TOTAL SYNTHESIS OF CHELONIN A, CHELONIN B AND BROMOCHELONIN B

A MSC DISSERTATION REPORT BY:

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CERTIFICATE

This is to certify that the dissertation entitled "Total Synthesis of Chelonin A, Cheonin B and Bromochelonin B" is bonified work carried out by Ms. Sindhuja Bhaskar Porob under my supervision in partial fulfilment of the requirement for the award of the degree of Master of Science in Chemistry at the School of Chemical Sciences, Goa University.

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STATEMENT

I hereby declare that the matter presented in this dissertation entitled, “TOTAL SYNTHESIS OF CHELONIN A, CHELONINB, AND BROMOCHELONIN B” is based on results of investigation carried out by me in the School of Chemical Sciences, Goa University, Goa under the supervision of Prof. Dr. Bidhan A Shinkre and the same has not been submitted elsewhere for the award of degree or diploma.

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CHAPTER I

1. INTRODUCTION

Alkaloid are naturally occurring nitrogenous compounds that represents a large and highly structurally diverse group of secondary metabolities.[1] Many marine organisms including sponges, algae, sea worms, tunicate and bacteria are capable of producing Indole alkaloids.[2 3] The alkaloids obtained from marine organisms frequently possess novel frameworks that is they have[2] indole ring system has become an important structural component in many pharmaceutical agents as substituted indoles are capable of binding to many receptors with high affinity.[4] The isolation of 3-indolyl-imidazol-4-one from the tunicate Dendrodoa grossularia was the very first reported 3 position substituted indole alkaloid.[5]

A great variety of simple and more complexely functionalized indole derivatives has tryptamine unit[6]. These marine indole alkaloids Tryptamine comprises of a large and steadily growing group of secondary metabolites.[1] Marine metabolites often possess complexities such as halogen substituents.[2] Their structure elucidation, chemical modification, stereochemistry, synthesis, and pharmacology have received a great attention from areas of research other than chemistry and include pharmacology, physiology, and medicine.[2] Indole alkaloids have been consider to exhibit cytotoxic, antineoplastic, antibacterial antiparasitics, anti-inflammatory, antiserotonin and antimicrobial activities.[2]

Some of the biological active indole alkaloids derived from sponges having tryptamine unit in their structures are Konbamidin[7], Chelonin A, Chelonin B[8 9], Chelonin C[10], and Bromochelonin B[11 9], as shown in Figure 1.

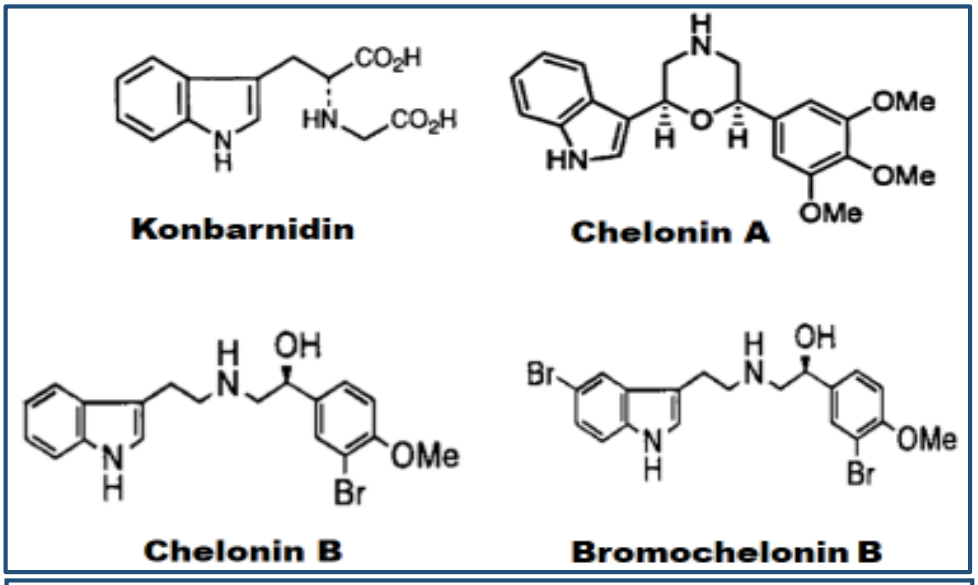


FIGURE 1: Examples of biological active Indole alkaloids having Tryptamine unit.

2. ISOLATION OF CHELONIN A, CHELONIN B, BROMOCHELONIN B

These were isolated by D. J. Faulkner and co-workers. They collected a small purple colour dendritic sponge Chelonaplysilla sp. by hand at a depth from a marine lake on Kaibaku Island, Iwayama Bay, Palau in 1981 and 1990.

The sponge was stored at -10^{0}C for approximately 2 weeks and then freeze-dried. The lyophilized sponge tissue (109.5 g) was extracted with dichloromethane (4 X 1 L) and methanol (3 X 1 L). The methanol extract (7.1 g) of the freeze-dried sponge tissue was triturated with dichloromethane (3 X 100 mL) to obtain a brown solid (1.3 g) that exhibited antimicrobial activity against *subtilis* and S. *auteus.* This mixture was separated on Sephadex LH-20 (column size 95 X 3 cm) using dichloro-methane/methanol (1: l) to elute the mated. The major fraction that exhibited antimicrobial activity (629 mg) was separated by flash chromatography on silica (Kieselgel 60, 230-400 mesh, column size 34 X 2.5 cm) using a solvent gradient from ethyl acetate/methanol (nl) to methanol to yield a number of bioactive fractions that appeared to contain mixtures of aromatic compounds as judged by 'H NMR spectroscopy. One of the fractions (173 mg) was subjected to centrifugal counter current chromatography (CCC) using a solvent system of hexane/ethyl acetate/methanol/water (3:7:55, upper phase stationary) to yield chelonin A (3, 69.8 mg, 0.06446 dry weight).

A second bioactive fraction (160 mg) from the silica flash chromatography was separated by CCC in hexane/ethyl acetate/methanol/water (3:7:5:5, upper phase stationary) to yield two mixtures that exhibited antimicrobial activity. The first fraction (71 mg) was separated by successive CCC in hexane/ethyl acetate/methanol/water (3:7:5:5 upper phase stationary once, lower phase stationary once) and ethyl acetate/95% ethanol/water (2:1:2, lower phase stationary) to yield a mixture of indole alkaloids. This mixture (57 mg) was separated by reversed-phase HPLC on µ Partisil C_{18} silica using methanol/water/diethylamine (75:25:1) as eluent followed by reversed-phase HPLC on a Dynamax CIS silica column using methanol/water (85:15) as eluent to yield chelonin B (4,9.5 mg, 0.009% dry weight).

The second bioactive fraction from the first CCC separation (32 mg) was separated by HPLC on a Selectosil NH_2 silica column using dichloromethane/methanol (97:3) as eluent to yield bromochelonin B (5,6.5 mg, 0.006% dry weight).

A third bioactive fraction (75 mg) from the original flash chromatography step was separated by HPLC on Selectosil NH_2 silica using dichloromethane/ methanol (96:4) as eluent to yield more chelonin A and an inactive compound identified as chelonin C (6,16.7 mg, 0.015% dry weight).[12]

Then after successful isolatation of 4 alkaloids from which three were indole derivatives, which had tryptamine and tyrosine units, namely Chelonin A, Chelonin B, and Bromochelonin B. The fourth alkaloid chelonin C, also contains this structural feature, tryptamine and tyrosine units but it does not contain an indole ring.[13]

3. CHARACTERISATION

3.1 CHELONIN A

IUPAC name of Chelonin A is 3-[(2R, 6S)-6-(3, 4, 5-Trimethoxyphenyl)-2-morpholinyl]-1H-indole. It is a colourless solid with melting point 180-182^{o}C. It is the first natural product to contain a 2, 6-disubstituted morpholine.[14] It has anti-inflammatory and antimicrobial properties. It further showed anti-inflammatory activity in vivo that is 60% inhibition against PMA induced inflammation in a mouse ear model.[14] It also exhibited activity against *B. subtilis* at a concentration of 100 µg/disk.[15]

The structure was proved using following techniques;

a. ^{1}H NMR data:

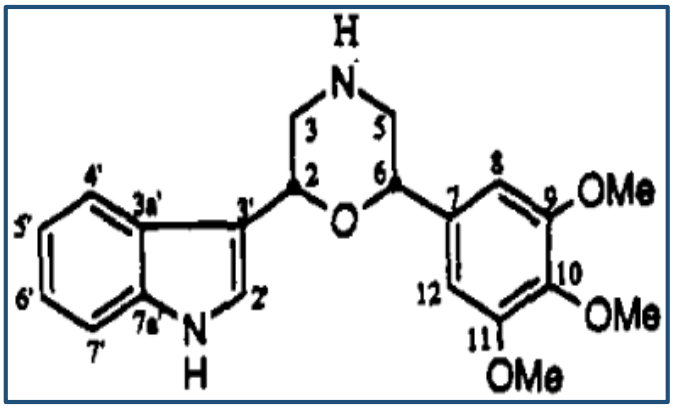


FIGURE 2: Structure of chelonin A.

Carbon numbers	1H NMR signal values (ppm)
2’	7.25 (s, 1H)
4’	7.77 (dd, 1H 6.9,1.0)
5’	7.01 (ddd, 1H, 6.9, 6.9, 1.2)
6’	7.10 (ddd, 1H,7.0,6.9,1.0)
7’	7.35 (dd, 1H, 7.0,1.2)
2	5.00 (br t, 1H, 6.8)
3	3.11 (br d, 2H, 6.8)
5	2.74 (dd, 1H,12.8, 10.6) 3.08 (dd, 1H, 12.8, 2.4)
6	4.70 (dd, 1H, 10.6, 2.4)
8	6.74 (s, 2H)
12	6.74 (s, 2H)
9-OMe	3.82 (s, 6H)
10-OMe	3.73 (s, 3H)
11-OMe	3.82 (s, 6H)

TABLE 1: ^{1}H NMR (200 MHz, Chemical Shift (δ), Multiplicity, Number of Hydrogens, and Coupling Constants (Hz) data for Chelonin A in CD_3OD

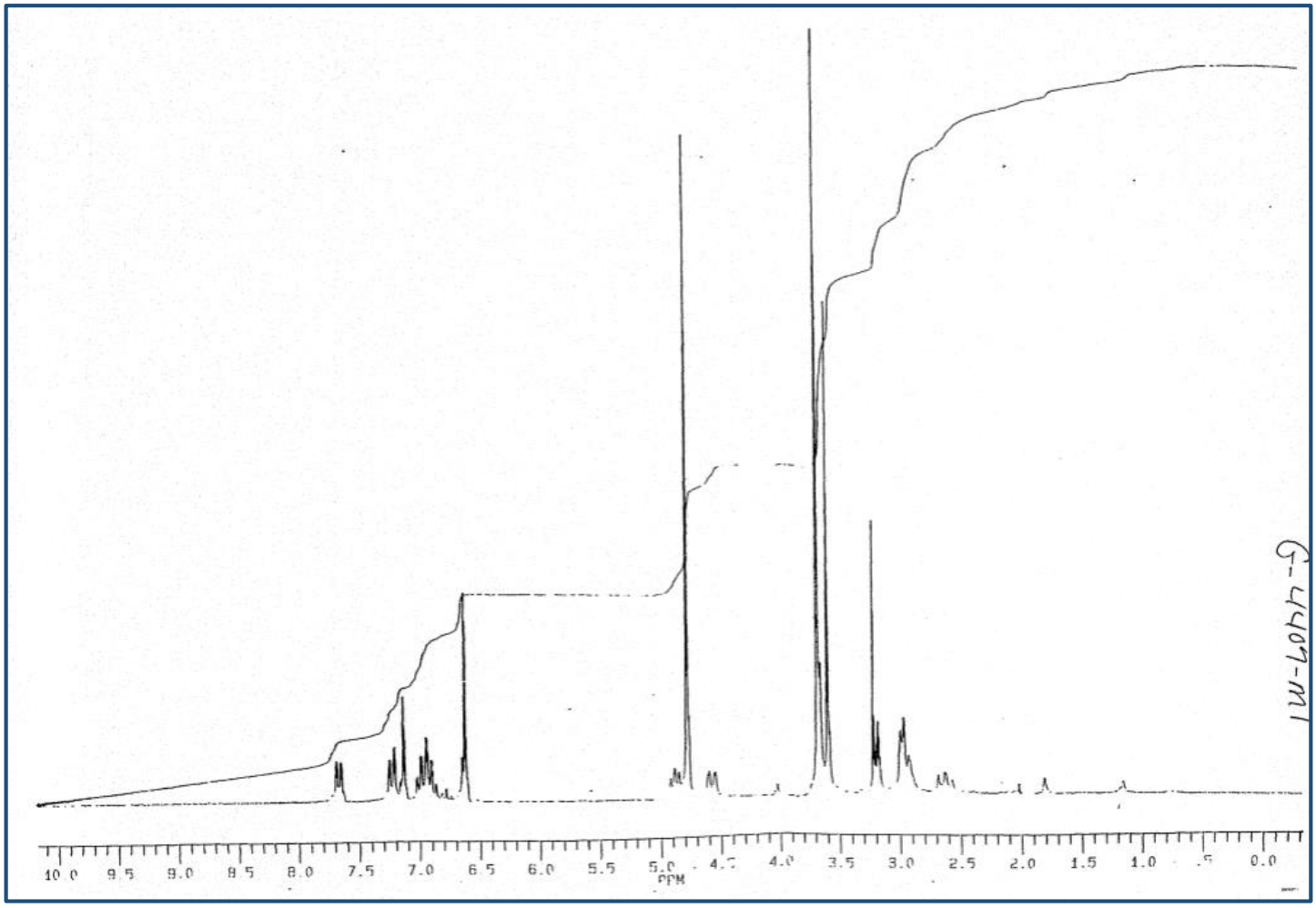


FIGURE 3: ^{1}H NMR Spectra (200MHz) of Chelonin A in CD_3OD solution.

The presence of a 3, 4, 5 - tri- methoxyphenyl subunit was indicated by ^{1}H NMR signals at δ 6.74 (s, 2 H), 3.82 (s, 6 H), and 3.73 (s, 3 H). The indole subunit was responsible for the five additional downfield signals in the ^{1}H NMR spectrum at δ 6 7.77 (dd, 1 H, J = 6.9, 1.0 Hz), δ 7.35 (dd, 1 H, J = 7.0, 1.2 Hz), δ 7.25 (s, 1 H), 7.10 (ddd, 1 H, J = 7.0, 6.9, 1.0 Hz), and δ 7.01 (ddd, 1 H, J = 6.9, 6.9, 1.2 Hz) as can be seen in Figure 3.[12] The cis orientation of the substituents on the morpholine ring was determined by irradiation of the ^{1}H NMR signal at δ 5.00 (br t, 1 H, J = 6.8Hz, H-2) to obtain an enhancement (16.1%) of the signal at 4.70 (dd, 1 H, J = 10.6, 2.4 Hz, H-6). [12]

b. ^{13}C NMR data

Carbon Numbers	^{13}C NMR signal values (ppm)
2’	123.3 (d)
3’	115.3 (s)
j3a’	127.3 (s)
4’	120.5 (d)
5’	120.1 (d)
6’	122.7 (d)
7’	112.7 (d)
7a’	138.4 (s)
2	75.1 (d)
3	51.1 (t)
5	52.8 (t)
6	80.0 (d)
7	137.8 (s)
8	104.4 (d)
9	154.4 (s)
10	138.1 (s)
11	154.4 (s)
12	104.4 (d)
9-OMe	56.5 (q)
10-OMe	61.1 (q)
11-OMe	56.5 (q)

TABLE 2: ^{13}C NMR (50 MHz, Chemical Shift (δ), and Multiplicity) data for Chelonin A in CD_3OD Solution.

The presence of a 3, 4, 5 – tri - methoxyphenyl subunit was indicated by the ^{13}C NMR signals at δ154.4 (s, 2 C), 138.1 (s), 137.8 (s), 104.4 (d, 2 C), 61.1 (q) and 56.5 (q, 2C). The indole subunit was responsible for the presence of eight additional downfield signals at δ 138.4 (s), 127.3 (s), 123.3 (d), 122.7 (d), 120.5 (d), 120.1 (d), 115.3 (s), and 112.6 (d) as can be seen in Figure 4.[12]

c. IR data: 3480, 1595, 1510, 1505, 1465, 1455, 1420, 1335, 1130, 1095 cm^{-1}.[12]

d. UV data : λmax values are 287, 276, 270, 206 nm recorded using MeOH.[12]

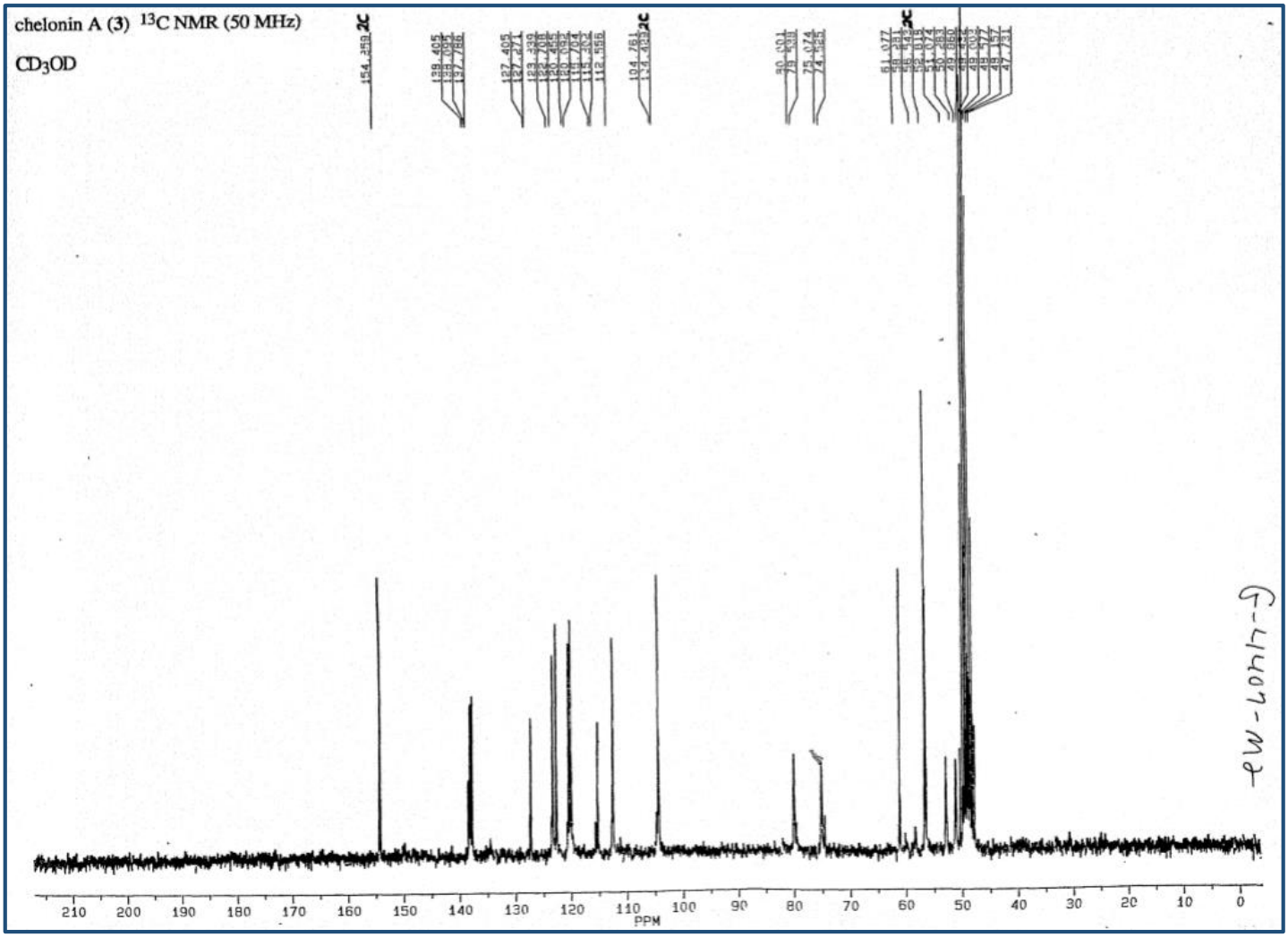


FIGURE 4: ^{13}C NMR Spectra (50MHz) of Chelonin A in CD_3OD solution.

e. **Mass Spectroscopy Data:** It exhibited a molecular ion at m/z = 368.1713(M^+), ($C_{21}H_{24}N_2O_4$) in the high - resolution mass spectrum. Prominent fragment ions at m/z = 194.0938 ($C_{11}H_{14}O_3$, 100%) and 143.0726 ($C_{10}H_9N$, 94%) were identified as (trimethoxyphenyl)ethylene and indolylethylene units, respectively.[12,16]

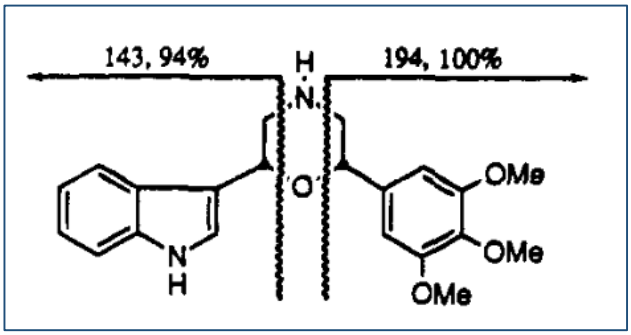


Figure 5: Prominent Fragment Ions in the Electron Impact Mass Spectra (70 eV, m/z, and Percent Base Peak) of Chelonin A.

3.2 CHELONIN B

The IUPAC name of chelonin B is (1S)-1-(3-Bromo-4-methoxyphenyl)-2-{[2-(1H-indol-3-yl) ethyl] amino} ethanol. The structure of chelonin B was revealed by both high resolution mass measurement and ^{1}H and ^{13}C NMR techniques. The specific rotation for it was never recorded and it is not yet been prepared by asymmetric synthesis. It is known to possess antimicrobial activity against Bacillus *subtilis.*

The structure was proved using following techniques;

a. **IR Analysis:** ($CHCl_3$) 3470, 3330 (br), 1605, 1500, 1460, 1445, 1420, 1285, 1260, 1055 cm^{-1}.
b. **UV Analysis:** (MeOH) 288, 280, 221, 208 nm
c. **^{1}H-NMR (CD_3OD) data:** These are the signal values as seen in (Figure 6), δ 2.75 (d, 1 H, J = 5.7 Hz), 2.76 (d, 1 H, J = 7.3 Hz), 2.96 (br s, 4H), 3.82 (s,3H), 4.66 (dd, 1 H, J = 7.3,5.7 Hz), 6.86 (d, 1 H, J = 8.5 Hz), 6.98 (ddd, 1 H, J = 7.3, 7.1, 1.0 Hz), 7.04 (8, 1 H), 7.04 (ddd, 1 H, J= 7.7, 7.3, 1.1

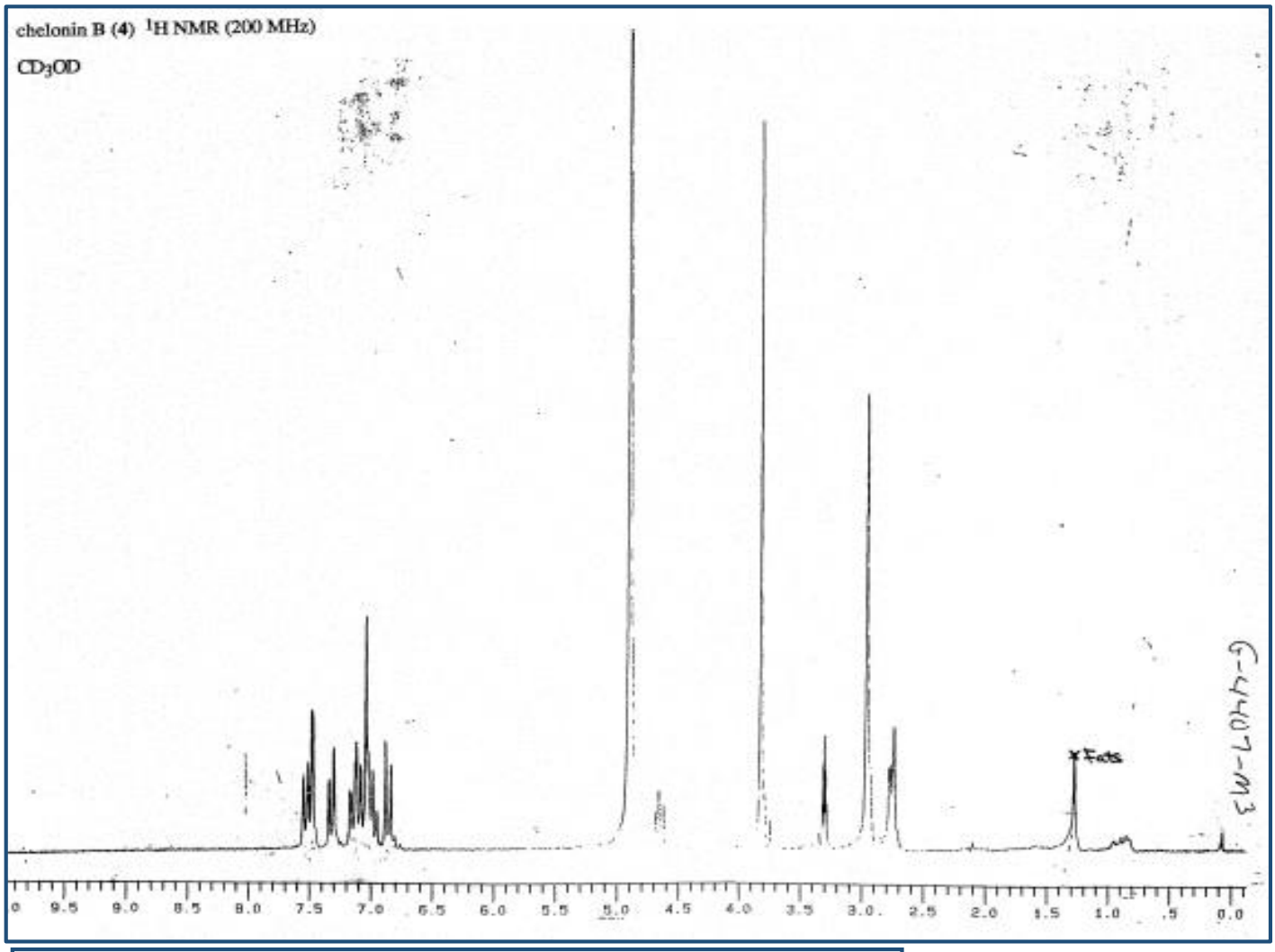


FIGURE 6: ^{1}H NMR Spectra (200MHz) of Chelonin B in CD_3OD solution.

Hz), 7.14 (dd, 1 H, J = 8.5, 2.0 Hz), 7.32 (dd, 1 H, J = 7.7, 1.1 Hz), 7.48 (d, 1H, J = 2.0 Hz), 7.52 (dd, IH, J = 7.1, 1.1, Hz). ^{1}H NMR signals at 6 7.48 (d, 1 H, J = 2.0 Hz, H-12), 7.14 (dd, 1 H, J = 8.5, 2.0 Hz, H-81, and 6.86 (d, 1 H, J = 8.5 Hz, H-9) indicated that a 1, 2, 4-trisubstituted benzene ring was present in chelonin B.[12, 16]

d. ^{13}C-NMR (CD_3OD) data:

δ 26.0 (t), 50.5 (t), 56.7 (q), 57.5 (t), 72.0 (d), 112.3 (d), 112.4 (s), 113.0 (s), 113.0 (d), 119.2 (d), 119.6 (d), 122.4 (d), 123.6 (d), 127.4 (d), 128.6 (s), 131.8 (d), 138.0 (s), 138.2 (s), 156.7 (s), are the signals values as seen in figure 7.[16] The absence of one of the carbon-oxygen bonds was confirmed by the observation of a methylene carbon signal at δ 26.0 (t, C-2).[12,17]

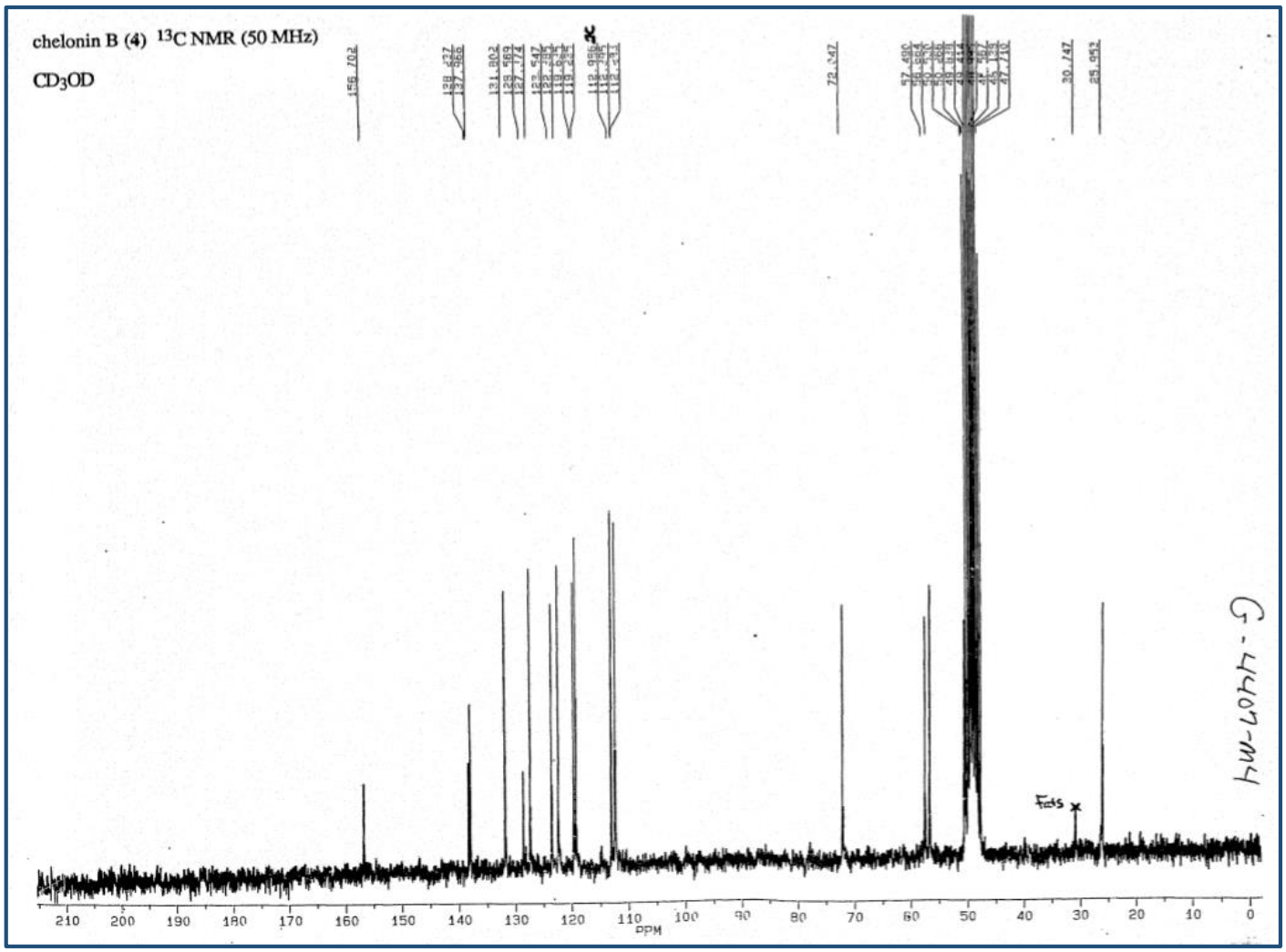


FIGURE 7: ^{13}C NMR Spectra (50MHz) of Chelonin B in CD_3OD solution.

e. Mass Spectroscopy Data:

Molecular formula $C_{19}H_{21}N_2O_2Br$ was determined by high-resolution mass measurement of the of fragment ion at m/z = 370.0681 $(M - H_2O)^+$. A fragment ion at m/z = 211.9857 (C_9H_9OBr, 7.5%) in the high-resolution mass spectrum suggested that these substituents were bromine, methoxy, and alkyl groups. The position of the hydroxyl group was determined by the observation of the dehydrated fragment ion at m/z = 240.00 ($C_{10}H_{11}NOBr$ 10%) as seen in Figure 8.[12] The molecular formula of chelonin B requires one less degree of unsaturation than Chelonin A, which indicates that morpholine ring of chelonin A was not present in chelonin B.

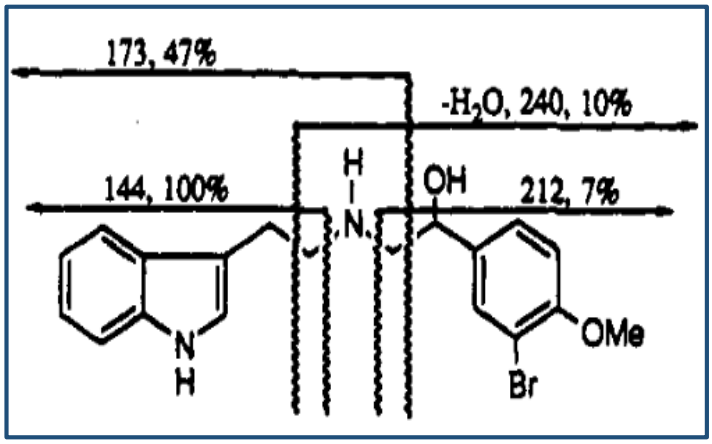


Figure 8: Prominent Fragment Ions in the Electron Impact Mass Spectra (70 eV, m/z, and Percent Base Peak) of Chelonin B.

3.3 BROMOCHEONIN B

The IUPAC name of bromochelnin B is (1S)-2-{[2-(5-Bromo-1H-indol-3-yl) ethyl] amino}-1-(3-bromo-4-methoxyphenyl) ethanol. It is known to possess antimicrobial activity against Bacillus subtilis.

The structure was proved using following techniques;

a. IR data Analysis: IR was recorded using KBr 3470, 3330 (br), 1605, 1500, 1460, 1445, 1420, 1285, 1260, 1055 cm-'

b. UV data Analysis: (DMSO) λmax 299, 287, 279, 221, 208 nm.

c. ^{1}H NMR data: (DMSO-d_6) δ 2.63(br d, 2H, J = 5.9 Hz), 2.79 (br s, 4H), 3.81 (s, 3H), 4.55 (br t, lH, J=5.9Hz), 5.25 (br, lH), 6.98(d, lH, J=8.4Hz), 7.13 (dd, 1H, J = 8.5, 1.6 Hz), 7.14 (br s, 1H),

7.23 (dd, 1 H, J = 8.4, 1.7 Hz), 7.28 (d, 1H, J = 8.5 Hz), 7.48 (d, 1 H, J = 1.7 Hz), 7.66 (d, 1 H, J = 1.6 Hz), 11.04 (br s, 1 H); as seen in Figure 9.

Irradiation of the resonance assigned to the carbinol proton at δ 4.55 (br t, 1 H, J = 5.9 Hz, H-6) produced enhancements of the signals at δ 7.48 (d, 1 H, J = 1.7 Hz, H-12, 2.7%) and 7.23 (dd, 1 H, J = 8.4, 1.7 Hz, H-8, 8.1%), indicating that these two aromatic protons were ortho to the side chain. Irradiation of the methoxyl signal at δ 3.81 produced an enhancement (13.1%) of the resonance at δ 6.98 (d, 1 H, J = 8.4 Hz, H-9), supporting the para position of the methoxy group. The coupling patterns of the remaining aromatic proton resonances indicated that the indole subunit possessed a bromine atom at either C-5' or C-6'. [12]

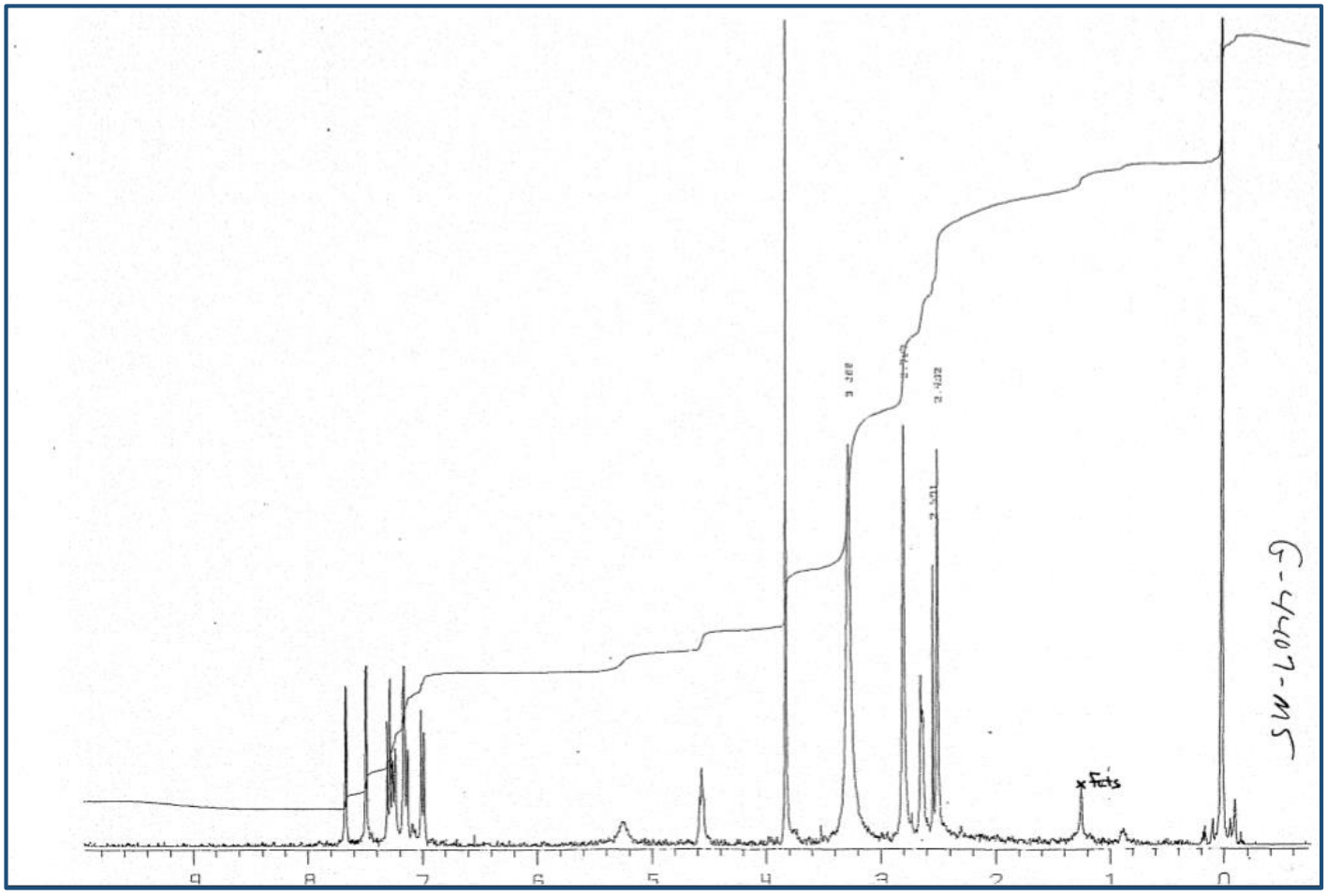


FIGURE 9: ^{1}H NMR Spectra (360MHz) of Bromochelonin B in DMSO-d_6

d. **^{13}C NMR data:** (DMSO-d_6) δ 24.7 (t), 49.4 (t), 56.1 (q), 56.7 (t), 69.9 (d), 110.2 (s), 110.9 (s), 112.0 (s), 112.1 (d), 113.3 (d), 120.6 (d), 123.2 (d), 124.4 (d), 126.4 (d), 129.1 (s), 130.3 (d), 134.9 (s), 154.2 (s), are the signal values as seen in Figure 10.

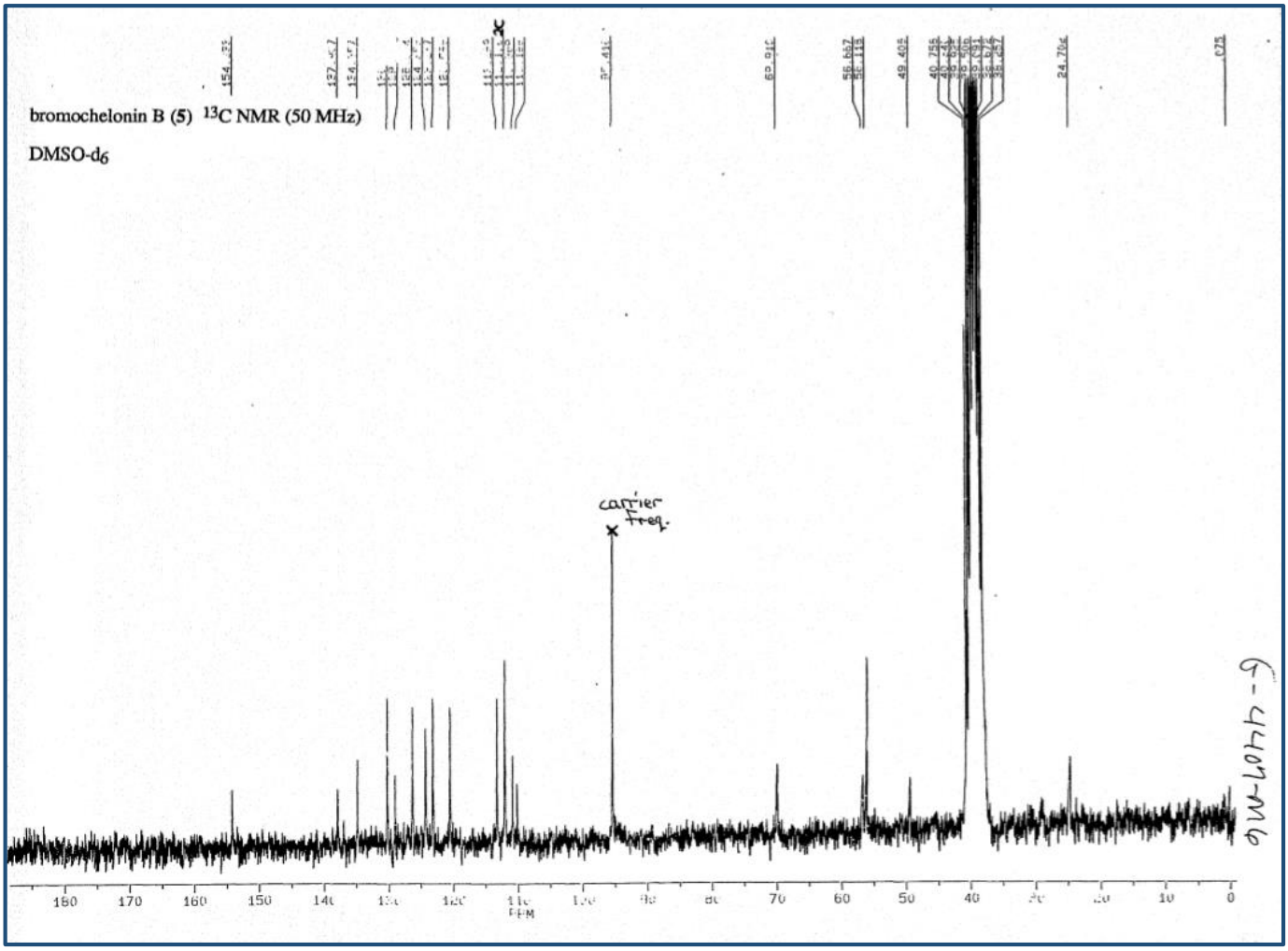


FIGURE 10: ^{13}CNMR Spectra (50MHz) of Bromochelonin B in DMSO-d_6

e. <u>Mass Spectroscopy Data</u>:

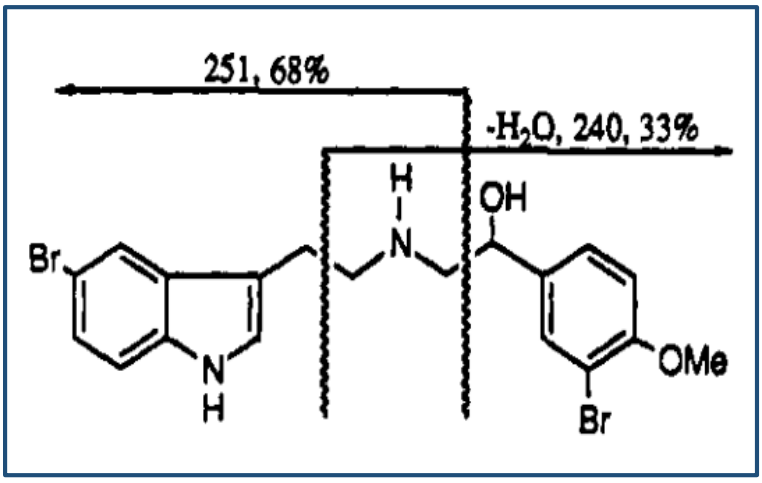


FIGURE 11: Prominent Fragment Ions in the Electron Impact Mass Spectra (70 eV, m/z, and Percent Base Peak) of Bromochelonin B.

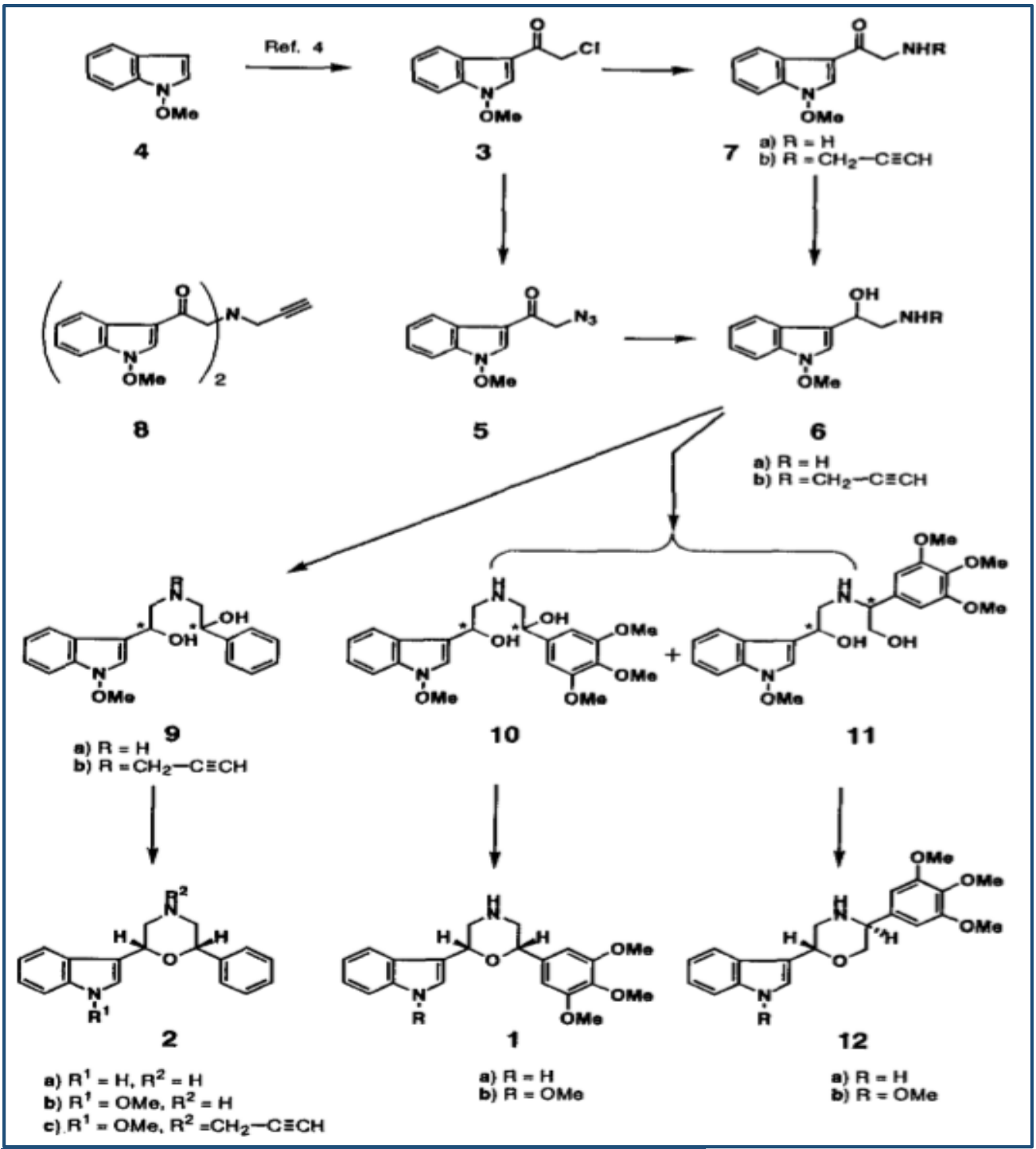
It determined to have a molecular formula of $C_{19}H_{20}N_2O_2Br_2$ from high-resolution mass measurement of the molecular ion at m/z = 465.9891. A prominent fragment ion in the high-resolution mass spectrum at m/z = 251.0117 ($C_{11}H_{12}N_2Br$, 68%) indicated a brominated indole subunit, while a fragment ion at m/z = 239.9997 ($C_{10}H_{11}NOBr$, 33%) supported the presence of a benzene subunit bearing methoxy and bromine substituents as seen in Figure 11.[12]

CHAPTER II

1. LITERATURE SURVEY

A. TOTAL SYNTHESIS OF CHELONIN A

a. First total synthesis of chelonin A and its analogs based on 1-Hydroxyindole



SCHEME 1: Total synthesis of Chelonin A using 1-hydroxyindole

The first total synthesis was reported by Masanori Somei, Kazuko Aoki, Yoshiyuki Nagahama, and Kyoko Nakagawa based on 1-hydroxyindole chemistry with total of 5 steps. [18]

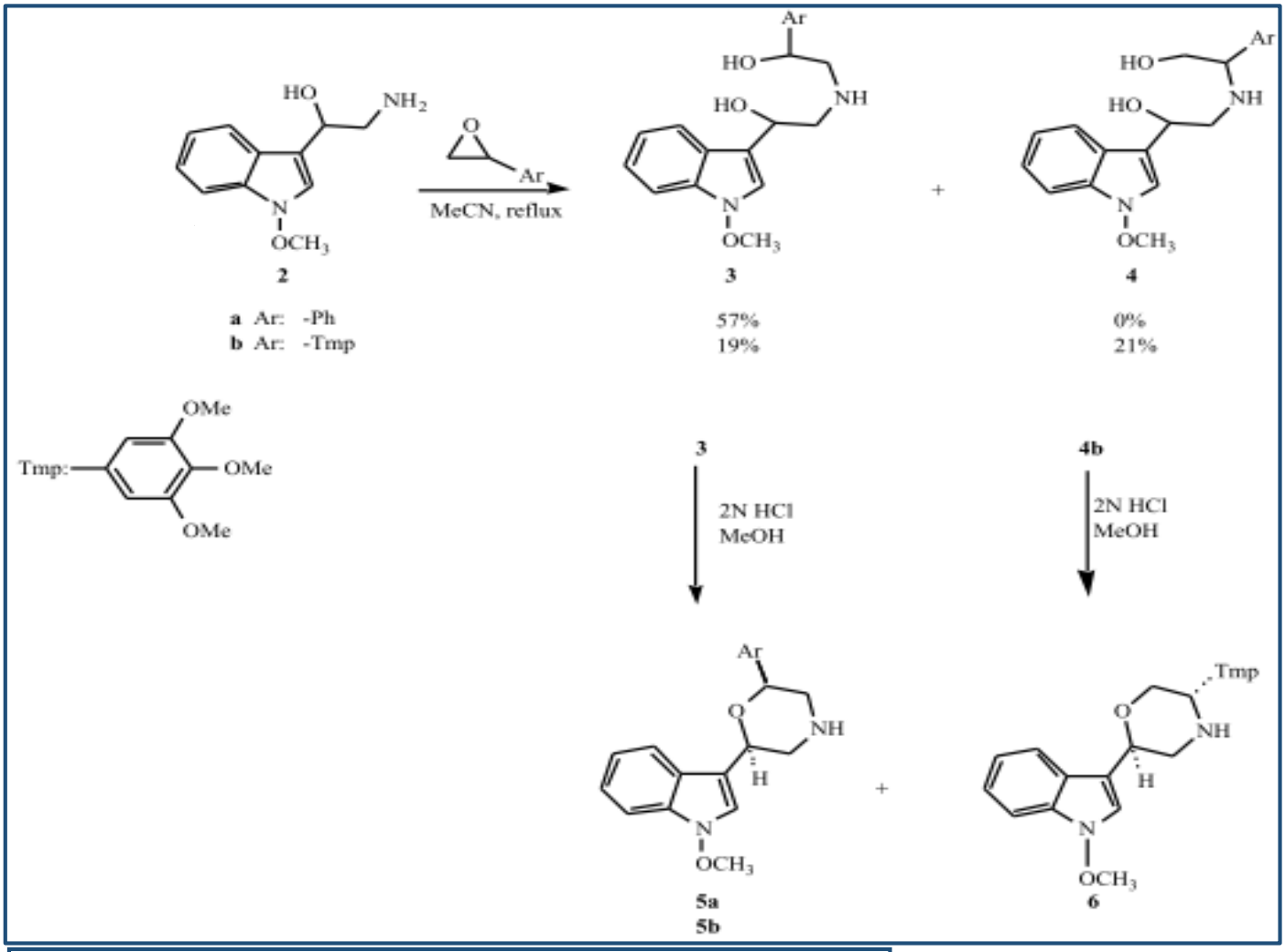
The synthesis of 2, 6-cis-2-(indol-3-y1)-6-phenylmorpholine **(2a)** and 2, 6-cis-2-(1-methoxyindol-3-y1)-6-phenyl-N- propargylmorpholine **(2c)** was done first. 3-(2-chloroacetyl)-1-methoxyindole4 **(3)**, available from 1-methoxyindole **(4)**, was converted to 3-(2-azidoacety1)-1-meth- oxyindole **(5)** in 87% yield by treatment with NaN_3 in CH_3CN-H_2O for 2 h under reflux. Reduction of **(5)** with $LiAlH_4$ in THF for 1 h at room temperature afforded **(6a)** in 40% yield. The compound **(6a)** was alternatively produced in 72% yield by the reduction of 3-(2-aminoacetyl)-1-methoxyindole4 **(7a)** with $NaBH_4$ in MeOH for 1 h at room temperature. when **(3)** was reacted with propargyl amine (excess) in MeOH for 1 h under reflux, monomer **(7b)** and dimer **(8)** were produced in 53% and 32% yields, respectively.

Reduction of **(7b)** with $NaBH_4$ in MeOH for 8 hr at room temperature afforded 57% yield of **(6b)**. Subsequent reaction of **(6a)** with styrene oxide in CH_3CN for 24 h under reflux produced **(9a)** as a 1: l mixture of diastereoisomers in 57% yield. Similar reaction of **(6b)** with styrene oxide afforded **(9b)** as a 1: l mixture of diastereoisomers in 80% yields. Treatments of **(9a)** and **(9b)** with 2N HC1 in MeOH for 1 h or 20 min at room temperature smoothly underwent cyclization to give the desired **(2b)** and **(2c)** as a single isomer in both cases, in 74 or 70% yields, respectively.

Catalytic hydrogenation of **(2b)** over 10% Pd/C at room temperature and 1 atm for 4 h produced **(2a)** in 51% yield. Based on the successful model experiments, **(6a)** was next treated with 3,4,5-trimethoxystyrene oxide under the similar reaction conditions as described above to give the regioisomers, **(10)** and **(11)** in 19 and 21% yields, respectively. Acid cyclizations of **(10)** and **(11)** formed the corresponding **(lb)** and **(12b)** in 89 and 81% yields, respectively. One pot preparations of **(lb)** and **(12b)** from **(6a)** were in 16 and 15% overall yields, respectively, when the reactions of **(6a)** with the epoxide and acid cyclization were carried out successively. Catalytic hydrogenation of **(lb)** over 10% Pd/C at room temperature and 1 atm for 4 h produced **(la)** in 59% yield, while the same reaction of **(12b)** afforded **(12a)** in 57% yield.

b. Total synthesis of Chelonin A using indolyl-aminoalcohol

Ulf Pindur and Thomas Lemster gave synthesis of Chelonin A in 2012 using indolyl-aminoachohol. These approach was completely different than the first reported synthesis.[19]



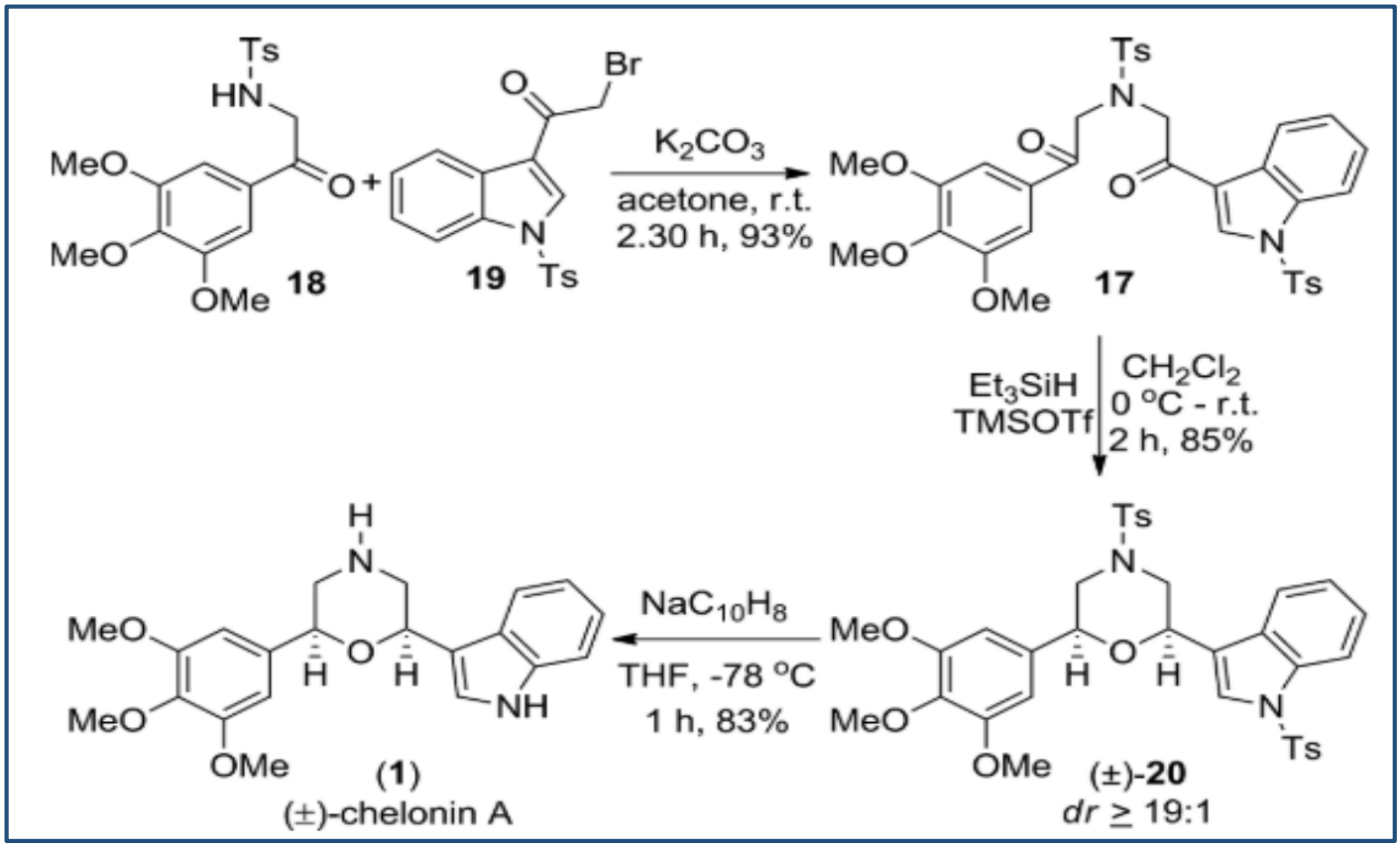
SCHEME 2: Total Synthesis of Chelonin A using indolyl-aminoachohol.

Firstly indolyl-aminoalcohol **(2)** reacted with aryl-oxirane to give rise to the indolyl-diols **(3)** and **(4)**. Compound **(3)** in particular was cyclised under proton acid catalysis to the 3-morpholinyl- indole **(5a)** (the natural origin) and **(5b)**, stereoselectively. In this context, compound **(4b)** was transformed additionally to the compound (**6)**

c. Total synthesis of Chelonin A through 1,5-diketones

Santosh J. Gharpure, Dandela Anuradha, Jonnalagadda V. K. Prasad, and Pidugu Srinivasa Rao synthesised cis-2, 6- disubstituted morpholines through Lewis acid catalysed reductive etherification strategy using 1, 5-diketones and this strategy was used in the total synthesis of morpholine-based natural products Chelonin A.[20]

Firstly diketone **(17)** was prepared by alkylation of amine **(18)** with the bromide **(19)**. This diketone **(17)** was subjected to reductive etherification reaction which gave the corresponding protected (±)-chelonin A **(20)** in good yield and excellent diastereoselectivity. Further deprotection of tosyl group in (±)-morpholine **(20)** was effected by using sodium naphthanalide to give (±) - chelonin A **(1)** as can be seen in Scheme 3.

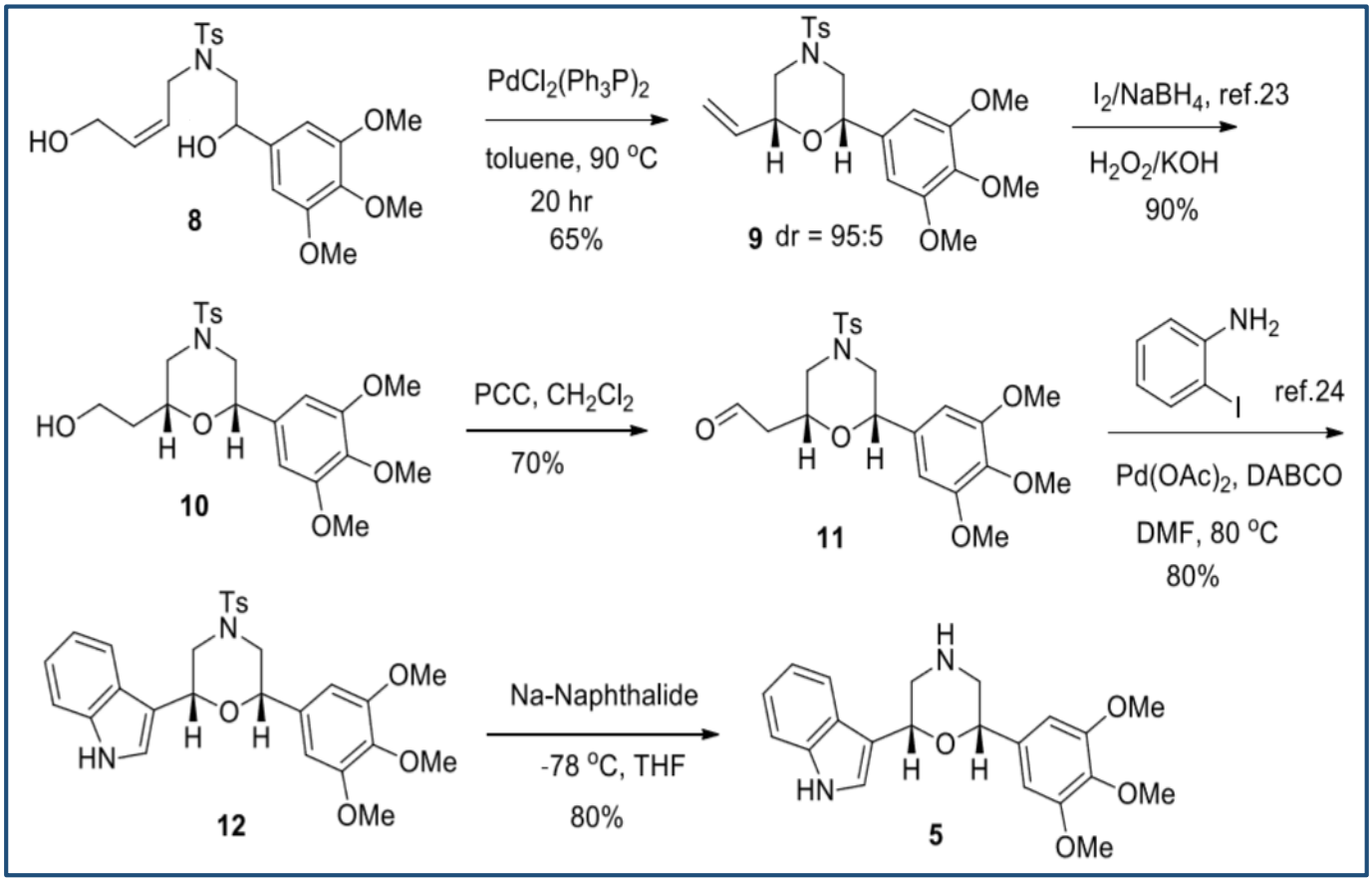


SCHEME 3: Total synthesis of Chelonin A through Lewis acid catalysed reductive etherification strategy using 1, 5-diketones.

d. Total synthesis of Chenolin A through substituted Morpholine

Madhurjya Borah, Upasana Borthakur, and Anil K. Saikia synthesised substituted morpholines through Intramolecular cyclization of nitrogen tethered alkenols catalyzed by palladium chloride. The reaction is compatible with a wide range of functional groups such as ether, -NO2, chloro, bromo and furan. The major advantage of this reaction is that it regioselectively generates a vinyl group at position

2 of the morpholine ring, which can be used for the synthesis of biologically active molecules (+)-chelonin A.[21]



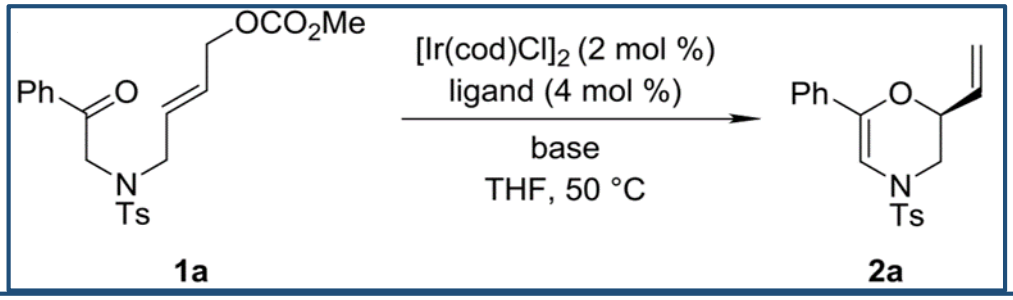
SCHEME 4: Total synthesis of Chelonin A through substituted Morpholine.

Firstly diol **(8)** was treated with palladium chloride to give diastereomeric mixture of morpholine **(9)** with a ratio of 95:5 in 65% yield along with 20% unreacted starting material. Conversion of the olefinic group of the major diastereomer of morpholine **(9)** into alcohol **(10)** followed by PCC oxidation gave aldehyde **(11)** as a single diastereomer in 70% yield. The aldehyde **(11)** was treated with 2- iodoaniline in the presence of palladium acetate to give tosylated (+)-chelonin A **(12)** in 80% yield. The final compound **(5)** was obtained by detosylation with sodium naphthalide in 80% yield and 26% overall yield as shown in scheme 4.

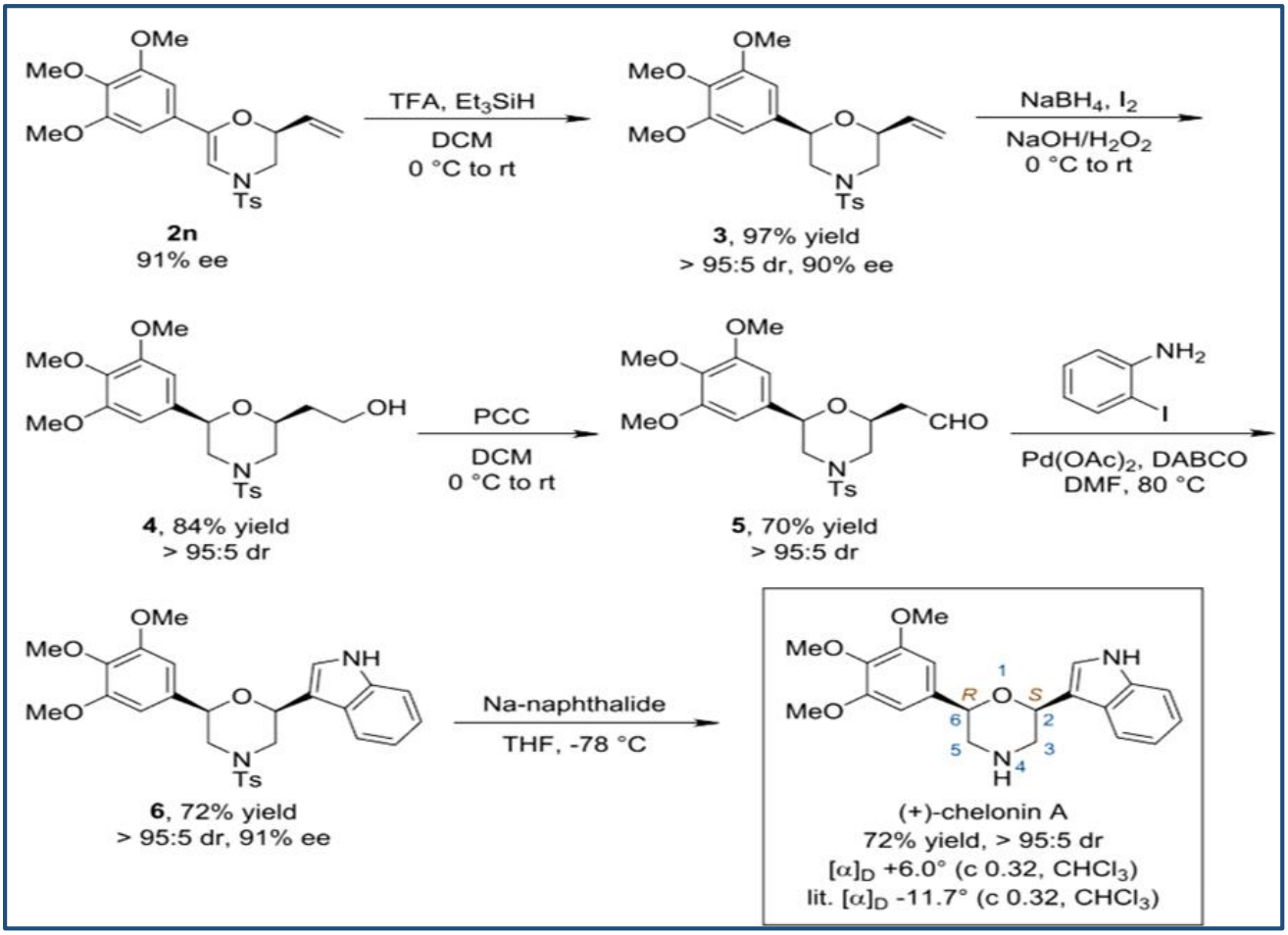
e. Enantioselective synthesis of (+)-Chelonin A

Here an intramolecular iridium catalyzed asymmetric allylic substitution reaction was carried out using a ketone or aldehyde moiety as an O-nucleophile. The products are readily transformed into chiral morpholines by simple reduction of the endocyclic double bond.[22]

Firstly the treatment of **(1a)** with Ir catalyst derived from [Ir (cod)Cl]$_2$ (2 mol %) and Feringa ligand L1 (4 mol %), and Cs_2CO_3 (1 equiv) in THF at 50^0C gave product **(2a)** in 34% as depicted in below scheme 5a. Finally, the synthetic utility of this Ir-catalyzed asymmetric allylic substitution reaction was demonstrated by the first asymmetric total synthesis of (+)-chelonin A.



SCHEME 5a: Intramolecular iridium catalyzed asymmetric allylic substitution reaction



SCHEME 5b: Enantioselctive synthesis of (+) - Chelonin A.

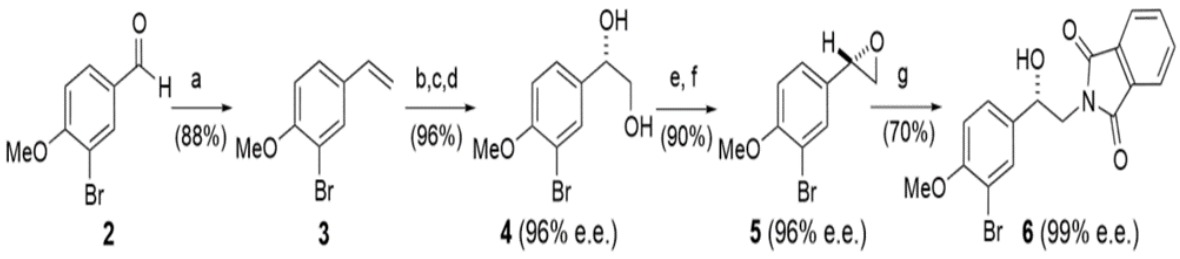
Treatment of **(2n)** (91% ee) with TFA/Et_3SiH afforded **(3)** in 97% yield with 90% ee and > 95:5 dr. Racemic **(3)** was a known intermediate in the total synthesis of (±)-chelonin A by Saikia and coworkers. Following Saikia's synthetic route, subsequent hydroboration/oxidation and PCC oxidation led to aldehyde **(5)**. The indole moiety was introduced by the condensation of **(5)** with 2-iodoaniline and subsequent Pd-catalyzed α-arylation. (+)- Chelonin A was obtained after the removal of the tosyl group by Na-naphthalide as seen in scheme 5b. Based on the comparison of the sign of the optical rotation, the absolute configuration of naturally occurring (-) - chelonin A was assigned as (2R, 6S).[22]

B. TOTAL SYNTHESIS OF CHELONIN B

A total synthesis would serve two purposes. Firstly, greater quantities of chelonin B and related derivatives would become available for further biological evaluation and secondly the stereochemistry of the natural product would be assigned.

a. First total synthesis of chelonin B

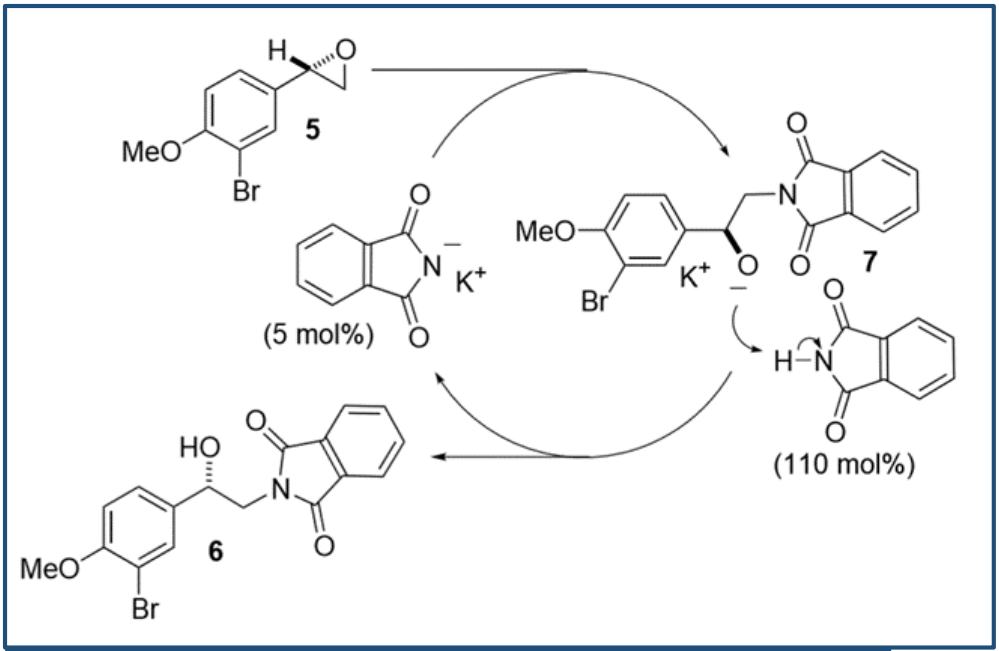
The first total synthesis of the marine natural product (S)-(+)-chelonin B is described below and the key reactions employed include Sharpless asymmetric dihydroxylation of a styrene derivative, catalytic ring-opening of an epoxide and sequential deprotection–rearrangement of a phthalimido indole acetate.[8]



Scheme 1. *Reagents and conditions*: (a) Ph_3PMeBr (1.1 equiv.), *n*-BuLi (1.1 equiv.), THF, 0°C to rt, 1 h; (b) $K_3Fe(CN)_6$ (3 equiv.), $K_2OsO_4{\cdot}2H_2O$ (0.2 mol%), $(DHQ)_2PHAL$ (1 mol%), H_2O/*tert*-BuOH (1:1, v/v), 0°C, 4 h; (c) rt, 0.5 h; (d) Na_2SO_3 (excess), 0°C, 1 h; (e) TMSCl (1.3 equiv.), $MeC(OMe)_3$, CH_2Cl_2, 40°C to rt, 1 h; (f) K_2CO_3 (1.5 equiv.), MeOH, rt, 2 h; (g) phthalimide (1.1 equiv.), potassium phthalimide (5 mol%), DMF, 90°C, 18 h.

SCHEME 1a: Involves the formation of bond via epoxide ring-opening and by intramolecular O-N acyl transfer.

Wittig methylenation of the commercially available benzaldehyde **(2)** gave **(3)**. Sharpless dihydroxylation of the substituted styrene **(3)** using the $(DHQ)_2$ PHAL ligand gave the diol **(4)**. Transformation of the (S)-diol **(4)** into the corresponding enantiomerically enriched (S)-isomer of oxirane **(5)** was achieved in 90% chemical yield, according to the method of Sharpless and co-workers. Introduction of the nitrogen atom at C-2 was achieved by reaction of the oxirane **(5)** with phthalimide. The use of potassium phthalimide alone was very inefficient and resulted in very poor yields of **(6)**.

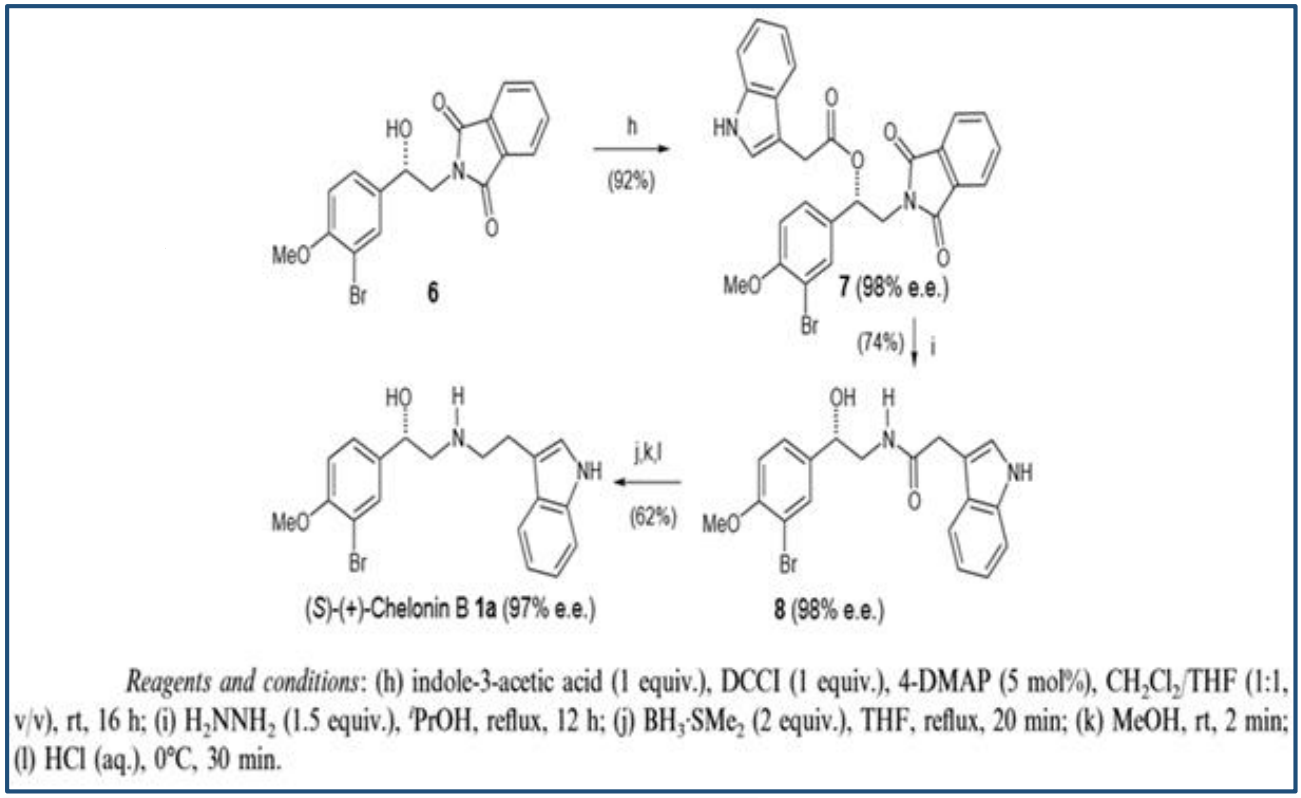


SCHEME 1b: Transfer of (5) to (6) using Potassium

Ideal conditions for the transformation **(5)** to **(6)** involved the use of catalytic potassium phthalimide in hot DMF. The alkoxide **(7)**, generated upon oxirane ring-opening in the presence of phthalimide, simply regenerates the potassium phthalimide as seen in Scheme 1b.

The indole acetyl group was then introduced via reaction of the C-1 hydroxyl group with inexpensive indole3-acetic acid. This was achieved efficiently by treatment of a 1:1 mixture of the alcohol **(6)** and indole-3-acetic acid with 1 equiv. of DCCI, in the presence of DMAP (5 mol%).14 Treatment of the ester **(7)** with hydrazine monohydrate, in refluxing isopropanol for 12 h, furnished the optically active amide (S)-**8** . It was clear that under these reaction conditions the desired O to N acyl transfer had also taken place.The absolute configuration of the C-1 chiral centre of **(8)** was indeed S, as expected from the initial Sharpless dihydroxylation reaction.

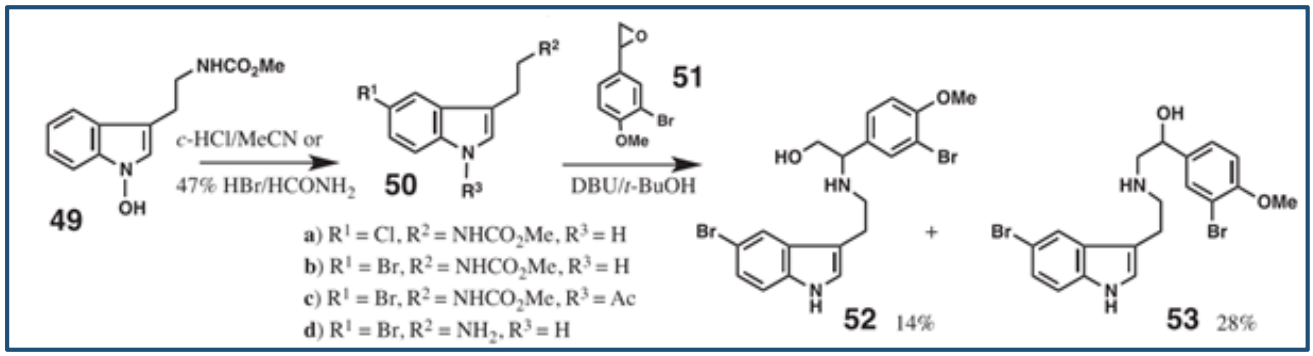
Finally, the chemoselective BH_3•SMe_2 reduction of **(8)**, using a protocol developed by Bussolari and co-workers, in refluxing THF, furnished the target natural product **(1a)** as seen in Scheme 1c.



SCHEME 1c: Final steps for synthesis of Chelonin B

b. Total synthesis of Chelonin B based on 1-hydroxyindole chemistry

chelonin B was prepared by applying nucleophilic substitution reaction of 1-hydroxyindole chemistry by K. Aoki, Y. Nagahama, K. Sugaya, Y. Maeda, H. Sato, K. Nakagawa (Goto), and M. Somei.[23]



SCHEME 2: synthesis of Chelonin B based on 1-hydroxyindole chemistry.

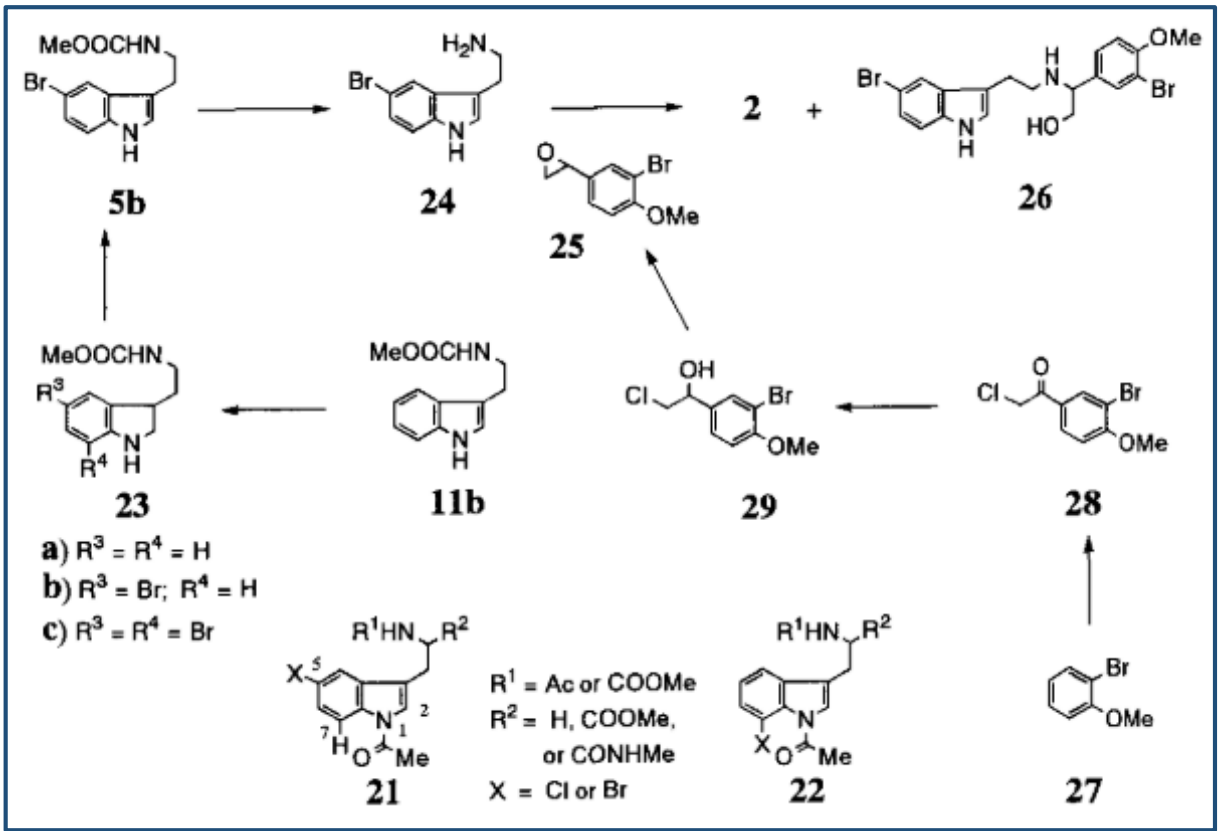
They started firstly with reaction with chloride and bromide with 1-hydroxy-Nb-methoxy-carbonyltryptamine **(49)** which produced 5-chloro- **(50a)** and 5-bromo-Nb-methoxycarbonyltryptamines **(50b)** in the respective yields of 61% and 39%, together with small amount of regioisomers, 7-chloro- and 7-bromo-Nb-methoxycarbonyltryptamines, respectively.

Then they structurally proved **(50b)** that was synthesised as follows. Introduction of acetyl group onto the indole nitrogen of **(50b)** by the reaction with NaH/AcCl produced **(50c)** in 65% yield. After which they did comparison of 1H-NMR spectra of **(50b)** and **(50c)**. It had showed that C(7)-proton of **(50b)** at 7.31 signal(1H, d, J = 8.6 Hz) shifted to the down field to 8.25 signal (1H, d, J = 8.8 Hz). Also the coupling constant and the anisotropy effect by the introduced acetyl group clearly showed that **(50b)** is a 5-substituted indole. Futher they had carried out hydrolysis of **(50b)** with 10% NaOH which gave 5-bromotryptamine **(50d)** in 88% yield. Subsequent reaction of **(50d)** with 2-bromo-3-methoxystyrene oxide **(51)** in the presence of DBU in t-BuOH produced (±)-Chelonin B **(52)** and its regio-isomer **(53)** in 14% and 28% yields, respectively, as seen in Scheme 2.[23]

C. TOTAL SYNTHESIS OF BROMOCHELONIN B

a. First Total synthesis of bromochelonin B

M.Hasegawa, K.Yamada, Y. Nagahama, and M. Somei had carried out preparation of 5-bromo-tryptamines and tryptophans and through its applicative study they synthesied Bromocheonin B.[11]



SCHEME 1: Synthesis of Bromochelonin B

Firstly they did reduction of **(11b)** to corresponding **23(a)** and again treating **(11b)** with bromine-AcOH which resulted in 5-bromo- **(23b)** and 5,7-dibromo derivatives **(23c)** in 61 and 31% yields,

respectively. After this they had carried out Salcomine catalyzed oxidation of **(23b)** with molecular oxygen which had resulted **(5b)** in 89% yield.

Then they started with bromo- anisole **(27)** and performed Friedel-Crafts chloroacetylation which resulted in **(28)**, this **(28)** was further reduced using $NaBH_4$ to chlorohydrin **(29)** in 98% yield and epoxide formation with tert-BuOK gave 3-hromo-4methoxystyrene oxide **(25)** in 47% yield.

In the final step they did hydrolysis of **(5b)** with 5% NaOH and MeOH at reflux which resulted 5-brornotryptamine **(24)** in 88% yield. Subsequent reaction of **(24)** with 3-hromo-4methoxystyrene oxide **(25)** in the presence of DBU in refluxing tBuOH provided them (+)-2 and its (±)-isomer **(26)** in 28 and 14 % yields, respectively, as seen in scheme 1.[11]

2. PREPARATION OF DERIVATIVES

2.1 Acetylation of Chelonin A

Procedure; Acetic anhydride (0.1 mL) was added to a stirred solution of chelonin A (l.l mg) in pyridine (1.0 mL), and the reaction was allowed to proceed for 17 h at room temperature. The solvents were removed from the reaction mixture in vacuo and the producta separated on a silica Sep-pak (Waters) using ethyl acetate/methanol (94:6) as eluent. The product appeared as a mixture by ^{I}H NMR spectroscopy, and separation was attempted by HPLC on µ-Partisil using ethyl acetate as eluant. This yielded a single peak, which was deter- mined to be a 6:4 mixture of syn and anti-isomers of the acetamide (0.9 mg, 73% yield).[12]

Results;

IR ($CHCl_3$) 3480, 1640, 1630, 1595, 1510, 1460, 1420, 1130 cm^{-1}.

1H NMR ($CDCl_3$) δ 2.18 (s,-1.8 H), 2.19 (s, -1.2 H), 2.74 (dd, 1 H, J = 13.5, 10.8 Hz),Hz), 3.54 (dd, 1 H, J = 13.0, l0.8 Hz), 3.80 (s, 3 H), 3.84 (s,3 H), 3.05 (dd, 1 H, J = 13.0, 11.0 Hz), 3.29 (dd, 1 H, J = 13.5, 11.6 3 Hz) 3.87 (s, 3 H), 4.84 (dd, 1 H, J = 11.6, 10.9 Hz), 4.95 (dd, 1 H, J= 11.0, 10.8 Hz), 6.68 (s, 2 H), 7.18 (m, 3 H), 7.37 (d, -0.4 H, J = 6.8 Hz), 7. 40 (d, -0.6 H, J 7.2 Hz), 7.79 (d, -0.4 H, J = 7.4 s, -0.6 Hz), 7.83 (d, 0.6 H, J =7.2Hz), 8.15 (br s, -0.4 H), 8.20 (br s, -0.6 H) are the signal values as seen in Figure 12.

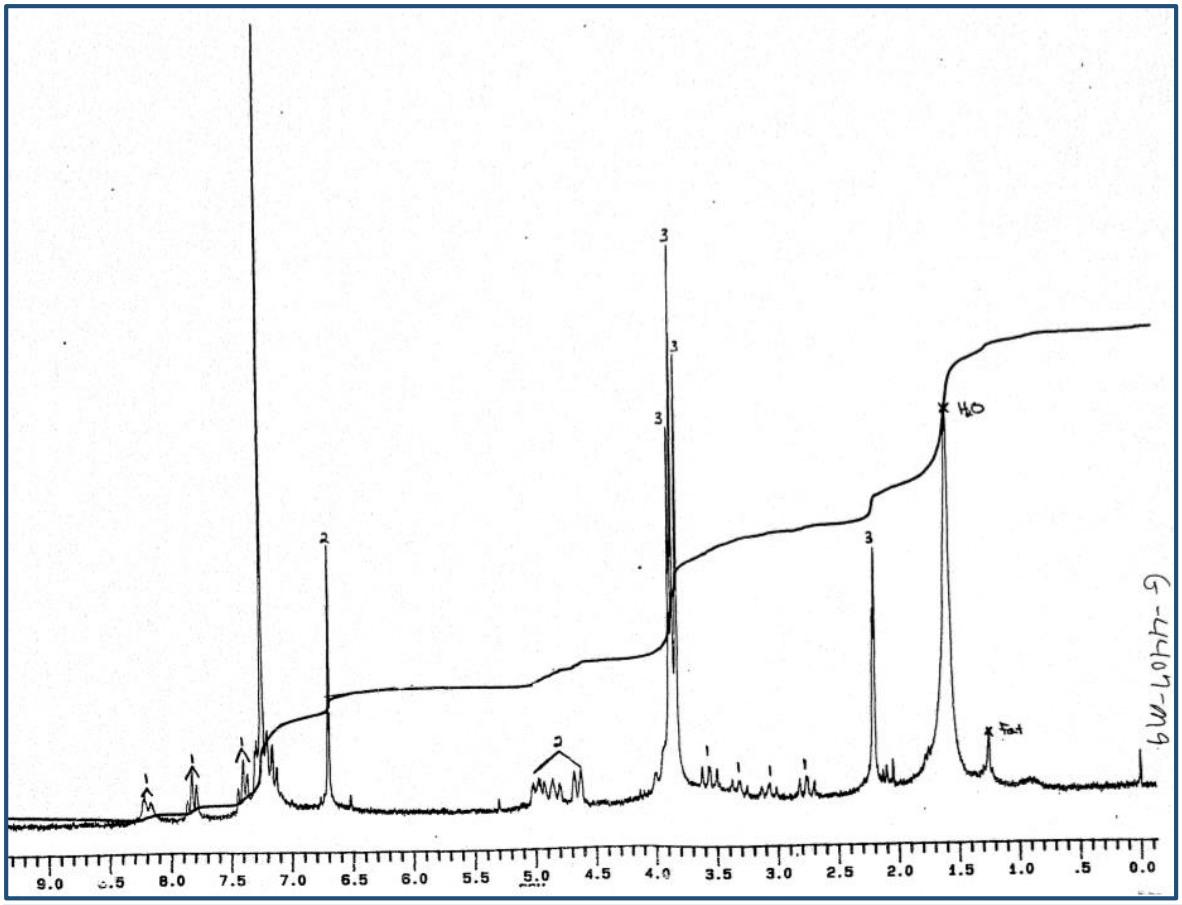


FIGURE 12: 1H NMR (200MHz) spectra of Chelonin A Acetamide in $CDCl_3$ solution.

2.2 Acetylation of Chelonin B

Procedure; Acetic anhydride (0.1 mL) was added to a stirred solution of chelonin B (1.7 mg) in pyridine (1.0 mL), and the reaction was allowed to proceed for 21 h at room temperature. The solvents were removed from the reaction mixture in vacuo and the products separated on a silica Sep-Pak (Waters) in ethyl acetate. The product was purified by HPLC on µ-Partisil using hexane/ethyl acetate (1:9) as eluant to obtain a single peak, which was determined to be a mixture of conformational isomers of the N, O-diacetate (1.7 mg, 84% yield).[12]

Results;

IR ($CDCl_3$): 3475, 1745, 1635, 1605, 1500, 1455, 1440, 1420, 1375, 1260, 1225, 1066, 905 cm^{-1}.

1H NMR: δ 1.93 (s, -2 H), 2.06 (s, 3 H), 2.09 (s, -1H), 2.99 (m, 3H), 3.14 (dd, 0.3H, J= 14.9, 4.6 Hz), 3.57 (m, 3H) 3.87 (s, 3H), 5.72 (dd, 0.4 H, J= 8.4, 4.8 Hz), 5.96 (dd, -0.6 H, J = 7.6,5.5 Hz), 6.81 (d, -0.4 H, J = 8.2 Hz), 6.84 (d, -0.6 H, J = 8.3 Hz), 6.97 (d, -0.6 H, J 2.3 Hz), 7.02 (d, -0.4 H, J = 2.0 Hz), 7.21 (m, 3 H), 7.38 (m, -1.4 HI, 7.51 (d, -0.6 H, J = 2.0 Hz), 7.56 (br d, -0.6 H, J = 8.4 Hz), 7.67 (br d, -0.4 H, J = 7.2 Hz), 8.00 (br 8,-0.4 HI, 8.07 (br s,0.6 H).

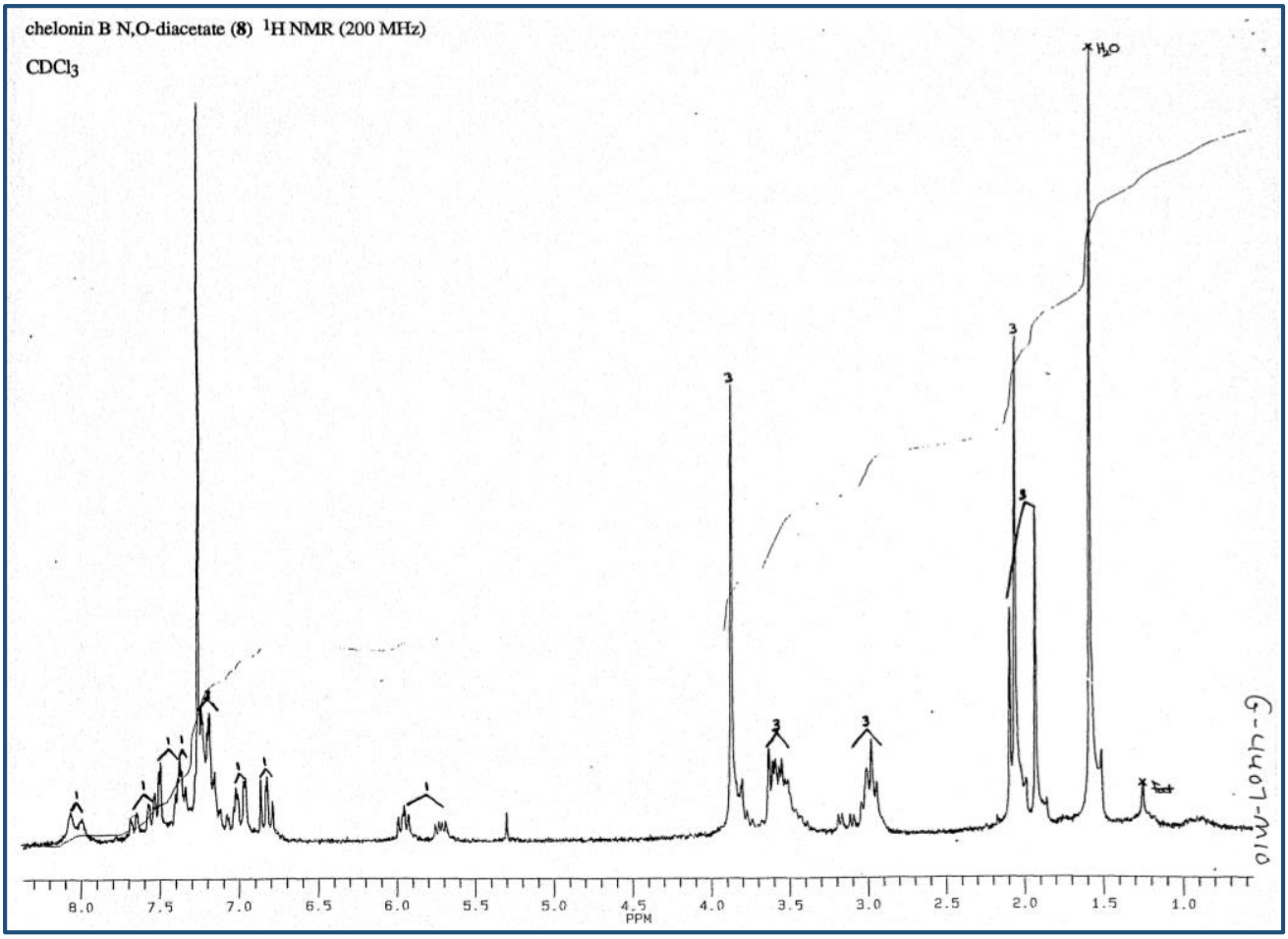


FIGURE 13: ^{1}H NMR (200MHz) spectra of Chelonin B N, O diacetate in $CDCl_3$

CHAPTER III

CONCLUSION:

Marine organisms provide a valuable source of natural products. In the last ten years a large number of heterocyclic alkaloids and related congeners have been isolated and characterised. From these compounds the indole derivatives have evoked special interest as new lead substances for drug design. Simply substituted indoles and peptides, which contain a tryptophan unit, have been characterised and tested for biological activity. Moreover, parallel to the studies about the characterisation of the marine natural products, synthetic studies were performed continuously to obtain more data for structure activity research in medicinal chemistry.

In this literature review we choose Total synthesis of Chelonin A that includes not more than 10 steps. The potential of scheme 1 was substantiated by the short synthesis with overall yield 59%. Scheme 2 was completely different approach staring from indolyl-aminoalcohol which gave racemic mixture under optimised reaction condition in just 3 steps.

Synthesis of Chelonin A from corresponding 1, 5 diketone (scheme 3) in which reaction proceeds via Lewis acid catalysed reductive etherification strategy gave product in good yield up to 83% and excellent diastereoselectivity. Scheme 4 regioselectively generates a vinyl group at position 2 of the morpholine ring, which was used for the synthesis of biologically active molecules (+)-chelonin A with overall yield of 80% under optimised reaction conditions with total of 5 steps.in (scheme 5a and 5b) they have developed the first iridium-catalyzed asymmetric allylic etherification reaction with ketones and aldehydes as enol O-nucleophiles. It afforded chiral 2H-1, 4-oxazine derivatives in good yields (up to 94%) with excellent enantioselectivity (up to 99% ee). The reaction could be scaled up to gram-scale with the catalyst loading lowered to 0.5 mol %. With this reaction as a key step, the first enantioselective synthesis of (+)-chelonin A was synthesised. Hence scheme 3 is excellent among other reported synthesis.

The first synthesis of Chelonin B, (Scheme 1a, 1b, 1c) were furnished with excellent yield of 97% under optimized reaction condition. (Scheme 2) 1-hydroxyindole method was no that effective as the yields of reaction were poor only 14%.

The first synthesis of Bromochelonin B was carried out under optimised reaction condition and overall yield of reaction was good that is 28%. In conclusion, regioselective introduction of either chlorine, bromine, hydroxy, or methoxy group onto the 5-position of tryptamines is now possible by the following sequence of reactions: 1) conversion of tryptamine to 2, 3-dihydroindole, 2) transformation

to 1-hydroxyindole, and 3) subsequent reaction with acids. The most impressive fact through these studies is that the 1-hydroxyindoles having C-C-Nb side chain at the 3-position can only undergo the acid promoted nucleophiiic substitution reactions effectively, otherwise other types of reactions such as pyrrolo indole formation, dimerization etc take place depending on the structures of substrates and reaction conditions. The reason why is an interesting subject for further invetigation. Furthermore, the present study suggest that use of acids for the isolation of indolic alkaloids and peptides should be done very carefully because if 1-hydroxy or 1-methoxy substituted tryptamines or tryptophans were involved as a component, they would be isolated as 5-substituted indole derivatives resulted by acid promoted nucleophilic substitution reactions.

Successful preparation of derivatives of Chelonin A and Chelonin B by Acetylation gave excellent results.

CHAPTER IV

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