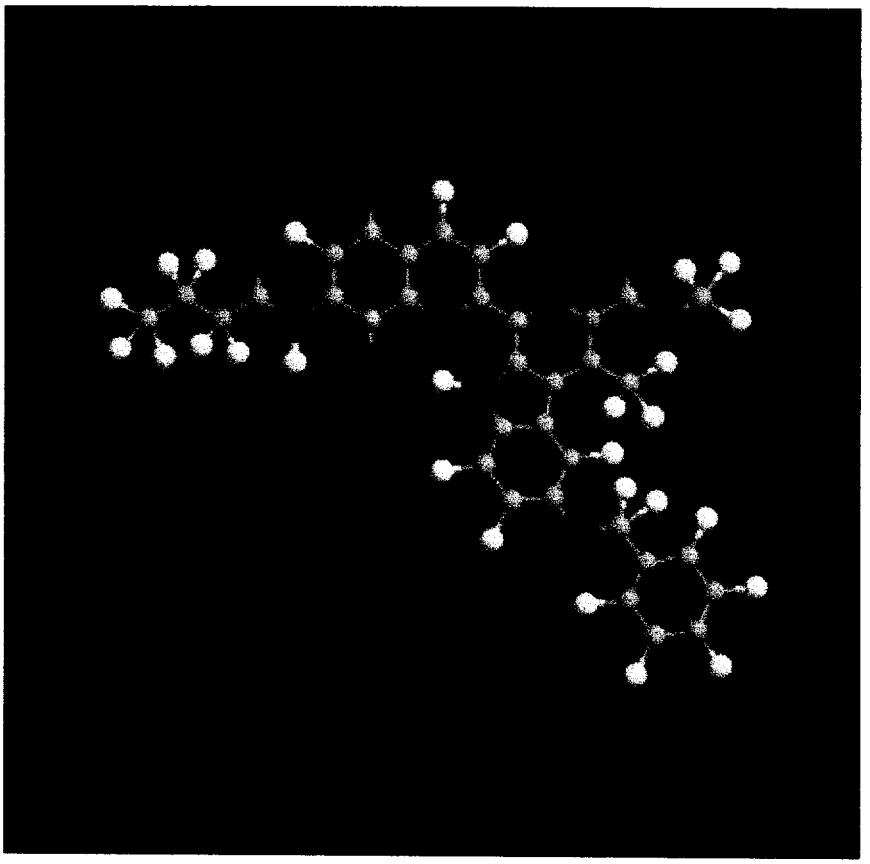
The Total Synthesis of 7-*N*-Butyryl-11'-benzyloxylavendamycin Methyl Ester

An Honors 499 Thesis by

C. Scott Proctor



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I. Abstract

This thesis is part of an ongoing research project, led by Dr. Behforouz, which studies the structure-activity relationship of various lavendamycin analogs as possible anti-tumor agents. The specific work contained in this thesis is directed toward the synthesis of 7-*N*-butyryl-11'-hydroxylavendamycin methyl ester but ends with the synthesis of 7-*N*-butyryl-11'-benzyloxy-lavendamycin methyl ester. By synthesizing these analogs and eventually testing their biological activity, a better understanding of how adding a benzyloxy or a hydroxy functional group affects the activity of the compound. The goal of these structure-activity relationship studies is to develop analogs of lavendamycin that have a high selective toxicity against cancer cells.

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II. ACKNOWLEDGMENTS

I would like to thank Dr. Mohammad Behforouz for the wonderful opportunity and experience he has provided through his research. I have gained invaluable knowledge by working on this project which has laid the groundwork for my career as a chemist. It is his guidance and friendship that have made my education complete.

I would also like to thank Mrs. Wen Cai and all of the members of our research team for their help and support. Wen Cai has always been a ready source of knowledge and advice and she is always willing to help. I would like to thank Rajesh Karki, a graduate student working on a very similar analog, for all of his help.

I would like to acknowledge the Ball State University Chemistry Department for my education., which I have found is a unique one. I feel that very few schools can provide the high quality education of large school while retaining a sturdy relationship between the students and the professors. All of the faculty should be commended for their efforts in providing students with a great atmosphere and an extensive education.

I would like to thank the American Cancer Society, whose funding made my research possible, as well as the National Institute of Health, Eli Lilly, and many other sources who have contributed to the ongoing research project.

Finally, I would like to thank my family for their unwavering love and support.

III. Background Information

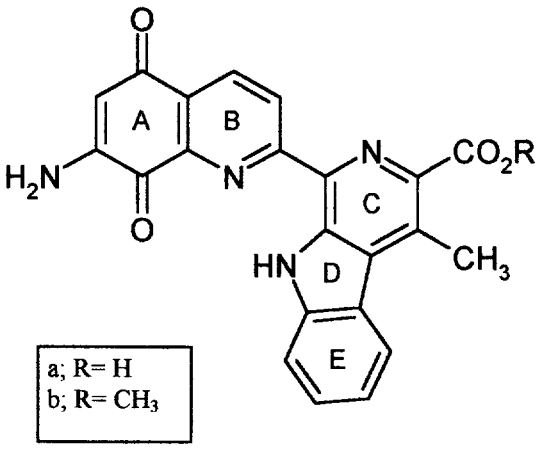


Figure 1 – Lavendamycin (a) and Lavendamycin Methyl Ester (b)

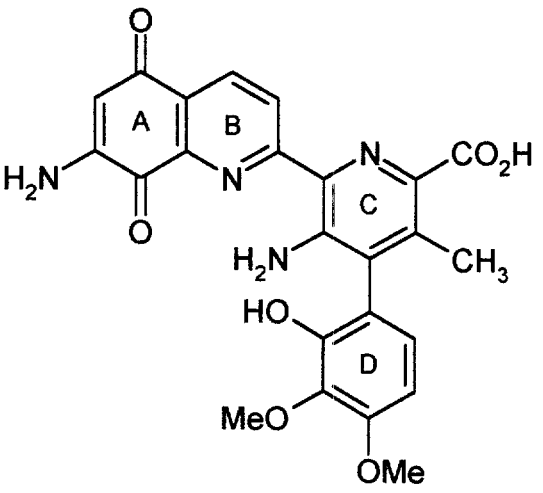


Figure 2 - Streptonigrin

Lavendamycin (Figure 1a) and streptonigrin (Figure 2) are two similar molecules that have been found to exhibit potent anti-tumor activity. Unfortunately, these two molecules are too toxic for clinical applications[1, 2, 3]. Analogs of lavendamycin, though, have shown a promising increase in the activity of the molecule as compared to its toxicity. One analog, lavendamycin methyl ester (Figure 1b), has particularly exhibited promising activity against certain types of lung cancer[4].

The goal of the research presented in this thesis was to synthesize an analog of lavendamycin methyl ester containing a hydroxyl group. The addition of a hydroxyl group to ring E of the lavendamycin produces a molecule reminiscent of streptonigrin, which contains several oxy- groups on ring D. Testing of hydroxy-analogs will thus aid in determining the role

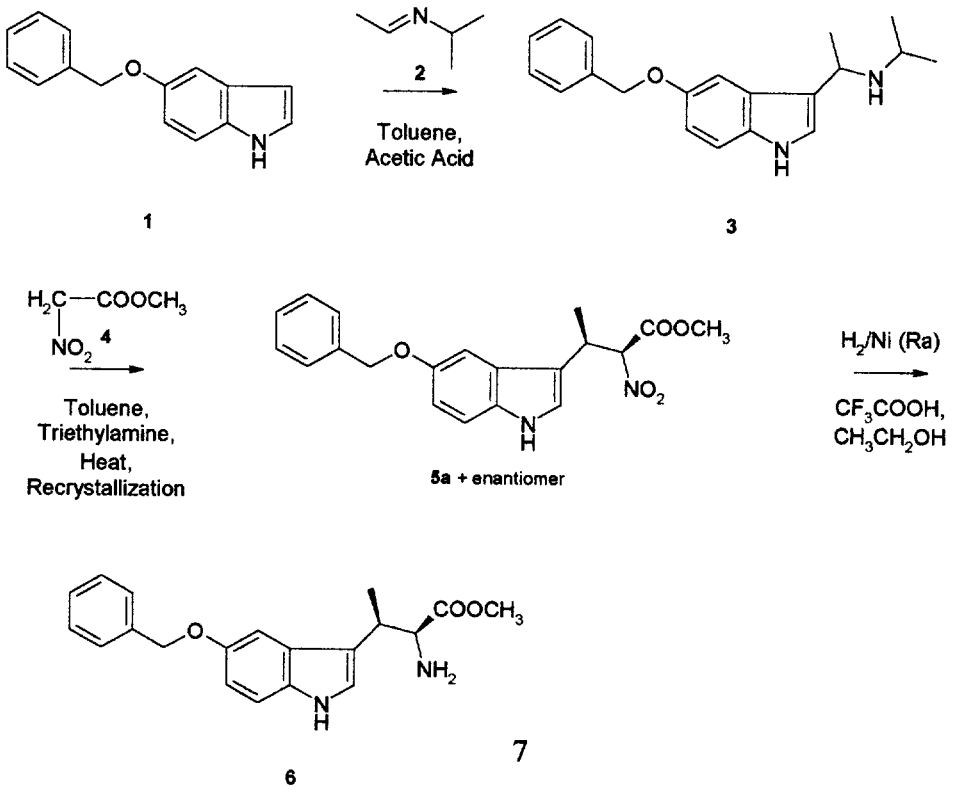
these groups play in the activity of the molecule. A possibility is that the hydroxy-analogs will exhibit some of streptonogrin's increased activity without the added effect of increased toxicity[5].

An additional purpose in synthesizing hydroxy-analogs of lavendamycin methyl ester is that they may show an increased solubility since most lavendamycin analogs exhibit very low solubility[6]. The hydroxyl group may also serve as a handle to add a phosphate group, which would allow for a further increase in solubility.

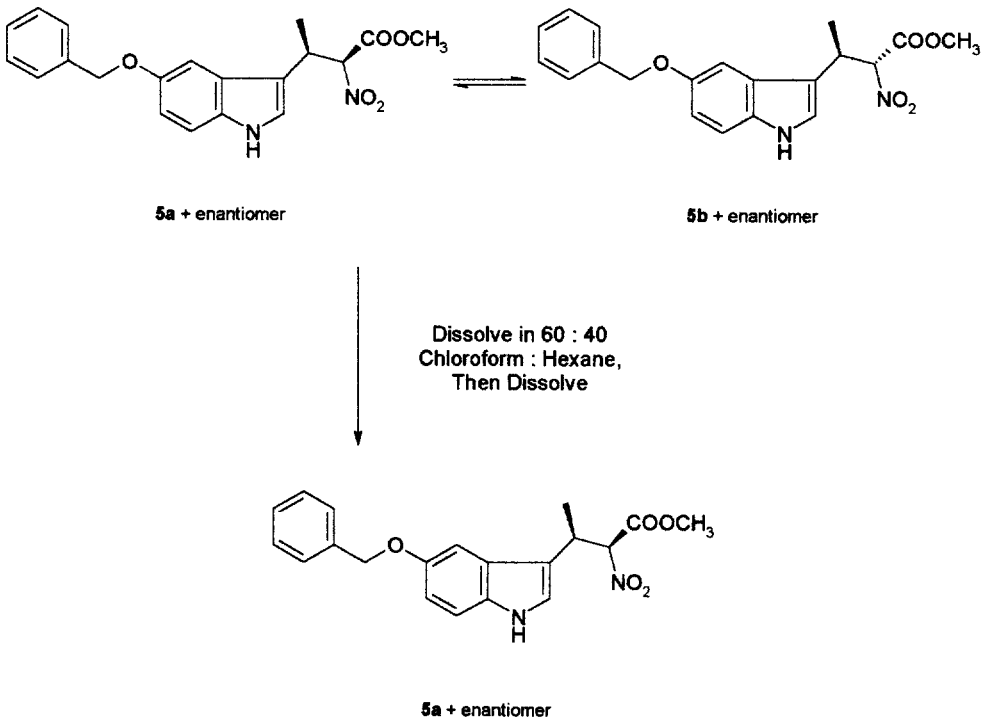
IV. Total Synthesis

For the specific lavendamycin analog 7-*N*-butyryl-11'-benzyloxylavendamycin methyl ester **(8)**, 7-Butyramido-2-formylquinoline-5,8-dione **(7)** was previously prepared according to the procedure by Stocksdale[7], and the methyl-2-amino-3-[3-(5-benzyloxyindole)]-butanoate **(6)** had to be synthesized. This was done using the commercially available 5-benzyloxyindole **(1)** as a starting material and following a procedure similar to the synthesis of β-methyl-tryptophan methyl ester[8, 9] (See Scheme 1). It is also possible to synthesize **1** according to a procedure by Stoll, et al[10].

Scheme 1 - Synthesis of β-Methyl-tryptophan Methyl Ester Analog



Scheme 2 – Isomers of Methyl-2-nitro-3-[3-(5-benzyoxyindolyl)]-butanoate



To a solution of 5-benzyloxyindole **(1)** in glacial acetic acid, a solution of freshly prepared ethylidene isopropylamine **(2)** in dry toluene was added, keeping the temperature below 10°C. Because this reaction is very exothermic, a salt-ice bath was used to keep the reaction temperature below 10°C . This mixture was allowed to stand in the refrigerator for 4 days, then it added to water and extracted with ether. The ethereal layer was washed with 1M potassium hydrogen sulfate. The aqueous solutions were then combined and basified to produce 3-(isopropylamino-ethylidene)-5-benzyloxyindole **(3)** crystals in 48% yield.

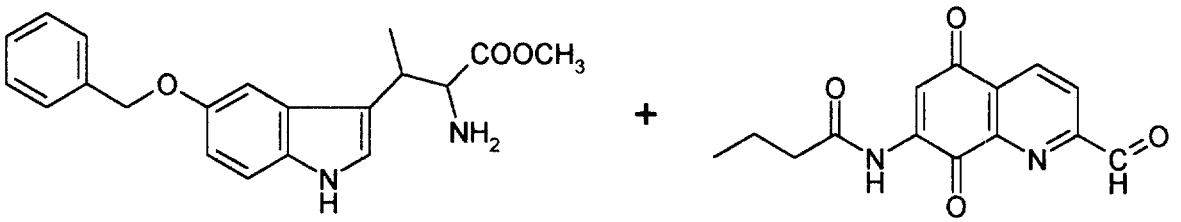
Compound **3** was placed in dry toluene, and to this triethylamine and methyl nitro-acetate **(4)** were dissolved. The solution was stirred at 95-105°C for 8 hours, then the toluene

was evaporated, leaving a racemic mixture of the two isomers of Methyl-2-nitro-3-[3-(5-benzyloxy-indolyl)]-butanoate **(5a** and **5b)** (see Scheme 2) with a yield of 75%. Since isomer **5a** is less soluble, the residue was dissolved in a 60 : 40 mixture of chloroform : hexane, which was then evaporated, pushing the equilibrium toward isomer **5a**. The repetition of this process yields very pure crystals of the isomer **5a** and its enantiomer, which were then recrystallized from chloroform and hexane.

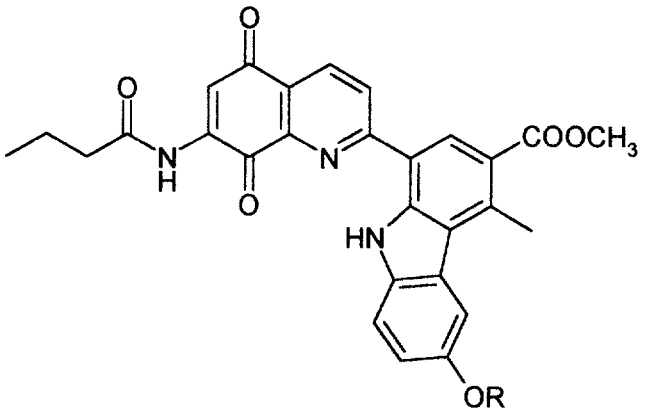
Compound **5a** was then dissolved in a solution of trifluoroacetic acid in absolute ethanol. Raney-Nickel catalyst was added to this solution, and hydrogenation was carried out at 40 psi at room temperature. After carefully filtering the Raney-Nickel catalyst, the solution was extracted with ether and aqueous ammonium hydroxide. The ether was evaporated to give a brown, oily residue. Methyl-2-amino-3-[3-(5-benzyoxyindolyl)]-butanoate **(6)** was obtained by dissolving the residue in anhydrous ether and evaporating it, producing light brown crystals with a 99% yield.

The synthesis of the benzyloxy analog **8** was carried out via a Pictet-Spengler condensation similar to the procedure used to make many lavendamycin methyl ester analogs[11, 12]. For this Pictet-Spengler condensation, compounds **6** and **7** were dissolved in dry xylene and refluxed for 2 hours (see Scheme 3). The xylene was evaporated, leaving a mixture of benzyloxy **(8)**, hydroxy **(9)**, and other products with a crude yield of 80%. The products were purified using a chromatography column, producing compound **8** and a small amount of compound **9**.

Scheme 3 – Pictet-Spengler Condensation



6 + **7**



8 , **9** , and **10**

8; R= $OCH_2C_6H_5$
9; R= OH
10; unknown compound

V. Experimental

A. General Information

Reagents: Isopropylamine, acetaldehyde, 5-benzyloxyindole, nitromethane, triethylamine, and trifluoroacetic acid were purchased from the Aldrich Chemical Company

Solvents: All solvents used were reagent grade. Exceptions to this are when the experiment called for either dry toluene or dry xylene (see Section B).

Melting Points: All melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected.

NMR Spectra: ^{1}H NMR Spectra were recorded on a Varian Gemini 200 Spectrometer in $CDCl_3$ or DMSO-D_6.

IR Spectra: IR Spectra were recorded on a Perkin Elmer FT-IR Spectrometer Spectrum 1000 using a KBr mull.

Thin-Layer Chromatography: Eastman silica gel strips with fluorescent were used to test the purity of all products.

B. Solvent purification

It was necessary to dry and purify toluene and xylene for some reactions. This was done by refluxing the solvent over sodium spheres until the metal had melted and appeared shiny. Benzophenone was added to the reflux mixture as an indicator, since dry benzophenone is a dark blue. Once the solvents were dried, they were then distilled.

C. Procedure

The procedures for the synthesis of methyl-2-amino-3-[3-(5-benzyoxyindolyl)]-butanoate **(6)** were similar to those used in the synthesis of β-methyl-tryptophan methyl ester[8, 9]. The procedure for the synthesis of 7-*N*-Butyryl-11'-benzyloxylavendamycin methyl ester **(8)** is similar to the procedure used to make many lavendamycin methyl ester analogs[11, 12].

1. **Ethylidene isopropylamine (2).** In a 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a condenser cooled with flowing ice-water, 85.0 mL of isopropylamine (59.0 g, 1.0 mol) was placed. The flask was cooled in an ice bath, and 55.8 mL of freshly distilled acetaldehyde (44.0 g, 1.0 mol) was added at 0°C over a period of 3 hr. The light orange solution was then stirred for an additional ½ hr. The solution was then transferred to a 500 mL Erlenmeyer flask and a sufficient amount of ground potassium flakes was added so that the solution separated into two distinct layers. The light orange organic layer (top layer) was separated from the clear aqueous layer, and the organic layer was placed in a 250 mL Erlenmeyer flask containing barium oxide and was allowed to stand in the refrigerator overnight. The barium oxide was filtered off, and the resulting yellow solution was distilled in a dry, base washed setup (5% NaOH) under reduced pressure (bp 22-24°C, 120 mm Hg) to yield 61.56 g of clear product (72%).

2. **3-(Isopropylaminoethylidene)-5-benzyloxyindole (3).** A solution of 5-benzyloxy-indole **(1)** (5.00 g, 0.0224 mol) dissolved in 80 mL of glacial acetic acid and 25 mL of dry toluene was placed in a 250 mL round-bottomed flask equipped with a magnetic stirrer, a

dropping funnel, and an ice-water cooled condenser with a calcium chloride drying tube. A solution of freshly distilled amine **2** (2.13 g, 0.0250 mol) in 40 mL of dry toluene cooled to 5°C was placed in the dropping funnel and it was added drop-wise over a period of ½ hr, maintaining an internal temperature below 15°C. The dark orange solution was allowed to stir for an additional 15 min, then it was placed in the refrigerator for 5 days. The resulting dark brown solution was poured into 150 mL of ice water and 50 mL of ether, and the mixture was stirred vigorously for 15 min. The yellow aqueous layer was extracted from the dark ethereal layer, and the ethereal layer was washed with 1M potassium hydrogen sulfate (3 x 50 mL). The combined aqueous solutions were basified to pH 13 with 10M sodium hydroxide solution, while keeping the temperature of the solution below 25°C using an ice bath. The crystals were filtered off and, to remove any sodium hydroxide crystals, suspended in cold water and filtered again. The product was dried under vacuum overnight to yield 3.31g (48%) of fine, white crystals. mp 139-142°C (sub). IR (KBr); 740.45, 795.18, 1037.67, 1194.68, 1382.37, 1452.84, 1463.80, 1581.49, 700.27 , 2966.59, 3431.00 cm^{-1}. NMR ($CDCl_3$); δ1.03 (q, J = 6.14 Hz, 6 H), δ1.47 (d, J = 6.60 Hz, 3 H), δ2.82 (m, J = 6.24 Hz, 1 H), δ4.16 (q, J = 6.60 Hz, 1 H), δ5.10 (s, 2 H), δ6.92 (d, J = 8.76 Hz, 1 H), δ7.06 (s, 1 H), δ7.22 - 7.49 (m, 7 H), δ7.85 (b, 1 H).

3. **Dipotassium Salt of Nitroacetic Acid.** 250 mL of 50% potassium hydroxide solution (4.456 mol) was placed in a 500 mL round-bottomed flask equipped with a condenser, a thermometer, a dropping funnel, and a magnetic stirrer, and the solution was heated to 60°C. 48.8 mL of nitromethane (55.0 g, 0.902 mol) was added drop-wise with vigorous stirring over a period of 45 min, causing the reaction temperature to rise to 90°C. Ammonia was liberated

during the reaction, and the condenser was removed after all of the nitromethane was added. The solution was heated to 100-115°C to boil off water until yellow crystals formed. The solution was allowed to cool to room temperature, then the crystals were filtered. The mother liquor was boiled again until more crystals formed then was allowed to cool, and the crystals were collected. The combined crystals were dried overnight under vacuum. Total yield was 79.28 g (97%).

4. **Methyl nitroacetate (4).** In a 1-L round-bottomed flask equipped with a mechanical stirrer, a thermometer, and a dropping funnel fitted with a calcium chloride drying tube was placed freshly ground, dry dipotassium salt of nitroacetic acid (77.65 g, 0.428 mol) and 600 mL of methanol. The solution was cooled well below -10°C using a salt-ice bath. Concentrated sulfuric acid (80.25 mL, 147.66 g, 1.48 mol) was placed in the dropping funnel and added dropwise with vigorous stirring over a 2 hr period, maintaining the reaction temperature below -10°C. After all of the sulfuric acid had been added, the mixture was slowly allowed to warm to room temperature over a 3 hr period and was allowed to stir at room temperature overnight. The white precipitate was filtered from the solution, and the orange filtrate was concentrated to 100 mL and then extracted with 150 mL of toluene. The organic layer was washed with water (6 x 100 mL) until the washes were no longer orange. The clear toluene solution was dried over anhydrous sodium sulfate and the toluene was rotoevaporated. The resulting yellow liquid was distilled under reduced pressure to yield 8.19 g (19 %) of clear liquid.

5. **Methyl-2-nitro-3-[3-(5-benzyoxyindolyl)]-butanoate (5).** A mixture of amino **3** (4.50 g, 0.0146 mol) and 100 mL of dry toluene was placed in a 1 L round-bottomed flask

equipped with a mechanical stirrer, an argon inlet, a thermometer, and a water cooled condenser connected to an oil bubbler. To this, triethylamine (1.47 g, 0.0145 mol) and methyl nitro-acetate **(4)** (1.75 g, 0.0170 mol) were added, and the mixture was stirred at room temperature for ½ hr. Dry toluene (300 mL) was then added and the mixture was stirred at 95-105°C for 12 hr. After allowing the reaction mixture to cool to room temperature the toluene was washed with 5% hydrochloric acid (3 x 50 mL) and water (3 x 50 mL) and dried over magnesium sulfate. The toluene was then evaporated , leaving a dark brown, sticky residue. This residue was dissolved entirely in 60 : 40 mixture of chloroform : hexane, then the solvent was evaporated, pushing the equilibrium toward isomer **5a** and producing dark brown crystals. Subsequent recrystallizations of this product from 60 : 40 chloroform : hexane eventually produced white crystals of pure isomer **5a**, which were recrystallized from chloroform and hexane. Crude yield was 4.02 g (75 %). mp 110°C. IR (KBr); 629.42, 726.65, 786.03, 797.59, 1216.82, 15.48.81, 1736.89, 3382.90 cm^{-1}. NMR ($CDCl_3$); δ1.51 (d, J = 6.96 Hz, 3 H), δ3.53 (s, 3 H), δ4.11 (m, J = 5.73 Hz, 1 H), δ5.11 (s, 2 H), δ5.36 (d, J = 9.00 Hz, 1 H), δ6.94 (d, J = 8.76 Hz, 1 H), δ7.05 (s, 1 H), δ7.13 (s, 1 H), δ7.23 - 7.51 (m, 6 H) δ8.00 (b, 1 H).

6. **Methyl-2-amino-3-[3-(5-benzyoxyindolyl)]-butanoate (6).** Nitro compound **5a** (1.360 g, 0.00369 mol), trifluoroacetic acid (1.208 g, 0.0106 mol), and 120 mL of absolute ethanol were placed in a 500 mL hydrogenation bottle and was stirred with a magnetic stirrer for ½ hr until all of nitro compound **5a** was dissolved. The magnetic stir bar was removed from the flask and 3.0 g of Raney nickel catalyst was added. Hydrogenation was carried out at 40 psi at room temperature for 2 hr. After hydrogenation, the mixture was filtered through celite and the filter cake was washed with absolute ethanol (3 x 10 mL). The filtrate was evaporated to almost

dryness, then it was extracted with 10 mL of ether, 5 mL of water, and 1.5 mL 14% ammonium hydroxide. The yellow ether layer was separated from the green aqueous layer. The aqueous layer extracted further with ether (4 x 10 mL), then the combined ethereal layers were washed with 5 mL of 10% solution of sodium chloride and was dried over magnesium sulfate for 1 hr. The ether was then evaporated off, leaving a light brown, sticky residue. It was possible to crystallize the product by repetitively dissolving it in anhydrous ether and evaporating the ether using a rotary evaporator, but it was highly resistant to forming crystals in any solvent so a true recrystallization of **6** was never achieved. Yield was 1.24 g (99%). IR (KBr); 721.91, 799.96, 1135.30, 1202.22, 1675.95, 1748.94, 2956.39, 3259.25, 3419.48 cm^{-1}. NMR ($CDCl^3$); δ1.37 (d, J = 7.04 Hz, 3 H), δ3.61 (s, 3 H), δ3.75 (q, J = 3.64 Hz, 1 H), δ4.15 (d, J = 3.96 Hz, 1 H), δ5.06 (s, 2 H), δ6.83 – 7.46 (m, 11 H), δ8.48 (b, 1 H).

7. **7-*N*-Butyryl-11'-benzyloxylavendamycin methyl ester (8).** For the Pictet-Spengler condensation, tryptophan **6** (100.6 mg, 0.2972 mmol) and aldehyde **7** (98.8 mg, 0.3629) were placed in 300 mL of dry xylene and stirred in a 500 mL round-bottomed flask equipped with a magnetic stirrer, an argon inlet, and a Liebeg condenser connected to an oil bubbler., and the mixture was heated to 30°C for ½ hr. The reaction temperature was slowly raised to 130°C over the period of two hours, then the reaction mixture was refluxed in an oil-bath for 2 hr. The reaction mixture was allowed to cool to room temperature and the dark brown crude product was filtered off. The filtrate was evaporated and more crude product was obtained, and the product was then dried under a vacuum at 50°C for 48hr. Total crude yield was 139.5 mg (80%).

TLC showed that the main product of this reaction was the benzyloxy analog **8**, but the reaction also produces some of the hydroxy analog **9** and a compound with very low solubility.

Flash chromatography using an effluent of 0.5% methanol in dichloromethane produced the benzyloxy analog **8** at over 90% purity, with a small amount of impurity which may be due to the hydroxy analog **9**. IR (KBr); 636.52, 798.62, 828.08, 1306.52, 1490.02, 1648.31, 1716.35, 2961.40, 3328.17 cm^{-1}. NMR ($CDCl_3$); δ1.05 (t, J = 7.37 Hz, 3 H), δ1.81 (q, J = 7.40 Hz, 2 H), δ2.53 (t, J = 7.40 Hz, 2 H), δ3.13 (s, 3 H), δ4.06 (s, 3 H), δ5.21 (s, 2 H), δ7.24 - 7.54 (m, 7 H), δ7.64 (d, J = 9.00 Hz, 1 H), δ7.85 (s, 1 H), δ7.97 (s, 1 H), δ8.38 (s, 1 H), δ8.48 (d, J = 8.34 Hz, 1 H), δ9.04 (d, J = 8.14 Hz, 1 H), δ11.73 (s, 1 H)

Conclusive NMR data was not available to identify the structure of the insoluble product **10** or the product collected from the second fraction from the chromatography column. The NMR data suggests, however, that the compound from the second fraction could be the hydroxy product **9**. This is important because it may be possible to modify the condensation so that the hydroxy product **9** is the main product formed.

APPENDIX A: **Molecular Formulas and Molecular Weights for Compounds.**

Isopropylamine	C_3H_9N	59.11 g/mol
Acetaldehyde	C_2H_40	44.05 g/mol
5-Benzyloxyindole **(1)**	$C_{15}H_{13}NO$	223.27 g/mol
Ethylidene isopropylamine **(2)**	$C_5H_{11}N$	85.15 g/mol
3-(Isopropylaminoethylidene)-5-benzyloxyindole **(3)**	$C_{20}H_{24}NO$	308.44 g/mol
Nitromethane	CH_3NO_2	61.04 g/mol
Dipotassium salt of nitroacetic acid	$C_2HNO_4K_2$	181.23 g/mol
Methyl nitroacetate **(4)**	$C_3H_5NO_3$	103.08 g/mol
Triethylamine	$C_6H_{15}N$	101.19 g/mol
Methyl-2-nitro-3-[3-(5-benzyoxyindolyl)]-butanoate **(5)**	$C_{20}H_{20}N_2O_5$	368.34 g/mol
Trifluoroacetic acid	$C_2HO_2F_3$	114.02 g/mol
Methyl-2-amino-3-[3-(5-benzyoxyindolyl)]-butanoate **(6)**	$C_{20}H_{22}N_2O_3$	338.41 g/mol
7-Butyramido-2-formylquinoline-5,8-dione **(7)**	$C_{14}H_{12}N_2O_4$	272.26 g/mol
7-*N*-Butyryl-11'-benzyloxylavendamycin methyl ester **(8)**	$C_{34}H_{28}N_4O_6$	588.62 g/mol
7-*N*-Butyryl-11'-hydroxylavendamycin methyl ester **(9)**	$C_{27}H_{22}N_4O_6$	498.50 g/mol

APPENDIX B: **NMR and IR Spectra for Compounds**

3-(isopropylaminoethylidene)-5-benzyloxyindole **(3)** - NMR ($CDCl_3$)

3-(isopropylaminoethylidene)-5-benzyloxyindole **(3)** - IR (KBr)

Methyl-2-nitro-3-[3-(5-benzyoxyindolyl)]-butanoate **(5)** - NMR ($CDCl_3$)

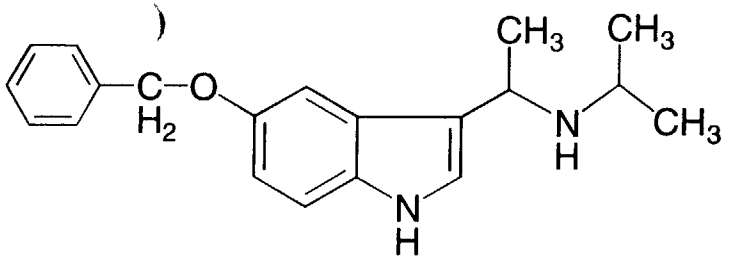
Methyl-2-nitro-3-[3-(5-benzyoxyindolyl)]-butanoate **(5)** - IR (KBr)

Methyl-2-amino-3-[3-(5-benzyoxyindolyl)]-butanoate **(6)** - NMR ($CDCl_3$)

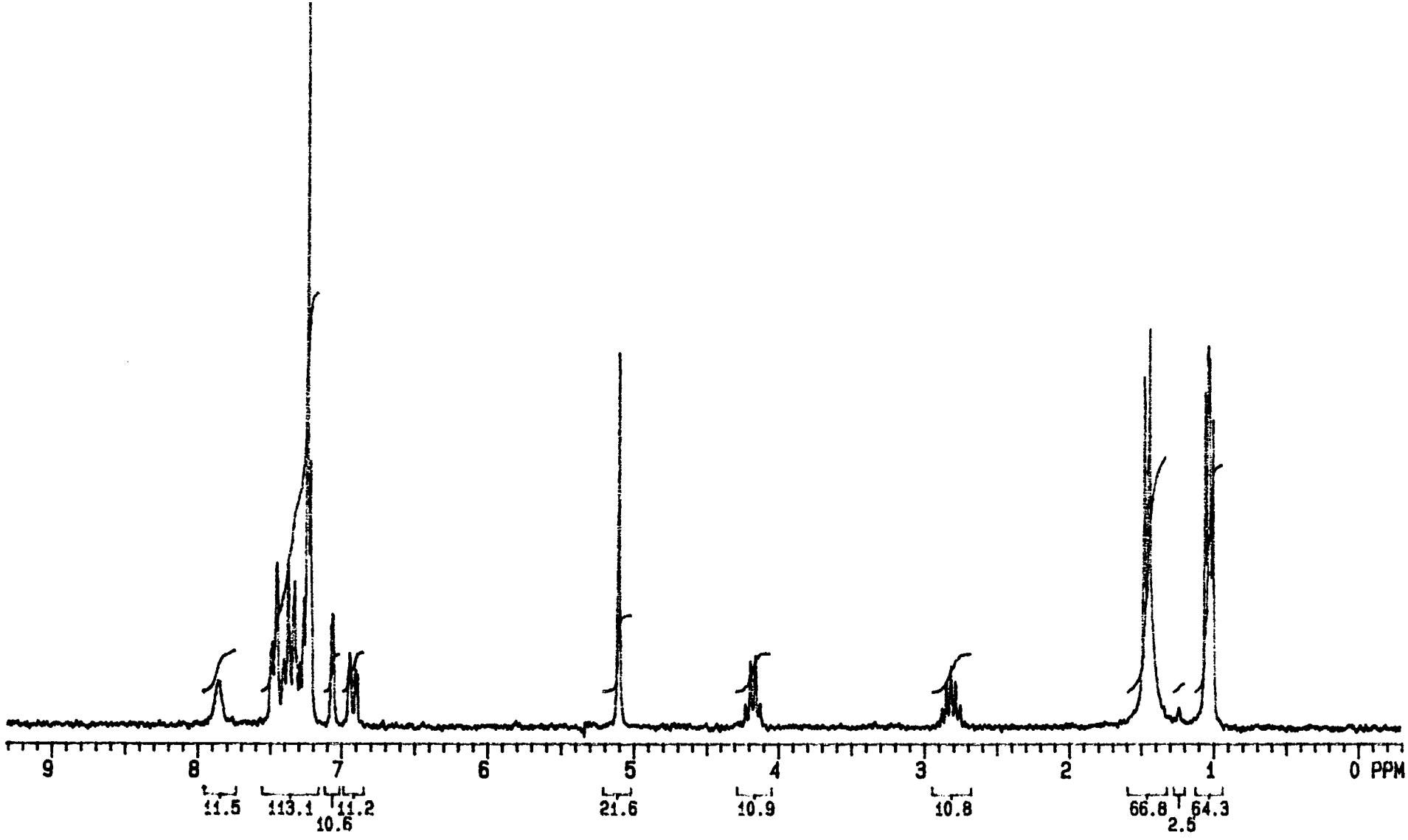
Methyl-2-amino-3-[3-(5-benzyoxyindolyl)]-butanoate **(6)** - IR (KBr)

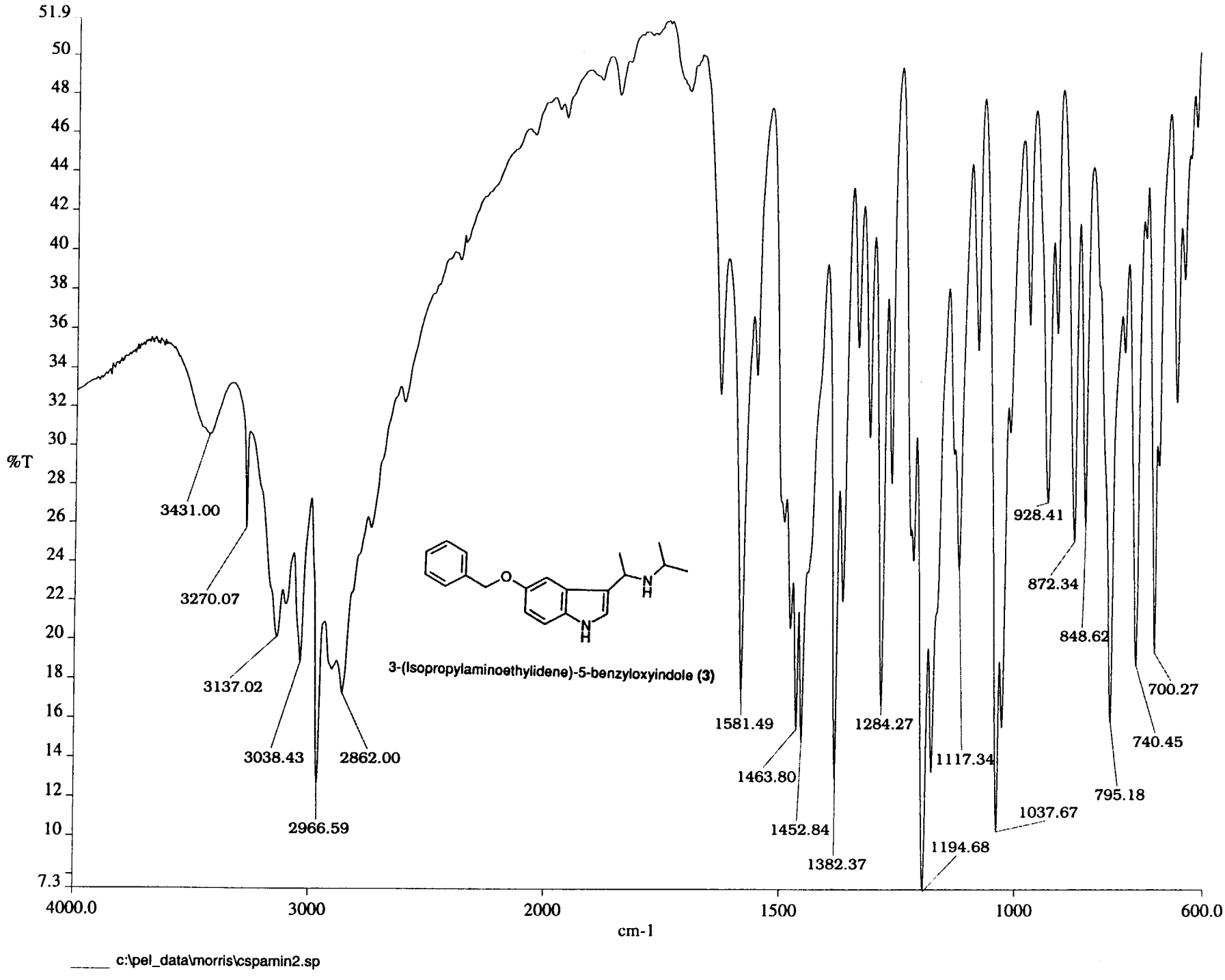
7-*N*-Butyryl-11'-benzyloxylavendamycin methyl ester **(8)** - NMR ($CDCl_3$)

7-*N*-Butyryl-11'-benzyloxylavendamycin methyl ester **(8)** - IR (KBr)



3-(Isopropylamino Ethyliedene)-5-Benzyloxyindole

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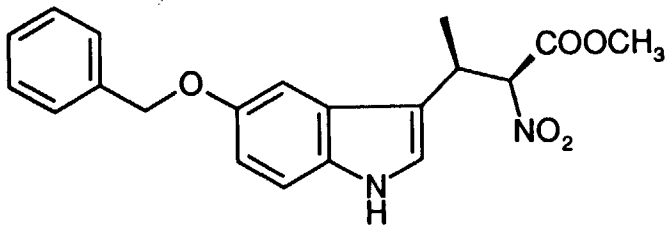
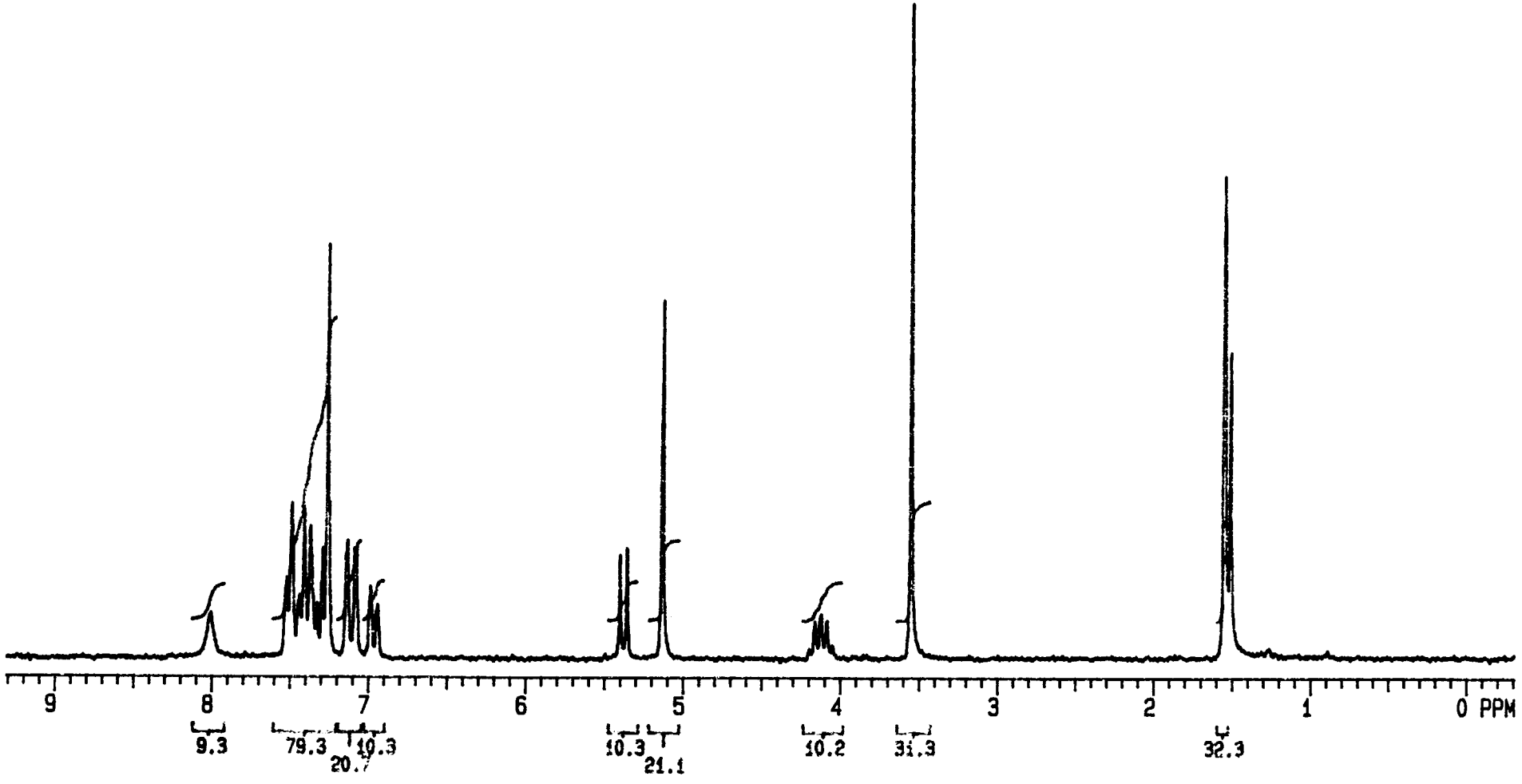
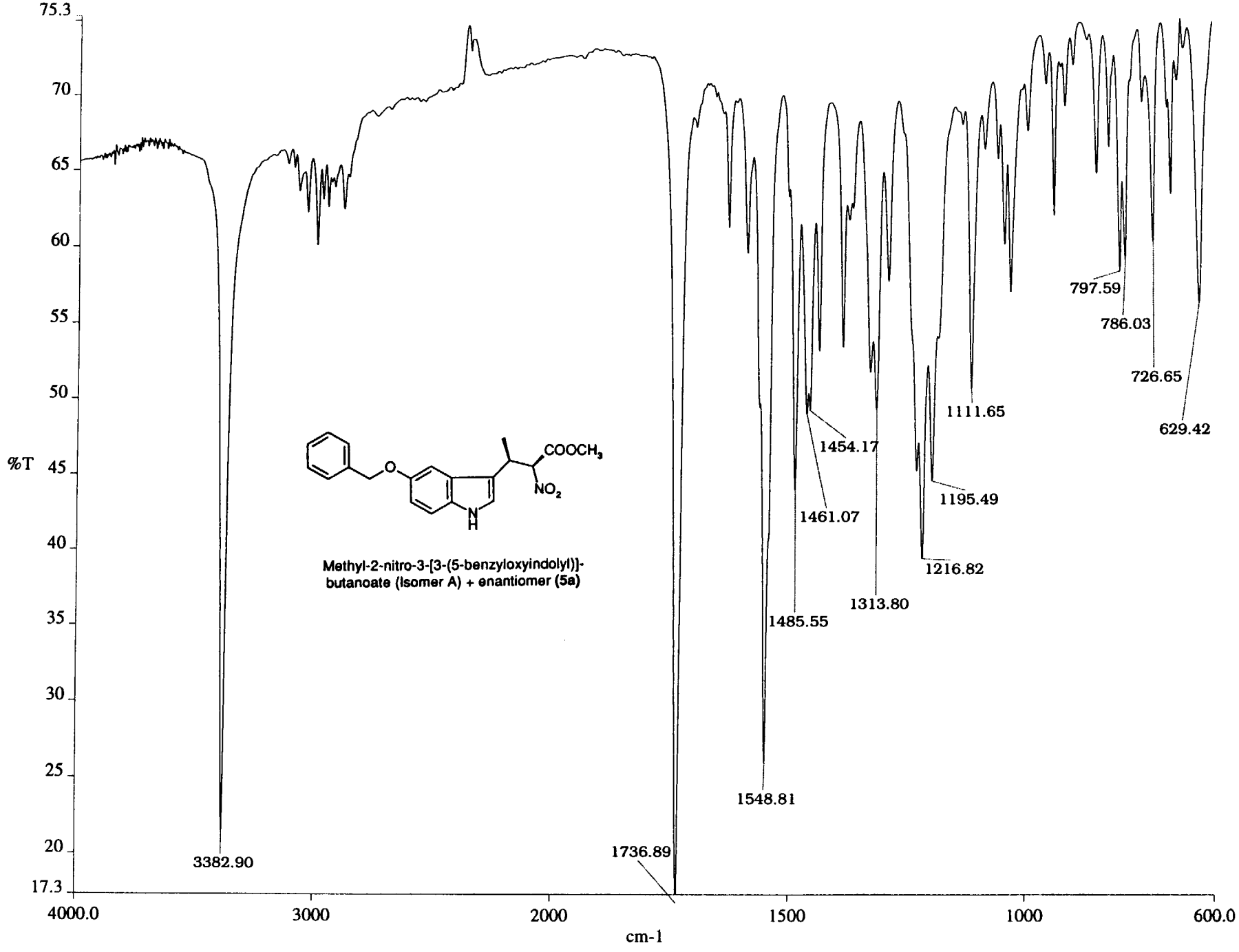


Methyl-2-nitro-3-[3-(5-benzyloxyindolyl)]-butanoate (Isomer A) + enantiomer **(5a)**

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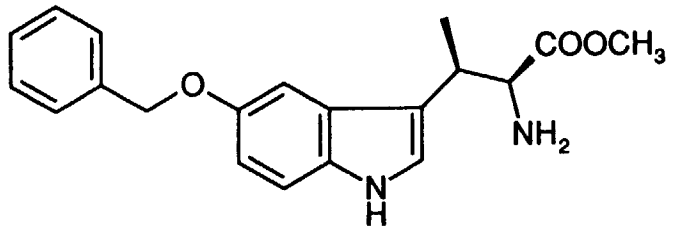
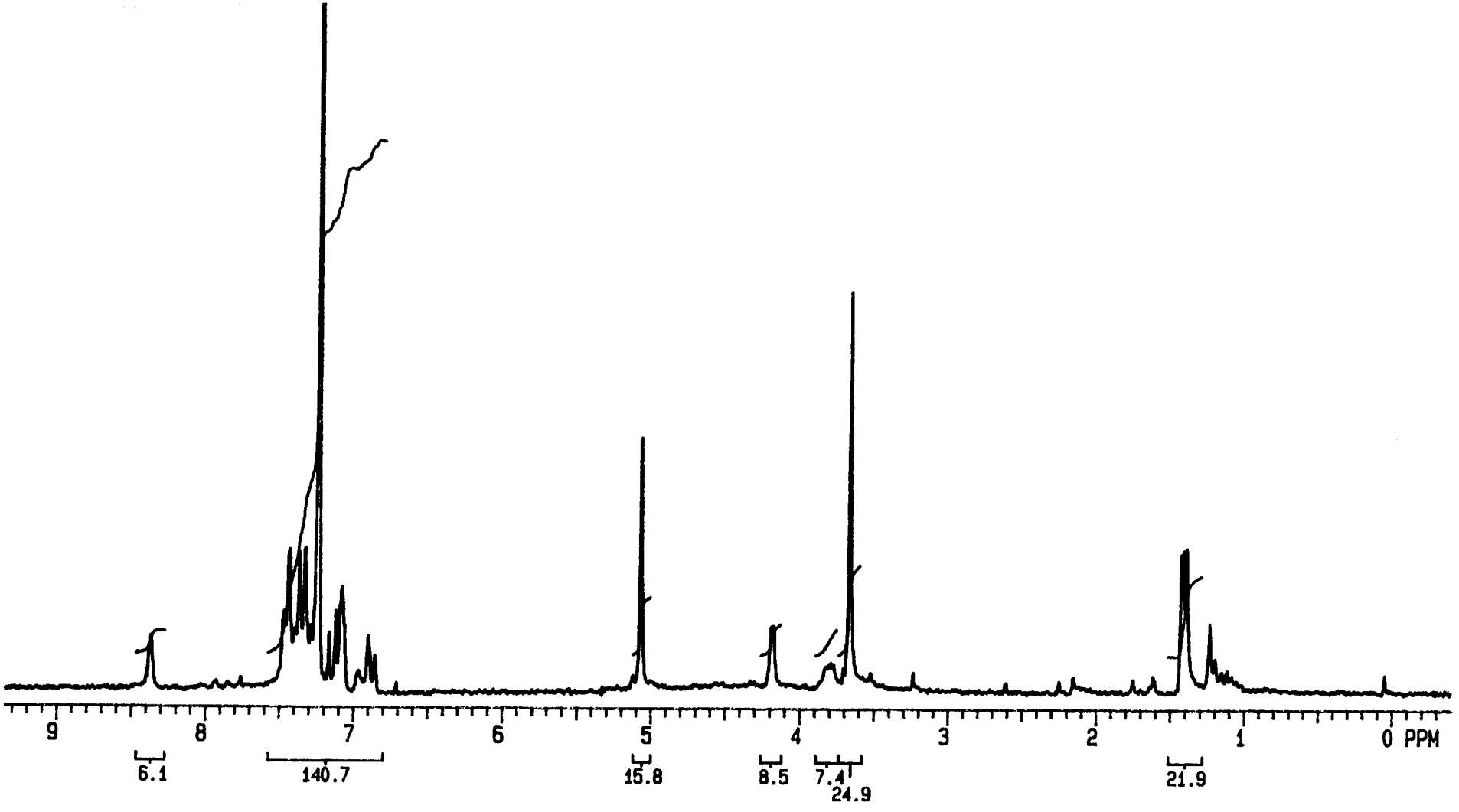
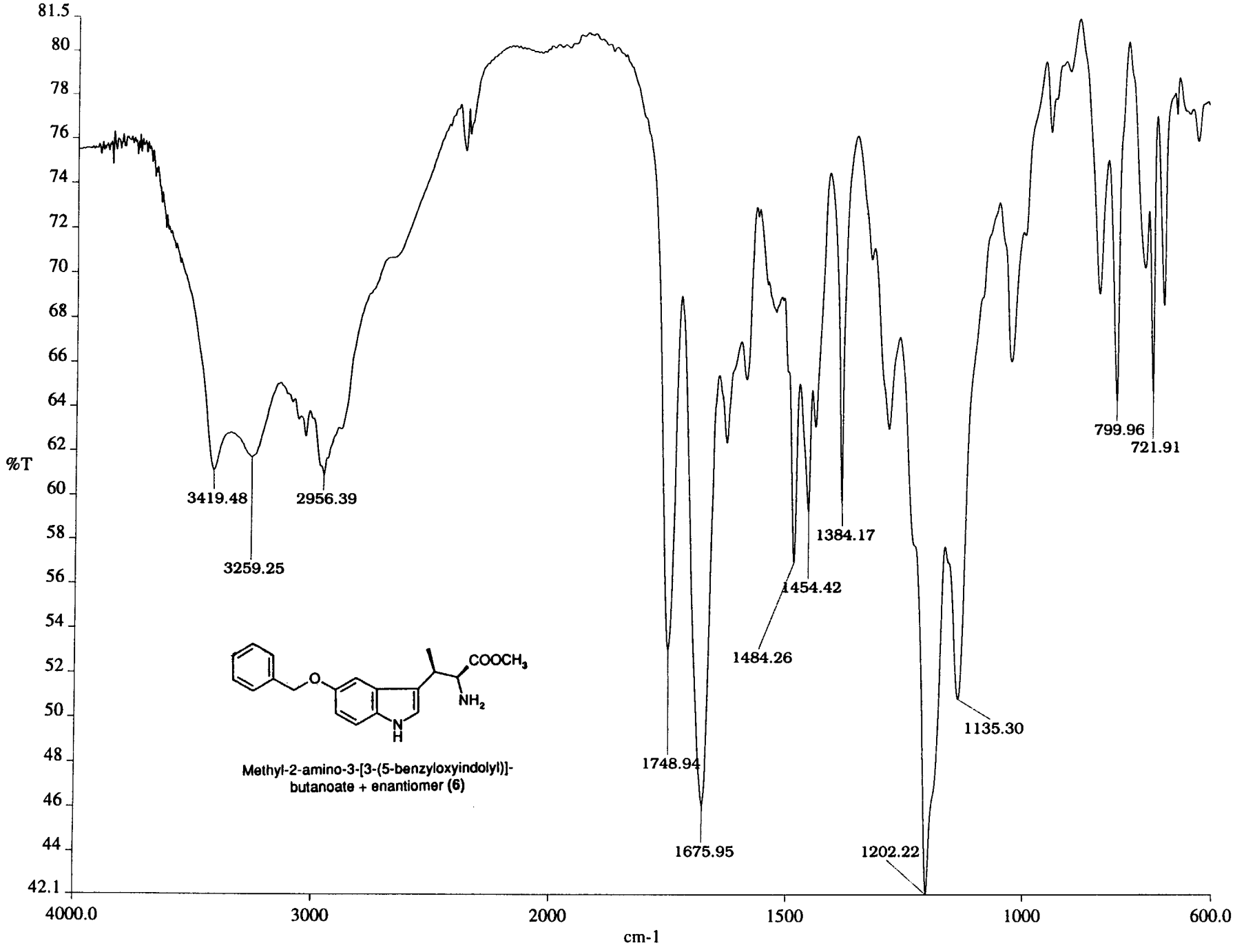
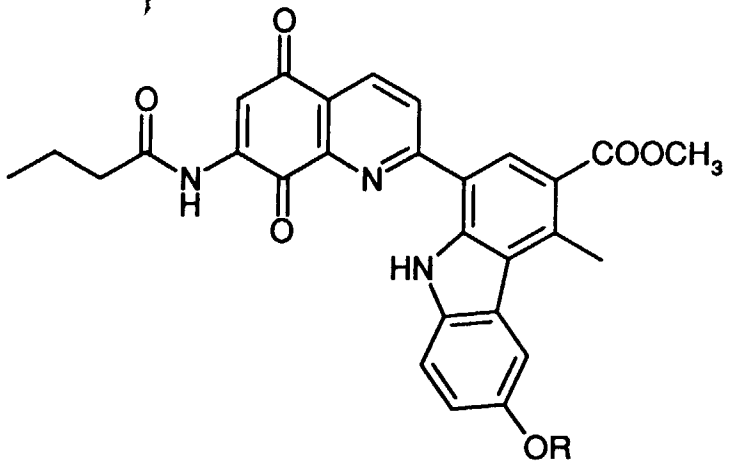
786.03
726.65
629.42
COOCH3
NO2
O
N
H
Methyl-2-nitro-3-[3-(5-benzyloxyindolyl)]-
butanoate (Isomer A) + enantiomer (5a)
c:\pel_data\morris\cspnitr2.sp



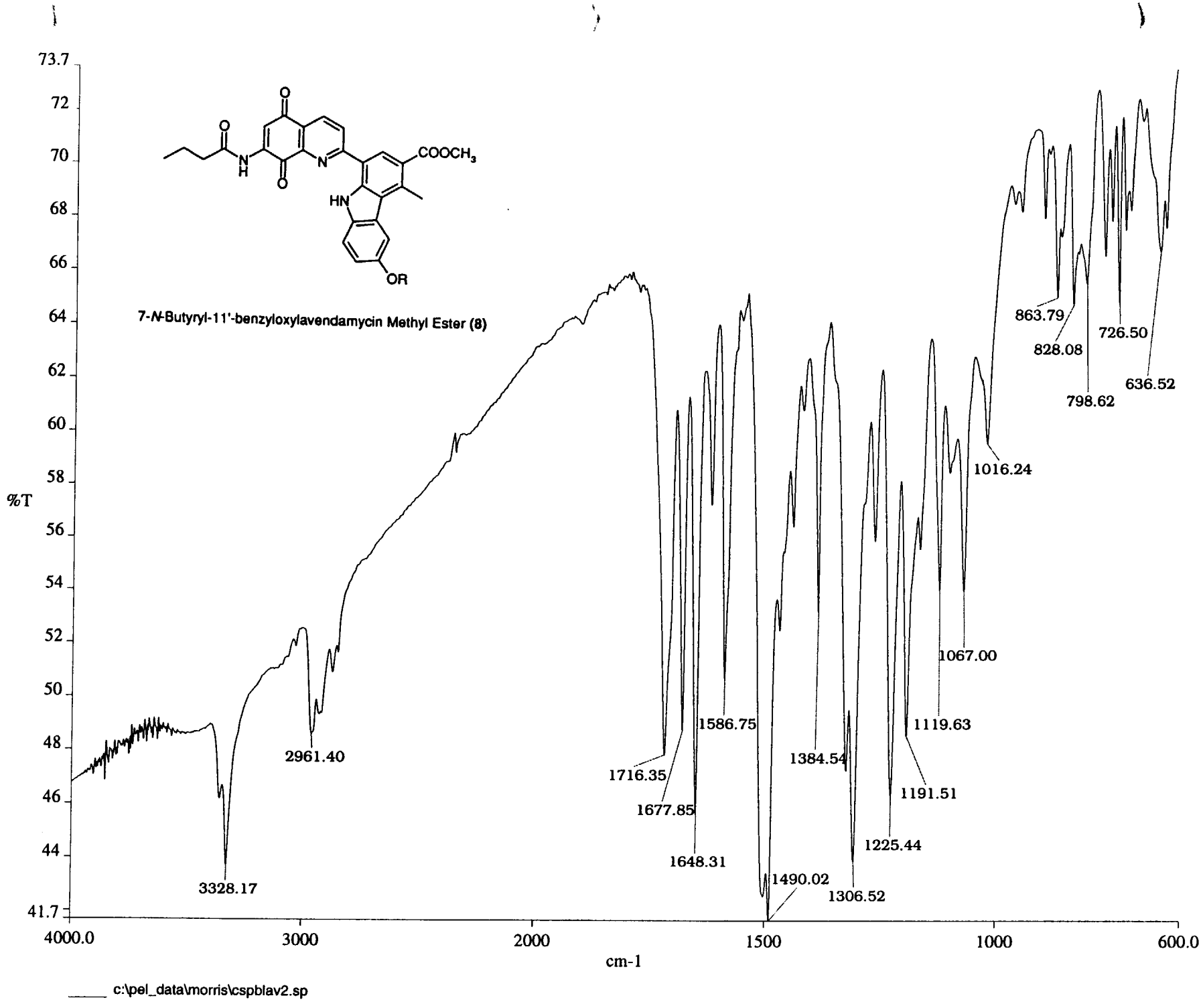
Methyl-2-amino-3-[3-(5-benzyloxyindolyl)]-
butanoate + enantiomer **(6)**




81.5
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42.1
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3419.48
3259.25
2956.39
1748.94
1675.95
1484.26
1454.42
1384.17
1202.22
1135.30
799.96
721.91
COOCH3
NH2
O
N
H
Methyl-2-amino-3-[3-(5-benzyloxyindolyl)]-
butanoate + enantiomer (6)
c:\pel_data\morris\csptrypt.sp



7-*N*-Butyryl-11'-benzyloxylavendamycin Methyl Ester **(8)**


7-N-Butyryl-11'-benzyloxylavendamycin Methyl Ester (8)
%T
cm-1
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2961.40
1716.35
1677.85
1648.31
1586.75
1490.02
1384.54
1306.52
1225.44
1191.51
1119.63
1067.00
1016.24
863.79
828.08
798.62
726.50
636.52
c:\pel_data\morris\cspblav2.sp

APPENDIX C: **Research Presentations**

The author of this thesis has presented his plans for and progress on this project on several occasions. One seminar was given to the Ball State Chemistry Department during the summer research program of 1997, and another seminar was given during the Indiana Academy of Science 113th Annual Meeting on October 31, 1997. A seminar was presented for the Discovery division of Eli Lilly & Company on January 15, 1998, and another was given the following day for the Chemical Process division. These presentations have served to help the author gain an understanding of his work in a very concise manner, as well as giving him valuable presentation skills.

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