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Pursuit of a Chiral Amino Aldehyde Intermediate in the Synthesis of (+)-Obafluorin, a B-Lactone Antibiotic

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Table of Contents

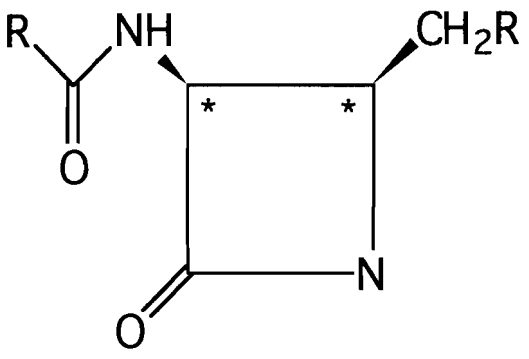
List of Spectral Data

Abstract

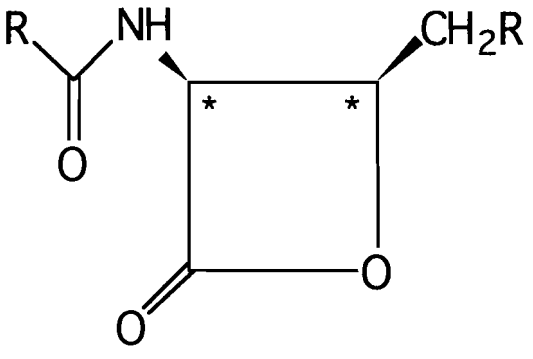
This research is focused on synthesizing a chiral amino aldehyde from L-Serine. The proposed synthesis of the amino aldehyde would yield a stereochemically pure product working through an L-Serine β-lactone intermediate. The amino aldehyde is a proposed intermediate in the synthesis of (+)-obafluorin, a β-lactone antibiotic of interest. The proposed synthesis might provide a simpler, more versatile way to synthesize obafluorin.

Background

In 1982, Wells *et al.*[1] were conducting experiments on a variety of organisms to test for the presence of novel molecules containing the β-lactam (1) moiety. Some naturally occuring antibiotics, including penicillin, were known to contain the β-lactam moiety and already many others had been isolated by searching for this structure. Most of the antibiotics had been discovered from fungi and actinomycetes. In this case, the researchers took a different route and applied a highly selective test to detect the presence of β-lactams in bacteria. To their suprise, their results showed that not only had they discovered some β-lactams produced by the bacteria, but also β-lactones (2). The two structures have the same relative stereochemistry (the chiral atoms are indicated by a *), and differ in only one atom of the four-membered ring.



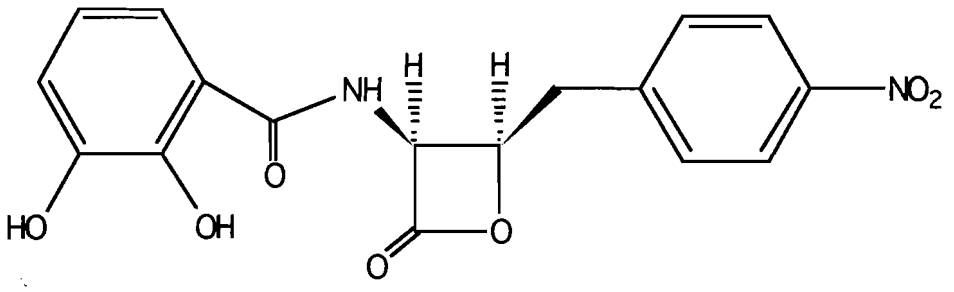
β-lactam(1)



β-lactone(2)

The sterochemistry of the β-lactams is extremely important to its role as an antibiotic. The β-lactams are inhibitors of D,D-carboxypeptidases, which catalyze a polymerization reaction in the formation of the cell wall in bacteria. If the inhibitor does not posess this stereochemistry, it will not fit into the active site of the enzyme and will not function.[2]

One of the β-lactone molecules discovered in 1982 was produced by the bacteria *Pseudomonas fluorescens* and was identified as (+)-obafluorin (3) by Wells *et al.*[3] in 1984. When tested by disk diffusion for its antibacterial activity, obafluorin was found to be about three times weaker than ampicillin, a β-lactam antibiotic. Also, it was the first β-lactone discovered that was susceptible to β-lactamases. Both these qualities created interest in the molecule because it was apparently functioning by the same mechanism as the β-lactam antibiotics since it has the same



(+)-Obafluorin(3)

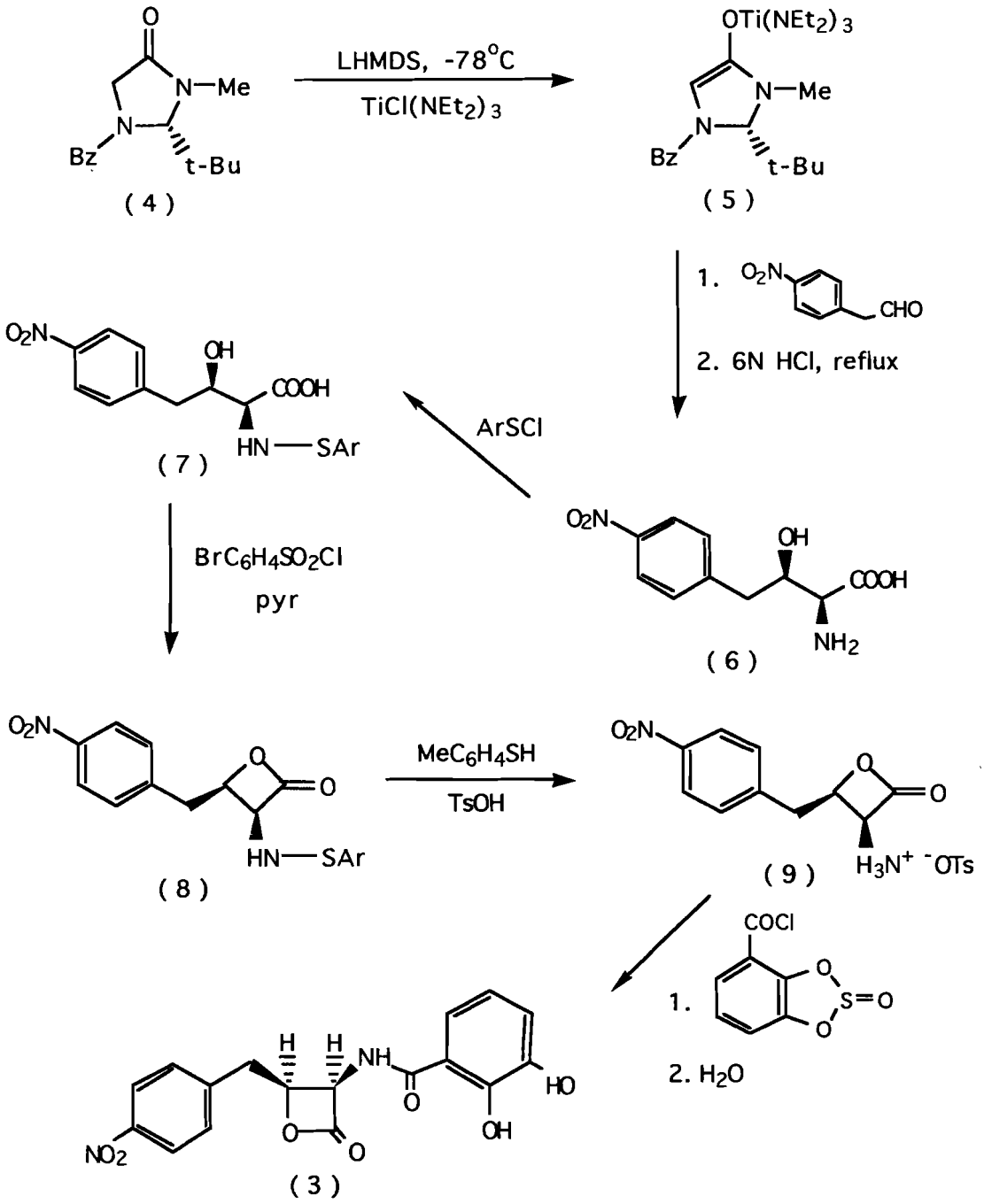
stereochemistry and was hydrolyzed by the same enzymes. This information spurred further research to discover its structure[4] and to synthesize it.

In addition to biosynthetic studies on obafluorin[5,6], the first laboratory synthesis was reported in 1992 by Lowe, Pu, *et al.*,[7] and again in 1994 by the same group.[8] The latter synthesis was an improvement upon the first, and is represented by Scheme I.

The synthesis started out with treatment of the imidazolidinone (4) with lithium hexamethyldisilylamide, followed by the addition of chloro [tris(diethylamino)] titanium to generate the titanium enolate (5). The addition of 4-nitrophenylacetaldehyde to the enolate produced two isomeric alcohols (not pictured). Acidic hydrolysis of the mixture, followed by ion exchange chromatography, produced pure *threo* β-hydroxy α-amino acid (6). The resulting amino acid was protected on the nitrogen with (2-nitrophenyl) sulfenyl chloride. The resulting protected amino acid (7) was converted to the N-protected β-lactone (8) by addition of (4-bromophenyl) sulfonyl chloride in pyridine. The (2-nitrophenyl) sulfenyl group is then removed with thiocresol, and then transformed using *p*-toluenesulfonic acid (TsOH) into the tosylate salt (9). An acid chloride was then added to produce optically pure (+)-obafluorin. The reported yields ranged from >60% to >80%, except for the lactonization at 24%. This route proved to be a flexible one yielding some analogs that displayed antibacterial activity.

The diversity of antibiotics is becoming a major issue today with the growing phenomenon of infectious diseases caused by organisms resistant to treatment. In an article appearing in the Chicago Tribune on January 17th[9], it was reported that 36 national and international medical journals that week had warned of overuse of antibiotics leading to resistant diseases. Joshua Lederberg, a Nobel laureate of Rockefeller University, warned that "the world's population had 'never been more vulnerable'

Scheme I



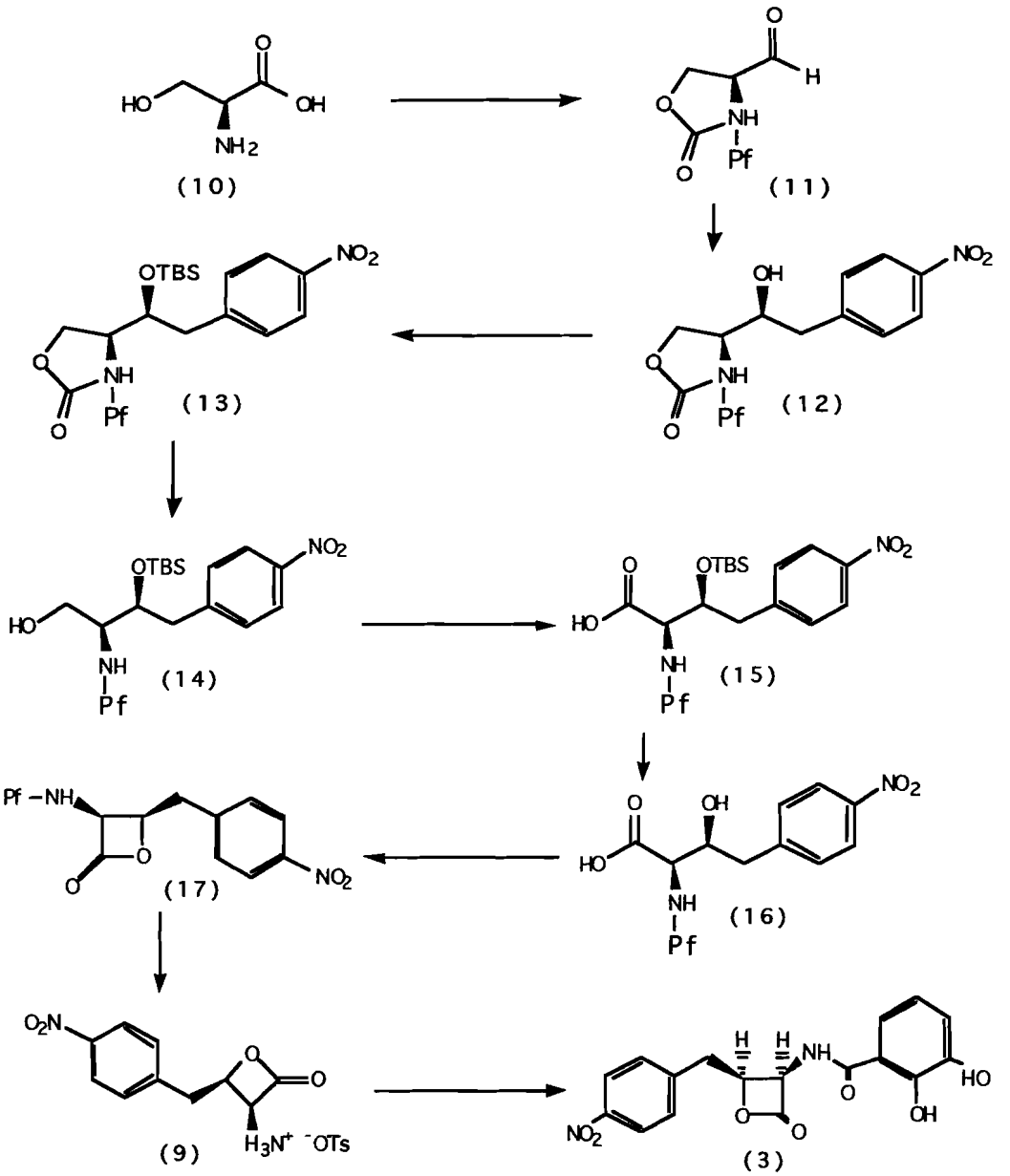
to the threat of emerging and re-emerging diseases."

As the number of resistant diseases grows, it is increasingly important that the diversity of antibiotics continues to grow also, so that medicine is given the necessary tools to fight today's changing diseases.

Introduction

The purpose of this research was to find an alternate synthesis for obafluorin. The objectives were twofold. First, a synthesis that is more versatile is desired which would open up the possibility for different analogs of obafluorin than the ones that have been previously synthesized by Pu *et al.*[8] Second, a synthesis that begins with a molecule readily available from the chiral pool would be less wasteful than the Pu synthesis since it starts with a chiral auxillary. Scheme II represents the proposed synthesis.

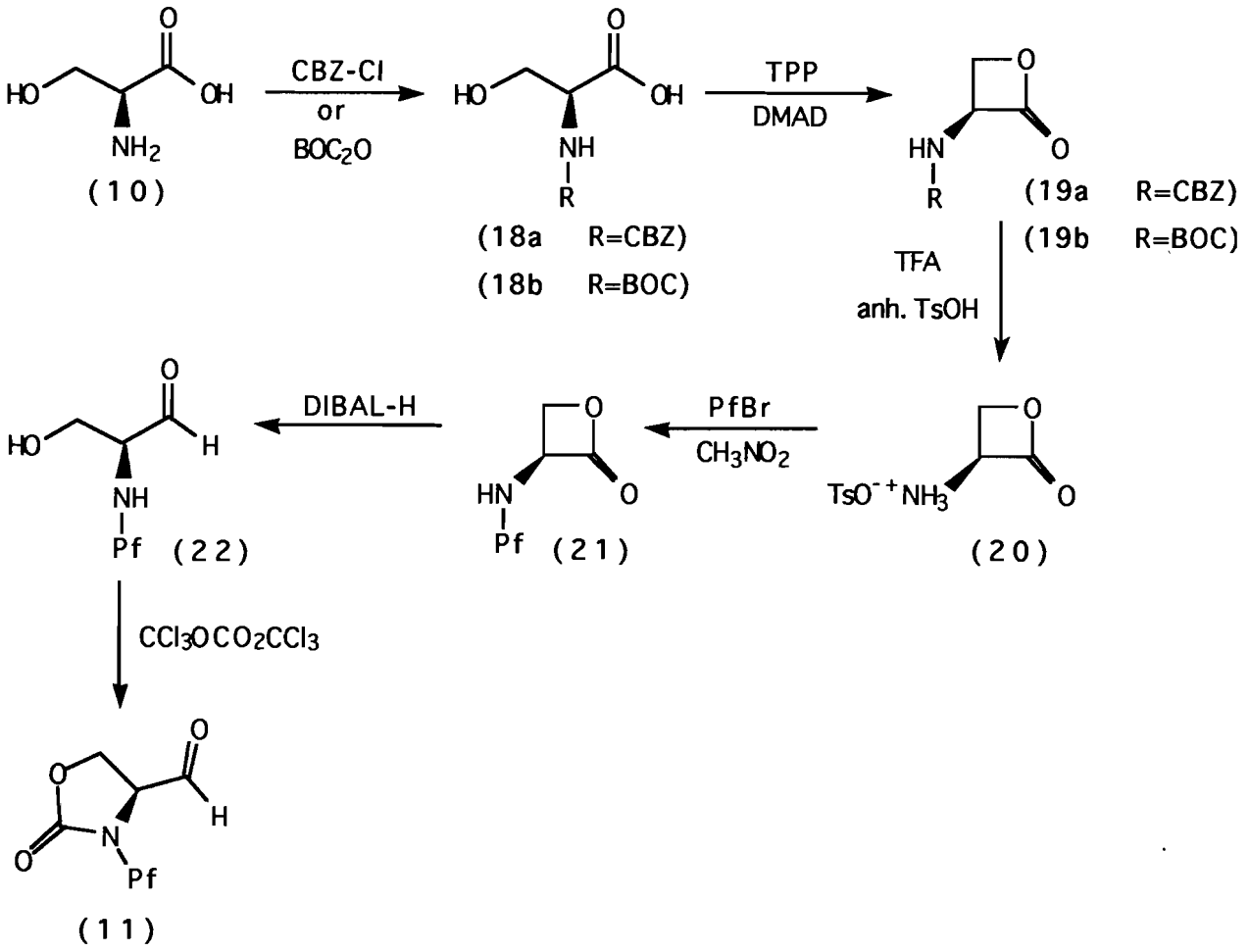
Scheme II



The proposed synthesis begins with an amino acid, L-Serine (10). Through a series of reactions that will be discussed in further detail, it is converted to an N-protected chiral amino aldehyde (11). The anion of *p*-nitrotoluene is then added to the aldehyde. The resulting compound (12) is then treated with *t*-butyl dimethylsilyl chloride in order to protect the hydroxyl group from the subsequent oxidation reaction. After reduction of the oxazolidinone the amino alcohol (14) is converted to the amino acid (15) by oxidation. The hydroxyl group is then deprotected and the β-lactone (17) is formed. At this point the schemes I and II are identical, converting to the β-lactone tosylate salt (9), and then to obafluorin (3).

The present focus of this research has been to convert L-Serine (10) to the amino aldehyde (11). The following scheme outlines the reactions proposed for this conversion.

Scheme III



L-Serine (10) is converted to the N-protected L-Serine (18b) by the addition of di-*t*-butyl dicarbonate. Lactonization takes places upon the addition of triphenylphosphine (TPP) and dimethylhydrazodicarboxylate (DMAD). The β-lactone tosylate salt (20) is formed by adding trifluoroacetic acid and anhydrous TsOH. To the tosylate salt 9-Bromo-9-phenylfluorene in nitromethane are added to hopefully produce the N-protected β-lactone (21). Reduction should occur upon addition of diisobutylaluminum hydride (DIBAL-H), and is followed by triphosgene to produce the stereochemically pure chiral amino aldehyde (11).

Experimental

General Information. All solvents used were reagent grade solvents and purchased from Fisher Scientific. All chemicals used in reactions were purchased from Aldrich Chemical Co, except for N-protected benzyloxycabonyl (CBZ)-L-serine β-lactone and 9-bromo-9-phenylfluorene which were obtained from previous researchers. A procedure for making the CBZ-lactone is outlined in Arnold *et al.*[10] A procedure for the synthesis of 9-bromo-9-phenylfluorene can be found in Lubell *et al.*[11] IR spectra were taken on an ATI Mattson Gensis Series Fourier Transform Infrared Spectrometer. NMR spectra were taken at Illinois State University on a Varian XL-300MHz Nuclear Magnetic Resonance Spectrometer. Reactions carried out under N_2 were done with a balloon/septum set-up. Methods for purification of solvents and reagents were found in Perrin *et al.*[12] TPP was recrystallized from ethanol and dried under vacuum for 72 hrs. in the presence of phosphorous pentoxide. Tetrahydrofuran (THF) was dried by adding 3 3/4 in. cubes of sodium and 5 grams of benzophenone to 800 mL of THF under N_2, and stirring with heat until a yellow to dark blue color change was observed. The THF was distilled from this mixture when needed. The monohydrate TsOH was dried by azeotropically distilling it from benzene, dissolved with the aid of ethyl acetate. Once the water was removed, the volume was distilled down to 10-15 mL and the acid was precipitated by the addition of excess benzene along with cooling. The crystals were filtered, dried under vacuum, and stored in a dessicator, limiting exposure to air as much as possible. A m.p. of anywhere between 94-98 ^{o}C was suitable for reaction. Diethyl ether was dried using sodium/benzophenone. Trifluoroacetic acid (TFA) , nitromethane and triethylamine were distilled.

Synthesis of N-Protected BOC-serine (18b). A solution of di-*t*-butyl dicarbonate (13.10 g, 0.120 mol) in dioxane (200 mL) was added to an ice-cold, magnetically stirred solution of L-serine (10.50 g, 0.100 mol) in 1 N NaOH (100 mL) and was allowed to stir at 0 ^{o}C for 1/2 hr. The reaction was then stirred at room temperature for 4 hrs, and monitored by TLC. After the reaction had gone to completion, the mixture was rotovaped at 40 ^{o}C to 1/2 its volume. The mixture was then cooled in an ice bath and acidified to pH 2-3 by adding 200 mL of 1N $KHSO_4$. This mixture was extracted with ethyl acetate (3 X 125 mL), and the organic layers were

pooled and dried over anhydrous Na_2SO_4. The ethyl acetate was filtered and rotovaped down to a yellow oil. The product was crystallized from ethyl acetate/hexane, and dried under vacuum. A 21% yield was obtained. R_f=0.80, 8:1:1 butanol/acetic acid/H_2O, nihydrin stain. m.p. 90-91 °C (dec) [std. m.p. 91 °C (dec)[13]; IR (KBr) 3420, 2981,1755, 1665, 1526, 1158 cm^{-1} (Appendix A-1); ^1H NMR (CD_3OD) δ 4.96 (s,1H), 4.19 (s,1H), 3.84 (dd, 2H) ppm (Appendix A-2, A-3).

Synthesis of N-Protected BOC-L-Serine β-lactone (19b). To a magnetically stirred solution of anhydrous TPP in dry THF (44 mL) at -78 °C was added DMAD (1.45 mL, 13.1 mmol) dropwise over 10 min. A solution of BOC-L-serine (2.50 g, 13.1 mmol) in dry THF (44 mL) was then added to the mixture dropwise over 15 min. The mixture was stirred for 20 min. at -78 °C, and then for 3 hrs. at room temperature. The reaction was monitored by TLC. The product was easily identified by TLC because it turned a bright yellow against a green background upon staining and heating. The reaction was rotovaped down to an oil and purified by column chromatography (90 g silica gel/6 hexane:4 ethyl acetate). Fractions containing the product were rotovaped to produce a yellow oil, which was crystallized from ethyl acetate/hexane. A 67% yield was obtained. R_f=0.50, 6:4 hexane/ethyl acetate, bromcresol green stain. m.p. 119.5-120.5 °C (dec) [119.5-120.5°C lit.value[14]; IR (KBr) 3358, 1844, 1680, 1532 cm^{-1} (Appendix A-4) [3358, 1836, 1678, 1533 cm^{-1}]][14].

Synthesis of L-Serine β-Lactone Tosylate Salt (20) *from BOC-Serine β-Lactone* (19b). BOC-serine β-lactone (605 mg, 3.23 mmol) and anhydrous TsOH were treated with distilled TFA at 0 °C for 15 min. The reaction was then rotovaped to remove the solvent, leaving a cream-colored solid. The solid was washed with dry diethyl ether, leaving a white solid, which was dried under vacuum. A 97% yield was obtained. Rf=0.0, ethyl acetate, bromocresol green stain. m.p. 131-132.5 °C (darken),155-160 °C (dec) [133-135 °C (darken),173 °C (rapid dec)[14,15]; IR (KBr) 3040, 1835, 1601, 1527 cm^{-1} (Appendix A-5) [IR (fluorolube mull) 3040, 1833, 1547 cm^{-1}]][14,15].

Attempted Synthesis of L-Serine β-Lactone Tosylate Salt (20) *from CBZ-Serine β-Lactone* (19a). CBZ-L-Serine β-lactone (0.100 g, 0.452 mmol), anhydrous TsOH (0.100 g, 0.526 mmol), palladium on charcoal (catalytic), and anhydrous methanol (10 mL) were added together and stirred magnetically. The mixture was stirred for 5 hrs. and monitored by TLC. The mixture was then filtered with celite, and the filtrate was rotovaped to produce white crystalline solid.

Attempted Synthesis of N-Protected 9-Phenylfluorenyl-L-Serine β-Lactone (21). BOC-L-serine tosylate salt (0.290 g, 1.10 mmol) and 9-bromo-9-phenylfluorene (0.420 g, 1.30 mmol) were dissolved in distilled nitromethane (4 mL) and treated with triethylamine (.44 mL, 3.10 mmol). The mixture was allowed to stir for 72 hrs. and turned light brown. The solvent was rotovaped down to produce a yellow oil. Ethyl acetate was added to precipitate a solid by product, the mixture was filtered, and the filtrate was rotovaped to produce a yellow oil. The oil was purified by column chromotography (30 g silica gel, 4:1 hexane/ethyl acetate). Fractions containing the suspected product were collected and rotovaped to produce a yellow oil, which was dried under vacuum.

Results and Discussion

Synthesis of BOC-L-Serine (18b). BOC-L-Serine (18b) was synthesized since it was rather expensive to purchase from Aldrich. One of difficulties run into was that there was no reference IR spectrum for this compound. Thus an IR spectrum of BOC-L-Serine from Aldrich was taken, and was used to compare with the spectrum of the synthesized product (Appendix A-1). One important feature of the spectrum is the carbonyl peak at 1755 cm^{-1}. The carbonyl of the lactone (Appendix A-4) appears around 1830-1845 cm^{-1}. A possible reason for the observed shift in carbonyl peaks can be accounted for by the existence of the keto and enol forms of serine. In the enol form, serine has a hydroxyl group where the carbonyl group existed. Thus, the resonance between these two forms would diminish the strength of the carbonyl bond in serine since in one of the forms it is only a single bond rather than a double bond. The serine carbonyl would be expected then to shift to a lower frequency since it is weaker than the carbonyl of the β-lactone. For this to be hold as a valid explanation, the resonance forms would have to be more prevalent in serine than for the β-lactone, which might or might not be true.

Another possible explanation is that carboxylic acids in the solid state (KBr pellet) can dimerize via hydrogen bonding. The dimerization weakens the carbonyl bond, and shifts the peak to a lower frequency.[16] This shift in frequency was very valuable information because it identified whether the lactone ring existed or was broken open in the reactions where it was supposed to stay closed.

Other characteristic features are the N-H peak and the O-H peak around 3420 cm^{-1}. The same procedure of making a standard spectrum and comparing it to the spectrum of the synthesized product was repeated for the NMR spectra (Appendix A-2, A-3).

Synthesis of BOC-L-Serine β-Lactone (19b). For the synthesis of BOC-L-Serine β-lactone (19b), the procedure from the Pansare *et al.*[14] was followed. One important tool that was helpful in identifying whether or not the lactone ring was still intact was the bright yellow spot it produced on a TLC plate after staining with bromocresol green and heating. The spot was distinctive because it did not turn yellow

immediately, it changed color just before the plate was finished developing, which set it apart from anything else that was encountered. The IR spectrum (Appendix A-4) shows the characteristic carbonyl peak at 1844 cm^{-1}, also indicating the presence of the lactone ring.

Synthesis of Anhydrous TsOH. Problems arose when attempting to dry the TsOH monohydrate to form the anhydrous acid. Several sources reported melting points for the anhydrous acid at 38 °C, 94-95 °C, 104-105 °C; the melting point of the monohydrate was 104-105 °C. The sources reporting the latter two melting points also synthesized the tosylate salt (20). Thus, it was not certain that it was even necessary to prepare the anhydrous acid since it appeared that one of the references successfully synthesized the tosylate salt (20) using the monohydrate, since their listed melting point for the anhydrous was the same as the monohydrate.[10]

The preparation of the anhydrous acid was attempted by two methods: 1) azeotropic distillation of the acid with benzene, and 2) heating the acid at 50 °C under vacuum for 4 hours. In both cases the monohydrate acid was obtained rather than the anhydrous acid. Dehydration did in fact occur during the distillaton because the water could be seen coming off in the arm opposite the sample flask, water being immiscible with benzene. However, the anyhydrous acid is extremely hygroscopic, and probably picked up water over the crystallization or the filtering processes. Preparation of the the anhydrous acid was attempted twice by this method and both attempts were unsuccessful. The monohydrate crystals melted and formed a block of solid when heating under vacuum, and became difficult to handle without exposing to the air for 2-3 minutes at a time. The melting point was taken and found to be 104-105 °C, so this method of dehydration was no more successful. Eventually, some crystals were used from the azeotropic distillation for the attempted synthesis of the tosylate salt (20) from CBZ β-lactone (19a), which were the monohydrate acid.

For the synthesis of the tosylate salt (20) from BOC β-lactone (19b), anhydrous TsOH was prepared successfully. The azeotropic distillation method was used, precipitating the anhydrous acid after distillation by the addition of excess benzene and cooling. In the first

attempt at preparation of the anhydrous acid, the distillate was rotovaped down and the product was recrystallized. In this attempt, no recrystallization was necessary since the acid was crystallied from the distillate. The extra handling and exposure to the air during the first attempt at making the anhydrous acid could have caused the anhydrous to pick up water again. The anhydrous acid was filtered and stored the crystals in a dessicator. A melting point of 94-95 °C was obtained.

Attempted Synthesis of the Tosylate Salt (20) *from CBZ-L-Serine β-Lactone* (19a). The synthesis of the CBZ β-lactone (19a) was completed successfully by a previous researcher. However, problems arose trying to make the tosylate salt (20) from CBZ-protected β-lactone. The IR spectrum from this reaction (Appendix A-8) shows a very prominent carboxyl peak at 3450 cm^{-1}. This peak indicates that the lactone ring was hydrolyzed and broken open. Also, the shift in the carbonyl peak to the around 1740 cm^{-1} was observed, supporting that conclusion.

One possible cause for the broken ring was the quality of the reagents used. The presence of H_2O from the monohydrate acid could have hydrolyzed the lactone ring. Also, it is possible that the methanol used was not properly dried. The methanol was dryed by stirring overnight in $CaCl_2$. Although, we did take an IR spectrum of the lactone after stirring in methanol for 24 hours (Appendix A-9), and found that it was stable in the methanol used. Thus the methanol was probably not the source of the problem.

Synthesis of Tosylate Salt (20) *from BOC-L-Serine β-Lactone* (19b). The prominent feature on IR spectrum of the tosylate salt (20) (Appendix A-5) is the carboxyl group peak at 3038 cm^{-1}. This peak is a result of the TsOH, not the breaking open of the lactone. The carbonyl peak at 1834 cm^{-1} indicates that the lactone ring was still intact. Again, the successful synthesis of our compound was confirmed by comparing our data with the data of the reference.[10]

Attempted Synthesis of 9-Phenyfluorene-L-Serine β-Lactone (21). The final part of the project was the attempted synthesis of N-protected 9-

phenylfluorene-L-serine β-lactone (21), which was probably not completed successfully. Upon inspection of the IR spectrum (Appendix A-10), it appeared that the lactone ring had broken open. The carbonyl peak was no longer around 1830 cm^{-1}, but at 1746 cm^{-1}, an indication that the lactone ring was no longer intact. It didn't make sense, though, that there was an alcohol peak rather than a carboxylic acid peak because an acid would have been formed had the ring been broken by water. It is uncertain at this point what product was formed.

Future Work

The continuation of this project would attempt to synthesize the N-protected 9-phenylfluorene-L-serine β-lactone(21). It is uncertain what this reaction has produced thus far, with the results showing at this point that the lactone ring was broken open but an acid was not made. Once this reaction has been completed, the synthesis of the aldehyde(22) seems promising after working with DIBAL-H in a model rxn, which successfully produced an aldehyde.

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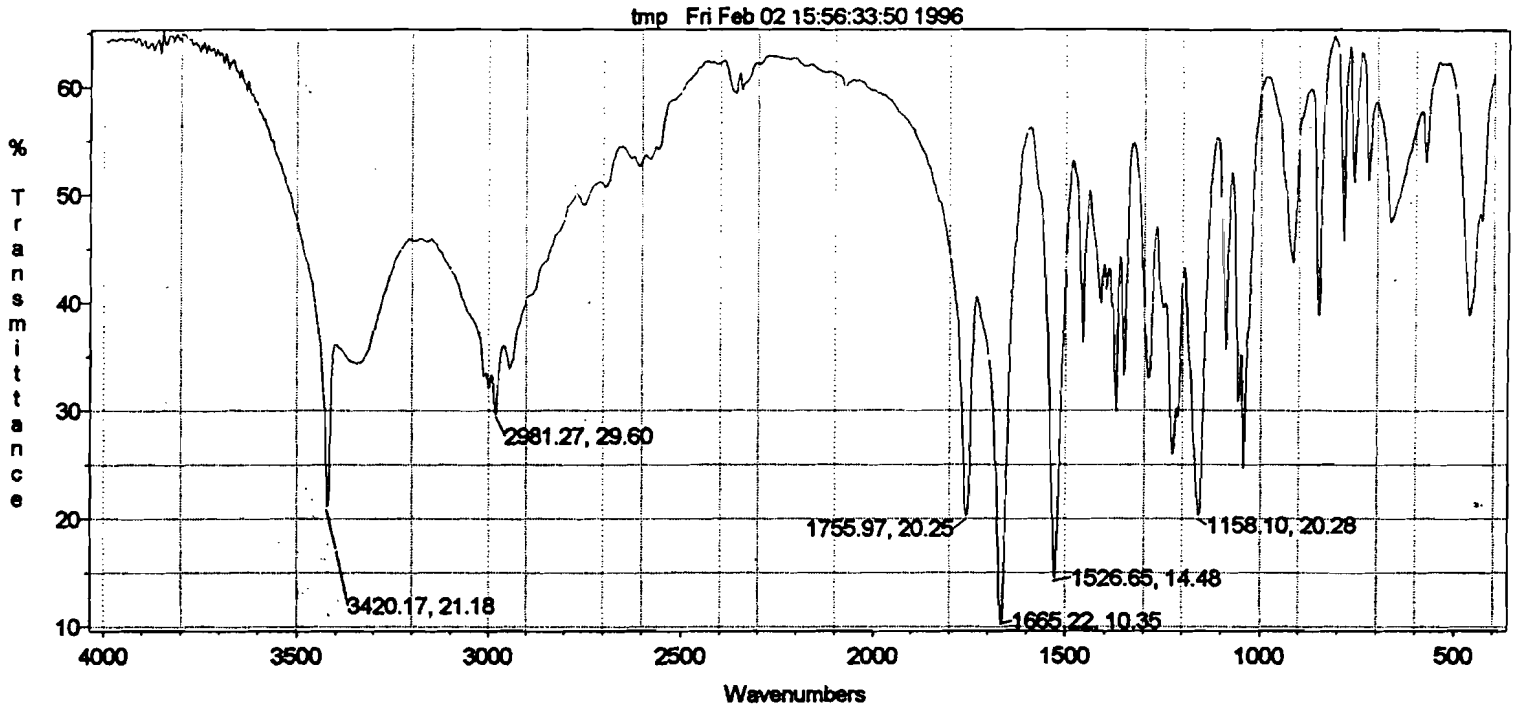

N-Protected BOC-L Serine (18b)

STANDARD 1H OBSERVE

Solvent: CD3OD
Ambient temperature
GEMINI-300BB "DOWN"

PULSE SEQUENCE
Pulse 88.0 degrees
Acq. time 1.003 sec
Wioth 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0685395 MHz
DATA PROCESSING
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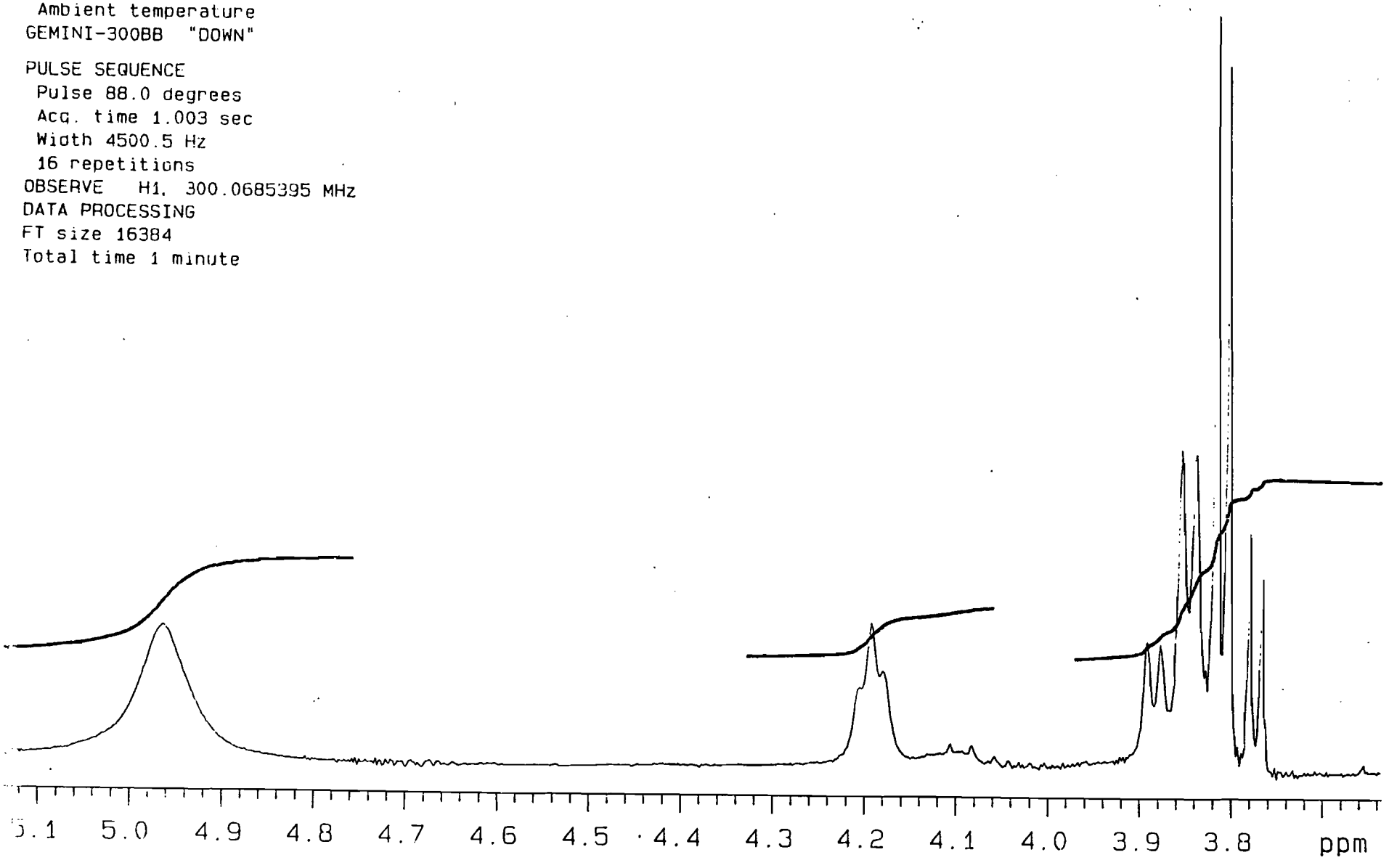
Total time 1 minute



A-2

N-Protected-BOC-L-Serine (18b)

STANDARD 1H OBSERVE

Solvent: CD3OD
Ambient temperature
GEMINI-300BB "DOWN"

PULSE SEQUENCE
Pulse 88.0 degrees
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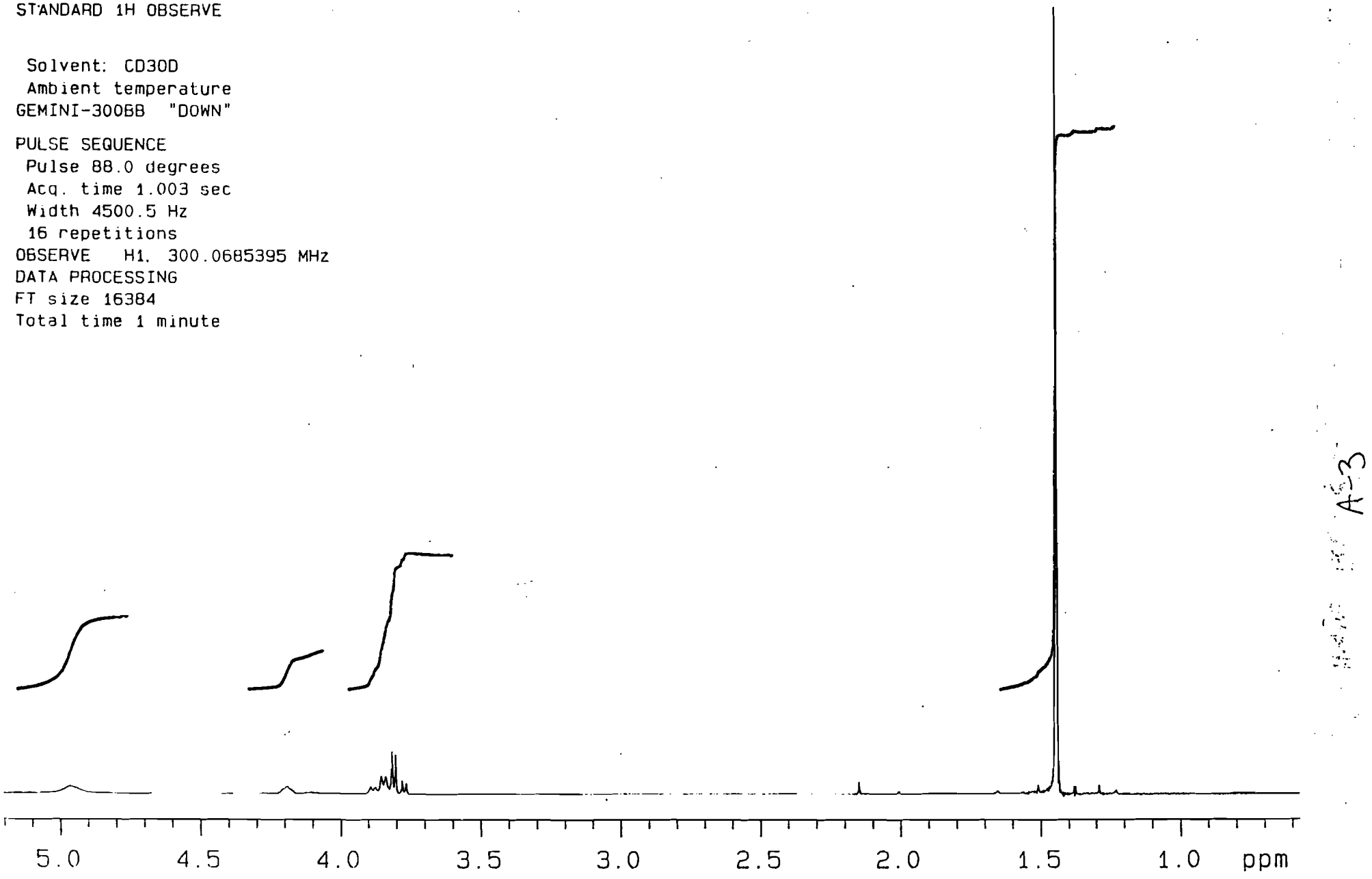
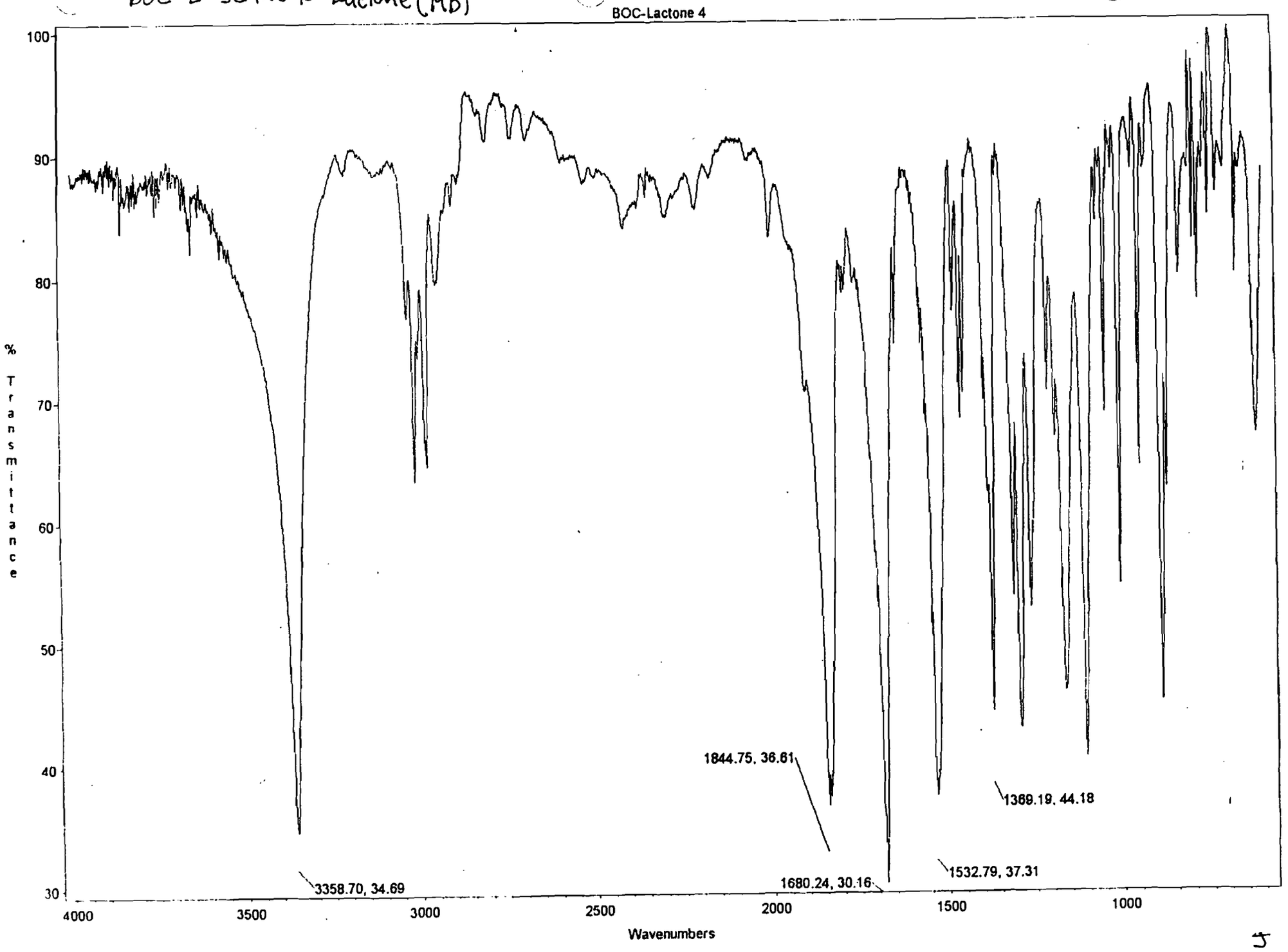
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0685395 MHz
DATA PROCESSING
FT size 16384
Total time 1 minute



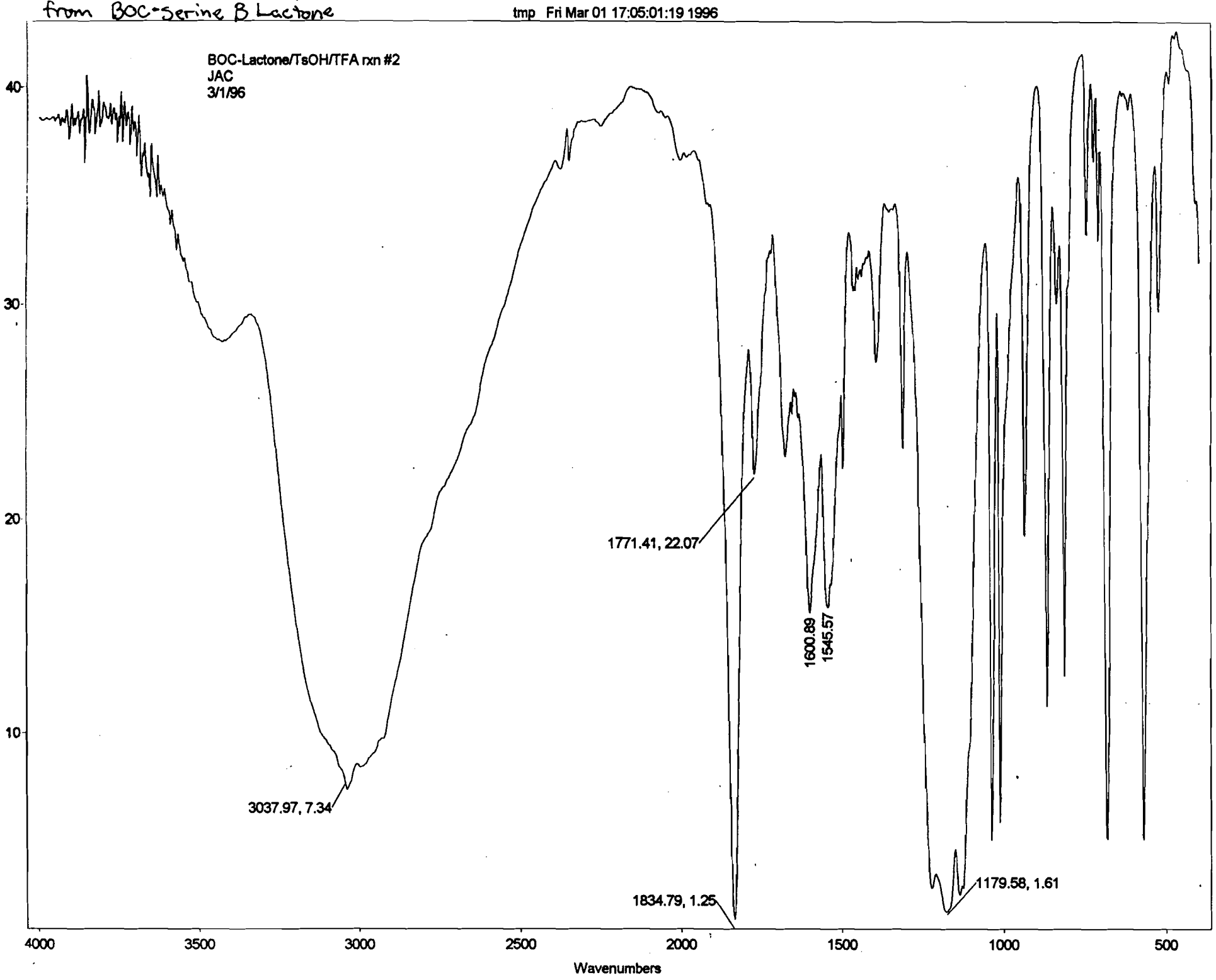
A-3

BOC-L-Serine (18b)

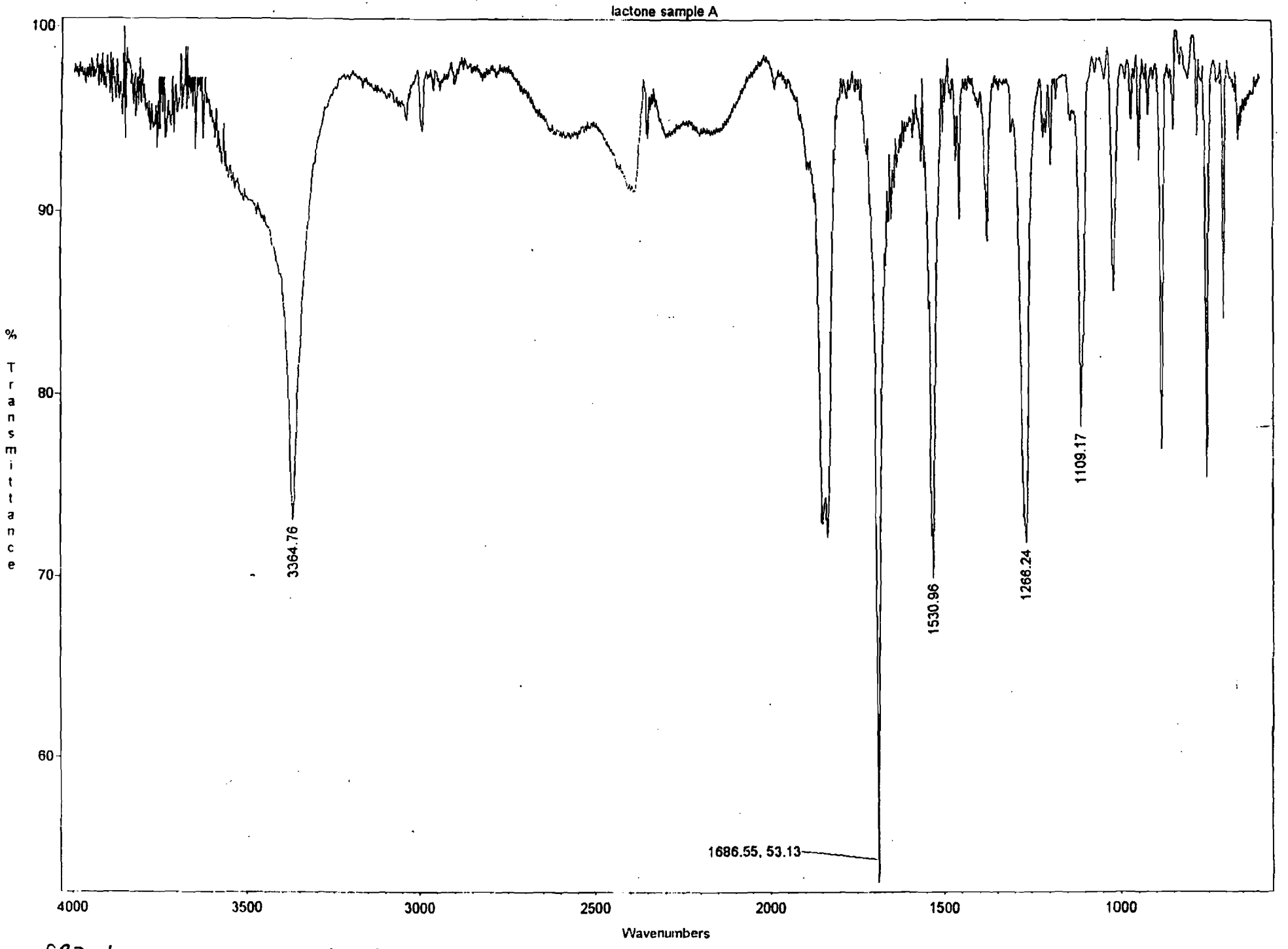
BOC L-Serine N Lactone (14b)



from BOC-Serine β Lactone

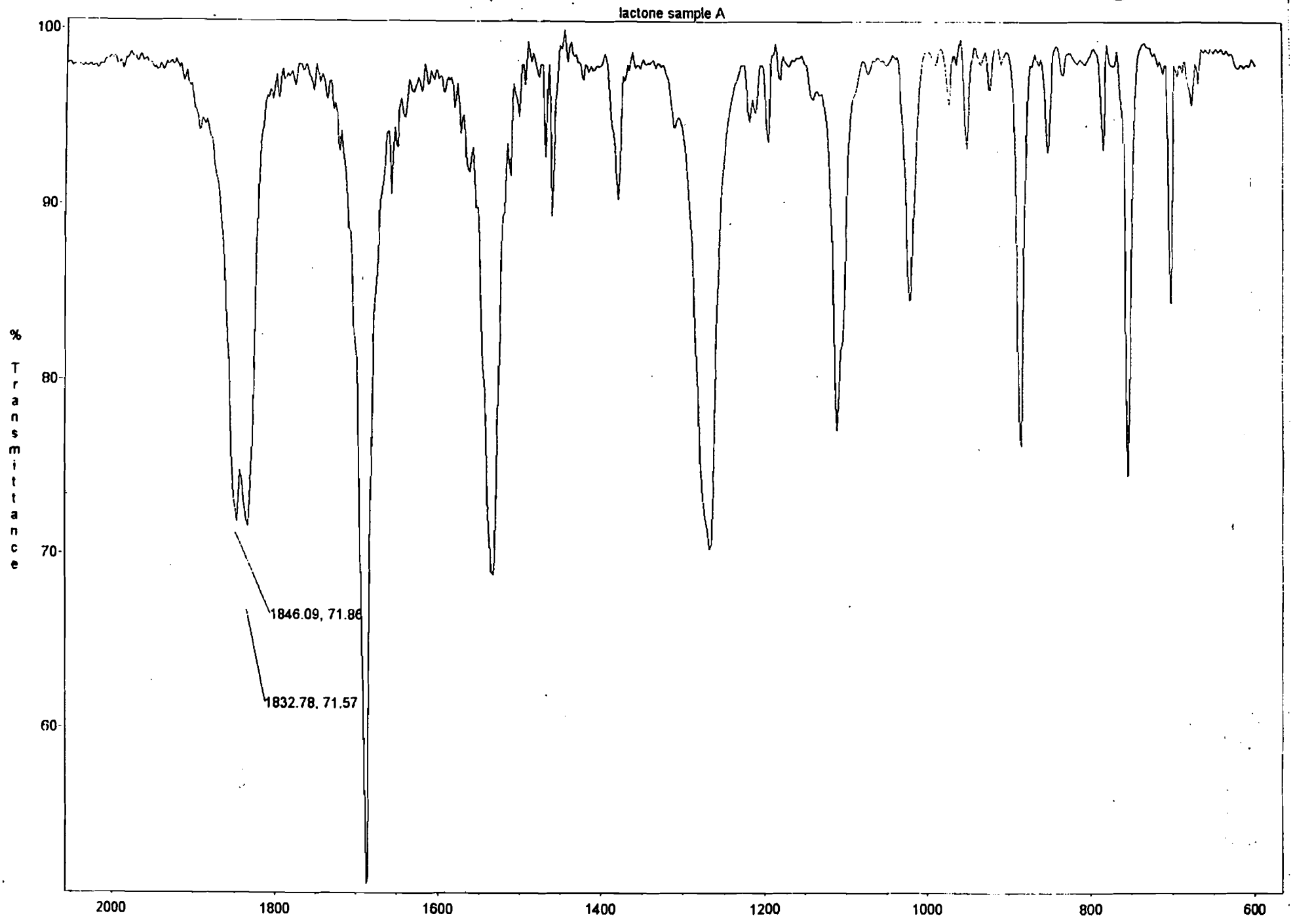


A-5



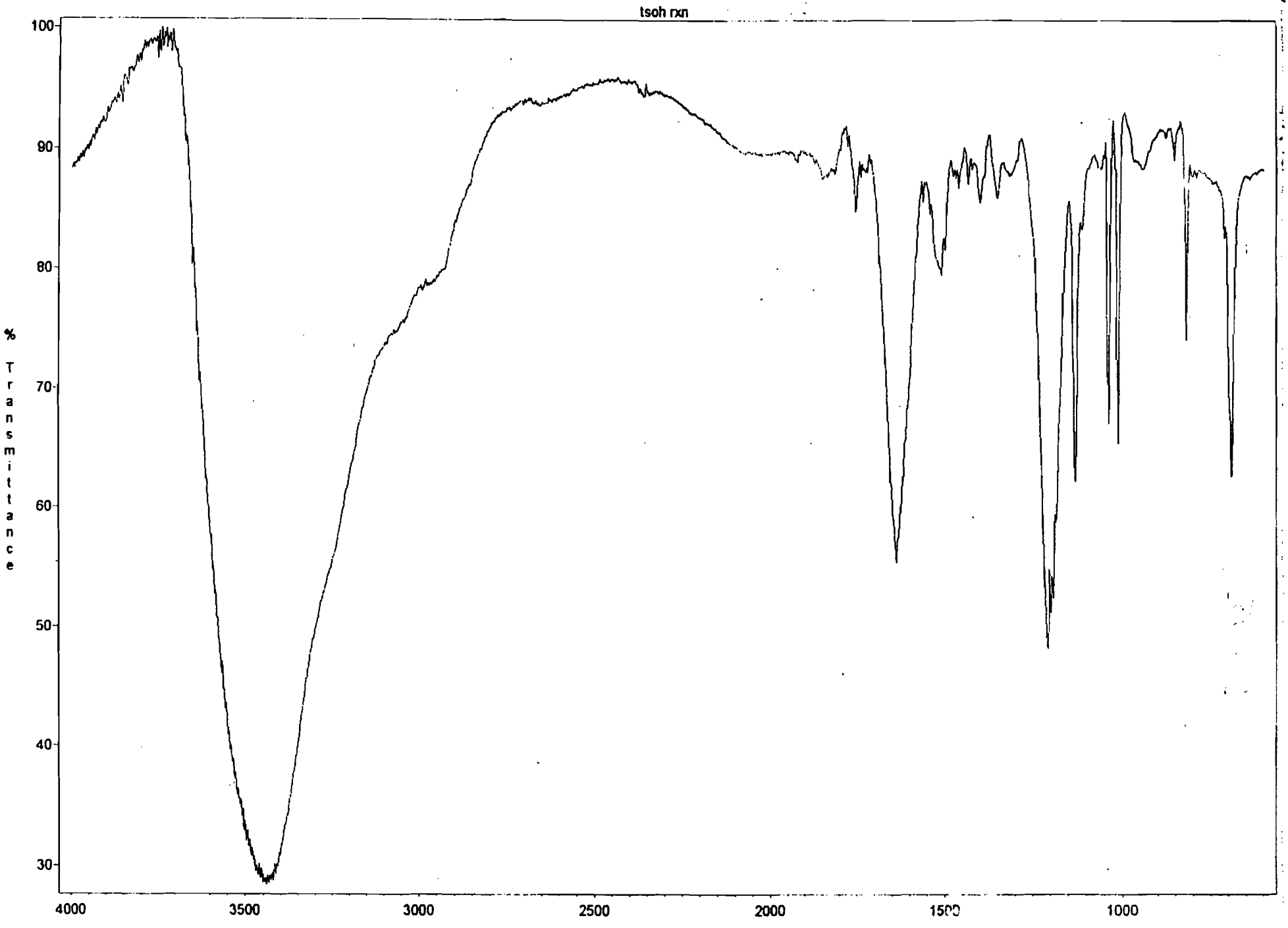
CBZ-L-Serine β-Lactone (19a)

A-9



CBZ-L-Serine β-Lactone (19a)

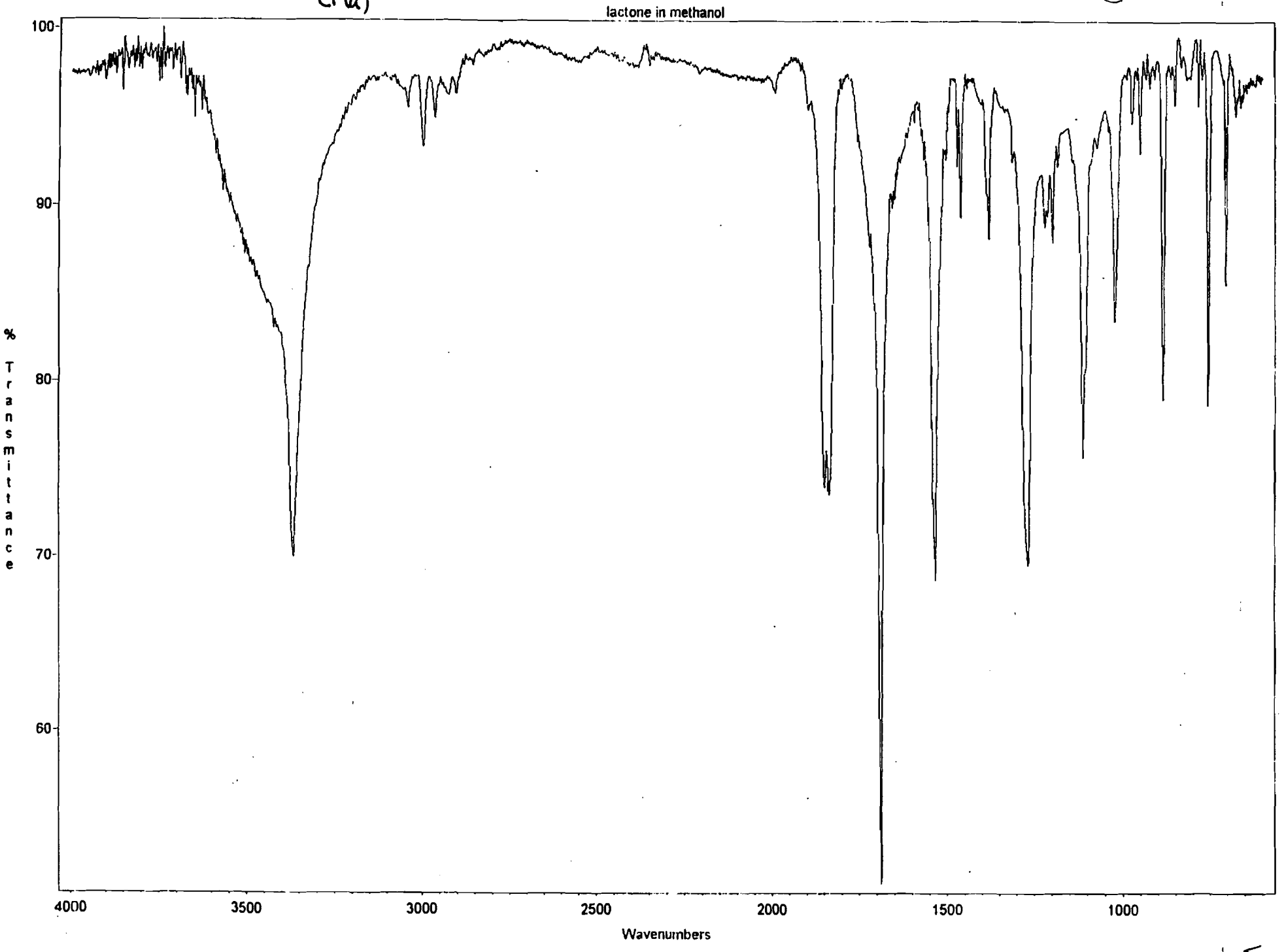
A-7



L-Serine β-Lactone Tosylate Salt
from CBZ-Serine β-Lactone (Attempted Synthesis)

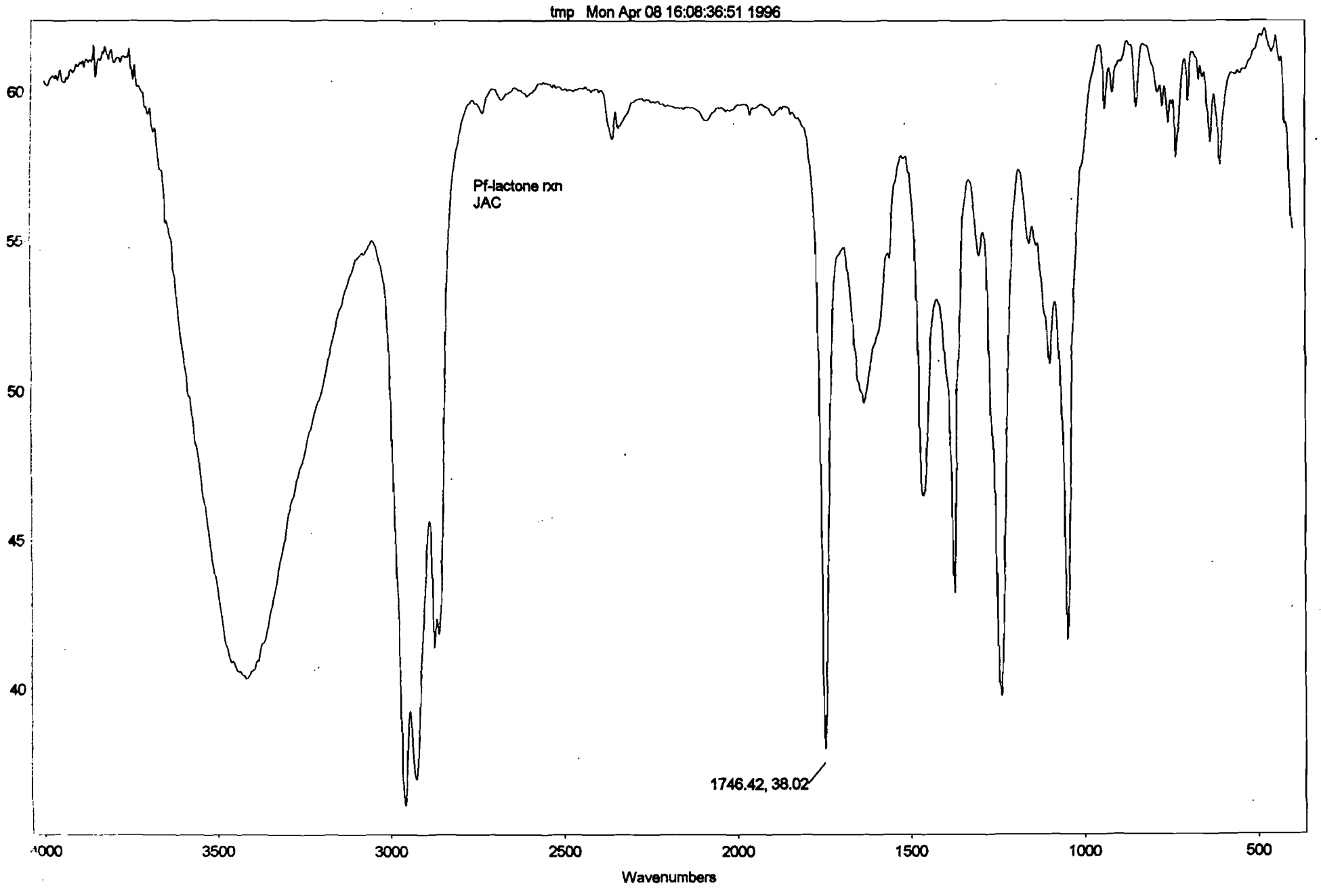
∞
1
A

(19a)


lactone in methanol
100
90
80
70
60
% Transmittance
4000
3500
3000
2500
2000
1500
1000
Wavenumbers

A-9

N-Protected 9-Phenylfluorene-L-Serine
β-Lactone (21) (Attempted Synthesis)



A-10

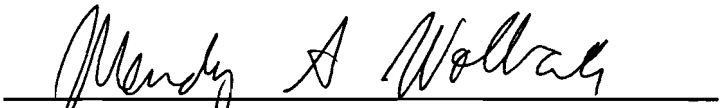
Approval Page
"Pursuit of a Chiral Amino Aldehyde Intermediate in the Synthesis of (+)-Obafluorin, a β-Lactone Antibiotic"
by Jim Cwik

A paper submitted in partial fulfillment of the requirements for Chemistry 499 and research honors in chemistry.

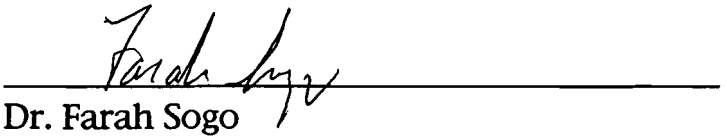
Approved, Honors Committee:

Dr. Jeffrey A. Frick, Research Advisor

Dr. Timothy R. Rettich



Dr. Wendy Wolbach



Dr. Farah Sogo

Illinois Wesleyan University
1996