt made above.

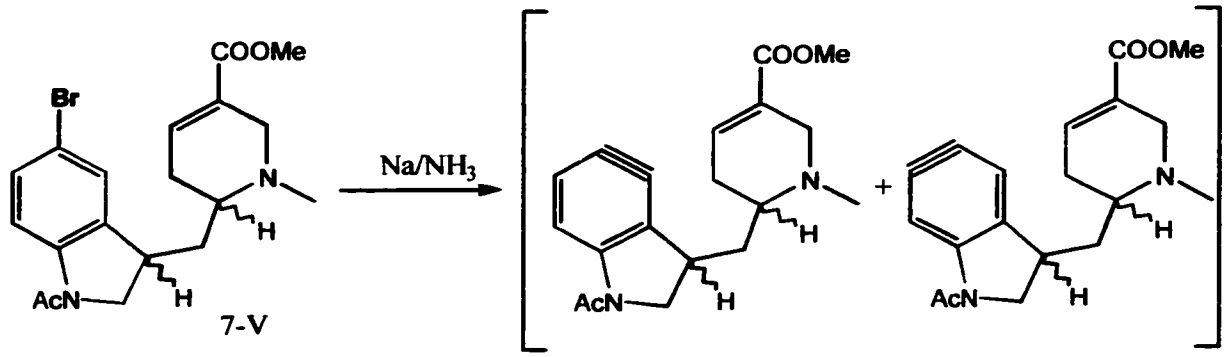
The indole pyridinium salt was dissolved in methanol and addition of $NaBH_4$ at 0°C rapidly gave the tetrahydropyridine compound in 52% yield. The desired product is a white solid (mp. 184.8-185.7 °C). Proton NMR showed that the pyridinium protons disappeared and the pattern of reduced pyridine protons was similar to that of arecoline (**18**) mentioned in chapter 1, section 2.3.



28 **29**

2.4 Attempts at Cyclization

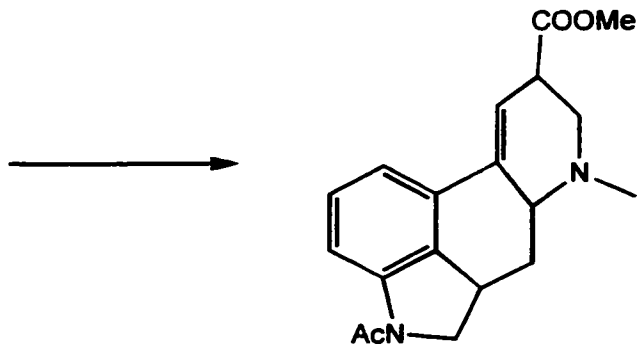
In Julia's synthesis of lysergic acid[14] discussed in the introduction chapter (section 2.7) the intermediate for cyclization had the same skeleton, with a tetrahydropyridine moiety and bromine on the 5-position of the indoline part. The cyclization was achieved via a benzyne intermediate, using Na/NH3 conditions. Since the elimination of the 5-bromo substituent can form two benzynes and only one can cyclize, the yield was only 15%. In our case the 4-iodo substituent can form only the desired benzyne for cyclization.



7-V

7-VI

7-VII

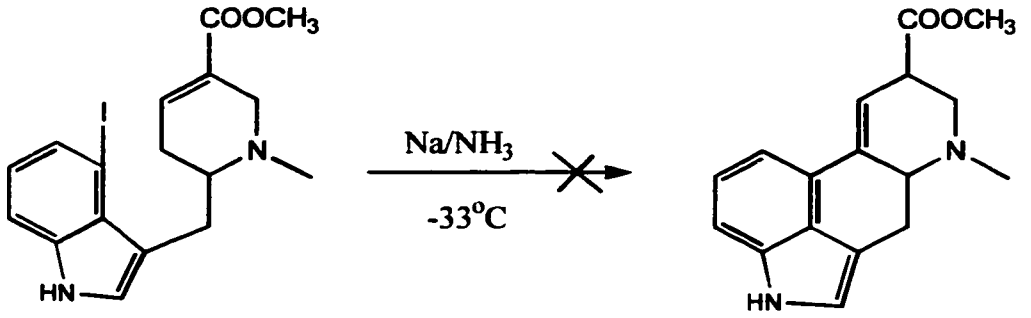


7-VIII

Scheme 20: Julia's cyclization

However, when Julia's protocol was applied to compound 30 using four equivalents of sodium amide, no desired cyclized product was obtained. After aqueous workup, the compounds which could be identified from the reaction were the starting material and the de-iodo compound from starting material in 65% yield.

The reason for this result may be that the N-protected indoline derivative used in Julia's synthesis only requires a mono-anion of the unsaturated ester to capture the benzyne formed. However, in our approach, since the indole is not protected, a dianion must be generated, and formation of the dianion in time to capture the benzyne could be difficult in this case. As we were reluctant to N-protect the indole and de-protect it later, we did not pursue this further.

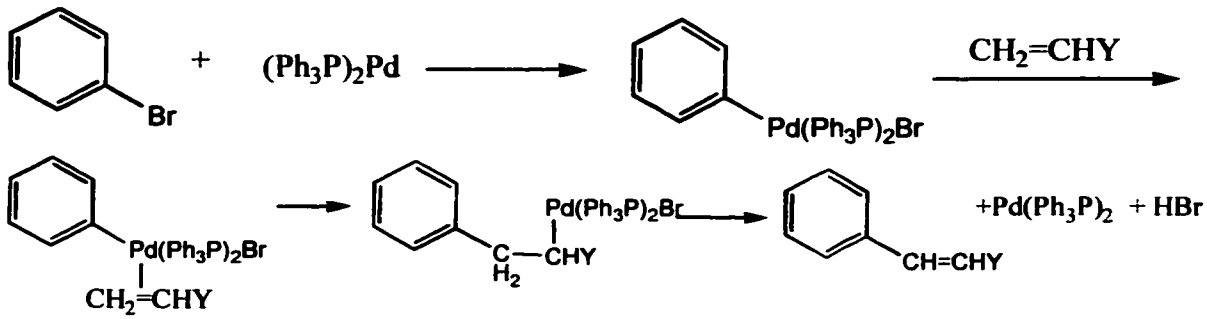


29 **30**

The Heck reaction is an important way to form carbon-carbon bonds. Aryl or alkenyl halides react with alkenes in the presence of catalytic amounts of palladium and mild bases to give net substitution of the halide by the alkenyl

group[33, 34, 35, 36]. The reaction is quite general and has been observed for simple alkenyl and cyclic alkenyl group substitution onto aryl or alkenyl halides.

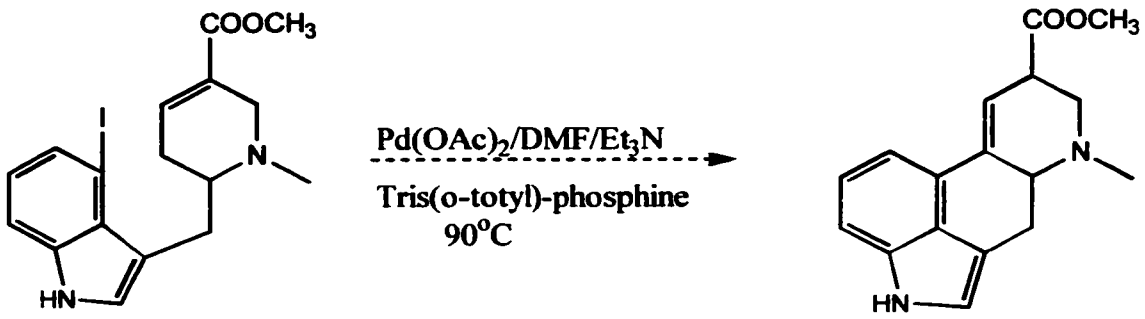
Usually, the reaction is carried out in the presence of a phosphine ligand, with tri-(*o*-tolyl) phosphine being preferred in many cases. The reaction is initiated by oxidative addition of the halide to a Pd(0) species generated in situ from the Pd(II) catalyst. The arylpalladium intermediate forms a complex with the alkene and this complex undergoes reductive elimination with carbon-carbon bond formation and regeneration of Palladium(0), presumably through a σ-bonded intermediate. The mechanism of a typical Heck Reaction is shown as the following.



Scheme 21: Mechanism for Heck Reaction

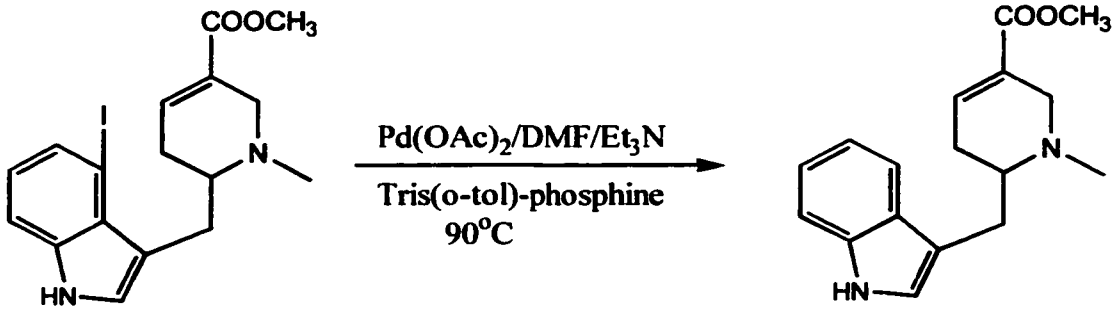
In our system for cyclization by the Heck Reaction the bond which needs to be formed is between C-10 and C-11. In our precursor the alkenyl group partner is not located in the right place. However, It is known that arecoline can be deconjugated[14] with base, i.e., with LDA, and quenched with HCl. In our case this would shift the double bond to C9-10 as required. Although the base used

in the Heck Reaction is mild, it should serve for equilibrium deconjugation *in situ* at the elevated temperature of the reaction, and so our precursor was used as is, without prior deconjugation.



29 **30**

When compound **29** was used as the starting material under the standard Heck reaction conditions, no desired cyclized product, namely, methyl lysergate, was obtained from the reaction. The major product was identified simply as de-iodinated starting material. Obviously, insertion of palladium into the phenyl halide moiety does happen, but no cyclization occurred. The indole N-H or the aqueous workup might be the proton source for this deiodination reaction.



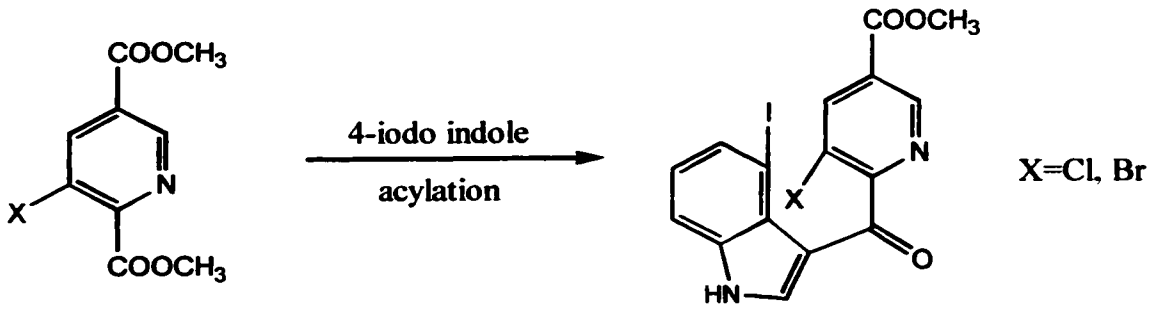
29 **31**

Again, in order to avoid the extra steps of protection-deprotection we did not pursue this reaction on an N-substituted indole.

3. Ring Closures with Both Rings Halogenated

So far in this project, it has been proven that bond a is difficult to build. If the pyridine is not to be reduced, formation of bond a can be considered as a cyclic diaryl coupling.

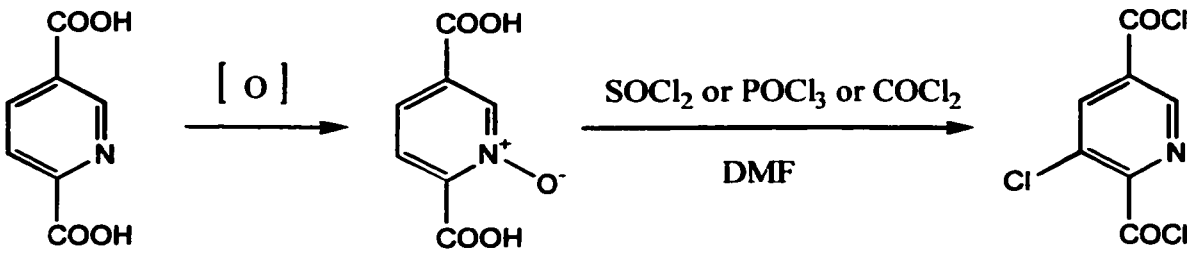
There are many methods to reductively couple aryl halides. Stanforth has a very extensive review of these reactions[37], which include the Suzuki cross-coupling reaction[38], Stille reaction[39], Negishi reaction[40] and the nickel-catalyzed cross-coupling reaction[41]. To perform any of these reactions in this synthesis, the 4-halo-indole is required as well as a 3-halo-pyridine. If a 3-halo-isocinchomeronic acid can be prepared, one could propose the following reaction to achieve the required dihalo compound, which could be the starting material for the several diaryl coupling reactions.



3.1 Preparation of 3-Chloro-isocinchomeronic Derivatives

3-Chloro-isocinchomeronic acid is a known compound and was reported in a patent[42], but the detailed protocol for its preparation was not fully presented

in that patent. The procedure is unusual in affording 3-chloro- instead of 4-chloro-substitution as commonly observed with pyridine N-oxides.



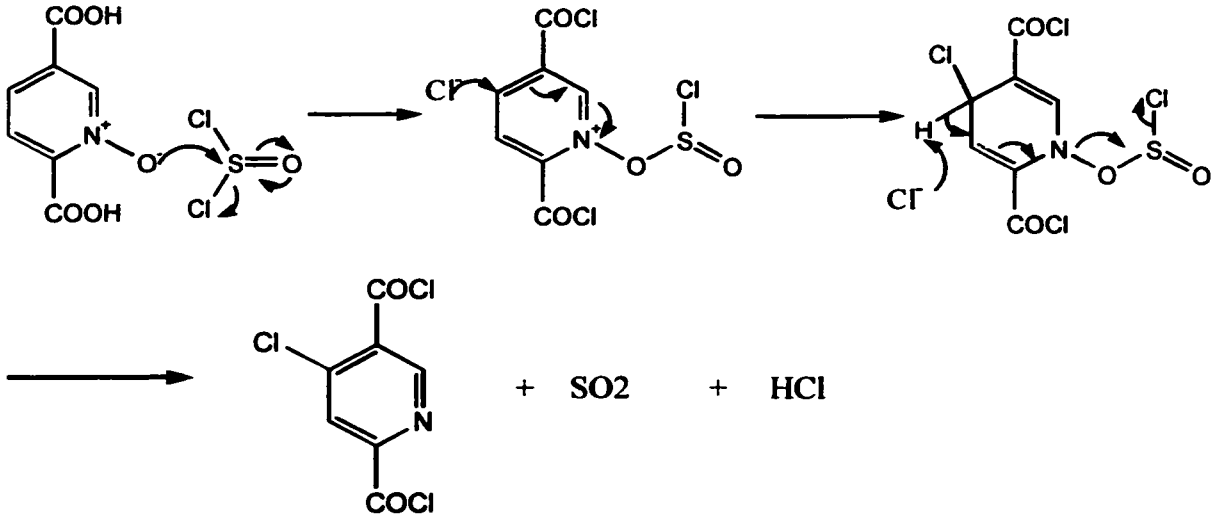
12 **32** **33**

No reaction occurred when isocinchomeronic acid was treated with standard oxidants such as mCPBA or H_2O_2/urea. Two carboxylic acid groups at the 2- and 5- positions of this pyridine ring are electron withdrawing and decrease the electron density on the pyridine nitrogen, making this otherwise routine oxidation a difficult one.

Finally, it was found that there are several methods in the literature[43, 44] to form isocinchomeronic acid N-oxide. The operation in the first is long and difficult, but the method in ref. 44 was successful. The acid was treated with H_2O_2 in the presence of catalytic Na_2WO_4 at 85°C using water as the solvent. After 10 hours, the product was collected as a white solid by filtering in 99% yield (mp. 253.2-254.1°C./dec.; Lit. 254°C./dec.). The proton NMR in DMSO-d6 showed two doublets and one singlet (δ 8.95, s, 1H; δ 8.38, d, 1H, J=6.4; δ8.25, d, 1H, J=6.4) as expected.

Although 3-chloro isocinchomeronic acid was reported in the patent, the detailed preparation was not given[42]. After several trials of the reaction of the N-oxide with thionyl chloride, it was found that the optimal conditions involved four equivalents of thionyl chloride with catalytic DMF in $CHCl_3$ at 0°C. followed by heating to 65°C. for two hours, then quenched with methanol. The 3-chloro-isocinchomeric methyl ester was obtained in good yield as a white solid. (mp. 126-127°C). The NMR data was in agreement with those in ref. 42. A small meta coupling (J=1.6 in $CDCl_3$) indicated chlorine substitution on the 3-position of the pyridine ring. Substitution on the 6-position would give a typical ortho coupling with J=6-9 Hz, while substitution on the 4-position would show essentially no coupling constant at all.

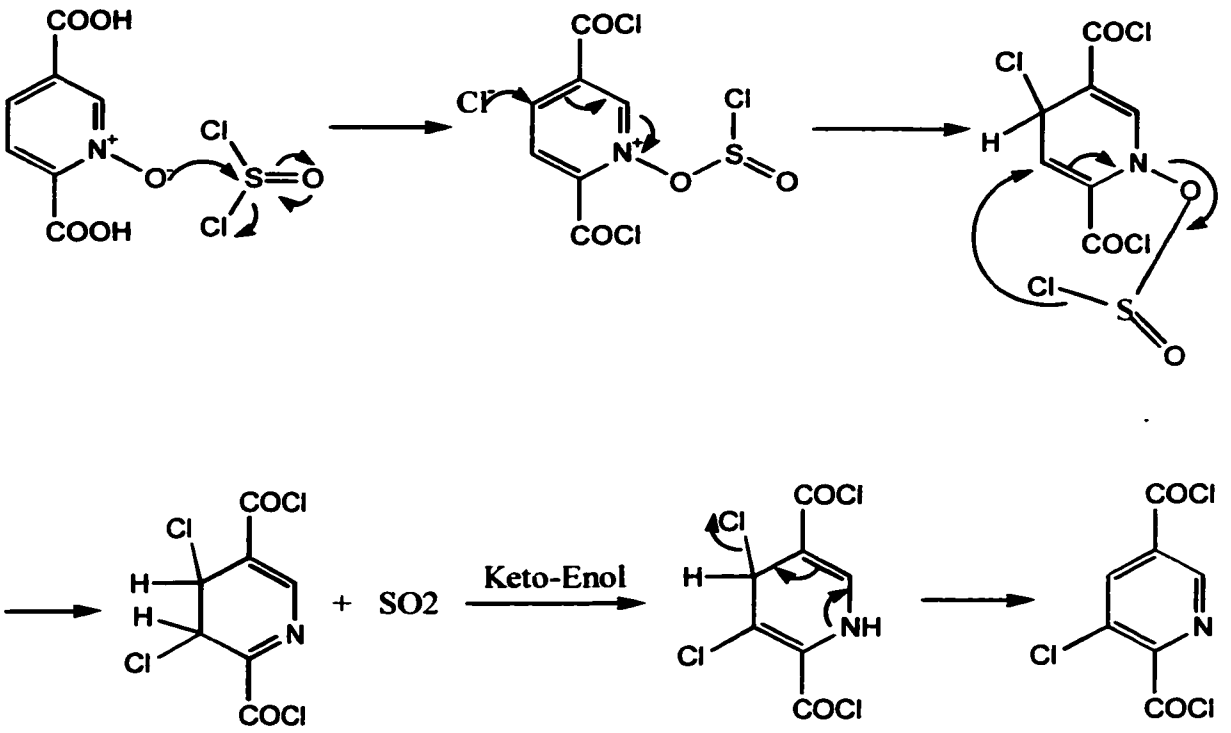
Normal mechanism:



Scheme 22: Normal Mechanism for chlorination of pyrinide N-oxide

However, it was a surprise to us that the chlorine substitution occurred at the 3- instead of 4-position. We proposed two mechanisms, for 3- or 4-substitution.

Present mechanism:

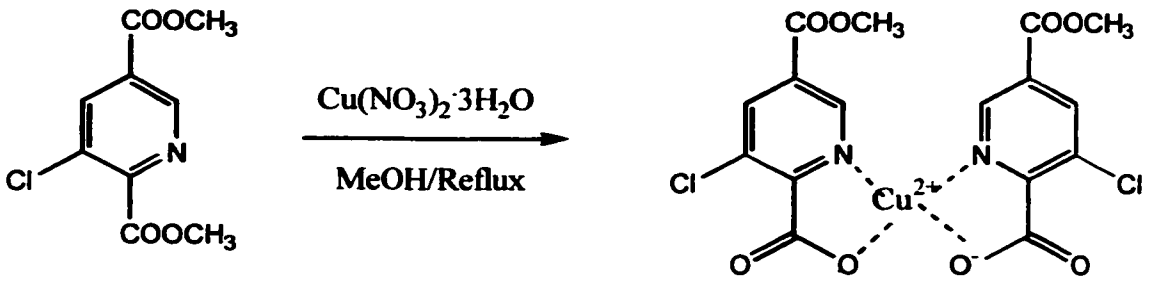


Scheme 23: Present mechanism for chlorination of pyridine N-oxide

3.2 Mono-Hydrolysis of the 3-Chloro Ester

The same protocol as described in chapter 1 (section 1.3) was used again to differentiate the two ester groups in 3-chloro- isocinchomeronic dimethyl ester[18].

This mono acid of isocinchomeronic methyl ester was obtained as a grayish white solid in 84.5% yield. Recrystallization from EtOH-H_2O afforded a white solid (mp. 192.2-193.4°C), while the NMR showed the disappearance of the methyl group in the ester at the 2-position, and a single methyl group at 4.03 ppm, with a pattern similar to the parent described in chapter 1, section 1.3. All these indicated the formation of the desired product.



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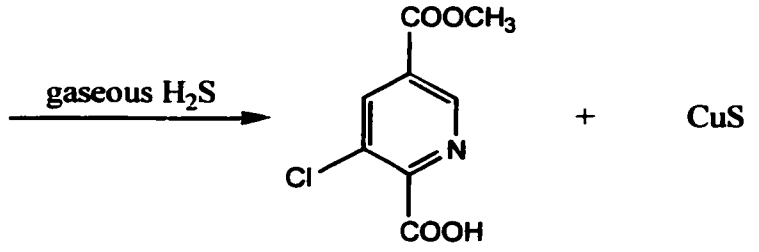

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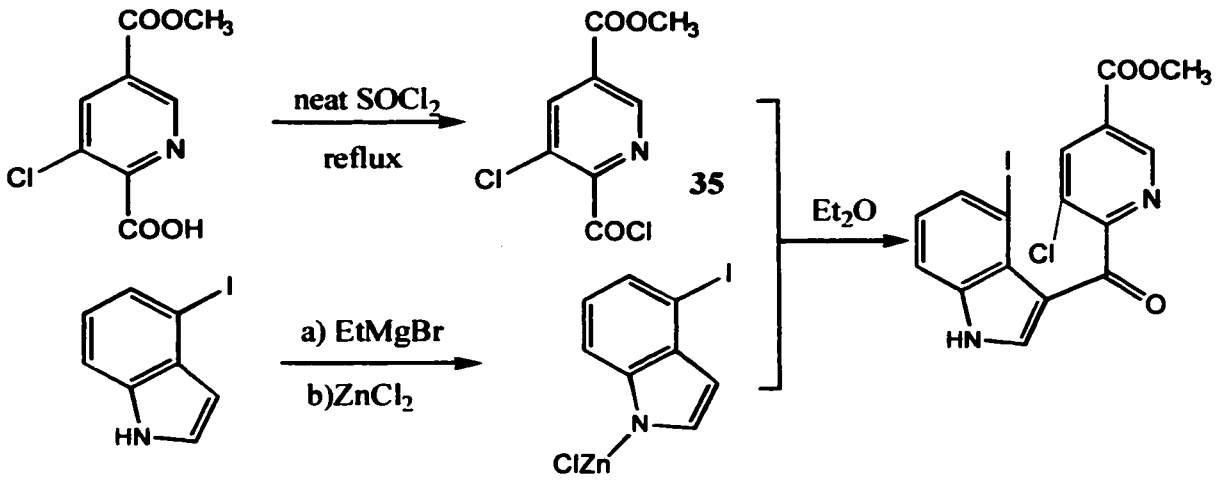
3.3 Acylations with the 3-chloro-pyridines

Following the same method described in chapter 1, section 1.4, the following reaction was carried out. The mono-acid was treated with $SOCl_2$. The corresponding acid chloride was obtained as a white solid (m. p. 168.2-170.2°C./dec.). After this acid chloride reacted with the zinc Grignard of 4-iodo indole as previously, the desired product was obtained as a pale yellow solid, recrystallization from acetone-water gave a yellow compound in 75% yield (mp. 245.2-245.8°C). The NMR spectrum showed the disappearance of the typical indole 3-H (6.3 ppm), which indicated the acylation had proceeded as before. The usual pattern of 4-substituted indole and pyridine protons was very well resolved and clearly confirmed the identity of the desired product.



22 36

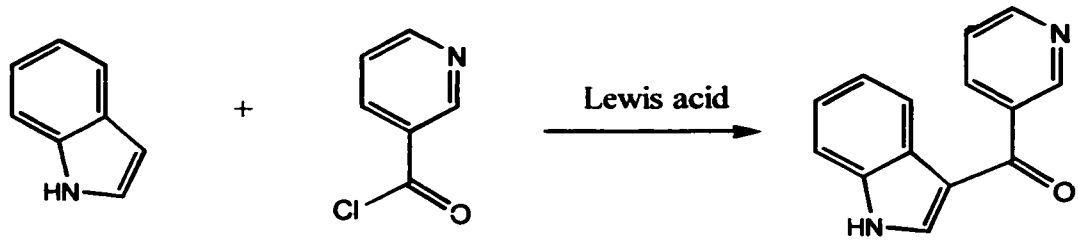
2.4. Comparison of Various Indole 3-acylations

Since indole 3-acylation is so heavily used in this project, it became worthwhile to investigate more alternatives for this reaction. Lewis acid catalysts were explored in different reactions. Overall, it was found that $SnCl_4$ is a better catalyst than the other Lewis acid catalysts, and it was easier to operate than the rest of the methods. However, in the acylation of 4-halo-indole and pyridine (both des-halo or halo substituted), it was found that Grignard/$ZnCl_2$ procedure gave a better yield than the $SnCl_4$ method and was chosen in the main synthesis. Following is the table summarizing the acylation results of various methods. Detailed experimental conditions are shown in the Experimental section.

Starting Materials	$AlCl_3$	$TiCl_4$	$SnCl_4$	MgEtBr /$ZnCl_2$
Indole + nicotinic acid chloride	45	42	90	85
Indole + isocinchomeronic monoacid chloride	65	-	75	71
4-iodo-indole + isocinchomeronic mono-acid chloride	-	-	62	70
4-bromo-indole + isocinchomeronic mono-acid chloride	-	45	65	70
4-iodo-indole + 3-chloro-pyridine mono-acid chloride	-	40	58	71

Table 2: Comparison of Acylation Methods

It was also found that $SnCl_4$ gave the best result when indole and nicotinic acid chloride were used as the starting material.



2 **5** **37**

3.5 Attempts at Cyclization via Diaryl Coupling

With the dihalo-ketone in hand, various attempts of cyclization were conducted. The results of these experiments are summarized in the following table.

#	Reaction Conditions	Results	Method . Ref
1	Cu(active), I_2, DMF, 160°C	Polymerization, or dehalogenation on both indole and pyridine	49
2	$(Me_3Sn)_2$, $Pd(PPh_3)_4$, toluene	dehalogenation on indole	46,47
3	$NiCl_2(PPh_3)_2$, Zn, Bu_4NI, THF	dehalogenation on both indole and pyridine	48,49
4	Pd/C, Zn, acetone/water	No reaction, SM recovered	50
5	$Pd(OAc)_2$,P(o-tolyl)$_3$, hydroquinone, K_2CO_3, DMA	No reaction, SM recovered	51
6	hv, 324 nM	Polymerization	52

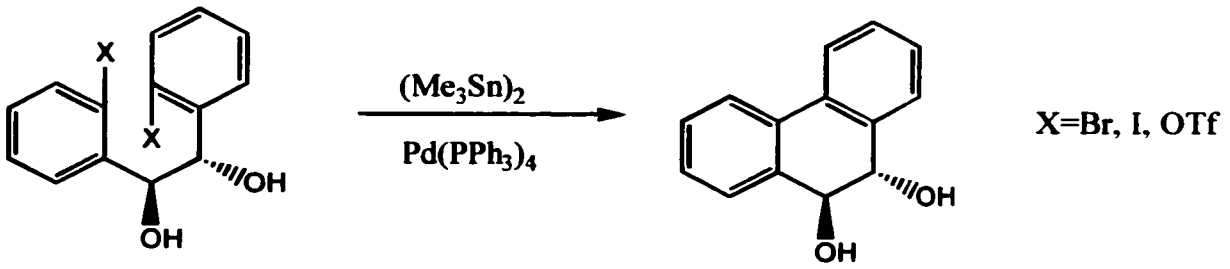
Table3: Attempted Intramolecular Biaryl Halides Coupling

Reaction 1: Organocopper intermediates are employed in several procedures for coupling of two organic reactants to form a new carbon-carbon bond. A classical example of this type of reaction is the Ullman Reaction of aryl halides, which is done by heating an aryl halide with a copper-bronze alloy[45]. Generally, there are two limitations to this type of reaction as used intermolecularly: 1) Only aryl halides with electron-withdrawing groups will react; 2) Homo-aryl halides coupling give a single product, while hetero-aryl halide coupling gives all three possible products in a non-selective manner. We

thought these two limitations would not cause problems in our case since: 1) electron-withdrawing groups are present in the starting material (ester group on pyridine and ketone between pyridine and indole); 2) Intramolecular coupling should be favored in competition with intermolecular coupling, so selectivity should not be an issue in this case.

However, when the reaction **1** conditions were applied to this starting material, the only identified product was the ketone compound with dehalogenation on both indole and pyridine, and this product only accounts for about 10% of the mass. In the crude NMR, aromatic peak broadening was observed and this accounts for the majority of the mass, which indicated that polymerization by hetero-coupling is still the dominant reaction pathway. This result might due to the fact that iodo-aryl is much more reactive than chloro-aryl in Ullman conditions, or it may simply be that the preferred conformation of the ketone places the pyridine anti to the indole ring.

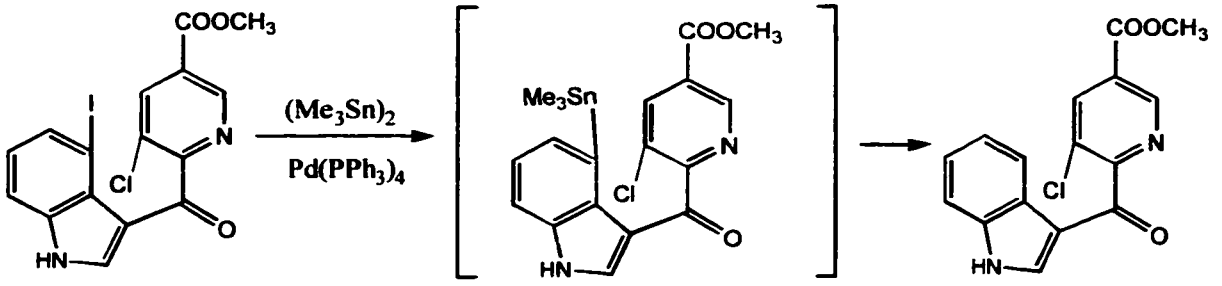
Reaction 2: Kelly reported an intramolecular biaryl coupling in Stille Coupling conditions[46] as shown in the following scheme. Structurally, this example bears common features with our case: 1) it is a intramolecular biaryl coupling; 2) a six-member ring is formed after cyclization.



Scheme 24: Biaryl coupling by Stille Reaction

In a 1994 paper by G. Ortar[47], indole stannyl species are used to couple with other aryl halide.

Based on this information we thought that the iodo-indole moiety would be more reactive than the chloro-pyridine, so that the intermediate shown below should be formed *in situ* which in turn would react intramolecularly to cyclize the ring.

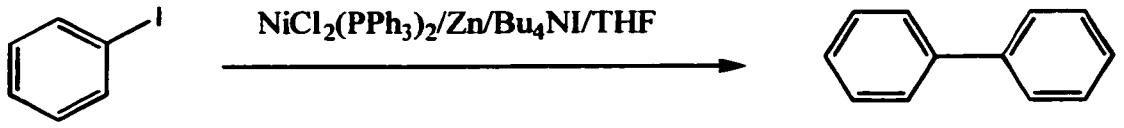


36 **38**

However, when this reaction condition was applied to our system, the product isolated from the reaction was simply the de-iodinated one shown above. NMR data clearly showed the two triplets and two doublets for the indole phenyl moiety and the slightly changed two meta-coupled pyridine proton peaks. This indicated dehalogenation only occurred on the indole part. This result might be due to the protonolysis of the intermediate. A similar observation was reported in a paper by R. Mook[53] in 1987. Again, the unprotected indole nitrogen proton might provide the proton source. It is difficult to tell at which stage of the reaction the protonolysis occurred, because the TLC plate after reaction might also be the proton source.

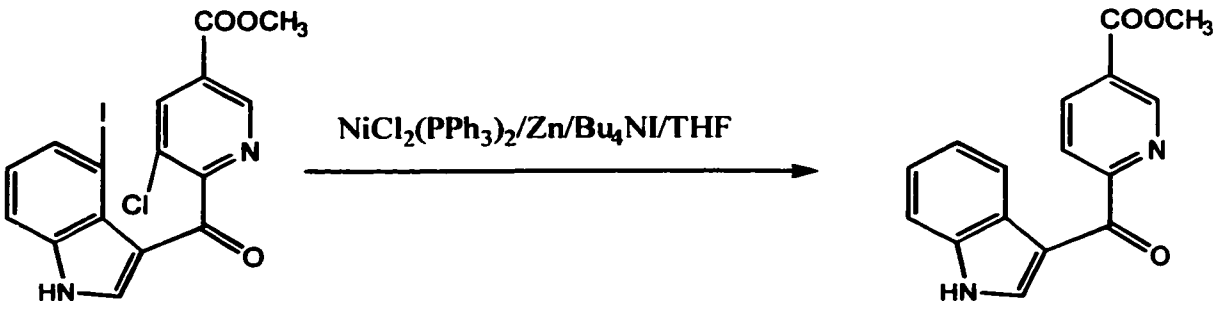
Reaction 3: The nickel-catalyzed coupling of aryl halides[41] has received considerable attention in recent years, because the reaction proceeds under very mild conditions compared with classical Ullmann conditions to give the corresponding biaryls in relatively good yield, and because many functional groups such as aldehyde, ketone and carboxylate ester do not interfere with the coupling reaction.

M. Iyoda[48] and K. Takagi[49] reported in 1990 and 1984 respectively that the following conditions could be applied to the nickel-catalyzed aryl halide coupling, where the aryl halides could be substituted phenyl or heteroaromatic halides. A typical example of this reaction is shown.



Scheme 25: Nickel_catalyzed biaryl coupling

However, when these reaction conditions were applied to our system, dehalogenation was the only result detected from the reaction. NMR data clearly was identical with the unsubstituted compound **4** made in chapter 1, section 1.4.



36 **4**

Reaction 4: A very mild conditions with zinc was successfully applied for biaryl coupling[50]. The reaction was done in acetone/water and was not air-sensitive. However, when the same conditions were applied to our system, only starting material was recovered.

Reaction 5: Pd(OAc)2 was also used to effect the diaryl coupling in basic condition[51]. When their conditions were applied to our system, however, only starting material was recovered from the reaction.

Reaction 6: Photochemistry has been extensively used in biaryl coupling[52]. Usually, the wavelength at which the molecule has a maximum UV absorption was chosen as the irradiation wavelength. The starting material molecule has an absorption peak at 282 nm, so this wavelength was chosen for the irradiation. Since the carbon-iodine bond is easier to break than the carbon-chlorine bond, the reaction was run at a highly diluted concentration (0.0005 M) to prevent the intermolecular homocoupling and enhance the possibility of intramolecular coupling.

After a short period of irradiation (2 min) in MeOH-d4, the NMR peaks in the aromatic region became very broad. The TLC also showed only a baseline spot using hexane and ethyl acetate (1:1) as the normal eluent, in which the starting material has an RF of 0.32. All of these indicated polymerization of the starting material in this reaction. So the reaction solution was diluted 10 more fold, but the same result was obtained at such a diluted concentration. We were

convinced that the intermolecular coupling competes and wins over the intramolecular coupling.

4. Conclusion

Various kinds of cyclization via route **B** on substituted aromatics were attempted without success so far, to close the last ring for the tetracyclic ring system. Halogens (bromo, iodo) were introduced onto the 4-position of the indole and chlorine was introduced onto the 3-position of the pyridine part of the precursor. Acylation of the indole was successful in the presence of halogens on the indole only or on both indole and pyridine. Julia's approach was tried on the arecoline type system, and various ring closures, such as Heck Reaction and radical coupling, were attempted on the partially reduced pyridine ketone compound. Various intramolecular biaryl coupling reactions were tried with halogen on both indole and pyridine, and no successful case has yet been achieved.

In all these cases it seems apparent that the preferred conformation of the substrate was one with the two rings *anti* to each other and so not in the required proximity for cyclization. There is a serious barrier to rotation from one conformer to the other in the ketones since the indole-ketone bond has substantial double bond character owing to the resonance in these vinylogous amides.

The two conformations are shown in section 1.1 in connection with the thallation failure. It is doubly unfortunate that the favored conformation of the

unsubstituted ketone appears to be that with the two aromatics *syn* to thwart the thallation and is *anti* in the halo-substituted cases to thwart cyclization! The latter cases may prefer the *anti* conformation because of that substitution, and indeed the failure of the thallation may simply be due to preferential complexation of thallium to the pyridine nitrogen, and not to conformation.

One possible avenue we have not explored is the diaryl coupling on the dihalogenated reduced ketone, which would at least remove the barrier to rotation in the ketone from one conformer to the other. However, since a number of these biaryl couplings seem to have failed because of the unprotected indole N-H, that freedom of rotation would still have been of no help.

All of these results suggest that there are serious difficulties in making bond **a** last. Accordingly, at this time we turned to the alternative Route A, making bond **a** first, en route to the tetracyclic ring system of lysergic acid. These experiments are discussed in chapter 3.

Chapter 3

Approach via Route A: Synthesis of Lysergic Acid

1. Formation of Bond a

As we know from chapter 2, bond **a** is very difficult to make. From the introduction chapter, we know that most of the previous syntheses of lysergic acid were focussed on the formation of bond **a** before the pyridine ring was made, as the chemistry was deliberately planned for the early formation of this difficult bond. Since we have encountered enormous difficulties to form bond **a** intramolecularly after bond **b** was formed, we decided to form bond **a** first. We hoped that our previous experience in the earlier stages of this project on intermolecular indole acylation to form bond **b** will help us to finish the analogous intramolecular ring closure smoothly. Another important reason to choose route A is that we were able to install the halogen on the indole 4-position and the pyridine 3-position, and we believed that one of the many existing methods for aryl halide coupling will successfully bring these building

blocks together intermolecularly. So the journey via route A was embarked at that point.

11. Stille Coupling Reaction Approach

Stille coupling is widely used in organic synthesis for carbon-carbon bond formation[39]. Examples of the palladium-catalyzed coupling of organotin compounds with carbon electrophiles were first reported in 1977 by Kosugi[53], Shimizu[54] and Migita[55]. The first study by Stille appeared in 1978[56]. In recognition of Stille's comprehensive synthetic and mechanistic studies since then, this coupling is now referred to as the Stille Reaction[57]. The Stille Reaction is schematically defined in the following Equation.

$$R^1Sn(R^2)_3 \quad + \quad R^3X \quad \xrightarrow{Pd(0)L_n} \quad R^1\text{-}R^3 \quad + \quad (R^2)_3SnX$$

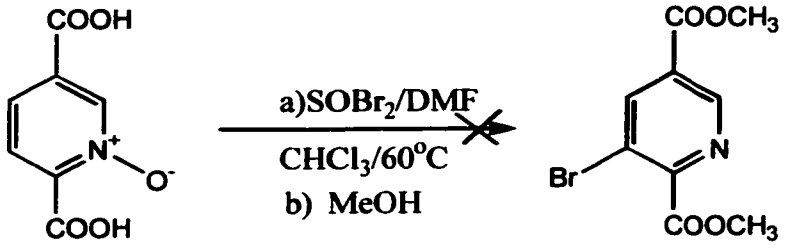
Scheme 26 : Stille Coupling Reaction

In this equation, R^1 is typically an unsaturated moiety (e.g., vinyl, aryl. heteroaryl, alkynyl, allyl), and R^2, the nontransferable ligand, is almost always butyl or methyl. Electrophiles participating in the coupling include halides (always bromides or iodides; no chloride has been reported so far). In our system, since we had halides on both indole and pyridine, we had two choices to apply this Stille reaction.

Choice 1: Indole bromide or iodide could be used as the electrophile and pyridine chloride could be converted into the pyridine-tin derivative. There is a problem with this choice. When halides are converted into their trialkyl-tin

derivatives, BuLi is usually used as the base, and this base is not compatible with the ester functional groups in the pyridine derivative. So this choice was deleted.

Choice 2: Pyridine halide could be used as the electrophile and indole bromide or iodide could be converted into trialkyl-tin derivatives. The only problem remaining in this choice is that pyridine chloride was never used as the electrophile in the Stille Reaction and all the Stille Reactions use bromides and iodides as the electrophile[39]. So we decided to try to make 3-bromo isocinchomeronic methyl ester via the same method by which 3-chloro isocinchomeronic methyl ester was made in chapter 2, section 3.1.



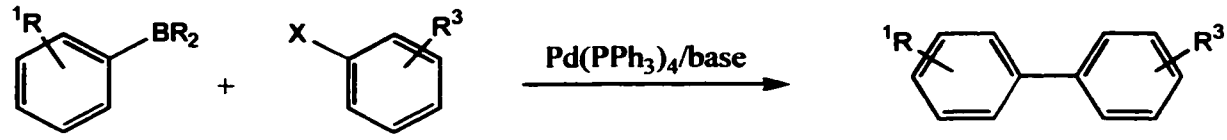
However, when isocinchomeronic acid was treated with thionyl bromide in the presence of DMF in chloroform followed by quenching with methanol, no expected product was detected. The crude NMR data showed several sets of aromatic pyridine proton peaks and many different methyl ester group singlets around 4 ppm. The TLC showed no movable spot in hexane and ethyl acetate (3:1) in which 3-chloro isocinchomeronic methyl ester has an R_F around 0.5. All

these suggested that thionyl bromide didn't play the same role as thionyl chloride did in the formation of 3-chloro isocinchomeronic methyl ester.

Since we couldn't prepare the requisite starting material for a Stille Reaction, this approach to form bond **a** was abandoned.

1.2 Suzuki Coupling Reaction Approach

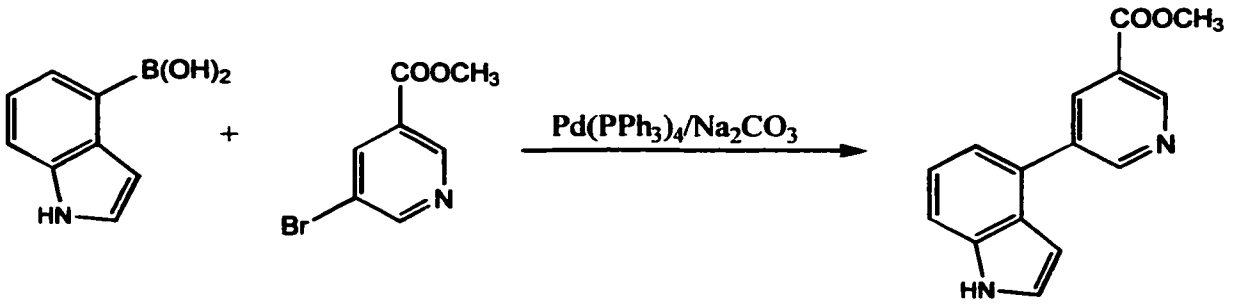
The preparation of biphenyls using the Suzuki Reaction is well documented in the literature[37,58,59]. A generic example of this reaction is shown in the following equation.



Scheme 27: Suzuki Coupling Reaction

Where R^1 could be ester, ketone and amide functional groups, R is usually a hydroxyl group or an n-butoxide group, R^3 could be ketone, ester and hydroxyl functional groups, and X could be bromide, iodide or triflate. The reactions are almost always catalyzed by $Pd(PPh_3)_4$ in the presence of mild base, such as Et_3N or K_3CO_3.The yields of product are invariably good to excellent.

As this work was underway a closely related example appeared in a note by Doll[16] who reported the following reaction in 1999.

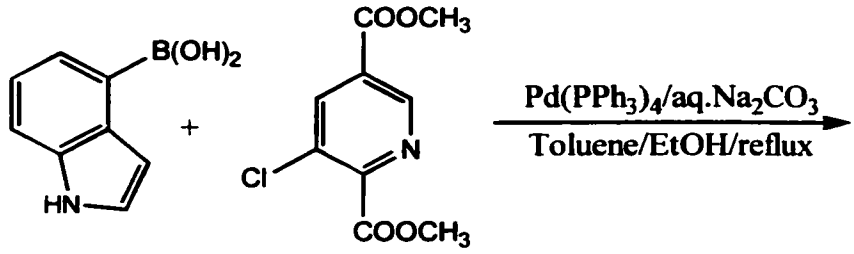


We were very encouraged by Doll's work. It showed that bond a could be formed by this Suzuki Reaction. One question remaining is that Doll used 5-bromo nicotinate as the Suzuki partner and we only had the access to the chloro-pyridine derivative. This remaining question was partially answered by the work of Lohse[60] in the same year. In that paper, he reported that chloro-pyridine derivatives could be used in the Suzuki Reaction as the aryl halide partner, but the chloride had to be in the *ortho* or *para* position. However, it was also addressed in the paper that electron-withdrawing groups on the pyridine will enhance the reactivity of these Suzuki Reaction partners.

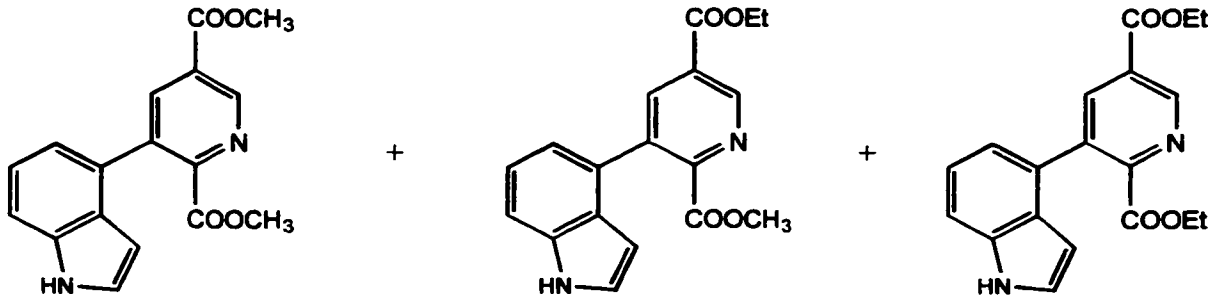
In our case, although the chlorine is on the *meta* position of pyridine derivative, two ester groups are present in this molecule, *ortho* and *meta* to chloride respectively. These two ester groups, acting as electron withdrawing groups, might enhance the reactivity of 3-chloro-isocinchomeronic methyl ester.

With these considerations, 4-bromo-indole was treated with an equivalent of KH in ether to deprotonate the indole N-H, followed by BuLi. The resulting dianion was quenched with tributyl borate. Hydrolysis of the resulting tributyl indole-4-borate in acid conditions gave indole-4-boronic acid as a beige solid. The NMR data in $CDCl_3$ were not very clear, due to the three possible forms of

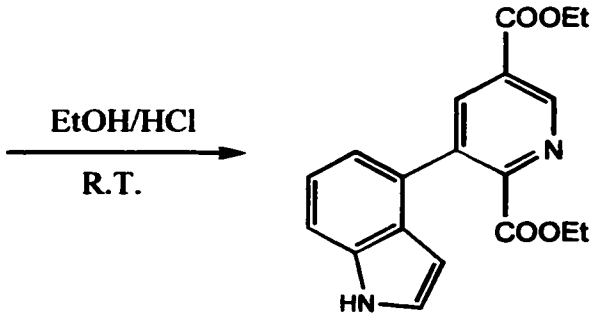
this compound from dissociation of the boronic acid protons. But when the NMR was taken in acetone-d6 and D_2O (4:1), the NMR data clearly showed a single compound with the desired peak pattern. With indole 4-boronic acid in hand , the Suzuki Reaction was carried out using the following standard conditions.



38 **34**



39 **40** **41**



41

Three products were obtained as indicated by the crude NMR data. They were all Suzuki Reaction products with ester exchange on one or two ester groups or with no ester exchange. The ratio of these three products indicated by the NMR was 3:1:1 in the order shown above. However, all three compounds could be used with no separation necessary for further action. The TLC clearly showed three different spots with very close R_F values.

The mixture of these three compounds was dissolved in EtOH in the presence of a catalytic amount of HCl in diethyl ether. This mixture was stirred at room temperature overnight, and the three compounds were consolidated into one single compound as shown in the above equation.

This compound was purified by recrystallization from EtOH. A pale yellow crystalline solid was obtained with mp. 212.3-213.0° C. The NMR data showed the presence of both indole and pyridine moieties, with 5 aromatic peaks from indole: δ_3 7.45 (d, 1H, J=8.4Hz), $\delta_{4\text{-}5}$ 7.25-7.30 (m, 2H), δ_6 7.08 (d, 1H, J=8.4Hz), δ_7 6.34 (m, 1H), and 2 aromatic peaks from pyridine: δ_1 9.25 (d, 1H, J=1.6Hz), δ_2 8.55 (d, 1H, J=1.6Hz). The overall yield in this sequence was 91%.

This was the first time we have seen bond **a** formed in this project. We were very encouraged by this result and hoped that intramolecular indole 3-acylation would now close the ring smoothly in the next step.

2. Intramolecular Ring Closure for Bond b

All the skeletal atoms of lysergic acid have now been assembled and only one cyclization remains to achieve its tetracyclic skeleton. We presumed that,

as an intramolecular reaction, the base-catalyzed acylation of the indole by the proximal ester on the pyridine should be a facile transformation.

In fact many reactions had to be tried to close the ring on the Suzuki product, with different oxidation states and functional groups on the pyridine-substituted carbon (C-4 in lysergic acid numbering). These different functional groups on C-4 were ester, acid, hydroxylmethyl (primary alcohol) and aldehyde. In this section, these efforts and experimental results will be discussed in detail.

2.1 Intramolecular Ring Closure on Diester

The intramolecular version of ester condensation is called the Dieckmann Condensation[61]. It is a very important method to form five- and six-member rings intramolecularly. Usually, strong base, such as NaH, is used to form an enolate as the nucleophile to attack the ester. In our system, the 3-position of indole can be considered as an enol, and deprotonation at the indole nitrogen would make this nitrogen enolate more nucleophilic.

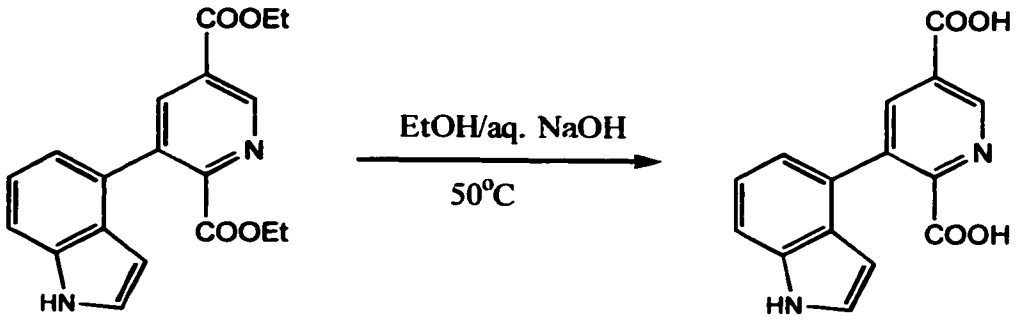
However, when the Suzuki diester was allowed to react with NaH in boiling xylene, no reaction occurred and only the starting material was recovered. When the reaction was run in refluxing ethylene glycol (mp. 197°C) with the same base, there was still no reaction.

2.2 Intramolecular Ring Closure on Diacid

We know from the past that isocinchomeronic acid can be converted into its diacid chloride with thionyl chloride and the acid chloride thus obtained can

acylate the indole on the 3-position in the presence of Lewis acids. If the Suzuki diester product is converted into its diacid derivative, such ring closure might be realized on the diacid chloride derivative. We also believed that this intramolecular ring closure should be regioselective, because only one of the two carbonyl groups (*ortho* to pyridine nitrogen) is accessible to the indole 3-position.

The Suzuki diester product was dissolved in alkaline aqueous ethanol and the mixture was heated at 50°C for 2 hours. Upon adjusting pH to 5, a red solid precipitates from the solution. Recrystallization from methanol of this solid material afforded a light red crystalline material with mp. 235.9-236.8°C. The NMR data in D_2O/NaOD showed the same pattern as the Suzuki diester in the aromatic region, and disappearance of the two ethyl ester groups. The yield for this step is 95%.



41 **42**

The very insoluble diacid was suspended in dichloroethylene, and two equivalents of thionyl chloride were added into this suspension. After heating at 60°C for 1 hour, the suspension became very dark. $SnCl_4$ was added at this point

and the mixture was heated at 40° C for another hour. The reaction was quenched with anhydrous methanol. After aqueous workup, no movable spot was observed on the TLC plate; the Suzuki diester moves at R_F 0.45 in hexane : ethyl acetate (1 : 1). A large amount (75%) of the starting diacid was recovered from the aqueous bicarbonate solution by methylene chloride extraction.

In another experiment, the diacid was suspended in neat thionyl chloride and the mixture was heated at 50° C. Again, the solution became very dark. Excess thionyl chloride was evaporated in vacuum and dichloroethylene was added to the dark residue. Addition of neat $SnCl_4$ as Lewis acid didn't lead to the desired product either after the reaction was quenched with anhydrous methanol. The difference from the last experiment was that the starting diacid was not recovered at all after aqueous workup. The crude NMR data showed many sets of the aromatic peaks for both indole and pyridine.

From the results of the last two experiments, we could tell that thionyl chloride didn't act in the desired way to simply form the diacid chloride. Thionyl chloride either didn't react with the insoluble acid functional group at all or it reacted with the other reaction site(s) in the molecule. To confirm this analysis, the following control experiment was conducted.

The diacid was mixed with excess neat thionyl chloride and the mixture was heated at 50°C for 2 hours. The excess thionyl chloride was evaporated and anhydrous methanol was added into this mixture. If the acid chloride was formed during this course, the Suzuki diester product should be formed after methanol

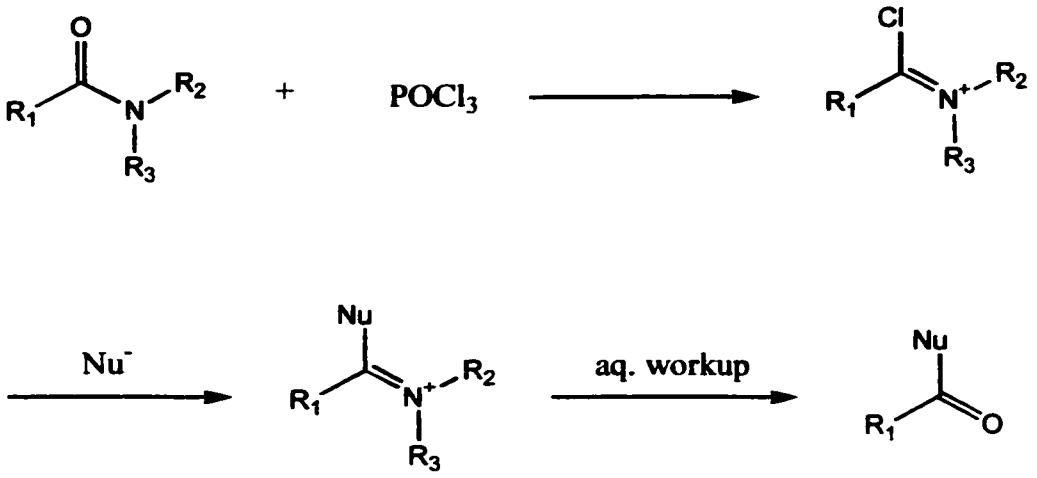
quenching. Not to our surprise, no Suzuki diester product was observed after such an operation and starting material diacid was recovered only in 10% yield.

Different methods for ring closure on the diacid compound were explored. An alternative acidic cyclization is in the literature using PPA (polyphosphoric acid)[62] or PPE (polyphosphoric ester)[63,64] as the internal acylating reagent. The diacid compound was suspended in chloroform and 2 equiv. of PPA was added into this suspension. No desired ring closure product was observed after the reaction was heated for two hours and quenched with anhydrous methanol. The starting diacid was recovered in 95% yield.

PPE was also tried as the acylating reagent. PPE was prepared from P_4O_{10} and diethyl ether in refluxing chloroform according to ref. 64. When the diacid starting material was added to the freshly made PPE reagent in chloroform, and the mixture was refluxed overnight, no desired product was observed and the starting material was recovered in 97% yield after aqueous workup. Trials on the diester compound using PPE also gave the starting material recovered from the reaction.

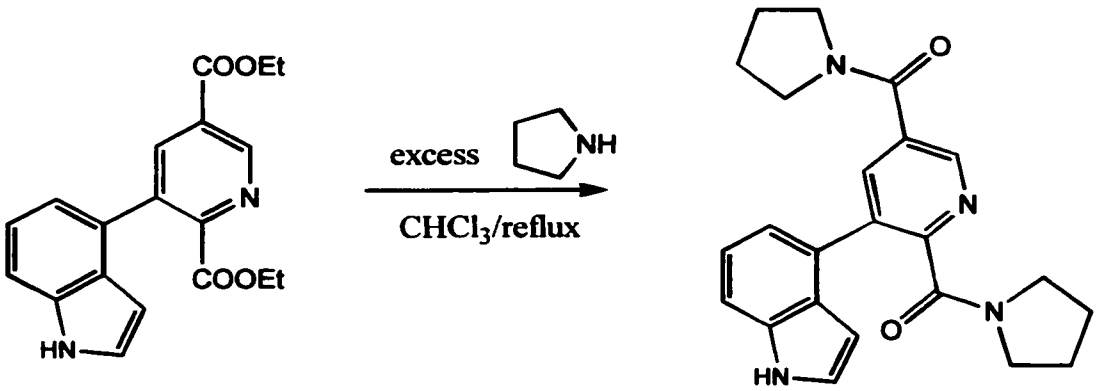
2.3 Vilsmeier Approach

The Vilsmeier Reaction is one of the most important methods for introducing formyl and acyl groups onto aromatic rings[65,66,67]. In this reaction an N, N-dialkylamide and phosphorus oxychloride react to give a chloroiminium ion, which is the reactive electrophile.



Scheme 28: Vilsmeier acylation reaction

If we could convert the ester groups in the Suzuki diester into an N,Ndialkylamide derivative, then treat this compound with $POCl_3$, the indole 3-position could act as the nucleophile in the Vilsmeier Reaction and the ring could be closed by internal Vilsmeier acylation.



41 **43**

The Suzuki Reaction product was dissolved in chloroform and a large excess of pyrrolidine was added. The reaction was refluxed for 12 hours and a single product was isolated as a white solid with a much lower R_F than the starting

material (m. p. 246.7-247.9°C). The NMR data showed the disappearance of the two starting ethyl ester groups, replaced by two pyrrolidine groups integrated at 16 protons.

The Vilsmeier Reaction was carried under the standard conditions. Three equivalents of $POCl_3$ were used in THF as the solvent. The reaction was quenched with anhydrous MeOH then with $NaHCO_3$. The crude NMR showed the disappearance of the C-3 proton on indole, but two pyrrolidine groups were still present. The peaks in the aromatic region were not well defined and irresolvable. This suggested that $POCl_3$ might have attacked the 3-position as an electrophile, with many complex subsequent reactions afterwards. It also suggested that the presence of any electrophilic reagents with this indole present may react with it instead of causing cyclization because the indole ring itself is very nucleophilic.

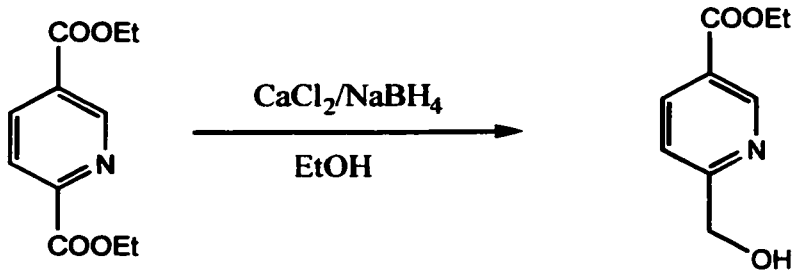
2.4 Selective Reduction of Ester Groups

Since ring closure was not successful on ester or carboxylate starting material, we decided to reduce the ester to alcohol, then try to close the ring from an alcohol compound, or oxidize that to the more reactive aldehyde for closure.

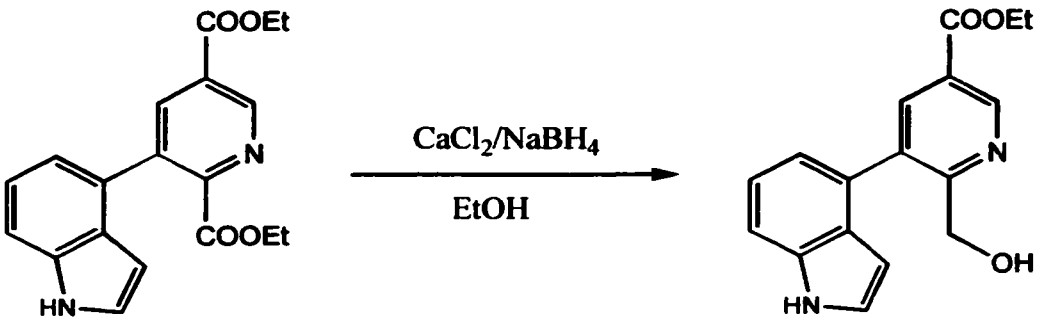
By the same argument used in the introduction chapter and early in this chapter, if we could reduce the two ester groups to hydroxymethyl groups, intramolecular alkylation on the indole 3-position would only happen at the carbon *ortho* to the pyridine nitrogen to form a six-membered ring, since the

other methyl is not accessible to the indole 3-position. However, if both carboxyl groups are reduced to hydroxymethyl groups, the closure product would be left with a primary alcohol group on the C-8 of the lysergic acid skeleton, and this is the wrong oxidation state. It would cost an additional oxidation step to change it back to the carboxyl group. Hence it will be a more efficient synthesis if we can first reduce the ester group selectively.

We found in a Japanese patent that isocinchomeronic methyl ester could be converted into its mono hydroxymethyl derivative by a combination of $CaCl_2/NaBH_4$ in ethanol[68].



The details of the reaction conditions were not discussed in that patent. So different reaction conditions were tried to apply the same method on our Suzuki diester product. Finally, the best result was obtained when 0.3 equivalents of $CaCl_2$ and 0.6 equivalents of $NaBH_4$ were used as the reagents, and the reaction was stirred at room temperature for 6 hours. The product was obtained as a colorless solid (m. p. 198.1-199.0°C) in 78% yield. NMR data showed the disappearance of one ester group corresponding to the ester group ortho to pyridine nitrogen, and a new methylene group (2H) was observed at 4.6 ppm. This clearly confirmed the identity of the desired product.



41 **44**

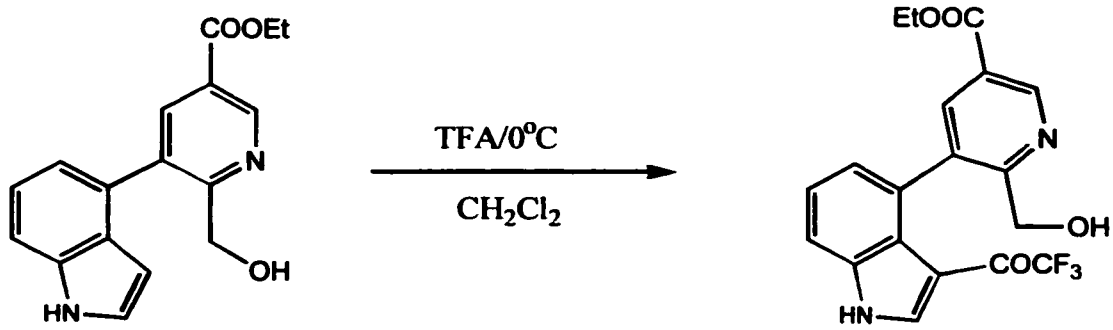
The patent did not discuss the mechanism of this selective reduction. We believe that $CaCl_2$ and $NaBH_4$ form a reagent $Ca(BH_4)_2$ *in situ*, and Ca^{2+} in this reagent chelates with the pyridine nitrogen; thus the hydride could be delivered onto the neighboring ester group faster and the reduction could happen regioselectively if no excess reducing reagent was used. When the reaction was carried out with 0.3 equivalents of $Ca(BH_4)_2$ in ethanol for the same period of time, the product was also obtained in an improved 84% yield.

2.5 Ring Closure on the Hydroxyl Compound

With the hydroxylmethyl compound in hand, we began the investigation of ring closure on this compound. Alkylation on the indole 3-position is a standard reaction and routinely performed[69]. If the alkylation is performed in basic media, the nitrogen of indole will be alkylated. However, if the alkylation is carried out in acidic conditions, the alkylation site will be the indole 3-position. In the latter case, the reactions are usually catalyzed by Lewis acid.

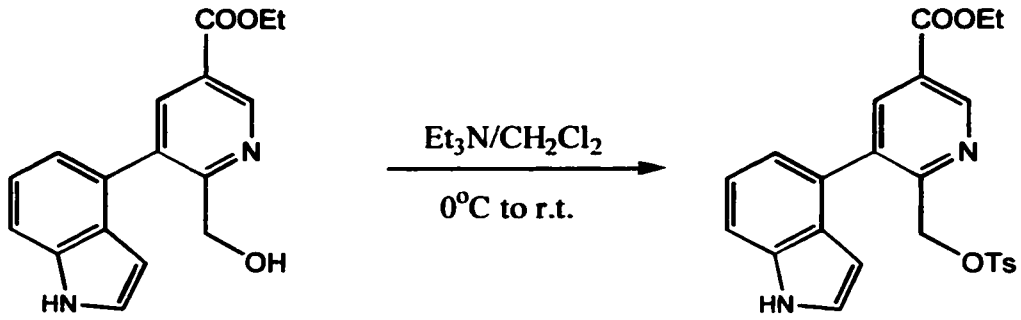
Different Lewis acid were used on the hydroxyl compound to effect the intramolecular alkylation. These Lewis acids Include $SnCl_4$, $AlCl_3$, BF_3, $TiCl_4$. Many reaction conditions were tried using different Lewis acids, in different solvents (THF, dichloro ethylene, methylene chloride, toluene) and at different temperatures (from 0°C to refluxing temperature). We always had the same result from this series of reactions, which was the recovery of the starting material.

Trifluoroacetic acid (TFA) was also used in this series on the hydroxylmethyl compound to effect the ring closure. The reaction was carried out in methylene chloride at 0°C. No desired intramolecular alkylation occurred, but instead the indole 3-position was acylated by TFA. The indole 3-H disappeared in the NMR spectrum, but the hydroxylmethyl group remained unchanged, and the -OH group was still present. If the ring had closed in the desired way, we would expect a significant shift of this methylene group in the NMR spectrum and disappearance of the hydroxyl group at 4.4 ppm. This is now another example of intermolecular acylation on the indole 3-position in preference to ring closure.



44 **45**

If the hydroxyl group is converted into its tosylate, we might be able to close the ring since we had a better leaving group. Accordingly, the hydroxyl compound was dissolved in methylene chloride and tosyl chloride was added in the presence of triethylamine as the base. The starting material was quantitatively converted into its tosyl derivative. The product was obtained as a light yellow solid (m. p. 234.1-235.2°C). The methylene group shifted from 4.62 ppm in the starting material to 5.07 ppm in product in NMR spectrum with little change in the other peaks, and the additional tosyl group peaks were also observed.

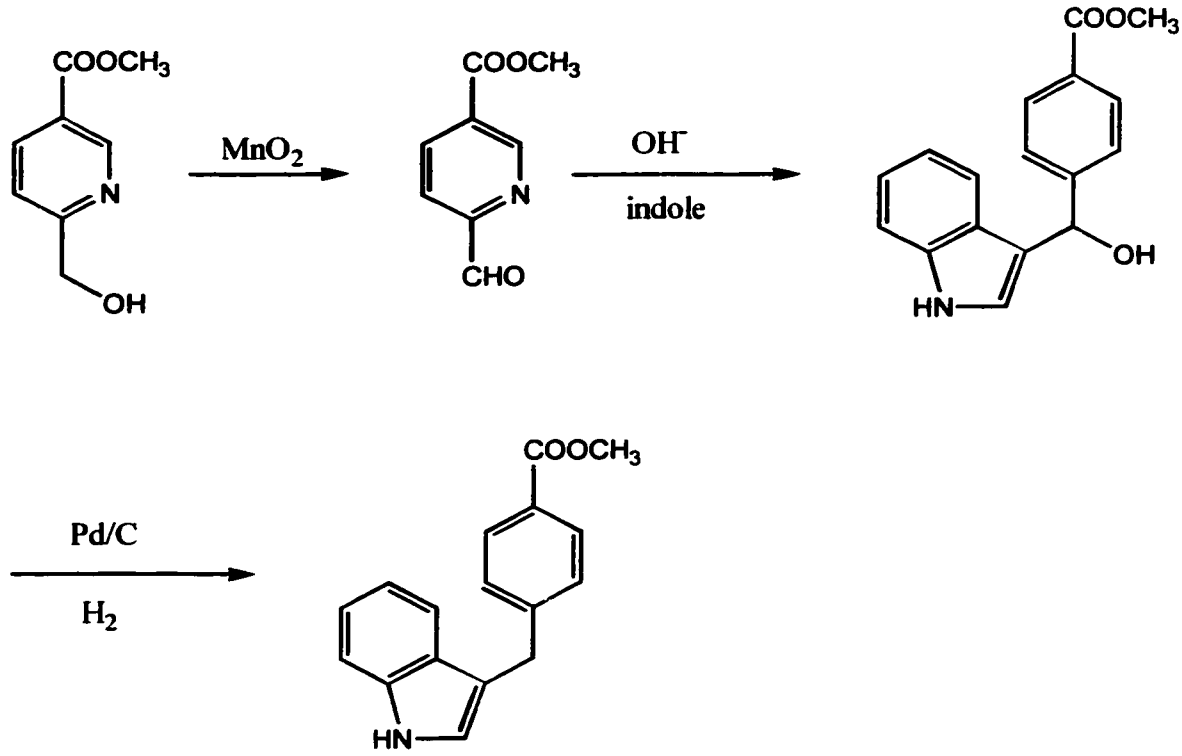


44 **46**

Different reaction conditions were used to close the ring from this tosylate. These conditions included LDA in THF, DBU in methylene chloride and EtMgBr/$ZnCl_2$ in ether. None of these reactions afforded the desired ring closure product, and only starting material was recovered from these reactions.

2.6 Ring Closure on the Aldehyde

So far, we have had enormous difficulties to form bond **b** after bond **a** was formed by the Suzuki Reaction. More literature precedents were sought for carbon-carbon bond formation on an indole 3-position. The following example, which was closely related to our case, was found in a 1975 paper by Potier[70].

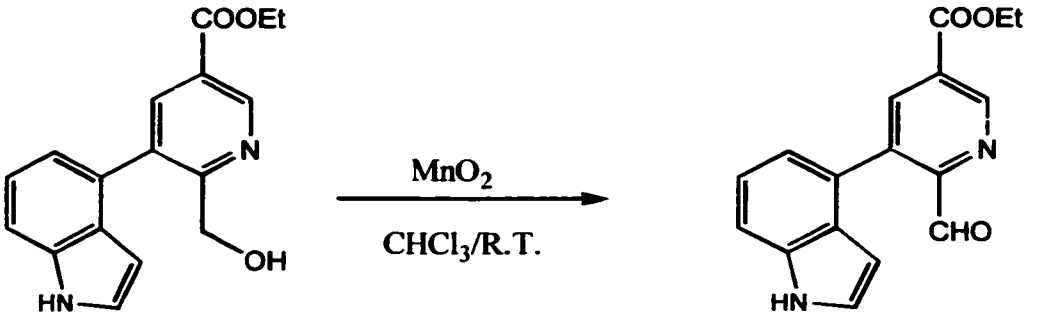


Scheme 28: Potier's Approach to make bond a

We were surprised by this 3-step reaction sequence since with the hydroxymethyl-pyridine in hand, they could have used this compound to alkylate the indole directly, and they would have obtained in one step the same product as the one obtained after this three-step sequence. Obviously, there must have been some reason for them to do this. One reason might be that they already

tried the direct alkylation and it didn't work for them, so they turned to this 3-step sequence. However, the reason why the direct alkylation didn't work is not clear and the paper itself does not discuss this at all.

Since we had the hydroxyl compound, it should be easy to prepare the aldehyde by their method and try the aldol reaction intramolecularly. The hydroxyl compound was dissolved in chloroform and an excess of freshly made MnO_2 was added into this solution. The reaction was stirred at room temperature for two hours and the aldehyde product was obtained as a yellow solid (mp. 198.4-199.2°C) in 92% yield after the manganese solids were filtered out through celite. The NMR of the product showed the characteristic peak of an aldehyde proton at 10 ppm, and disappearance of the methylene and hydroxyl group absorptions.



44 **47**

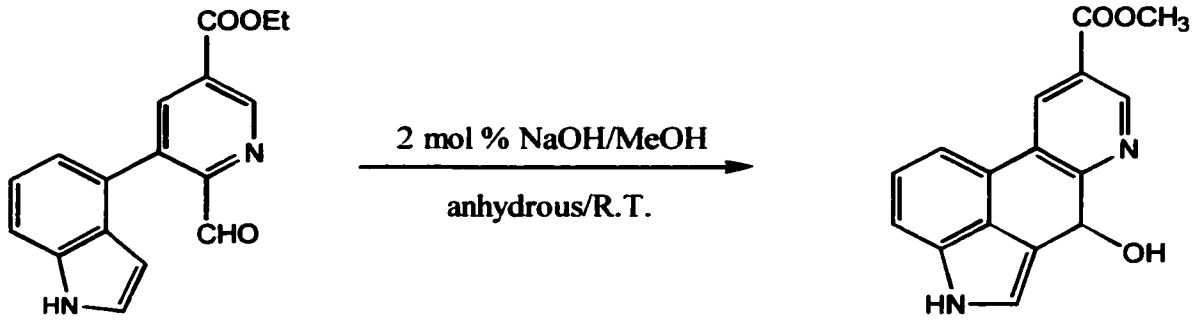
This aldehyde was dissolved in methanol and 10 mol % of aqueous 1N NaOH solution was added into the reaction solution at 0°C and stirred at 0°C. After 12 hours, precipitation was observed from the reaction mixture. This solid

was separated from the mother liquid by filtration. The TLC of the mother liquid showed only two spots, the one with higher R_F identical with the starting aldehyde and the one with lower R_F identical with that of the solid material precipitated from the solution. A reaction has happened but not finished. The solid material accounted for 30% of the total mass.

If the reaction was left for longer periods of time, more solid product could be obtained during the course of the reaction but it took more than one week for the reaction to finish completely. After running this reaction at different temperatures and concentration with different relative amounts of base, we found that temperature played a very important role. If the reaction was carried out at room temperature, it only took 2 hours for the reaction to go to completion, even with only 2 mol % of base. The yield for this reaction was almost quantitative under these conditions. In this case, the NaOH was directly added into methanol to make an alkaline solution, instead of adding aqueous 1N NaOH solution into methanol. Alternatively, sodium methoxide in methanol solution (anhydrous) could be used as the base, and the same quantitative result could also be achieved.

The solid product was recrystallized from methanol and a beige crystalline solid was obtained (mp. 234.6-235.8°C). The NMR data showed that the aldehyde proton had disappeared and a new peak at 6.5ppm was observed. This new peak could be the methine proton if the ring is closed. The ethyl ester group was swept out, and instead, a single methyl ester group was observed. This ester exchange was caused by the alkaline methanol solution. A new broad

peak at 5.2 ppm suggested the presence of a hydroxyl group, and this broad peak was eliminated when a drop of D_2O was added into the NMR solution. All these data suggested that the desired ring closure product was finally obtained.



47 48

3. Final Transformation to Lysergic Acid

After considerable exploration we had at last cyclized our intermediate into the tetracyclic skeleton of Lysergic Acid. While it has been all too evident that this cyclization is difficult, implying serious steric strain to closing the last ring, we were still surprised at how easily the aldol reaction on the aldehyde finally worked.

Examination of models seemed to suggest that in the cyclization of a pyridine –CO-X or CH_2-X group onto the 3-position of the indole there is a very considerable hindrance of the X-atom to reaching the necessary transition state for the C-C bond formation. In such a case it is perhaps reasonable that only the aldehyde case of X=H surmounts this strain barrier. Even so, the extent of

the difference in the facility of the aldehyde over the intractability of the others surprised us.

There now remained only the refunctionalization of the cyclized product to finish the synthesis. This work involves the removal of the cyclized hydroxyl, methylation of the pyridine nitrogen, and reduction of the pyridine ring. The reduction of the hydroxyl group was successfully achieved by Potier via hydrogenation, and the methylation and reduction was known from the arecoline formation (chapter 2) and from our own results in chapter 2, section 2.3. It was already known that the double bond in Lysergic Acid readily isomerizes in base from the position $\alpha.\beta$- to the ester, as in arecoline, to the more stable and more substituted β,γ-position in Lysergic Acid[71].

3.1 Reduction of the Cyclized Hydroxy Compound

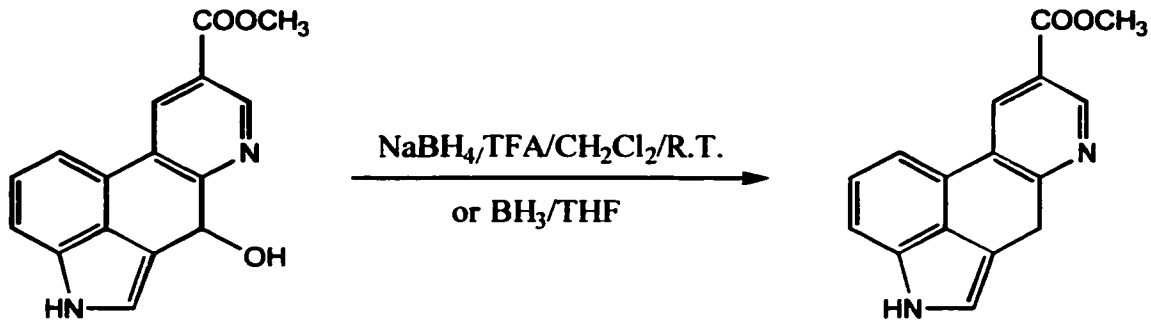
In the Potier paper[70], the hydroxyl adduct was reduced to the methylene derivative by hydrogenation on Pd/C. When his reaction conditions were applied to our system, over-reduction was observed even with a very short period of time. The crude NMR showed multiple sets of aromatic peaks and the indole 2-H integrated for less than one proton. Additional aliphatic protons were also observed. This indicated the over- reduction of the indole. Since the TLC showed many closely spaced spots, this hydrogenation was abandoned and different reduction conditions were explored.

We discussed the mechanism of reduction of the ketone compounds in chapter 2, section 2.1. By that mechanism, the ketone was first reduced to

hydroxyl. The second reduction happened only after this hydroxyl compound was dehydrated via elimination in acidic conditions and this double bond then further reduced to an indole. By this mechanism, the hydroxyl compound was an intermediate in the reduction, and our current cyclized hydroxyl compound should also be reduced to the cyclic methylene compound the same way.

Two sets of reaction conditions were used to reduce the ketone compound in chapter 1. When $NaBH_4$ was used as the reducing reagent together with TFA, the desired methylene product was obtained in 35% yield. However, when BH_3 in THF was used as the reducing reagent, the best yield was 41%. The yield of this BH_3 reduction varied with different scales, the smaller the scale, the better the yield. We also found that a better result was obtained if the reaction was carried out at lower concentration and at room temperature.

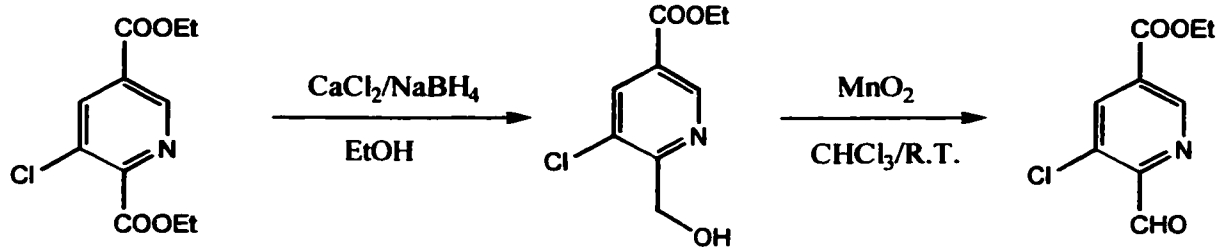
However, it was found that the methylene product was not very stable. If it was left in the air for 2 hours, it developed a dark color and the TLC showed a baseline spot developing besides the original spot. If the compound was left for about 4 hours, the original spot disappeared completely, leaving only the baseline spot on the TLC. The NMR of this degraded material also showed the disappearance of the original product and many unrecognizable peaks in the aromatic region as well as several methyl ester peaks. We suspected that the methylene group in this compound is very susceptible to oxidation, but storage of this compound with an anti-oxidant such as 1,4-hydroquinone did not stop this degradation. As a result the reduction product was used immediately for the next step, discussed in section 3.3.



48 **49**

3.2 Suzuki Reactions at Different Stages of the Synthesis

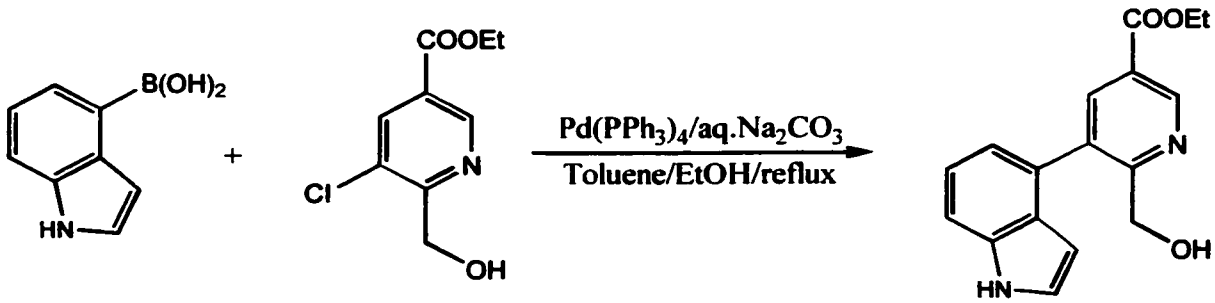
In principle the Suzuki Reaction could be performed at a different stage of the synthesis. The route would be more efficient if the aldehyde required for the final cyclization were already present in the chloro-pyridine used in the Suzuki Reaction. Here 3-chloro-isocinchomeronic ester would be reduced first to its hydroxymethyl derivative and this in turn would be used as the Suzuki Reaction starting material. Alternatively, the hydroxymethyl derivative could be oxidized to aldehyde and this aldehyde could also be used as the Suzuki Reaction starting material. It seemed worthwhile to investigate and compare the results of Suzuki Reaction at these different stages to optimize the synthetic route.



50 51 52

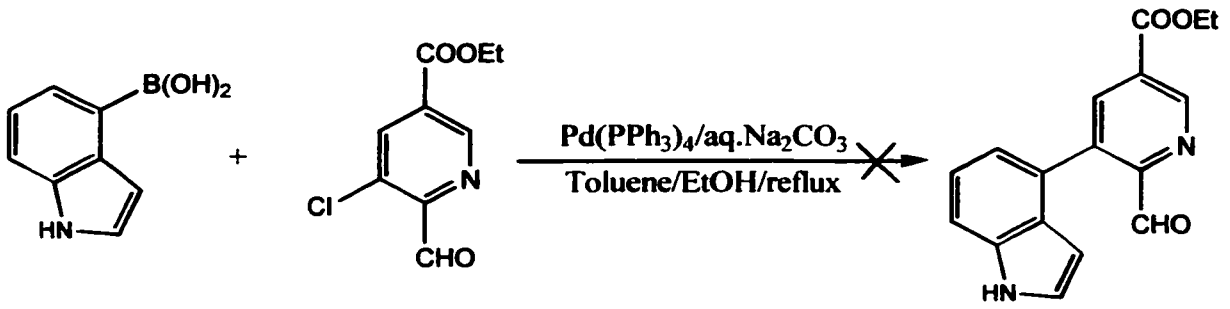
3-Chloro-isocinchomeronic diethyl ester was selectively reduced to its methyl alcohol using the same $Ca(BH_4)_2$ conditions as for the selective reduction of the Suzuki coupling product. This was successful and the product was obtained as a white solid (mp. 167.5-168.6°C) in 89% yield. As expected the NMR spectrum of this compound showed the disappearance of the lower ester group; it also showed the expected methylene group at 4.5 ppm. This alcohol was oxidized to the aldehyde by $MnO_2/CHCl_3$ as in the preparation of the cyclization starting material. The product was a light yellow solid (mp. 145.0-146.3°C), with the expected NMR spectrum showing the aldehyde proton at 9.8 ppm and disappearance of the methylene and hydroxyl group peaks.

With these starting materials in hand, we carried out two more different Suzuki Reactions as shown in the following two equations.



38 51 44

In the Suzuki Reaction on the hydroxymethyl derivative above, the product was obtained in 63% yield, and had an identical mp. and NMR spectrum as that of the selective reduction product in section 2.4 above. As discussed above, the electron withdrawing group on the pyridine plays an important role and enhances the reactivity of the starting material. Replacement of the ester group (electron withdrawing) with the methyl alcohol group apparently lowered the reactivity of the Suzuki starting material and the yield of the reaction decreased.



38 **52** **47**

However, when the chloro-pyridine aldehyde was used in the Suzuki Reaction, neither desired product was obtained nor could starting materials be recovered. The disappearance of the starting materials suggested that the Suzuki Reaction might have happened. If the Suzuki Reaction did happen, the product could have also cyclized to the cyclic alcohol in section 2.6 of this chapter. No such product was suggested by the crude NMR of the reaction. The TLC showed a streak of spots and the identification of the many products from this reaction proved to be too difficult.

From these two experiments, we concluded that the original Suzuki Reaction with the diester still constituted the best synthetic route.

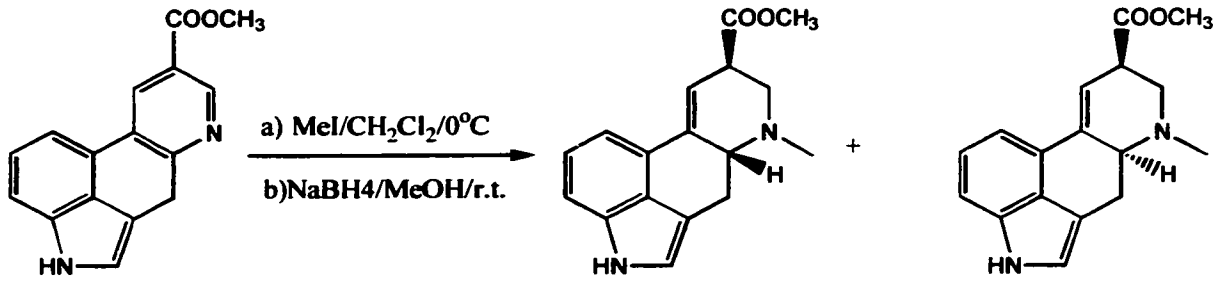
3.3 The End Game

A methyl group on the pyridine nitrogen now needs to be installed to finish the lysergic acid skeleton, and the resulting pyridinium salt should be reduced to methyl lysergate according to previous study.

The reduced tetracyclic pyridine was dissolved in methylene chloride and 2 equivalents of iodomethane was added at 0°C. The TLC showed the disappearance of starting material within 2 hours and no precipitation was observed. The NMR of the resulting crude material clearly showed two downshifted pyridine aromatic peaks and a new methyl group. However, the NMR also showed some of the peaks encountered above for the slow degradation of the reduction product, and so the methylation was not quick enough to avoid some of this concomitant degradation.

The resulting crude methylation product was not purified but immediately subjected to the final reduction reaction. The product was dissolved in methanol and excess $NaBH_4$ was added. A new spot was observed on TLC immediately and did not become more intense with longer reaction time or more $NaBH_4$. Isolation of this new spot on TLC afforded a light yellowish solid. The NMR of this new material showed it to be a mixture of two compounds in a 6 : 1 ratio. The major compound was methyl lysergate with the correct stereochemistry and

the minor one was the diastereomeric methyl isolysergate. The NMR of this mixture was identical to that prepared by I. Ninomyia[9] in 1985.



6 : 1

49 **53** **54**

Isolation of this mixture was not attempted as these esters are known to be somewhat unstable[71], and so the whole batch was subjected to the hydrolysis of the methyl ester. The mixture obtained above was dissolved in a mixture of ethanol and 1N NaOH solution. Hydrolysis was complete in two hours at 35°C, as indicated by TLC. The pH was adjusted to 6 and a solid material precipitated out. Recrystallization of this solid material from ethanol afforded a light brownish crystalline solid. The NMR of this material showed a single diastereomer and it was in agreement with the NMR of the lysergic acid made by I. Ninomyia[9]. By this hydrolysis and recrystallization process, the minor diastereomer was removed and pure lysergic acid was obtained. The NMR (1H and 13C) was identical to that of lysergic acid synthesized by Ninomyia and was also in agreement with that of the authentic sample acquired from Dr. David Nichols from the Department of Pharmacy at Purdue University. We wish to express our gratitude to Prof. Ninomyia and Dr. Nichols for these comparison spectra and sample.

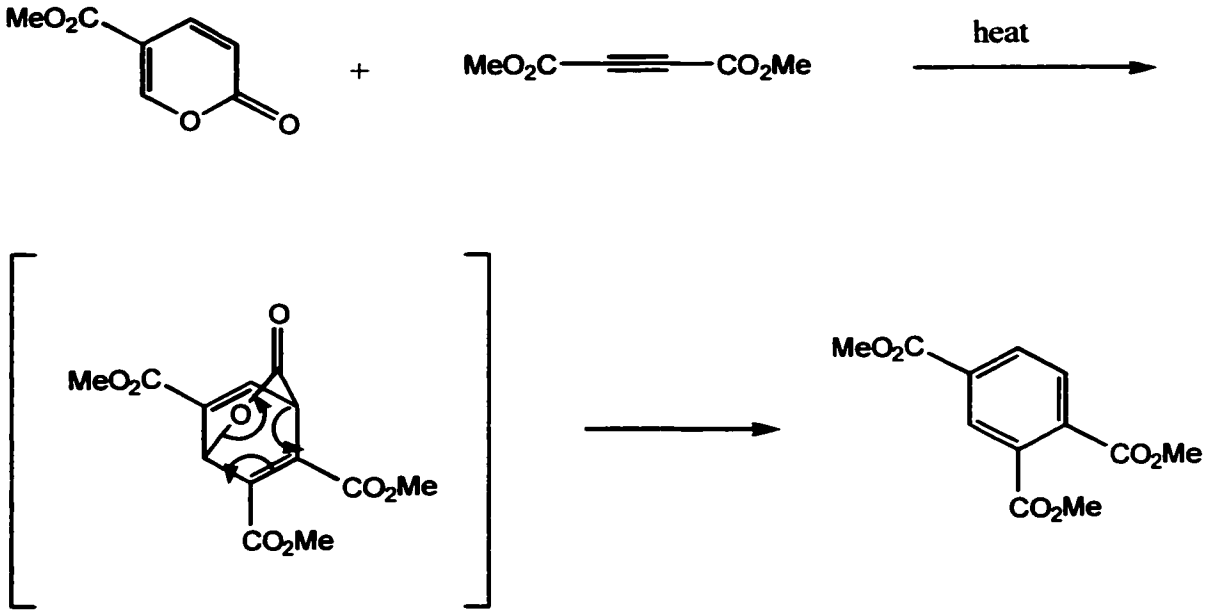
4. Conclusion

In this chapter, lysergic acid was obtained via route A (bond **a** then bond **b**). Different diaryl halide coupling reactions (Stille Reaction, Negishi Reaction and Suzuki Reaction) were tried and the Suzuki Reaction proved to be the only successful way to form the bond **a** between indole-4-boronic acid and 3-chloro-isocinchomeronic diethyl ester. The formation of bond **b** in this route was not successful on the diester product or several of its derivatives. Finally, bond **b** was formed from the aldehyde derivative. Reduction of the cyclized alcohol and subsequent methylation, reduction and hydrolysis afforded lysergic acid. The obtained lysergic acid was identical to the natural material by ^{1}H NMR and ^{13}C NMR. The Suzuki Reaction using other derivatives of the pyridine starting material proved not to be preferable. and the best result was obtained when indole-4-boronic acid and 3-chloro-isocinchomeronic diethyl ester were used as the starting materials.

Chapter 4

A New Synthesis of Pyridines by the Diels-Alder Reaction

The Diels-Alder reaction is one of the most important reactions in organic chemistry and has been the object of extensive theoretical and mechanistic study, as well as synthesis application[72-81].

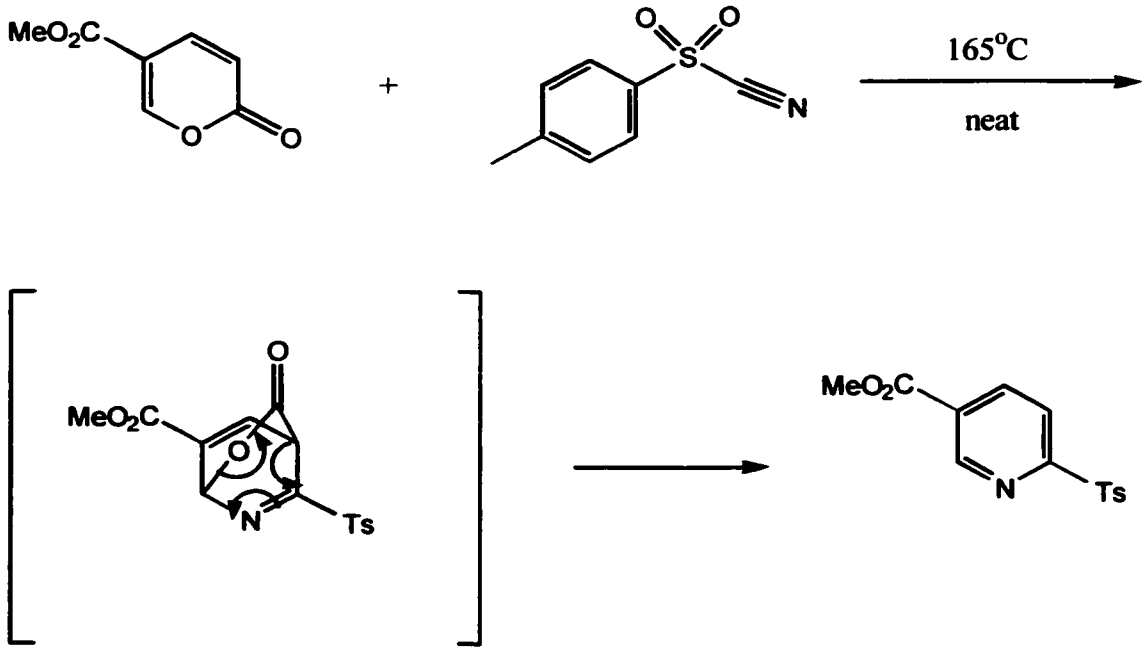


Scheme 29: Diels-Alder reaction precedent

An interesting variant is the formation of benzene rings by the reaction of an acetylenic dienophile with an α-pyrone. The reaction shown below has two

pericyclic stages, the first a Diels-Alder reaction on the diene part of the pyrone, the second a retro-Diels-Alder to release carbon dioxide and form the aromatic. This aromatization presumably constitutes the driving force for the overall reaction.

When this reaction was described in Professor Hendrickson's heterocyclic chemistry course, it occurred to me that it might be modified to create pyridine aromatics as well, but this variant has apparently not been reported before. The necessary dienophile would then be a cyanide with an attached electron-withdrawing group, as with tosyl cyanide, which is commercially available. This has the added advantage that the tosyl group on the newly formed pyridine could be a leaving group, and so different pyridine derivatives could be formed by displacing the tosyl group with different nucleophiles.

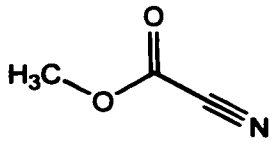


55

This was tried with methyl coumalate, which was mixed with a slight molar excess of tosyl cyanide (1.2 equiv.) without solvent and heated at 165°C. After two hours, the tosyl cyanide had disappeared from the TLC, but methyl coumalate was still present in the reaction mixture. The crude product was purified by chromatography and a white crystalline solid was obtained (mp. 189.1-190.2°C) in 54% yield.

The NMR of this product showed one singlet at 8.8ppm and two doublets at 8.1ppm and 8.5ppm respectively (J=9.6 Hz). This result is characteristic for pyridine derivatives having this substitution pattern. The NMR also showed the presence of a methyl ester at 3.8ppm and the characteristic methyl and aromatic doublet of the tosyl group. All these results suggested the successful formation of the proposed product.

Different available pyrone derivatives were also subjected to this new reaction conditions using tosyl cyanide as the dienophile. Some of them gave the desired product and some of them did not. The results are summarized in the table 4.



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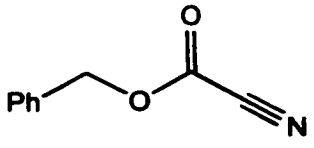


When tosyl cyanide was heated alone, decomposition occurred above 150°C. Therefore, different dienophiles were also tried with methyl coumalate. When above cyanoformate dienophiles were used, however, no desired product was obtained even at 210°C.

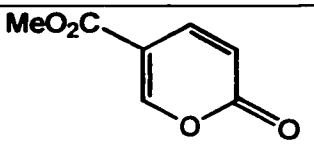
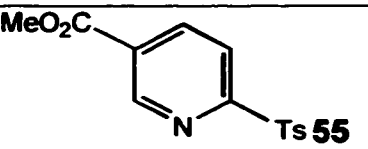
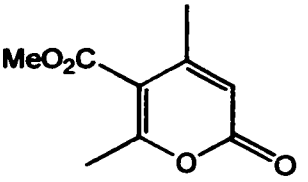
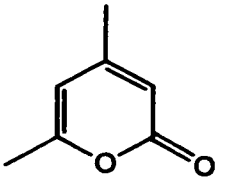
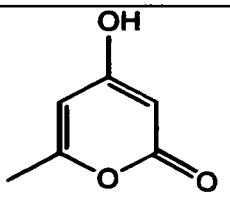
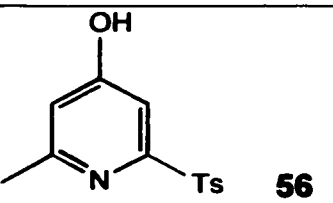
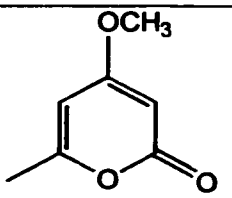
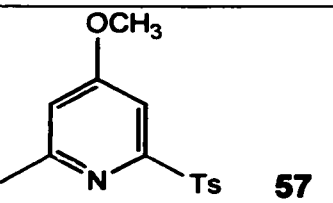
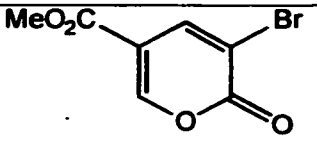
diene	temperature	product	yield
	165°C	 **55**	54%
	180°C	no product formed, decomposition of tosyl cyanide	
	120°C	no product formed, decomposition of tosyl cyanide	
	125°C	 **56**	49%
	165°C	 **57**	60%
	180°C	no product formed, decomposition of tosyl cyanide	

Table 4: Diels-Alder Reaction Results

4.2 Optimized Diels-Alder Reaction Conditions

As we can see from the above discussion, this new Diels-Alder reaction proceeded at a relatively high temperature, very close to the decomposition of tosyl cyanide itself. This may account for the imperfect yield of the reaction. If we could use milder reaction conditions, the yield of the reaction might be improved and some of the unsuccessful cases could become successful.

Methyl triflate was tried to methylate the tosyl cyanide nitrogen in order to activate this dienophile. When equal moles of methyl triflate, methyl coumalate and tosyl cyanide were dissolved in $CDCl_3$, the NMR spectrum showed no change of the starting materials. Heating of this mixture at 60°C in a sealed vessel led only to general decomposition.

Lewis acid catalysis is known for many Diels-Alder reactions[82]. The commonly used Lewis acids are $AlCl_3$, $TiCl_4$, BF_3 and $ZnCl_2$. These Lewis Acids were tested in the reaction of methyl coumalate and tosyl cyanide and the results are summarized in the table below. These reactions were all run in solvents as indicated. 1.0 equivalent of methyl coumalate, 1.2 equivalents of tosyl cyanide and 20 mol % of the Lewis Acid were used in all the reactions, which were run in anhydrous conditions and under nitrogen. The yields are calculated based on methyl coumalate.

From the table 5, we can see that $TiCl_4$ gave quite superior performance. The decomposition of tosyl cyanide was observed in all cases, with the reaction catalyzed by $AlCl_3$ the most serious decomposition. This result is explained by

the longer reaction time and higher temperature and thus subsequent decomposition of the tosyl cyanide.

Lewis Acid	$AlCl_3$	$TiCl_4$	BF_3	$ZnCl_2$	None
Temperatures	100°C	65°C	65°C	65°C	165°C
Solvents	toluene	Dichloro ethane	THF	THF	neat
Duration of Reaction	4 hours	1 hour	2 hours	2 hours	2 hours
Yields	32%	82%	53%	58%	54%

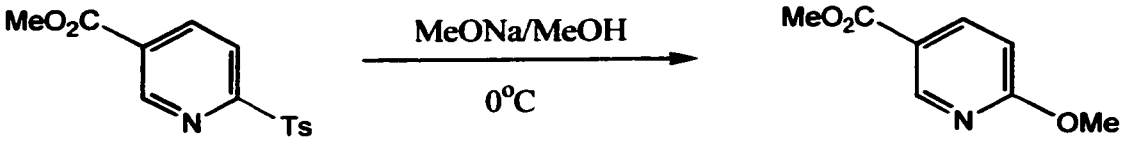
Table 5: Diels-Alder Reaction by Lewis Acid

From the above table, we can see that $TiCl_4$ gave quite superior performance. The decomposition of tosyl cyanide was observed in all cases, with the reaction catalyzed by $AlCl_3$ the most serious decomposition. This result is explained by the longer reaction time and higher temperature and thus subsequent decomposition of the tosyl cyanide.

The optimized reaction conditions with $TiCl_4$ as the Lewis Acid were also applied to the cases in which the earlier neat conditions did not work. Unfortunately, none of these reactions delivered any desired product under the optimized conditions for methyl coumalate and tosyl cyanide.

4.3 Pyridine Derivatives by Nucleophilic Displacement

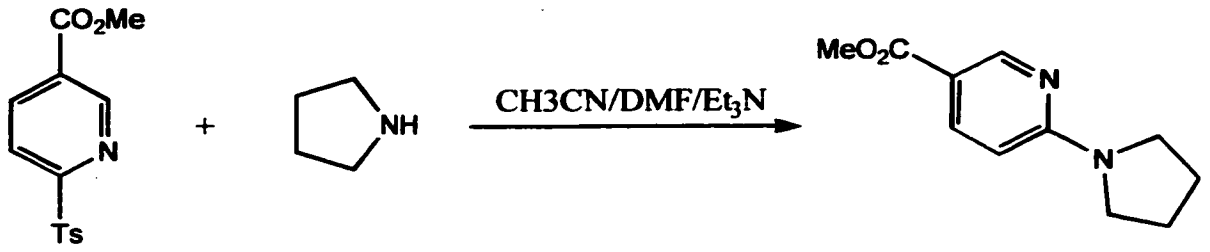
Since tosyl is a reasonably good leaving group, different nucleophiles were used to displace the tosyl on pyridine in order to form new pyridine derivatives which might not be accessible by other synthetic methods.



55 **58**

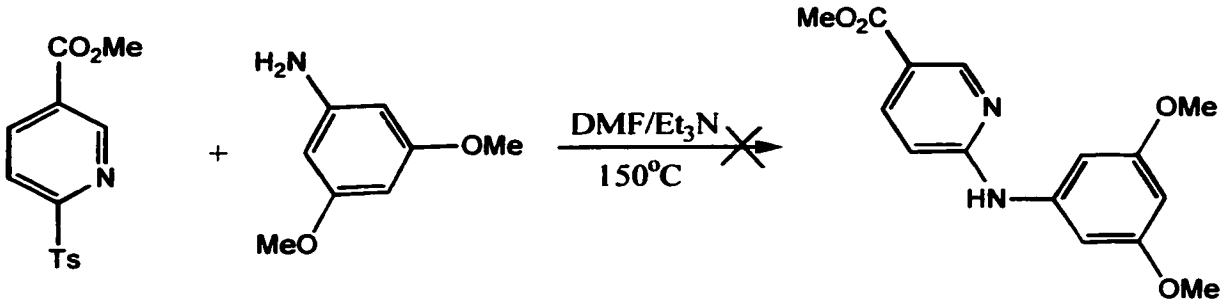
Displacement of the tosyl group by sodium methoxide in methanol at 0°C afforded the 6-methoxy-nicotinate as a white solid (mp. 145.9-146.7°C). The NMR of this compound was similar, with the disappearance of the tosyl group and appearance of the methoxyl group at 4.2 ppm. The yield of this reaction is 89%.

Nitrogen was also used as the displacing nucleophile. In the following two examples, both aromatic and aliphatic amines were used to displace the tosyl group on the Diels-Alder product. With pyrrolidine the indicated displacement of the tosyl group took place at r.t. in 4 hours to yield the product shown as a solid (mp. 122.6-123.6°C) in 85% yield. The NMR showed the expected loss of the tosyl protons and the addition of pyrrolidine protons and a small upfield shift of the three aromatic protons.

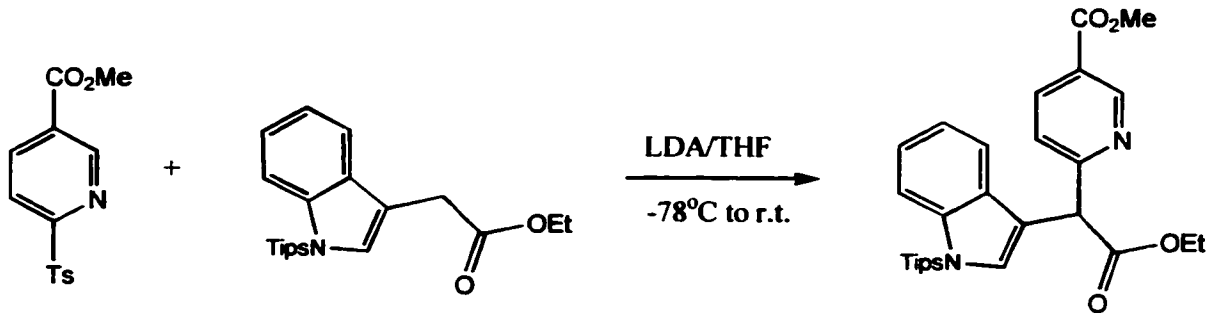


55 **59**

With 3,5-dimethoxy aniline, the displacement reaction didn't proceed even at elevated temperature. This might be due to the weaker nucleophilicity of the aniline.



We saw this simple preparation of a substituted nicotinate as a potential start for another synthesis of lysergic acid. The indole nitrogen of the commercial indole 3-acetic ester was blocked with a tri-isopropyl-silyl group and treated with LDA at –78°C to form the enolate anion. Without the addition of the tosyl-nicotinate the enolate apparently eliminates ethoxide to form a ketene and reacts further with itself, as indicated by the fact that the indole starting material disappeared in the TLC. When the tosyl-nicotinate is present during the addition of LDA, however, the expected displacement of tosyl occurred smoothly as shown.



54 **58**

The obtained compound is a oil, the NMR of which showed the presence of both the characteristic indole protons and the pyridine moiety as well as a new methine singlet at 4.5 ppm. All these data supported the formation of the expected product.

It is dramatic that if this pyridine product is methylated, it acquires all the atoms of the complete skeleton for lysergic acid. If the bond **a** could be formed after the formation of this bond linking the two aromatics, the product could be used as a precursor for a short lysergic acid synthesis! However, our experience in chapters 1 and 2 with closing bond **a** discouraged us from pursuing this avenue further for total synthesis.

4.4 Conclusion

A new Diels-Alder reaction, using an α-pyrone as diene and tosyl cyanide as dienophile, with or without $TiCl_4$ as a catalyst, was proposed and successfully developed. The loss of carbon dioxide from the Diels-Alder adduct intermediate and subsequent formation of pyridine aromaticity is the driving force for the formation of the proposed product. $TiCl_4$ catalysis could be used to achieve

milder reaction conditions and improve the yield. Attempts to use other dienophiles containing nitrile groups, however, failed. Displacements of the tosyl group from the tosyl-pyridine product by various nucleophiles containing carbon, oxygen and nitrogen lead to new substituted pyridines that may otherwise not be easily accessible by other synthetic methods.

This suggests that this newly developed Diels-Alder reaction is an important and useful method for forming substituted pyridines.

Experimental Section

The solvents and reagents were purified by the following methods:

Diethyl ether, glyme and THF were distilled from sodium with benzophenone as an indicator. DMF, CH_2Cl_2 and xylene were distilled from calcium hydride. Benzene and toluene were distilled from P_2O_5. Methanol and ethanol were dried over magnesium[83]. Triglyme was distilled from $LiAlH_4$. Trimethylamine was distilled from NaOH. Anhydrous $CaCl_2$ refers to $CaCl_2$ that has been roasted in a crucible and allowed to cool in a desiccator.

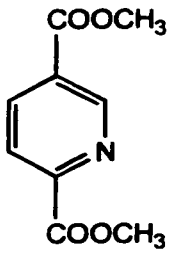
Analyses were performed on the following instruments:

1H NMR & 13C NMR: VARIAN UNITY INOVA 400 MHz

Mass Spectrometry: Micromass QUATTRO II

Unless otherwise specified, the 1H data refers to the 400 MHz spectrum data. In the description of the spectra, s = singlet, d = doublet, t = triplet, m = multiplet. The prefix b is used to describe a broad peak. The chemical shift is given in ppm.

1. Preparation of **pyridine-2,5-dicarboxylic acid dimethyl ester(3):**



Pyridine-2,5-dicarboxylic acid (5.43g, 30.0 mmol) was dissolved in 300ml anhydrous methanol in a 1 liter round bottom flask. To this solution was added 3 drops of conc. H_2SO_4. The reaction vessel was equipped with a reflux condenser and a stirring bar. The reaction was refluxed and stirred over 12 hours and was cooled to r.t. The solvent was evaporated *in vacuo* and a light yellowish oil was obtained. This oil material was dissolved in 200 ml CH_2Cl_2 and washed with aq. $NaHCO_3$(Sat., 150ml) then H_2O (200 ml). The organic phase was dried over Na_2SO_4. Removal of solvent *in vacuo* afforded 5.75 g (98.2% yield) product as a white crystalline material (mp. 182.1-182.9°C).

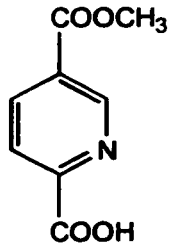
^1H NMR ($CDCl_3$): δ 9.30 (s, 1H), 8.49 (d, 1H, J=2.8Hz), 8.20 (d, 1H, J=2.8Hz), 3.98 (s, 3H), 4.03 (s, 3H)

^{13}C NMR ($CDCl_3$): δ 165.2, 165.2, 152.2, 151.4, 138.5, 129.7, 125.2, 60.6, 52.3.

Mass Spectrum (ES^+): Expected for $C_9H_9NO_4$: 195.05. Found: 196.05.

Elemental Analysis: Calcd. For $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.19; H, 4.69; N, 7.33.

2. **pyridine-2,5-dicarboxylic acid 5-methyl ester(10)**:



To a solution of pyridine-2,5-dicarboxylic acid dimethyl ester (5.91g, 30 mmol) in 100 ml methanol was added copper(II) nitrate trihydrate (14.5g, 60 mmol) in a 500 ml round bottom flask equipped with a reflux condenser and a stirring bar. The reaction was refluxed for 80 mins. A deep violet-blue precipitation was observed after 20 mins and lasted throughout the course of the reaction. The reaction was cooled to r.t., and the reaction mixture was reduced to 1/3 of its original volume. The deep violet-blue solid was collected by filtration and washed with cold methanol then cold water. This solid material was dissolved in 50 ml glyme, and H_2S gas was bubbled into the solution. The black precipitate was formed in 2 mins, and the deep violet-blue solid disappeared after 15 mins. The black precipitate was filtered out through a plug of celite and the filtrate was concentrated to 20 ml. Excess hexanes were added into this solution, and a white solid was formed. The white solid was collected by filtration. Recrystallization of this solid from acetone afforded 4.83g product in 88.9% yield (mp. 194.1-195.1°C).

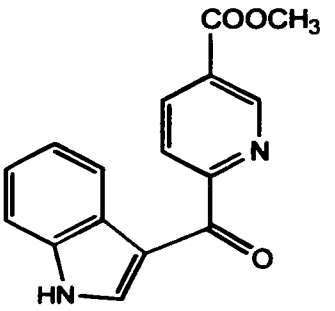
^{1}H NMR ($CDCl_3$): δ 9.21 (s, 1H), 8.60 (d, 1H, J=2.9Hz), 8.23 (d, 1H, J=2.9Hz), 4.00 (s, 3H).

^{13}C NMR ($CDCl_3$): δ 172.4, 165.3, 154.3, 150.4, 139.2, 129.3, 122.9, 52.3.

Mass Spectrum (ES^+): Expected for $C_8H_7NO_4$: 181.04. Found: 182.04.

Elemental Analysis: Calcd. For $C_8H_7NO_4$: C, 53.04; H, 3.89; N, 7.73. Found: C, 52.91; H, 3.88; N, 7.86.

3. Preparation of **6-(1*H*-indole-3-carbonyl)-nicotinic acid methyl ester(4)**:



This compound was made by two different methods (**A** & **B**):

Method A:

To a solution of pyridine-2,5-dicarboxylic acid 5-methyl ester (3.62g, 20.0 mmol) in 100 ml anhydrous THF was added 60% of NaH in mineral oil (0.84g, 21.0 mmol). The solvent was removed *in vacuo* and a white solid was obtained. To a suspension of this white solid in 50 ml anhydrous dichloroethane was added $POCl_3$ (1.23g, 8.0 mmol) and 0.5 ml DMF. The resulting mixture was heated at 45°C in an oil bath with stirring for 2 hours. $AlCl_3$ (3.2g, 24 mmol) was added to the reaction mixture at r.t. The resulting mixture was added portionwise to a solution of indole (2.81g, 24 mmol) in 20

ml anhydrous dichloro- ethane via an addition funnel at 0°C. A bright red color was observed immediately and reaction was heated at 40-45°C with vigorous stirring for 1 hour. The reaction mixture was cooled to r.t. and poured onto 100 g of ice cubes in a 500 ml beaker. The material was partitioned between CH_2Cl_2 and aq. NH_4Cl (sat.) and extracted with CH_2Cl_2 (100ml x 3). The organic phase was washed with water (200 ml) and dried over Na_2SO_4. The solvent was removed in vacuo and a yellowish solid was obtained. Recrystallization of this solid from acetone afforded 3.64 g product as an off-white solid (mp.215.7-216.8°C) in 65.0% yield.

^1H NMR ($CDCl_3$): δ 9.25 (s, 1H), 8.88 (d, 1H, J=2.1Hz), 8.75 (bs, 1H), 8.60 (d, 1H, J=5.5Hz), 8.46 (d, 1H, J=5.5Hz), 8.23(d, 1H, J=8.1Hz), 7.43(d, 1H, J=8.1Hz), 7.33(m, 2H), 4.02 (s, 3H).

^{13}C NMR (Acetone-d6): δ 185.0, 165.1, 159.8, 149.3, 144.2, 141.1, 137.7, 136.6, 130.9, 127.7, 123.1, 122.4, 122.1, 114.7, 112.0, 52.2.

Mass Spectrum (ES^+): Expected for $C_{16}H_{12}N2O_3$: 280.08. Found: 281.07.

Elemental Analysis: Calcd. For $C_{16}H_{12}N2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.39; H, 4.17; N, 9.81.

Method B:

Pyridine-2,5-dicarboxylic acid 5-methyl ester (2.85g, 15.7 mmol) was suspended in 20 ml thionyl chloride in a 100 ml round bottom flask equipped with a reflux condenser and a stirring bar. The reaction was refluxed and stirred until the solid went into solution completely. The reaction was cooled

to r.t., and thionyl chloride was removed *in vacuo*. Traces of thionyl chloride were chased by CCl_4 (20 ml x 2) *in vacuo*. A white solid was obtained (3.14g) in quantitative yield (mp. 156.1-157.4°C). This material was used directly in the following reaction.

For analytical purpose, the above material was allowed to react with methanol in anhydrous acetonitrile at 0°C. The NMR of the resulting product was identical with that of pyridine-2,5-dicarboxylic acid dimethyl ester obtained in experiment 1. This confirmed the identity of the product as 6-chlorocarbonyl-nicotinic acid methyl ester.

^{1}H NMR ($CDCl_3$): δ 9.22 (s, 1H), 8.52 (d, 1H, J=8.6Hz), 8.19 (d, 1H, J=8.6Hz), 4.04 (s, 3H).

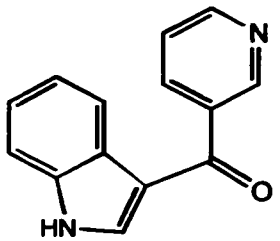
Elemental Analysis: Calcd. For $C_8H_6ClNO_3$: C, 48.14; H, 3.03; N, 7.02. Found: C, 48.30; H, 3.16; N, 6.88.

To a solution of EtMgBr (10 ml, 1.575 M in ether, 15.75 mmol) was added a solution of indole (1.755g, 15.0 mmol) in ether (anhydrous, 20 ml). The resulting two-phase system was allowed to stand for 15 min under stirring, whereafter $ZnCl_2$ (15 ml, 1.0m in ether, 15.0 mmol) was added with stirring. The two-phase system was allowed to stand for 30 min when 6-chlorocarbonyl-nicotinic acid methyl ester (3.14g, 15.75 mmol) in anhydrous ether (10 ml) was added rapidly under vigorous stirring. The reaction mixture was allowed to stand for 2 hours whereupon NH_4Cl (aq. sat. 25 ml) was added. The organic layer was separated, and the aqueous layer was

extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was washed with $NaHCO_3$ (aq. sat. 25 ml) followed by brine (25 ml), dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded a yellowish solid. Recrystallization of this solid from acetone afforded 2.99g of the desired crystalline product in 71.2% yield.

^1H NMR ($CDCl_3$), ^{13}C NMR ($CDCl_3$), Mass Spectrum (ES^+), Elemental Analysis and mp. of this product were identical to that of the product obtained by method A.

4. **Preparation of (1H-indol-3-yl)-pyridin-3-yl-methanone(37):**



General procedure using $AlCl_3$, $TiCl_4$, $SnCl_4$ and $EtMgBr/ZnCl_2$ method:

To a solution of nicotinic acid chloride (1.37g, 10.0 mmol) in dichloro-ethane was added various Lewis acid (12.0 mmol) at 0°C. The mixture was stirred at r.t. for 30 min and indole (1.17g, 10.0 mmol) was added into the mixture at 0°C. The reaction was warmed to r.t. and heated at 45°C for 2 hours. The reaction was poured into 100g ice cube and the mixture was extracted with ethyl acetate (100 ml x 3) from aqueous $NaHCO_3$ (sat., 100 ml). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude was passed through a short plug of silica gel and recrystallized from acetone.

Compound could also be made following the method described in above $EtMgBr/ZnCl_2$ method.

From above reactions, solid products were obtained. Mp. Of these compound are in the range of 189.2-192.4°C.

Yield: $AlCl_3$: 45%; $TiCl_4$: 42%; $SnCl_4$: 90%; $EtMgBr/ZnCl_4$: 85%.

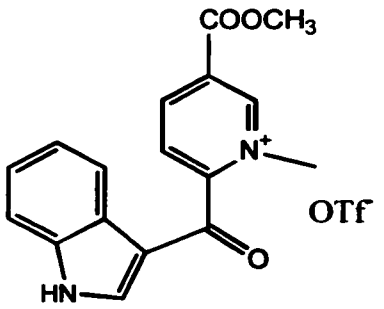
^1H NMR (acetone-d6): δ 11.4 (bs, 1H), 9.01 (s, 1H), 8.77 (d, 1H, J=4.0Hz), 8.40 (t, 1H, J=4.0Hz), 8.18 (d, 1H, J=4.0Hz), 8.01 (d, 1H, J=2.8Hz), 7.56 (m, 2H), 7.32 (m, 2H)

^{13}C NMR (Acetone-d6): δ 189.2, 152.9, 150.5, 138.3, 137.6, 136.9, 136.7, 127.8, 124.8, 124.6, 123.4, 123.2, 117.3, 113.3

Mass Spectrum (ES^+): Expected for $C_{14}H_{10}N_2O$: 222.08. Found: 223.08.

Elemental Analysis: Calcd. For $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.51; H, 4.39; N, 12.66

5. Preparation of **6-(1*H*-indole-3-carbonyl)-nicotinic acid methyl ester trifluoromethanesulfonate salt(16):**



To a solution of 6-(1*H*-indole-3-carbonyl)-nicotinic acid methyl ester (1.40g, 5.0 mmol) in 50 ml $CH_2Cl_2$was added MeOTf (1.64g, 1.13 ml, 10.0 mmol) at 0°C. The reaction was stirred at 0°C under N_2. A precipitate was observed during the reaction and starting material disappeared after 30 min. The reaction was warmed to r.t., and the solid was collected by filtration. The solid was washed with minimal cold water then cold methanol. A yellowish crystalline was obtained (2.18g) in 98.3% yield (mp. 245.3-244.2°C).

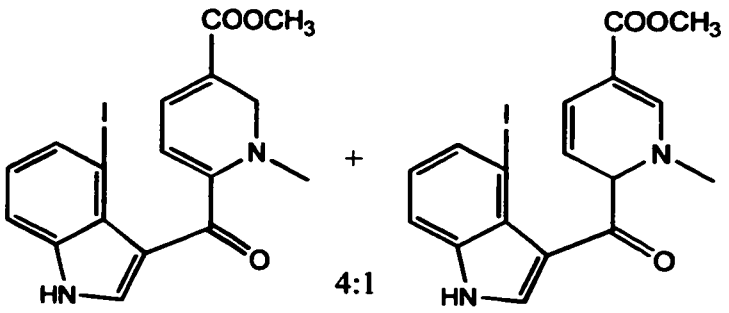
^{1}H NMR (acetone-d6): δ 9.78 (s, 1H), 9.29 (d, 1H, J=8.4Hz), 8.61 (d, 1H, J=8.4Hz), 8.35 (t, 1H, J=8.8Hz), 8.15 (d, 1H, J=3.2 Hz), 7.68(dd, 1H, J=6.4, 3.2Hz), 7.43(d, 1H, J=9.2Hz), 7.43(d, H, J=2.4Hz), 4.65 (s, 3H), 4.09 (s, 3H).

^{13}C NMR (Acetone-d6): δ 180.5, 163.0, 154.8, 150.6, 147.7, 141.2, 138.9, 131.7, 129.0, 126.8, 126.1, 124.9, 122.9, 116.7, 114.2, 54.4, 48.2, 36.2.

Mass Spectrum (ES^+): Expected for $C_{17}H_{15}N_2O_3$: 295.05. Found: 296.05.

Elemental Analysis: Calcd. For $C_{18}H_{15}F_3N_2O_6S$: C, 48.65; H, 3.40; N, 6.30. Found: C, 48.48; H, 3.33; N, 6.18

6. Preparation of **dihydro-compounds(19 + 20):**



To a solution of 6-(1*H*-indole-3-carbonyl)-nicotinic acid methyl ester trifluoromethanesulfonate salt ((0.44 g, 1.0 mmol) in methanol (5 ml) was added $NaBH_4$ (0.19 g, 5.0 mmol) at r.t. The reaction was stirred at r.t. for 10 min, and H_2O (15 ml) was added into the reaction mixture dropwise. A red precipitation was observed and collected by filtration . The solid was washed with minimal amount of cold H_2O and cold methanol. The solid was dried in vacuum and weighed at 0.26 g (87% yield).

NMR of this solid in CDCl3 showed that it is a mixture of two compounds in 4:1 ratio.

Major compound:

^1H NMR ($CDCl_3$): δ 9.72 (bs, 1H), 7.63 (d, 1H, J=8.4Hz), 7.45 (d, 1H, J=3.2Hz), 7.32 (d, 1H, J=7.2Hz), 7.30 (d, 1H, J=8.4Hz), 7.15 (t, 1H, J=8.4Hz), 7.15=0 (t, 1H, J=8.4Hz), 6.10 (d, 1H, J=7.2Hz), 3.88 (s, 3H), 3.23 (m, 1H), 2.97 (m, 1H), 2.54 (s, 3H)

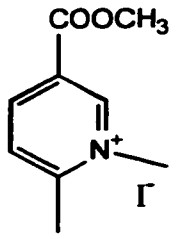
Minor compound:

^1H NMR ($CDCl_3$): δ 9.72 (bs, 1H), 7.92 (d, 1H, J-3.2Hz), 7.61 (d, 1H, J=8.4Hz), 7.28 (d, 1H, J=8.4Hz), 7.10 (t, 1H, J=8.4Hz), 7.02=0 (t, 1H, J=8.4Hz), 6.88 (s, 1H), 6.22 (d, 1H, J=6.8Hz), 5.67 (d, 1H, J=6.8Hz), 4.10 (m, 1H), 3.86 (s, 3H), 2.51 (s, 3H)

Mass Spectrum (ES^+): Expected for $C_{17}H_{16}N_2O_3$: 296.12. Found: 297.12.

Elemental Analysis: Calcd. For $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.09; H, 5.37; N, 9.43

7. Preparation of **5-methoxycarbonyl-1,2-dimethyl-pyridinium iodide(17):**



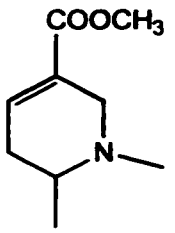
To a solution of 6-methyl nicotinic methyl ester (0.22g, 2.0mmol) was added MeI (0.59g, 4.0 mmol). The reaction was stirred at r.t. under N_2. A white precipitate was formed after 15 min. The starting material disappeared completely after 6 hours, indicated by TLC. The solid material was collected by filtration and washed with cold ether. A white crystalline solid (mp. 192.1-193.3°C) was obtained (0.58g) in 98.9% yield.

^{1}H NMR (CD_3CN): 9.41 (s, 1H), 8.92 (d, 1H, J=8.4Hz), 8.1 (d, 1H, J=8.4Hz), 4.39 (s, 3H), 4.05 (s, 3H).

Mass Spectrum (ES^+): Expected for $C_9H_{12}NO_2$: 166.09. Found: 167.09.

Elemental Analysis: Calcd. For $C_9H_{12}INO_2$: C, 36.88; H, 4.13; N, 4.78. Found: C, 36.68; H, 4.07; N, 4.86

8. Preparation of **arecoline(18):**

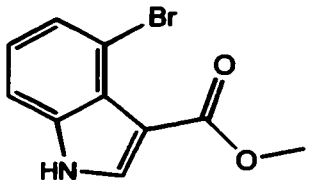


To a suspension of the **17** (0.29g, 1.0 mmol) in 20 ml methanol was added $NaBH_4$ (0.19g, 5.0 mmol) at r.t. A yellow color was generated immediately after the addition of $NaBH_4$. After 5 mins, the reaction was complete as indicated by TLC. Water (50 ml) was added, and the reaction was extracted with CH_2Cl_2 (30 ml x 3). The combined organic phases were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded a light yellow oil. Purification by silica gel using hexane: ethyl acetate (3 : 1) afforded a colorless oil (127.4 mg) in 75.3% yield.

^1H NMR ($CDCl_3$): δ 6.95 (bs,1H), 3.78 (s, 3H), 3.46 (d, 1H, J=16.0Hz), 3.05 (d, 1H, J=16.0Hz), 2.48 (m, 1H), 2.38 (s, 3H), 2.33 (m, 1H), 2.10 (m, 1H).

^{13}C NMR (Acetone-d6): δ 168.4, 137.6, 128.6, 53.2, 52.5, 51.7, 41.6, 34.3, 17.3.

9. Preparation of **4-bromo-1H-indole-3-carboxylic acid methyl ester(61):**



To a solution of 3-methoxycarbonylindole (7.0g, 40.0mmol) in TFA was added Thallium (III) trifluoroacetate (32.6g, 60.0 mmol) in TFA (140 ml), and

the mixture was stirred for 2 hours at r.t. After TFA was evaporated *in vacuo*, a dark brown oil material was obtained. This oil was dissolved in DMF (ml) and $CuBr_2$ (35.8g, 160.0 mmol) was added. The reaction was stirred at 120°C for 1 hour then was cooled and CH_2Cl_2 : MeOH (95 : 5, v/v) (300 ml) was added. Insoluble precipitates were filtered off through a plug of celite. The filtrate was washed with brine (100 ml x 2), and the organic layer was dried over $NaSO_4$. A crystalline material (7.60m g) was obtained in 63.1 yield after the removal of solvent in reduced pressure. This material was directly subjected to the decarboxylation for the preparation of 4-bromo-indole. For analytical purpose, this material was purified by silica gel using hexane : ethyl acetate (5 : 1). A white solid was obtained (mp. 125.8-126.8°C, Lit. 125.0-126.0°C).

^1H NMR ($CDCl_3$): δ 9.14 (bs, 1H), 7.87 (d, 1H, J=2.8Hz), 7.47 (d, 1H, J=8.0 Hz), 7.36 (d, 1H, J=8.0Hz), 7.07 (t, 1H, J=8.0Hz), 3.91 (s, 3H)

^{13}C NMR ($CDCl_3$): δ 164.7, 137.7, 132.5, 127.4, 124.6, 124.0, 114.1, 111.1, 109.5, 51.5.

Mass Spectrum (ES^+): Expected for $C_{10}H_8BrNO_2$: 252.97. Found: 253.98.

Elemental Analysis: Calcd. For $C_{10}H_8BrNO_2$: C,47.27; H, 3.17; N, 5.51. Found: C, 47.43; H, 3.03; N, 5.46.

10. Preparation of **4-bromo-1H- indole(21):**

To a solution of 4-bromo-1H-indole-3-carboxylic acid methyl ester (5.06g,20.0 mmol) in 200 ml methanol was added 200 ml of 40% aq. NaOH. The reaction was refluxed for 1.5 h with stirring. After evaporation of the solvent, the residue was poured into 200 ml water, and the mixture was extracted with CH_2Cl_2-MeOH (95 : 5, v/v; 200 ml x 3). The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an brown oil. Purification by chromatography using hexane : ethyl acetate (6:1) afforded a light colored oil (2.68 g) in 69.1% yield.

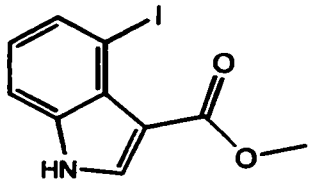
^{1}H NMR ($CDCl_3$): δ 6.62 (t-like m, 1H), 7.05 (dd, 1H, J=8.2, 8.2Hz)), 7.24 (m, 1H,), 7.30 (d, 1H, J=8.2Hz), 7.34(d, 1H, J=8.2Hz), 8.28 (bs, 1H).

^{13}C NMR ($CDCl_3$): δ 136.7, 128.2, 125.5, 123.1, 122.9, 115.2, 111.0, 103.5.

Mass Spectrum (ES^+): Expected for C_8H_6BrN: 194.97. Found: 195.97.

Elemental Analysis: Calcd. For C_8H_6BrN: C, 49.01; H, 3.08; N, 7.14. Found: C, 48.83; H, 3.07; N, 7.28.

11. Preparation of **4-iodo-1H-indole-3-carboxylic acid methyl ester(62):**



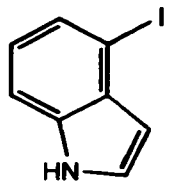
To a solution of 3-methoxycarbonylindole (7.0g, 40.0mmol) in TFA was added Thallium (III) trifluoroacetate (32.6g, 60.0 mmol) in TFA (140 ml), and the mixture was stirred for 2 hours at r.t. After TFA was evaporated in *vacuo*, a dark brown oil material was obtained. This oil was suspended in 450 ml H_2O, and KI (19.9 g, 120.0 mmol) was added to this suspension. The reaction was stirred at r. t. for 2 hours. CH_2Cl_2 : MeOH (95 : 5, v/v) (300 ml) was added to the reaction mixture and insoluble precipitates were filtered off through a plug of celite. The organic layer was separated and washed with aq. sodium thiosulfate then brine. Removal of the solvent left a brownish solid. Quick purification by a short plug of silica gel afforded a white solid (8.68g) in 72.1% yield. For analytical purpose, this material was purified by chromatography using hexane : ethyl acetate (6 : 1). A white solid was obtained after this (mp. 142.5-143.0°C, Lit. 138.5-139.5°C).

^{1}H NMR ($CDCl_3$): δ 8.93 (bs, 1H), 7.56-7.76(m, 2H,), 7.24 (dd, 1H,J=8.0, 0.8Hz), 6.75 (dd, 1H, J=8.0, 7.2Hz), 3.85(s, 3H)

Mass Spectrum (ES^+): Expected for $C_{10}H_8INO_2$: 300.96. Found: 301.97.

Elemental Analysis: Calcd. For $C_{10}H_8INO_2$: C, 39.89; H, 2.68; N, 4.65. Found: C, 40.12; H, 2.71; N, 4.51.

12. Preparation of **4-iodo-1H- indole(22):**



To a solution of 4-iodo-1H-indole-3-carboxylic acid methyl ester (6.02g, 20.0 mmol) in 200 ml methanol was added 200 ml of 40% aq. NaOH. The reaction was refluxed for 1.5 h with stirring. After evaporation of the solvent, the residue was poured into 200 ml water, and the mixture was extracted with CH_2Cl_2-MeOH (95: 5, v/v; 200 ml x 3). The extract was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to leave an off-white solid. Purification by chromatography using hexane : ethyl acetate (6 : 1) afforded a white crystalline solid (3.51g) in 72.3% yield.

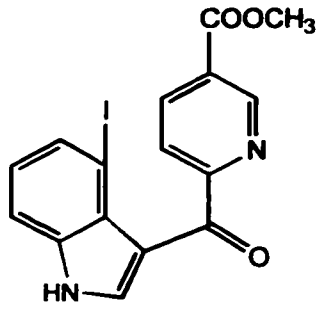
^1H NMR ($CDCl_3$): δ 8.30 (bs 1H), 7.52 (d, 1H, J=8.4Hz), 7.34 (d, 1H, J=8.4Hz), 7.20 (m, 1H), 6.92 (t, 1H, J=8.4Hz), 6.48 (t-like m, 1H).

^{13}C NMR ($CDCl_3$): δ 135.4, 133.2, 130.1, 125.2, 124.1, 111.8, 107.1, 88.2.

Mass Spectrum (ES^+): Expected for C_8H_6IN: 242.95. Found: 243.95.

Elemental Analysis: Calcd. For C_8H_6IN: C, 39.53; H, 2.49; N, 5.76. Found: C, 39.67; H, 2.59; N, 5.75.

13. Preparation of **6-(4-iodo-1H-indole-3-carbonyl)-nicotinic acid methyl ester(23):**



To a solution of EtMgBr (10 ml, 1.575 M in ether, 15.75 mmol) was added a solution of 4-iodo-1H-indole (3.65g, 15.0 mmol) in ether (anhydrous, 20 ml). The resulting two-phase system was allowed to stand for 15 min under stirring whereupon $ZnCl_2$ (15 ml, 1.0m in ether, 15.0 mmol) was added with stirring. The two-phase system was allowed to stand for 30 min when 6-chlorocarbonyl-nicotinic acid methyl ester (3.14g, 15.75 mmol) in anhydrous ether (10 ml) was added rapidly under vigorous stirring. The reaction mixture was allowed to stand for 2 hours whereupon NH_4Cl (aq. sat. 25 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was washed with $NaHCO_3$ (aq. sat. 25 ml) followed by brine (25 ml), dried over Na_2SO_4. Removal of the solvent in vacuo afforded a yellowish solid. Recrystallization of this solid from acetone afforded 4.25g of the desired crystalline product (mp. 245.7-246.8°C) in 69.8% yield.

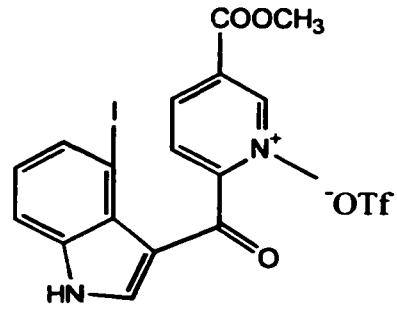
^1H NMR ($CDCl_3$): δ 9.17 (d, 1H, J=1.2Hz), 8.52 (dd,1H, J=8.0, 1.2 Hz), 8.28 (d, 1H, J=2.4Hz), 8.22 (d, 1H, J=8.0Hz), 7.75 (d, 1H, J=8.0Hz), 7.63 (d, 1H, J=8.0Hz), 7.00 (t, 1H, J=8.0Hz),

^{13}C NMR (Acetone-d6): δ 186.1, 164.5, 160.8, 148.8, 142.7, 140.8, 138.2, 137.2, 134.4, 127.7, 123.4, 122.8, 114.9, 111.4, 87.2, 52.2

Mass Spectrum (ES^+): Expected for $C_{16}H_{11}IN_2O_3$: 405.98. Found: 406.98.

Elemental Analysis: Calcd. For $C_{16}H_{11}IN_2O_3$: C, 47.31; H, 2.73; N, 6.90. Found: C, 47.50; H, 2.60; N, 6.88.

14. Preparation of **6-(4-iodo-1H-indol-3-ylmethyl)-1-methyl-nicotinic acid methyl ester trifluoromethanesulfonate acid salt(24):**

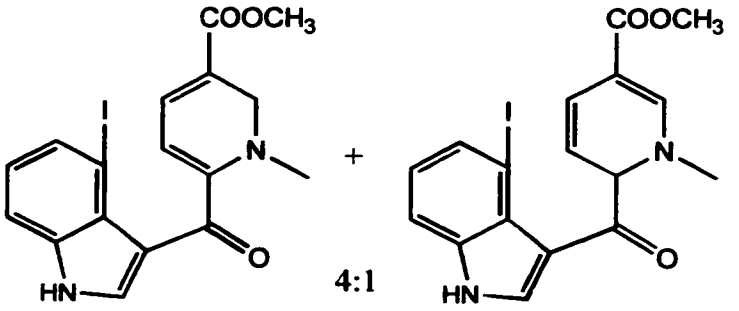


To a solution of 6-(4-iodo-1H-indole-3-carbonyl)-nicotinic acid methyl ester (2.03g, 5.00 mmol) in 50 ml anhydrous CH_2Cl_2 was added MeOTf (1.70 ml, 15.0 mmol). The reaction was stirred at r.t. under N_2 for 2 hours at 0°C. During the course of the reaction, yellowing precipitation was formed and the reaction was completed in 2 hours as indicated by TLC. The solid material was collected by filtration and was washed with minimal cold water then cold methanol. A yellowish crystalline solid was obtained (2.80g) in 98.3% yield.

^{1}H NMR (CD_3CN): δ 11.3 (bs, 1H), 9.34 (s, 1H), 8.96 (d, 1H, J=7.2Hz), 8.22 (d, 1H, J=7.2Hz), 7.90 (d, 1H, J=8.4Hz), 7.85 (d, 1H, J=3.2Hz), 7.70, (d, 1H, J=8.4Hz), 7.12 (t, 1H, J=8.4Hz), 4.38 (s, 3H), 4.06 (s, 3H)

^{13}C NMR (CD_3CN): δ188.4, 166.9, 162.1, 149.9, 143.7, 142.1, 139.7, 138.6, 136.7, 129.8, 126.6,123.5, 122.9, 111.8, 86.4, 52.2, 40.1

15. Preparation of **iodo-dihydro-compounds(25+26):**



To a solution of 6-(4-iodo-1H-indol-3-ylmethyl)-1-methyl-nicotinic acid methyl ester trifluoromethanesulfonate acid salt (0.57 g, 1.0 mmol) in methanol (5 ml) was added $NaBH_4$ (0.19 g, 5.0 mmol) at r.t. The reaction was stirred at r.t. for 10 min, and H_2O (15 ml) was added into the reaction mixture dropwise. A light red precipitation was observed and collected by filtration . The solid was washed with minimal amount of cold H_2O and cold methanol. The solid was dried in vacuum and weighed at 0.35 g (82% yield).

NMR of this solid in CDCl3 showed that it is a mixture of two compounds in 4:1 ratio.

Major compound:

^{1}H NMR ($CDCl_3$): δ 8.80 (bs, 1H), 7.82 (d, 1H, J=3.2Hz), 7.52 (d, 1H, J=8.0Hz), 7.34 (d, 1H, J=8.0Hz), 7.02 (m, 1H), 6.92 (t, 1H, J=8.0Hz), 5.92 (m, 1H), 3.88 (s, 3H0, 3.29 (m, 1H), 2.87 (m, 1H), 2.52 (s, 3H)

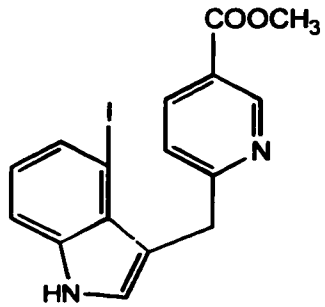
Minor compound:

^{1}H NMR ($CDCl_3$): δ 8.80 (bs, 1H), 8.10 (d, 1H, J=3.2Hz), 7.57 (d, 1H, J=8.4Hz), 7.23 (d, 1H, J=8.4Hz), 7.00 (t, 1H, J=8.4Hz), 6.82 (s, 1H), 6.02 (d, 1H, J=7.2Hz), 5.47 (d, 1H, J=7.2Hz), 4.29 (m, 1H), 3.83 (s, 3H), 2.51 (s, 3H)

Mass Spectrum (ES^+): Expected for $C_{17}H_{15}IN_2O_3$: 422.01. Found: 423.01.

Elemental Analysis: Calcd. For $C_{17}H_{15}IN_2O_3$:C, 48.36; H, 3.58; N, 6.63. Found: C, 48.18; H, 3.51; N, 6.48

16. **6-(-iodo-1H-indol-3-ylmethyl)-nicotinic acid methyl ester(27):**



Method A: To a solution of 6-(4-iodo-1H-indole-3-carbonyl)-nicotinic acid methyl ester (2.03g, 5.00 mmol) in 50 ml anhydrous THF was added BH_3 in THF solution (1.0 M, 10.0 ml, 10.0 mmol) via a syringe at r.t. The reaction was stirred and heated at 60°C for 2 hours under N_2. The reaction was

cooled to r.t. and poured into cold MeOH at 0°C. The solvent was removed *in vacuo,* and the material was partitioned between aq. $NaHCO_3$ (sat., 50 ml) and CH_2Cl_2 and extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was dried over Na_2SO_4 and concentrated. Purification of the crude by silica gel using hexane : ethyl acetate (3: 1 to 2: 1) afforded a white crystalline solid (1.27g, mp. 189.2-190.3°C) in 65% yield.

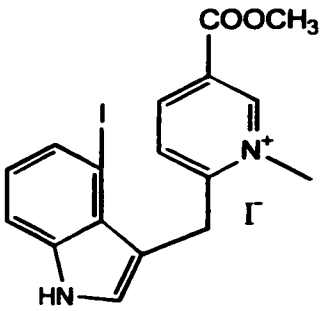
^1H NMR ($CDCl_3$): δ 9.3 (bs, 1H), 9.10 (s, 1H), 8.74 (d, 1H, J=7.6Hz), 8.02 (d, 1H, J=7.6Hz), 7.79 (d, 1H, J=8.4Hz), 7.55, (d, 1H, J=8.4Hz), 7.15 (d, 1H, J=2.4Hz), 7.12 (t, 1H, J=8.4Hz), 4.45 (s, 2H), 3.88 (s, 3H)

Mass Spectrum (ES^+): Expected for $C_{16}H_{13}IN_2O_2$: 392.00; Found: 393.00.

Elemental Analysis: Calcd. for $C_{16}H_{13}IN_2O_2$: C, 49.00; H, 3.34; N, 7.14. Found: C, 49.23; H, 3.33; N, 6.94

Method B: A solution of 6-(4-iodo-1H-indole-3-carbonyl)-nicotinic acid methyl ester (2.03g, 5.00 mmol) in 50 ml CH_2Cl_2 was added into another preformed solution of $NaBH_4$ (0.76 g, 20.0 mmol) in 10 ml TFA at r.t. The resulting mixture was stirred at r.t. for 4 hours. The volatiles were removed *in vacuo* and the crude was partitioned between aq. $NaHCO_3$ (sat., 50 ml) and CH_2Cl_2 and extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was dried over Na_2SO_4 and concentrated. Purification of the crude by silica gel using hexane : ethyl acetate (3: 1 to 2: 1) afforded a white crystalline solid (1.22g, mp. 189.0-190.4°C) in 65% yield. The ^1H and ^{13}C NMR of this material were identical to that prepared by method A.

17. **6-(-iodo-1H-indol-3-ylmethyl)-nicotinic acid methyl ester methyl iodide salt(28):**



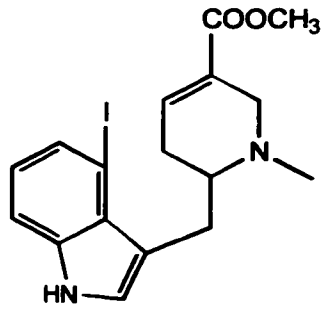
To a solution of 6-(-iodo-1H-indol-3-ylmethyl)-nicotinic acid methyl ester (0.78g, 2.0 mmol) in 10 ml anhydrous CH_2Cl_2 was added MeI (0.57g, 4.0 mmol). The reaction was stirred at r.t. under N_2 for 2 hours at 0°C. During the course of the reaction, yellowing precipitation was formed and the reaction was completed in 2 hours as indicated by TLC. The solid material was collected by filtration and was washed with minimal cold water then cold methanol. A crystalline solid was obtained (1.03g) in 96.8% yield (mp. 213.9-215.1°C).

^{1}H NMR (Acetone-d_6): δ 11.95 (bs, 1H), 9.76 (s, 1H), 9.22 (d, 1H, J=7.2Hz), 8.58 (d, 1H, J=7.2Hz), 8.14 (d, 1H, J=2.4Hz), 7.92 (d, 1H, J=8.4Hz), 7.76 (d, 1H, J=8.4Hz), 7.12 (t, 1H, J=8.4Hz), 4.69 (s, 2H), 4.06 (s, 3H)

Mass Spectrum (ES^+): Expected for $C_{17}H_{16}IN_2O_2$: 407.03; Found: 408.03.

Elemental Analysis: Calcd. for $C_{17}H_{16}I_2N_2O_2$: C, 38.20; H, 3.00; N, 5.24. Found: C, 38.10; H, 3.18; N, 5.32.

18. Preparation of **6-(4-iodo-1H-indol-3-ylmethyl)-1-methyl-1,2,5,6-tetrahydro-pyrodine-3-carboxylic acid methyl ester(29):**



To a suspension of 6-(-iodo-1H-indol-3-ylmethyl)-nicotinic acid methyl ester methyl iodide salt (534mg, 1.0 mmol) in 10 ml methanol was added $NaBH_4$ (113mg, 3.0mmol) at r.t. A yellow color was generated immediately after the addition of $NaBH_4$. After 5 mins, the reaction was completed as indicated by TLC. Water (25 ml) was added, and the reaction was extracted by CH_2Cl_2 (20 ml x 3). The combined organics were washed with brine and dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded an off-white solid. Purification by silica gel using hexane: ethyl acetate (3 : 1) afforded a white crystalline material (mp. 184.8-185.7°C, 214mg) in 52.4% yield.

^1H NMR ($CDCl_3$): δ 8.85 (bs,1H), 7.56 (d, 1H, J=8.4Hz), 7.25 (d, 1H, J=8.4Hz), 7.00 (s, 1H0, 6.98 (bs, 1H), 6.80 (t, 1H, J=8.4Hz), 3.78 (s, 3H),

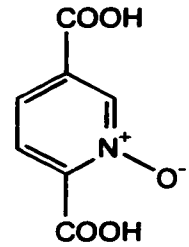
3.46 (m, 2H), 3.40 (m, 1H), 3.11 (m, 1H), 2.76 (m, 1H), 2.60 (s, 3H), 2.11 (m, 2H).

^{13}C NMR (Acetone-d6): δ 166.7, 138.0, 137.2, 131.5, 128.1, 128.1, 125.6, 123.3, 113.9, 111.8, 85.1, 57.9, 51.9, 51.6, 40.9, 28.6, 25.7

Mass Spectrum (ES^+): Expected for $C_{17}H_{19}IN_2O_2$: 410.05. Found: 411.05.

Elemental Analysis: Calcd. for $C_{17}H_{19}IN_2O_2$: C, 49.77; H, 4.67; N, 6.83. Found: C, 49.45; H, 4.88; N, 6.92.

19. **Pyridine-2,5-dicarboxylic acid N-Oxide(32):**



Pyridine-2,5-dicarboxylic acid (8.35g, 50.0 mmol) was suspended in 250ml 0.2% (w/w) aq. Na_2WO_4 (0.5g) in a 1 liter round bottom flask. To this soiution was added H_2O_2 in water (30% w/w, 8.5g, 75.0 mmol). The resulting mixture was stirred and heated at 80-85°C for 10 hours. The resulting solid was collected by filtration and washed with cold water. Drying of the material under vacuum overnight yielded 9.06 g product solid (mp. 253.2-254.1°C, dec; Lit. 254°C, dec.) in 99% yield.

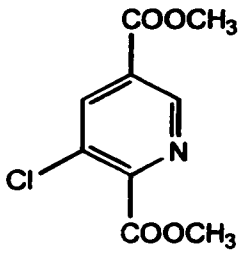
^{1}H NMR (DMSO-d6): δ 14.48 (bs, 2H), 8.95 (s,1H), 8.38 (d, 1H, J=6.4Hz), 8.25 (d, 1H, J=6.4Hz)

^{13}C NMR (DMSO-d6): δ 176.5, 174.9, 153.6, 151.2, 139.0, 132.5, 125.7

Mass Spectrum (ES^+): Expected for $C_7H_5INO_5$: 183.02. Found: 184.02.

Elemental Analysis: Calcd. for $C_7H_5INO_5$: C, 45.91; H, 2.75; N, 7.65. Found: C, 45.86; H, 2.67; N, 7.82.

20. Preparation of **3-chloro-pyridine-2,5-dicarboxylic acid dimethyl ester(34):**



To a solution of thionyl chloride (9.52g, 5.84 ml, 80 mmol) in 200 ml CH_3Cl was added DMF (2 ml) at 0°C. Pyridine-2,5-dicarboxylic acid N-oxide (3.66g, 20.0 mmol) was added into this mixture portionwise. The resulting mixture was heated at 65°C for 2 hours. The reaction was cooled to r.t. then placed in an ice-bath. The reaction was quenched with methanol (30 ml) slowly at 0°C. The solvent was removed *in vacuo* and the crude was partitioned between CH_2Cl_2 (100 ml) and aq. $NaHCO_3$ (sat. 50 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (100 ml x 2). The combined organic layer was dried over Na_2SO_4 and the solvent

was removed *in vacuo*. Purification of the crude oil by a short plug of silica gel using hexane : ethyl acetate (2 : 1) afforded a white solid (3.73g, mp. 126.0-127.0°C) in 81.2% yield.

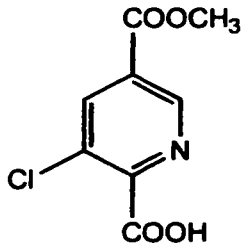
^{1}H NMR ($CDCl_3$): δ 9.12 (d, 1H, J=1.6Hz), 8.41 (d, 1H, J=1.6Hz), 4.04 (s, 3H), 4.00 (s, 3H)

^{13}C NMR ($CDCl_3$): δ 164.2, 164.0, 151.8, 148.0, 139.9, 131.2, 128.3, 53.2, 53.0

Mass Spectrum (ES^+): Expected for $C_9H_8ClNO_4$: 229.01. Found: 230.01.

Elemental Analysis: Calcd. for $C_9H_8ClNO_4$: C, 47.08; H, 3.51; N, 6.10. Found: C, 47.21; H, 3.56; N, 6.27.

21. Preparation of **3-chloro-pyridine-2,5-dicarboxylic acid 5-methyl ester(35):**



To a solution of 3-chloro-pyridine-2,5-dicarboxylic acid dimethyl ester (6.89g, 30 mmol) in 100 ml methanol was added copper(II) nitrate trihydrate (14.5g, 60 mmol) in a 500 ml round bottom flask equipped with a reflux condenser and a stirring bar. The reaction was refluxed for 80 mins. A violet-blue precipitate was observed after 30 min and lasted throughout the course of

the reaction. The reaction was cooled to r.t., and the reaction mixture was reduced to 1/3 of its original volume. The violet-blue solid was collected by filtration and washed with cold methanol then cold water. This solid material was dissolved in 50 ml glyme, and H_2S gas was bubbled into this solution. The black precipitate was formed in 2 min, and the deep violet-blue solid disappeared after 15 min. The black precipitate was filtered out through a plug of celite and the filtrate was concentrated to 20 ml. Excess hexanes were added into this solution, and a white solid was formed and collected by filtration. Recrystallization of this solid from EtOH-H_2O afforded 5.46g product in 84.5% yield (mp. 192.2-193.4°C).

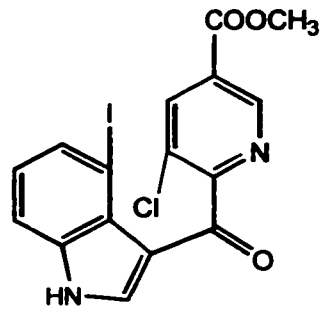
^{1}H NMR (CD_3CN): δ 9.05 (d, 1H, J=1.6Hz), 8.44 (d, 1H, J=1.6Hz), 3.98 (s, 3H)

^{13}C NMR (CD_3CN): δ 172.3, 163.0, 153.6, 149.1, 143.7, 132.5, 129.8, 52.7

Mass Spectrum (ES^+): Expected for $C_8H_6ClNO_4$: 215.00. Found: 216.00.

Elemental Analysis: Calcd. For $C_8H_6ClNO_4$: C, 44.57; H, 2.81; N, 6.50. Found: C, 44.72; H, 2.87; N, 6.67.

22. Preparation of **5-chloro-6-(4-iodo-1H-indole-3-carbonyl)-nicotinic acid methyl ester(36):**



3-chloro-Pyridine-2,5-dicarboxylic acid 5-methyl ester (3.38g, 15.7 mmol) was suspended in 20 ml thionyl chloride in a 100 ml round bottom flask equipped with a reflux condenser and a stirring bar. The reaction was refluxed and stirred until the solid went into solution completely. The reaction was cooled to r.t., and thionyl chloride was removed *in vacuo*. Traces of thionyl chloride were chased by CCl_4 (20 ml x 2) *in vacuo*. A white solid was obtained (3.66g) in quantitative yield with (mp. 168.2-170.2°C, dec.). This material was used directly in the following reaction.

For analytical purpose, above material was allowed to react with methanol in anhydrous acetonitrile at 0°C. NMR of the resulting product was identical with that of 3-chloro-pyridine-2,5-dicarboxylic acid dimethyl ester obtained in experiment 16. This confirmed the identity of the product as 6-chlorocarbonyl-nicotinic acid methyl ester.

^{1}H NMR ($CDCl_3$): δ 9.17 (d, 1H,J=1.6Hz), 8.42 (d, 1H, J=1.6Hz), 4.00 (s, 3H)

Elemental Analysis: Calcd. For $C_8H_5Cl_2NO_3$: C, 41.06; H, 2.15; N, 5.98. Found: C, 40.89; H, 2.29; N, 6.12.

To a solution of EtMgBr (10 ml, 1.575 M in ether, 15.75 mmol) was added a solution of 4-iodo-1H-indole (3.65g, 15.0 mmol) in ether (anhydrous, 20 ml). The resulting two-phase system was allowed to stand for 15 min under stirring whereupon $ZnCl_2$ (15 ml, 1.0m in ether, 15.0 mmol) was added with stirring. The two-phase system was allowed to stand for 30 min when 6-chlorocarbonyl-nicotinic acid methyl ester (3.66g, 15.75 mmol) in anhydrous ether (10 ml) was added rapidly under vigorous stirring. The reaction mixture was allowed to stand for 2 hours whereupon NH_4Cl (aq. sat. 25 ml) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 ml x 3). The combined organic layer was washed with $NaHCO_3$ (aq. sat. 25 ml) followed by brine (25 ml), dried over Na_2SO_4. Removal of the solvent *in vacuo* afforded a yellowish solid. Recrystallization of this solid from acetone-water afforded 2.99g of desired crystalline product in 71.2% yield (245.2-245.8°C).

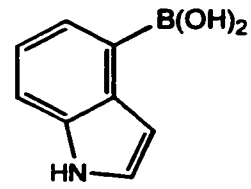
^1H NMR ($CDCl_3$): δ 9.15 (bs, 1H), 9.08 (d, 1H, J=1.6Hz), 8.42 (d, 1H, J=1.6Hz), 7.81 (d, 1H, J=8.4 Hz), 7.58 (d, 1H, J=2.4Hz), 7.39 (d, 1H, J=8.4Hz), 6.94 (t, 1H, J=8.4Hz)

^{13}C NMR (Acetone-d6): δ 184.8, 165.4, 161.3, 152.7, 143.2, 141.1, 136.3, 135.4, 133.4, 132.7, 126.5, 121.8, 113.6, 110.9, 88.1, 53.4

Mass Spectrum (ES^+): Expected for $C_{16}H_{10}ClIN_2O_3$: 439.94. Found: 440.95.

Elemental Analysis: Calcd. for $C_{16}H_{10}ClIN_2O_3$: C, 43.61; H, 2.29; N, 6.36. Found: C, 43.48; H, 2.19; N, 6.32.

23. Preparation of **indole-4-boronic acid(38):**



To a suspension of KH (4.57 g of a 30% suspension in mineral oil, 32.9mmol) was added a solution of 4-bromo-indole (5.88g, 30.0 mmol) in anhydrous ether (25 ml). The reaction was stirred at r.t. for 30 min under N_2 and the reaction was cooled in an acetone-dry ice bath (-78°C) with stirring. Precooled *t*-BuLi solution (33.0 ml, 66.0 mmol) was cannulated into the reaction and the reaction was kept stirring for another 20 min. Neat B(*n*-BuO)$_3$ (24.1 ml, 90.0 mmol) was added into the reaction by a syringe under vigorous stirring. The reaction mixture became thick when it was allowed to warm to r.t., and more anhydrous ether (30 ml) was added under N_2. The reaction was allowed to stand overnight at r.t. with vigorous stirring. The thick reaction mixture was diluted by more anhydrous ether and then transferred into 1 M aqueous H_3PO_4 (300 ml) at 0°C slowly. The mixture was stirred at r.t. for 40 min, and was extracted with ether (100 ml x 30). The combined organic layer was extracted with 1 N NaOH (50 ml x 3). Ether (100 ml) was added to this aqueous solution and the mixture was acidified to pH = 2 using 1M H_3PO_4. The organic layer was separated and the aqueous layer was extracted with ether (100 ml x 2). The combined ether layer was dried over Na_2SO_4 and evaporation of solvent *in vacuo* left a beige solid (4.24g, 88.0%).

^{1}H NMR (acetone-d_6 80% + D_2O 20%): δ 7.56 (dd, 1H, J=7.0, 1.0Hz), 7.53 (dd, 1H, J=8.4, 1.0Hz), 7.34 (d, 1H, J=3.2Hz), 7.21 (dd, 1H, J=8.4, 70Hz), 6.96 (d, 1H, J=3.2Hz).

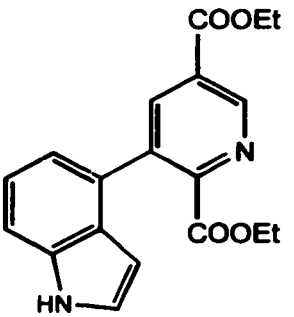
^{13}C NMR (acetone-d_6 80% + D_2O 20%): 136.2, 132.8, 126.6, 125.5, 124.9, 120.2, 112.8, 103.4.

For analytical purposes, the material was converted into its diethanolamine derivative according to a literature procedure[86]. The product was recrystallized from EtOH/acetone/water: mp. 271.0-272.1°C, dec. (Lit. 272.7-273.1°C, dec.)

Mass Spectrum (ES^+): Expected for $C_{12}H_{15}BN_2O_2$: 230.11. Found: 231.12.

Elemental Analysis: Calcd. for $C_{12}H_{15}BN_2O_2$: C, 62.55; H, 6.57; N, 12.18. Found: C, 62.33; H, 6.58; N, 12.32.

24. Preparation of **3-(-1H-indol-4-yl)-pyridine-2,5-dicarboxylic acid diethyl ester(41):**



Into 500 ml anhydrous toluene in a 1 liter round bottom flask equipped with stirring bar was bubbled in a stream of argon via a needle for 30 min.

$Pd(PPh_3)_4$ (0.878g, 0.75 mmol) and 3-chloro-pyridine-2,5-dicarboxylic acid diethyl ester (3.44g, 15.0 mmol) were added into this solvent and the resulting mixture was stirred at r.t. under argon for 1 hour. A solution of indole 4-boronic acid (1.86g, 11.5 mmol) in 50 ml EtOH and a solution of 2 M aqueous Na_2CO_3 (11.5 ml) was added into the reaction mixture at r.t. under argon. The mixture was heated under argon with vigorous stirring at 105°C for 8 hours. The reaction mixture was cooled and brine (200 ml) was added. The organic layer was separated and aqueous layer extracted with additional CH_2Cl_2 (100 ml x 2). The combined organic layer was dried over Na_2SO_4 and evaporation of the solvent left a yellowish solid. Purification of the crude material by a short plug of silica gel (hexane : ethyl acetate, 1:2) afforded a yellow solid. The TLC of this material showed it to be a mixture of three different compounds due to ester exchange. This solid was dissolved in 500 ml EtOH and the solution was stirred overnight at r.t. in the presence of cat. HCl in diethyl ether. A single compound (3.54g) was obtained (mp. 212.3-213.0oC) in 91.0% yield.

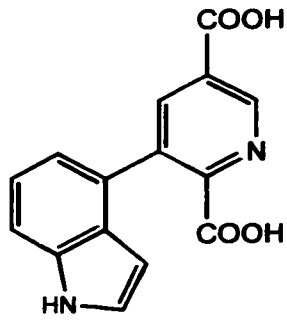
^1H NMR ($CDCl_3$): δ 9.25 (d, 1H, J=1.6Hz), 8.55 (d, 1H, J=1.6Hz), 8.43 (bs, 1H), 7.45 (d, 1H, J=8.4Hz), 7.25-7.30 (m, 2H), 7.08 (d, 1H, J=8.4Hz), 6.34 (m, 1H), 4.42 (q, 2H, J=7.2Hz), 4.06 (q, 2H, J=7.2Hz), 1.41 (t, 3H, J=7.2Hz), 0.90 (t, 3H, J=7.2Hz).

^{13}C NMR ($CDCl_3$): δ 166.4, 164.8, 142.8, 149.0, 140.1, 136.3, 135.8, 129.8, 127.6, 126.4, 125.1, 122.3, 120.2, 111.6, 100.9, 61.1, 61.2, 14.1, 13.7

Mass Spectrum (ES^+): Expected for $C_{19}H_{18}N_2O_4$: 338.13. Found: 339.13.

Elemental Analysis: Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.64; H, 5.24; N, 8.15.

25. Preparation of **3-(-1H-indol-4-yl)-pyridine-2,5-dicarboxylic acid(42):**



To a mixture of ethanol (10 ml) and 1 N NaOH (5 ml) was added 3-(-1H-indol-4-yl)-pyridine-2,5-dicarboxylic acid diethyl ester (776mg, 2.0 mmol). The resulting mixture was heated at 50 °C for two hours. The reaction mixture was cooled and the pH was adjusted to 5.0 using 1N aqueous HCl. A red solid was precipitated from the solution and it was collected by filtration. The solid was recrystallized from methanol to afford a light solid (535 mg, mp. 235.9-236.8°C) in 95.0% yield.

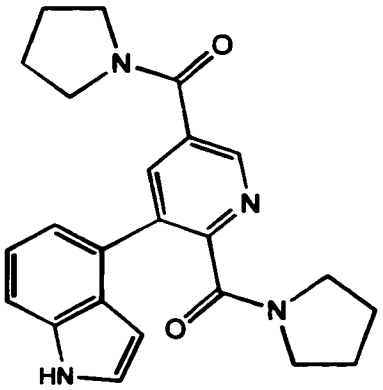
^{1}H NMR ($NaOD/D_2O$): δ 8.68 (s, 1H), 8.16 (s, 1H), 7.36 (d, 1H, J=9.2Hz), 7.21 (d, 1H, J=2.4Hz), 7.09 (t, 1H, J=9.2Hz), 6.95 (d, 1H, J=9.2Hz), 6.27 (d, 1H, J=3.2Hz).

^{13}C NMR ($NaOD/D_2O$): δ 173.2, 172.8, 149.8, 144.3, 139.1, 135.7, 134.5, 129.4, 126.7, 125.5, 124.5, 123.2, 122.4, 112.1, 103.6,

Mass Spectrum (ES^+): Expected for $C_{15}H_{10}N_2O_4$: 282.06. Found: 283.06.

Elemental Analysis: Calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.57; N, 9.93. Found: C, 63.67; H, 3.76; N, 8.35.

26. Preparation of **[3-(1H-indol-4-yl)-5-(pyrrolidine-1-carbonyl)-pyridin-2-yl]-pyrrolidin-1-yl-methanone(43):**



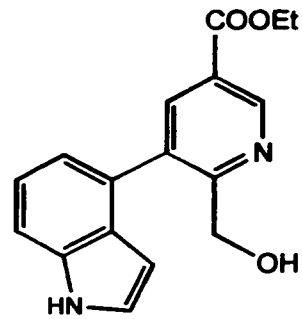
To a solution of 3-(-1H-indol-4-yl)-pyridine-2,5-dicarboxylic acid diethyl ester (0.34 g, 1.0 mmol) in chloroform (50 ml) was added pyrrolidine (1.42 g, 20.0 mmol). The mixture was refluxed for 12 hours. The reaction was cooled to r.t., and the organic volatiles was remove in vacuo. The crude material was partitioned between ethyl acetate (100 ml) and brine (50 ml). The organic layer was separated and extracted with additional ethyl acetate (100 ml x 2). The combined organic layers were dried over Na_2SO_4. The solvent was removed and the crude was purified by silica gel using CH_2Cl_2-MeOH (98 : 2). A yellow solid was obtained (mp. 246.7-247.9°C, 0.33 g) in 84.3% yield.

^1H NMR ($CDCl_3$): δ 8.86 (bs, 1H), 8.78 (d, 1H, J=1.6Hz), 8.08 (d, 1H, J=1.6Hz), 7.36 (d, 1H, J=8.4Hz), 7.20-7.10 (m, 3H), 6.41 (m, 1H), 3.65 (t, 2H, J=14.8Hz), 3.43 (t, 2H, J=14.8Hz), 3.36 (t, 2H, J=14.8Hz), 2.89 (t, 2H, J=14.8Hz), 1.90 (m, 4H), 1.62 (m, 2H), 1.45 (m, 2H)

Mass Spectrum (ES^+): Expected for $C_{23}H_{24}N_4O_2$: 388.19. Found: 389.19.

Elemental Analysis: Calcd. for $C_{23}H_{24}N_4O_2$: C, 71.11; H, 6.23; N, 14.42. Found: C, 71.00; H, 6.26; N, 14.58

27. Preparation of **6-hydroxymethyl-5-(1H-indol-4-yl)-nicotinic acid ethyl ester(44):**



To a solution of 3-(-1H-indol-4-yl)-pyridine-2,5-dicarboxylic acid diethyl ester (0.34g, 1.0 mmol) in anhydrous EtOH (10 ml) was added $Ba(BH_4)_2$ (24.6mg, 0.65 mmol) followed by $CaCl_2$ (44.3mg, 0.4 mmol) at 0°C. The reaction was warmed to r.t. and stirred for 2 hours. 1 M H_2SO_4 (1 ml) was added to the reaction, and resulting white precipitation ($CaSO_4$) was filtered out through a plug of celite. The filtrate was concentrated and partitioned between ethyl acetate (20 ml) and $NaHCO_3$ (aq. 15 ml). The organic layer was separated and the aqueous layer was extracted with additional ethyl acetate (20 ml x 2). The combined organic layer was dried over Na_2SO_4, and the solvent was removed. The crude material was purified by silica gel using hexane-ethyl

acetate (3 : 1 to 1 : 1). A colorless solid (mp. 198.1-199.0°C) was obtained (231 mg) in 78% yield.

^{1}H NMR ($CDCl_3$): δ 9.22 (d, 1H, J=1.6Hz), 8.72 (bs, 1H), 8.34 (d, 1H, J=1.6Hz), 7.46 (d, 1H, J=8.0Hz), 7.23 (t, 1H, J=8.0Hz), 7.22 (m, 1H), 6.98 (d, 1H, J=8.0Hz), 6.15 (m, 1H), 4.66 (s, 2H), 4.39 (bs, 1H), 4.42 (q, 2H, J=7.2Hz), 1.40 (t, 3H, J=7.2Hz).

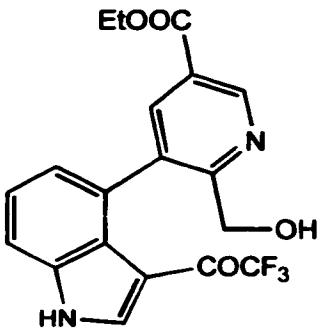
^{13}C NMR ($CDCl_3$): δ 165.2, 160.4, 148.0, 138.8, 136.0, 134.2, 128.4, 126.9, 125.4, 125.3, 122.2, 120.3, 111.4, 100.8, 62.4, 60.9, 14.2

Mass Spectrum (ES^+): Expected for $C_{17}H_{16}N_2O_3$: 296.12. Found: 297.12.

Elemental Analysis: Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 69.13; H, 5.26; N, 9.33.

Alternatively, the product could also be made using Ca(BH4)2 (0.32 equivalent) as the reducing reagent in the same solvent, at same temperature and for same period of reaction time. The NMR, mass spectrum, elemental analysis and mp. of this product were identical to that of the product obtained by the previous method. The yield of this reaction was 85% at the same scale as the previous reaction.9.33.

28. Preparation of **6-hydroxymethyl-5-(3-trifluoroacetyl-1H-indol-4-yl)-nicotinic acid ethyl ester(45):**



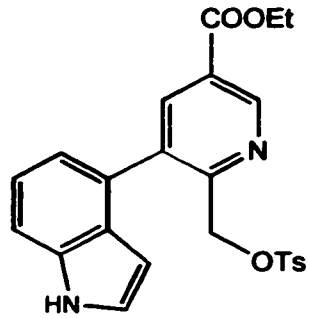
To a solution of 6-hydroxymethyl-5-(1H-indol-4-yl)-nicotinic acid ethyl ester (148 mg, 0.50 mmol) in CH2Cl2 (10 ml) was added TFA (0.4 ml) at 0°C and the reaction was stirred at 0°C for 1 hours. The reaction was warmed to r.t., and the solvent was removed. The crude material was partitioned between CH_2Cl_2 (30 ml) and aq. $NaHCO_3$ (sat., 30 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (30 ml x 2). The combined organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude material was purified by a short plug of silica gel using hexane-ethyl acetate (2:1). A solid material was obtained (mp. 232.6-233.9°C, 122 mg) in 62.1% yield.

^1H NMR ($CDCl_3$): δ 9.60 (bs, 1H), 9.21 (d, 1H, J=1.6Hz), 8.14 (m, 1H), 8.06 (d, 1H, J=1.6Hz), 7.53 (d, 1H, J=8.0Hz), 7.42 (t, 1H, J=8.0Hz), 7.13 (d, 1H, J=8.0Hz), 4.60 (bs, 1H), 4.39 (q, 2H, J=7.6Hz), 4.36 (s, 2H), 1.38 (t, 3H, J=7.6Hz)

Mass Spectrum (ES^+): Expected for $C_{19}H_{15}F_3N_2O_4$: 392.05. Found: 393.05.

Elemental Analysis: Calcd. for $C_{19}H_{15}F_3N_2O_4$: C, 58.11; H, 3.82; N, 7.13. Found: C, 57.95; H, 3.97; N, 7.12

29. Preparation of **5-(1H-indol-4-yl)-6-(toluene-4-sulfonyloxymethyl)-nicotinic acid ethyl ester(46):**



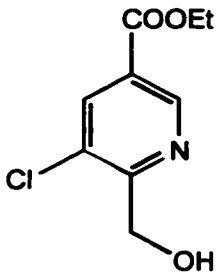
To a solution of 6-hydroxymethyl-5-(1H-indol-4-yl)-nicotinic acid ethyl ester (148 mg, 0.50 mmol) in anhydrous CH_2Cl_2 (10 ml) was added Et_3N (115 mg, 1.2 mmol) and tosyl chloride (115 mg, 0.6 mmol) at 0°C. The reaction was warmed to r.t. and stirred for 1 hour. The solvent was removed in vacuo and the crude material was partitioned between CH_2Cl_2 (20 ml) and aq. $NaHCO_3$ (sat., 20 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (20 ml x 2). The combined organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. The crude material was purified by a short plug of silica gel using hexane-ethyl acetate (1:1). A solid material was obtained (mp. 216.8-217.9°C, 210 mg) in 93.2% yield.

^1H NMR ($CDCl_3$): δ 9.18 (d, 1H, J=1.6Hz), 8.46 (bs, 1H), 8.32 (d, 1H, J=1.6Hz), 7.59 (d, 2H, J=8.8Hz), 7.43 (d, 1H, J=8.4Hz), 7.22-7.18 (m, 4H), 6.93 (d, 1H, J=8.4Hz), 6.08 (m, 1H), 4.39 (q, 2H, J=7.2Hz), 2.38 (s, 3H), 1.37 (t, 3H, J=7.2Hz)

Mass Spectrum (ES^+): Expected for $C_{24}H_{22}N_2O_5S$: 450.12. Found: 451.12.

Elemental Analysis: Calcd. for $C_{24}H_{22}N_2O_5S$: C, 63.98; H, 4.92; N, 6.22. Found: C, 64.12; H, 4.91; N, 6.34.

30. Preparation of **5-chloro-6-hydroxymethyl-nicotinic acid ethyl ester(51):**



The above compound was made from 3-chloro-pyridine-2,5-dicarboxylic acid diethyl ester using $Ca(BH_4)_2$ as described in experiment 22. The product was obtained as a white solid (mp.167.5-168.6°C) in 89% yield.

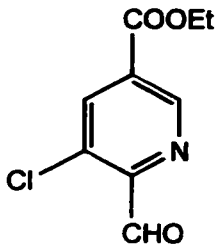
^1H NMR ($CDCl_3$): δ 9.10 (d, 1H, J=1.6Hz), 8.30 (d, 1H, J=1.6Hz), 4.64 (s, 2H), 4.40 (bs, 1H), 4.40 (q, 2H, J=7.2Hz), 1.40 (t, 3H, J=7.2Hz).

^{13}C NMR ($CDCl_3$): δ 167.3, 158.2, 147.8, 135.6, 128.4, 120.6, 62.1, 60.8, 13.8.

Mass Spectrum (ES^+): Expected for $C_9H_{10}ClNO_3$: 215.03. Found: 215.04.

Elemental Analysis: Calcd. for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.67; N, 6.50. Found: C, 50.29; H, 4.73; N, 6.52.

31. Preparation of **5-chloro-6-formyl-nicotinic acid ethyl ester(52):**



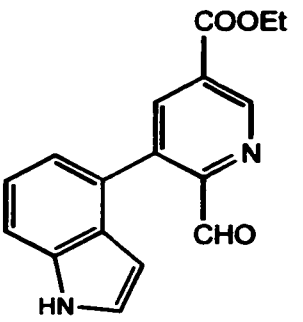
To a solution of 5-chloro-6-hydroxymethyl-nicotinic acid ethyl ester (431 mg, 2.0 mmol) in chloroform (20 ml) was added freshly made MnO_2[87] (1.74 g, 20.0 mmol). The reaction was stirred at r.t. for 2 hours then solid was removed from the solution by a plug of celite. The filtrate was concentrated in vacuo. Purification of the crude material by silica gel chromatography using hexane-ethyl acetate (3 : 1) afforded a yellow solid (mp. 126.1-127.0°C, 402 mg) in 94% yield.

^{1}H NMR ($CDCl_3$): δ 10.30 (bs, 1H), 9.20 (d, 1H, J=1.6Hz), 8.39 (d, 1H, J=1.6Hz), 4.42 (q, 2H, J=7.6Hz0, 1.40 (t, 3H, J=1.6Hz)

Mass Spectrum (ES^+): Expected for $C_9H_8ClNO_3$: 213.02. Found: 214.02.

Elemental Analysis: Calcd. for $C_9H_8ClNO_3$: C, 50.60; H, 3.77; N, 6.56. Found: C, 50.42; H, 3.61; N, 6.65

32. Preparation of **6-formyl-5-(1H-indole-4-yl)-nicotinic acid ethyl ester(47):**



To a solution of 6-hydroxymethyl-5-(1H-indol-4-yl)-nicotinic acid ethyl ester (148 mg, 0.5 mmol) in 5 ml CH_3Cl was added freshly made MnO_2[87] (435 mg, 5.0 mmol). The reaction was stirred at r.t. for 2 hours then filtered from the solution by a plug of celite, and the solvent was removed. Purification of the crude material by silica gel chromatography using hexane-ethyl acetate (2 ; 1) afforded a yellow solid (135.4 mg, 92%) with mp. 198.4-199.2°C.

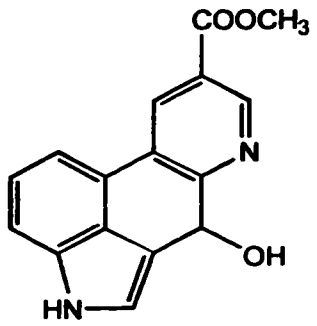
^1H NMR ($CDCl_3$): δ 10.03 (s, 1H), 9.22 (d, 1H, J=1.6Hz), 8.61 (d, 1H, J=1.6Hz), 8.47 (bs, 1H), 7.56 (d, 1H, J=8.0Hz), 7.35-7.25 (m, 2H), 7.08 (d, 1H, J=8.0Hz), 6.26 (m, 1H), 4.42 (q, 2H, J=7.2Hz), 1.42 (t, 3H, J=7.2Hz).

^{13}C NMR ($CDCl_3$): δ 190.8, 164.2, 150.8, 149.6, 140.9, 140.1, 136.7, 128.4, 127.8, 127.2, 126.1, 122.1, 121.9, 112.0, 100.6, 61.7, 14.2

Mass Spectrum (ES^+): Expected for $C_{17}H_{14}N_2O_3$: 294.10. Found: 295.10.

Elemental Analysis: Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.58; H, 4.83; N, 9.64.

33. Preparation of **6-hydroxy-4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic methyl ester(48):**



To a solution of 6-formyl-5-(1H-indole-4-yl)-nicotinic acid ethyl ester (58.9 mg, 0.2 mmol) in anhydrous methanol (0.5 ml) in a 2 ml conical vial was added 0.5 M NaOMe/MeOH (8.0 μl, 0.004 mmol). The reaction was stirred at r.t. for 2 hours. Solid precipitated out of the solution during the course of the reaction, and the starting material disappeared completely after 2 hours as indicated by TLC. The solution was cooled to 0°C and the liquid was removed with a pipette. The remaining solid was recrystallized from MeOH to afford 51.0 mg yellow crystalline solid (mp. 234.6-235.8°C) in 91% yield.

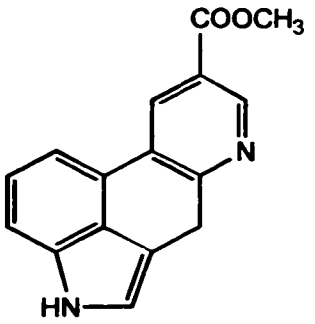
^{1}H NMR ($CDCl_3$): δ 9.52 (d, 1H, J=1.6Hz), 9.45 (d, 1H, J=1.6Hz), 8.55 (bs, 1H), 7.96 (s, 1H), 7.82 (d, 1H, J=8.0Hz), 7.58 (t, 1H, J=8.0Hz), 6.81 (d, 1H, J=8.0Hz), 6.54 (bs, 1H), 5.22 (bs, 1H), 4.05 (s, 3H),

^{13}C NMR ($CDCl_3$): δ 166.1, 152.3, 149.4, 148.2, 142.8, 133.8, 131.6, 128.1, 125.9, 123.9, 122.6, 121.0, 111.2, 104.1, 90.4, 52.2

Mass Spectrum (ES^+): Expected for $C_{16}H_{12}N_2O_3$: 280.08. Found: 281.08.

Elemental Analysis: Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.43; H, 4.48; N, 10.19.

34. Preparation of **4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic acid methyl ester(49):**



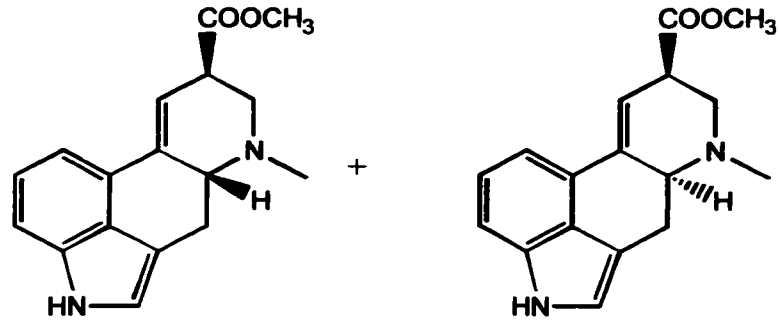
To a solution of 6-hydroxy-4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic methyl ester (45 mg, 0.16mmol) in 10 ml anhydrous THF was added BH_3 in THF (1.0 M, 0.32 ml, 0.32mol) under argon. The resulting mixture was stirred at r.t. for 2 hours. The TLC showed the disappearance of the starting material and a new fluorescent spot under UV on TLC. The solvent was removed *in vacuo* and the crude material was partitioned between CH_2Cl_2 (3 ml) and aq. $NaHCO_3$ (sat., 2 ml). The organic layer was separated and the aqueous was extracted with additional CH_2Cl_2 (3 ml x 2). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel PTLC using CH_2Cl_2 : MeOH (98 : 2). A white solid was obtained (mp. 212.9-213.9°C, 17.6 mg) in 41% yield.

^1H NMR ($CDCl_3$): δ 9.44 (d, 1H, J=1.6Hz), 9.40 (d, 1H, J=1.6Hz), 8.07 (bs, 1H), 7.75 (d, 1H, J=8.0Hz), 7.70 (s, 1H), 7.54 (t, 1H, J=8.0Hz), 6.78 (d, 1H, J=8.0Hz), 4.98 (s, 2H), 4.04 (s, 3H),

^{13}C NMR ($CDCl_3$): δ 164.0, 149.6, 147.2, 146.1, 141.0, 135.2, 129.3, 126.4, 124.2, 122.6, 120.9, 119.8, 110.1, 103.6, 55.2, 51.4

Mass Spectrum (ES^+): Expected for $C_{16}H_{12}N_2O_2$: 264.09. Found: 265.09. Elemental Analysis: Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.58; H, 4.72; N, 10.68.

35. Preparation of 7-methyl-4,6,6a-hexahydro-indolo[4,3-fg]quinoline carboxylic acid methyl ester (methyl-lysergate & methyl-isolysergate, 53 + 54):



To a solution of 4,6-dihydro-indolo[4,3-fg]quinoline-9-carboxylic acid methyl ester (14.6 mg, 0.058 mmol) in CH_2Cl_2 (1ml) was added MeI (16.5 mg, 7.3 μl, 0.12 mmol) at 0°C. The reaction was stirred at 0°C for 2 hours and the starting material disappeared after 2 hours as indicated by TLC. The solvent was removed *in vacuo* and the crude was dissolved in methanol (1 ml). To that mixture was added $NaBH_4$ (7.6 mg, 0.2 mmol) and the reaction was stirred at r.t. for 5 min. The organic solvent was removed *in vacuo* and the remaining solution was partitioned between CH_2Cl_2 (2 ml) and water (2 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (3 ml x 2). The organic layers were combined and dried over Na_2SO_4. The solvent was removed and the crude material was purified

by PTLC (CH_2Cl_2 : MeOH, 98 : 2). A white solid was obtained (10.7 mg, 65%). ^1H NMR showed it is a mixture of methyl lysergate and methyl isolysergate in 6 : 1 ratio using N-methyl as the integration indicator.

^1H NMR ($CDCl_3$) of methyl lysergate: δ 7.90 (bs, 1H), 7.15-7.25 (m, 3H), 6.92 (t, 1H, J=2.0Hz), 6.62 (bs, 1H), 3.78 (s, 3H), 3.75 (m, 1H), 3.52 (dd, 1H, J=14.0, 6.0Hz), 3.29 (br dd, 1H, J=11.0, 5.0Hz), 3.22 (m, 1H), 2.72 (ddd, 1H, J=14.0, 12.0, 2.0Hz), 2.70 (t, 1H, J=11.0Hz), 2.62 (s, 3H)

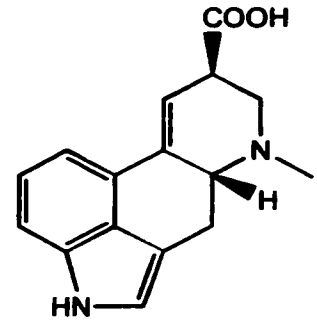
^1H NMR ($CDCl_3$) of methyl isolysergate: δ 7.90 (bs, 1H), 7.15-7.25 (m, 3H), 6.90 (t, 1H, J=2.0Hz), 6.56 (br d, 1H, J=4.0Hz), 3.72 (s, 3H), 3.42 (dd, 1H, J=14.0, 5.0Hz), 3.35 (m, 1H), 3.30 (m, 1H), 3.30 (m, 1H), 3.20 (m, 1H), 2.73 (ddd, 1H, J=14.0, 11.0, 2.0Hz), 2.74 (m, 1H), 2.57 (s, 3H)

These ^1H NMR data are in agreement with that of methyl lysergate and methyl isolysergate synthesized by Ninomyia[9] , whom we thank for providing comparison spectra.

Mass Spectrum (ES^+): Expected for $C_{17}H_{18}N_2O_2$: 282.14. Found: 283.14.

Elemental Analysis: Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.20; H, 6.41; N, 10.05.

36. Preparation of ±lysergic acid(1):



To a solution of methyl lysergate & methyl isolysergate (6 : 1 mixture above, 7.8 mg, 0.028 mmol) in ethanol (0.5 ml) was added 1 N NaOH (0.5 ml). The reaction was heated at 35°C for two hours. 1 N HCl solution was used to adjust the pH to 6 and the solid material was collected by removing the liquid. The solid was recrystallized from ethanol to afford 6.1 mg, 95%, of lysergic acid.

^{1}H NMR (pyridine-d_5) of ± lysergic acid: δ 7.44 (d, 1H, J=8.4Hz), 7.42 (d, 1H, J=8.4Hz), 7.31 (t, 1H, J=8.4Hz), 7.25 (t, 1H, J=1.6Hz)), 7.20 (bs, 1H), 4.05 (m, 1H), 3.63 (dd, 1H, J=14.4, 6.4Hz), 3.52 (dd, 1H, J=11.2, 5.2Hz), 3.29 (m, 1H), 2.93 (ddd, 1H, J=14.4, 11.2, 2.0Hz), 2.71 (t, 1H, J=11.2Hz), 2.50 (s, 3H)

^{1}H NMR (methanol-d_4) of ±lysergic acid: δ 7.22 (d, 1H, J=8.4Hz), 7.18 (d, 1H, J=8.4Hz), 7.12 (t, 1H, J=8.4Hz), 7.05 (t, 1H, J=2.0Hz), 6.65 (bs, 1H), 4.15 (m, 1H), 3.70 (m, 3H), 3.42 (t, 1H, J=11.2Hz), 2.91 (ddd, 1H, J=14, 12, 2Hz)

^{13}C NMR (pyridine-d_5) : δ 174.9, 137.2, 136.4, 130.2, 128.9, 127.3, 119.8, 119.6, 112.0, 111.5, 111.3, 63.5, 56.1, 43.8, 43.4, 27.3

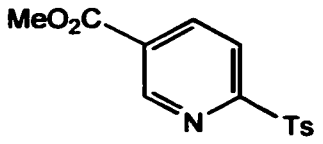
Mass Spectrum (ES^+): Expected for $C_{16}H_{16}N_2O_2$: 268.12. Found: 269.12

Elemental Analysis: Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.54; H, 5.88; N, 10.31

37. General procedure for the Diels-Alder reaction (without solvent):

Tosyl cyanide (1.2 equiv.) and α-pyrone (1.0 equiv.) were placed in a flask equipped with condenser, and the reaction was heated at elevated temperature in an oil bath under N_2. The crude mixture was purified by silica gel. The following is a typical example:

Preparation of **6-(toluene-4-sulfonyl-nicotinic acid methyl ester(55):**



Methyl coumalate (0.77 g, 5.0 mmol) and tosyl cyanide (1.09 g, 6.0 mmol) were placed in a 50 ml flask equipped with a condenser. The mixture was heated at 165°C in an oil bath with vigorous stirring under N_2 for two hours. The mixture was partitioned between CH_2Cl_2 (30 ml) and aq. $NaHCO_3$ (sat. 20 ml). The organic layer was separated and the aqueous was extracted with additional CH_2Cl_2 (30 ml x 2). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude material was purified on silica gel using hexane : ethyl acetate (3 : 1). A white crystalline product was obtained (mp. 189.1-190.2°C) in 54% yield.

^{1}H NMR ($CDCl_3$): δ 9.10 (s, 1H), 8.48 (d, 1H, J=8.0Hz), 8.22 (d, 2H, J=8.0Hz), 7.92 (d, 1H, J=8.0Hz), 7.34 (d, 2H, J=8.0Hz), 3.94 (s, 3H), 2.40 (s, 3H)

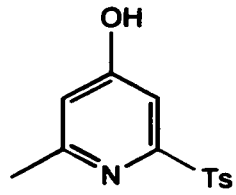
^{13}C NMR (pyridine-d5): δ 164.2, 162.1, 151.4, 145.3, 139.4, 135.1, 129.9, 129.2, 128.4, 121.5, 52.9, 21.7

Mass Spectrum (ES^+): Expected for $C_{14}H_{13}NO_4S$: 291.06. Found: 292.06

Elemental Analysis: Calcd. for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50; N, 4.81. Found: C, 57.59; H, 4.43; N, 4.73

The same method was used to prepare the following two compounds:

2-methyl-6-(toluene-4-sulfonyl)-pyridin-4-ol(56):



^{1}H NMR ($CDCl_3$): δ 7.84 (d, 2H, J=8.0Hz), 7.36 (s, 1H), 7.26 (d, 2H, J=8.0Hz), 6.76 (s, 1H), 5.2 (bs, 1H), 2.54 (s, 3H), 2.38 (s, 3H)

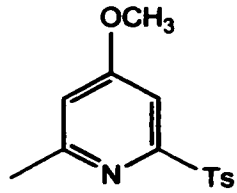
^{13}C NMR (pyridine-d5): δ 164.7, 160.8, 160.4, 143.9, 135.1, 129.8, 129.2, 114.3, 104.6, 22.9, 21.5

Mass Spectrum (ES^+): Expected for $C_{13}H_{13}NO_3S$: 263.06. Found: 264.06

Elemental Analysis: Calcd. for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32. Found: C, 59.17; H, 4.99; N, 5.20

Mp. 167.3-168.2°C, yield: 49%

4-methoxy-2-methyl-6-(toluene-4-sulfonyl)-pyridine(57):



^{1}H NMR ($CDCl_3$): δ 7.88 (d, 2H, J=8.0Hz), 7.56 (s, 1H), 7.29 (d, 2H, J=8.0Hz), 6.98 (s, 1H), 5.2 (bs, 1H), 3.70 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H)

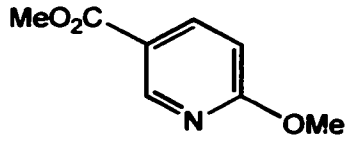
^{13}C NMR (pyridine-d_5): δ 165.1, 161.3, 160.4, 144.2, 135.9, 131.8, 129.0, 113.2, 105.7, 55.6, 22.6, 21.3

Mass Spectrum (ES^+): Expected for $C_{14}H_{15}NO_3S$: 277.08. Found: 278.08

Elemental Analysis: Calcd. for $C_{14}H_{15}NO_3S$: C, 60.63; H, 5.45; N, 5.05. Found: C, 60.76; H, 5.33; N, 5.15

Mp. 154.9-156.0°C, yield: 60%

38. Preparation of **6-methoxy-nicotinic acid methyl ester(58)**:



To a solution of 6-(toluene-4-sulfonyl)-nicotinic acid methyl ester (146 mg, 0.5 mmol) in methanol (5 ml) was added NaOMe/MeOH solution (0.5 M, 2.0 ml, 1.0 mmol) at r.t. The reaction was stirred at r.t. under N_2. The reaction was complete in 30 min as indicated by TLC. The solvent was removed *in vacuo* and the crude was partitioned between CH_2Cl_2 (10 ml) and H2O (5 ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (10 ml x 2). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The crude was passed

through a short plug of silica gel and a colorless oil was obtained (78.5 mg, 97.5%).

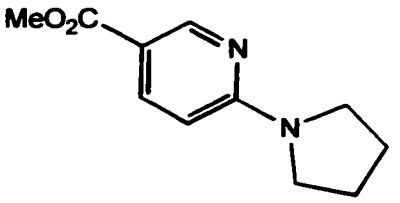
^{1}H NMR ($CDCl_3$): δ 8.90 (d, 1H, J=2.0Hz), 8.15 (dd, 1H, J=8.0, 2.0Hz), 6.77 (d, 1H, J=8.0Hz), 4.00 (s, 3H0, 3.91 (s, 3H)

^{13}C NMR ($CDCl_3$): δ 166.2, 150.2, 139.7, 125.9, 119.8, 110.9, 54.2, 52.3

Mass Spectrum (ES^+): Expected for $C_8H_9NO_3$: 167.06. Found: 168.06

Elemental Analysis: Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.65; H, 5.30; N, 8.50

39. Preparation of **6-pyrrolidin-1-yl-nicotinic acid methyl ester(59):**



To a solution of 6-(toluene-4-sulfonyl-nicotinic acid methyl ester (146 mg, 0.5 mmol) in CH_3CN/DMF (5 ml, v/v 1 : 1) was added pyrrolidine (106.7 mg, 125 μl, 1.5 mmol) via a syringe and a spatula of K_2CO_3. The reaction was stirred at r.t for 4 hours. Water (10 ml) was added to the mixture and extracted with ethyl acetate (5 ml x 3). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude material was purified by silica gel

chromatography using CH_2Cl_2-MeOH (98 : 2). A white solid was obtained (mp. 122.6-123.6°C, 87.7 mg) in 85% yield.

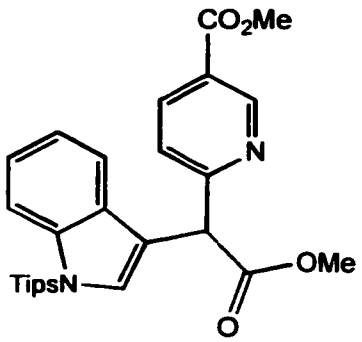
^1H NMR ($CDCl_3$): δ 9.11 (d, 1H, J=2.0Hz), 7.82 (dd, 1H, J=8.0, 2.0Hz), 6.82 (d, 1H, J=8.0Hz), 3.91 (s, 3H), 2.82 (t, 4H, J=7.2Hz), 1.62 (m, 4H)

^{13}C NMR ($CDCl_3$): δ 165.3, 148.5, 138.2, 124.6, 117.5, 106.8, 53.5, 52.1, 22.5

Mass Spectrum (ES^+): Expected for $C_{11}H_{14}N_2O_2$: 206.11. Found: 207.11

Elemental Analysis: Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.17; H, 6.99; N, 13.43

40. Preparation of **C-substituted Nicotinic Acid Methyl Ester(60):**



To a solution of 6-(toluene-4-sulfonyl-nicotinic acid methyl ester (146 mg, 0.5 mmol) in anhydrous THF was added N-triisopropylsilyl-3-indoleacetic acid methyl ester (207 mg, 0.6 mmol). The reaction was cooled in an acetone-dry ice bath (-78°C). To this mixture was cannulated a solution of LDA (1.5 M, 0.5 ml, 0.75 mmol) in THF (5 ml) at –78°C. The reaction was stirred at –78°C for 30min. The reaction was removed from the acetone-dry ice bath and warmed to r.t. with stirring at r.t. for additional 1 hour. The reaction was concentrated and the crude was partitioned between CH_2Cl_2 (20 ml) and aq. NH_4Cl (sat. 15

ml). The organic layer was separated and the aqueous layer was extracted with additional CH_2Cl_2 (15 ml x 2). The combined organic layers were dried over Na_2SO_4 and the crude was purified by silica gel using hexane-ethyl acetate (3 : 1). A colorless oil was obtained (182.4 mg, 76%).

^1H NMR ($CDCl_3$): δ 9.18 (d, 1H, J=1.6Hz), 8.16 (dd, 1H, J=8.4, 1.6Hz), 7.50 (d, 1H, J=8.4Hz), 7.44 (d, 1H, J=8.0Hz), 7.39 (s, 1H), 7.30 (d, 1H, J=8.0Hz), 7.16 (t, 1H, J=8.0Hz), 7.06 (t, 1H, J=8.0Hz), 5.55 (s, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 1.71 (m, 3H), 1.10 (s, 18H)

Mass Spectrum (ES^+): Expected for $C_{27}H_{36}N_2O_4Si$: 480.24. Found: 481.24

Elemental Analysis: Calcd. for $C_{27}H_{36}N_2O_4Si$: C, 67.47; H, 7.55; N, 5.83. Found: C, 67.51; H, 7.67; N, 5.97

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