Synthesis of Horsfiline and Coerulescine

A MSc Dissertation report by

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Introduction

An alkaloid is a class or naturally occurring organic nitrogen-containing compounds that are frequently found in plant kingdom.[1] A huge number of alkaloids have been isolated from plants, bacteria, and animals.[2] In addition, they have several attractive properties, such as potent bioactivity for development of drugs, and unique architecture for total synthesis.[1] Indole and indoline alkaloids exist widely in nature and these alkaloids are mainly derived from tryptophan, which is one of the essential amino acids in biosynthesis as a secondary metabolite. Several important bioactivities of these alkaloids have been reported and a number of important naturally occurring indole and indoline alkaloids, such as Vinblastine, Vincristine, Reserpine, and Physostigmine are employed in medicines for human health.[1] Indole alkaloid act on central and peripheral nervous system.[1]

Pyrrolizines have been found to be promising scaffolds for anticancer drugs.[3] Some alkaloids are used to treat diseases including malaria, diabetics, cancer, cardiac dysfunction etc.[1] Large numbers of oxindole alkaloids have been isolated from nature and several biological activities have been reported.[4] Oxindole alkaloids are monoterpene group of alkaloids that exhibits an oxindole moiety(N-C=O) in the ring B of its structure.[1] Usually, in biosynthesis oxindoles are synthesized by an oxidation reaction of indole alkaloids. Therefore, oxindole alkaloids are also classified as indole alkaloids. Horsfiline and Coerulescine are spiropyrrolidinyl-oxindole skeleton alkaloids, which are also known as spirooxindoles alkaloids.[5] In spiro compounds each ring contributing to its structure is unique or identical, spiro-ring fusion provides a useful method of increasing molecular complexity and may offer greater benefit than the introduction of flat rings.[6]

Several synthetic approaches are available in the literature for the synthesis of both racemic and enantiomeric Horsfiline and Coerulescine.[7] Spirooxindoles are important class of compounds and have been extensively studied in the fields of synthetic and pharmaceutical chemistry.[8] A number of oxindole have a chiral quarternary carbon centre at the 3-position of the oxindole moiety.[9] The unique three-dimensional spiro system may be the main cause for the bioactivities of spirooxindoles.[10] They have been considered to exhibit antitumor, antimicrobial, antioxidant, anti-inflammatory, antiviral and other bioactivities. [11]

Some representative examples of bioactive spirooxindoles are Horsfiline, Coerulescine, Rhynchophylline and Spirrotrryprostatin A. Elacomine and Rhynchophylline have more complex structures than Horsfiline and Coerulescine. Horsfiline is an intoxicating snuff, Rhynchophylline is potent towards various cancer cell lines, Spirotryprostatin A prevents G2M progression in mammalian tsFT210 cells.[11] Due to the pharmaceutical potencies of spirooxindole derivatives, chemists have been inspired to establish various synthetic routes for this class of compounds.[11]

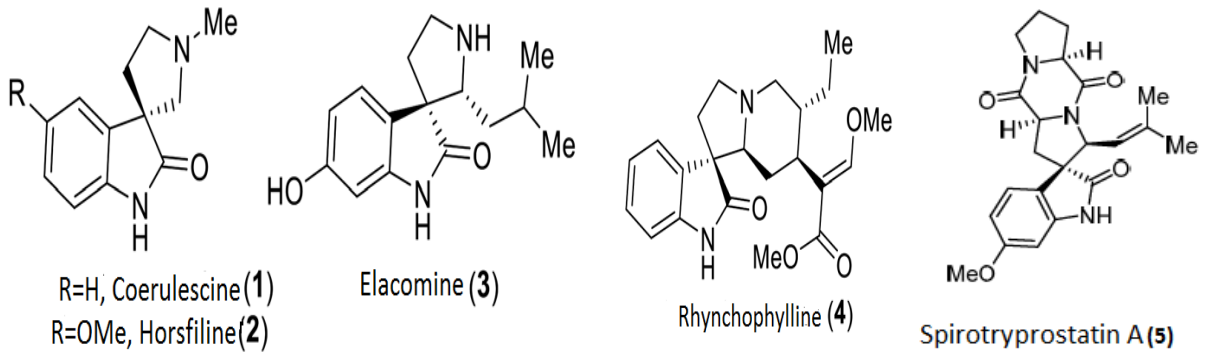
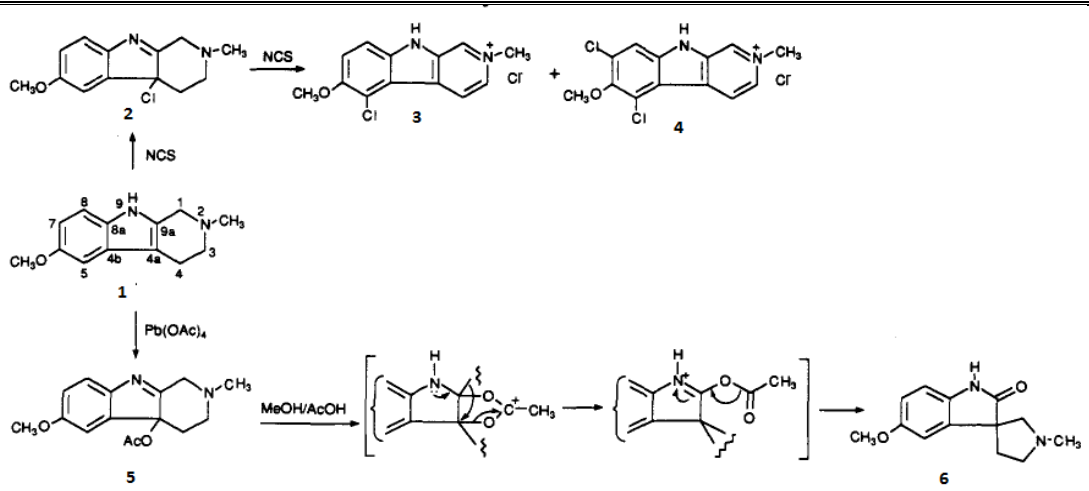


Figure 1: Examples of Spiroxindoles (1–5).

Literature Review

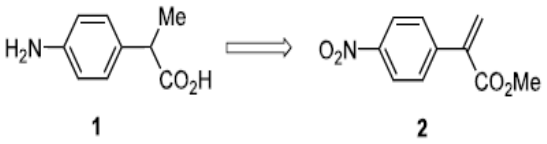
While going through lot of journals I got to know that there are various synthetic routes which have been established for the synthesis of Horsfiline and Coerulescine derivatives. Horsfiline was the first alkaloid isolated in 1991, among other known alkaloids, from a Malaysian medicinal tree Horsfieldia Superba Warb belonging to the Horsfieldia genus by Bodo and co-workers.[12] In 1998, Colegate and co-workers isolated a related oxindole alkaloid Coerulescine from the blue canary grass, Phalaris Coerulescens.[2] Horsfiline had attracted wide attention from synthetic chemists and many methodologies were applied to its synthesis.[13]



Scheme 1: Synthesis of Horsfiline by Bodo

Extraction of alkaloids was carried out in the usual way and the three main constituents of the alkaloid fraction were separated by column chromatography and further purified by TLC or crystallization.[12] 6-methoxy-2-methyl-1,2,3,4-tetrahydro-beta-carboline (**1)** was identified on the basis of their spectral data. Oxidation of **1** with N-chlorosuccinimide gave chlorinated and dehydrogenated derivatives **3** and **4** and was confirmed by NMR and mass spectrum. The reaction of tetrahydro-beta-carboline **1** with lead tetraacetate, furnished 4a-acetoxyindolenine **5** which was isolated by silica gel chromatography. Then 4a-acetoxyindolenine **5** was further converted into the oxindole Horsfiline **6** by an acid-catalyzed rearrangement (Scheme **1**) and was obtained as a racemic mixture, mp 156-157 °C and identified by NMR and mass spectral data.[12,13]

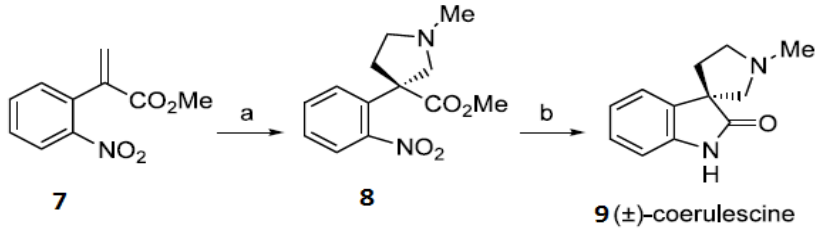
Scheme **2**, **3** and **4** shows the shorter routes for the synthesis of Horsfiline and Coerulescine.[14,11] Scheme **2** shows the short and direct synthesis of 2-arylpropenoic acid esters that possess nitro groups in their phenyl ring using common and less expensive reagents was done by N. Selvakumar along with 4 others.[14] 2-Arylpropenoic acids signify a medicinally important class of non-steroidal anti-inflammatory agents. 2-Arylpropenoic acids possessing nitro groups in their aromatic rings such as **2** (figure **1**) are potential starting materials for the preparation of several analgesic and anti-inflammatory 2-(4-aminophenyl)propionic acid derivatives.[14]



1 2

Figure 1

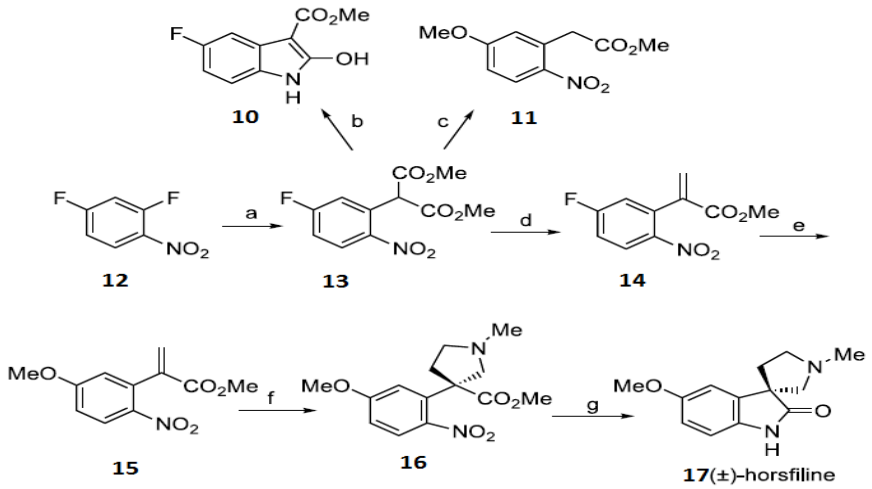
The synthesis was started from commercially available aromatic nitro compounds having leaving groups in either the *ortho* or *para* position with respect to the nitro group.[14] The 2-arylpropenoic acid ester **7** obtained in two steps was converted to (±)-Coerulescine **9** in two steps using the route which was reported by Palmisano and co-workers.[15,16] The pyrrolidine nitro ester **8** which was generated by 1,3-dipolar cycloaddition of nitro ester **7** and N-methyl-azomethine ylide was formed in good yields. (±)-Coerulescine **9** was obtained in two steps by hydrogenation of the compound resulted in cyclization leading to. Thus, the synthesis of (±)Coerulescine was achieved from commercially available material with an overall yield of 45%.[14]



7 8 9 (±)-coerulescine

Scheme 2:. Reagents and conditions: (a) Sarcosine, $(CH_2O)n$, 3 A_ molecular sieves, toluene, reflux 86%; (b) H_2, 10% Pd/C, MeOH, 84%.

The synthesis of (±)-Horsfiline **17** includes the synthesis of nitro-ester **7** possessing a methoxy group in the aromatic ring starting from the synthesis of 2,4-difluoronitrobenzene (Scheme **3**).[14] The treatment of dimethyl malonate with 2,4-difluoronitrobenzene and NaH was carried out and one isomer **13** was obtained in good yield. Treatment of **14** with NaOMe in methanol cleanly gave the desired methoxy nitro-acrylate **15** in 76% yield. The synthesis of (±)-Horsfiline was achieved in five steps from a commercially available substance with an overall yield of 24%. The spectral data of synthetic (±)-Coerulescine **9** and (±)-Horsfiline **9** were comparable in all respects with those of literature values.[14]



Scheme 3: *Reagents and conditions*: (a) NaH, dimethyl malonate, THF, rt, 73%; (b) H_2, 10% Pd/C, MeOH, 62%; (c) NaH, MeOH, rt then 60°C, 51%; (d) K_2CO_3, formalin, 60°C, 80%; (e) NaH, MeOH, rt, 76%; (f) Sarcosine, $(CH_2O)n$, 3 A_ molecular sieves, toluene, reflux 66%; (g) H_2, 10% Pd/C, MeOH, 83%.

In 2021, Manda Sathish along with 4 others published a synthesis on Trichloroisocyanuric acid (TCCA), a reagent with three reactive centers, which was employed in the synthesis of spirooxindoles through the oxidative rearrangement of various N-protected tetrahydro-beta-carbolines.[11] Low equivalents of TCCA were required to access spirooxindoles (up to 99% yield). Several approaches have been proposed in the literature to build spirooxindoles, which mainly involve two ways: (i) multistep synthesis and (ii) oxidative rearrangement. However, oxidative rearrangement reaction is more beneficial than multistep synthesis, because it only involves a single step, avoids the use of various toxic reagents, and ultimately time saving. The use of mild organic oxidants such as oxone, N-bromosuccinimide(NBS), t-BuOCl and transition metal oxidants such as $Pb(OAc)_4$, CrO_3 and OsO_4 are more likely to produce highly toxic by-products.

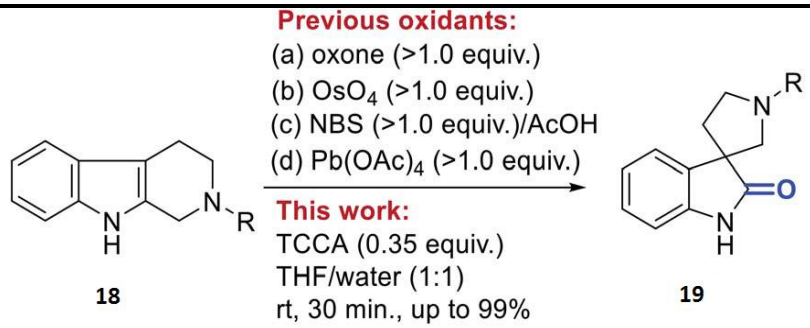
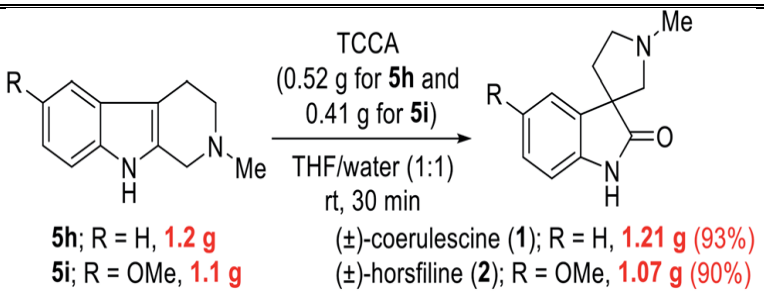


Figure 2:

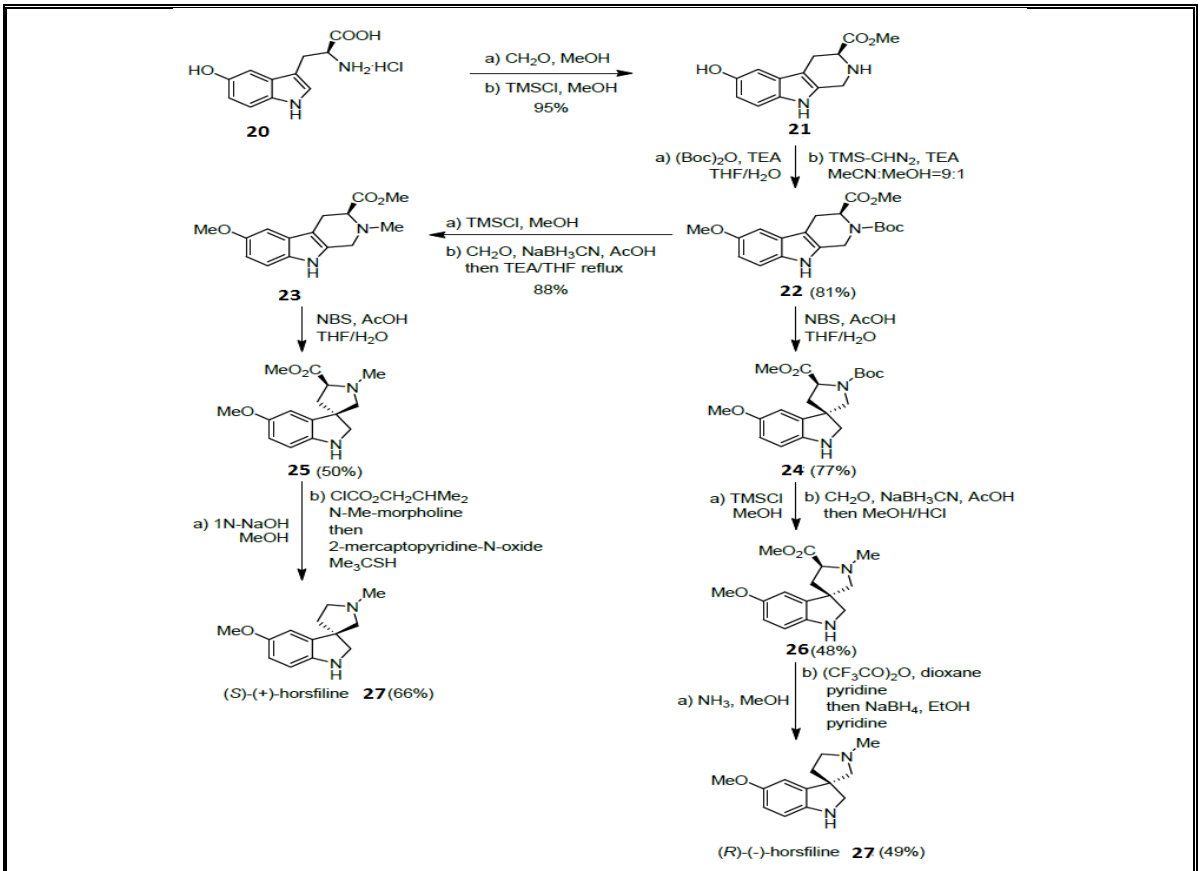
TCCA requires less equivalents(0.33-0.5g), inexpensive and produces essentially the non-toxic cyanuric acid as a by-product, which can be easily separated from the reaction mixture.[11] The gram-scale total synthesis of two bioactive spirooxindole natural products, (±)-Coerulescine (**1**) and (±)-Horsfiline (**2**) as shown in Scheme **3**. The gram-scale reaction of bioactive natural products is highly desirable from a commercial perspective. Specifically, 5h (1.2 g) and 5i (1.1 g) were reacted with TCCA to produce(±)-Coerulescine (**1**) and (±)-Horsfiline(**2**) in high yields (1.21 g, 93% and 1.07 g, 90%, respectively). It is important to know that the quantity of TCCA used for this gram-scale synthesis is very low (0.52 g for 5h and 0.41 g for 5i), whereas these reactions need large quantities of other earlier reported oxidants when performing gram-scale synthesis (>1 g).[11]



Scheme 4: Gram scale synthesis of (±)-Coerulescine and (±)-Horsfiline

In 1994, Borschberg et al. confirmed the absolute configuration of Horsfiline by the synthesis of both enantiomers through diastereoselective oxidative rearrangement of chiral tetrahydro-β-carboline precursors, derived from (L)-5-hydroxytryptophan.[13] Borschberg et al. have synthesized both optical antipodes of Horsfiline (**27**) with satisfactory overall yields ((–)-Horsfiline, 14%; (+)-Horsfiline, 22%) from the same enantiomer of the starting tryptophan derivatives.

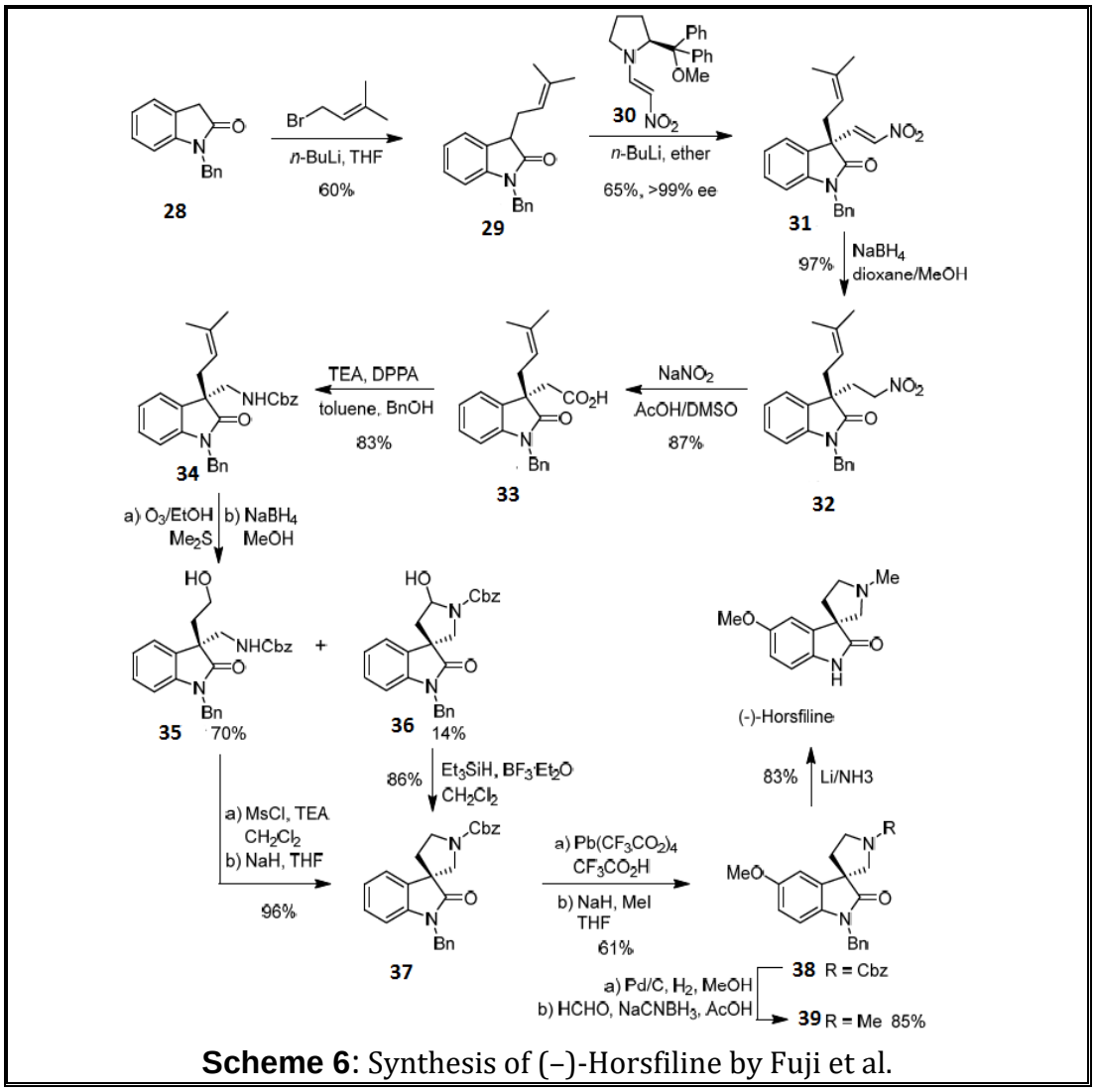
Because the absolute configuration of **27** was not known at that time, they attempted to develop an unambiguous enantioselective synthesis which would furnish both optical antipodes of Horsfiline with established absolute configurations.[13]The key step was the one-pot oxidation-rearrangement of optically pure tetrahydro-β-carboline derivatives (**22**, **23**) which furnished the desired oxindoles with diastereoface selectivity.[13] The relative configuration of the resulting isomers **25** and **26** were analyzed by NOE spectroscopy to deduce the absolute configuration of natural Horsfiline in comparison with final products. The required intermediates **22** and **23** were prepared in optically pure form as shown in Scheme **5**. Using a modified version of Brossi's protocol, the hydrochloride of the commercially available (*S*)-5-hydroxytryptophan **20** was transformed into **21** in virtually quantitative yield. Then, *N*-Boc-protection and *O*methylation of **21** and **22** proceeded with very high yield. The *N*-methyl analogue **23** was prepared from **22** through deprotection followed by reductive amination. The diastereoselective oxidative rearrangement of **22** and **23** gave diastereomers **24** and **25**, respectively.[13]



Scheme 5: Synthesis of (+)-Horsfiline and (–)-Horsfiline by Borschberg et al.

Diastereoisomer **24** was analyzed after deprotection and *N*-methylation, as was **25**. After analyzing **25** and **26** using NOE spectroscopy, the removal of the carbomethoxy group was performed using a different method. Eventually, the natural (–)-Horsfiline was compared with the obtained final products to confirm the optical configuration as *R*.[13]

Fuji et al. developed synthetic route to (–)-Horsfiline using asymmetric nitroolefination as the key step in 1999.[17] They reported an efficient asymmetric nitroolefination of oxindole derivatives using chiral nitroenamine **30,** and a similar strategy involving the asymmetric nitroolefination of **29** was expected to be well suited to the synthesis of (–)-Horsfiline (Scheme **6**). Oxindole **26** was prepared from **28**, which was readily available from isatin through a known method. A phenyl group was introduced into **28** by treating with 1-bromo-3-methyl-2-butene to furnish **29**, which was followed by asymmetric nitroolefination using chiral nitroenamine **30** to afford **31** in 65% yield with >99% ee. With compound **31** available with high enantiomeric excess, they started to construct the spiropyrrolidine ring system. The nitroolefin was reduced with $NaBH_4$ to give **32** in high yield. The attempted conversion of the nitro group of **32** into a carboxyl group using DMSO/$NaNO_2$/AcOH conditions was successful, giving **33** in 87% yield. Thermal Curtius rearrangement of **33** in benzyl alcohol furnished the corresponding benzoxy carbamate **34** in 83% yield. Ozonolysis of **34** followed by reduction with $NaBH_4$ afforded primary alcohol **35** and cyclic secondary alcohol **36** in 70% and 14% yields, respectively. The mesylation of **35** followed by base treatment afforded spiropyrrolidine **37**, while reduction of **36** with Et_3SiH in the presence of BF_3OEt_2 gave **37**. [17]



Scheme 6: Synthesis of (–)-Horsfiline by Fuji et al.

The regioselective oxidation of **37** at the 5-position was achieved by treatment with $Pb(CF_3CO_2)_4$ in TFA to give a crude phenolic compound which, upon Omethylation, gave **38** in 61% yield.[17] Then, the Cbz group was removed under neutral conditions (Pd-C,H_2, MeOH) at room temperature to yield the free amine. Without purification, the amine was methylated using formaldehyde and $NaCNBH_3$ at room temperature to furnish **39**. Finally, debenzylation was achieved using Li/NH_3 to give **27,** which had an optical rotation and melting point identical to those of natural (*R*)-(–)-Horsfiline.[17]

Takasuke Mukaiyama developed the synthetic to (-)Horsfiline and (-)Coerulescine by three one pot synthesis which was published on 2014.[18] In Michael reaction of α, β-unsaturated aldehyde and nitromethane, they found that unreactive β, β-

disubstituted α, β-unsaturated aldehyde is also a useful Michael acceptor for the construction of quaternary chiral centers with excellent enantioselectivity (figure **3**). Using this reaction as a key step, they had synthesized (–)-horsfiline (**50**) and (–)-coerulescine (**51**) in three pots.[18]

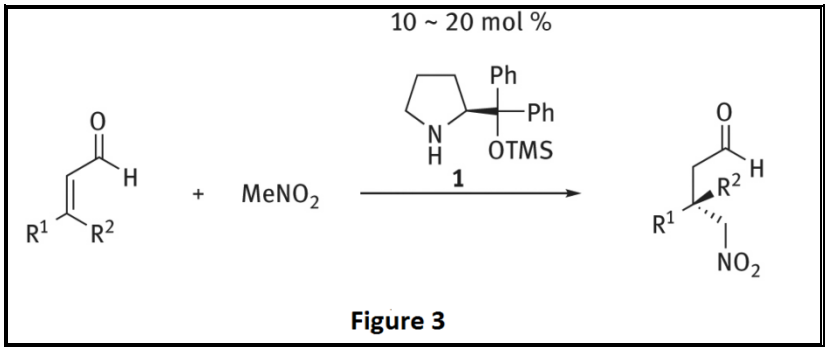
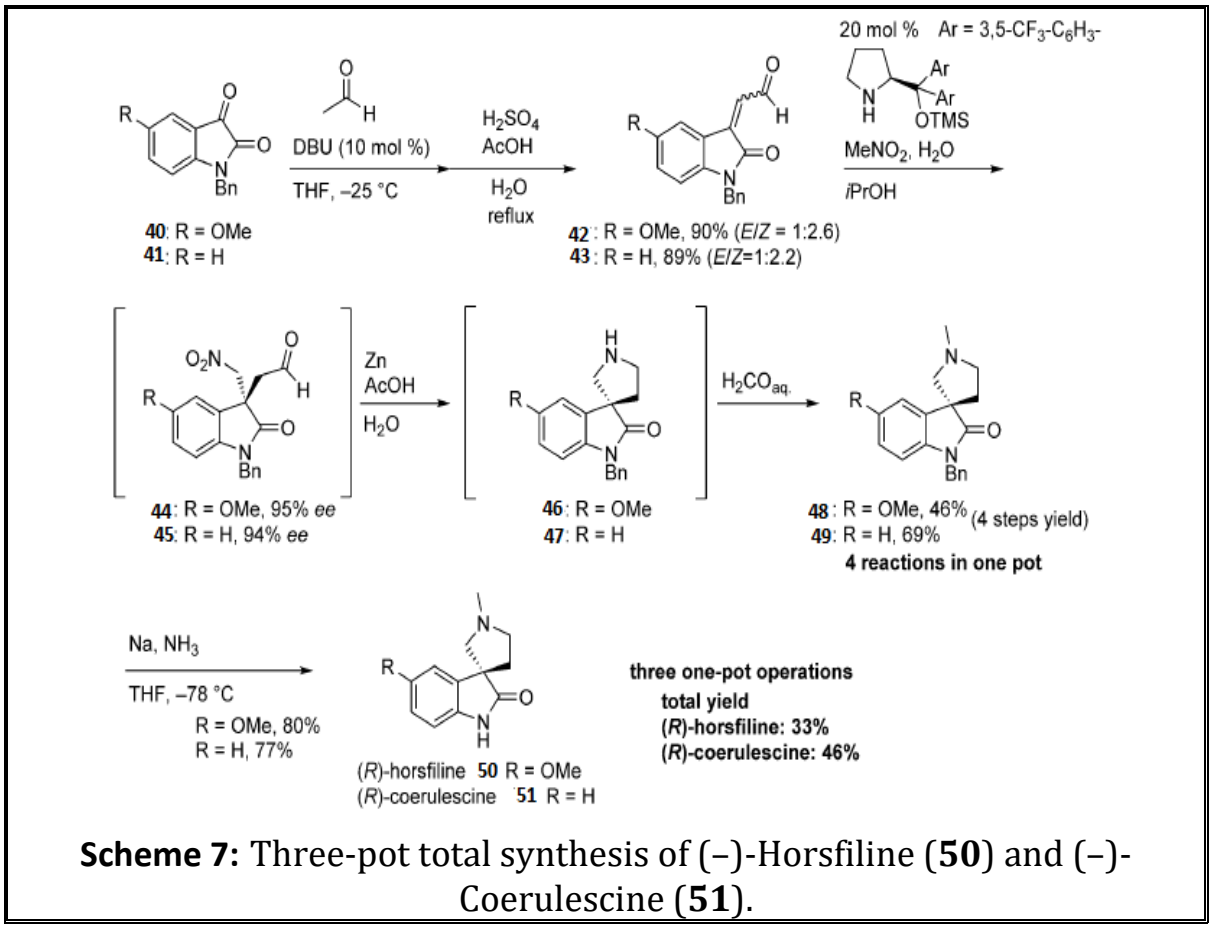


Figure 3

The first reaction is an aldol condensation reaction of acetaldehyde and isatin derivatives **40**, **41**. β, β-Disubstituted α, β-unsaturated aldehydes **42**, **43** were obtained in good yield.[18] The next reaction is a key asymmetric reaction catalyzed by diarylprolinol silyl ether of β, β-disubstituted α, β- unsaturated aldehydes **42**, **43** with nitromethane to afford the Michael products **44**, **45**. By treatment of **44**, **45** with Zn and CH_3CO_2H, a domino reaction comprising the reduction of nitro group and reductive amination was proceeded to afford **46, 47**. Second reductive amination occurred by the further addition of formaldehyde in the same reaction vessel to provide *N*-methyl amines **48**, **49**. Deprotection of Bn-protecting group provided (–)-horsfiline (**50**) and (–)-coerulescine (**51**) in good yield.[18]



Scheme 7: Three-pot total synthesis of (–)-Horsfiline (**50**) and (–)-Coerulescine (**51**).

In 2006, B. M. Trost and co-workers reported the asymmetric allylic alkylation of the protected oxindole **52** with allyl acetate using chiral ligand **53** in a palladium catalyzed reaction.[9] The enantiomeric excess of **54** was 84% with tetrabutylammoniumdifluorotriphenylsilicate (TBAT) as a fluoride source in toluene (Figure **4**). The major enantiomer of **54** could be purified to 98% ee in 69% yield by recrystallizing the major enantiomer pair using heptane or cyclohexane.[9]

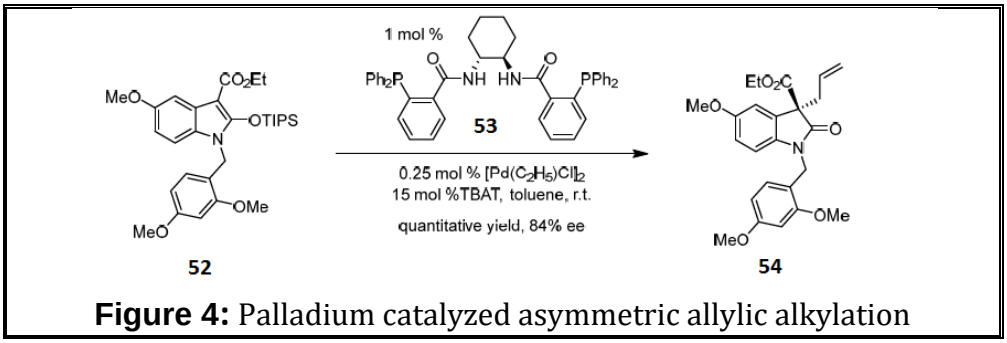
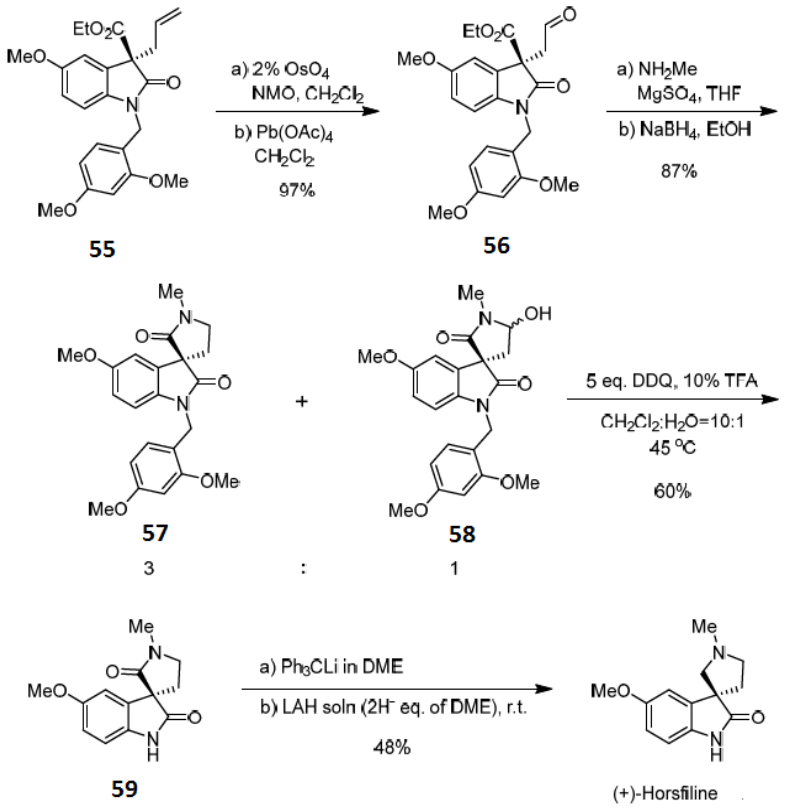


Figure 4: Palladium catalyzed asymmetric allylic alkylation

With the enantiomerically enriched **45**, oxidative cleavage of the allyl group was done using catalytic osmium tetraoxide and *N*-methylmorpholine *N*-oxide (NMO) followed by cleavage of the diol with lead tetraacetate in methylene chloride (Scheme **8**).[9] Reductive amination in a two-step procedure, by first forming the imine in dry THF with $MgSO_4$ and then reducing with $NaBH_4$ in ethanol, provided lactam **57** in 65% yield. The byproduct of the reaction was the lactam alcohol **58**, which presumably forms from cyclization of the hemiaminal onto the ester. Once lactam **57** was formed, only deprotection and a chemoselective reduction remained. Removal of the 2,4-dimethoxybenzyl group from the oxindole nitrogen was accomplished in 60% yield using DDQ in refluxing aqueous methylene chloride.[9]



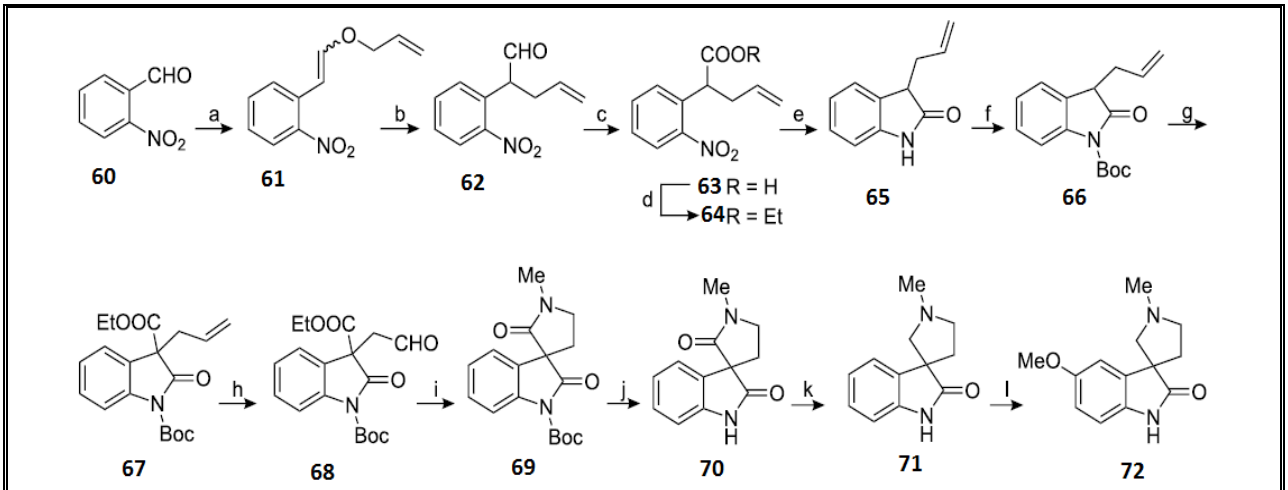
Scheme 8: Completion of (+)-Horsfiline by Trost et al.

The chemoselective reduction of **59** was proved to be a difficult challenge. It was finally found that the addition of 2 hydride equivalents of the LAH solution to a prepared solution of **59** and tritylllithium in DME at 0 °C afforded unnatural

(+)-Horsfiline in 45% yield. With unnatural (+)-Horsfiline, a first catalytic total synthesis of the enantiomerically enriched Horsfiline was achieved successfully in eight steps and in 11.1% yield.[9]

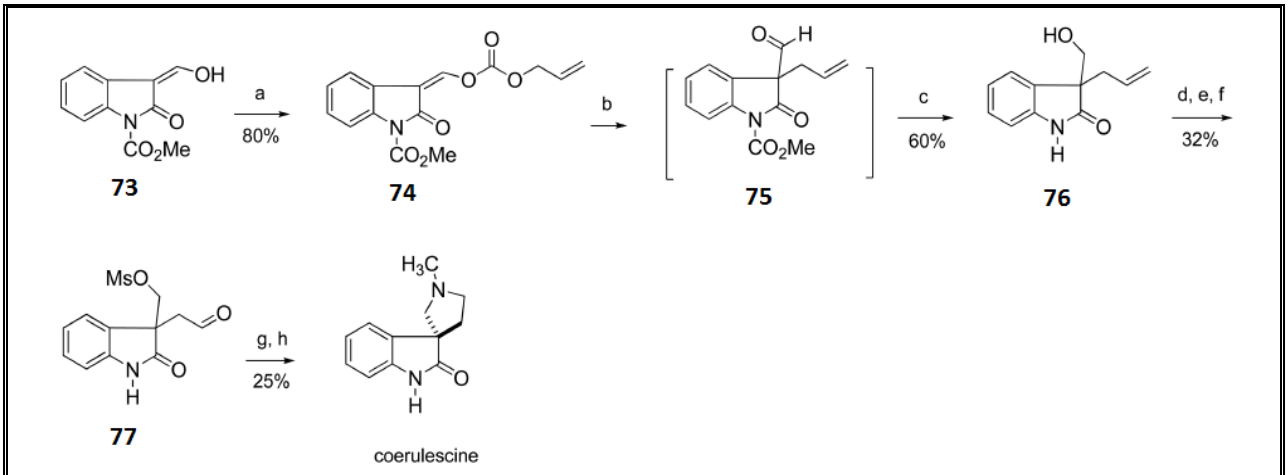
The total synthesis of Coerulescine and Horsfiline remain attractive targets for demonstrating the efficacy of newer synthetic protocols.[19] Several synthetic approaches have been developed for the synthesis of the spiro[pyrrolidin-3,3'-oxindole] framework for Horsfiline and Coerulescine, both in racemic and enantiomeric forms.[19] In 2010, total synthesis was published by Mukund Kulkarni on Wittig olefination–Claisen rearrangement which was applied to obtain 3-allyl oxindole. This oxindole was then converted to (±)-Coerulescine and (±)-Horsfiline. As shown below in scheme **9** the Wittig olefination of *o*-nitrobenzaldehyde with allyloxymethylenetriphenylphosphorane under standard conditions gave the corresponding allyl vinyl ether **61** as an inseparable mixture of two isomer with one as the major one. The mixture of allyl vinyl ethers was heated in refluxing xylene to give the Claisen rearrangement to obtain 4-pentenal **62** in 85% yield. Jones oxidation was done to convert aldehyde **62** into acid **63**, which was immediately converted to the ethyl ester **64**. Reduction of the compound **63** with Zn and NH_4Cl resulted in clean cyclization leading to oxindole **65**. After protecting the amide nitrogen with Boc, the oxindole **66** was treated with NaH, followed by ethyl chloroformate at 0 °C to give **67** in 80% yield.[19]

Oxidative cleavage of the allyl group was accomplished by catalytic osmium tetroxide and *N*-methylmorpholine *N*-oxide (NMO), followed by cleavage of the diol with sodium metaperiodate on silica in methylene chloride.[19] Reductive amination of the aldehyde **50** was conducted using methylamine hydrochloride and $NaBH_3CN$ and gave spirooxindole **51**. The Boc group of **51** was removed by treatment with 2.5 M HCl to give **52**. Finally, chemoselective reduction of amide **52** with *n*-BuLi and LAH under certain conditions gave Coerulescine. Coerulescine, on treatment with *N*-bromosuccinimide, gave the 5-bromo derivative, which upon heating with sodium methoxide in the presence of cuprous iodide gave Horsfiline in 60% yield. The physical data of synthetic Coerulescine and Horsfiline were comparable in all respects with the literature data.[19]



Scheme 9: Reagents and conditions: a) CH_2=$CHCH_2OCH_2P$+ Ph3Cl−, *t*-BuO− Na+, THF, 0 °C; b) xylene, reflux; c) Jones reagent, acetone, d)H_2SO_4, EtOH, e) Zn, NH_4Cl, EtOH, reflux, f) NaH, $(Boc)_2O$, THF, 0 °C, g) NaH, ethyl chloroformate, THF, 0 °C, h) K_2OsO_4, NMO, $NaIO_4{\cdot}SiO_2$, DCM,i) $MeNH_2{\cdot}HCl$, $NaCNBH_3$, THF j) 2.5 M HCl aq. THF, reflux; k) *n*-BuLi, LAH, THF, l) NBS, NaOMe, CuI, reflux.

Intramolecular allylation to Coerulescine was published on 2012 by Minhye Kim and Guncheol Kim.[20] The allyl enol carbonate precursor **74** was obtained in 80% yield using a general reaction condition for carbonate formation from the intermediate **73** obtained via a known reaction. Tsuji allylation gave the allylic aldehyde **75**. The allyl enol carbonate **74** was treated with $Pd_2(dba)_3$ and PPh_3 in THF, prompt filtration and concentration was followed by reduction of the crude product under $NaBH_4$ in MeOH at 0 ^{0}C. The careful and rapid two step process afforded compound **76** in 60% yield. Spontaneous deprotection of methyl carbamate group on nitrogen was shown in the two steps. Mesylation of **76** was followed by oxidative cleavage of the allylic double bond to aldehyde **77** using OsO_4 and $Pb(OAc)_4$ in 32% yield in 2 steps. The final transformation of **77** to coerulescine was carried out via sequential treatment with $MeNH_2$ and $NaBH_4$ to ensure reductive amination and the following cyclization in 25%. The spectral data of coerulescine were identical to those published.[20]



Scheme 10: Reagents and conditions: (a) allyl chloroformate, $NaHCO_3$, DMF (b) $Pd_2(dba)_3$, Ph_3P, THF (c) $NaBH_4$, LiCl, THF EtOH (d) MsCl, TEA, CH_2Cl_2 (e) OsO_4, NMO, CH_2Cl_2 (f) $Pb(OAc)_4$ (g) $MeNH_2$, $MgSO_4$, THF (h) $NaBH_4$, EtOH.

Conclusions

Bodo and his co-workers were the first one to synthesize Horsfiline, from a Malaysian medicinal tree Horsfieldia Superba Warb as shown in scheme **1.**[12] Scheme **2** and **3** synthesis involves commercially available starting materials and use of less expensive reagents. This methodology would be useful in the preparation of analogues of anti-inflammatory drugs. The potential of this method was substantiated by the short syntheses of the oxindole alkaloids (±)-coerulescine and (±)-horsfiline in excellent overall yields from commercially available starting materials and the syntheses should be amenable for the preparation of the natural products in large scale for biological evaluation.[14]

Synthesis of of spirooxindoles from the corresponding tetrahydro-beta-carbolines (THBCs) using the inexpensive TCCA(scheme **4**) in which the reaction proceeds via oxidative rearrangement and produced spirooxindoles in good to excellent yields (up to 99%).Substituted spirooxindoles and naturally occurring , (±)-coerulescine and (±)-horsfiline were furnished in excellent yields using the optimized reaction conditions. To demonstrate the commercial importance of this protocol, they carried out gram-scale reactions to produce (±)-coerulescine and (±)-horsfiline with yields of 93% and 90%, respectively. In addition, this synthetic strategy is amenable for the generation of a library spiro-compounds and their derivatives, which can be further utilized in the drug discovery process.[11]

Both optical antipodes of Horsfiline have been synthesized by Borschberg et al in about 10 steps and with satisfactory overall yields ((–)-Horsfiline 14%; (+)-Horsfiline, 22%) from the same enantiomer of the starting tryptophan derivative (Scheme **5**).[13] Fuji et al has developed two synthetic routes to (-)-Horsfiline using asymmetric nitroolefination as the key step (Scheme **6**). A three one-pot sequential synthesis of both (-)-Horsfiline and (-)-Coerulescine was achieved by Mukaiyama (Scheme **7**).[17]d This method allowed a mixture of E/Z isomers to be used as the starting material to give the product in excellent enantioselectivity (yields were good).[18] A concise total synthesis of Horsfiline was achieved in 8 steps with 11.1% yield by Barry Trost (Scheme **8**). A palladium-catalyzed asymmetric allylic alkylation was used to set the spiro(pyrrolidine-oxindole) stereogenic center.[9]

Mukund Kulkarni developed the synthesis in which Wittig olefination and Claisen rearrangement was applied to obtain 3 allyl oxindole. The oxindole was then converted to (±)-coerulescine and (±)-horsfiline (Scheme **9**). Horsfiline was obtained in about 60% yield.[19] Intramolecular allylation to Coerulescine was done by Minhye Kim and Guncheol Kim (Scheme **10**).Tsuji allylation was done and the product Coerulescine was obtained in 25% yield.[20]

Bibiliography

1. Ishikawa, H. & Shiomi, S. Biomolecular Chemistry amine organocatalysts. (2015). doi:10.1039/c5ob02021b

2. Chang, M., Pai, C. & Kung, Y. Synthesis of (±) -coerulescine and a formal synthesis of. **46**, 8463–8465 (2005).

3. Romo, P., Quiroga, J. & Glidewell, C. Regio- and stereospecific assembly of dispiro- simple precursors using a one-pot procedure : synthesis , spectroscopic and structural character- ization , and a proposed mechanism of formation research papers. 779–785 (2020). doi:10.1107/S2053229620009791

4. Smith, G., Wang, E., Bartley, J. P. & Raymond, C. organic papers. 973–975 (2001). doi:10.1107/S1600536801015252

5. White, J. D., Li, Y. & Ihle, D. C. Tandem Intramolecular Photocycloaddition - Retro-Mannich Fragmentation as a Route to Spiro [pyrrolidine-3 , 3 0 - oxindoles] . 3569–3577 (2010). doi:10.1021/jo1002714

6. Sharma, S., Brahmachari, G. & Gupta, V. K. One-pot green synthesis of biologically relevant zoles] and studies on their spectral and X-ray crystallographic behaviors research papers. 1–9 (2016). doi:10.1107/S2052520616005060

7. Murphy, J. A. & Khan, T. A. Novel Phosphorus Radical-Based Routes to Horsfiline. 6–8 (2005).

8. Marti, C. & Carreira, E. M. Construction of Spiro [pyrrolidine-3 , 3 J - oxindoles] ⁒… Recent Applications to the Synthesis of Oxindole Alkaloids. 2209–2219 (2003). doi:10.1002/ejoc.200300050

9. Trost, B. M., Brennan, M. K. & V, S. U. Palladium Asymmetric Allylic Alkylation of Prochiral Nucleophiles : Horsfiline. 4–7 (2006).

10. Lizos, D. E. & Murphy, J. A. Concise synthesis of (±) -hors fi line and (±) -

coerulescine by tandem cyclisation of iodoaryl alkenyl azides †. 117–122 (2003).

11. Sathish, M., Sakla, A. P., Nachtigall, F. M. & Santos, L. S. spirooxindoles and the total synthesis of. 16537–16546 (2021). doi:10.1039/d1ra02381k

12. Jossang, A., Jossang, P., Hadi, H. A., Sbvenet, T. & Bodo, B. ["id +5.6". **6530**, 6527–6530 (1991).

13. Pellegrini, C., Sthissler, C., Weber, M. & Borschberg, H. Synthesis of the Oxindole Alkaloid (-)-Horsfiline. **5**, 1979–1992 (1994).

14. Selvakumar, N., Azhagan, A. M., Srinivas, D. & Krishna, G. G. A direct synthesis of 2-arylpropenoic acid esters having nitro groups in the aromatic ring : a short synthesis of (±) -coerulescine. **43**, 9175–9178 (2002).

15. Palmisano, G. *et al.* Oxindole Alkaloids . A Novel Non-biomimetic Entry to (-) -Horsfiline . **7**, 1–4 (1996).

16. Cravotto, G., Giovenzana, G. B., Pilati, T., Sisti, M. & Palmisano, G. Azomethine Ylide Cycloaddition / Reductive Heterocyclization Approach to Oxindole Alkaloids : Asymmetric Synthesis of (-) -Horsfiline. 8447–8453 (2001).

17. Lakshmaiah, G. & Kawabata, T. Total Synthesis of (-) -Horsfiline via Asymmetric Nitroolefination. **517**, 1699–1704 (1999).

18. Mukaiyama, T., Ogata, K., Sato, I. & Hayashi, Y. Asymmetric Organocatalyzed Michael Addition of Nitromethane to a 2-Oxoindoline-3-ylidene Acetaldehyde and the Three One-Pot Sequential Synthesis of (À) -Horsfiline and (À) -Coerulescine. 1–7 (2014). doi:10.1002/chem.201403932

19. Kulkarni, M. G. *et al.* Total synthesis of (±) -coerulescine and (±) -horsfiline. 876–879 (2010). doi:10.3762/bjoc.6.103

20. Kim, M. & Kim, G. Intramolecular Allylation to Coerulescine and a New Route to Formal Synthesis of Horsfiline. **33**, 1821–1822 (2012).