Chapter 3

Total synthesis of (±)-Coerulescine and (±)-Horsfiline
INTRODUCTION

The oxindole alkaloids are a subclass of the indole alkaloids, a family of heterocyclic alkaloids. Indole alkaloids comprise alkaloids that contain the indole or a structural element derived from indole like in the structures shown in Figure 1.

![Figure 1: structural motifs of some indole alkaloids.](image)

The first oxindole alkaloids were isolated from the roots of *Gelsemium sempervirens*, and are classified as *Gelsemium* alkaloids. Later on some novel oxindoles were isolated from *spidosperma, Mitragyna, Ourouparia, Rauwolfia* and *Vinca*.¹ Most of these alkaloids possess a common basic framework derived from tryptamine and are characterized by a unique spiro pyrrolidine ring connected to the 3-position of the oxindole core. They can be
Further classified into two substructural classes: the tetracyclic secoyohimbane type [e.g. rhynchophylline 374] and the pentacyclic heteroyohimbane type [e.g. formosanine 375]. Other spiro[pyrrolidine-3,3'-oxindole] alkaloids that have been isolated are exemplified by (-)-horsfiline 376², spirotryprostatin A 377, spirotryprostatin B 378³ and (+)-elacomine 379⁴ (Figure 2).

![Chemical structures]

Figure 2: Spiro[pyrrolidine-3,3'-oxindole] alkaloids

The spiro[pyrrolidin-3,3'-oxindole] ring system is a widely distributed structural framework present in a number of cytostatic alkaloids such as spirotryprostatins A, B and strychnophylline.⁵,⁶ Among them, coerulescine 380 and horsfiline 376 represent the simplest prototype members of this subfamily. The unique structural array and the unusual biological activity displayed by this class of compounds have made them attractive synthetic targets.⁷,⁸
Horsfiline 376 was isolated in 1991 by Bodo and co-workers from the Malaysian tree *Horsfieldia superb*, an important source of medicinal extracts and snuffs in the local medicine. Coerulescine 380 had been already synthesized in pilot studies toward the synthesis of horsfiline 9 and vincadifformine 10 even before it was isolated and characterized from the natural resources (i.e. *Phalaris coerulescens*). The findings of Danishefsky et al. are particularly interesting in this regard; they tested compounds 381 and 382 (both diastereomers) (Figure 3) and reported significant activity against human breast cancer cells. Several synthetic approaches have been developed for the construction of the spiro[pyrrolidin-3,3'-oxindole] framework of coerulescine and horsfiline, both in racemic as well as enantiomeric forms.

![Figure 3: spiropyrrolidinoxindoles.](image)

Bernard Bodo 2 reported the first synthesis of racemic horsfiline 376 from either of the two achiral metabolites 383 and 384, co-isolated with horsfiline itself from the same species. The two step conversion of 383 into (±)-376 by treatment with lead tetraacetate furnished a 4a-acetoxyindolenine 385. Acid-catalyzed rearrangement of 385 gave horsfiline 376 (Scheme 1).
The synthetic route to (±)-horsfiline \( \text{376} \) by Jones and Wilkinson\(^{13} \) employed radical cyclization reaction as a key step. Cbz-protected glycine ethyl ester \( \text{386} \) was treated with ethyl acrylate to give the compound \( \text{387} \). The compound \( \text{387} \) was reduced with sodium cyano borohydride to give the alcohol \( \text{388} \). The alcohol \( \text{388} \) was treated with BzCl and DBU refluxing in toluene, afforded the dehydrating product \( \text{389} \). Hydrolysis of ester group by treating with KOH furnished the compound \( \text{390} \). Reaction of 2-bromo-4-methoxyaniline with \( \text{390} \) furnished the precursor \( \text{391} \) for the radical cyclization. Protection of the indole nitrogen, followed by treating the compound with tributyl tinhydride and AIBN furnished the compound \( \text{393} \). Deprotection of \( \text{393} \) and its \( N \)-methylation of the intermediate \( \text{394} \) under Eschweiler–Clarke conditions furnished (±)-Horsfiline \( \text{376} \) in good yield (Scheme 2).
Laronze$^{14}$ synthesized horsfiline following two different strategies. In one of the approach, tetrahydro-γ-carboline 395 was treated with tBuOCl to get chloroindolenine 396 via oxidative rearrangement which on in situ treatment with NaOH furnished a mixture of (±)-horsfiline 376, 397 and 398. Compounds 397 and 398 can be easily converted into desired (±)-horsfiline 376 by sequentially treating them with NaOMe and p-TsOH. The other route involves oxidation of 5-methoxy-N$_2$-methyl-tryptamine 399 with DMSO-HCl to oxo-5-methoxytryptamine 400. Treatment of the 400 with an excess of formaldehyde in acetic acid in the presence of NaCNBH$_3$ gave (±)-horsfiline 376 in 35% overall yield (Scheme 3).
The first chiral synthesis of (-) and (+)-horsfiline was reported by Borschberg. This also established the absolute configuration of the natural product as (-)-horsfiline. Starting from the commercially available (S)-5-hydroxytryptophan 401, the compound (-)-402 was obtained by treating 401 with CH$_2$O under the modified version of Brossi's protocol. Alicyclic N-H in (-)-402 was converted to its Boc derivative. It was then treated with TMS-diazomethane in the presence of Hunig's base to afford the O-methylated product (+)-404. Oxidative rearrangement of (+)-404 with NBS and AcOH furnished a diastereomeric mixture of the corresponding oxindoles. The major diastereoisomer (-)-405 was deprotected and subsequently N-methylated to give (-)-406. The compound (-)-406 was treated with NH$_3$, (CF$_3$CO)$_2$O, pyridine, in 1,4-dioxane to furnish the cyano derivative 407. Reductive removal of the cyano group with provided (-)-horsfiline 376. When the N-methyl derivative (-)-408, obtained from (+)-404 was subjected to the Oxidative rearrangement using NBS and AcOH the oxindole (-)-409 was obtained. Hydrolysis of the ester...
in 409 gave the acid 410. Removal of the carbonyl group by Barton method\textsuperscript{19} furnished the corresponding (+)-horsfiline 376 (Scheme 4).

[Diagram of the synthesis of (+)-horsfiline 376]

Giovanni Palmisano\textsuperscript{20} and co-workers have reported the synthesis of (-)-horsfiline by using 1,3-dipolar cycloaddition reaction. Wittig olefination of 411 with (5R)-menthyl (triphenylphosphoranylidene)acetate in refluxing diglyme afforded the compound 412. The compound 412 was treated with N-methyl-azomethine ylide (thermally generated \textit{in situ} from sarcosine and formaldehyde)\textsuperscript{21} to give two chromatographically separable oxindoles as (-)-(3S,4'R)-413 and (-)-(3R,4'S)-414. Cleavage of the chiral auxiliary in 414 with
KOH, 18-crown-6(cat) and subsequent removal of the CO$_2$H function according to the Barton radical protocol$^{19}$ furnished the (-)-horsfiline 376 (Scheme 5).

Scheme 5

Kaoru Fuji$^{22}$ and co-workers have reported the synthesis of (-)-horsfiline via asymmetric nitroolefination. Selective O-methylation of 415, obtained from $p$-anisidine,$^{23}$ was achieved by using dimethyl sulfate in the presence of potassium hydroxide to afford 416. A prenyl group was introduced into 416 by treating it with 1-bromo-3-methyl-2-butene to furnish 417. After the protection of amide nitrogen with TBDMSI, the oxindole 418 was treated with $n$-BuLi followed by chiral nitroenamine 419 to give 420. The TBDMS group of 420 was removed with HCl to give 421. The nitroolefin was reduced with NaBH$_4$ to give 422. The amide was protected with a benzyl group to afford
Conversion of nitro group in 423 into a carboxylic acid by using DMSO, NaNO₂, CH₃COOH consecutively afforded the compound 424. Thermal Curtius rearrangement of 424 using benzyl alcohol furnished the corresponding carbamate 425. Ozonolysis of 425 followed by reduction of the resulting aldehyde with NaBH₄ produced alcohol 426. The hydroxyl group of 426 was mesylated, and the crude residue was directly treated with NaH/THF at room temperature to afford spiropyrrolidine 427. Then the Cbz group was deprotected under neutral conditions (Pd/C, H₂) to yield the free amine. Without purification, it was methylated using formaldehyde and NaCNBH₃ to furnish 428. Finally, debenzylation, using Li/NH₃ gave 376 (Scheme 6).
Erick M. Carreira and co-workers have reported the synthesis of (±)-horsfiline through the MgI₂-catalyzed ring-expansion reaction. N-benzylation of the commercially available 5-methoxyisatin 429 furnished 430. Subsequent Wolff-Kishner reduction of 430 afforded oxindole 431. The compound 431 underwent alkylative cyclization with 1,2-dibromoethane to afford the compound 432. Treatment of 432 with 1,3,5-trimethyl-1,3,5-triazinane 433 and MgI₂ furnished the desired spiro[indole-pyrrolidin]-2-one 428. Removal of the N-Bn protecting group was effected by subjecting 428 to dissolving metal reduction, affording (±)-horsfiline 376 (Scheme 7).
Giovanni Palmisano\textsuperscript{26} and co-workers have reported the synthesis of (-)-horsfiline by using azomethine ylide cycloaddition. The Claisen condensation of 2-nitro-5-methoxytoluene 434 with diethyl oxalate furnished ethyl 2-nitro-5-methoxyphenopyruvate, which was oxidatized with Blaikie and Perkin conditions\textsuperscript{27} (NaOH, H\textsubscript{2}O\textsubscript{2}) to give acid 435. Esterification of acid 435 in MeOH, and Amberlyst 15 gave 436. Treatment of 436 with paraformaldehyde in the presence of K\textsubscript{2}CO\textsubscript{3} and tris[2-(2-methoxyethoxy)-ethyl]amine] (TDA-1)\textsuperscript{28} as a solid-liquid phase-transfer catalyst furnished the acrylate 437. Hydrolysis of ester 437 gave the acid 438. Reaction of acid 438 with chiral auxiliary 439 in presence of HOBt, DCC and DMAP provided the compound 440. 1,3-dipolar cycloaddition of N-methylazomethine ylide from sarcosine (N-methylglycine) and paraformaldehyde in the presence of 440 yielded the desired pyrrolidine 441. Finally, catalytic hydrogenation of the nitro gave (-)-horsfiline 376 (Scheme 8).
Hiriyakkanavar Junjappa\textsuperscript{29} and co-workers have reported the synthesis of (±)-horsfiline via iodide ion induced rearrangement. α-oxoketene dithioacetals 442 obtained from 2-oxindole.\textsuperscript{30} Compound 442 was treated with an equimolar quantity of aziridine to afford the corresponding 3-[[N-aziridinomethylthio)methylene]oxindole 443. When 443 was reacted with potassium iodide under nitrogen atmosphere, the reaction mixture furnished a yellow crystalline solid 2'-methylthio-2-oxospiro-(3H-indole-3,3'-1'-pyrroline) 444. Reductive dethiomethylation of 444 with Raney nickel in refluxing methanol also effected N-methylation with methanol to directly give (±)-horsfiline 376. Replacing 442 with 445 in the synthetic scheme, furnished (±)-coerulescine 380 (Scheme 9).

\[
\begin{align*}
\text{Scheme 9}
\end{align*}
\]

John A. Murphy\textsuperscript{31,32} and co-workers have reported the synthesis of (±)-coerulescine and (±)-horsfiline by using a tandem radical cyclization as the key step. Dilithiated t-Boc-p-anisidine 446 (prepared from p-anisidine) was iodinated\textsuperscript{33} with 1,2-diiodoethane to afford the compound 447. Deprotection of the t-Boc group and reductive amination with benzaldehyde yielded the N-benzyl derivative 448. Coupling of itaconic acid derivative\textsuperscript{34} to the amine 448,
affording amide 449. The compound 449 was treated with thiophenol to give the compound 450. Reduction of 450 with DIBAL-H afforded the alcohol 451. Oxidation of the sulfide and thermal elimination of the resulting sulfoxide yielded the desired alcohol 452. It was smoothly converted to the azide 453 with diphenylphosphoryl azide. Cyclisation with tris(trimethylsilyl)silane (TTMSS) followed by in situ methylation afforded the tricycle 428. Finally, this was debenzylated to afford (±)-coerulescine 380 and (±)-horsfiline 376 (Scheme10).

\[
\text{Scheme10}
\]

N. Selvakumar\textsuperscript{37} and co-workers have reported the synthesis of (±)-coerulescine and (±)-horsfiline. The aromatic nucleophilic substitution of
dimethyl malonate onto 2-fluoronitrobenzene 454 afforded the nitro-malonate 455. Treatment of nitromalonate 455 with aq. formaldehyde afforded the nitroaryl propenoate 456. The 1,3-dipolar cycloaddition of the nitro-ester 456 to a N-methylazomethine ylide, generated from N-methylglycine and paraformaldehyde, afforded the pyrrolidine nitro-ester 457. Subsequent hydrogenation of the compound 457 resulted in lactam formation leading to (±)-coerulescine 380. The treatment of dimethyl malonate with 2,4-difluoronitrobenzene 458 gave the compound 459. The treatment of nitromalonate 459 with aq. formaldehyde afforded the compound 460. Treatment of 460 with NaOMe in methanol gave the desired methoxy nitro-acrylate 437. Adopting the same sequence of reactions as employed in the synthesis of coerulescine 380, the synthesis of (±)-horsfiline 376 was completed (Scheme 11).

![Scheme 11](image)

John A. Murphy and co-workers have reported the synthesis of horsfiline by using diethylphosphine oxide (DEPO) to generate radical from a
selenide derivative. Reaction of the pyrrolidine ester 461, prepared from pyrrolidine,\textsuperscript{41} with LDA and the phenylselenyl chloride gave the α-selenylated compound which was directly reacted with o-anisidine in the presence of trimethylaluminum\textsuperscript{42} to give amide 462. The amide nitrogen of 462 was protected with benzyl group to produce the compound 463. The compound 463 was treated with DEPO and AIBN in refluxing dry benzene, the substrate underwent smooth radical cyclization to obtain cyclized product 427. As mentioned, 427 is an advanced precursor of horsfiline 376 (Scheme 12).

\[
\text{Scheme 12}
\]

Meng-Yang Chang\textsuperscript{43} and co-workers have reported the synthesis of (±)-coerulescine by using intramolecular electrophilic cyclization as a key step. Reaction of benzoxycarbonylation of amine 464 with triethylamine and benzoxycarbonyl chloride, followed by oxidation with Jones reagent afforded the compound 465. Grignard addition of ketone 465,\textsuperscript{44} followed by dehydration of the resulting tertiary alcohols with boron trifluoride etherate furnished the compound 466. Dihydroxylation of olefins 466\textsuperscript{45} with N-methylmorpholine N-
oxide and a catalytic amount of osmium tetroxide gave the compound 467. Rearrangement of diols 467 with boron trifluoride etherate furnished 3-aryl-3-formylpyrrolidines 468. Aldehyde 468 was transformed into acid 469 by Jones oxidation. Treatment of acid 469 with DCC and benzylamine gave a benzyl amide product. Intramolecular electrophilic cyclization of the benzyl amide with tert-butylhypochlorite followed by zinc acetate gave the compound 470. Hydrogenation of compound 470 with hydrogen in the presence of a catalytic amount of 10% Pd/C, followed by N-methylation with formaldehyde and sodium borohydride furnished (±)-coerulescine 380 (Scheme 13).

![Scheme 13](image)

Barry M. Trost and co-workers have reported the synthesis of horsfiline by using palladium asymmetric allylic alkylation. p-Anisidine 471 was treated with 2,4-dimethoxybenzaldehyde 472 and sodium borohydride to furnished amine 473. Acylation of 473 with the acid chloride derivative of ethyl
diazoacetate in the presence of triethylamine led to the formation of amide 474. The amide 474 was treated with Rh\(_2\)(CF\(_3\)CONH\(_2\))\(_4\) to effect Rh mediated C-H insertion occurred to give the corresponding oxindole which was directly treated with TIPSOTf to yield 475. Asymmetric allylic alkylation of 475 in presence of [Pd(C\(_2\)H\(_5\))Cl] and TBAT afforded the alkylated product 476. Oxidative cleavage of the allyl group was accomplished with catalytic osmium tetraoxide and lead tetraacetate to give aldehyde 477. Reductive amination of 477 with methyl amine, followed by reduction with NaBH\(_4\) provided lactam 478. Removal of 2,4- dimethoxybenzyl group was effected by subjecting 478 to DDQ, affording the compound 479. The chemoselective reduction of 479 with LAH in presence of \(n\)-BuLi furnished horfsline 376 (Scheme14).
Scheme 14

Hongbin Zhang and co-workers have reported the synthesis of horsfiline by using oxidative carbon-carbon bond formation. 4-(benzylamino) phenol was treated with 480 to give amide 481. Oxidation of amide 481 with iodobenzene diacetate (IBD), followed by Michael addition was achieved by the addition of DBU in dichloromethane to furnish 4-methoxyl cyclohexadienenones 482. The crude product was treated with TsOH to afford the oxindole 483. Oxindole was treated with K$_2$CO$_3$, methyl iodide to give the precursor 476 of the horsfiline 376 (Scheme 15).

Scheme 15
Luc Neuville and co-workers have reported the synthesis of horsfiline via intramolecular palladium-catalyzed domino Heck–cyanation. Reaction of triethyl phosphonoacetate with formaldehyde in the presence of potassium carbonate provided 484. Hydrolysis of the ester followed by protection of the primary alcohol as tert-butylidimethylsilyl ether afforded compound 485. Coupling of 485 and 486 was best realized in the presence of Mukaiyama’s reagent (2-chloro-N-methyl pyridinium iodide, tributylamine in refluxing toluene) to afford the desired amide 487. Finally, protection of the secondary amide 487 with SEM group afforded the ortho-idoanilide 488. Attempted enantioselective Heck–cyanation of 488 in presence of Pd(OAc)$_2$, K$_4$[Fe(CN)$_6$] afforded 489. Selective reduction of the nitrile function in 489 with CoCl$_2$·6H$_2$O, NaBH$_4$, afforded amine 490. Removal of O-TBS protecting group from 490 under acidic conditions, followed by treatment with t-Boc afforded the amino alcohol 491. Treatment of 491 with methanesulfonyl chloride afforded the corresponding mesylate, which was treatment with NaH to afford the spirooxindole 492. Removal of the N-SEM group, followed by deprotection of the N-Boc function afforded compound 394. Treatment of 394 with an excess of formaldehyde in acetic acid in the presence of NaBH$_3$CN furnished 493. Hydrolysis of the hemiaminal function under basic reaction condition afforded the horsfiline 376 (Scheme 16).
Christopher J. Douglas\textsuperscript{51} and co-workers have reported the synthesis of (-)-coerulescine and (+)-horsfiline by employing intramolecular cyanoamidation. \textit{N}-Boc-protected 2-bromoanilines 494 or 495 was treated with iodoalkene 496 by using Pd-catalyzed Suzuki coupling reaction\textsuperscript{52} furnished the compound 497. Boc-deprotection with TBSOTf in 2,6-lutidine generated the free amine, which was treated with tetracyanoethylene oxide (TCEO) and dimethyl sulfide\textsuperscript{53} to give cyanoformamides 498. Intramolecular cyanoamidation provided the oxindole 499 by using palladium catalysts with chiral phosphoramidite ligand. The silyl ether was deprotected with TBAF, and the resulting alcohol was converted to the corresponding mesylate 500. Reduction of nitrile with NaBH\textsubscript{4}/CoCl\textsubscript{2}.6H\textsubscript{2}O, followed by reductive amination furnished the corresponding (-)-coerulescine 380 and (+)-horsfiline 376 (Scheme 17).
Most of the syntheses discussed above are a result of demonstration of efficiency of methodologies developed by various workers. We have successfully achieved a total synthesis of coerulescine and horsfiline by applying Wittig Olefination Claisen rearrangement protocol, developed in our laboratory previously. The results of these efforts are discussed in the following section.
EXPERIMENTAL DISCUSSION

In the proposed synthetic plan, the synthesis of coerulescine and horsfiline could be achieved from a key intermediate, namely, a 4-pentenal derivative. Such a 4-pentenal derivative could be prepared via Wittig Olefination - Claisen rearrangement protocol, which is now a well established theme in our laboratory.

![Scheme 3](image)

**Scheme 3**

Form the retro synthetic analysis given above (Scheme 3), the coerulescine and horsfiline synthesis begins with the Wittig Olefination of the 2-nitrobenzaldehyde using the Wittig reagent derived from allyloxymethylenetriphenylphosphonium chloride in presence of tert-butoxide in dry THF. On completion of the reaction (TLC check), normal aqueous extractive work-up gave the crude product. Purification of the crude product on silica gel column chromatography using ethyl acetate - hexane gave the allyl vinyl ethers in good yields. The TLC showed a homogenous spot for resulting possible E-and Z-isomers.
The IR spectrum of this compound showed a strong absorption band at 1525 cm\(^{-1}\), indicating the presence of the nitro group in compound. The weak absorption bands in the IR spectrum at 1681 cm\(^{-1}\) and 1653 cm\(^{-1}\) corresponded to two olefins. A strong absorption band at 916 cm\(^{-1}\) is typically of a terminal olefin. The \(^1\)H NMR spectrum showed two sets of signals indicating that compound is probably a mixture of \(E\)- and \(Z\)-geometrical isomers. The \(^1\)H NMR spectrum the compound showed two doublets at \(\delta\) 5.75 and \(\delta\) 6.50 with coupling constant of 7.3 Hz and 12.9 Hz respectively corresponded to the benzylic proton of \(Z\)- and \(E\)-geometrical isomer in ratio 0.33:0.67. The corresponding carbon appeared at \(\delta\) 99.12 and \(\delta\) 101.86 in the \(^{13}\)C NMR spectrum. The two doublets appearing at \(\delta\) 6.42 and \(\delta\) 7.08, with coupling constant of 7.3 Hz and 12.9 Hz respectively were assigned to the enol ether proton of \(Z\)- and \(E\)-geometrical isomer in ratio 0.33:0.67. The corresponding carbon appeared at \(\delta\) 148.93, \(\delta\) 150.93 in the \(^{13}\)C NMR spectrum. A doublet at \(\delta\) 4.45 with coupling constant 5.2 Hz, another doublet appeared at \(\delta\) 4.50 with coupling constant of 5.0 Hz, was attributed to the allylic methylene protons for \(E\)- and \(Z\)- isomer in ration 1.34:0.66. The corresponding allylic methylene carbon appeared at \(\delta\) 70.80 and \(\delta\) 74.22 in \(^{13}\)C NMR spectrum. A multiplet at \(\delta\) 5.34-5.50 integrating for two protons corresponded to the terminal protons of the unconjugated olefin. The corresponding terminal carbon of the unconjugated olefin appeared at \(\delta\) 118.21, \(\delta\) 118.30 in the \(^{13}\)C NMR spectrum. A multiplet at \(\delta\) 5.97-6.12 integrating for one proton corresponded to the internal proton of the unconjugated olefin. The corresponding internal carbon of
Chapter 3

$\text{H NMR (300 MHz) Spectrum of the compound 501}$

$\text{C NMR (75 MHz) Spectrum of the compound 501}$
the unconjugated olefin appeared at $\delta$ 131.72 and $\delta$ 132.02 in the $^{13}$C NMR spectrum. A multiplet at $\delta$ 7.27-7.35 integrating for one proton corresponded to the aromatic protons para to the nitro group. A multiplet at $\delta$ 7.49-7.58 integrating for two protons corresponded to the aromatic protons meta to the nitro group. Two doublets at $\delta$ 7.92 and $\delta$ 8.19 integrating for one proton (ratio 0.67:0.33), with coupling constant 8.0 Hz was attributed to the aromatic proton ortho to the nitro group in $^1$H NMR spectrum. The aromatic carbons appeared at $\delta$ 124.12, 124.83, 125.91, 126.24, 126.91, 129.76, 130.91, 132.43, 132.71 and 147.14. The mass spectrum of this compound showed a molecular ion peak at m/z 205(M$^+$) corresponding to the molecular weight of the compound. Elemental analysis also supported the molecular formula C$_{11}$H$_{11}$NO$_3$ for the compound. Thus from the above data it is clear that in the Wittig reaction the allyl vinyl ether 501 was indeed formed and it was obtained as an inseparable mixture of $E$-and $Z$-isomers in a 2:1 ratio.

![Image of chemical structure](image)

501

The Claisen Rearrangement of the mixture of $E$- and $Z$-allyl vinyl ethers 501 was effected by heating the solution of allyl vinyl ether in dry xylene at reflux for 6-7 h. The crude product was purified by silica gel column chromatography with hexane-ethyl acetate mobile phase to afford the Claisen Rearrangement product (85%) as a yellow thick liquid.
The IR spectrum of the compound showed strong absorption bands at 1726 cm$^{-1}$ and 732 cm$^{-1}$, which confirmed the presence of carbonyl group in the compound. A singlet at $\delta$ 9.78 in $^1$H NMR spectrum, integrating for one proton was typical for an aldehyde proton, thus confirming the aldehyde group. This was further supported by the presence of a peak at $\delta$ 198.29 in $^{13}$C NMR spectrum. In the $^1$H NMR spectrum, a multiplet at $\delta$ 4.99-5.05 integrating for two protons corresponded to the olefinic protons on the terminal carbon of the olefin. A multiplet at $\delta$ 5.63-5.77 integrating for one proton, attributed to the internal olefinic proton. The terminal olefinic carbons resonated at $\delta$ 117.89 and $\delta$ 133.85 in $^{13}$C NMR spectrum. Two multiplets appearing at $\delta$ 2.50-2.60 and $\delta$ 2.90-2.99 and integrating for one proton each corresponded to the allylic protons. The allylic carbon in the $^{13}$C NMR spectrum appeared at $\delta$ 33.69. A multiplet at $\delta$ 4.28-4.33 integrating for one proton, attributed to the benzylic proton. The benzylic carbon appeared at $\delta$ 53.41 in $^{13}$C NMR spectrum. Two doublets at $\delta$ 7.28 and $\delta$ 7.97 integrating for one proton each with coupling constant 8.2 Hz and 8.0 Hz respectively were due to the aromatic protons. Another two triplets at $\delta$ 7.45 and $\delta$ 7.61 with coupling constant 8.0 Hz and 7.4 Hz respectively integrating for one proton each were attributed to the aromatic protons. The aromatic carbons appeared at $\delta$ 124.93, 128.34, 130.85, 131.02, 133.13, and 149.69 in the $^{13}$C NMR spectrum. The mass spectrum of this compound showed a molecular ion peak at m/z 205(M$^+$) corresponding to the molecular weight of the compound. Elemental analysis also supported the molecular formula C$_{11}$H$_{11}$NO$_3$ for the compound.
$^1$H NMR (300 MHz) Spectrum of the compound 502

$^{13}$C NMR (75 MHz) Spectrum of the compound 502
Thus the above spectral data confirmed the structure of the aldehyde 502.

\[
\begin{align*}
\text{CHO} \\
\text{NO}_2
\end{align*}
\]

502

In the next step aldehyde 502 was oxidized with Jones reagent in acetone at 0°C. The acetone was decanted and the green salt washed with acetone. After evaporation of the combined organic layers, water was added, and the crude product was extracted with ethyl acetate. After purification of the crude product on a silica gel column the pure product was obtained in 80% yield.

The IR spectrum the compound showed a broad absorption band at 3325 cm\(^{-1}\), 1710 cm\(^{-1}\), which indicated the presence of the acid group in the compound. In the \(^1\)H NMR spectrum a broad exchangeable singlet at \(\delta\) 9.17 integrating for one proton, corresponded to the acid proton. In the \(^{13}\)C NMR spectrum showed the peak at \(\delta\) 177.53 corresponded to the carbonyl carbon of the acid. In the \(^1\)H NMR spectrum, a multiplet at \(\delta\) 4.98-5.06 integrating for two protons corresponded to the olefinic protons on the terminal carbon of the olefin. A multiplet at \(\delta\) 5.70-5.78 integrating for one proton, attributed to the internal olefinic proton. The terminal olefinic carbons resonated at \(\delta\) 117.92 and \(\delta\) 134.13 in \(^{13}\)C NMR spectrum. Two multiplets at \(\delta\) 2.65 and \(\delta\) 2.90 each integrating for one proton were attributed to the allylic protons and the corresponding carbon resonated at \(\delta\) 36.21. A triplet at \(\delta\) 4.32, integrating for
one proton was attributed to the benzylic proton. The benzylic carbon appeared at $\delta$ 46.38 in $^{13}$C NMR spectrum. A triplet at $\delta$ 7.43, integrating for one proton, with coupling constant of 8.2 Hz, corresponded to the aromatic proton meta to the nitro group. A doublet at $\delta$ 7.52 integrating for one proton, with coupling constant of 7.6 Hz, was assigned to the aromatic proton meta to the nitro group. A triplet at $\delta$ 7.59 integrating for one proton, with coupling constant of 7.6 Hz, was attributed to the proton para to the nitro group. A doublet at $\delta$ 7.90 integrating for one proton, with coupling constant of 8.2 Hz, was assigned to the proton ortho to the nitro group. The aromatic carbons appeared at $\delta$ 124.80, 128.31, 130.42, 132.34, 133.10 and 149.13. The mass spectrum of the compound showed a molecular ion peak at m/z 221 (M$^+$) which corresponded to the molecular weight of the compound and the elemental analysis confirmed the molecular formula C$_{11}$H$_{11}$NO$_4$ for the compound. Thus the above data confirms the structure of the acid 503.

\[ \text{COOH} \]
\[ \text{NO}_2 \]

503

In the next step, esterification of acid 503 under usual conditions using ethanol and concentrated sulphuric acid gave the corresponding ethyl ester. The crude product was purified by column chromatography using ethyl acetate - hexane solvent system to furnish the pure product in quantitative yield.
Chapter 3

\[ \text{\( ^1H \) NMR (300 MHz) Spectrum of the compound 503} \]

\[ \text{\( ^{13}C \) NMR (75 MHz) Spectrum of the compound 503} \]
The IR spectrum of the compound showed, absence of the acid hydroxyl stretching and a strong absorption band at 1735 cm\(^{-1}\), which clearly indicated the formation of the ester. The \(^{13}\)C NMR spectrum showed the peak at \(\delta\) 171.92 corresponded to the carbonyl carbon of the ester. The methyl protons of the ester functionality appeared as a triplet at \(\delta\) 1.17-1.22 with coupling constant 7.1 Hz, and corresponding carbon resonated at \(\delta\) 13.91. Methylene protons of the ester functionality appeared as quartered at \(\delta\) 4.09-4.17 with coupling constant 4.4 Hz, and corresponding carbon resonated at \(\delta\) 61.11. In the \(^1\)H NMR spectrum, a multiplet at \(\delta\) 4.98-5.08 integrating for two protons corresponded to the olefinic protons on the terminal carbon of the olefin. A multiplet at \(\delta\) 5.70-5.79 integrating for one proton, attributed to the internal olefinic proton. The terminal olefinic carbons resonated at \(\delta\) 117.56 and \(\delta\) 134.45 in \(^{13}\)C NMR spectrum. Two multiplets at \(\delta\) 2.57-2.67 and \(\delta\) 2.87-2.96 each integrating for one proton were attributed to the allylic protons and corresponding carbon resonated at \(\delta\) 36.70. A triplet at \(\delta\) 4.26-4.31 with coupling constant 7.7Hz, integrating for one proton, attributed to the benzylic proton. The benzylic carbon appeared at \(\delta\) 46.10 in \(^{13}\)C NMR spectrum. A triplet at \(\delta\) 7.39-7.44, integrating for one proton, with coupling constant 7.2 Hz, corresponded to the aromatic proton \textit{meta} to the nitro group. A multiplet at \(\delta\) 7.52-7.61 integrating for two protons, was assigned to the aromatic proton \textit{meta} and para to the nitro group. A doublet at \(\delta\) 7.87-7.90 integrating for one proton, with coupling constant 8.2 Hz, was assigned to the aromatic proton \textit{ortho} to the nitro group. The aromatic carbons appeared at \(\delta\) 124.60, 127.97, 129.97, 132.83, 132.93 and 149.23.
Chapter 3

$\text{COOEt}$

$\text{NO}_2$

$\text{H NMR (300 MHz) Spectrum of the compound 504}$

$\text{COOEt}$

$\text{NO}_2$

$\text{C NMR (75 MHz) Spectrum of the compound 504}$

$\text{1H NMR (300 MHz) Spectrum of the compound 504}$

$\text{13C NMR (75 MHz) Spectrum of the compound 504}$
Molecular ions peak at m/z 249 and the elemental analysis correlated to the molecular formula C_{13}H_{15}NO_{4} for the compound. The above spectral information confirmed the structure of the compound of the ester 504.

In the next step reduction of nitro group in 504 with zinc and ammonium chloride in refluxing aqueous ethanol was carried out. After the reaction is over (monitored by TLC), the mixture was filtered, and the filtrate was evaporated under reduce pressure. The crude product was extracted with ethyl acetate and washed with brine, dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure, the crude product was purified by column chromatography using ethyl acetate - hexane solvent system to furnish the pure product in quantitative yield.

The IR spectrum the compound showed a broad absorption bands at 3280 cm^{-1}, 1708 cm^{-1}, which indicated the presence of the lactam in the compound. In the {^1}H NMR spectrum a broad exchangeable singlet at δ 9.85 integrating for one proton, corresponded to the oxindole N-H proton. In the {^{13}}C NMR spectrum showed the peak at δ 180.53 corresponded to the carbonyl carbon of the lactam. In the {^1}H NMR spectrum, a multiplet at δ 5.69-5.83 integrating for one proton, attributed to the internal olefinic proton. A multiplet at δ 5.02-5.14 integrating for two protons corresponded to the olefinic protons on
the terminal carbon of the olefin. The terminal olefinic carbons resonated at δ 117.93 and δ 133.74 in $^{13}$C NMR spectrum. Two multiplets at δ 2.53-2.63 and δ 2.79-2.87 each integrating for one proton were attributed to the allylic protons and corresponding carbon resonated at δ 34.58. A triplet at δ 3.50-3.54, integrating for one proton, with coupling constant 6.6 Hz, was attributed to the benzylic proton. The benzylic carbon appeared at δ 45.71 in $^{13}$C NMR spectrum. A multiplet at δ 6.91-7.01, integrating for two protons, corresponded to the aromatic protons. A multiplet at δ 7.16-7.25, integrating for two protons, corresponded to the aromatic protons. The aromatic carbons appeared at δ 109.86, 121.99, 124.17, 127.81, 129.12 and 141.70. The mass spectrum of the compound showed a molecular ion peak at m/z 173 (M$^+$) which corresponded to the molecular weight of the compound and the elemental analysis confirmed the molecular formula C$_{11}$H$_{11}$NO for the compound. Thus the above data confirms the structure of the oxindole 505.
Chapter 3

$\text{NH}_2\text{ONH}$

$^1\text{H NMR (300 MHz) Spectrum of the compound 505}$

$\text{NH}_2\text{ONH}$

$^{13}\text{C NMR (75 MHz) Spectrum of the compound 505}$
In the next step the nitrogen of oxindole 505 was to be protected with Boc. For this purpose, the oxindole 505 was treated with Boc anhydride in presence of DMAP in DCM at room temperature. On completion of the reaction (TLC check), normal aqueous extractive work-up gave the crude product. Purification of the crude product on silica gel column chromatography using hexane gave the pure product in good yield.

The IR spectrum the compound showed strong absorption bands at 1734 cm\(^{-1}\), 1772 cm\(^{-1}\) and 1795 cm\(^{-1}\), which indicated the presence of the lactam and an ester group in the compound. This indicated that the compound carries two, rather than one Boc group. In the \(^{13}\)C NMR spectrum showed the peak at \(\delta\) 166.68 and \(\delta\) 141.46 corresponded to the carbonyl carbon of the Boc, and \(\delta\) 172.12 corresponded to the carbonyl carbon of the lactam. In the \(^1\)H NMR spectrum, two singlets at \(\delta\) 1.36 and \(\delta\) 1.64 each integrating for nine protons corresponded to the methyl protons of the \(t\)-Boc group. The corresponding carbon resonated at \(\delta\) 27.48 and \(\delta\) 28.03. This further supported the notion that the compound contains two Boc groups. A multiplet at \(\delta\) 5.32-5.53 integrating for one proton was attributed to the internal olefinic proton. A multiplet at \(\delta\) 4.92-5.10 integrating for two protons corresponded to the olefinic protons on the terminal carbon of the olefin. The terminal olefinic carbons resonated at \(\delta\) 118.20 and \(\delta\) 134.75 in \(^{13}\)C NMR spectrum. A doublet at \(\delta\) 2.93-2.97 integrating for two protons was attributed to the allylic protons and corresponding carbon resonated at \(\delta\) 38.40. A multiplet at \(\delta\) 7.12-7.37, integrating for three protons, corresponded to the aromatic protons. A doublet at \(\delta\) 7.81-7.5, integrating for one proton, with coupling constant 8.0 Hz,
corresponded to the aromatic proton. The aromatic carbons appeared at δ 115.86, 122.42, 124.17, 126.18, 129.39 and 140.87. The $^1$H NMR spectrum was conspicuously absent with a signal corresponding to the benzylic proton. This further reinforced the conclusion that the compound contains two Boc groups and that the second Boc group is present at the benzylic position. The mass spectrum of the compound showed a molecular ion peak at m/z 373 which did not correspond to the molecular weight of the expected compound 506. On the other hand the molecular ion peak at m/z 373 matched well with, among other possible molecular formulae, a molecular formula C$_{21}$H$_{27}$NO$_5$. Elemental analysis also supported this molecular formula. On the basis of the above information structure 507 was assigned to the compound.

![Structure 506 and 507](image)

This is a rather unusual and potentially useful observation and more importantly this saved us one step, as in the next step introduction of a one carbon unit at the benzylic position was planned. In order to construct the 3,3-spiro-oxindole skeleton of coerulescine and horsfiline, it was essential to oxidatively cleave the double in the compound 507. This operation was effected with ozone in DCM at 0°C. After the reaction was over, excess ozone was
$^{1}H$ NMR (200 MHz) Spectrum of the compound 507

$^{13}C$ NMR (75 MHz) Spectrum of the compound 507
removed by purging the reaction mixture with nitrogen and then the ozonide was treated with excess dimethyl sulfide to get the pure product in 80% yield after silica gel column chromatographic purification.

The IR spectrum of the compound showed one extra strong absorption band, apart from those for the lactam and ester carboxyls, at 1707 cm\(^{-1}\) which clearly indicated the presence of the aldehyde. A singlet at \(\delta\) 9.65 in \(^1\)H NMR spectrum, integrating for one proton was typical for an aldehyde proton, thus confirming the aldehyde group. This was further supported by the presence of a peak at \(\delta\) 197.04 in \(^{13}\)C NMR spectrum. The methylene protons alpha to the aldehyde group appeared as a singlet at \(\delta\) 3.39. The corresponding carbon appeared at \(\delta\) 47.28 in the \(^{13}\)C NMR spectrum. Two singlets at \(\delta\) 1.33 and \(\delta\) 1.65 each integrating for nine protons corresponded to the methyl protons on the t-Boc and corresponding carbon appeared at \(\delta\) 27.45 and \(\delta\) 28.00 in the \(^{13}\)C NMR spectrum. The tertiary carbons of the t-Boc appeared at \(\delta\) 83.67 and \(\delta\) 84.46 in the \(^{13}\)C NMR spectrum. The \(^{13}\)C NMR spectrum showed the peak at \(\delta\) 172.04 corresponded to the carbonyl carbon of the lactam, \(\delta\) 166.51 corresponded to the carbonyl carbon of the Boc, and \(\delta\) 149.05 corresponded to the carbonyl carbon of the N-Boc. The benzylic carbon appeared at \(\delta\) 57.05 in \(^{13}\)C NMR spectrum. A multiplet at \(\delta\) 7.11-7.20, integrating for two protons, corresponded to the aromatic protons. A triplet at \(\delta\) 7.32-7.37 integrating for one proton, with coupling constant 7.3 Hz, was attributed to the aromatic proton. A doublet at \(\delta\) 7.87-7.90 integrating for one proton, with coupling constant 8.3 Hz, was assigned to the aromatic proton.
\[ \text{Boc} - \text{CHO} \]

\[ \text{Boc} \]

\[ \text{N} \]

\[ \text{Boc} \]

\[ \text{CHO} \]

\[ \text{Boc} \]

\[ \text{Boc} \]

\[ \text{N} \]

\[ \text{Boc} \]

\[ \text{H NMR (300 MHz) Spectrum of the compound 508} \]

\[ \text{Boc} - \text{CHO} \]

\[ \text{Boc} \]

\[ \text{N} \]

\[ \text{Boc} \]

\[ \text{CHO} \]

\[ \text{Boc} \]

\[ \text{N} \]

\[ \text{Boc} \]

\[ \text{C NMR (75 MHz) Spectrum of the compound 508} \]
The aromatic carbons appeared at δ 115.46, 122.27, 124.51, 126.52, 129.32 and 140.46. Molecular ions peak at m/z 375 and the elemental analysis correlated to the molecular formula C_{20}H_{25}NO_{6} for the compound. The above spectral information confirmed the structure of the compound 508.

![Chemical Structure](image)

**508**

In the next step reductive amination in *situ* cyclization of aldehyde 508 by using methylamine hydrochloride, followed by reduction with sodium cyano borohydride in THF at 0°C gave crude product. The crude product was purified by silica gel column chromatography with hexane - ethyl acetate to afford pure product as a yellow thick oil 50% yield.

The IR spectrum the compound showed a strong absorption band at 3405 cm\(^{-1}\) which indicated the presence of the secondary amine group in the compound. In the \(^1\)H NMR spectrum a broad exchangeable singlet at δ 8.61 integrating for one proton, corresponded to the amino N-H proton. A singlet at δ 2.93 integrating for three protons corresponded to the N-methyl protons. The corresponding N-methyl carbon appeared at δ 39.69 in the \(^{13}\)C NMR spectrum. The methylene protons alpha to the amine gave two multiplets at δ 2.85 and δ 2.97 each integrating for one proton. The corresponding methylene carbon appeared at δ 51.63 in the \(^{13}\)C NMR spectrum. The methylene protons beta to the amine appeared as a multiplet at δ 2.42-2.48, integrating for two protons in
the \( ^1H \) NMR spectrum. The corresponding methylene carbon appeared at \( \delta \) 34.55 in the \( ^{13}C \) NMR spectrum. Two singlets at \( \delta \) 1.41 and \( \delta \) 1.48 each integrating for nine protons corresponded to the methyl protons on the Boc and corresponding carbon resonated at \( \delta \) 27.47 and \( \delta \) 28.34 in the \( ^{13}C \) NMR spectrum. The tertiary carbons of the \( t \)-Boc appeared at \( \delta \) 82.12 and \( \delta \) 83.99 in the \( ^{13}C \) NMR spectrum. The \( ^{13}C \) NMR spectrum showed the peak at \( \delta \) 172.65 corresponded to the carbonyl carbon of the lactam, \( \delta \) 171.73 corresponded to the carbonyl carbon of the Boc and \( \delta \) 154.03 corresponded to the carbonyl carbon atom of the \( N \)-Boc. The benzylic carbon appeared at \( \delta \) 60.39 in \( ^{13}C \) NMR spectrum. A triplet at \( \delta \) 7.09-7.14, integrating for one proton, with coupling constant 7.3 Hz, corresponded to the aromatic proton. A multiplet at \( \delta \) 7.22-7.33 integrating for two protons was attributed to the aromatic protons. A doublet at \( \delta \) 7.64-7.66 integrating for one proton, with coupling constant 6.1 Hz, was assigned to the aromatic proton. The aromatic carbons appeared at \( \delta \) 124.65, 126.08, 126.33, 128.58, 130.08 and 137.25. Molecular ions peak at m/z 390 and the elemental analysis correlated to the molecular formula \( C_{21}H_{30}N_2O_5 \) for the compound. The above spectral information confirmed the structure of the compound 509.

![Structure 509](image1)

![Structure 510](image2)
$^1$H NMR (300 MHz) Spectrum of the compound 509

$^{13}$C NMR (75 MHz) Spectrum of the compound 509
During the above operation reductive amination in \textit{situ} cyclization to compound \textbf{510} was expected. However from the analytical data for the compound \textbf{509} it is clear that the desired five-member lactam product was not obtained. Probably the steric bulk of the Boc group prevented the lactam formation to yield the compound \textbf{509} rather than compound \textbf{510}. To circumvent the problem, it became necessary selectively effect N-Boc formation and then introduce an ethyl/methyl ester group at the benzylic position so that the required compound \textbf{510} will be obtained. For this purpose, the compound \textbf{505} was treated with \((\text{Boc})_2\text{O}\) using 1eq. of NaH in THF at 0°C for 5 min. After removal of THF under reduced pressure, reaction mixture was diluted with water and extracted in ethyl acetate. Ethyl acetate layer dried over sodium sulphate and solvent was evaporated. The crude product was purified by silica gel column chromatography with acetone - hexane solvent system to afford the pure product \textbf{506} in (70%) yield.

The IR spectrum of the compound showed two strong absorption bands at 1732 cm\(^{-1}\) and 1767 cm\(^{-1}\), which indicated the presence of the lactam and ester group in the compound. This indicated that the compound carry one Boc group. The \(^{13}\text{C}\) NMR spectrum showed the peak at \(\delta\) 149.02 corresponded to the carbonyl carbon of the Boc. The methyl protons of the Boc functionality appeared as a singlet at \(\delta\) 1.64, and corresponding carbon resonated at \(\delta\) 27.89. This further supported the notion that the compound contains only one Boc group. A triplet at \(\delta\) 3.59-3.63, integrating for one proton, with coupling constant 6.5 Hz, was attributed to the benzylic proton. The benzylic carbon
appeared at $\delta$ 45.48 in $^{13}\text{C}$ NMR spectrum. The olefinic protons on the terminal carbon of the olefin appeared as a multiplet at $\delta$ 5.05-5.14, while the internal olefinic proton appeared as a multiplet at $\delta$ 5.68-5.79. The terminal olefinic carbons resonated at $\delta$ 114.70 and $\delta$ 133.27 in $^{13}\text{C}$ NMR spectrum. Two multiplets at $\delta$ 2.58-2.68 and $\delta$ 2.79-2.88 each integrating for one proton was attributed to the allylic protons and corresponding carbon resonated at $\delta$ 35.25. A triplet at $\delta$ 7.11-7.16, integrating for one proton, with coupling constant 7.6 Hz, corresponded to the aromatic proton. A multiplet at $\delta$ 7.27-7.32 integrating for two protons was assigned to the aromatic protons. A doublet at $\delta$ 7.79-7.82 integrating for one proton, with coupling constant 8.2 Hz, was attributed to the aromatic proton. The aromatic carbons appeared at $\delta$ 118.36, 123.82, 123.96, 127.20, 127.96, and 139.88 Molecular ions peak at m/z 273 and the elemental analysis correlated to the molecular formula $\text{C}_{16}\text{H}_{19}\text{NO}_3$ for the compound. The above spectral information confirmed the structure 506 for the compound in hand.

\[ \text{506} \]

In the next step in order to construct the 3,3-spiro-oxindole skeleton of coerulescine and horsfiline, it was essential to effect carboxylation at C-3 position in compound 506.
Chapter 3

$\text{Boc}$

$\text{H NMR (300 MHz) Spectrum of the compound 506}$

$\text{Boc}$

$\text{C NMR (75 MHz) Spectrum of the compound 506}$

225
This was realized with ethyl cloroformate in presence of the NaH in dry THF at 0°C. After removal of THF under reduced pressure, reaction mixture was diluted with water and extracted in ethyl acetate. Ethyl acetate layer dried over sodium sulphate and solvent was evaporated. The crude product was purified by silica gel column chromatography with acetone - hexane solvent system to afford the pure product in (80%) yield.

The IR spectrum of the compound showed strong absorption bands at 1735 cm\(^{-1}\), 1775 cm\(^{-1}\) and 1798 cm\(^{-1}\) which clearly indicated the presence of additional ester group in the compound. The \(^{13}\)C NMR spectrum showed a peak at \(\delta\) 148.78 corresponded to the carbonyl carbon of the ethyl ester. The methyl protons of the ester functionality appeared as a triplet at \(\delta\) 1.37-1.42, with coupling constant 7.0 Hz. The corresponding carbon resonated at \(\delta\) 14.04. Methylene protons of the ester functionality appeared as quartered at \(\delta\) 4.31-4.38, with coupling constant 7.6 Hz, and corresponding carbon resonated at \(\delta\) 65.53. In the \(^1\)H NMR spectrum, a singlet at \(\delta\) 1.63 integrating for nine protons corresponded to the methyl protons on the Boc and corresponding carbon appeared at \(\delta\) 28.03 in the \(^{13}\)C NMR spectrum. The tertiary carbon of the Boc appeared at \(\delta\) 84.17 in the \(^{13}\)C NMR spectrum. The \(^{13}\)C NMR spectrum showed the peak at \(\delta\) 152.27 and \(\delta\) 137.91 corresponded to the carbonyl carbon of the lactam and Boc respectively. In the \(^1\)H NMR spectrum, a multiplet at \(\delta\) 5.03-5.16 integrating for two protons corresponded to the olefinic protons on the terminal carbon of the olefin. A multiplet at \(\delta\) 5.86-5.99 integrating for one proton, attributed to the internal olefinic proton. The
terminal olefinic carbons resonated at \( \delta \) 115.31 and \( \delta \) 132.20 in \(^{13}\)C NMR spectrum. A doublet at \( \delta \) 3.36-3.38 with coupling constant 5.9 Hz, integrating for two protons was attributed to the allylic protons and corresponding carbon resonated at \( \delta \) 26.78. The benzylic carbon appeared at \( \delta \) 106.10 in \(^{13}\)C NMR spectrum. A multiplet at \( \delta \) 7.20-7.34, integrating for two protons, corresponded to the aromatic proton. A doublet at \( \delta \) 7.46-7.49 integrating for one proton, with coupling constant 7.0 Hz, was assigned to the aromatic proton. A doublet at \( \delta \) 8.06-8.08 integrating for one proton, with coupling constant 8.2 Hz, was attributed to the aromatic proton. The aromatic carbons appeared at \( \delta \) 115.95, 118.98, 122.77, 124.22, 126.91 and 134.75. Molecular ions peak at m/z 345 and the elemental analysis correlated well with the molecular formula \( \text{C}_{19}\text{H}_{23}\text{NO}_5 \) for the compound. The above spectral information confirmed the structure of the compound 511.

![511](image)

In the next step, oxidative cleavage of double in 511 with catalytic potassium osmate and NMO in aq. THF furnished the diol. The cleavage of this diol with sodium metaperiodate in aqueous solution was reported\(^{47}\) to be a complex reaction giving little expected product, if any. To avoid this problem this diol was cleaved under nonaqueous conditions with sodium metaperiodate adsorbed on silica to get the crude product.
$^{1}H$ NMR (300 MHz) Spectrum of the compound 511

$^{13}C$ NMR (75 MHz) Spectrum of the compound 511
The crude product was purified by silica gel column chromatography with acetone - hexane solvent system to afford the pure product in (80%) yield.

The IR spectrum of the compound showed one extra strong absorption band at 1735 cm$^{-1}$ which clearly indicated the presence of the aldehyde in the compound. A singlet at δ 9.66 in $^1$H NMR spectrum, integrating for one proton was typical for an aldehyde proton, thus confirming the presence of the aldehyde group. This was further supported by the presence of a peak at δ 197.80 in $^{13}$C NMR spectrum. The methylene protons alpha to the aldehyde group appeared as a doublet at δ 3.64-3.65 with coupling constant 2.4 Hz. The corresponding carbon appeared at δ 37.51 in the $^{13}$C NMR spectrum. The methyl protons of the ester functionality appeared as a triplet at δ 1.38-1.43, with coupling constant 7.3 Hz. The corresponding carbon resonated at δ 14.00. Methylene protons of the ester functionality appeared as quartet at δ 4.33-4.40, with coupling constant 7.3 Hz, and corresponding carbon resonated at δ 65.96. In the $^1$H NMR spectrum, a singlet at δ 1.65 integrating for nine protons corresponded to the methyl protons on the Boc and corresponding carbon appeared at δ 28.03 in the $^{13}$C NMR spectrum. The tertiary carbon of the Boc appeared at δ 84.79 in the $^{13}$C NMR spectrum. The $^{13}$C NMR spectrum showed the peak at δ 152.15 corresponded to the carbonyl carbon of the lactam, δ 148.52 corresponded to the carbonyl carbon of the ethyl ester group and δ 139.47 corresponded to the carbonyl carbon of the Boc group. The benzylic carbon appeared at δ 99.55 in $^{13}$C NMR spectrum. A multiplet at δ 7.26-7.41, integrating for three protons, corresponded to the aromatic protons.
A doublet at δ 8.07-8.10 integrating for one proton, with coupling constant 7.3 Hz, was assigned to the aromatic proton. The aromatic carbons appeared at δ 115.52, 118.40, 123.29, 124.78, 126.39 and 132.14. Molecular ions peak at m/z 347 and the elemental analysis correlated to the molecular formula C_{18}H_{21}NO_{6} for the compound. The above spectral information confirmed the structure of the compound 512.

After the successful preparation of aldehyde 512 in an efficient manner, its further conversion of coerulescine and horsfiline was carried out by following the reported procedure of Barry M. Trost.\textsuperscript{47} Thus the aldehyde 512 was subjected to reductive amination in situ cyclization by using methylamine hydrochloride salt and MgSO\textsubscript{4} in dry THF. The reaction mixture was stirred for 2 hr at room temperature. Then sodium cyanoborohydride was added at 0°C and then stirred at room temperature for 2h. On completion of the reaction, the reaction mixture was filtered, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with hexane - ethyl acetate to afford the pure product in (60%) yield.
Chapter 3

\[ \text{EtOOC} \quad \text{CHO} \quad \text{Boc} \]

$^{1}H$ NMR (300 MHz) Spectrum of the compound 512

\[ \text{EtOOC} \quad \text{CHO} \quad \text{Boc} \]

$^{13}C$ NMR (75 MHz) Spectrum of the compound 512
The IR spectrum of the compound showed strong absorption band at 1712 cm\(^{-1}\) which clearly indicated the presence of the amide in the compound. In the \(^1\)H NMR spectrum, showed a singlet at $\delta$ 2.95 integrating for three protons, corresponded to the \(N\)-methyl protons. The corresponding carbon appeared at $\delta$ 30.85. The methylene protons at C-4' # position gave two multiplets at $\delta$ 2.37 and $\delta$ 3.13 each integrating for one proton. The corresponding C-4' carbon appeared at $\delta$ 29.15 in the \(^{13}\)C NMR spectrum. The methylene protons at C-3' position appeared as a multiplet separately one at $\delta$ 3.54 and other proton appeared as a multiplet at $\delta$ 4.00. The corresponding C-3' carbon appeared at $\delta$ 47.05 in the \(^{13}\)C NMR spectrum. A singlet at $\delta$ 1.53 integrating for nine protons corresponded to the methyl protons on the \(N\)-Boc and corresponding carbon resonated at $\delta$ 28.05 in the \(^{13}\)C NMR spectrum. The tertiary carbon of the \(N\)-Boc appeared at $\delta$ 84.50 in the \(^{13}\)C NMR spectrum. The \(^{13}\)C NMR spectrum showed the peak at $\delta$ 174.23 and $\delta$ 159.78 corresponding to the carbonyl carbon of the lactam, and $\delta$ 147.55 corresponded to the carbonyl carbon of the \(N\)-Boc. The benzylic carbon appeared at $\delta$ 95.21 in \(^{13}\)C NMR spectrum. A triplet at $\delta$ 7.09-7.14, with coupling constant 7.3 Hz, integrating for one proton, corresponded to the aromatic protons. A doublet at $\delta$ 7.22-7.25 integrating for one proton, with coupling constant 8.6 Hz, was assigned to the aromatic proton. A triplet at $\delta$ 7.28-7.33 integrating for one proton, with coupling constant 7.3 Hz, was attributed to the aromatic proton.

# the numbering of the atoms follows the standard horsfiline numbering.
$^1$H NMR (300 MHz) Spectrum of the compound 510

$^{13}$C NMR (75 MHz) Spectrum of the compound 510
A doublet at $\delta$ 7.75-7.78 integrating for one proton, with coupling constant 8.2 Hz, was assigned to the aromatic proton. The aromatic carbons appeared at $\delta$ 115.80, 118.40, 123.50, 124.95, 127.20, and 136.71. Molecular ions peak at m/z 316 and the elemental analysis correlated to the molecular formula C$_{17}$H$_{20}$N$_2$O$_4$ for the compound. The above spectral information confirmed the structure of the compound 510.

![Structure](image)

510

In the next step removal of Boc group from the oxindole nitrogen was accomplished by using 2.5 M HCl in THF refluxing for 30 min (TLC check) to give the crude product. The crude product was purified by silica gel column chromatography with chloroform – methanol to yield pure product.

The IR spectrum of the compound showed absorption bands at 3215 cm$^{-1}$ and 1708 cm$^{-1}$, this indicated that the Boc group from the oxindole nitrogen has been removed. In the $^1$H NMR spectrum a broad exchangeable singlet at $\delta$ 8.10 integrating for one proton, corresponded to the $N$-H proton. A singlet at $\delta$ 2.91 integrating for three protons corresponded to the $N$-methyl protons. The corresponding carbon appeared at $\delta$ 31.58. The methylene protons at C-4′ position gave two multiplets, one at $\delta$ 2.32 and another at $\delta$ 3.01, each integrating for one proton. The corresponding C-4′ carbon appeared
at δ 30.11 in the $^{13}$C NMR spectrum. One of the methylene proton at C-3′ position appeared as a multiplet at δ 3.51 and the other appeared as a multiplet at δ 3.91. The corresponding C-3′ carbon appeared at δ 48.36 in the $^{13}$C NMR spectrum. The $^{13}$C NMR spectrum showed the peak at δ 176.31 and δ 170.54 corresponded to the carbonyl carbon of the lactam. The benzylic carbon appeared at δ 84.50 in $^{13}$C NMR spectrum. A multiplet at δ 6.77 integrating for two protons corresponded to the aromatic protons. A triplet at δ 7.03 integrating for one proton was attributed to the aromatic proton. A doublet at δ 7.28 integrating for one proton was assigned to the aromatic proton. The aromatic carbons appeared at δ 118.10, 121.08, 124.17, 127.81, 130.93, and 140.70. Molecular ions peak at m/z 216 and the elemental analysis correlated to the molecular formula C$_{12}$H$_{12}$N$_{2}$O$_{2}$ for the compound. The above spectral information confirmed the structure of the compound 513.
$^1$H NMR (300 MHz) Spectrum of the compound 513

$^{13}$C NMR (75 MHz) Spectrum of the compound 513
For completing the synthesis of Coerulescine 380, compound 513 was subject to the chemoselective reduction of lactam reported by Barry M. Trost\textsuperscript{47} by using \textit{n}-butyl lithium and lithium aluminum hydride. Initially deprotonating of lactam 513 with \textit{n}-butyl lithium at 0\degree C, then the LAH was added at 0\degree C and then warmed to room temperature and stirred for 1 h. The reaction was then quenched with water, and then filtered over Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The crude product was purified by silica gel column chromatography to yield coerulescine 380 as pale yellow gum.

The IR spectrum of the compound showed absorption bands at 3212 cm\textsuperscript{-1} and 1709 cm\textsuperscript{-1} indicating the presence of the lactam in the compound. In the \textsuperscript{1}H NMR spectrum a broad exchangeable singlet at δ 8.61 integrating for one proton, corresponded to the N-H proton. In the \textsuperscript{13}C NMR spectrum the carbonyl carbon of the lactam appeared at δ 183.28. \textit{N}-methyl protons appeared as a singlet at δ 2.48 and corresponding carbon resonated at δ 41.78. The methylene protons at C-4' position gave two multiplets at δ 2.07 and δ 2.40 each integrating for one proton and corresponding carbon appeared at δ 37.88. The signals appearing between δ 2.75-3.05 and integrating for four protons corresponded to methylene protons at C-3' and C-1' and corresponding carbons appeared at δ 56.68 and δ 66.12. The benzylic carbon appeared at δ 53.65 in the \textsuperscript{13}C NMR spectrum. A doublet at δ 6.89 integrating for one proton with a coupling constant 7.8 Hz, was attributed to the aromatic proton. A triplet at δ 7.04 with coupling constant 7.3 Hz, integrating for one proton, was assigned to the aromatic proton. A triplet at δ 7.20 integrating for one proton,
with coupling constant 7.5 Hz, corresponded to the aromatic proton. A doublet at $\delta$ 7.41 with coupling constant 7.3 Hz, integrating for one proton, was attributed to the aromatic proton. The aromatic carbons appeared at $\delta$ 109.75, 122.84, 123.29, 127.81, 136.02 and 140.38. The structure of the compound was further confirmed by the mass spectrum, wherein the molecular ion peak was observed at $(M^+) 202$. Elemental analysis also supported the molecular formula $C_{12}H_{14}N_2O$. The above spectral data of the coerulescine was well in accordance with the reported values.\textsuperscript{29,32,37}

This completed the total synthesis of (±)-coerulescine. To complete the synthesis of horsfiline 376, the compound 380 was treated with $N$-bromosuccinimide in DMF at 0°C for 2 hr. After addition of water, the aqueous solution of water was extracted with ether. Ether part of the extract was dried over sodium sulphate and concentrated. In the next steps the crude product was treated with CuI and sodium methoxide solution in DMF at 120°C for 2 hr, the crude reaction mixture was cooled and the insoluble materials were filtered off, extracted with ether and concentrated.
Chapter 3

$^1$H NMR (300 MHz) Spectrum of the compound 380

$^{13}$C NMR (75 MHz) Spectrum of the compound 380
Chapter 3

The crude product was purified by silica gel column chromatography to yield horsfiline 376 as light yellow crystals mp 152-154° C (lit. 156-157° C).²

The IR spectrum of the compound showed absorption bands at 3215 cm⁻¹ and 1708 cm⁻¹ indicating the presence of the lactam in the compound. In the ¹H NMR spectrum a broad exchangeable singlet at δ 8.20 integrating for one proton, corresponded to the lactam N-H proton. In the ¹³C NMR spectrum the carbonyl carbon atom of the lactam appeared at δ 182.95. ¹H NMR spectrum the compound showed a singlet at δ 3.80 integrating for three protons corresponding to the methoxy protons. The corresponding methoxy carbon appeared at δ 56.58. N-methyl protons appeared as a singlet at δ 2.49 and corresponding carbon resonated at δ 41.78. The methylene protons at C-4' position gave two multiplets at δ 2.07-2.12 and δ 2.37-2.45 each integrating for one proton and corresponding carbon appeared at δ 38.25. The methylene protons at C-3' appeared as two multiplets at δ 2.77-2.83 and δ 2.99-3.07 each integrating for one proton, and corresponding carbon appeared at δ 56.02. The methylene protons at C-1' position gave a singlet at δ 2.88 integrating for two protons and corresponding carbon appeared at δ 66.30. The benzylic carbon appeared at δ 54.18 in the ¹³C NMR spectrum. A doublet at δ 6.72 integrating for one proton with a coupling constant 8.0 Hz, was attributed to the aromatic proton. A doublet at δ 6.78 with coupling constant 8.0 Hz, integrating for one proton, was assigned to the aromatic proton. A doublet at δ 7.05 integrating for one proton, with coupling constant 2.0 Hz, corresponded to the aromatic proton. The aromatic carbons appeared at δ 156.28, 137.31,
133.47, 112.53, 110.27 and 109.92. The structure of the compound was further confirmed by the mass spectrum, wherein the molecular ion peak was observed at (M+)^+ 232. Elemental analysis also supported the molecular formula C_{13}H_{16}N_{2}O_{2}. The above spectral data of the horsfiline 376 was well in accordance with the reported values.\textsuperscript{2,29,32,37,40.}

Thus one of the shortest and most efficient total synthesis of the (±)-horsfiline has been achieved.
\(^1\)H NMR (300 MHz) Spectrum of the compound 376
EXPERIMENTAL SECTION

All solvents were distilled before use. Dry THF was prepared by distilling over sodium and benzophenone, under dry nitrogen atmosphere and stored over sodium wire and was freshly distilled before use. All the liquid reagents were distilled and stored under anhydrous and nitrogen atmosphere. Dry benzene was prepared by washing it with conc. H₂SO₄ and distilling over sodium and was stored over sodium wire by similar treatment toluene and xylene were rendered dry. Dry acetone was obtained by refluxing over KMnO₄ till permanent pink color persisted (6h to 8h) and then refluxed over anhydrous K₂CO₃ for 4 h, distilled and stored over anhydrous K₂CO₃. Tert. butanol was dried by refluxing and distilling over calcium hydride and was stored over molecular sieves (4Å). Dry diglyme was prepared by refluxing over calcium hydride for 7-8 h and was distilled and stored over molecular sieves (4Å). All the anhydrous reactions were carried out under dry nitrogen atmosphere. IR spectra were recorded on Shimadzu 8400 FT-IR instrument. ¹H NMR and ¹³C NMR spectra [ppm, TMS-internal standard] in CDCl₃ were recorded on Varian Mercury 300 instrument. Mass spectra were recorded at ionization energy of 70 eV on Shimadzu GCMS-QP5050A automated GC/MS instrument and mass values are expressed as (m/z). Silica gel (100-200 mesh) was used for column chromatography.
To a suspension of \( o \)-nitro benzaldehyde (6.62 mmol) and allyloxymethylenetriphenylphosphonium chloride (7.94 mmol) in dry THF at 0\(^\circ\)C was dropwise added a solution of \( t \)-BuO\(^-\)Na\(^+\) (7.94 mmol) in dry THF. After 45-50 min (TLC check) THF was removed under vacuum. The crude allyl vinyl ether was extracted with ethyl acetate (3 × 10 ml). The combined organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and evaporated off under vacuum. The crude product was purified by column chromatography using appropriate mobile phase (Ethylacetate- Hexane) pure allyl vinyl ether \(501\) was obtained as an inseparable mixture of geometrical isomers in good yield.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 4.45 (d, \(J = 5.2\) Hz, 1.34H, -\(\text{CH}_2\text{CH}=\text{CH}_2\)) \(E\)-isomer, 4.50 (d, \(J =5.2\) Hz, 0.66H, -\(\text{CH}_2\text{CH}=\text{CH}_2\)) \(Z\)-isomer, 5.34-5.50 (m, 2H, \(\text{CH}=\text{CH}_2\)), 5.75 (d, \(J =7.3\) Hz, 0.33H, -\(\text{CH}=\text{CH}-\text{O}-\)), 5.97-6.12 (m, 1H, \(\text{CH}=\text{CH}_2\)), 6.42 (d, \(J =7.3\) Hz, 0.33H, -\(\text{CH}=\text{CH}-\text{O}-\)), 6.50 (d, \(J =12.9\) Hz, 0.67H, -\(\text{CH}=\text{CH}-\text{O}-\)), 7.08 (d, \(J =12.9\) Hz, 0.67H, -\(\text{CH}=\text{CH}-\text{O}-\)), 7.27-7.35 (m, 1H, Ar-\(\text{H}\)), 7.49-7.58 (m, 2H, Ar-\(\text{H}\)), 7.92 (d, \(J =8.0\) Hz, 0.67H, Ar-\(\text{H}\)), 8.19 (d, \(J =8.0\) Hz, 0.33H, Ar-\(\text{H}\)).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 150.93, 148.93, 147.14, 132.71, 132.43, 132.02, 131.72, 130.91, 129.76, 126.91, 126.24, 125.91, 124.83, 124.12, 118.30, 118.21, 101.86, 99.12, 74.22, 70.80.
IR (Neat): 2922, 2856, 1681, 1525, 1352, 916, 732 cm.\textsuperscript{1}

GCMS (rel. intensity) m/z: 205.

Anal. Calcd for C\textsubscript{12}H\textsubscript{13}NO\textsubscript{3}: C, 64.38; H, 5.40; N, 6.83. found: C, 64.50; H, 5.33; N, 6.86.

2-(2-nitrophenyl)-pent-4-enal 502.

The allyl vinyl ether 501 obtained from Wittig Olefination was refluxed in xylene for 6-7h. Complete consumption of the starting material was observed (TLC check). At this stage the reaction mixture was cooled at room temperature and stripped off the solvent under reduced pressure. The crude product was purified by silica gel column chromatography with hexane-ethyl acetate mobile phase to afford 502 (85\%) as a yellow thick liquid.

\( ^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \): 2.50-2.60 (m, 1H, -CH\textsubscript{2}CH=CH\textsubscript{2}), 2.90-2.99 (m, 1H, -CH\textsubscript{2}CH=CH\textsubscript{2}), 4.28-4.33 (m, 1H, Ar-CH), 4.99-5.05 (m, 2H, CH=CH\textsubscript{2}), 5.63-5.77 (m, 1H, CH=CH\textsubscript{2}), 7.28 (d, \( J = 8.2 \) Hz, 1H, Ar-H), 7.45 (t, \( J = 8.0 \) Hz, 1H, Ar-H), 7.61 (t, \( J = 7.4 \) Hz, 1H, Ar-H), 7.97 (d, \( J = 8.0 \) Hz, 1H, Ar-H), 9.78 (s, 1H, CHO).

\( ^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \): 198.29, 149.69, 133.85, 133.13 131.02, 130.85, 128.34, 124.93, 117.89, 53.41, 33.69.

IR (Neat): 2928, 2858, 2719, 1726, 1641, 1527, 1357, 921, 732 cm.\textsuperscript{1}

GCMS (rel. intensity) m/z: 205.
Anal. Calcd for C\textsubscript{11}H\textsubscript{11}NO\textsubscript{3}: C, 64.38; H, 5.40; N, 6.83. found: C, 64.51; H, 5.30; N, 6.87.

2-(2-nitrophenyl)pent-4-enoic acid 503.

![2-(2-nitrophenyl)pent-4-enoic acid](image)

A solution of aldehyde 502 (4.87 mmol) in acetone Jones reagent was added drop wise at 0\(^\circ\) C and the resulting mixture was stirred at room temperature. The acetone was decanted and the green salt washed with acetone. After evaporation of the combined organic layers, water was added, and the product was extracted with ethyl acetate. Evaporation of the solvent and chromatography on silica with ethyl acetate - hexane afforded (80%) of acid 503.

\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 2.65 (m, 1H, \(-\text{CH}_2\text{CH}=\text{CH}_2\)), 2.90 (m, 1H, \(-\text{CH}_2\text{CH}=\text{CH}_2\)), 4.32 (t, \(J = 7.0\) Hz, 1H, Ar-CH), 4.98-5.06 (m, 2H, CH=CH\textsubscript{2}), 5.70-5.78 (m, 1H, CH=CH\textsubscript{2}), 7.43 (t, \(J = 8.2\) Hz, 1H, Ar-H), 7.52 (d, \(J = 7.6\) Hz, 1H, Ar-H), 7.59 (t, \(J = 7.6\) Hz, 1H, Ar-H), 7.90 (d, \(J = 8.2\) Hz, 1H, Ar-H), 9.17 (bs, 1H, COOH).

\(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 177.53, 149.13, 134.13, 133.10, 132.34, 130.42, 128.31, 124.80, 117.92, 46.38, 36.21.

IR (Neat): 3325, 2980, 2928, 1710, 1527, 922. cm\(^{-1}\)

GCMS (rel. intensity) m/z: 221.
Anal. Calcd for C\textsubscript{11}H\textsubscript{11}NO\textsubscript{4}: C, 59.73; H, 5.01; N, 6.33. found: C, 59.89; H, 4.98; N, 6.36.

**Ethyl2-(2-nitrophenyl)pent-4-enoate 504**

![Chemical Structure](image)

A solution of acid 503 in dry ethanol was added catalytic amount of concentrated sulphuric acid, the resulting mixture reflux for 1h. The methanol was evaporated under reduced pressure. The residue was extracted with ethyl acetate, washed with brine, dried on anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified on a silica chromatography using ethyl acetate – hexane to furnish the ester 504 in 82% yield.

\(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 1.19 (t, \(J = 7.1\) Hz, 3H, -CH\textsubscript{2}CH\textsubscript{3}), 2.57-2.67 (m, 1H, -CH\textsubscript{2}CH=CH\textsubscript{2}), 2.87-2.96 (m, 1H, -CH\textsubscript{2}CH=CH\textsubscript{2}), 4.09-4.17 (q, \(J = 4.4\) Hz, 2H, -CH\textsubscript{2}CH\textsubscript{3}), 4.29 (t, \(J = 7.7\) Hz, 1H, Ar-CH), 4.98-5.08 (m, 2H, CH=CH\textsubscript{2}), 5.70-5.79 (m, 1H, CH=CH\textsubscript{2}), 7.39-7.44 (t, \(J = 7.2\) Hz, 1H, Ar-H), 7.52-7.59 (m, 2H, Ar-H), 7.87-7.90 (d, \(J = 8.2\) Hz, 1H, Ar-H).

\(^13\)C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 171.92, 149.23, 134.45, 132.93, 132.83, 129.97, 127.97, 124.60, 117.56, 61.11, 46.10, 36.70, 13.91.

IR (Neat): 2982, 1735, 1529, 1352, 916, 736. cm\(^{-1}\)

GCMS (rel. intensity) m/z: 249.
Anal. Calcd for C\textsubscript{13}H\textsubscript{15}NO\textsubscript{4}: C, 62.64; H, 6.07; N, 5.62. found: C, 62.73; H, 6.01; N, 5.66.

3-allyliindolin-2-one 505.

A solution of the compound 504 (4.01 mmol) in ethanol 8ml and water 2ml, ammonium chloride (16.04 mmol) and zinc powder (12.03 mmol) was added, the mixture was stirred vigorously at refluxing. After reaction is over (TLC check), the mixture was filtrate, and removed ethanol under reduced pressure. The residue was extracted with ethyl acetate, washed with brine, dried over anhydrous sodium sulphate. After removal of solvent under reduced pressure, the residue was purified by a column chromatography using ethyl acetate to give the corresponding oxindole 505 in 78% yield.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 2.53-2.63 (m, 1H, -CH\textsubscript{2}CH=CH\textsubscript{2}), 2.79-2.87 (m, 1H, -CH\textsubscript{2}CH=CH\textsubscript{2}), 3.50-3.54 (t, \(J = 6.6 \text{ Hz}\), 1H, Ar-CH), 5.02-5.14 (m, 2H, CH=CH\textsubscript{2}), 5.69-5.83 (m, 1H, CH=CH\textsubscript{2}), 6.91-7.01 (m, 2H, Ar-H), 7.16-7.25 (m, 2H, Ar-H), 9.85 (bs, 1H, NH).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 180.53, 141.70, 133.74, 129.12, 127.81, 124.17, 121.99, 117.93, 109.86, 45.71, 34.58.

IR (Neat): 3280, 2922, 1708, 1620, 1469, 750. cm\textsuperscript{-1}

GCMS (rel. intensity) m/z: 173.
Anal. Calcd for C₁₁H₁₁NO: C, 76.28; H, 6.40; N, 8.09. found: C, 76.41; H, 6.33; N, 8.15.

Di-tert-butyl 3-allyl-2-oxoindoline-1,3-dicarboxylate 507.

A solution of 505 (2.89 mmol) in dichloromethane was added DMAP (3.17 mmol), followed by Boc anhydride (3.17 mmol) at 0°C. The resulting solution was stirred for 1 h at room temperature and poured into a saturated NaHCO₃ (100 ml) solution. The aqueous layer was extracted with ether (3 x 100 ml). The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, hexane- acetone) to give 507 as yellow thick oil in 70% yield.

¹H NMR (200 MHz, CDCl₃) δ: 1.36 (s, 9H, -OCC₃), 1.64 (s, 9H, -OCC₃), 2.93-2.97 (d, J = 8 Hz, 2H, -CH₂CH=CH₂), 4.92-5.10 (m, 2H, CH=CH₂), 5.32-5.53 (m, 1H, CH=CH₂), 7.12-7.37 (m, 3H, Ar-H), 7.81-7.85 (d, J = 8.0 Hz, 1H, Ar-H).

¹³C NMR (75 MHz, CDCl₃) δ: 172.12, 166.68, 141.46, 140.87, 134.75, 129.39, 126.18, 124.17, 122.42, 118.20, 115.86, 85.01, 84.32, 38.40, 28.03, 27.48.

IR (Neat): 2980, 1795, 1772, 1734, 1477, 1149, 738 cm⁻¹.

GCMS (rel. intensity) m/z: 373.
Anal. Calcd for C_{21}H_{27}NO_{5}: C, 67.54; H, 7.29; N, 3.75. found: C, 67.71; H, 7.18; N, 3.78.

**Di-tert-butyl 2-oxo- 3-(2-oxoethyl)indoline-1,3-dicarboxylate 508.**

![Diagram of the molecule](image)

Ozone gas was passed into a solution of above compound 507 (1.34 mmol) in DCM at 0°C. The flow of ozone was stopped after 20 min. After the reaction was over (TLC check), excess ozone was removed by purging the reaction mixture with nitrogen and then the ozonide was treated with excess dimethyl sulfide (2.68 mmol) and the resulting mixture was stirred for 2 h at room temp. Removed DCM, reaction mixture was diluted with water and extracted in ether (3 x 15 ml). Ether part of the extract was dried over sodium sulphate and concentrated. The crude product was purified by silica gel column chromatography with hexane - ethyl acetate to afford 508 with 88% yield as a faint yellow thick liquid.

^1^H NMR (300 MHz, CDCl3) δ: 1.33 (s, 9H, -OCC\textsubscript{3}H\textsubscript{3}), 1.65 (s, 9H, -OCC\textsubscript{3}H\textsubscript{3}), 3.39 (s, 2H, CH\textsubscript{2}CHO), 7.11-7.20 (m, 2H, Ar-H), 7.32-7.37 (t, J = 7.3 Hz, 1H, Ar-H), 7.87-7.90 (d, J = 8.3 Hz, 1H, Ar-H), 9.65 (s, 1H, CHO).

^13^C NMR (75 MHz, CDCl3) δ: 197.04, 172.04, 166.51, 149.05, 140.46, 129.32, 126.52, 124.51, 122.27, 115.46, 84.46, 83.67, 57.05, 47.28, 28.00, 27.45.

IR (Neat): 2982, 1772, 1737, 1707, 1363, 1246, 756 cm.\textsuperscript{-1}

GCMS (rel. intensity) m/z: 375.
Anal. Calcd for C\textsubscript{20}H\textsubscript{25}NO\textsubscript{6}: C, 63.99; H, 6.71; N, 3.73. found: C, 64.08; H, 6.66; N, 3.76.

\textbf{Di-\textit{tert}-butyl 3-(2-(methylamino)ethyl)-2-oxoindoline-1,3-dicarboxylate 509.}

A solution of the compound 508 (0.53 mmol) in THF (20 ml) was cooled to 0\(^\circ\) C. Then magnesium sulfate (5.30 mmol) followed by methylamine hydrochloride (2.12 mmol) was added. The reaction mixture was stirred for 1.5 h at room temperature. Then sodium cyanoborohydride (0.79 mmol) was added at 0\(^\circ\) C and then stirred at room temperature. The reaction mixture was then quenched with 1 M NaOH and extracted with DCM (3 x 10ml). The combined DCM portions were then dried over magnesium sulfate, filtered and concentrated \textit{in vacuo}. The crude material was then purified via silica gel chromatography ethyl acetate – hexane system to afford 509 in 50% as a yellow thick oil.

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\): 1.41 (s, 9H, -OC\textsubscript{H}\textsubscript{3}), 1.48 (s, 9H, -OC\textsubscript{H}\textsubscript{3}), 2.42-2.48 (m, 2H, CH\textsubscript{2}CH\textsubscript{2}NH), 2.85 (m, 1H, -CH\textsubscript{2}CH\textsubscript{2}NH), 2.93 (s, 3H, NH\textsubscript{CH}\textsubscript{3}), 2.97 (m, 1H, -CH\textsubscript{2}CH\textsubscript{2}NH), 7.09-7.14 (t, \(J = 7.3\) Hz, 1H, Ar-\textbf{H}), 7.22-7.33 (m, 2H, Ar-\textbf{H}), 7.64-7.66 (d, \(J = 6.1\) Hz, 1H, Ar-\textbf{H}), 8.61 (bs, 1H, NH).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\): 172.65, 171.73, 137.25, 130.08, 128.58, 126.33, 154.03, 126.08, 124.65, 83.99, 82.12, 60.39, 51.63, 39.69, 34.55, 28.34, 27.47.
IR (Neat): 3405, 2982, 1809, 1737, 1369, 1118, 844 cm\(^{-1}\)

GCMS (rel. intensity) m/z: 390.

Anal. Calcd for C\(_{21}\)H\(_{30}\)N\(_2\)O\(_5\): C, 64.59; H, 7.74; N, 7.17. found: C, 64.74; H, 7.65; N, 7.19.

*tert*-butyl 3-allyl-2-oxoindoline-1-carboxylate 506.

![Chemical Structure]

To an ice cold suspension of sodium hydride (5.78 mmol) in a solution of 505 (5.78 mmol) in THF was added Boc anhydride (5.78 mmol) in a dropwise manner at 0\(^{\circ}\) C. The resulting solution was stirred for 5 min at 0\(^{\circ}\) C and poured into cold water. The aqueous layer was extracted with ethyl acetate (3 x 100 ml). The organic layer was dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, acetone- hexane) to give 506 in 70% as a Pale yellow thick oil.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.64 (s, 9H, OCC\(_3\)), 2.58-2.68 (m, 1H, -CH\(_2\)CH=CH\(_2\)), 2.79-2.88 (m, 1H, -CH\(_2\)CH=CH\(_2\)), 3.59-3.63 (t, \(J = 6.5\) Hz, 1H, Ar-CH), 5.05-5.14 (m, 2H, -CH=CH\(_2\)), 5.68-5.79 (m, 1H, -CH=CH\(_2\)), 7.11-7.16 (t, \(J = 7.6\) Hz, 1H, Ar-H), 7.27-7.32 (m, 2H, Ar-H), 7.79-7.82 (d, \(J = 8.2\) Hz, 1H, Ar-H).
\(^{13}\text{C}\) NMR (75 MHz, CDCl\(_3\)) \(\delta\): 175.29, 149.02, 139.88, 133.27, 127.96, 127.20, 123.96, 123.82, 118.36, 114.70, 84.03, 45.48, 35.25, 27.89.

IR (Neat): 2926, 1767, 1732, 1462, 1151, 736 cm\(^{-1}\).

GCMS (rel. intensity) m/z: 273.

Anal. Calcd for C\(_{16}\)H\(_{19}\)NO\(_3\): C, 70.31; H, 7.01; N, 5.12. found: C, 70.39; H, 6.94; N, 5.16.

1-tert-butyl 3-ethyl 3-allyl-2-oxoindoline-1,3-dicarboxylate 511.

![Chemical Structure](image)

To an ice cold suspension of sodium hydride (3.66 mmol) in a solution of 506 (3.66 mmol) in THF was added ethyl chloroformate (3.66 mmol) in a dropwise manner at 0\(^{\circ}\) C. The resulting solution was stirred for 2 hr at room temperature. After 2 hr (TLC check) THF was removed under vacuum. The crude reaction mixture was extracted with ethyl acetate (3 × 25 ml). The combined organic layer was washed with brine, dried over anhydrous Na\(_2\)SO\(_4\) and evaporated off under vacuum. The residue was purified by column chromatography (silica gel, ethyl acetate-hexane) to afford compound 511 in 80% as yellow thick liquid.

\(^{1}\text{H}\) NMR (300 MHz, CDCl\(_3\)) \(\delta\): 1.37-1.42 (t, \(J = 7.0\) Hz, 3H, -OCH\(_2\)CH\(_3\)), 1.63 (s, 9H, OCCH\(_3\)), 3.36-3.38 (d, \(J = 5.9\) Hz, 2H, -CH\(_2\)CH=CH\(_2\)), 4.31-4.38 (q, \(J = 7.6\) Hz, 2H, -OCH\(_2\)CH\(_3\)), 5.03-5.16 (m, 2H, CH=CH\(_2\)), 5.86-5.99 (m, 1H, CH=CH\(_2\)),
7.20-7.34 (m, 2H, Ar-H), 7.46-7.49 (d, $J = 7.0$ Hz, 1H, Ar-H), 8.06-8.08 (d, $J = 8.2$ Hz, 1H, Ar-H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 152.27, 148.78, 137.91, 134.75, 132.20, 126.91, 124.22, 122.77, 118.98, 115.95, 115.31, 106.10, 84.17, 65.53, 28.03, 26.78, 14.04.

IR (Neat): 2926, 1798, 1775, 1735, 1462, 1151., 736 cm.$^{-1}$

GCMS (rel. intensity) m/z: 345.

Anal. Calcd for C$_{19}$H$_{23}$NO$_5$: C, 66.07; H, 6.71; N, 4.06. found: C, 66.19; H, 6.68; N, 4.10.

1-tert-butyl 3-ethyl 2-oxo-3-(oxoethyl)indoline-1,3-dicarboxylate 512.

To a stirred solution of 511 (2.60 mmol) in aqueous THF at room temperature was added catalytic amount of potassium osmate (1 mol%) and $N$-methylmorpholine-$N$-oxide (5.21 mmol). The solution was stirred for 6 h at room temperature. After 6 hr (TLC check) THF was removed under vacuum. The crude reaction mixture was extracted with ethyl acetate (3 × 25 ml). The combined organic layer was dried over anhydrous Na$_2$SO$_4$ and evaporated off under vacuum to give crude diol. To a stirred solution of diol in DCM at room temperature was added sodium periodate on silica (2.60 mmol). The reaction was stirred for 15 min and then filtered through a silica gel plug with ethyl
acetate. The ethyl acetate was then removed \textit{in vacuo} to obtain crude product. The crude product was purified by column chromatography (silica gel, ethyl acetate-hexane) to afford compound \textbf{512} in 80\% as yellow thick liquid.

$^1$H NMR (300 MHz, CDCl$_3$) \(\delta\): 1.38-1.43 (t, \(J = 7.3\) Hz, 3H, OCH$_2$CH$_3$), 1.65 (s, 9H, OCC(CH$_3$)$_2$), 3.64-3.65 (d, \(J = 2.4\) Hz, 2H, CH$_2$CHO), 4.33-4.40 (q, \(J = 7.3\) Hz, 2H, OCH$_2$CH$_3$), 7.26-7.41 (m, 3H, Ar-H), 8.07-8.10 (d, \(J = 7.3\) Hz, 1H, Ar-H), 9.66 (s, 1H, CHO).

$^{13}$C NMR (75 MHz, CDCl$_3$) \(\delta\): 197.80, 152.15, 148.52, 139.47, 132.14, 126.39, 124.78, 123.29, 118.40, 115.52, 99.55, 84.79, 65.96, 37.51, 28.03, 14.00.

IR (Neat): 2982, 1778, 1775, 1735, 1458, 1246., 756 cm.$^{-1}$

GCMS (rel. intensity) m/z: 347.

Anal. Calcd for C$_{18}$H$_{21}$NO$_6$: C, 62.24; H, 6.09; N, 4.03. found: C, 62.32; H, 5.99; N, 4.08.

tert-butyl 1'-methyl-2,2'-dioxospiro[indoline-3,3'-pyrrolidine]-1-carboxylate \textbf{510}.

A solution of aldehyde \textbf{512} (1.44 mmol) in THF was cooled to 0\degree C. Then magnesium sulfate (14.4 mmol) followed by methylamine hydrochloride salt (5.76 mmol) was added. The reaction mixture was stirred for
1.5 h at room temperature. Then sodium cyanoborohydride (2.88 mmol) was added at 0°C and then stirred at room temperature for 2 hr. The reaction mixture was then quenched with 1 M NaOH and extracted with DCM (3 x 10ml). The combined DCM portions were then dried over sodium sulfate, filtered and concentrated in vacuo. The crude material was then purified via silica gel chromatography to afford 510 in 60% as pale yellow thick oil.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 1.53 (s, 9H, -OCC$_3$H$_3$), 2.37 (m, 1H, C-4'-H), 2.95 (s, 3H, NCH$_3$), 3.13 (m, 1H, C-4'-H), 3.54 (m, 1H, C-3'-H), 4.00 (m, 1H, C-3'-H), 7.09-7.14 (t, $J$ = 7.3 Hz, 1H, Ar-H), 7.22-7.25 (d, $J$ = 8.6 Hz, 1H, Ar-H), 7.28-7.33 (t, $J$ = 7.3 Hz, 1H, Ar-H), 7.75-7.78 (d, $J$ = 8.2 Hz, 1H, Ar-H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 174.23, 159.78, 147.55, 136.71, 127.20, 124.95, 123.50, 118.40, 115.80, 95.21, 84.50, 47.05, 30.85, 29.15, 28.05.

IR (Neat): 2980, 1732, 1460, 1240, 760 cm$^{-1}$.

GCMS (rel. intensity) m/z: 316.

Anal. Calcd for C$_{17}$H$_{20}$N$_2$O$_4$: C, 64.54; H, 6.37; N, 8.86. found: C, 64.73; H, 6.27; N, 8.80.

$1'$-methylspiro[indoline-3,3'-pyrrolidine]-2,2'-dione 513.
To a stirred solution of **510** (0.63 mmol) in THF was added 2.5M HCl (2ml) and refluxed for 30 min. The reaction mixture was then quenched with saturated NaHCO₃ and extracted with EtOAc (3 x 100 ml). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated off under vacuum. The crude material was purified by chromatography (silica gel, methanol – chloroform) to afford **513** 86% as a yellow viscous oil.

\[ ^1H \text{ NMR (300 MHz, CDCl}_3 \text{)} \delta: 2.32 \text{ (m, 1H, C-4’-H)}, 2.91 \text{ (s, 3H, NCH}_3 \text{)}, 3.01 \text{ (m, 1H, C-4’-H)}, 3.51 \text{ (m, 1H, C-3’-H)}, 3.91 \text{ (m, 1H, C-3’-H)}, 6.77 \text{ (m, 2H, Ar-H)}, 7.03 \text{ (t, } J = 8.8 \text{ Hz, 1H, Ar-H)}, 7.28 \text{ (d, } J = 8.2 \text{ Hz, 1H, Ar-H)}, 8.10 \text{ (bs, 1H, NH).} \]

\[ ^{13}C \text{ NMR (75 MHz, CDCl}_3 \text{)} \delta: 176.31, 170.54, 140.70, 130.93, 127.81, 124.17, 121.08, 118.10, 84.50, 48.36, 31.58, 30.11. \]

IR (Neat): 3215, 2982, 1710, 1469, 1240, 750 cm⁻¹

GCMS (rel. intensity) m/z: 216.


**Coerulescine 380.**

To an ice cold solution of **513** (0.23 mmol) in dry THF was added \( n \)-butyl lithium (0.23 mmol) and the reaction mixture was stirred at 0°C for 30 min. Then the LAH (0.46 mmol) was added at 0°C and then warmed to room
temperature and stirred for 1 h. The reaction was then quenched with water and then filtered over Na₂SO₄ and concentrated *in vacuo*. The crude material was then purified via silica gel chromatography (chloroform – methanol) to yield coerulescine 30% as a pale yellow gum.

¹H NMR (300 MHz, CDCl₃) δ: 2.07 (m, 1H, C-4'-H), 2.40 (m, 1H, C-4'-H), 2.48 (s, 3H, NCH₃), 2.75-3.05 (m, 4H, C-1' & C-3'-H), 6.89 (d, J = 7.8 Hz, 1H, Ar-H), 7.04 (t, J = 7.3 Hz, 1H, Ar-H), 7.20 (t, J = 7.5 Hz, 1H, Ar-H), 7.41 (d, J = 7.3 Hz, 1H, Ar-H), 8.61 (bs, 1H, NH).

¹³C NMR (75 MHz, CDCl₃) δ: 183.28, 140.38, 136.02, 127.81, 123.29, 122.84, 109.75, 66.12, 56.68, 53.65, 41.78, 37.88.

IR (Neat): 3212, 2978, 1709, 1465, 1238, 760 cm⁻¹

GCMS (rel. intensity) m/z: 202.


**Horsfiline 376.**

![Horsfiline 376](image)

*N*-Bromosuccinimide (0.27 mmol) was added to a solution of 380 (0.24 mmol) in DMF (2 ml) at 0°C. The mixture was stirred for 2 h at 0°C. After addition of water, the aqueous solution was extracted with ether. Ether
part of the extract dried over sodium sulphate and concentrated. To a suspension of the crude product and Cul (0.27 mmol) in DMF (2 ml) was added a sodium methoxide solution (0.36 mmol). After the resulting mixture was stirred at 120°C for 2 hr., the reaction mixture was cooled and the insoluble materials were filtered off. The filtrate was concentrated in vacuo and water was added to the residue. The aqueous layer was extracted with ether and the extract was washed with brine and dried over sodium sulphate and concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel with methanol- chloroform to give horsfiline as light yellow crystal mp 152-154°C (lit 156-157°C).²

¹H NMR (300 MHz, CDCl₃) δ: 2.07-2.12 (m, 1H, C-4'-H), 2.37-2.45 (m, 1H, C-4'-H), 2.49 (s, 3H, NCH₃), 2.77-2.83 (m, 1H, C-3'-H), 2.88 (s, 2H, C-1'-H), 2.99-3.07 (m, 1H, C-3'-H), 3.80 (s, 3H, OCH₃), 6.72 (d, J = 8.0 Hz, 1H, Ar-H), 6.78 (d, J = 8.0 Hz, 1H, Ar-H), 7.05 (d, J = 2.0 Hz, 1H, Ar-H), 8.20 (bs, 1H, NH).

¹³C NMR (75 MHz, CDCl₃) δ: 182.95, 156.28, 137.31, 133.47, 112.53, 110.27, 109.92, 66.30, 56.58, 56.02, 54.18, 41.78, 38.25.

IR (Neat): 3215, 2950, 1708, 1482, 760 cm⁻¹

GCMS (rel. intensity) m/z: 232.

Anal. Calcd for C₁₃H₁₄N₂O₂: C, 67.22; H, 6.94; N, 12.06. found: C, 67.36; H, 6.80; N, 12.12.
References


Chapter 3


