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Total Synthesis of Mansouramycin A

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TOTAL SYNTHESIS OF MANSOURAMYCIN A

A Thesis

by

ABIGAIL M. ZEPEDA

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ABSTRACT

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In 2009 bioactive compounds from marine *Streptomyces* species was isolated which resulted in deriving four isoquinoline-quinone alkaloids known as Mansouramycins A-D. There have been reports that there are 36 non-small cancer cells against cytotoxicity in Mansouramycins A-C in lung cancer, breast cancer, melanoma, and prostate cancer cells. Reports that have conducted total syntheses were all specific to a single compound only Mansouramycin A and D. However, in precedent methods, to obtain the derivatives with different substituents are limited when the substituents are on the fused-pyridine ring. Thus, a develop a systematic synthetic method of isoquinoline-quinones, which are to be able to obtain the natural Mansouramycins and their derivative by the usage of different amino acids via synthesis the aminoacetals.

DEDICATION

The completion of my master's studies would not have been possible without the support of my parents, Mario and Patricia Zepeda. My brothers, Diego and Jose and the support of my friends Tien Tran, Mitzin Conteras, Gabriela Cruz and Araceli Luna. Without their support and motivation, I would not have been able to achieve all the goals I have accomplish and want to move forward. Thank you for your love and support.

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CHAPTER I

INTRODUCTION

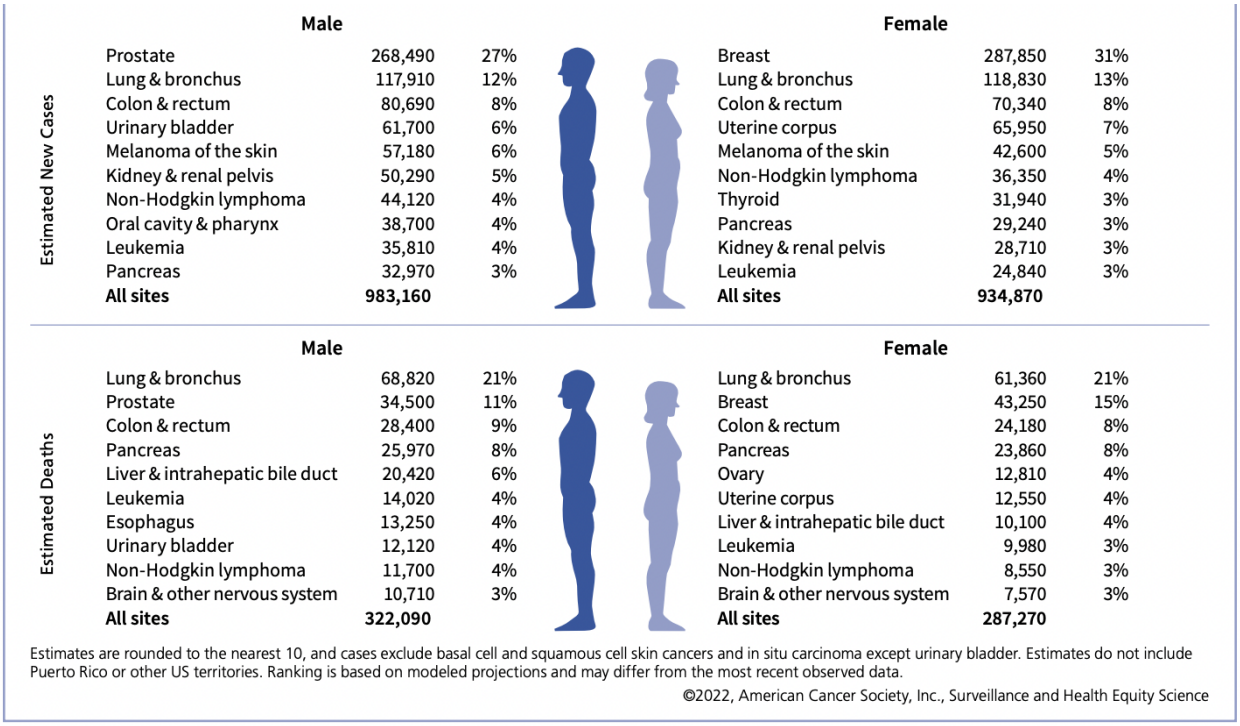
1.1 Cancer background

Cancer is known to be deadly in a human's body. According to the United States of American Cancer Society there is about 1,806,590 new cases in the year of 2020.[7] From 2020 to 2022 The American Society has estimated that there is of 2022 1.9 new million cases that have been diagnosed and with about 609,360 deaths in the United States.[8] However, some type of tumors can be benign and other can be very harmful to the body. It also depends on when the cancer is found in the body.

In figure one it shows an estimate on where the cancer is found in both male and female in 2022. For women the most area that has cancer is their breast with 31 % and the death rate is roughly 21%. In male where is mostly found is in their prostate with a 27% and the death rate being around 21%.[1] There are four different stages of cancer; Stage 1 is when cancer is found early on, and stage 4 is where the cancer has not only spread in the first area it was discovered but to more areas and can be too late for treatment. According to the cancer society, cancer is a disease in which some of the body cell growth uncontrollably and spread to other organs in the body.[1]

Treatments for cancer can be known to be expensive, especially for those who do not have the insurance to cover for it. According to the national expenditure for cancer in 2001 has reported that just for research on cancer is roughly around $ 57 billion and slowly increases as the years go by.[3] As the country progresses there is more and more studies being down on how to help cure this deadly diagnose.

However, some of the treatments and with America's health care system sometimes depending on an individual's financial status and where they live may or may not have the privilege to get rightfully treated. Which is why it is important that there is more research so there can be different ways to cure cancer that are more affordable and convenient for today's society.



Estimated New Cases	Male			Female		
	Prostate	268,490	27%	Breast	287,850	31%
	Lung & bronchus	117,910	12%	Lung & bronchus	118,830	13%
	Colon & rectum	80,690	8%	Colon & rectum	70,340	8%
	Urinary bladder	61,700	6%	Uterine corpus	65,950	7%
	Melanoma of the skin	57,180	6%	Melanoma of the skin	42,600	5%
	Kidney & renal pelvis	50,290	5%	Non-Hodgkin lymphoma	36,350	4%
	Non-Hodgkin lymphoma	44,120	4%	Thyroid	31,940	3%
	Oral cavity & pharynx	38,700	4%	Pancreas	29,240	3%
	Leukemia	35,810	4%	Kidney & renal pelvis	28,710	3%
	Pancreas	32,970	3%	Leukemia	24,840	3%
	All sites	**983,160**		**All sites**	**934,870**	

Estimated Deaths	Male			Female		
	Lung & bronchus	68,820	21%	Lung & bronchus	61,360	21%
	Prostate	34,500	11%	Breast	43,250	15%
	Colon & rectum	28,400	9%	Colon & rectum	24,180	8%
	Pancreas	25,970	8%	Pancreas	23,860	8%
	Liver & intrahepatic bile duct	20,420	6%	Ovary	12,810	4%
	Leukemia	14,020	4%	Uterine corpus	12,550	4%
	Esophagus	13,250	4%	Liver & intrahepatic bile duct	10,100	4%
	Urinary bladder	12,120	4%	Leukemia	9,980	3%
	Non-Hodgkin lymphoma	11,700	4%	Non-Hodgkin lymphoma	8,550	3%
	Brain & other nervous system	10,710	3%	Brain & other nervous system	7,570	3%
	All sites	**322,090**		**All sites**	**287,270**	

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Estimates do not include Puerto Rico or other US territories. Ranking is based on modeled projections and may differ from the most recent observed data.

Figure 1. Female and Male sites of cancer cases and deaths[2]

1.2 Isolation of the Isoquinoline-quinone

Some of the most known cancer diagnoses are lung cancer, breast cancer, melanoma cancer and prostate cancer. In 2009, there was bioactivity found in the marine *Streptomyces* in the specific strain of Mei37 that resulted in the isolation of four isoquinoline-quinone which are known as Mansouramycin A-D.[10] These four compounds have been reported to have cytotoxicity to 36 non-cancer cells to lung cancer, breast cancer, melanoma cancer and prostate cancer. [1]

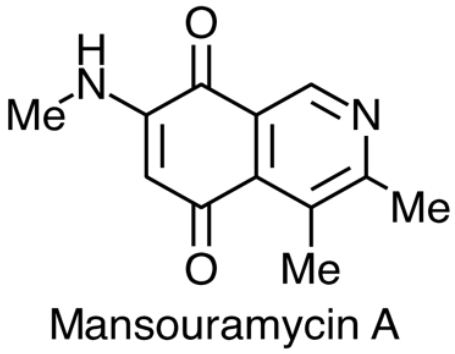


Figure 2. Mansouramycin A (1)

There have been other reports of isoquinlinequinones have been found in marine sponges such as cribostatins, renierone, etc.[1] In the German North Sea Coast, the strain of Mei37 was found in sea sponges that can be found there. The researchers had isolated the strain and were able to derive the compounds that are known as Mansouramycins A-D where can be shown in figure 2, 4, 5, and 6. In Figure 3 shows an SEM image of the species streptomyces that the Mansouramycincs A-D were isolated from.

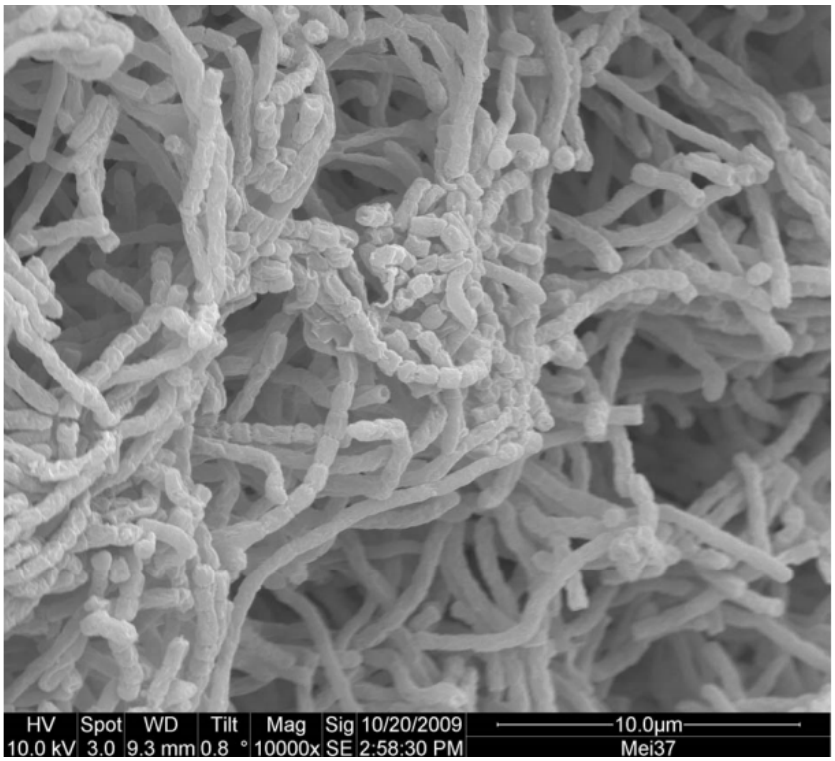


Figure 3: *Streptomyces* sp. Mei37 high resolution SEM image[4]

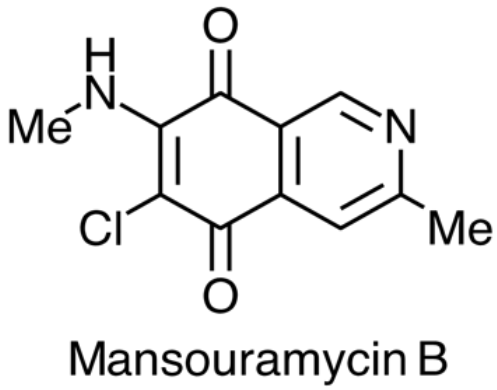
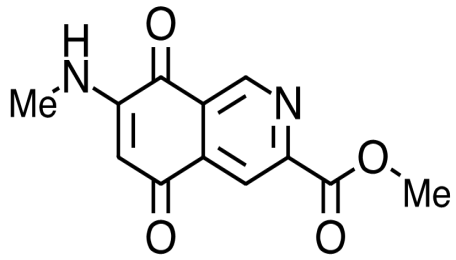
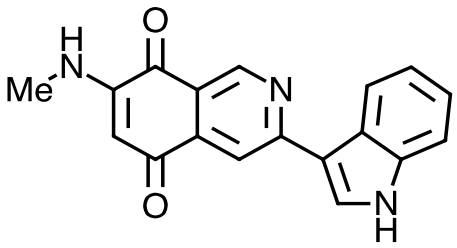


Figure 4: Structure of Mansouramycin B (2)



Mansouramycin C

Figure 5. Structure of Mansouramycin C (3)



Mansouramycin D

Figure 6. Structure of Mansouramycin D (4)

In other papers, the synthesized compound was then confirmed as Mansouramycin D via ^{1}H NMR spectrum of the natural product that was obtained.[1] This methodology for the synthesis of Mansouramycin D could also be applied to synthesize the other isoquinoline that have alkaloids that also show the same biological activities. Synthetic methods for these compounds require for the amine of the amino acid derivative to be protected with carboxybenzyl group, followed by coupling, protection, hydrogenation, reductive animation, and modified Pomeranz-Fritsch to help achieve Mansouramycin A.

The goal for this research is that Mansouramycin A could be synthesized from the amino acid alanine amino acetal. By using modification general methods of isoquinoline-quinones it should be able to obtain the total synthesis of the Mansouramycin natural compounds and their derivative by the usage of different amino acids to synthesis the amino acetals. The general methods can be shown in the figure 7. The next amino acids that are to be use is serine for Mansouramycin C and tryptophan for Mansouramycin D and to see if other amino acids can be used to get more derivatives of the amino acetals.

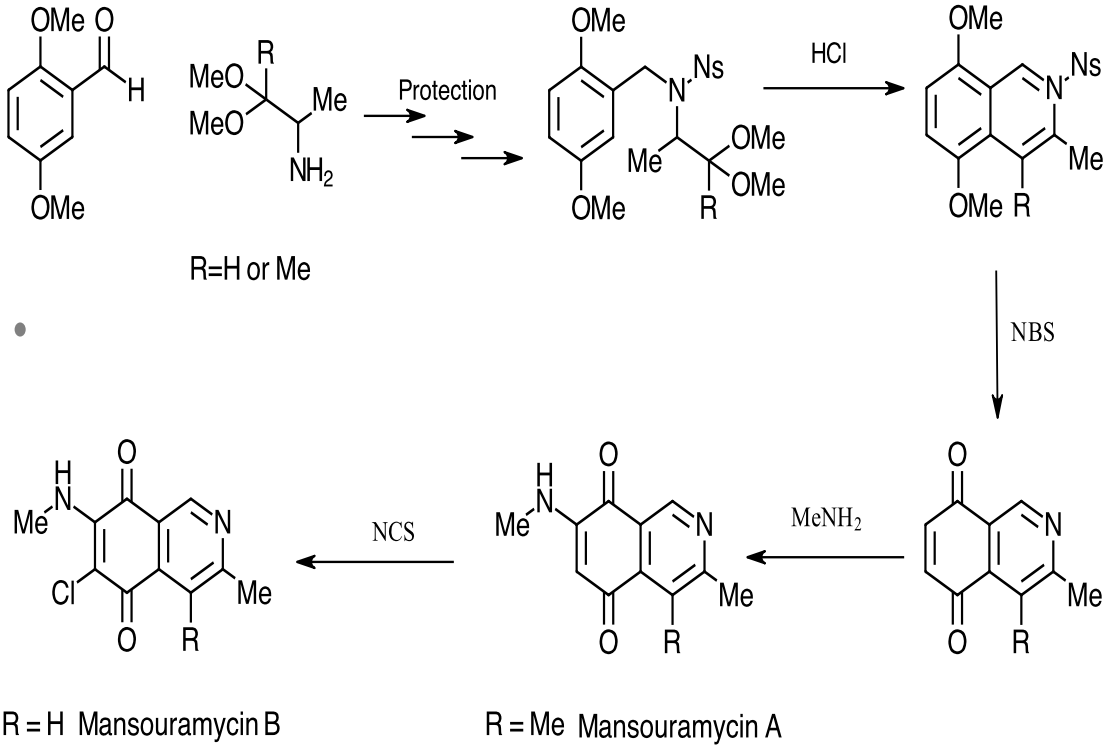


Figure 7. General methods of Mansouramycin A

CHAPTER II

REVIEW OF LITERATURE

Alkaloids are nitrogen compounds in natural resources such as plants, bacterial, fungal, etc. Alkaloids have a wide range of usage such as anticancer, antibacterial, and antiasthma. The species *Streptomyces* can be found in algae and sponges that are found in the sea. *Streptomyces* is known to be one of the largest Actinobacteria.[4] The Streptomyces were isolated and resulted in deriving five isoquinoline-quinone alkaloids that have been obtained through ethyl acetate extracts from *Streptomyces* Mei37.[4]

Where the sponge was found from the research with Hwas was in the German bay area. Because of the sea salt of the water that is where the algae and the sea sponges will be found in the bottom of the sea. The research then took those sponges and decided to isolate the *Streptomyces* Mei37.[4]

Streptomyces sp. Isolated Mei37 samples were incubated on a calcium carbonate medium and isolated by solid phase and ethyl acetate extraction as an oily extract. The extract yielded quinoline-quinones after separating through preparative thin layer chromatography. The mansouramycins A was obtained as a red like powder and mansouramycins B-D were a darker red powder. Further purification via HPLC to extract yielded mansouramycins A.

Hawas et. al. was the one that did the isolation and the chemical screening of the five compounds were extracted by ethyl acetate and were assigned the name Mansouramycin A, B, C, D, and 3-methyl-7-(methylamino)-5,8-isoquinoline.[4] They have become an interest due to their biological activities. Some of the biological activity that have been tested with the mansouramycins are antifungal, antitumor, antimicrobial, insecticidal, and cytotoxic properties. The four mansouramycins compounds underwent cytotoxic profiling against a total of 36 tumor cell lines of 4 different tumor types, which were prostate cancer, melanoma cancer, lung cancer, and breast cancer.[4] Mansouramycins compounds went through MTT cell proliferation assay.

What MTT is the measurement of the proliferation and the reduction in cell viability resulting in a form of apoptosis and or necrosis.[2] Usually the basic protocol for MTT is the cells are plated 1.000 to 100,000 per wall then they are left to incubate for 6 to 24 hours at 37 C. Then the MTT reagent is added which is roughly 10 µl, then is left to incubate for another four hours and is left to sit in a dark room temperature setting. Once that is complete the absorption will be recorded at 570 nm.[12]

The importance of the toxicity profiling of the mansouramycins compounds is because it will determine what is the difference of the substitution patterns that can affect the bioactivity that is being shown from the difference compounds.[2]

Tumor cells were welled and incubated for 24 h at 37 Celsius. Yellow tetrazolium MTT reagent was added by another incubation period until the MTT reagent was reduced by active cells resulting in a purple formazan dye and quantified through spectrophotometric analysis.[5]

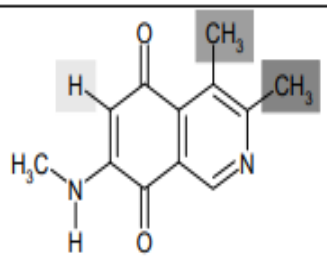
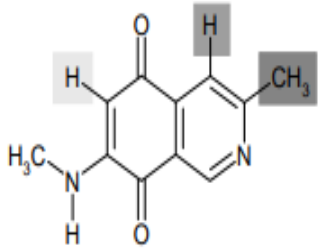
Compound	Structure	FA potency (mean IC_{50}, µM)	FA selectivity (n, %)
Mansouramycin A (**1**)		13.44	6/36 17
3-methyl-7-(methyl-amino)-5,8-isoquinoline-dione (**2**)		3.49	6/36 17

Table 1: FA potency IC_{50} and FA selectivity[2]

The main quinone isolated from Mei37 strain, Mansouramycin C, proved to be the most cytotoxic with a mean of IC_{50} value of 0.089 M, which is shown in table 2 and displayed a pronounced selectively towards 10 out of 36 cell lines: bladder cancer, glioblastoma, lung cancer, mammary cancer, melanoma, ovarian cancer, renal caner, and uterus cancer.[6] Cancer treatment has always been a very interesting topic in chemistry research as it is one of the leading causes of death worldwide. From table 2 it is showing that the one that was the most potent from the mansouramycins was mansouramycin C and the one that was the most selective out of all of them was also mansouramycin C. It shows that mansouramcyin C has an above average of about 10 out of the 36 tumor cell lines.

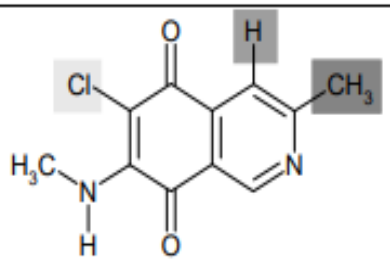
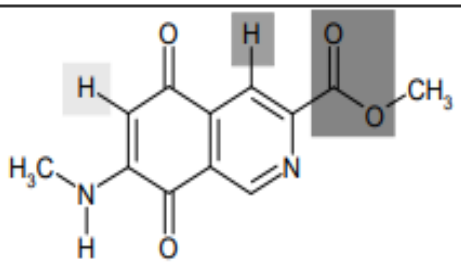
Mansouramycin B (**3**)		2.7	1/18 6
Mansouramycin C (**4**)		0.089	10/36 28

Table 2: FA potency IC_{50} and FA selectivity[2]

In table 3 it displays the tumor cell line derivatives, and it compares 14 solid tumor types. Some of the tumors had a pronounced selectivity.[10] These certain tumor types were also the main ones that were mentioned that are known as some of the cancers that are mostly diagnosed in the United States. The tumor cells that were known to have above average activity was breast cancer (SF-268), melanoma cancer (MEXF 2761, NEXF 514L, 520L) and prostate cancer (DU-145) as shown in table 3.

Tumor type	Cell line	IC_{50} [μM]			
		1	**2**	**3**	**4**
Bladder	BXF 1218L	28.19	10.26	1.38	0.134
	BXF T24	12.58	0.61	n.d.[a]	0.008
Glioblastoma	CNXF 498NL	14.39	5.21	1.34	0.130
	CNXF SF268	14.41	1.8	n.d.	0.008
Colon	CXF HCT116	9.11	3.62	n.d.	0.114
	CXF HT29	4.63	1.98	n.d.	0.146
Stomach	GXF 251L	31.9	3.6	1.75	0.167
Head & neck	HNXF 536L	0.71	0.38	n.d.	0.146
Lung	LXF 1121L	27.14	6.56	n.d.	0.150
	LXF 289L	19.05	3.04	5.96	0.130
	LXF 526L	18.99	10.62	n.d.	0.110
	LXF 529L	12.42	4.88	1.54	0.089
	LXF 629L	4.1	1.18	1.23	0.016
	LXF H460	7.11	3.92	n.d.	0.134
Breast	MAXF 401NL	47.76	17.31	3.55	0.195
	MAXF MCF7	2.34	1.11	n.d.	0.012
Melanoma	MEXF 276L	2.44	0.35	0.36	0.008
	MEXF 394NL	15.57	5.72	n.d.	0.106
	MEXF 462NL	49.93	18.97	5.64	0.179
	MEXF 514L	2.6	2.02	n.d.	0.012
	MEXF 520L	5.45	0.24	n.d.	0.012
Ovary	OVXF 1619L	13.15	4.01	n.d.	0.045
	OVXF 899L	34.89	6.6	13.91	0.134
	OVXF OVCAR3	32.31	7.64	2.0	0.012
Pancreas	PAXF 1657L	26.03	4.93	1.81	0.061
	PAXF PANC1	26.75	3.83	n.d.	0.549
Prostate	PRXF 22RV1	21.74	4.69	5.67	0.671
	PRXF DU145	1.25	0.34	n.d.	0.992
	PRXF LNCAP	21.67	6.36	n.d.	1.431
	PRXF PC3M	32.56	6.04	3.23	0.215
Mesothelioma	PXF 1752L	46.3	6.02	5.19	0.130
Kidney	RXF 1781L	16.36	9.89	n.d.	0.114
	RXF 393NL	18.65	4.16	1.57	0.122
	RXF 486L	59.14	50.62	17.89	1.646
	RXF 944L	18.1	5.43	n.d.	0.020
Uterus	UXF 1138L	18.02	2.23	1.68	0.012
Mean		13.44	3.49	2.7	0.089
Selectivity[b]		6/36	6/36	1/18	10/36

Table 3: Cytotoxic activity against the tumor cell lines[2]

Mansouramycins contain isoquinoline skeletons which can be synthesized through there common classical methods which were Bischler-Napieralski reaction, Pomeranz-Fritch reaction, picet-spengler reaction and Pictet-Games.[9] The pictet-spengler cyclization had been previously applied to the synthesis of Mansouramycin D however, it was unsuccessful.

Nagarajan and Prakash[6] attempted to synthesize of Mansouramycin D starting with a Sonogashira coupling of 2-bromo-3,6-dihydroxybenzaldehyde and Boc protected 3-ethynyl-1H-

indole but were unsuccessful starting perhaps because of the free hydroxyl groups. The free hydroxyl groups were then protected with MOM groups resulting in the successful Sonogashira coupling and synthesizing the full Mansouramycin D compound in three sequential steps iminoannulation of 2-alkylbenzaldehyde, oxidation/deprotection, and oxidative animation.[6]

CHAPTER III

METHODOLOGY

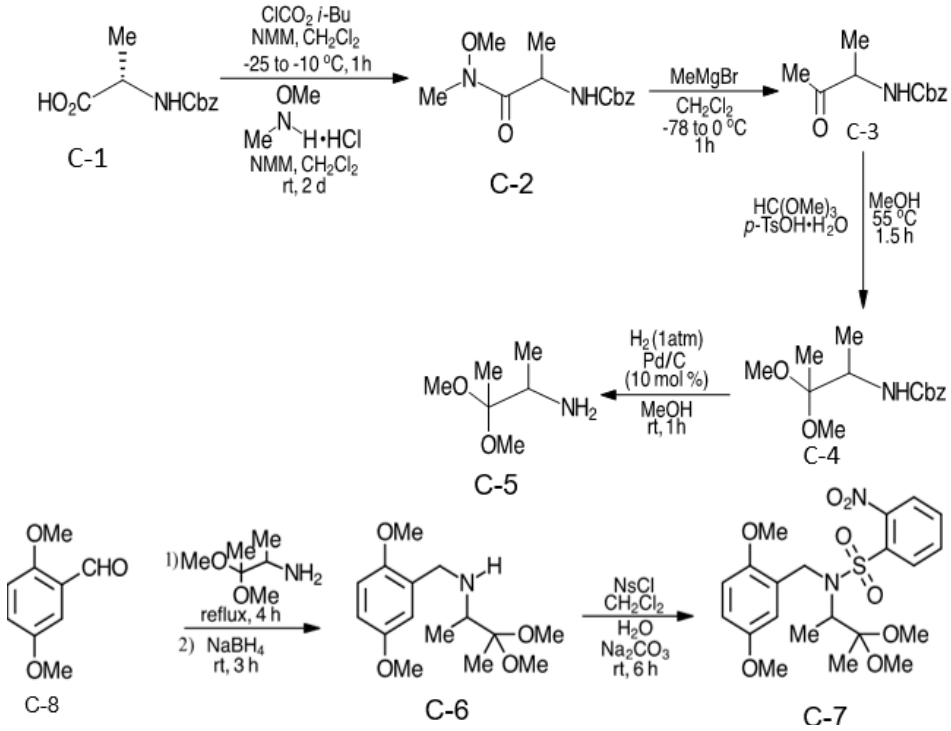


Figure 8: General scheme of C-1 – C-7 for Mansouramycin A

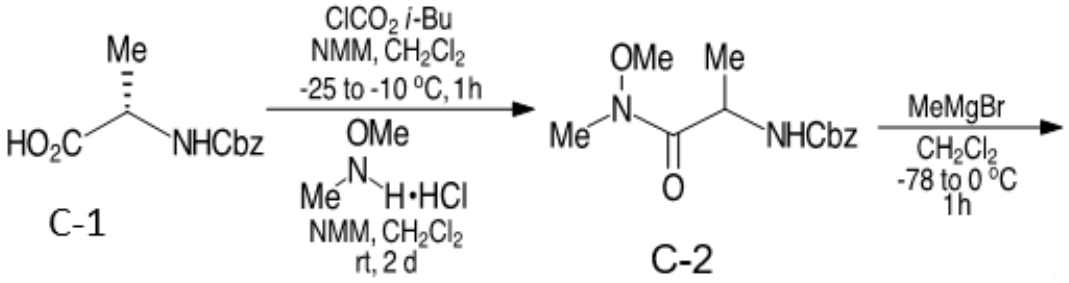


Figure 9: Step one reaction

N-Carboxybenzoyl alanine was coupled with N–Methoxy N–Methylamine hydrochloride to produce Benzyl 1-[methoxy(methyl)amino]-1-oxopropan-2-ycarbamate C-1. A two neck round bottom flask was heated with a heat gun equipped with a magnetic stirring bar. In the solution the L-alanine CBZ was added (1.02 g, 4.55 mmol) with about 7 ml of dichloromethane. To the mixture N-methylmorpholine (NMM) (462.0 mg, 4.55 mmol) as well as isobutyl chloroformate (0.0600 mL, 4.55 mmol). These two solutions were added at a -25 C temperature and was left to stir for about an hour at –10 C.

After the hour has passed N-methoxy N-methylamine hydrochloride (490 g, 5.07 mmol) and NMM (5.10 mg, 5.07 mmol) was added to the mixture along with 5 ml of DCM at the same temperature. The reaction was left to stir for 2 days at room temperature, once checked with TLC the reaction was quenched with saturated aqueous NH_4Cl. It was then extracted with DCM three times and the organic extracted was washed with water and saturated aqueous $NaHCO_3$. The organic extract was dried with anhydrous sodium sulfate, filtered and evaporated. A yellow oil

was obtained and columned with silica gel using the eluent hexane/AcOEt 30:70 to produce a white solid.

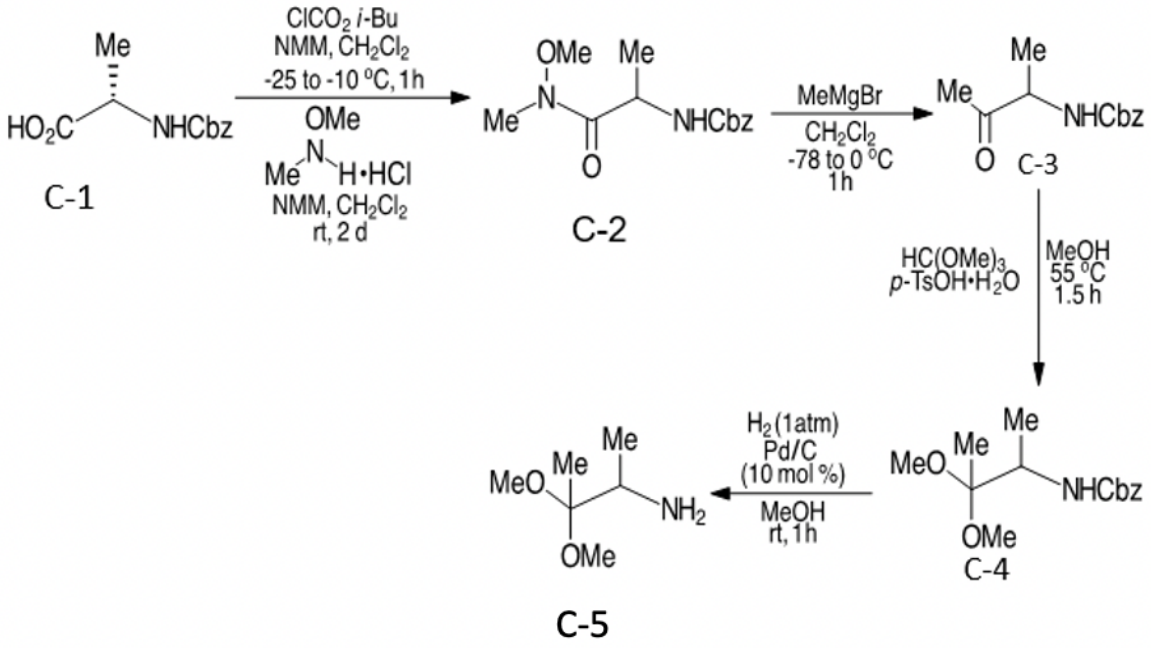


Figure 10: 3 step process to achieve pure amine

A 50 mL, flame dried, two neck-round bottom flasked equipped with stirring bar was charged with a Weinreb amide C-2 (535 mg, 2.01 mmol) and DCM. To the mixture Grignard (1.67 mL, 5.02 mmol) was added dropwise at -78 °C. The reaction was left to stir for an hour at 0°C, the reaction was quenched with AcOEt and saturated NH_4Cl(aq). Organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and vacuum under pressure to obtain a crude ketone C-3 as a pale-yellow oil. The crude ketone went on to the next reaction without further purification.

A 50 mL, flame dried, two neck-round bottom flasked equipped with stirring bar was charged the crude ketone C-3, trimethyl orthoformate (0.267 mL, 2.41 mmol), tosic acid (0.36 g,

0.189 mmol) and methanol (16.7 mL). The reaction was left stirring for 1.5 h at 55 °C, the reaction was quenched with saturated $NaHCO_3$(aq) and DCM. The organic extracts were washed with brine, dried with anhydrous sodium sulfate, and vacuum under pressure to obtain the crude acetal C-4. The crude acetal went on to the next reaction without further purification.

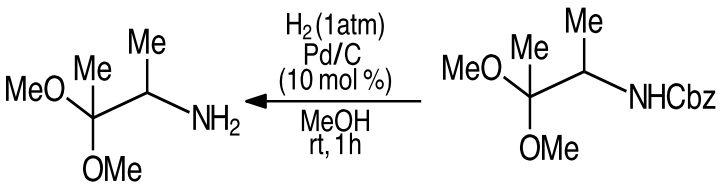


Figure 11: Hydrogenation reaction

A 50 mL, flame dried, two neck-round bottom flasked equipped with stirring bar was charged the crude acetal C-4, 10% Palladium with activated carbon (164 mg, 0.154 mmol) and methanol (20 mL). The mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 1 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to afford analytically pure amine C-5. (108 mg, 80% yield for three steps)

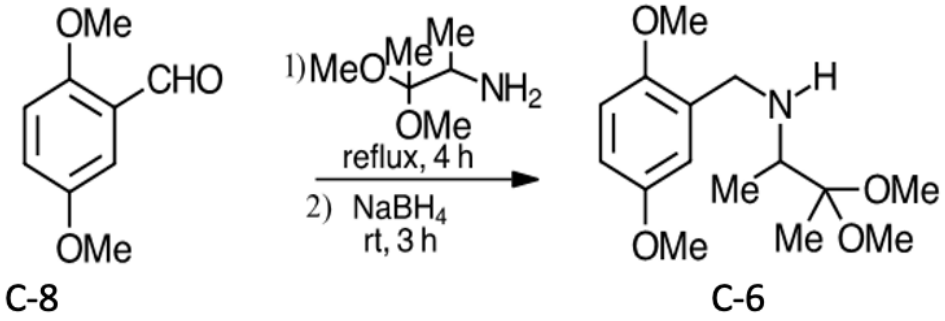


Figure 12: Modified Pomeranz-Fritsch

A 50 mL, flame dried, two neck-round bottom flask, equipped with stirring bar was charged with 2,5-dimethoxybenzaldehyde C-8 (216 mg, 1mmol) in 5 mL of dry toluene was added 1.0 mmol of C-5. The solution was boiled under reflux for 4 h. The solvent was under reduced pressure to obtain the Schiff's base. The isolated benzlideneamino acetal was used without further purification.

The isolated intermediate was dissolved in 5 mL of methanol and sodium borohydride (0.189 g, 5 mmol) was added to the mixture at room temperature. The reaction was stirred for 3 h and the organic solvent was evaporated in vacuum. Addition of saturated $NaHCO_3$(aq) and DCM followed by drying with sodium sulfate, and vacuum under reduced pressure to obtain a yellow oil. The residue obtained was purified by column chromatography AcOEt/MeOH (90:10) yield a yellow oil (96.8 %).

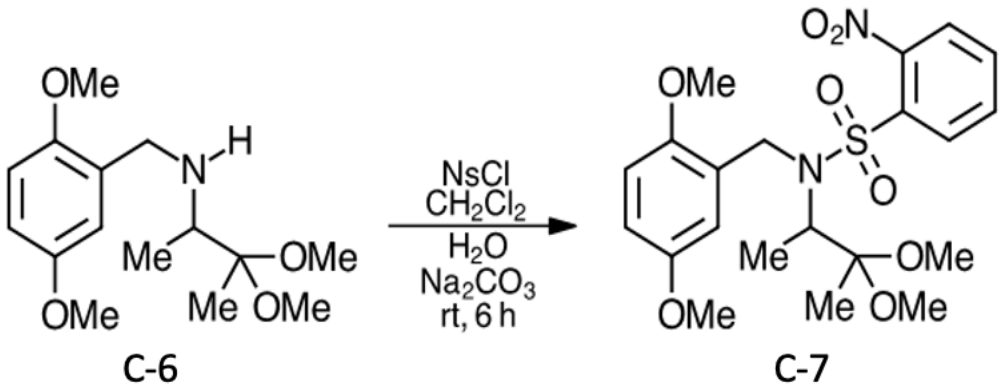


Figure 13: Modified Pomeranz-Fritsch part 2

A 50 mL, flame dried, two neck-round bottom flask equipped with stirring bar was charged with 8.0 mL of DCM solution of C-6 (255.0 mg, 1.0 mmol) were added a solution of sodium carbonate (10%, 5mL) and 0.215 mL of nitrobenzene sulfonyl chloride. The resulting mixture was stirred at room temperature for 6 h. The organic layer was separated dried and vacuum under reduced pressure and purified by column chromatography hexane/AcOEt (70:30) to yield a yellow oil (60% yield)

A two neck 100 ml round bottom flask was used equipped with a magnetic stir bar, glass was dry with oven over night. Equipped with a nitrogen balloon. In the round bottom flask (440.0 mg; 1.0 mmol) in 25 mL of dioxane/HCL 1 M. Left under reflux and under dark setting by using aluminum foil to wrap up the reaction was left to run four about 8 hours. After reaction completed, the pH of the reaction mixture was adjusted to 8 with Na_2CO_3 and was extracted with 150 ml of DCM. The combined extracts were dried over anhydrous $MgSO_4$, filtered, and

evaporated which received a light brown oil. To purify from any impurities using a column chromatography hexane/AcOEt (60:40).

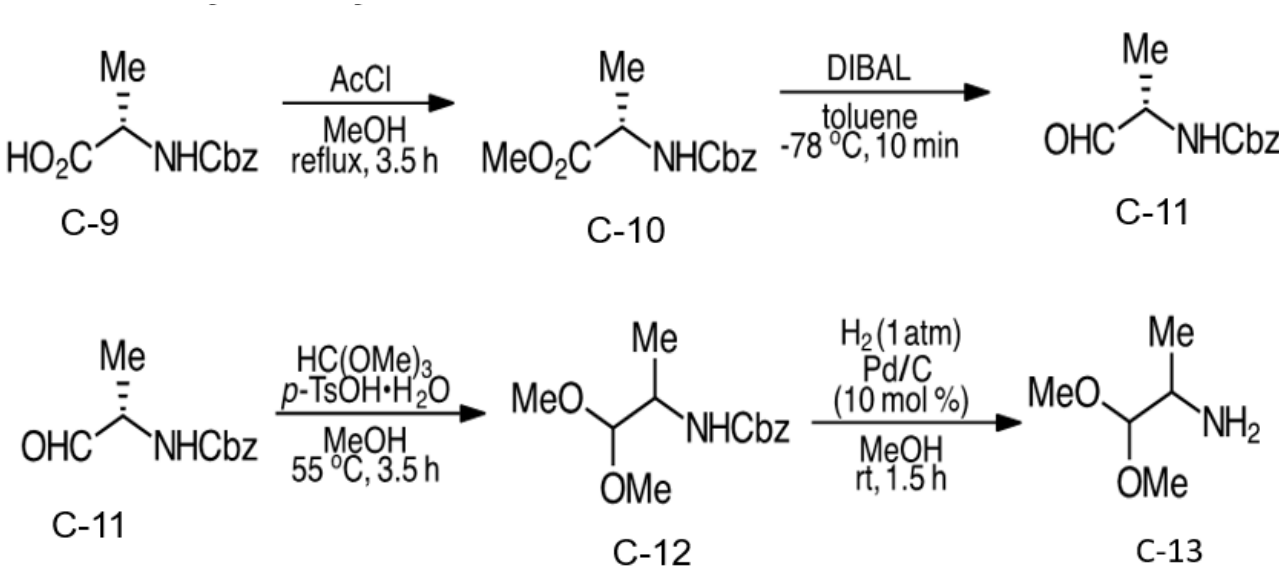


Figure 14: Mansouramycin B steps

Carboxylic acid group of N-Carboxybenzoyl alanine was esterified using acetyl chloride to produce Methyl N-carboxybenzoyl alanine.

Ester group of S-4 was reduced to an aldehyde group using DIBAL to obtain benzyl 1-methyl-2-oxoethylcarbamate (C-10).

Aldehyde group protection was obtained with substitution of aldehyde group with ester groups from trimethyl orthoformate in a tosic acid catalyzed reaction resulting in synthesis of N-Carboxybenzoylalaninal dimethylacetal (C-11).

Amine group was deprotected by the removal of the Cbz protection group through a hydrogenation reaction to produce 2-Amino-3,3-dimethoxypropane (C-12).

CHAPTER IV

DISCUSSION AND CONCLUSION

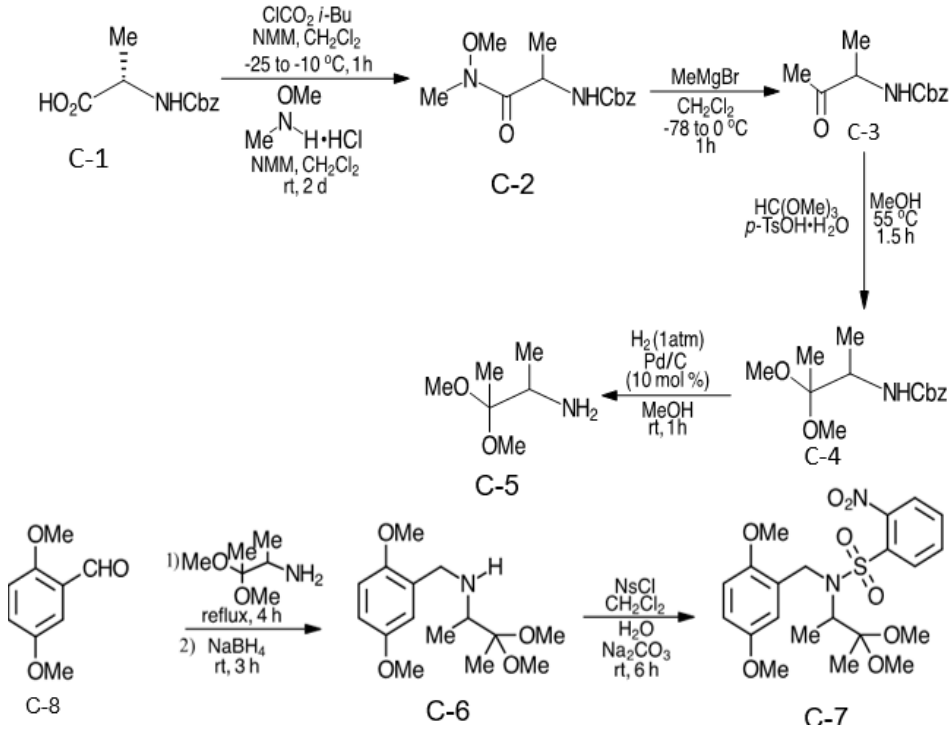


Figure 15: Mansouramycin A C-1 – C-8

The compound N-Carboxybenzoyl alanine was coupled with N–Methoxy N–Methylamine hydrochloride to produce Benzyl 1-[methoxy(methyl)amino]-1-oxopropan-2-ycarbamate known as C-2. To ensure that the final product would be pure with no other products

as well, C-2 was purified with a column chromatography and was confirmed that the product was pure by using nuclear magnetic resonance. C-2 percent yield was 86 % yield which was able to obtain a white solid. Some implications that could have happen to not obtain 100% yield is loss of product while transferring the product and losing some product while running the column chromatography.

The following procedures was a three-step process to keep on moving to the next reaction without further purification. The amide group of C-2 was substituted with a methyl group via Grignard reaction added dropwise to obtain the crude ketone C-3 as a yellow oil. The crude ketone was subjected to protection reaction without purification with tosic acid to produce C-4 crude acetal that obtained as a yellow oil. The crude acetal of S-10 was then continued with a hydrogenation. To ensure that the hydrogenation did not combust was that the round bottom flask was filled with Nitrogen to be able to be at nitrogen atmosphere.

Once the nitrogen balloon was on in the round bottom flask for about 15 minutes and the nitrogen was vacuumed out and the hydrogen balloon was then added once most of the nitrogen was out. The reaction was left for an hour to stir and once the reaction came to completion the solution was filtered through celite to produce the 2-amino-3,3-dimetoxybutane C-5 as a brown yellow which had 80.5 % percent yield. Reasons on why there may have not been a 100% yield is due to some lost of product when moving the stuff is being moved from one vial to another.

The pure amine C-5 was added to 2,5-dimethoxybezaldehyde to do a reductive animation reaction. The reaction was refluxed for four hours and once the reaction came to a complete it the solvent was evaporated and moved on to the next reaction with sodium borohydride. The reaction was then purified with a purified column chromatography after the solvent was checked

with a TLC plate to show there was two spots on the TLC plate. To confirm that the product was pure the product was checked with NMR. The percent yield for this end product was 96.8 %.

The last reaction for Mansouramycin A was a Pomeranz-Fritsch reaction and failed to receive the product. This waws run three times using different acid quantities. The first trial was with 25 mL of dioxane/HCL 1 M. Reason why it may have not work is because it was at a lower M than what the original procedures had. On the original procedure they had used 6 M of HCL and that type of concentration was not available. The second trial that was conducted was with dioxane/sulfuric acid 1:4 ratio. When check with NMR it was shown the sulfuric acid did not do protonate the compound and did not go through. The last one was with sulfuric acid in less quantity 1:3 to see if it will make a difference. NMR shows that it was unsuccessful.

The reaction was conducted with a dark setting due to it be light sensitive. The reaction was covered with tin foil to make sure that no light would go through. However, since this is just by covering the instruments with foil and not using a proper dark room there can be areas where light could have gone through while running the reaction. For future attempts there will be trials on using different acids that will hopefully help the reaction successfully go through.

The starting material that was done from the other graduate student working on the same project for Mansouramycin B was run by doing a reaction by an esterification process through a carboxylic acid group N-Carboxybenzoyl alanine by using acetyl chloride to produce methyl N-carboxybenzoyl alanine C-9 Which yield a 81.2 %. The esterification was followed by a reduction using the ester group and it was reduced to an aldehyde group by using DIBAL to obtain bezyl-1-methyl-2-oxoethylcarbamate C-10. The C-10 compound yield 33 %.

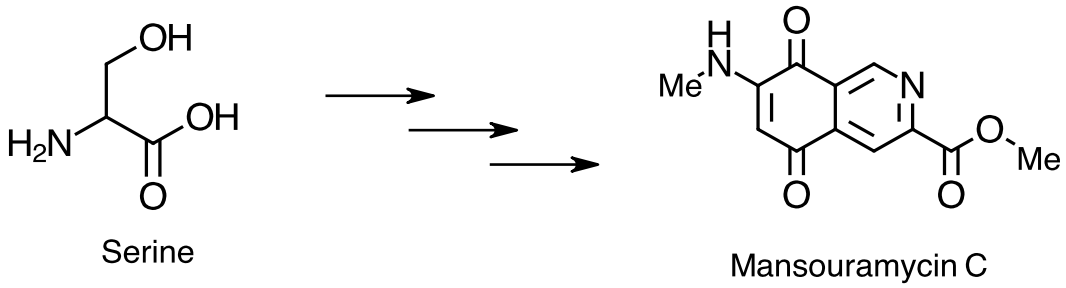


Figure 16: Future work on Mansouramycin C

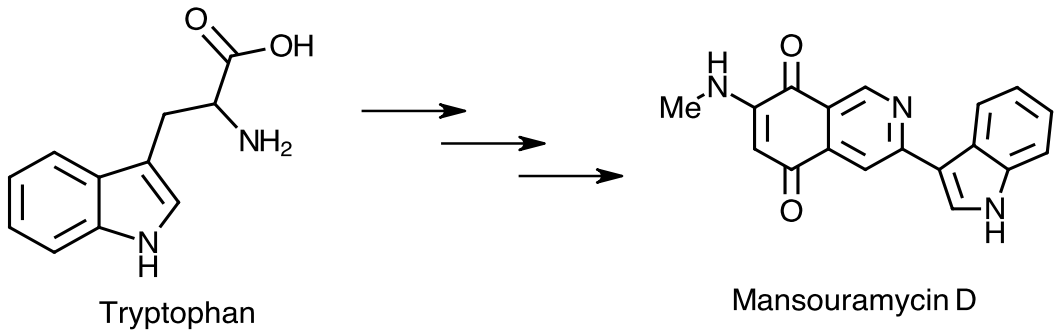


Figure 17: Future work on Mansouramycin D

The antitumor compounds of Mansouramycin A-D can be useful in the presence of cytotoxicity of 36 small for four different types of cancer which were lung, breast, melanoma, and prostate cancer. C-2 and C-5 were able to obtain 80-86% yield and the reductive animation reaction also obtained a high yield 96.8 %. NMR was used to confirm that all the products are pure. General procedures of the isoquinoline-quinones are to be able to obtain the total synthesis of the mansouramycins natural compounds and their derivative by the usage of different amino acids to synthesis the amino acetals. In the future work of this project is to start working with Mansouramycin C while using the amino acid serine and Mansouramycin D with the amino acid

tryptophan and to try different ways to obtain reaction 8 by using different acids. The project will continue on to see if by using a different acid the reaction will complete so it can move forward and successfully achieve mansouramycin A.

4.1 NMR SPECTRAS

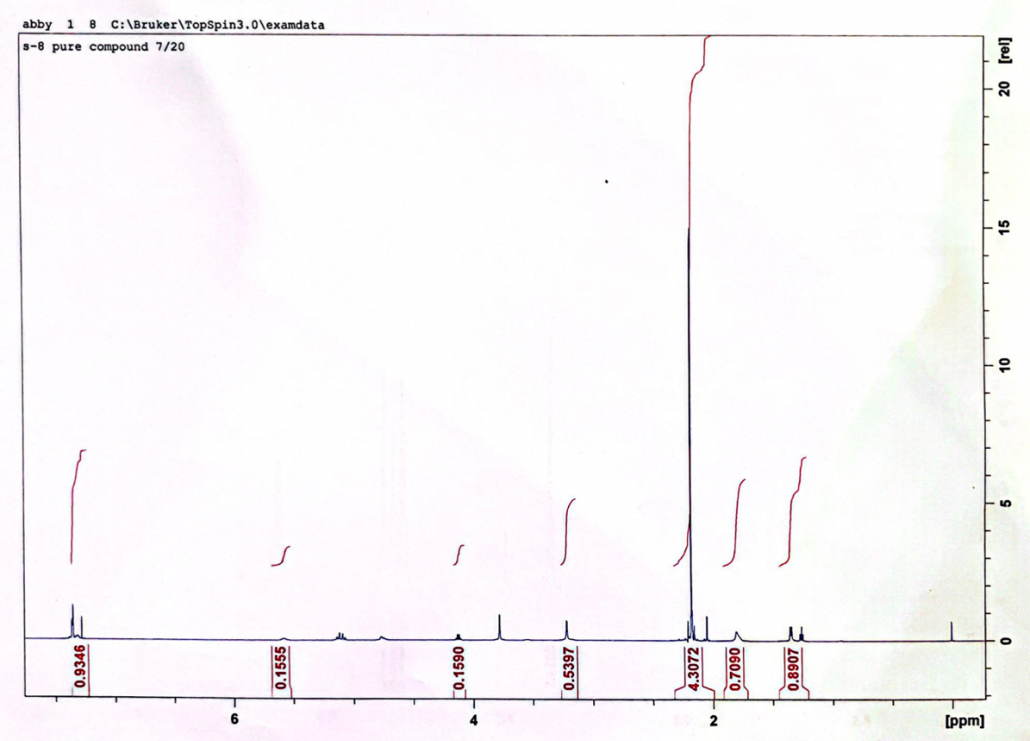


Figure 18: Pure NMR spectra for compound 2

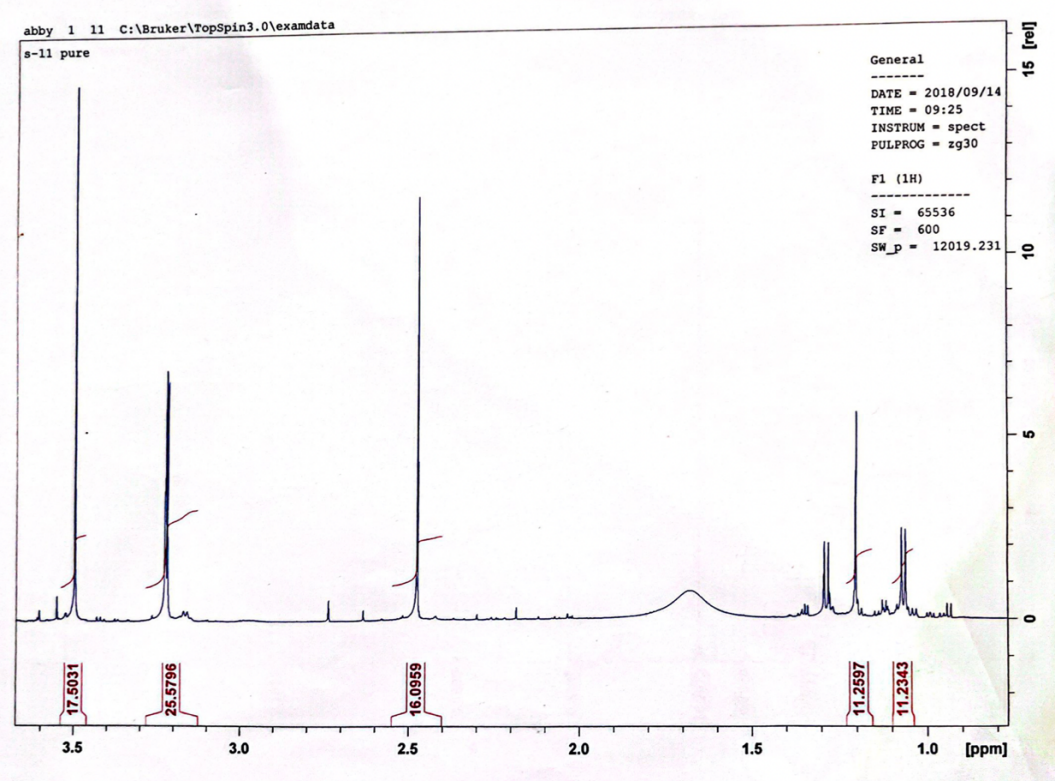


Figure 19: Pure NMR spectra of compound 5

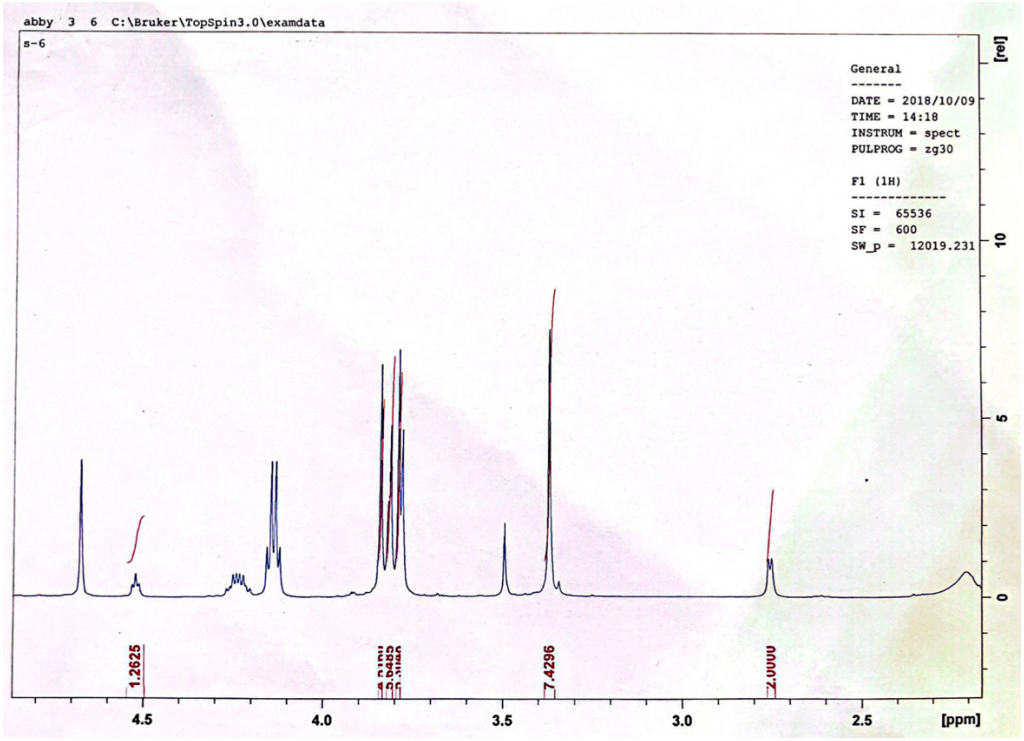


Figure 20: Pure NMR spectra of compound 6

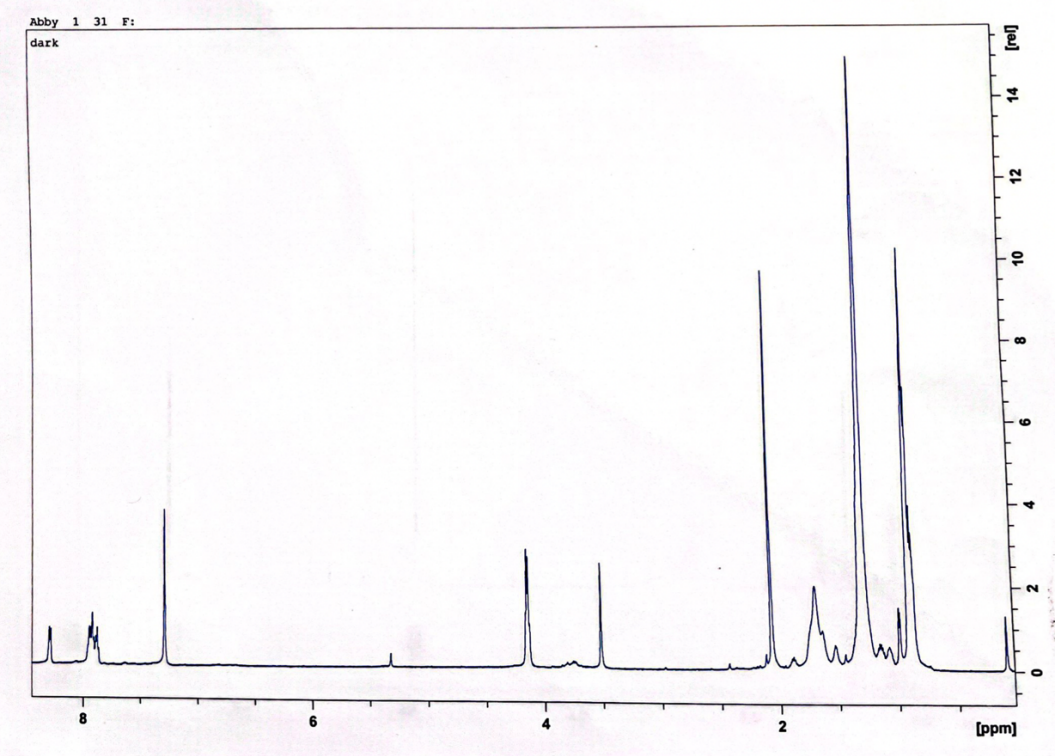


Figure 21: Failed spectra of last reaction

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BIOGRAPHICAL SKETCH

Abigail Milagros Zepeda graduated with her high school diploma at Weslaco high school in 2013. She went to the University of Texas at Rio Grande Valley to get her bachelor's degree in the school of science, majoring in Chemistry. She graduated from UTRGV in the spring of 2019. During her undergrad she worked under Dr. Jason Parsons and published her work in his lab in 2018. In the fall of 2020, she started working on her master's degree in chemistry. She did her research with Dr. Shizue Mito and received her Master of Science in Chemistry from the University of Texas Rio Grande Valley in May 2022. She can be access via email at abbymiracle17@gmail.com.