The Thesis Committee for Kyle David Marks
Certifies that this is the approved version of the following thesis:

The Total Synthesis of (±)Stepharine

APPROVED BY
SUPERVISING COMMITTEE:

Supervisor:

Philip Magnus

Eric Anslyn

The Total Synthesis of (±)Stepharine

by

Kyle David Marks, B.S.

Thesis

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Dedication

This work is dedicated to my wife Sara, whose love and nearly boundless understanding have made this possible.

Acknowledgements

I first want to thank my parents, Mitch and Roberta, whose love, support, and unyielding demand that I make every effort my best, have made it possible for me to get this far.

I would also like to thank Dr. Philip Magnus for taking me into the group and giving me the resources I needed to grow as a scientist. I truly appreciate you allowing me to make some wrong turns in figuring things out with this synthesis, it truly speaks to your confidence in me. Thank you for everything.

Bahman Ghavimi, thank you for all the helpful advice both in regards to chemistry and life. It was a pleasure having you as a labmate.

Finally thank you to the entirety of the Magnus Lab: Will, Tim, Charlie, Alan and, James. All of you have helped me develop the ideas for my chemistry and without your assistance this work would not be nearly as strong.

Abstract

The Total Synthesis of (±)Stepharine

Kyle David Marks, MA

The University of Texas at Austin, 2013

Supervisor: Philip Magnus

Herein is described work culminating in the total synthesis of the proaporphine alkaloid (±)stepharine. The first chapter discusses some of the background information regarding the molecule's isolation, biological activity, and previous syntheses. Chapter 2 tells of our initial attempts at synthesizing the molecule leading to the assembly of (±)stepharine's tetrahydroisoquinoline structure. Chapter 3 recounts the completion of the synthesis using an alternate route. Also described in this chapter is the use of a CsF induced intramolecular phenolic alkylation to form (±)stepharine's spiro cross conjugated dienone structure. Experimental details and characterization are included as well.

Table of Contents

Chapter 1: Background Information

1.1 Stepharine: Isolation and Classification

Stepharine **1** is a member of the proaporphine alkaloid family (**Figure 1.1**). Differing by only a methyl group, is its cousin pronuciferine **2**, which when it was isolated in 1963, was the first of this alkaloid family to be discovered. One year later, stepharine was found in the vine *Stephania galabra*. As their structures imply the proaporphine alkaloids derive their biosynthetic origin from a benzyl tetrahydroisoquinoline, via a phenolic oxidative coupling (**Scheme 1.1**)[1].

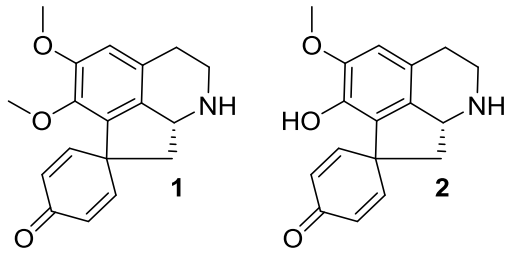
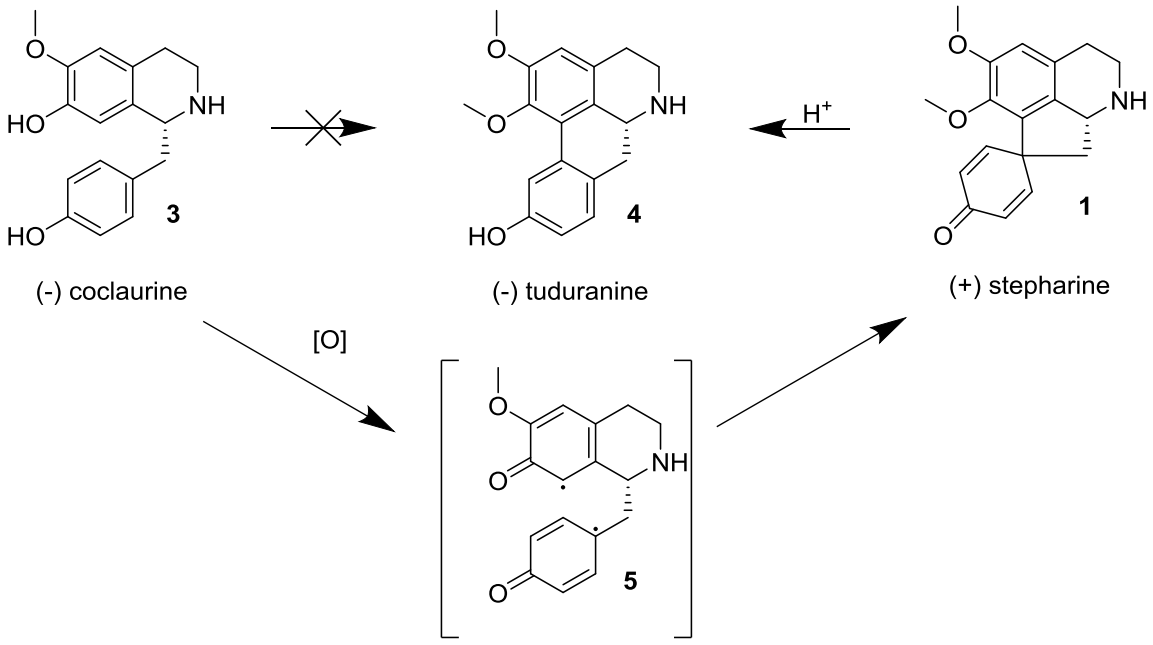


Figure 1.1: Stepharine and pronuciferine.

The proaporphine alkaloids were first described in Derik Barton's 1957 work on phenolic oxidative couplings, several years before any members of the family had been isolated[2]. In this work, he noted that certain aporphine alkaloids were the result of an apparent ortho-meta phenolic oxidative coupling. These couplings are unknown, as phenolic radicals delocalize from the oxygen to the ortho and para positions only. This suggests that the biosynthesis goes through a spirocyclic

intermediate which, in acidic conditions, undergoes a dienone phenol rearrangement to give the respective aporphine (**Scheme 1.1**). These intermediates were given the name proaporphines. Once stepharine **1** was isolated, it was subjected to aqueous acidic conditions and shown to undergo rearrangement to tuduranine **4**; strongly supporting Barton's theory.



Scheme 1.1: Barton's proposed biosynthesis of aporphine alkaloids via rearrangement of a spirocyclic proaporphine intermediate.

1.2 Biological Activity of Stepharine

Stepharine has been shown to have potent anti-cholinesterase effects. It was shown that stepharine sulfate suppresses the growth of post operative peripheral nervous system scar tissue growth in human patients. These patients were given 5 mg intramuscular injections of stepharine sulfate 2-3 times a day. After a month, 75% of the patients showed decreased fibrous tissue growth and had recovered pain and tactile sensations in the affected area. Of those patients in the treatment group, 37.5% had recovered at least two weeks faster than the control group, which was given galanthamine[3].

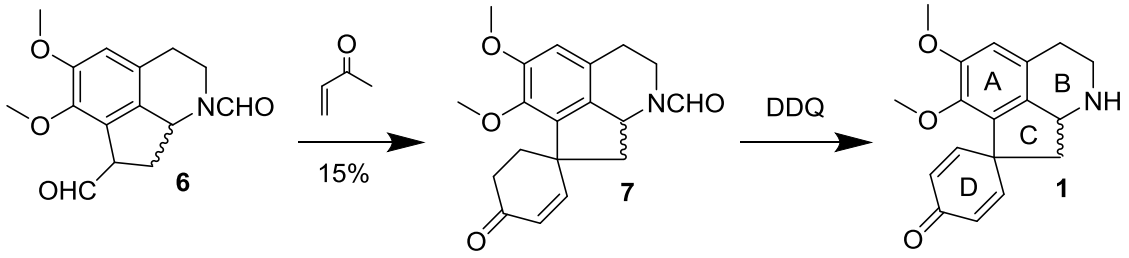
Stepharine has been shown to promote the remylination of damaged neurons in mice. Mice given 0.1-1mg/kg doses of stepharine sulfate were shown to have complete remylination and a return of normal impulse passage speeds after 60-80 days. Mice in the control group, which were given no treatment had not fully recovered even after 120 days. This study indicated that stepharine may be useful in treating degenerative neurological disorders such as amyotrophic syndrome[4].

Stepharine has shown mild cytotoxic activity against human breast cancer cell lines[5]. It has also shown some mild *in vitro* anti fungal activity against *Cladosporium cladosporides*[6].

1.3 Bernaur's Total Synthesis of Stepharine

The first synthesis of stepharine was in 1968 by Bernaur *et al*. Through a series of four steps, he formed the ABC ring structure **6**, shown in **Scheme 1.2**.

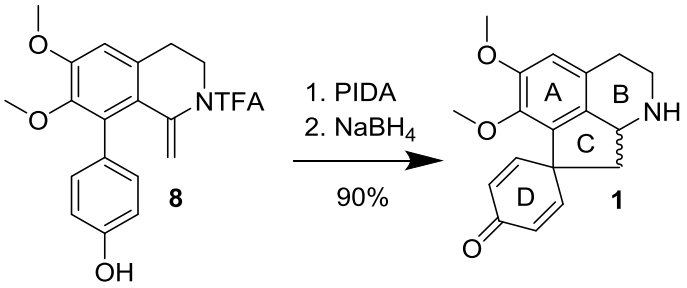
Using the aldehyde as a handle, the core structure of stepharine was formed using a Robinson Annulation with methyl vinyl ketone. The synthesis was concluded via oxidation to the cross conjugated dienone with DDQ. This overall synthesis took six steps and had a 4.5% yield[7].



Scheme 1.2: Stepharine's first synthesis by Bernaur wherein the core structure is formed by Robinson Annulation.

1.4 HONDA'S TOTAL SYNTHESIS OF STEPHARINE

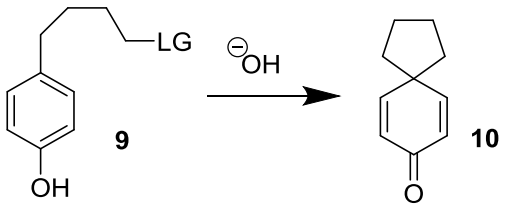
The most recent total synthesis of stepharine was in 2010 by Honda *et al*. In it, the ABD ring structure was formed with a strategically placed exocyclic double bond on the B ring. Periodobenzene diacetate (PIDA) was used to oxidize the phenol, allowing nucleophilic attack by the acyl enamide, subsequently forming the spiro center. In the same pot, sodium borohydride was added to reduce the resultant acyliminium ion. Honda synthesized the molecule in nine steps with an overall yield of 29.0% (**Scheme 1.3**)[8].



Scheme 1.3: Honda's method of forming stepharine's core structure.

1.5 PHENOLIC ALKYLATION STRATEGY

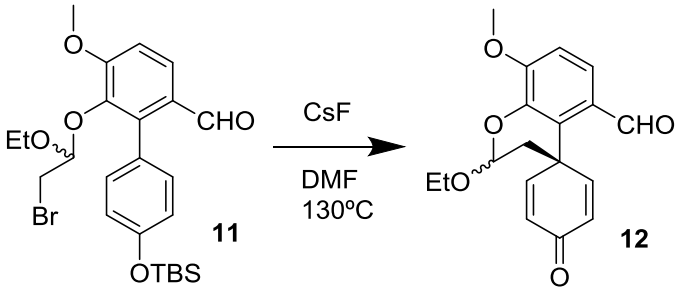
Our plan was to utilize a phenolic alkylation strategy to form the cross conjugated dienone system. The earliest known example of this is in the 1957 work by Weinstein[9] (**Scheme 1.4**).



Scheme 1.4: An example of Weinstein's us of a phenolic alkylation to form a spirocyclic system.

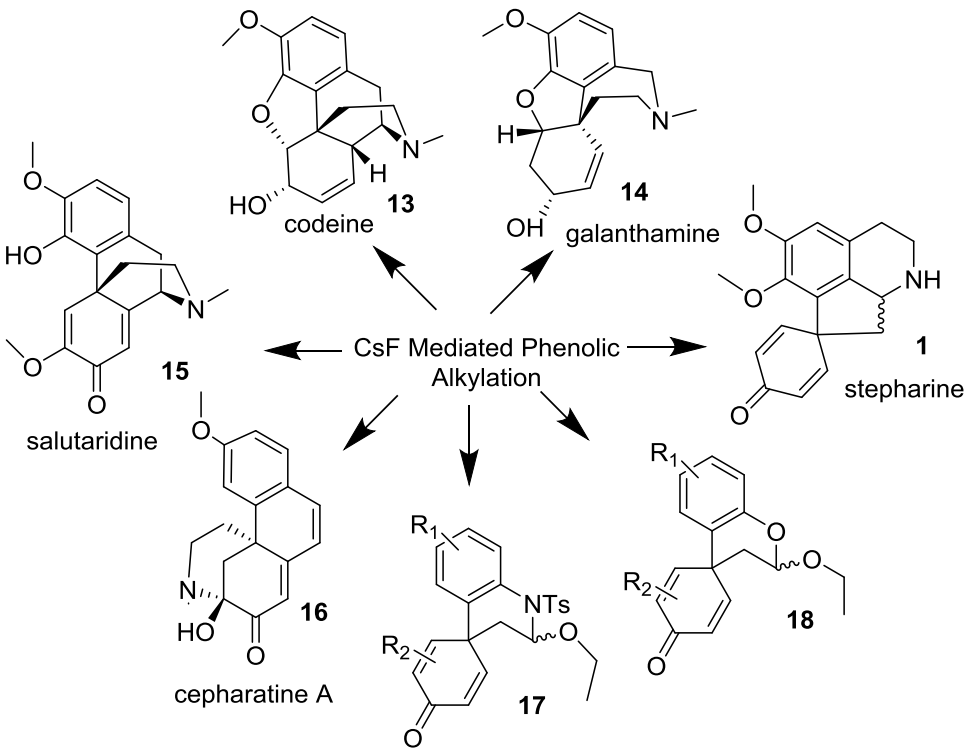
A recent modification to this was utilized by Magnus *et al.* in the 2009 synthesis of codeine and galanthamine. This modification involved using a silyl protected phenol that in the presence of CsF in dry DMF which formed a phenolate and displaced a leaving group[10] (**Scheme 1.6**). This approach was utilized because

the traditional strong basic conditions were found to be insufficient to induce phenolic C-alkylation on their systems[11].



Scheme 1.6: The first reported example of a CsF mediated desilylation of a phenol to form a cross conjugated dienone system.

Much of the recent work in our group has been devoted to expanding the scope of this methodology (**Scheme 1.7**). Following the codeine and galantamine work, the Magnus group has produced a total synthesis of cepharatine A[12]. Additionally several papers utilizing this methodology are in preparation, including the total synthesis of salutaridine, and two projects exploring substituent effects on the phenolic alkylation reaction[13]. Finally, there is this work, which aims to show the versatility of the reaction for the total synthesis of proaporphine alkaloids.



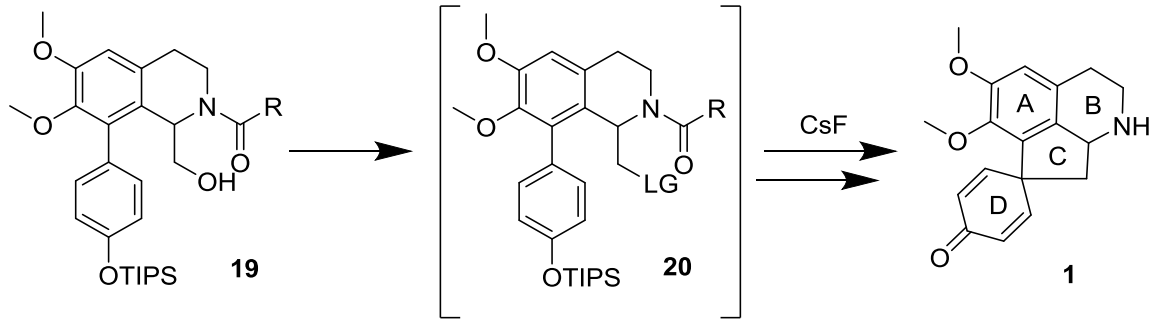
Scheme 1.7: Magnus lab applications of CsF mediated phenolic alkylation methodology.

1.6 Application of Phenolic Alkylation Strategy to Stepharine

Our strategy for the synthesis of stepharine was to make intermediate **19** as a substrate for activation and then intramolecular phenolic alkylation (**Scheme 1.8**). This would represent the first example CsF induced intramolecular phenolic alkylation being used to form a five membered ring. Additionally it would be the first example of fully carbocyclic ring formation using this methodology.

As the dienone in stepharine can rearrange under acidic conditions **(Scheme 1.1**), it was our intention to form it late in the synthesis. Application of the phenolic

alkylation on stepharine would demonstrate its utility on the most complex substrate to date.

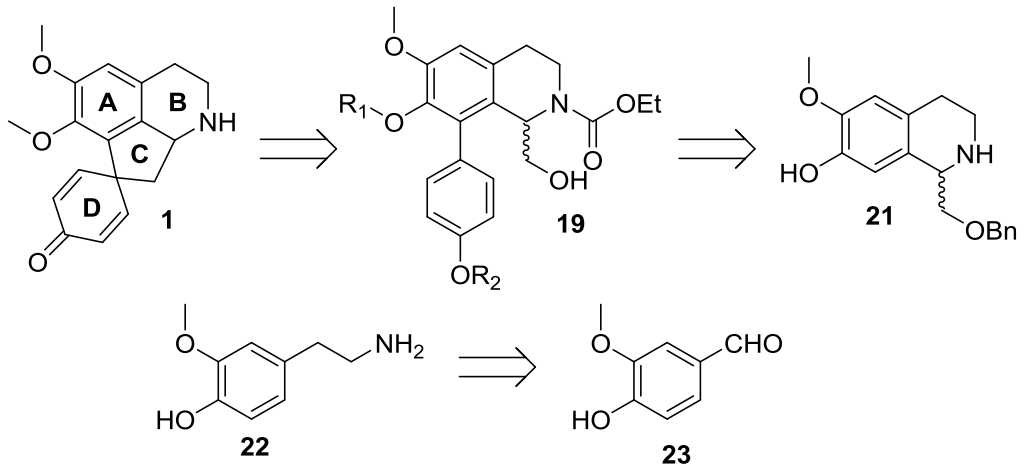


Scheme 1.8: Formation of the cross conjugated dienone via phenolic alkylation of stepharine.

Chapter 2: Synthetic Route to (±)Stepharine I

2.1 RETROSYNTHESIS

The retrosynthetic analysis addressed the four main challenges associated with the synthesis (**Scheme 2.1**). The first of these is the intramolecular phenolic affording the dienone. As this forms the quaternary center it represents the key step of the synthesis. Alcohol **19a** can be obtained from a Suzuki Cross Coupling Reaction of the AB ring system **21** and the appropriate silyl protected boronic ester. The tetrahydroisoquinoline system could be obtained from vanillin **23** via the primary phenethylamine **22**. Though two different routes were utilized, their chief differences lie in the order in which these challenges were addressed.

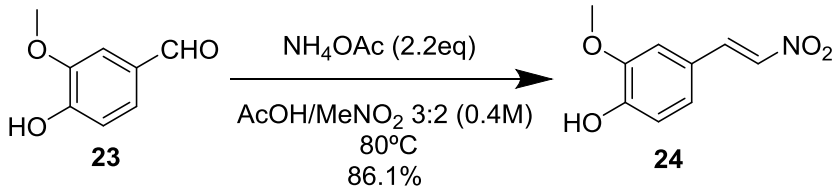


Scheme 2.1: Original retrosynthetic analysis of stepharine used.

Previous work in our lab[14] on the proaporphine alkaloids produced alcohol **20a** in 1.04% over 14 steps and, although this previous attempt proved insufficient to finish the synthesis, our hope was to salvage the route to **19** with only minor adjustments..

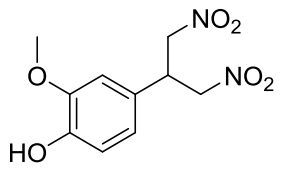
2.2 FORMATION OF NITROSTYRENE 24

Vanillin was transformed into the corresponding nitrostyrene with ammonium acetate in a 3:2 mixture of acetic acid and nitromethane. This was heated to 80 ºC for 2 hours, giving **24** in 86.1% (**Scheme 2.2)**.



Scheme 2.2: Formation of nitrostyrene **24** via a Henry reaction.

Care had to be taken with the reaction length; as prolonged heating would allow an additional equivalent of nitromethane to add, giving the dinitropropane product[15] (**Figure 2.1**).



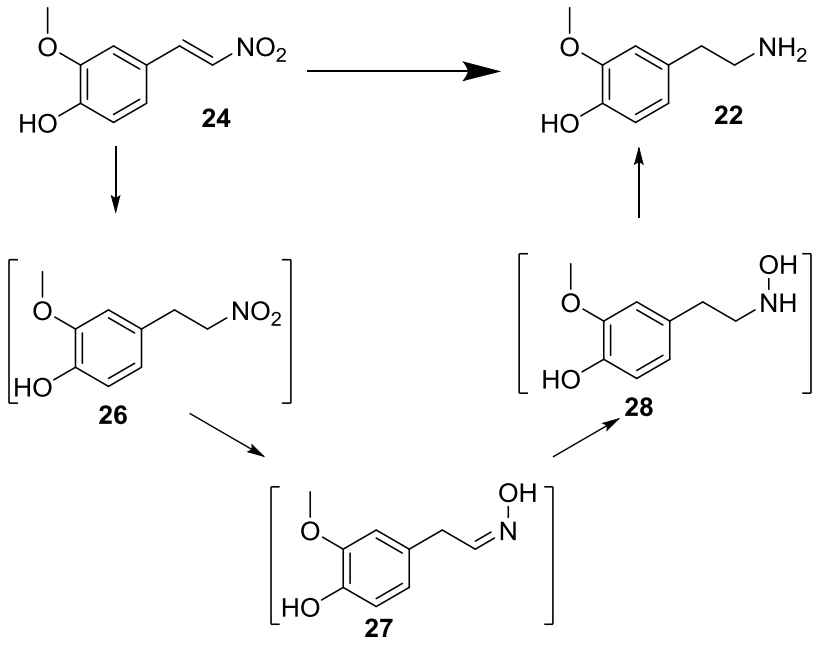
25

Figure 2.1: Proposed overreaction product due to a conjugate addition of nitromethane to nitrostyrene **24**.

The reaction scaled well and was run on scales as large as 30 g. Purification was facile due to the product's propensity to crystallize from methanol.

2.3 Reduction to Create Primary Phenethylamine 22

Reduction of nitrostyrene **24** provided the first real challenge in this route. Before getting into the strategies used to overcome this problem, a look at the transformation itself may prove insightful.



Scheme 2.3: Stages of nitrostyrene reduction to give a primary phenethylamine.

The transformation entails four total changes in oxidation state.[16] The first reduction from the nitrostyrene gives nitroalkane **26**. From there the oxime **27** and then, hydroxylamine **28** can be obtained. Finally, the amine **22** is formed after one last reduction. From this alone, we get five possible species in solution at any one time. Under anionic conditions, **24**, **26**, and **27** are nucleophilic, and because the starting material and all intermediates are hydride acceptors they may also act as electrophiles. Together these factors can lead to polymerization.[17]

Another complication arises from the acidic phenol. Upon deprotonation it can deactivate the nitrostyrene system to hydride attack. Additionally when **22** is formed, the pka's of the phenol and amine are approximately equivalent[18,19] (**Figure**

2.2) leading to the possibilty of zwitterionic species making extractions from water difficult.

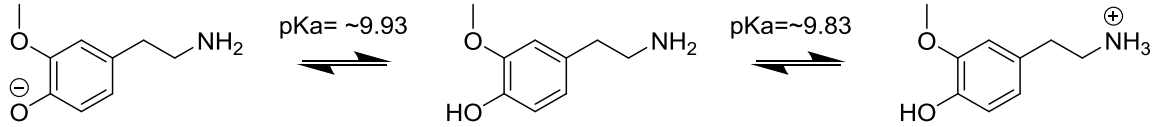
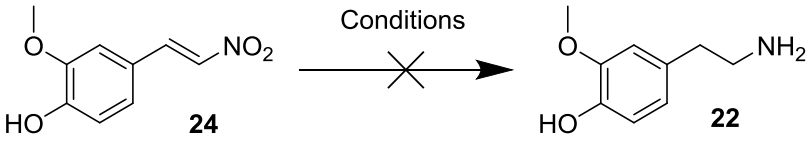


Figure 2.2: Proposed zwitterionic species

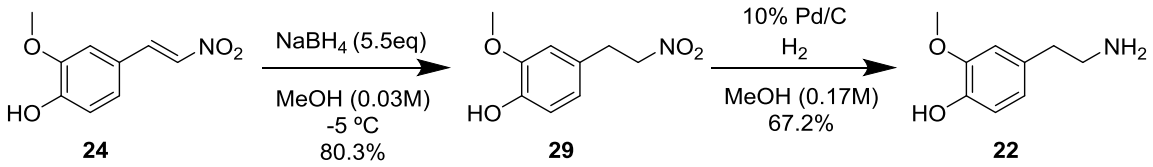
LAH [20]and Red-Al[21] both gave complex mixtures by LCMS which were inseparable. This was also the case with *in situ* generated Ni_2B[22]. Other methods for the generation of H_2 *in situ* (Zn[23]/Rainy Ni[24]/Pd on C[25]) gave partial reduction to the oxime stage even when heated (**Scheme 2.4)**.



Scheme 2.4: Early attempts to obtain **22** directly were unsuccessful.

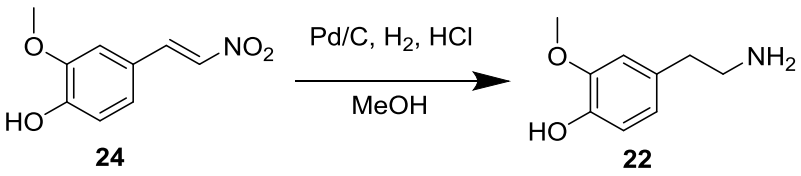
A stepwise approach provided the first traces of success (**Scheme 2.5**). Nitrostyrene **24** was taken to the nitroalkane **29** using sodium borohydride in methanol.[26] Care was taken to keep the reaction mixture below -5 ºC and dilute (0.03M) in order to prevent polymerization. This reaction was scaled to as large as 3 g, above which maintaining consistent internal reaction temperature became difficult due to the decreased surface area to volume ratio of the flask.

Nitroalkane **29** was then reduced to the amine **22** using Pd/C under an atmosphere of hydrogen over the course of 72 hours. One benefit of this method was that after the Pd/C was filtered off, **22** could be precipitated from cold (-78 ºC) methanol and used without further purification. This avoided the loss associated with the amine sticking to silica gel during column chromatography.



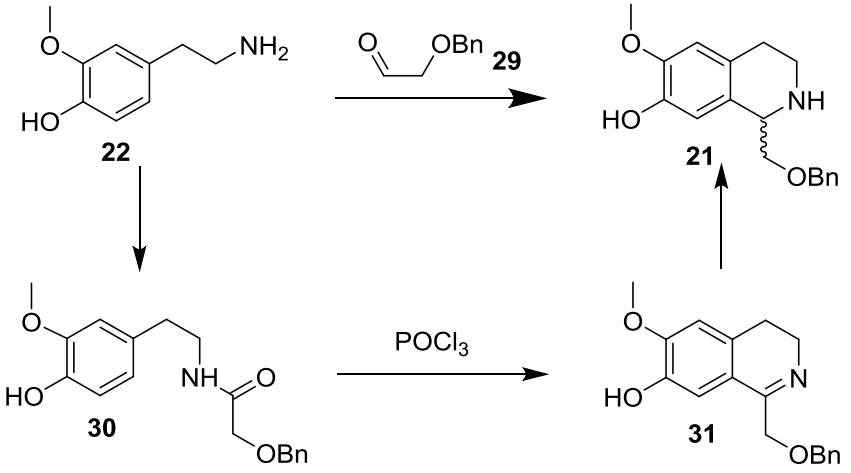
Scheme 2.5: A stepwise approach to reduction provided the first success in isolating **22**.

At length it was found that a 1:1 mixture of 6N HCl and methanol allowed Pd/C in a hydrogen atmosphere to reduce **24** to **22** in a single step in 78.8% yield (**Scheme 2.6**)[27]. In this reaction the acid not only activated the substrate for reduction but also protonated the product **22,** preventing it from poisoning the catalyst.



Scheme 2.6: Direct hydrogenation in acidic media provided **22** in 78.8% yield in 6 hours.

2.4 FORMATION OF TETRAHYDROISOQUINOLINE 21

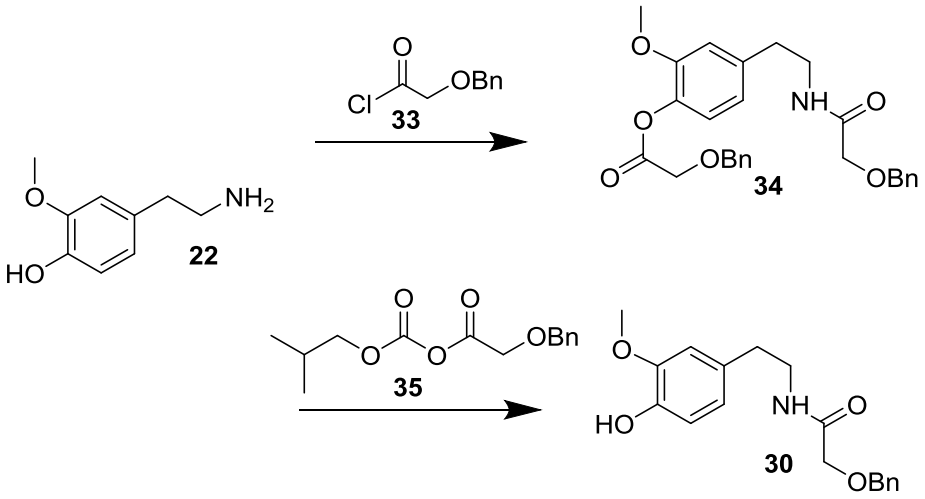


Scheme 2.7: Two methods for forming tetrahydroisoquinoline **21** from the parent amine **22**. Top: Pictet-Spengler Reaction. Bottom: Formation of amide **30**, Bischler -Napieralski, and finally reduction.

Having phenethylamine **22** in hand we turned our attention to forming the tetrahydroisoquinoline system. Two of the common methods for this transformation are the Bischler Napieralski and Pictet Spengler reactions (**Scheme 2.7)**. The Pictet Spengler has the advantage of being one step as well as keeping the substrate in the correct oxidation state. The major shortcoming with the Pictet Spengler is the possibility of overreaction and the use of aldehyde **29** as a reactant. Aldehyde **29** is problematic due to the increased acidity of its alpha carbon (**Figure 2.3)** leading to self condensation.

Figure 2.3: Aldehyde **29** and its enol tautomer **32**.

With the knowledge that aldehyde **29** would be prone to self aldol condensation and the minor success of previous work[14] the Bischler Napieralski was pursued first. Initial attempts used acyl chloride **33** to form the amide however it was found that the di-acylation product **34** dominated (**Scheme 2.8**). While saponification to remove the phenolic carbonate was an option, the strong basic conditions required could further complicate the transformation.



Scheme 2.8: Use of acid chloride **33** gave the di-acylated species **34,** while the mixed anhydride gave the desired product **30**.

It was found that activating acid **36** with isobutyl chloroformate to give the mixed anhydride provided a suitably mild coupling partner. Anhydride **35** was formed *in situ* using acid **36** and isobutyl chloroformate. Upon the consumption of acid **36** the amine was added giving **30** as the dominate product in 68.6% yield. Peptide coupling reagents such as EDC were also explored, however, the organic soluble, stoichiometric byproducts complicated isolation of the amide.

Cyclization of **30** was accomplished using phosphorus oxychloride in acetonitrile. The active species for this reaction is the acyl iminium ion which is obtained though dehydration of the amide (**Figure 2.4)**.

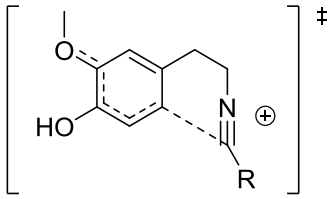


Figure 2.4: Nitrilium transition state for the Bischler-Napieralski reaction.

Modest yields were obtained from this reaction. We theorized that this may be due to the phenolic oxygen of **30** attacking $POCl_3$ and, pulling electron density out of the aromatic system making it less reactive towards electrophilic aromatic substitution (**Figure 2.5)**.

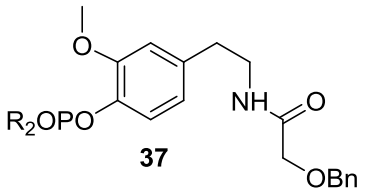
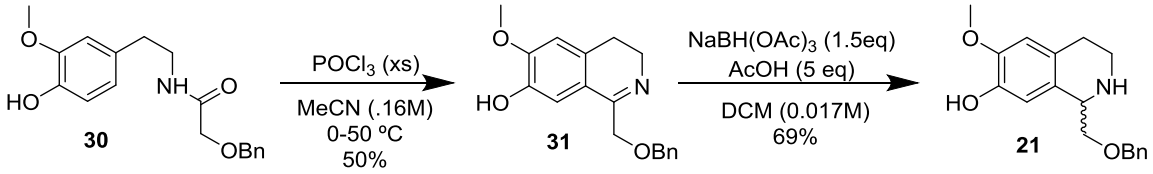


Figure 2.5: Proposed deactivated species for the Bischler Napieralski reaction of **30**.

This theory is supported by the observation that the starting material would appear consumed by TLC but, upon aqueous bicarbonate work up could be

recovered. This could be from hydrolysis of the phosphate ester and rehydration of the nitrilium ion.

The final step to obtaining **21** was to reduce imine **31** (**Scheme 2.9**). It was found that triacetoxyborohydride with acetic acid gave **21** upon workup. The overall yield for this process was 23.5% from **23**. Due to the low yield, additional steps required, and change in oxidation state, the Pictet Spengler reaction was pursued as an alternative.

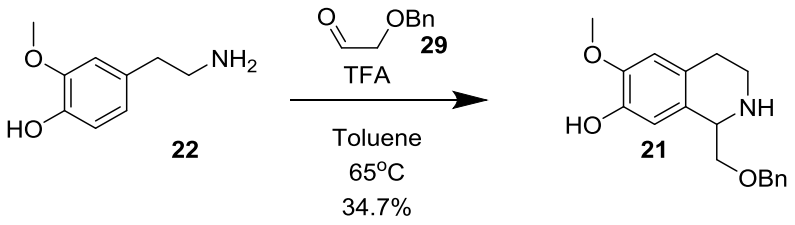


Scheme 2.9: Formation **21** using $POCl_3$ to induce cyclization and $NaBH(OAc)_3$ to reduce the imine.

2.5 Pictet Spengler Formation of Tetrahydroisoquinoline 21

The Pictet Spengler reaction proved a slightly more fruitful route. Amine **29** along with the benzyl substituted aldehyde **29** were dissolved in toluene with TFA and heated to 65 ºC, giving amine **21** in 34.7% (**Scheme 2.10**). The low yield was due the interplay between at least two factors. The first of which was aldehyde **29**'s propensity to polymerize under the reaction conditions. The second was **21**'s ability to react with a second equivalent of aldehyde. Along with the polymeric product of

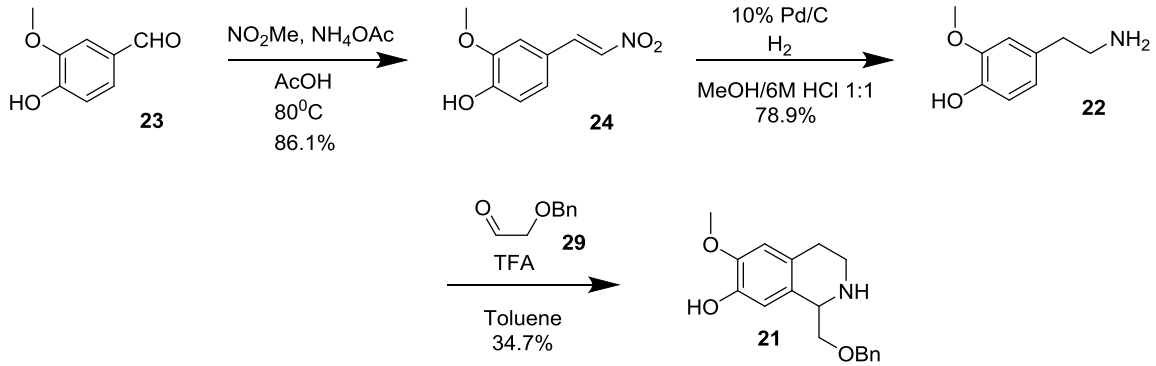
29, LCMS also showed masses corresponding to an second addition of aldehyde to **21** however, these products were not isolated.



Scheme 2.10: Formation of **21** using the Pictet Spengler reaction.

2.6 TERMINATION OF ROUTE I

Although this route cut out two steps and managed to almost double the yield (**Scheme 2.11**) over previous efforts in obtaining **21**, it was still an unsuitable method for reaching stepharine. At this point it was decided to change the starting material in order to avoid some of the issues caused by having the free phenol.

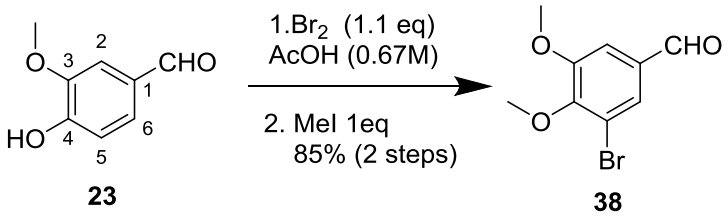


Scheme 2.11: Final result of the first route attempted to synthesize stepharine. Intermediate **21** was formed in 23.6% yield over three steps.

Chapter 3: Synthetic Route to (±)Stepharine II

3.1 A Change in Starting Material

Upon termination of the previous route our goal was to mitigate the issues of selectivity, and isolation of polar intermediates encountered due to the phenol. Vanillin derivative **38** was used in order to achieve these ends. Taking advantage of vanillin's predisposition to substitution ortho to the phenol, it was brominated then alkylated; reversing the order of these reactions gave bromination at the 6 position[28]. While synthesized in our lab **38** is commerically available and is thus considered our starting material for this route.



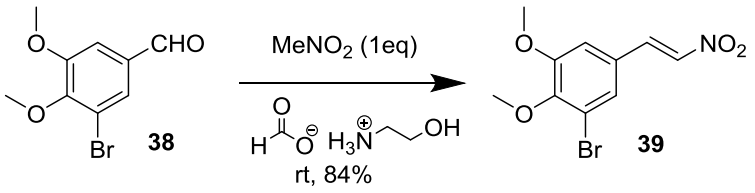
Scheme 3.1: Formation of starting material **36** from vanillin.

3.2 Henry Reaction to form Nitrostyrene 39

The aim for this route was to follow the same general retrosynthetic pathway as shown in **Scheme 2.1**, keeping the order in which each of the major structures are constructed the same. As such, this route began by attempts to form the primary phenethylamine.

From the outset, it was found that the presence of the aryl bromide complicated our efforts. The first problem arose in using the standard Henry Reaction conditions described in **Scheme 2.2**. It was found that hot acetic acid led to ipso protonation of the ring displacing the bromine.

The solution to this problem was in using a simple ionic liquid first described by Kuenburg *et al.*[29] and developed by Alizadeh *et al.*[30] as a solvent/catalyst for the Henry Reaction. In it they showed that simple nitrostyrenes could be formed at room temperature with only one equivalent of nitromethane by running the reaction in an ionic liquid composed of a 1:1 mixture of formic acid and ethanol amine ([FA][EA]).



Scheme 3.3: Ionic liquid mediated Henry Reaction to form **39**.

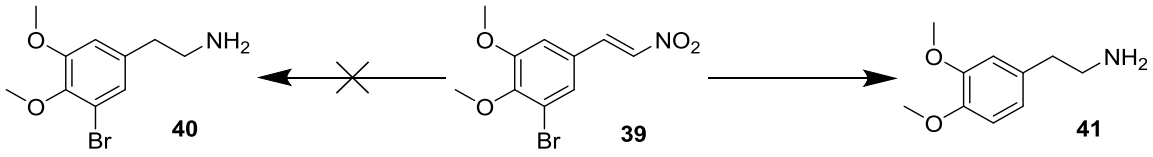
On our system, it was found to produce **39** in 84% yield (**Scheme 3.3**). Nitrostyrene **39** crashed out of solution over the course of the reaction, which pushed the equilibrium forward, prevented over reaction, and simplified the work up to require only filtration. The product was then crystallized from methanol giving the nitrostyrene as a pure canary yellow solid. The ionic liquid could then be reused for

subsequent reactions. This procedure was scaled effectively to 20 mmoles with consistent yields.

We speculate that this system proceeded by having the reactants highly concentrated in a system that worked as a proton shuttle, facilitating both attack of nitromethane on **38** and elimination of water to form the nitrostyrene. The product was significantly more lipophilic and thus crashed out of the highly polar ionic liquid.

3.3 Reduction of Nitrostyrene 39

The next problem faced was the reduction of **39** to form amine **40**. Each method attempted (LAH, Red-Al, catalytic hydrogenation) reduced the aryl bromide bond along with forming the amine (**Scheme 3.4**).



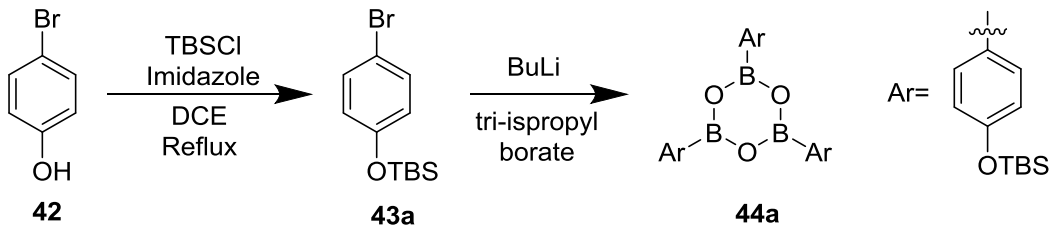
Scheme 3.4: Dehalogenation occurred in each method giving phenethylamine **39**.

By cooling the reactions down to 0 ºC, we observed that the removal of the bromine was occurring more rapidly than the reduction of the nitrostyrene functionality. This made attempts to stop the reaction before dehalogenation futile.

Realizing that this would not be trivial to fix, the issue was circumvented all together by performing the Suzuki reaction immediately following the formation of **38**.

3.4 BORONIC ESTER FORMATION

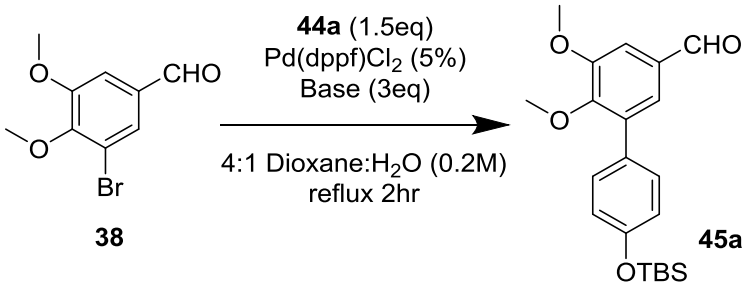
The Suzuki coupling partner was formed from 4-bromophenol **42** which was protected using TBS-Cl with imidazole as a base/catalyst. Butyl lithium was used to perform a metal exchange to give the boronic acid. This was immediately condensed under azeotroping conditions to give boronic ester **44** (**Scheme 3.5**). The boronic ester was used because of its comparative bench top stability to the acid.



Scheme 3.5: Formation of boronic ester trimer **42a**.

3.5 SUZUKI CROSS COUPLING YIELDING BIARYL 45A

Using standard Suzuki Reaction conditions[11] with K_2CO_3 as the base proved too slow and the reaction stalled out by precipitation of palladium black, giving poor yields. Progressively stronger bases were shown to speed up the reaction giving complete consumption of starting material. Tri-basic potassium phosphate gave nearly quantitative conversion to the biaryl system (**Scheme3.6)**.

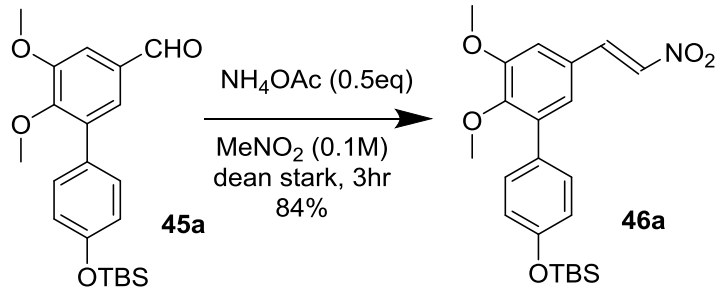


Scheme 3.6: By altering the base strength the yield for the Suzuki reaction was brought up to 96% for **45a**.

3.6 HENRY REACTION ON THE BIARYL SYSTEM

Attempting to recreate the success of the Henry Reaction in [FA][EA] on **38** (**Scheme 3.3**) **43** was subjected to ionic liquid Henry Reaction conditions. Due to the increased lipophilicity of the starting material it was insoluble in the ionic liquid and thus the **45a** failed to react. Reaction conditions using ammonium acetate in acetic acid and nitromethane led to diminished yields due to removal of the TBS protecting group.

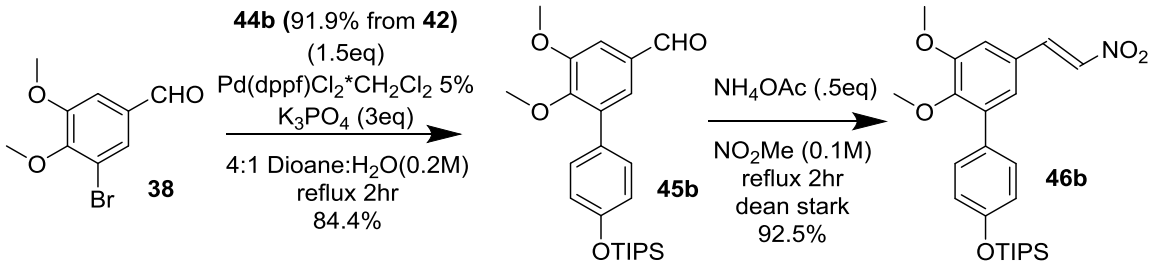
A biphasic system using [FA][EA] and nitromethane was set up which was effective, in forming **45a**, but required a 12 hour reflux to complete the reaction. Likewise, it was found that using 0.5 equivalents of ammonium acetate in refluxing nitromethane gave conversion of the starting material in 12 hours however, by employing a dean stark apparatus to remove the water produced and thus pushing the reaction forward, reaction times were cut to a mere 3 hours (**Scheme 3.7**).



Scheme 3.7: Nitrostyrene **46a** could be obtained in 84% yield in 3 hours by azeotroping off the water formed in the reaction.

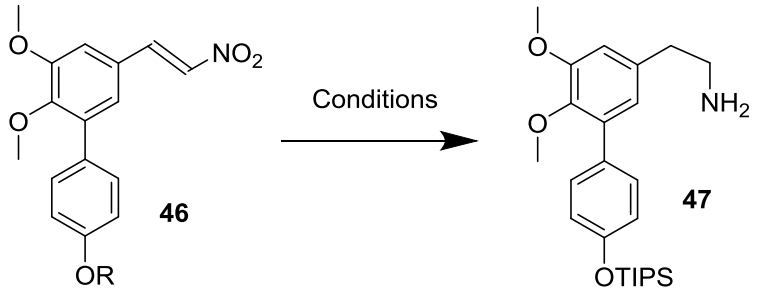
3.7 A SWITCH TO TIPS PROTECTION OF THE PHENOL

The reduction of the biaryl nitrostyrene **46a** proved difficult. LAH and Red-Al were too strongly nucleophilic and resulted in removal of the TBS group. Catalytic hydrogenation under acidic conditions was attempted as well, but also caused TBS hydrolysis. It was decided at this point that the protecting group should be changed to TIPS due to its increased stability and relatively minor changes to the molecule's stereoelectronic environment. The synthesis up to the point of reduction required little to no adjustment upon change of protecting groups (**Scheme 3.9**).



Scheme 3.9: TIPS modified synthesis to obtain nitrostyrene **46b**.

While yields of catalytic hydrogenation improved with the more acid stable TIPS group, they were still below 50%. It was at this point we came across a paper by Vinogradova *et. al* that showed DIBAL was a suitable reductant for nitrostyrenes[31]. With this method yields improved to 80% (**Scheme 3.10**).

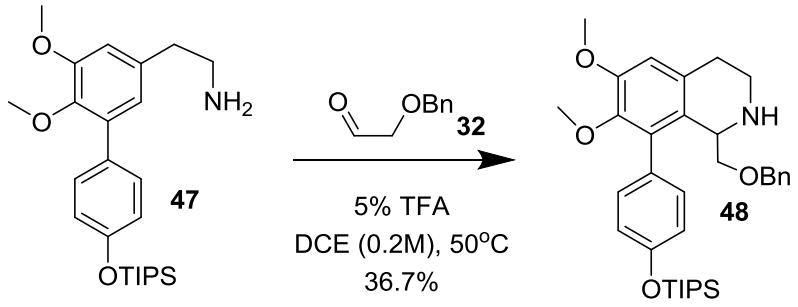


Reductant	R=TBS	R=TIPS
LAH	Silyl Deprotection	Silyl Deprotection
HCl, Pd/C, H_2 rt	Silyl Deprotection	/
HCl, Pd/C, H_2 0°C	/	29%
AcOH, Pd/C, H_2, rt	/	Slow
MsOH, Pd/C, H_2, 0°C	/	42%
DIBAL	Silyl Deprotection	80%

Scheme 3.10: It was found that DIBAL gave 47 in 80% yield, a vast improvement over previous methods.

3.7 Formation of Biaryl Tetrahydroisoquinoline

Initial attempts at the Pictet Spengler were comparable to results with **22** described previously. In DCE with aldehyde **29** and catalytic TFA the reaction suffered from low yields, issues with polymerization and over reaction, and difficulty in isolation (**Scheme 3.11**).



Scheme 3.11: Initial success using Pictet Spengler conditions.

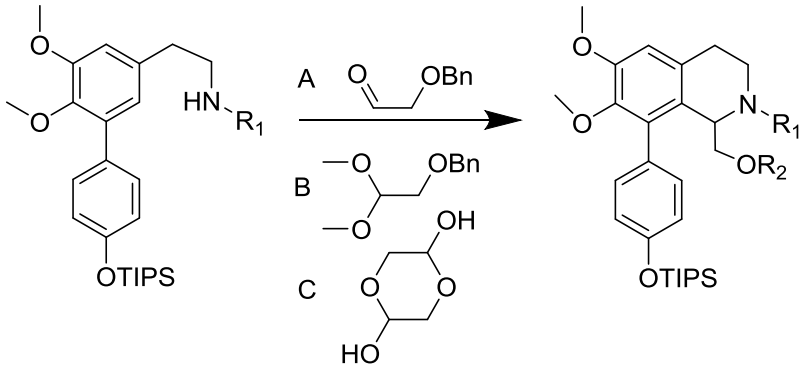
The first of these challenges to be addressed was the issue of aldehyde **29** polymerizing. This was temporarily solved by eliminating the acid catalyst and using a slightly acidic solvent such as trifluoroethanol (pka~12.5)[32]. With a pKa of ~8, the imine had an equilibrium ratio between its protonated and deprotonated forms of ~1:32,000. Once protonated cyclization was able to occur, driving the equilibrium forward[33]. TFE was not acidic so acidic that it readily enolized **29**. Using TFE gave much better yields but there was still overreaction and difficulty in purification.

We then looked to using an acyl Pictet Spengler reaction where the carbamate would first be formed, and then condensed with an aldehyde source. Unfortunately the carbamate nitrogen was not nucleophilic enough to attack the aldehyde without

an additional acid catalyst[34]. With TFA added, the reaction produced product but, not without significant aldehyde polymerization, making purification difficult. We believed this might be avoided by creating the aldehyde *in situ* from the dimethyl acetal[35]. This proved successful.

The final incarnation of Pictet-Spengler used was another change in aldehyde source. Since it was established the *in situ* opening of an acetal was successful on this system, we attempted to perform the reaction on the cyclic glycolaldehyde dimer. This gave free alcohol **19b** in 78.1% (**Scheme 3.12**) without requiring protection of the alcohol.

The evolution of the transformation from **47** to **19b** is particularly significant. First and foremost, the cyclization yield was more than doubled from route I. Additionally, the end result left the synthesis with two fewer amine purifications, as **47** could be trapped as the ethyl carbamate **49**, and **48** was no longer part of the synthesis. Finally, the synthesis benefited from having one fewer step as a result of using glycolaldehyde dimer as the aldehyde source. This eliminated the necessity of removing the benzyl group in the following step.



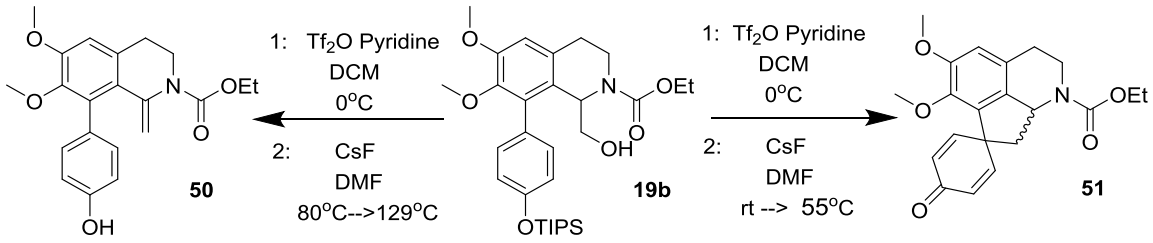
Condition	Aldehyde Source	R1	Solvent	Acid	Yield
1	A	H	DCE	TFA	36.7%
2	A	H	TFE	-	77.0%
3	A	CO_2ET	TFE	-	np
4	B	CO_2ET	TFE	-	np
5	B	CO_2ET	TFE	TFA	73.0%
6	C	CO_2ET	TFE	-	np
7	C	CO_2ET	TFE	TFA	78.1%

Scheme 3.12: Acyl Pictet Spengler using glycolaldehyde dimer as an aldehyde source gave the best yields at 78.1%.

3.8 Activation of 19b and Phenolic Alkylation

At this point we were just a few short steps from the product with our next task formation of the leaving group. Owing to the more demanding nature of the phenolic alkylation, compared to previous examples in the group[10,12,13], it was

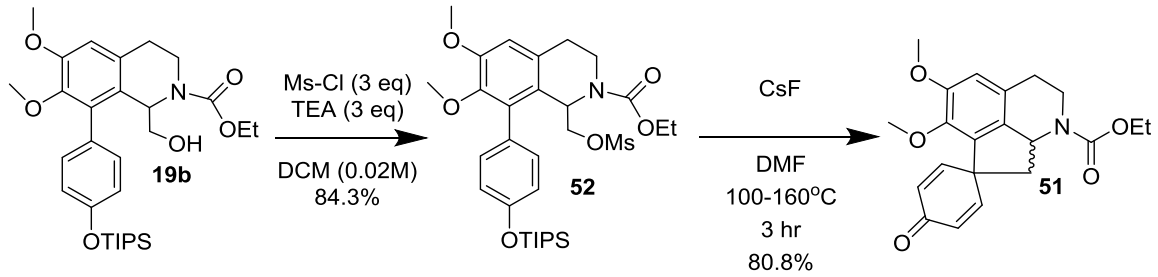
decided to use triflic anhydride to activate the alcohol. This was performed in DCM with pyridine as a proton scavenger. This was worked up and submitted to the standard quaternary center conditions developed by Faber11. However At 130 °C it was shown that the triflate eliminated (**Scheme 3.13**) giving **50**.



Scheme 3.13: Use of triflic anhydride to activate the alcohol was unsuitable.

The phenolic alkylation was then attempted on the triflate at 40 °C. After 12 hours, LCMS showed a trace peak corresponding to the product, but with only ~10% conversion of starting material. When the temperature was warmed to 55 °C, elimination products started to form. The rate of alkylation at 40 °C was too slow so a less reactive leaving group, the mesylate was used. This was obtained from the alcohol in 84% yield. Subjecting **52** to the standard phenolic alkylation conditions it was found CsF in DMF at 80-130 °C for 3 h succeeded in giving the cyclized product **51**, as well as an abundance of de-silylated starting material which was the product of quenched phenolate. Longer reaction times did not significantly increase the yield but gave rise to decomposition products. Trying to speed the reaction up, **52** was subjected to CsF in n-methylpyrrolidinone, which could be heated above 130 °C and

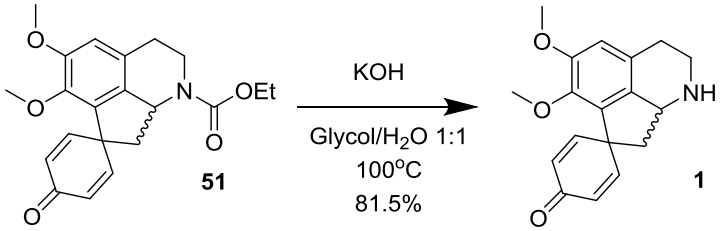
remain stable. The reaction was taken to 150 °C and was complete in 3.5 hours giving the product in 80.8% yield **(Scheme 3.14)**.



Scheme: 3.14: Activation of **19b** using mesyl chloride and then subjecting the product **52** to CsF in NMP gave the phenolic alkylation product **51**.

3.9 DEPROTECTION TO FORM STEPHARINE

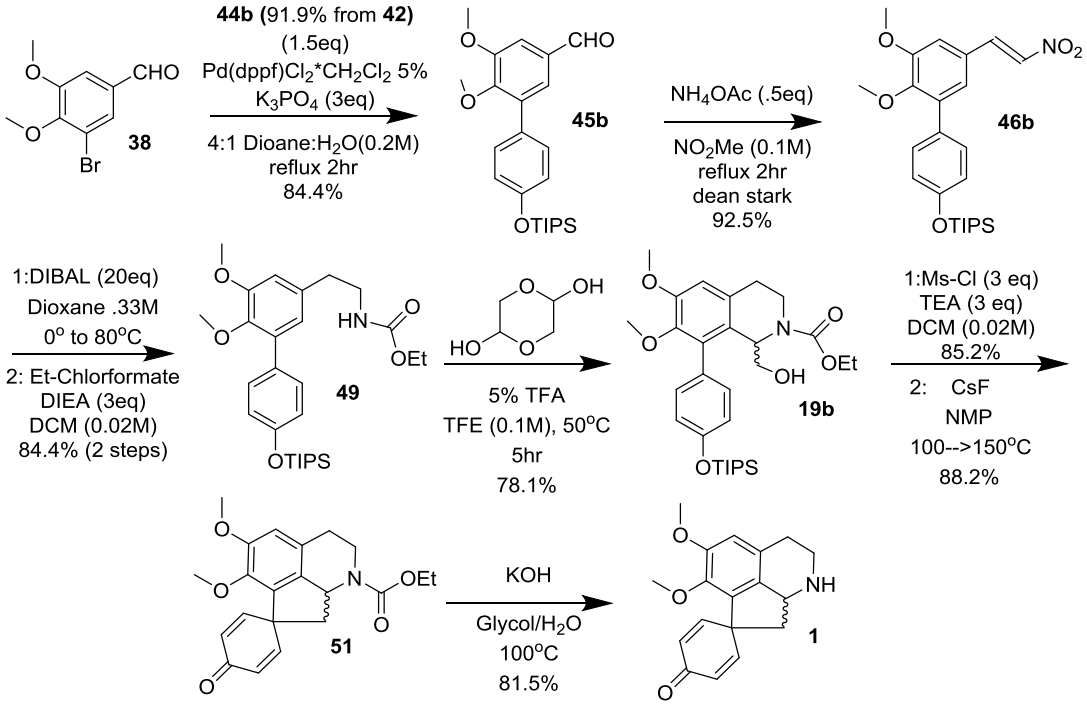
The final step in finishing the synthesis was to remove the protecting group. This was accomplished by heating the carbamate in a mixture of glycol and water with KOH over a period of 12 hours (**Scheme 3.15**). This gave stepharine in 81.5% with an overall yield of 26.4%.



Scheme 3.15: Stepharine was formed via saponification and decarboxylation of **51**.

3.10 A Recap of the Final Synthesis

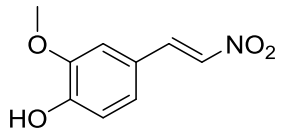
Stepharine was synthesized in an overall yield of 29.0% over 10 steps (**Scheme 3.16**). It is our hope that this work has shown the synthetic utility of the intramolecular phenolic alkylation methodology for the synthesis of alkaloids. Furthermore, this synthesis shows the general utility of this reaction for complex substrates.



Scheme 3.16: The full synthesis of stepharine **1** from **38** with an overall 29.0% yield.

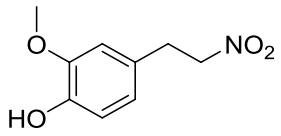
Supporting Information

2-methoxy-4-(2-nitrovinyl)phenol (24)



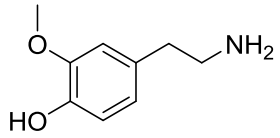
Vanillin (3.04 g, 20 mmol) and ammonium acetate (1.56 g 2.02 mmol) were dissolved into a mixture of nitromethane (20 mL) and acetic acid (30 mL) and warmed to 80°C. The solution was allowed to stir until starting material was gone by TLC (~3 h). Methanol (50 mL) was added to the solution and it was kept 12 h at 4 °C. A crude yellow solid was filtered off and then recrystallized in methanol giving **24** as a yellow crystalline solid (3.36 g 86.1%). ^{1}HNMR (400 MHz $CDCl_3$) δ 8.28 (s, 1H), 7.86 (d, *J*=13.6 Hz, 1H), 7.46 (d, *J*=13.6 Hz, 1H), 7.01 (dd J_1=8.4 Hz, J_2=2 Hz, 1H), 6.87 (d, *J*=2 Hz, 1H), 6.86 (d, *J*= 8.4 Hz, 1H), 3.84 (s, 3H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 150.7, 147.8, 139.7, 134.3, 124.8, 121.6, 115.7, 110.6, 55.8.

2-methoxy-4-(2-nitroethyl)phenol (26)



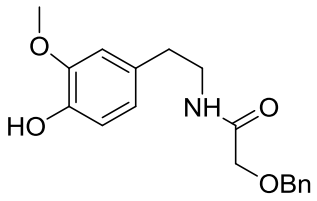
Nitrostyrene **24** (1 g, 5.128 mmol) was dissolved in methanol (150 mL) and cooled to -10 °C with a brine ice bath. Sodium borohydride (1.08 g, 30 mmol) was added portionwise to the solution keeping the internal temperature below -5 °C. The solution was allowed to stir 3 h. The reaction was quenched using saturated ammonium chloride. The methanol was removed under vacuum and the solution was extracted with dichloromethane (3X50 mL). The combined organic extracts were washed with brine (2X50 mL) and dried with sodium sulfate. The solution was concentrated under vacuum and purified by column chromatography giving **26** as pale oil (0.812 g 80.3%). ^{1}HNMR (400 MHz $CDCl_3$) δ 6.78 (d, *J*=8 Hz, 1H), 6,65 (m, 2H), 4.52 (t, *J*=7.2 Hz, 2H), 3.79 (s, 3H), 3.19 (t, *J*=7.2 Hz, 2H).

4-(2-aminoethyl)-2-methoxyphenol (22)



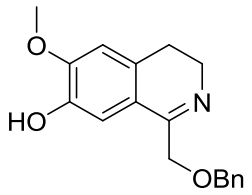
Nitrostyrene **24** (2.77 g, 14.2 mmol) and 10% Pd/C (0.7 g) were dissolved in a mixture of methanol (20 mL) and 6N HCl (20mL). The solution was stirred under an atmosphere of hydrogenation for 6 h, wherein the starting material was gone by TLC. The product was filtered through Celite and poured into saturated bicarbonate solution (30 mL). The amine was extracted with chloroform (3x50 mL) and concentrated. The crude oil was dissolved in methanol and precipitated out at -78 ºC as an amorphous solid (1.87g , 11.2 mmol, 78.9%) which was used without further purification. ^{1}HNMR (400 MHz $CDCl_3$) δ 6.70-6.50 (m, 3H), 3.73 (s, 3H), 3.29 (s, 2H), 2.80 (t, *J*=6.8 Hz, 2H), 2.56 (t, *J*=6.8 Hz, 2H).

2-(benzyloxy)-N-(4-hydroxy-3-methoxyphenethyl)acetamide (30)



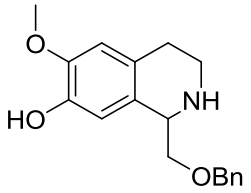
In dichloromethane (90 mL) isobutyl chloroformate (0.654 g, 4.8 mmol), triethylamine (0.483 g, 4.8 mmol) and acid **36** were stirred at -5 °C for an hour. At this time **36** was gone by TLC. Amine **22** (0.720 g, 4.3 mmol) was added to the solution and allowed to stir 4 h at -6 °C. The reaction mixture was then concentrated under vacuum and the crude oil was purified by silica gel chromatography yielding amide **30** (0.932 g, 68.6%).[1]HNMR (400 MHz $CDCl_3$) δ 7.38-7.22 (m, 5H), 6.84 (d, *J*=7.6 Hz, 1H), 6.67 (m, 3H), 5.56(s, 1H), 4.50 (s, 1H), 3.97 (s, 2H), 3.83 (s, 3H), 3.52 (m, 2H), 2.76 (t, *J*= 6.8 Hz).

1-((benzyloxy)methyl)-6-methoxy-3,4-dihydroisoquinolin-7-ol (31)



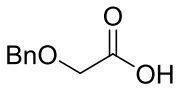
In acetonitrile (1 mL) at 0 ºC was added amide **30** (50 mg, 0.159mmol). To this suspension was added phosphorus oxychloride (0.5 ml 5.30 mmol) dropwise. The flask was then warmed to 50 ºC and allowed to stir for ~3 h until starting material was gone by TLC. The reaction mixture was concentrated and then diluted with dichloromethane and washed with a saturated solution of sodium bicarbonate and a saturated solution of brine. The organic layer was then dried with sodium sulfate and concentrated to a crude oil. This was chromatographed using silica gel giving **31** (24 mg, 50.8%). ^{1}HNMR (400 MHz $CDCl_3$) δ 7.25-7.14 (m, 6H), 6.57 (s, 1H), 4.52 (s, 2H), 4.42 (s, 2H), 3.84 (s, 3H), 3.63(t, *J*=7.6 Hz, 2H), 2.56 (t, *J*=7.6 Hz, 2H). ^{13}CNMR (400M Hz, $CDCl_3$) δ 164.4, 148.9, 144.3, 137.7, 130.5, 128.4, 128.0, 127.7, 120.8, 112.6, 109.7, 72.9, 72.4, 56.0, 46.7, 25.5.

1-((benzyloxy)methyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-ol (21)



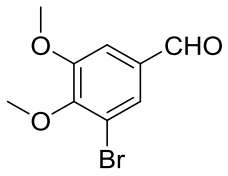
In dichloromethane (10ml) imine **31** (50 mg, 0.168 mmol) was added along with glacial acidic acid (0.05ml 0.83mmol). Triacetoxyborohydride (53 mg, 0.253 mmol) was added to the solution and allowed to stir at room temperature for 1 h. The reaction mixture was concentrated under vacuum and purified by preparative thin layer chromatography giving amine **21** (35 mg, 64.7%). ^{1}HNMR (400 MHz $CDCl_3$) δ 7.35 (m, 5H), 6.60 (s, 1H), 6.65(s, 1H), 4.60-4.53 (m, 2H), 4.01 (m 1H), 3.70 (s, 3H), 3.71-3.58 (m, 2H), 3.15 (m, 1H), 2.95 (m, 1H), 2,73 (m, 2H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 145.5, 143.8, 138.1, 128.4, 127.8, 127.7, 127.3, 126.9, 112.2, 111.2, 73.3, 72.7, 55.8, 54.8, 40.0, 29.1.

2-(benzyloxy)acetic acid (36)



To a solution of benzyl alcohol (20.0 mL, 185 mmol) in toluene (250 mL) at 0 °C sodium hydride (8.0 g, 200 mmol) was added portionwise with vigorous stirring. The mixture was warmed to room temperature and stirred until a homogenous solution was obtained. Ethyl bromoacetate was then added dropwise using an addition funnel over the course of 0.5 hr. The solution was then heated to reflux 3 hours. A mixture of methanol (50 mL), water (50 mL), and potassium hydroxide (20.0 g) were added to the solution and heated at reflux 12 h. The reaction mixture was then concentrated, dissolved in water and extracted with ethyl acetate which was then discarded. The aqueous media was then acidified with 6N hydrochloric acid and extracted with ethyl acetate (3X150 mL). The second set of organic extracts were washed with brine, dried with sodium subphase and concentrated. The crude old was then purified using short path distillation giving **36** as a clear oil. ^{1}HNMR (400 MHz $CDCl_3$) δ 7.38-7.35 (m, 5H), 4.65 (s, 2H), 4.15 (s, 2H).

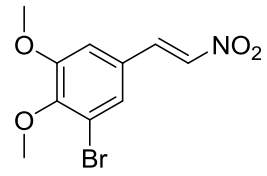
3-bromo-4,5-dimethoxybenzaldehyde (38)



Vanillin (6.08 g, 40 mmol) was stirred into acetic acid (60 mL). Bromine (6.4 g, 40 mmol) was then added dropwise. The reaction was allowed to stir for 3.5 h wherein the starting material was gone by TLC. The solution was poured into ice to precipice out the intermediate This was filtered and washed with cold water and dried.

The intermediate (9.1 g) was dissolved into dimethylformamide (200 mL) with potassium carbonate (14 g, 101 mmol). Iodomethane (0.4 mL, 64.3 mmol) was added dropwise and the reaction mixture was stirred 16 h. The reaction mixture was concentrated, poured into brine (200 mL), and extracted with methyl-tert butyl ether (4X50 mL). The combined organic extracts were dried with sodium sulfate and concentrated. The resulting solid was recrystallized from hexanes giving **38** (8.576 g, 87.5%). ^{1}HNMR (400 MHz $CDCl_3$) δ 9.78 (s, 1H), 7.58 (s, 1H), 7.32 (s, 1H), 3.88 (s, 6H).

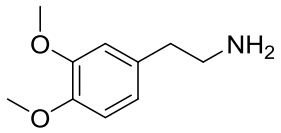
1-bromo-2,3-dimethoxy-5-(2-nitrovinyl)benzene (39)



38 (6.125 g, 25 mmol) and nitromethane (1.65 g, 25 mmol) were dissolved in [FA][EA] (25ml) and allowed to stir 2 h. The reaction was poured into ice, and the product filtered off. The crude product was crystallized from methanol giving **39** (5.81 g, 80.7%)

^{1}HNMR (400 MHz $CDCl_3$) δ 6.78 (m, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.98 (t, *J*=9.2 Hz, 2H), 2.68 (t, *J*=9.8 Hz, 2H), 2.07 (s, 2H).

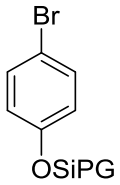
2-(3,4-dimethoxyphenyl)ethan-1-amine (41)



^{1}HNMR (400 MHz $CDCl_3$) δ 6.78 (m, 3H), 3.84 (s, 3H), 3.80 (s, 3H), 2.98 (t, *J*=9.2 Hz, 2H), 2.68 (t, *J*=9.8 Hz, 2H), 2.07 (s, 2H).

(4-bromophenoxy)(tert-butyl)dimethylsilane (43a)

(4-bromophenoxy)triisopropylsilane (43b)

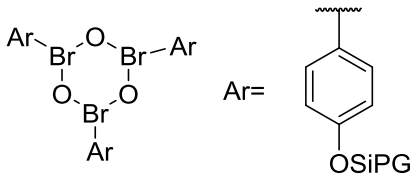


Typical Procedure:

4-Bromophenol (20 g, 115.6 mmol), TIPS-Cl (24.5 g, 127 mmol) and imidazole (19.7 g, 289 mmol) was added to dichloroethane (200 mL). The solution was heated to reflux for 3 hours. The reaction mixture was poured into saturated ammonium chloride and extracted with dichloromethane (3X100 mL). The combined extracts were washed with brine, dried with sodium sulfate and concentrated. The crude oil was purified by silica gel cromatography giving **43b** (38.03 g, 99.8%) as a clear oil. **43a** (400M Hz $CDCl_3$) δ 7.32 (d, *J*=9.2 Hz, 2H), 6.71 (d, *J*=9.2Hz, 2H), .97 (s, 9H), 0.18 (s, 6H) ^{13}CNMR (400 MHz, $CDCl_3$) δ 132.3, 121.9, 25.6, 18.2, -.45.

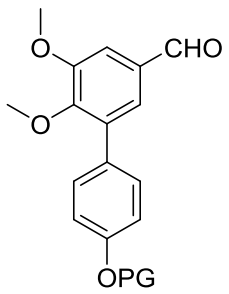
43b. (400 MHz $CDCl_3$) 7.31 (d, *J*=8.8 Hz, 2H), 6.77 (d, *J*=8.8 Hz, 2H), 1.27-1.21 (m, 3H), 1.08 (s, 18H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 125.2, 114.7, 10.9, 5.6.

Boronic Ester Trimer (44)



Butyl lithium (46 mL, 2.5M) was added dropwise to a stirred solution of **43b** (14.5g, 44 mmol) in THF (40 mL) at -78°C under argon. This was allowed to stir for 0.5 hours at which point triisopropyl borane (52.8 mL 229 mmol) was added to the solution dropwise at -78°C. This was allowed to stir and warm to room temperature overnight. The reaction mixture was quenched by pouring it into 10% aqueous potassium hydrogen sulfate (60 mL) This was extracted with ethyl acetate (3X150 mL). The combined organic extracts were washed with brine, dried with sodium sulfate and concentrated. The crude solid was purified by column chromatography giving **44b** (11.2 g, 92.1%) as a pale oil that crystallized upon standing. ^{1}HNMR (400 MHz $CDCl_3$) δ 8.11 (d, 8.4 Hz, 6H), 16.99 (d, 8.8 Hz, 6H), 1.33-1.10 (m, 63H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 160.1, 137.4, 119.6, 17.9, 12.7. IR thin film: 2944, 2867, 1597, 1374, 1239. HRMS calc for $C_{45}H_{75}B_3O_6Si_3$ (M^+) 828.5151, found 828.5166.

4'-((tert-butyldimethylsilyl)oxy)-5,6-dimethoxy-[1,1'-biphenyl]-3-carbaldehyde (45a)
and
5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-carbaldehyde (45b)



a. PG = TBS
b. PG = TIPS

Typical procedure for Suzuki Reaction:

A solution of dioxane (40 mL) and water (10 mL) was degassed for 1 h. Aldehyde **38** (2.45 g, 10 mmol), boronic ester **44a** (2.81g, 4 mmol), tri-basic potassium phosphate (8.0 g 30 mmol), and Pd(dppf)Cl_2*DCM (0.4 g, 0.49 mmol) were added to the solution. This was stirred for two hours at 80 °C under argon wherein starting material was gone by TLC. The solution was quenched with saturated ammonium chloride (100 mL) and extracted with ethyl acetate. The organic extracts were washed with brine, dried with sodium sulfate and concentrated. The crude oil was purified by column chromatography giving **45a** (3.575 g, 96.1%) as a clear oil. ^{1}HNMR (400 MHz $CDCl_3$) δ 9.92 (s, 1H), 7.44 (m, 4H), 6.91 (d, *J*=8.8 Hz, 2H), 3.96 (s, 3H), 3.66 (s, 3H), 1.00 (s, 9H), 0.24 (s, 6H).

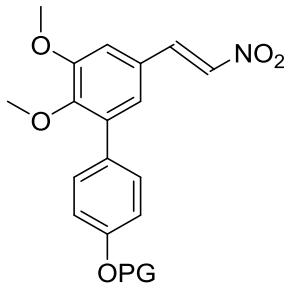
^{13}CNMR (400 MHz, $CDCl_3$) δ 191.1, 155.4, 153.8, 151.9, 135.8, 132.3, 130.2, 129.9, 127.4, 119.9, 109.0, 60.6, 56.1, 25.7, 18.2, -4.4.

45b. ^{1}HNMR (400 MHz $CDCl_3$) 9.92 (s, 1H), 7.47-7.26 (m, 4H), 6.94 (d, *J*=2 Hz, 2H), 3.96 (s, 3H), 3.49 (s, 3H), 1.18-.926 (m, 21H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 191.3, 155.8, 153.7, 151.9, 135.8, 132.3, 130.2, 129.65, 127.3, 115.9, 119.7, 108.9, 60.5, 56.0, 17.9, 12.6. IR thin film: 2944, 2867, 1699, 1606, 15.12. HRMS calculated for $C_{24}H_{34}NaO_4Si$ (MH^+) 473.2119, found 437.2119.

(E)-tert-butyl((2',3'-dimethoxy-5'-(2-nitrovinyl)-[1,1'-biphenyl]-4-yl)oxy)dimethylsilane (46a)

and

(E)-((2',3'-dimethoxy-5'-(2-nitrovinyl)-[1,1'-biphenyl]-4-yl)oxy)triisopropylsilane (46b)



Typical procedure for Henry Reaction.

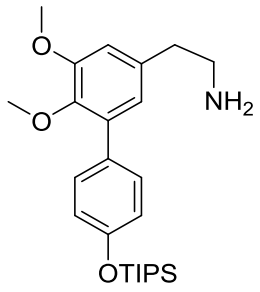
Biaryl aldehyde **45b** (4.4 g, 1.1 mmol) and ammonium acetate (0.2 g, 2.59 mmol) were added to nitromethane (35 mL) and heated to reflux. Water formed in the reaction was collected using a dean stark trap. After 3 h, TLC indicated the disappearance of starting material. The crude mixture was poured into brine (100 mL) and extracted with ethyl acetate (3X60 mL). The combined organic extracts were washed with brine, dried with sodium sulfate and concentrated. The crude oil was purified by column chromatography giving **46b** as a yellow oil that solidified upon sitting for 60 h into a crystalline yellow solid**.**

46a (400 MHz $CDCl_3$) δ 7.98(d, *J*=13.2, 1H), 7.55, (d, *J*=13.2 Hz, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 7.16 (d, *J*=2 Hz, 1H), 7.01 (d, *J*=1 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 2H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 155.5, 153.6m 150.1, 139.1, 136.4, 136.3, 130.2,

129.7, 125.6, 124.9, 119.9, 110.5, 60.7, 56.1, 25.6, 18.2, -4.4. HRMS calculated 438.1701 $C_{22}H_{29}NNaO_5Si$ (MH^+), found 438.1701.

45b. ^{1}HNMR (400 MHz $CDCl_3$) δ 7.98 (d, *J*=13.6 Hz, 1H), 7.56, (d, *J*=16.6 Hz, 1H), 7.39 (d, *J*=8.8 Hz), 7.17 (d, *J*=2 Hz, 1H), 7.01 (d, *J*=2 Hz, 1H), 6.95 (d, *J*=8.8 Hz, 2H), 3.94 (s, 3H), 3.62 (s, 3H), 1.34-1.08 (m, 21H) ^{13}CNMR (400 MHz, $CDCl_3$) δ 155.9, 153.6, 150.1, 149.7, 149.6, 139.1, 136.4, 136.2, 130.1, 129.4, 125.6, 124.9, 120.5, 119.8, 115.8, 110.5, 60.5, 56.1, 17.8, 12.6. IR thin film: 2944, 2867, 1511, 1335, 1263. HRMS calc 480.2178 $C_{25}H_{35}NNaO_5Si$(MH^+), found 480.2176. Melting point: 69-70ºC.

2-(5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-yl)ethan-1-amine (47a)

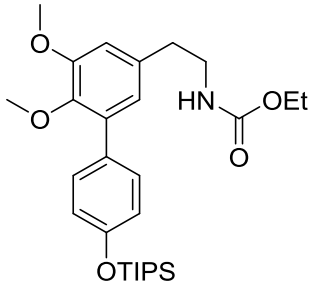


Diisobutylaluminum hydride (DIBAL) as a 1M solution in hexanes (40 mL, 40 mmol) was added to a flame dried flask under argon and cooled to 0 ºC. Dry dioxane (20 mL) was added dropwise with stirring over a period of 10 min. Nitrostyrene **46b** (0.886 g, 0.194 mmol) was dissolved in dry dioxane (20 mL) and then added to the DIBAL solution dropwise over 10 minutes. The reaction was warmed to room temperature and allowed to stir 3 h. The solution was cooled to 0 ºC, diluted with ether (100 mL) and water (0.8 mL), 15% NaOH (0.8 mL) and then water (2 mL) were added to the solution dropwise. The quenched reaction was allowed to warm to room temperature and stir an additional 30 min. The slurry was then filtered through a pad of Celite to remove aluminium precipitate. The solution was dried with sodium sulfate, concentrated, and then azeotroped with toluene to give a pale oil which was used without further purification.

^{1}HNMR (400 MHz $CDCl_3$) δ 7.41 (d, *J*=8.4 Hz, 2H), 6.90 (d, *J*=8.4 Hz, 2H), 6.74 (d, *J*=20 Hz, 2H), 3.87 (s, 3H), 3,50 (s, 3H), 3.03 (t, *J*=7.2 Hz, 2H), 2.79 (t, *J*=7.2 Hz, 2H) 1.30- 1.10 (m, 21H). ^{13}CNMR (400 MHz, $CDCl_3$) 155.3, 153.0, 144.9,

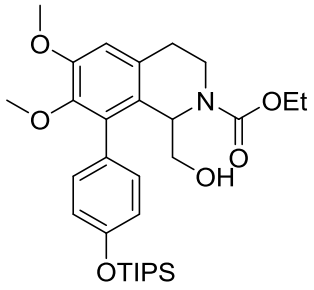
135.4, 134.6, 130.7, 130.1, 122.5, 119.5, 111.5, 60.2, 55.9, 42.8, 38.3, 17.9, 12.6.. IR thin film: 3362, 2945, 2867, 1607, 1513, 1263. HRMS calc for $C_{25}H_{40}NO_3Si$ (MH^+) 430.2772 found 430.2781.

ethyl (2-(5,6-dimethoxy-4'-((triisopropylsilyl)oxy)-[1,1'-biphenyl]-3-yl)ethyl)carbamate (49)



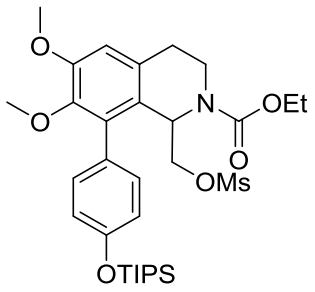
Crude amine (theoretical 1.94mmol) and diisopropylethylamine (0.877 g, 6.79 mmol) were dissolved in dichloromethane (100 mL) in a flame dried flask and cooled to 0 °C. Ethyl chloroformate (0.629 g, 5.82 mmol) was added dropwise with stirring. The solution was allowed to warm to room temperature and stir 3 h. The reaction mixture was diluted with ether and washed with a saturated solution of bicarbonate, then brine. The organic extracts were dried with sodium sulfate and concentrated under vacuum. The crude oil was purified using silica gel chromatography to give the product (0.823 g, 1.64 mmol, 84.5% over two steps) as a clear oil. ^{1}HNMR (400 MHz $CDCl_3$) δ 7.41 (d, *J*=8.4 Hz, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 6.76 (d, *J*=2 Hz, 1H), 6.70 (s, 1H), 4.73 (s, br, 1H), 4.11 (dd, J_1=14 Hz, J_2=7.2 Hz, 2H), 3.88 (s, 3H), 3.45 (dd, J_1=13 Hz, J_2=6.4 Hz, 2H), 2.79 (t, *J*=14 Hz, 2H), 1.33-1.10 (m, 24H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 156.6, 155.4, 153.0, 145.0, 135.5, 134.5, 130.7, 130.2, 122.5, 119.6, 111.4, 60.7, 60.3, 55.9, 40.1, 63.0, 17.8, 14.6, 12.6. IR thin film: 3345, 2944, 2867, 1700, 1512. HRMS calc for $C_{28}H_{43}NO_5Si$ (MH^+) 502.2983, found 502.2975.

ethyl 1-(hydroxymethyl)-6,7-dimethoxy-8-(4-((triisopropylsilyl)oxy)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (19b)



Carbamate **47b** (0.10 g, 0.199 mmol) and glycolaldehyde dimer (0.018g, 0.15 mmol) were dissolved in trifluoroethanol (0.5 mL). To the solution was added trifluoroacetic acid (2 drops). The solution was heated to 55°C and allowed to stir. After 5 hours the starting material was gone by LCMS. The crude mixture was concentrated under vacuum and purified by silica gel chromatography giving **47** (83 mg, 78.1%). ^{1}HNMR (400 MHz $CDCl_3$) δ 7.13 (t, *J*=7.2 Hz, 2H), 6.97 (d, *J*=7.6 Hz, 2H), 6.70 (s, 1H), 5.21 (m, 1H), 4.15 (m, 2H), 3.86 (s, 3H), 3.76-3.34 (m, 6H), 2.88 (d, *J*=7.4 Hz, 2H), 1.33-1.11(m, 24H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 155.4, 151.8, 131.7, 131.1, 129.9, 124.7, 120.1, 119.7, 119.8, 118.8, 111.5, 71.1, 65.5, 61.5, 60.4, 55.8, 54.4, 39.7, 28.6, 28.1, 17.9, 14.6, 12.6. IR thin film: 3447, 2943, 2867, 1684, 1512. HRMS calc for $C_{30}H_{45}NO_6Si$ (MNa^+) 566.2908, found 566.2911.

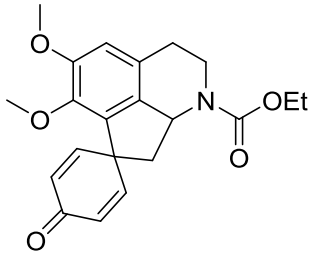
ethyl 6,7-dimethoxy-1-(((methylsulfonyl)oxy)methyl)-8-(4-((triisopropylsilyl)oxy)phenyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (52)



Alcohol **19b** (0.205 g, 0.409 mmol) and dry triethylamine (0.041 g, 0.405 mmol) were added to a flame dried flask charged with dichloromethane (50ml) and the mixture was cooled to 0 ºC. Freshly distilled methanesulfenylchloride (0.065 g, 0.607 mmol) was added to the solution dropwise. The reaction was allowed to stir at 0 ºC for 3 h wherein the staring material was consumed as shown by LCMS. The crude mixture was poured into a saturated solution of bicarbonate and entranced with ether. The organic extract was washed with saturated ammonium chloride then brine, dried with sodium sulfane and then concentrated. The crude material was purified by chromatography on neutral alumina giving the product **52** (0.214 g, 85.2%) as a clear oil. ^{1}HNMR (400 MHz $CDCl_3$) δ 7.20-6.96 (m, 4H), 6.70 (d, *J*=0.8 Hz, 1H), 5.56-5.40 (m, 1H), 4.17-4.02 (m, 4H), 3.90-3.87 (m, 4H), 3.41 (m, 4H), 2.87 (m, 2H), 2.64 (d, *J*=12.8 Hz, 3H) 1.31-1.11 (m, 24H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 155.7, 133.2, 131.9, 131.8, 131.5, 129.9, 127.6, 122.6, 120.3, 120.1, 120.0, 111.8, 105.0, 77.2, 69.0, 61.6, 60.4, 55.8, 50.9, 38.2, 37.1, 28.2, 17.9, 14.6,

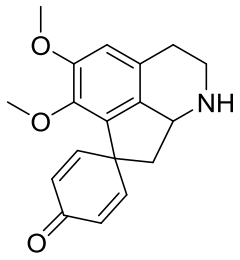
12.6. IR thin film: 2934, 2867, 1701, 1511, 1176. HRMS calc for $C_{31}H_{47}NO_8SiS$ (M^+) 621.2792, found 621.2783.

ethyl 5',6'-dimethoxy-4-oxo-2',3',8',8a'-tetrahydro-1'H-spiro[cyclohexane-1,7'-cyclopenta[ij]isoquinoline]-2,5-diene-1'-carboxylate (51)



Mesylate **52b** (50 mg 0.0860 mmol) was dissolved in dry n-methylpyrrolidone (1.5 mL) and warmed to 100 ºC. Excess cesium fluoride was flamed dried under vacuum and added to the solution. The reaction mixture was heated to 150 ºC and allowed to stir for 3.5 h wherein the staring material had disappeared by LCMS. The solution was allowed to cool to room temperature and was poured into brine, extracted with ether, and dried with sodium sulfate. This was concentrated under vacuum and purified on basic alumina giving the cyclized product **51** (28 mg, 0.0759 mmol, 88.2%) ^{1}HNMR (400 MHz $CDCl_3$) δ 7.02 (dd, J_1=10 Hz, J_2=2.8 Hz, 1H), 6.85 (dd, J_1=9.8 Hz, J_2=2.8 Hz, 1H), 6.71 (s, 1H), 6.41 (dd, J_1=9.8 Hz, J_2=1.6 Hz, 1H), 6.32 (dd, J_1=9.6 Hz, J_2=2.8 Hz, 1H), 4.98 (m, 1H) 4.24-4.16 (m, 3H), 3.84 (s, 3H), 6.63 (s, 3H), 2.93-2.64 (m, 4H), 2.33 (dd, J_1=12.4 Hz, J_2=10.4 Hz, 1H), 1.30 (t, J=13.2 Hz, 3H). ^{13}CNMR (400 MHz, $CDCl_3$) δ 186.0, 156.3, 152.8, 149.5, 144.8, 132.9, 132.1, 130.9, 125.3, 127.7, 115.5, 61.5, 60.9, 56.3, 55.0, 50.8, 49.7, 42.5, 28.7, 14.7. IR thin film: 2948, 2932, 1694, 1664, 1282. HRMS calc for $C_{21}H_{23}NO_5$ (MH^+) 370.1649, found 370.1647.

5',6'-dimethoxy-2',3',8',8a'-tetrahydro-1'H-spiro[cyclohexane-1,7'-cyclopenta[ij]isoquinoline]-2,5-dien-4-one (stepharine) (1)



Cyclized product (5 mg, 0.0136 mmol) and potassium hydroxide (100 mg, 1.78 mmol) were dissolved in a mixture of water (1.5ml) and ethylene glycol (1.5ml) and heated to 100 °C. The solution was allowed to stir 12 h. The crude reaction mixture was diluted with chloroform and extracted with water and then brine. The organic extract was dried with sodium sulfated and concentrated under vacuum. The product was purified using preparative TLC giving stepharine **1** (3.3 mg, 0.0111 mmol, 82.3%)**.** Spectra matching literature values. ^{1}HNMR (400 MHz $CDCl_3$) δ 7.02 (d, *J*=10.4 Hz, 1H), 6.89 (d, J= 9.6 Hz, 1H), 6.64 (s, 1H), 6.41 (d, J=10.8 Hz, 1H), 4.33 (m, 1H), 3.88-3.71 (m, 3H), 3.60 (s, 3H), 3.51 (m, 1H), 3.21-3.08 (m, 1H), 2.85-2.74 (m, 1H), 2.45-2.39 (m, 1H), 2.27-2.23 (m, 1H). IR thin film: 3584, 2923, 1662, 1490, 1261. HRMS calc for $C_{18}H_{19}NO_3$ (MH^+) 298.1438, found 298.1434.

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