# Stony Brook University

# Asymmetric Synthesis of Novel Fluorine-Containing *β*-Lactams for Application to Unnatural *β*-Amino Acid Synthesis

A Thesis Presented

by

**Wen Chen**

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Abstract of the Thesis

**Asymmetric Synthesis of Novel Fluorine-Containing *β*-Lactams for Application to Unnatural *β*-Amino Acid Synthesis**

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**Master of Science in Chemistry**

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*β*-Lactams are four-membered cyclic amides which can be found in many biologically active compounds. *β*-Lactams may possess two stereocenters. In enantiopure form, *β*-lactams can be used as chiral building blocks for the synthesis of various biologically relevant compounds, such as antibacterial drugs, antitumor agents, peptides, peptidomimetics and enzyme inhibitors. In addition, fluorine-containing *β*-lactams have drawn substantial interests among bioorganic and medicinal chemists. Studies have shown that the incorporation of fluorine efficiently blocks metabolism of the drug molecules, especially by cytochrome P-450 family of enzymes, providing improved pharmacokinetic properties.

Different diastereomers of fluorine-containing *β*-lactams with high enantiopurity were synthesized utilizing a base-catalyzed C4-specific epimerization. Highly enantioenriched *cis*-*β*-lactams were obtained using the Staudinger [2+2] ketene-imine cycloaddition reaction, followed by kinetic enzymatic resolution. Ozonolysis of an exocyclic double bond of the enantioenriched *cis*-*β*-lactam afforded the key intermediate for selective epimerization, i.e., a C4-formyl-β-lactam. The epimerization reaction was optimized for the isolation of *trans*-*β*-lactams. A difluorovinyl group was incorporated through a Wittig reaction, and subsequent modification of the substituents gave the desired 4-difluorovinyl-*β*-lactams. Using this protocol, a novel *trans*-difluorovinyl-β-lactam, (3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one with excellent enantiopurity, was obtained. These novel *cis*- and *trans*-fluorine-containing *β*-lactams can be used for the synthesis of fluorine-containing *α*-hydroxy-*β*-amino acids and their congeners or for the incorporation of fluorines into biologically

active compounds via the *β*-lactam synthon method to investigate the effects of the fluorine moieties on their biological activities.

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## List of Abbreviations

| | | |
|---|---|---|
| Ac | - | acetyl |
| Bn | - | benzyl |
| Boc | - | *tert*-butyloxycarbonyl |
| CAN | - | ammonium cerium(IV) nitrate |
| $CH_2Cl_2$ | - | dichloromethane |
| d | - | doublet |
| DAST | - | diethylaminosulfur trifluoride |
| DBU | - | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DMAP | - | 4-Dimethylaminopyridine |
| DMF | - | Dimethylformamide |
| ee | - | enantiomeric excess |
| $Et_3N$ | - | triethylamine |
| FIA | - | flow-injection analysis |
| g | - | grams |
| h | - | hour |
| HMPT ($P(NMe_2)_3$) | - | hexamethylphosphorous triamide |
| HPLC | - | high performance liquid chromatography |
| Hz | - | hertz |
| kJ | - | kilo joules |
| KOH | - | potassium hydroxide |
| LDA | - | lithium diisopropylamide |
| LiHMDS | - | lithium bis(trimethylsilyl)amide |
| M | - | molarity |

| | | |
|---|---|---|
| Me | - | methyl |
| $Me_2S$ | - | dimethyl sulfide |
| MeOH | - | methanol |
| mg | - | miligrams |
| MHz | - | mega hertz |
| mL | - | milliliter |
| Mmol | - | millimole |
| mp | - | melting point |
| NaOH | - | sodium hydroxide |
| NMR | - | nuclear magnetic resonance |
| PBS | - | phosphate buffered saline |
| Ph | - | phenyl |
| PMP | - | *p*-methoxyphenyl |
| PPM | - | part per million |
| s | - | singlet |
| $R_f$ | - | fluorine-containing group |
| r.t. | - | room temperature |
| t | - | triplet |
| TEA | - | triethylamine |
| THF | - | tetrahydrofuran |
| TIPS | - | triisopropylsilyl |
| TIPSCl | - | triisopropylchlorosilane |
| TLC | - | thin-layer chromatography |
| TMS | - | trimethylsilyl |

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# § 1.1 Introduction

## § 1.1.1 Structure and Reactivity of *β*-Lactams

*β*-lactams are four-membered cyclic amides (**Figure 1**) which can be found in many biologically active compounds. *β*-lactams may possess two stereocenters. *β*-lactams with high enantiopurity are beneficial as chiral synthons for the synthesis of stereospecific compounds. Cleaving any of the C-C or C-N bonds can resolve chiral precursors for several syntheses. The strain in the *β*-lactam ring makes the azetidin-2-one core prone to nucleophilic attack at the C2 carbonyl. The C2 carbonyl is also the most exploited nucleophilic center as the N1-C2 amide bond is susceptible to a variety of nucleophilic reagents. Notably, cleavage of N1-C2 bond yields enantiopure *β*-amino acids, while the reductive cleavage of the N1-C4 bond leads to formation of *α*-amino acids and *α*-hydroxy acids.[1] Thus, *β*-lactams are very useful in the synthesis of various *α*- and *β*-amino acids, which are the building blocks for many potential therapeutic drugs.

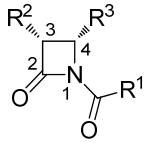



**Figure 1:**Azetidin-2-one

## § 1.1.2 Applications of *β*-Lactams in Biologically Active Compounds

Since the development of the *β*-lactam synthon method, *β*-lactams have drawn great interest from scientists for the synthesis of antibacterial drugs, antitumor agents, peptides, peptidomimetics and protease inhibitors.[2] For example, *β*-lactams have been used for the synthesis of antibiotics for decades. These antibiotics include penicillins, cephalosporins, carbapenems, and monobactams.[2] Moreover, antitumor agents such as Taxol® (paclitaxel) (**4**) as shown in **Figure 2** and Taxotère® (docetaxel) have utilized *β*-lactams as intermediates to introduce the C13 side chain isoserine (*α*-hydroxy-*β*-amino acid) moiety. The isoserine moieties (**1**) are obtained through the cleavage of the N1-C2 bond of C3-hydroxy *β*-lactams. These isoserine units are essential for the cytotoxicity of taxoids.[3]

*β*-lactams have also been used as intermediates in the synthesis of biologically active peptides. For example, the stereoselective synthesis of Bestatin (**2**) can be accomplished through the *β*-lactam synthon method.[4] Bestatin functions as an aminopeptidase inhibitor and has been used for the treatment of various forms of cancers such as chronic myelogenous leukemia,[5] and early lung cancer.[6] Peptidomimetics such as Kinostatin-227 (**3**),[7-8] an anti-HIV agent and

microginin (**5**)[9], an angiotensin-converting-enzyme inhibitor, have been successfully synthesized using *β*-lactams as intermediates.

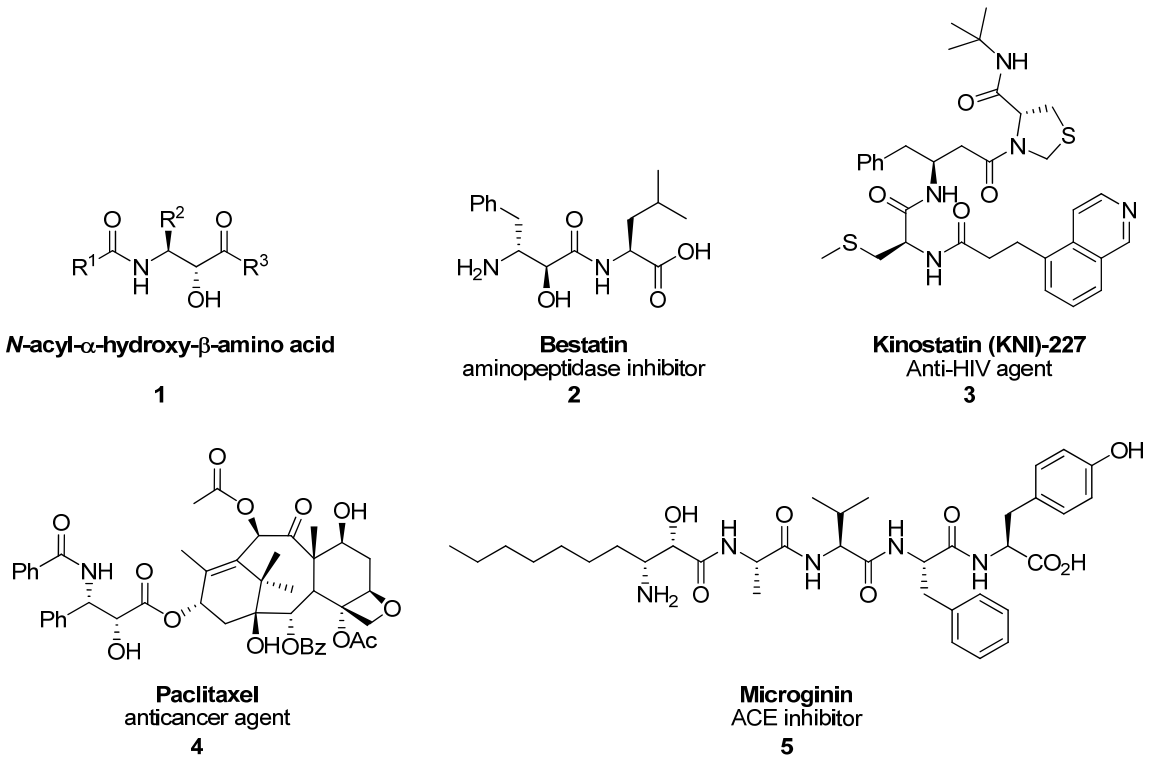



**Figure 2:** Examples of bioactive compounds containing α-hydroxy-β-amino acid unit

## § 1.1.3 Synthetic Methods Towards *β*-lactams

Two major synthetic methods have been developed to synthesize enantiomerically enriched *β*-lactams. The Staudinger [2+2] ketene-imine cycloaddition reaction is the first reported synthesis of *β*-lactams. *β*-lactams could be synthesized in racemic form and the enantiomers may be separated by means of enzymatic resolution.[10] The ester enolate-imine cyclocondensation was one of the first asymmetric syntheses reported for the preparation of *β*-lactams. By using a chiral auxiliary in the starting material, *β*-lactams can be synthesized with high enantiopurity.

## § 1.1.3.1 Staudinger Reaction

The *β*-lactam core can be achieved by the Staudinger [2+2] ketene-imine cycloaddition reaction, which was first reported by Staudinger in 1907. In this first example, a Schiff base derived from aniline and benzaldehyde underwent a [2+2] cycloaddition with diphenylketene (**Figure 3**).[11]

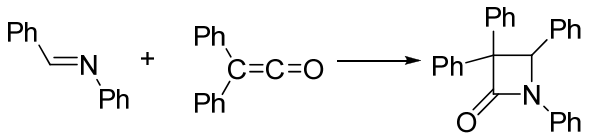



**Figure 3:** Staudinger reaction between imine and ketene

Although the Staudinger [2+2] ketene-imine cycloaddition reaction has been widely used for the synthesis of various *β*-lactams, the detailed mechanism has remained controversial. Several experiments and computational analyses have revealed that the Staudinger reaction undergoes a two-step process. The reaction involves the nucleophilic attack of an imine to a ketene, generating a zwitterionic intermediate. The zwitterionic intermediate then undergoes a four-electron conrotatory electrocyclization to form the *β*-lactam ring.[12] In the cycloaddition process, two stereocenters can be produced in the ring. As a result, both *cis*- and *trans*-*β*-lactam products can be obtained.

The stereoselectivity of *β*-lactams can be controlled by various factors such as the order of addition of the reagents and the electronic nature of the substituents.[13] Three pathways have been proposed for the formation of the *cis*- and *trans*-*β*-lactam diastereomers. As shown in Pathway I (**Figure 4**), after the formation of the zwitterionic intermediate, it can have two fates. If the ring closing happens faster than the isomerization of the zwitterionic intermediate, a *cis*-*β*-lactam product is formed. Alternatively, if the zwitterionic intermediate is relatively stable, an isomerization may occur which allows rotation around the N-C bond, thus the *trans*-*β*-lactam product is formed. Pathway III gives a similar prediction for the formation of the two diastereomers, however, the nucleophilic attack of the acyl chloride by the imine happened first. Pathway II suggests a stabilization of the zwitterionic intermediate by chlorine which can later behave as a leaving group at the ring closing step and give the two diastereomers. In general, (*E*) imines lead preferentially to the more hindered *cis*-*β*-lactams, while (*Z*) imines give predominantly the *tran*-isomers.[12] The two products can be isolated by means of column chromatography or recrystallization. Enantiomerically enriched *β*-lactams can also be achieved by incorporating chiral imines or ketenes in the synthesis.

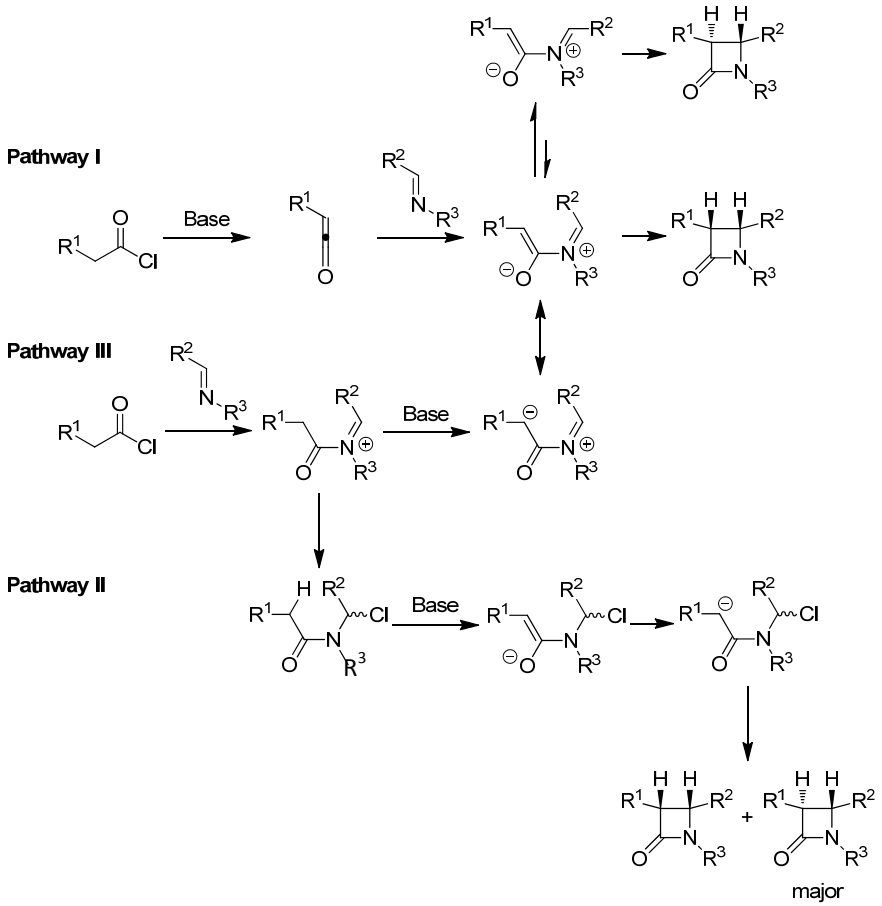
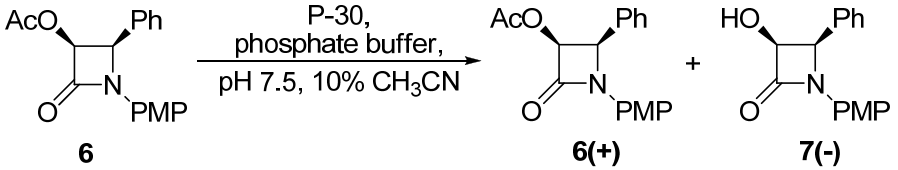



**Figure 4:** Proposed pathways in the Staudinger [2+2] reaction leading to the formation of both *cis*- and *trans*-*β*-lactams[12]

## § 1.1.3.2 Enzymatic Optical Kinetic Resolution

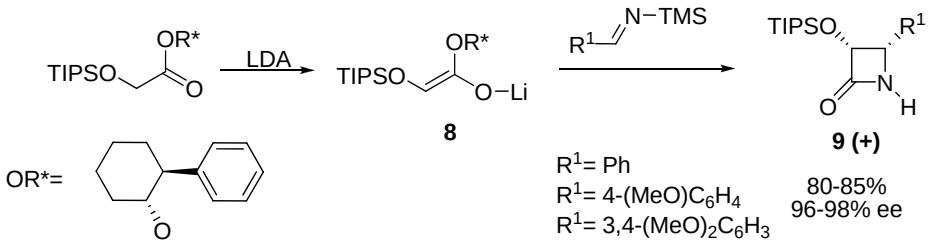
In most cases, the Staudinger reaction affords a racemic mixture of *β*-lactam. If there is a hydroxyl group at C3, the two enantiomers can be separated and isolated via an enzymatic kinetic resolution using lipases. Lipases have been employed for the kinetic resolution of racemic alcohols and carboxylic esters. Due to the commercial availability and the relative stability of the lipases, they have been utilized to synthesize *β*-lactams with excellent enantiomeric excess.[14] For example, Sih *et. al.* applied P-30 lipase to catalytically hydrolyze the racemic *β*-lactam (**6**) and obtained **6(+)** as the remaining substrate with an absolute configuration of (3*R*, 4*S*) (**Scheme 1**).[14]




**Scheme 1:** Application of enzymatic kinetic resolution on racemic *cis*-1-(*p*-methoxyphenyl)-3-acetoxy-4-phenylazetidin-2-one

## § 1.1.3.3 Chiral Ester Enolate-Imine Cyclocondensation

An alternative method towards the synthesis of enantiomerically enriched *β*-lactams is through the chiral ester enolate-imine cyclocondensation reaction.[15-16] An example of this reaction proceeds, by forming a chiral lithium ester enolate (**8**) that contains Whitesell's chiral auxiliary followed by cyclocondensation with *N*-trimethylsilylimines (**Scheme 2**). After acidic workup highly stereospecific *β*-lactams **9(+)** are obtained in good yield and high enantiopurity.




**Scheme 2:** Chiral ester enolate-imine cyclocondensation

In the chiral ester enolate-imine cyclocondensation reaction, an *E*-enolate is preferentially formed first. The *E*-enolate is the kinetically favored product as compared to the *Z*-enolate. Moreover, Ojima *et. al.* carried out calculations which proved that the *E*-enolate is also the thermodynamically favorable product.[16] The cyclocondensation reaction between the *E*-enolate and the imine can undergo two possible transition states. For the first transition state, the enolate has a chair like conformation (**A**), whereas in the other transition state the enolate takes on a boat like conformation (**B)** (**Figure 5**). Transition state **A** is kinetically favored, and thus the *cis*-product is formed instead of the *trans*-product, provided that care is taken during addition to maintain the temperature at -78 °C.[16] The transition state also explains the high enantioselectivity of the reaction. The chiral auxiliary blocks the front side of the ester enolate causing the imine to approach only from the back side, thus giving the highly enantiomerically enriched *cis*-product.

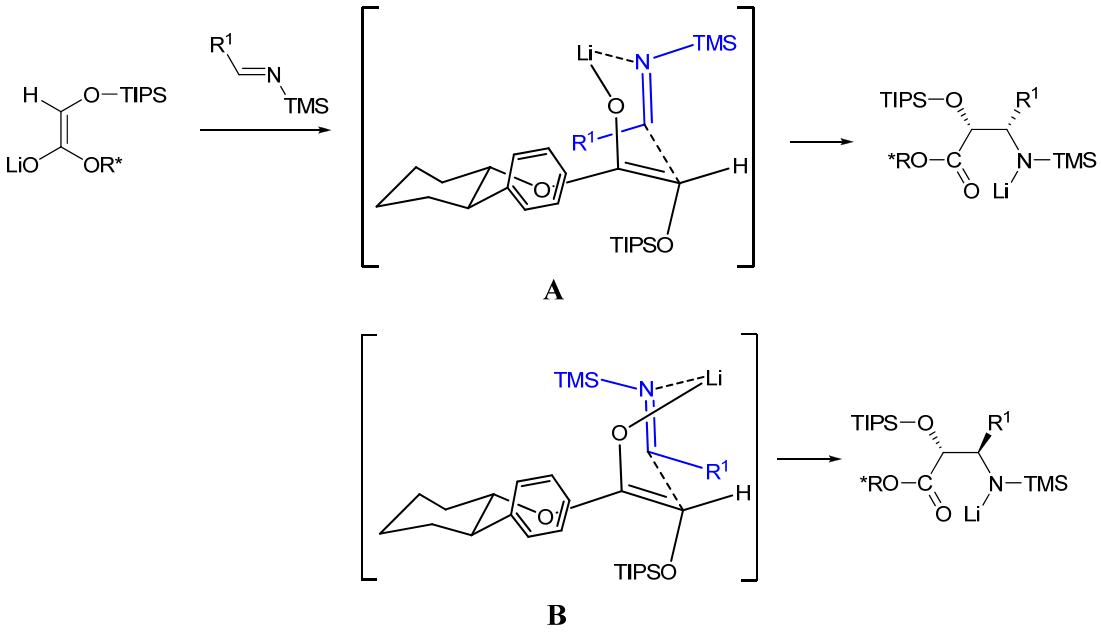



**Figure 5:** Mechanism of chiral ester enolate-imine cyclocondensation[16]

### § 1.1.4 Introduction of Fluoro-β-Lactams

Fluorine containing *β*-lactams have drawn a substantial amount of interest from scientists, as these *β*-lactams can be used for the synthesis of biologically relevant compounds. Studies have shown that the incorporation of fluorine moieties often improves the activity of bioactive drugs. Fluorine is the most electronegative atom, thus the C-F bond is stronger than the C-H bond. As a result, fluorine provides higher oxidative stability. Molecules without fluorine often contain active moieties that can be oxidized by the cytochrome P450 enzyme to allow excretion. This oxidation would terminate the drug action and influence the compound's residence time. The incorporation of fluorine efficiently blocks the oxidation at the active moieties of the drug molecule providing improved pharmacokinetic properties. Furthermore, fluorine is also isoelectronic to oxygen ions and hydroxyl groups, which can have profound effects on binding affinities of the drug to the protein. Moreover, incorporation of fluorine increases the lipophilicity of the drug, thus improving membrane permeability.[17]

From an analytical point of view, fluorine possesses large $^{19}F$-$^{1}H$ coupling constants and has better sensitivity in $^{19}F$ NMR spectroscopy, simplifying the analysis of complex molecules. In addition, due to the fact that fluorine is absent in human tissues, the activities of fluorine-containing molecules in a biological environment (i.e. protein) can be observed easier.[18]

Therefore, the synthesis of fluoro-*β*-lactams is very beneficial as intermediates for the synthesis of fluoro-*β*-amino acids.

## § 1.1.4.1 Applications of Fluorine in Biologically Active Compounds

In the past decade, many fluorine-containing drugs have been widely applied in experimental and clinical use. These fluorine-containing drugs have been used as treatments for various diseases. For example, Roflumilast (**10**) has been used to inhibit phosphodiesterase enzymes that inactivate cAMP and cGMP. These proteins are responsible for the regulation of autocoids, drugs, hormones and neurotransmitters. Roflumilast and related compounds are considered useful for the treatment of inflammatory diseases such as asthma, allergic rhinitis and pulmonary hypersensitivity, as well as central nervous system disorders. BMS 201038 (**11**) is a potent inhibitor of the microsomal triglyceride transfer protein, which is beneficial in lowering cholesterol level. Eflornithine (**12**) has been designed as an ornithine decarboxylase inhibitor and can be used to cure infections caused by *Trypanosoma gambiense*.[19]

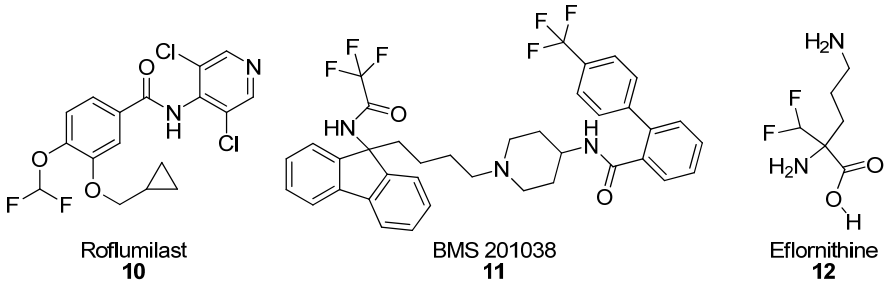
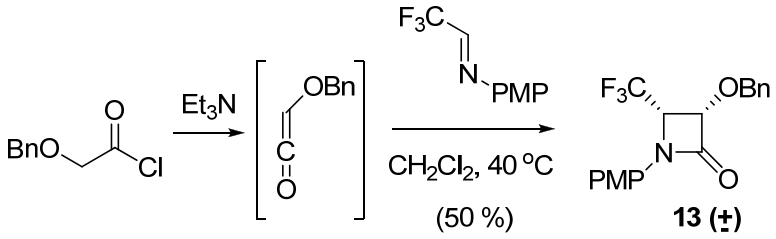



**Figure 6:** Fluorine-containing drugs[19]

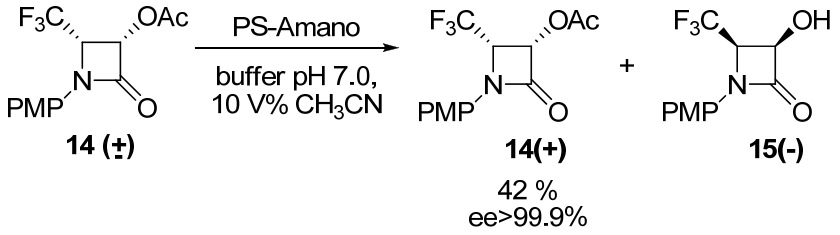
## § 1.1.4.2 Synthesis of Fluorine-Containing *β*-Lactams

All the synthetic methods described previously for general *β*-lactams can be applied for the synthesis of fluorine-containing *β*-lactams. In 1996, Bonnet-Delpon *et al.* reported the synthesis of *syn*-*α*-hydroxy-*β*-trifluoromethyl-*β*-amino acid using the Staudinger reaction (**Scheme 3**). Racemic *cis*-*β*-lactam (**13**) was obtained in 50 % yield.[20]



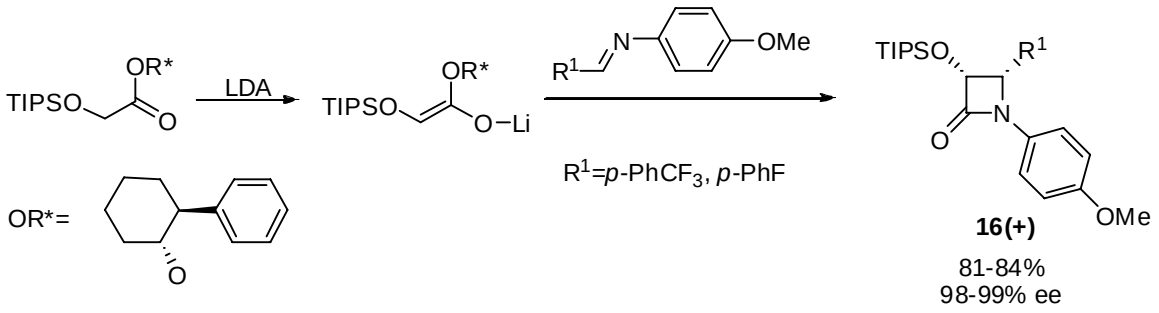

**Scheme 3:** Formation of racemic *cis*-3-benzyloxy-4-trifluoromethylazetidin-2-one using Staudinger reaction

In 1997, Ojima *et al.* utilized kinetic optical resolution on acetyl protected *β*-lactam **14(±)** in the presence of PS-Amano lipase and buffer (pH 7) at 50 $^{o}$C to give **14(+)** in high enantiopurity with 42% yield (50% was the theoretical yield). **15(-)** with high enantiopurity could not be isolated due to hydrolysis of **6(+)** to alcohol (**Scheme 4**). Careful temperature control and PS-Amano lipase activity may prevent over hydrolysis.[18]



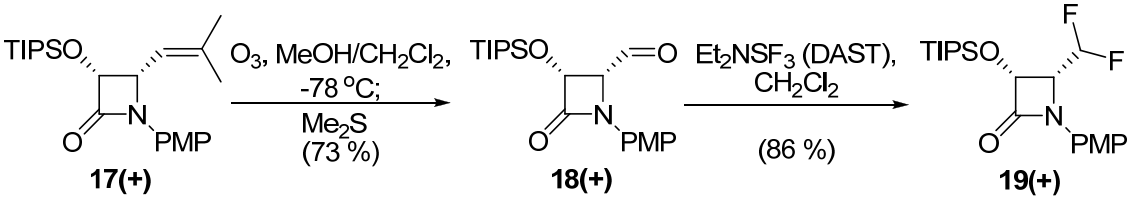

**Scheme 4:** Enzymatic kinetic resolution of racemic 3-AcO-4-$CF_3$-*β*-lactam

Ojima *et al.* successfully applied the chiral ester enolate-imine cyclocondensation strategy to synthesize the fluoro-*β*-lactams **16(+)** with very high enantioselectivity (**Scheme 5)**.[16]



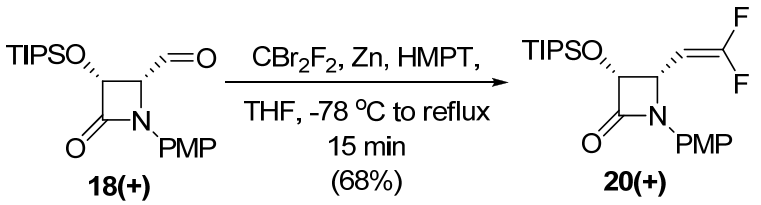

**Scheme 5:** Chiral ester enolate-imine cyclocondensation with fluorine

Furthermore, in 2000 Ojima *et al.* subjected TIPS-protected *β*-lactam **17(+)** to an ozonolysis reaction to give aldehyde **18(+)**. The aldehyde was then treated with excess dialkylaminosulfur trifluorides (DAST) to afford the 4-difluorinated-*β*-lactam **19(+)** (**Scheme 6**).[21]




**Scheme 6:** Formation of 4-difluoromethylazetidin-2-one

Recently in 2009, Ojima patented a new synthetic method exploiting the Wittig reaction by using the TIPS-protected **18(+)** and obtained 4-difluorovinyl-*β*-lactam **20(+)** in moderate yield (**Scheme 7**).[22]



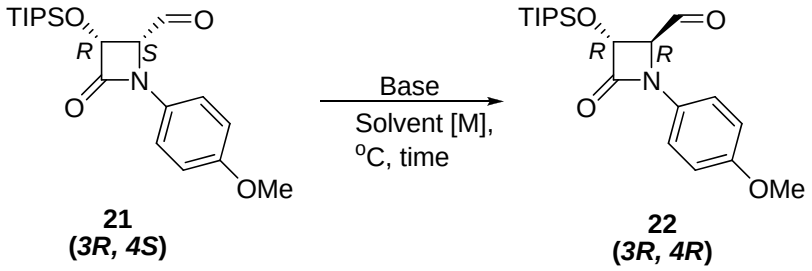

**Scheme 7:** Wittig reaction on (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one

## § 1.1.5 Epimerization of Enantiomerically Enriched *cis*-*β*-Lactams into *trans*-*β*-Lactams

To synthesize *trans*-*β*-lactams with high enantiomeric excess, two strategies can be applied starting with a *cis*-*β*-lactam possessing high enantiopurity. The first strategy involves the use of a base to epimerize the aldehyde and the second strategy involves the formation of a Schiff base, followed by epimerization and hydrolysis.

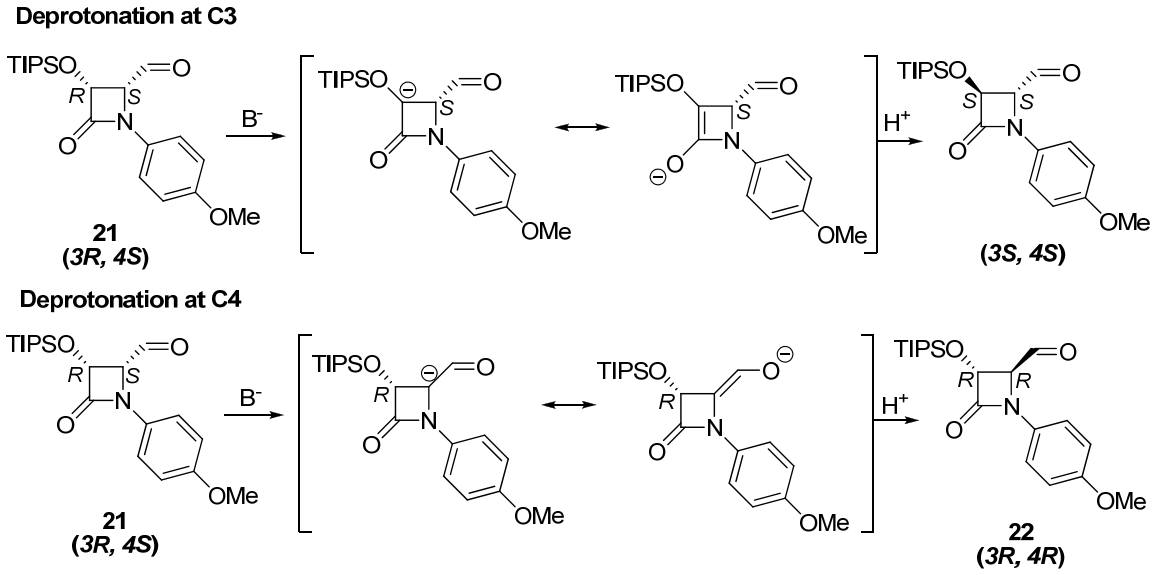
### § 1.1.5.1 Epimerization using Treatment of Base

*β*-lactam (**21**) contains two acidic protons at C3 and C4, thus it can be used as the key intermediate for the epimerization step. It is proposed that after deprotonation by base and careful control of reaction conditions, the *trans*-diastereomers (**22**) were expected to be the major products as they are thermodynamically more stable than *cis*-diastereomers (**Scheme 8**).




**Scheme 8:** Epimerization of (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one using treatment of base

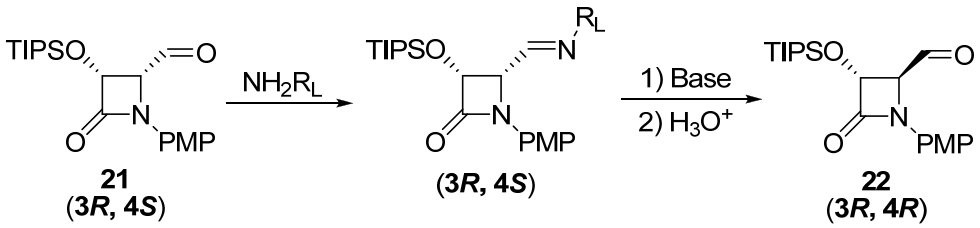
As shown in **Scheme 9**, deprotonation at C3 would generate a highly unstable charged intermediate. After deprotonation, the intermediate has a double bond in the four-membered β-lactam ring introducing more strain into the already highly strained ring. Alternatively, when the C4 proton is deprotonated a more stable intermediate is formed. After deprotonation, C4 changes its hybridization from $sp^3$ to $sp^2$, allowing a change of the stereocenter at the re-protonation step and forming the (3*R*, 4*R*) *trans*-diastereomer as the expected product.




**Scheme 9:** Possibilities of deprotonation at C3 and C4 of (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one

## § 1.1.5.2 Epimerization using Formation of Schiff Base

An alternative method for the epimerization is to employ a Schiff base strategy. A bulky amine could be reacted with the aldehyde to give an imine, which would epimerize after treating with a base (**Scheme 10**). The epimerization is facilitated by the steric hindrance between the TIPS group and the bulky imine moiety. As a result, a *trans*-imine could be formed to avoid steric interactions between bulky groups at C3 and C4 (**Figure 7**). Finally, hydrolysis would give the aldehyde with desired stereochemistry. Similarly, upon the addition of base, deprotonation at C3 would generate an unstable intermediate thus is not favorable.




**Scheme 10:** Epimerization of (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one

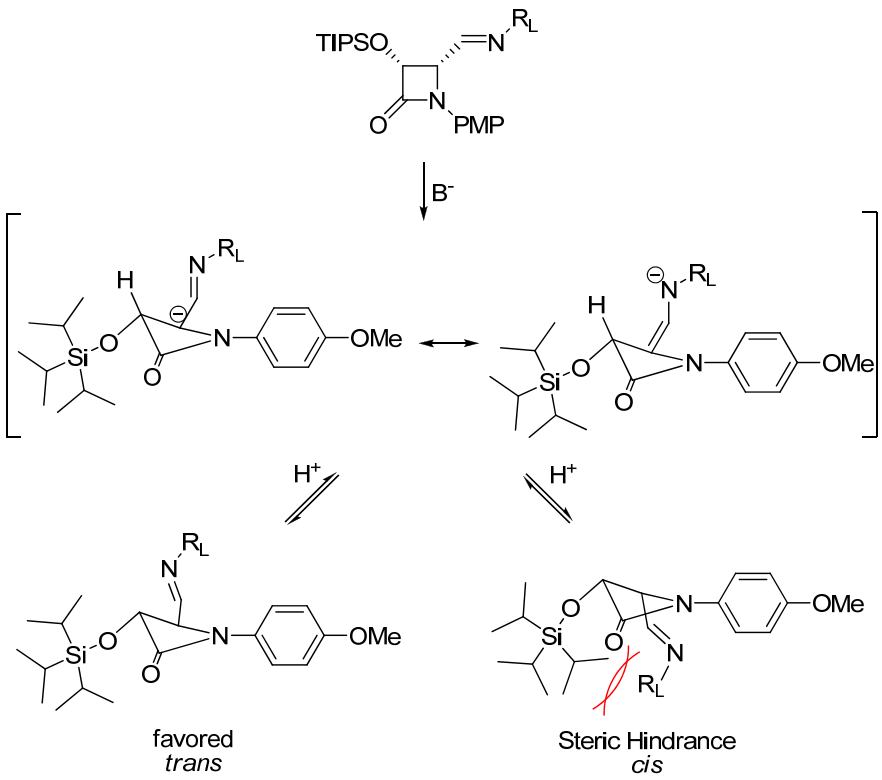


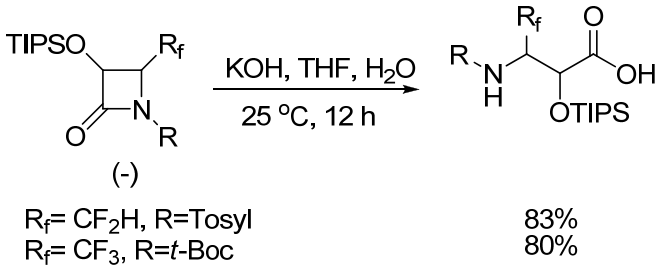

**Figure 7:** Epimerization mechanism of (3*R*,4*S*)-1-PMP-3-TIPSO-4-formylazetidin-2-one

Once the stereochemistry has been established, the fluoro-*trans*-*β*-lactams can be synthesized using the Wittig reaction, followed by CAN-mediated deprotection and Boc protection.[22] The fluoro-*β*-lactams with high enantiomeric excess can be used as precursors for the synthesis of fluoro-*α*-hydroxy-*β*-amino acids with high enantiopurity.

## §1.1.6 Asymmetric Synthesis of Fluoro-*α*-Hydroxy-*β*-Amino Acids

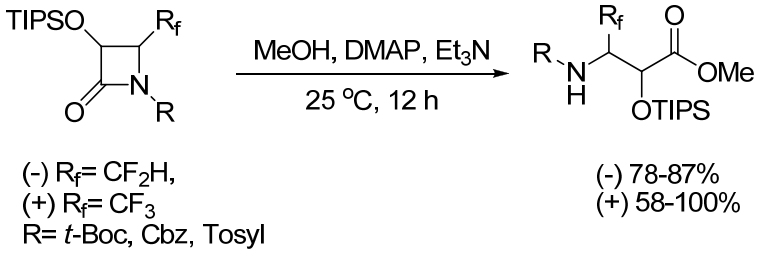
Fluorine-containing *β*-amino acids have drawn a substantial amount of interest in the last two decades due to the unique and intrinsic properties of fluorine. As mentioned previously, *α*-hydroxy-*β*-amino acids (isoserines) could be found in many biologically active compounds. The *β*-lactam synthon method is especially useful in the synthesis of isoserines. Utilizing the ring strain of the four-membered *β*-lactam ring, a ring-opening reaction would give chemically important isoserines. Therefore, to obtain stereospecific fluoro-*α*-hydroxy-*β*-amino acids fluoro-*β*-lactams could be used as versatile synthetic building blocks.[23]

Isoserines can be obtained from fluoro-*β*-lactams using various methods. A facile ring-opening hydrolysis was reported by Ojima *et al.*[21] (**Scheme 11**) which gave the *β*-$CF_2H$- and $CF_3$-*α*-TIPSO-*β*-amino acids in good yields.[23]



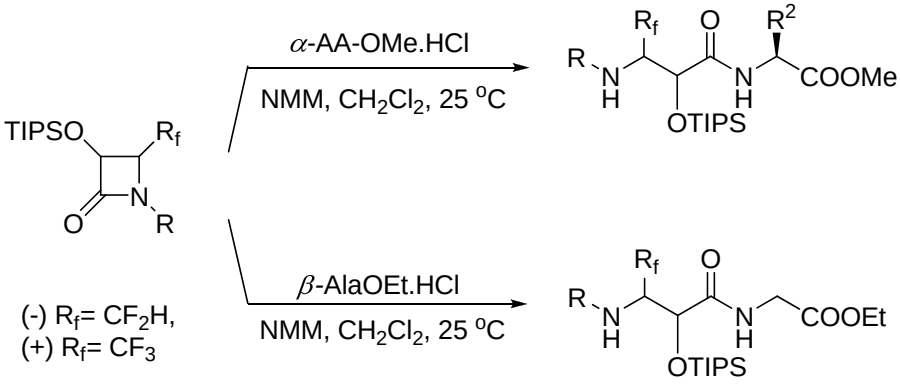

**Scheme 11:** Ring-opening hydrolysis of $R_f$-$\beta$-lactams

Another method was reported for the synthesis of $\beta$-$CF_2H$- and $CF_3$-$\alpha$-TIPSO-$\beta$-amino acids methyl ester through a facile methanolysis of $R_f$-$\beta$-lactams with good to excellent yield (**Scheme 12**).[23]




**Scheme 12:** Methanolysis of $R_f$-$\beta$-lactams

The synthesis of $R_f$-containing isoserine dipeptides was also reported and synthesized through a ring-opening coupling reaction. The isoserine dipeptides were obtained with good to excellent yields. This method was done without any peptide coupling reagents such as *N.N*-dicyclohexylcarbodiimide (DCC) and *N,N*-diisopropylcarbodiimide (DIC), and therefore provides a much easier method to the formation of dipeptides.[23]




**Scheme 13:** Ring-opening coupling of $R_f$-$\beta$-lactams with amino acid esters

### § 1.1.7 Applications of Fluoro-*α*-Hydroxy-*β*-Amino Acids

Fluoro-*α*-hydroxy-*β*-amino acids can be found in many biological applications, thus fluoro-*β*-lactams are very useful intermediates for the facile synthesis of biologically active molecules such as dipeptides, depsipeptides and peptidomimetics. Fluoro-*β*-lactams also can be used as building blocks for fluorine-containing hydroxyethylene, dihydroxylethylene, and hydroxyethylamine dipeptide isosteres.[23]

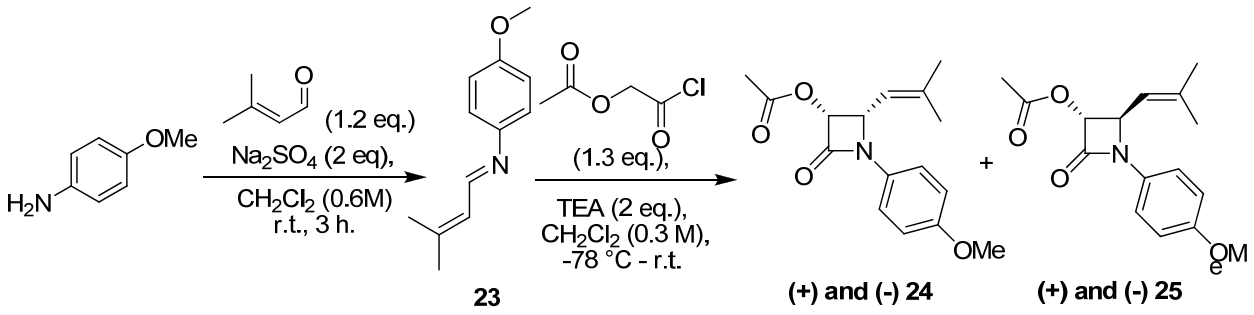
Ojima *et al.* used *β*-lactams as versatile intermediates in the synthesis of taxoids using the Ojima-Holton coupling. The isoserine moiety can be conveniently introduced in one step in which the *β*-lactam ring opens after coupling with a modified-baccatin core in the presence of base. The isoserine moiety at the C-13 side chain of taxoids is essential for the cytotoxicity of the taxoids.[24] A series of 3′-$CF_3$-docetaxel congeners, $CF_2H$- and $CF_3$-containing taxoids, and C-3′-difluorovinyl-taxoids have been synthesized. The cytotoxicity assay against different human cancer cell lines showed that fluoro-taxoids are significantly more potent than paclitaxel and docetaxel. [22-23, 25]

## § 1.2 Results and Discussion

The synthesis of fluoro-*β*-lactam diastereomers for the preparation of various fluoro-*β*-amino acids is the focus of the present study. *β*-amino acids are constituents of proteins and peptides, and *β*-amino acids moieties can be found in many biologically active compounds.[18] It is proposed that different fluoro-*α*-hydroxy-*β*-amino acids with high enantiopurity could be synthesized by utilizing 1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-(2,2-difluorovinyl)azetidin-2-one as the key intermediate. Both enantiopure (+) and (-) *cis*-diastereomers can be obtained using enzymatic resolution, while their corresponding *trans*-diastereomers could be achieved using epimerization. The synthetic method of achieving (+) and (-) *trans*-diastereomers from *cis*-*β*-lactams was explored in the present study.

### § 1.2.1 Synthesis of *β*-lactams

The synthesis of *β*-lactams with excellent enantionmeric excess begins with the construction of the four-membered heterocyclic ring core. Using the Staudinger [2+2] ketene-imine cycloaddition reaction, imine **23** was obtained in the condensation reaction of 3-methyl-2-butenal in the presence of *p*-anisidine and a desiccating reagent (**Scheme 14**).[26]



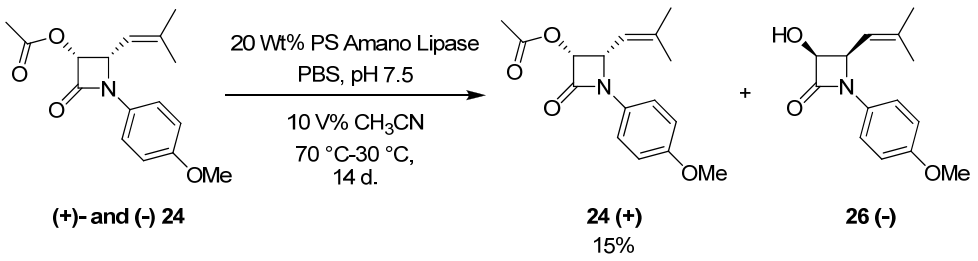

**Scheme 14:** Staudinger [2+2] ketene-imine cycloaddition reaction

Imine **23** is highly unstable. To prevent loss of the imine due to decomposition or isomerization, the condensation reaction was done in the dark. Upon completion of the reaction, the reaction mixture was filtered; the solvent was evaporated under vacuum pressure at room temperature. Without further purification the resulting material was carried onto the next step. The [2+2] cycloaddition between imine **23** and acetoxyacetyl chloride generated a racemic mixture of **24** accompanied by a racemic mixture of **25**.[26]

The -78 °C temperature had to be maintained to prevent *trans*-isomer formation of the *β*-lactam. This temperature was achieved using acetone with a cryocool. However, instead of adding acetoxyacetyl chloride dropwise against the sides of the reaction vessel to further assure the cold temperature was maintained, it was added dropwise directly into the solution which may account for the generation of **25** *trans*-*β*-lactam isomer. The temperature was held at -78 °C for at least 2 hours after the addition of the chloride. After 7 hours, the reaction was allowed to slowly warm to room temperature. *β*-lactam **24** was purified by column chromatography, however, trace amounts of the *trans*-*β*-lactam isomer were still present. Half of the product mixture was therefore carried to the next step. At the same time, recrystallization was performed to further purify the other half of the mixture. The purified **24** was eventually added to the next reaction.

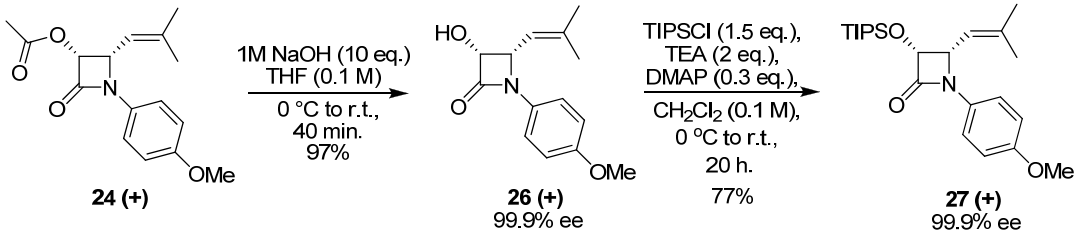
The Ojima-Holton protocol requires *β*-lactam **24(+)** with high enantiomeric excess. This can be achieved *via* enzymatic resolution using PS-Amano lipase.[14] Ideally, the lipase should preferentially cleave the acetate group of the **(-)** enantiomer leaving the **(+)** enantiomer intact. The reaction was monitored by $^{1}$H NMR and was quenched when the ratio of the acetate to alcohol was 1:1.[27] The ideal yield for **24(+)** should be 50%, but only a 15% yield was obtained experimentally after 3 steps. This poor yield could be due to the high temperature at the

beginning of the reaction which promoted enough energy for the enzyme to hydrolyze the **(+)** enantiomer. Moreover, residual *trans*-diastereomer may also account for the low yield.



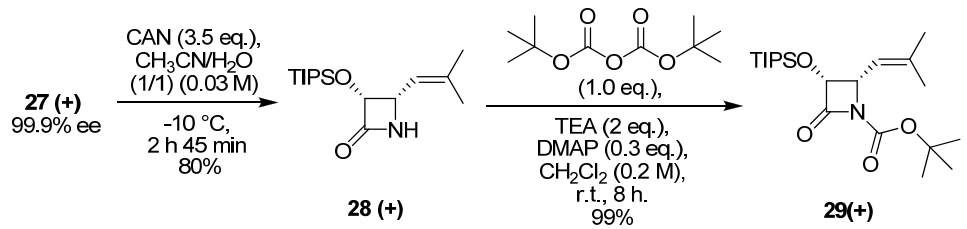

**Scheme 15:** Enzymatic kinetic resolution on (±)-1-(4-Methoxyphenyl)-3-acetoxyl-4-(2-methylprop-1-enyl)azetidin-2-one [**24(±)**]

Later, the desired **24(+)** was converted to an alcohol **26(+)** using base-hydrolysis and the alcohol was protected with a TIPS moiety to give **27(+)**.[28]




**Scheme 16:** Hydrolysis of (+) 2-2 followed by TIPS-protection

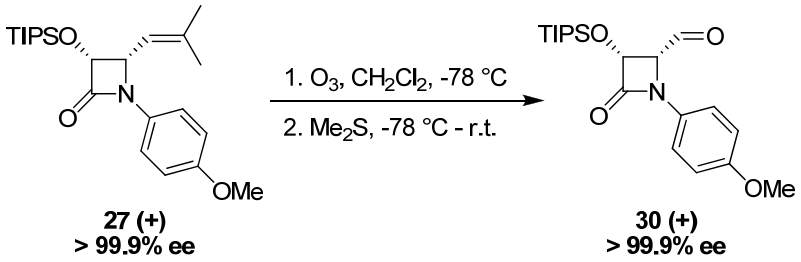
Further modification of **27(+)** involved the deprotection of the *p*-methoxyphenyl (PMP) moiety in the presence of ceric ammonium nitrate (CAN).[28] The mechanism for the removal of PMP involves two Single Electron Transfers. Cerium (IV) takes a single electron from the PMP group forming a radical cation intermediate that is susceptible to a nucleophilic attack by water. After the nucleophilic attack, another electron is transferred to another cerium molecule to give a quinone like radical which is then cleaved by the addition of a second water molecule producing the free amine, quinone and methanol as the primary products. After CAN-mediated deprotection, the amine was protected with Boc to yield **29(+)**. Following Boc protection, **29(+)** can be used in various stereospecific syntheses (**Scheme 17)**. For example, it could be coupled to a modified baccatin core to yield a highly potent 2nd generation taxoid, SB-T-1214.[28]




**Scheme 17:** CAN-mediated deprotection followed by Boc protection to give (3*R*,4*S*)-1-*t*-Boc-3-TIPSO-4-(2-methyl-1-propenyl)azetidin-2-one [**29(+)** ] with high enantiopurity

## § 1.2.2 Synthesis of Fluoro-*β*-lactams

The synthesis of fluoro-*β*-lactams began with subjecting **27(+)** to an ozonolysis reaction (**Scheme 18**). In the reaction, a malozonide would be formed as the first intermediate followed by decomposition into Criegee zwitterion and a carbonyl. Another cycloadditon between the two species would give rise to the ozonide intermediate. Due to the fact that the malozonide is very unstable and may be explosive, the reaction has to take place at low temperature. Upon workup with dimethylsulfide the ozonide can be reduced to give **30**.



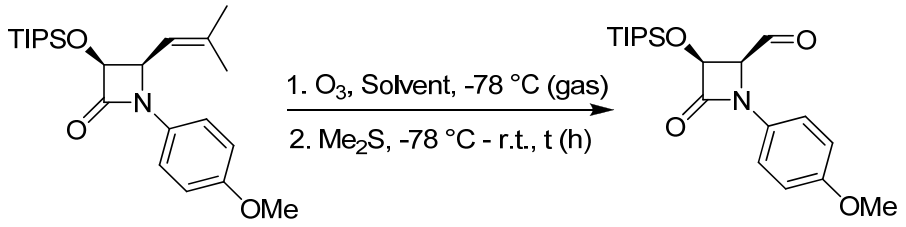

**27 (+)**
**> 99.9% ee**

**30 (+)**
**> 99.9% ee**

**Scheme 18:** Ozonalysis of **(+) 27**

Several ozonolysis reactions were carried out using **(-) 27** with low % ee to test the reaction conditions and to see if literature reported results are reproducible. The results are shown in **Table 1**. Although the same reaction conditions were followed according to literature procedure, the ozonolysis reaction gave poor to moderate yields. Unfortunately, the yield for ozonolysis could not be improved despite various changes in the reaction conditions. For example, a stream of $N_2$ instead of $O_2$ was bubbled into the reaction to clear excess $O_3$ in the solution, as shown in entries 4 to 5 and 7 to 8; a new bottle of dimethyl sulfide was used; the amount of time that the reaction was quenched, and the amount of dimethyl sulfide were varied; the solvent was changed based on another literature procedure,[21] a mixture of dichloromethane and methanol was used (entries 5 to 6 and 8). However, not much improvement in the yield was observed. No obvious trend was observed for the poor to moderate yield, therefore the next reaction was carried on.

**Table 1:** Screening reaction conditions for improving the yield of the ozonolysis product **30**

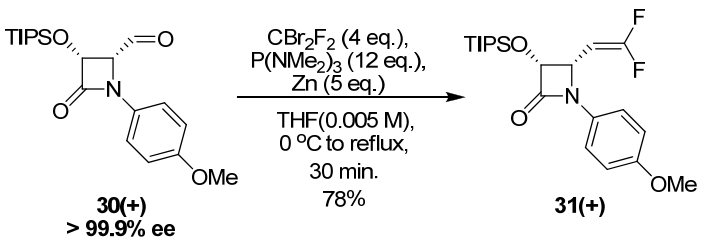



**27** **30**

| Entry | 27 | Solvent | Gas[1] | $Me_2S$ (eq.) | Time (h)[3] | Isolated Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **27(-)** | $CH_2Cl_2$ | $O_2$ | 5 | 6 | 80 |
| 2 | **27(-)** | $CH_2Cl_2$ | $O_2$ | 5 | 4 | 42 |
| 3 | **27(-)** | $CH_2Cl_2$ | $O_2$ | 10 | 7 | 45 |
| 4 | **27(-)** | $CH_2Cl_2$ | $N_2$ | 10 | 3 | 68 |
| 5 | **27(-)** >99.9 %ee | $CH_2Cl_2$/MeOH (2/1)[4] | $N_2$ | 10[2] | 4 | 61 |
| 6 | **27(-)** >99.9 %ee | $CH_2Cl_2$/MeOH (2/1)[4] | $O_2$ | 10[2] | 18 | 38 |
| 7 | **27(+)** >99.9 %ee | $CH_2Cl_2$ | $N_2$ | 10[2] | 2 | 25 |
| 8 | **27(+)** >99.9 %ee | $CH_2Cl_2$/MeOH (2/1)[4] | $N_2$ | 10 + 10[2] | 16 | 61 |

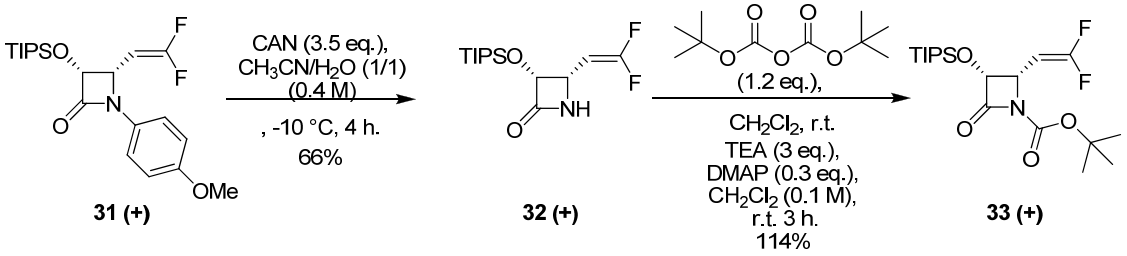
[1]Gas used to get rid off excess $O_3$ in the reaction
[2]A new bottle of dimethyl sulfide was purchased and used
[3]The amount of time allowed for $Me_2S$ to quench the reaction
[4]The solvent was changed according to the literature[21]

The fluorovinyl-*β*-lactam **30(+)** was obtained using a Wittig reaction. The reaction involved the *in situ* generation of (bromodifluoromethyl)triphenylphosphonium bromide by adding hexamethylphosphorous triamide to a solution of dibromodifluoromethane in THF under 0 $^{o}$C. The *in situ* mixture was then added to a mixture of zinc metal and **30(+)** solution in THF which was also cooled to 0 $^{o}$C. The presence of zinc metal promoted dehalogenation to form difluoromethylene triphenylphosphonium ylide ($Ph_3P^{+}$-$CF_2^{-}$) and zinc bromide ($ZnBr_2$). Reaction of the ylide with the aldehyde gave **31(+)** in good yield.



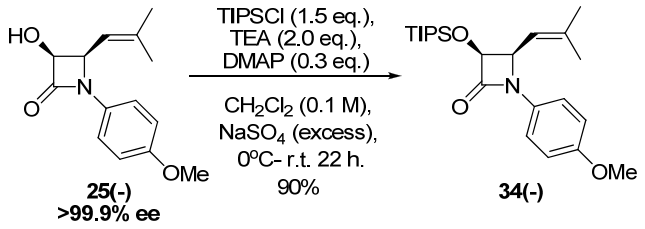

**Scheme 19:** Formation of 1-*p*-Methoxyphenyl-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [**31(+)**] via the Wittig reaction

The CAN-mediated deprotection of **31(+)** in acetonitrile and water under -10 $^{o}$C gave **32(+)** in good yield. The Boc protection on **32(+)** in the presence of TEA and DMAP, however, gave **33(+)** in an over quantitative yield (114%) (**Scheme 20**). The $^{1}$H-NMR showed the presence of *p*-methoxyphenyl group which may explain excess weight of the final product. Several attempts of purification were done by using column chromatography on silica gel, but they all failed. The final purification on alumina gel eventually caused the decomposition of **33(+)**, only 12 mg of the pure starting material **32(+)** was recovered.




**Scheme 20:** CAN-mediated deprotection followed by Boc-protection on **31(+)**

Highly enantiopure **25(-)** was obtained from enzymatic kinetic resolution. The TIPS protection on the alcohol **25(-)** gave **34(-)** in high yield (**Scheme 21**).




**Scheme 21:** TIPS-protection on high enantiomerically excess **25(-)**

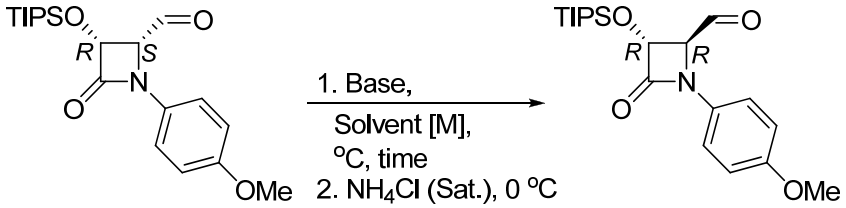
## § 1.2.3 Optimization of Epimerization reactions

### § 1.2.3.1 Epimerization using Treatment of Base

To initiate the epimerization reactions, experiments were carried out to find a suitable base for the deprotonation of the C4 proton of the aldehyde-bearing enantiomerically enriched *β*-

lactam **30(+)**, which was synthesized by a previous group member. As shown in **Table 2**, deprotonation with 1,8-diazabicycloundec-7-ene (DBU) gave *trans*-*β*-lactam to *cis*-*β*-lactam in a 7:3 ratio according to the crude $^{1}$H-NMR (entry 1). When NaH was applied, after 24 h the reaction gave a very messy result with neither *trans*- nor *cis*-*β*-lactam observed (entry 2). Another reaction with NaH was carried out, however, at lower concentration and shorter time (entry 3). The crude $^{1}$H-NMR again showed no *trans*- nor *cis*-*β*-lactam. In another reaction, LiHMDS was used for deprotonation. Unfortunately, after 2 h only a trace amount of *cis*-*β*-lactam was observed (entry 4). From this initial study, it was found that NaH and LiHMDS were not suitable for the deprotonation of **30(+)**. A moderately strong base, DBU, was found to be a potential base for the epimerization reaction.

**Table 2:** Epimerization reactions of **30(+)** using various bases




**30(+)** (*3R, 4S*) → **35** (*3R, 4R*)

| Entry | 30(+) (mg) | Base (eq.) | [M] | T. ($^{o}$C) | Time (h) | *Cis* 30(+)[1] | *Trans* 35[1] |
|---|---|---|---|---|---|---|---|
| 1 | 50 | DBU (2) | 0.44 | 22 | 16 | 29 | 71 |
| 2 | 50 | NaH (1.5) | 0.1 | 22 | 24 | N/O[2] | N/O |
| 3 | 50 | NaH (1.5) | 0.05 | 22 | 5 | N/O | N/O |
| 4 | 25 | LiHMDS (1.1) | 0.1 | -30 – 0 | 2 | trace | N/O |

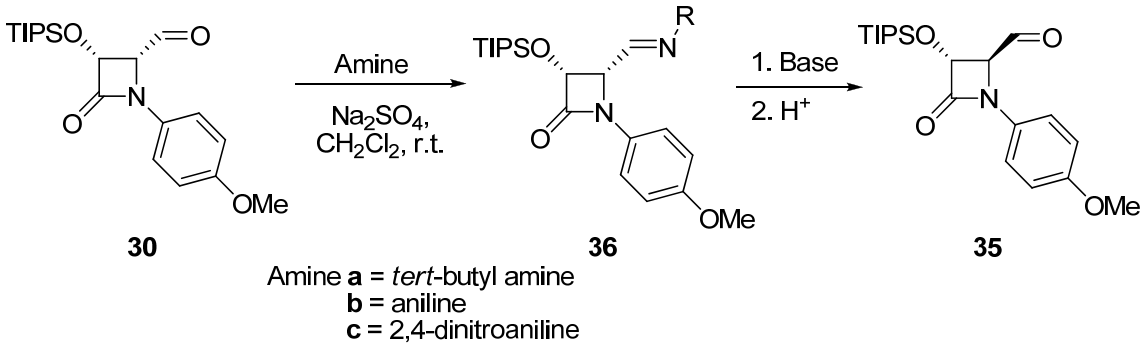
[1]The ratio of **30(+)** and **35** were determined by crude $^{1}$H-NMR based on H3, H4 or H5.
[2]N/O indicates not observed

## § 1.2.3.2 Epimerization using Formation of Schiff Base

In a parallel study, the possibility of epimerization through formation of a Schiff base was explored. As shown in **Table 3**, imine **36a** was first synthesized using *cis*-1-PMP-3-TIPSO-4-formylazetidin-2-one **30** in the presence of *t*-butyl amine and sodium sulfate at room temperature. Due to the expected instability of the imine species, no purification was done to the

crude. Minimum light exposure was also ensured while handling the reaction. The low boiling point of *t*-butyl amine (44-46 $^{o}$C) allowed the excess to be evaporated under reduced pressure, thus provided a clean imine which was carried to the next step. Upon treatment with 2 equivalents of DBU, followed by workup using saturated $NH_4Cl$, surprisingly, the crude $^{1}$H-NMR showed no hydrolysis at all (entry 1). Only clean imine was observed. Therefore, excess DBU was used to force the reaction (entry 2) affording a trace amount of *trans*-product (**35**) and some *cis*-product (**30**) in a 1:9 ratio. The ratio of unreacted imine (**36a**) to **30** was 2:1.

**Table 3:** Epimerization of **30** using the formation of Schiff base followed by hydrolysis




**30** **36** **35**

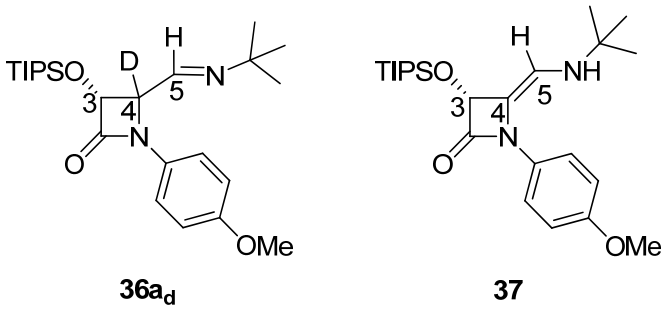
Amine **a** = *tert*-butyl amine
**b** = aniline
**c** = 2,4-dinitroaniline

| Entry | Imine | Base (eq.) | Time (h) | Workup | **30 : 35 : 36** ***cis*** **:** ***trans*** **: imine** **Crude $^{1}$H-NMR ratio[4]** |
|---|---|---|---|---|---|
| 1 | **36a** | DBU (2) | 16 | $NH_4Cl$ (sat.) | 0 : 0 : 1 |
| 2 | **36a** | DBU (7) | 12 | $NH_4Cl$ (sat.) | 9 : 1 : 18 |
| 3[1] | **36a** | LiHMDS (1.3+1.3) | 4.5 | $D_2O$ | - |
| 4 | **36a** | LiHMDS (1.3) | 6 | $H_2O$ | 1 : 0 : 7 |
| 5[2] | **36a** | LiHMDS (1.3) | 16 | 1N HCl | 4 : 0 : 1 |
| 6 | **36b** | DBU (2) | 14 | $NH_4Cl$ (sat.) | 0 : 0 : 1 |
| 7[3] | **36b** | LiHMDS (1.3) | 4 | $NH_4Cl$ (sat.) | - |

[1] An enamine formation as observed from the coupling in $^{1}$H-NMR
[2] Messy reaction, other side products were formed.
[3] Crude $^{1}$H-NMR showed messy peaks, no cis-, trans-, or imine β-lactams were observed
[4]The crude $^{1}$H-NMR ratio were determined based on H3, H4 or H5.

Disappointed by the result obtained from DBU, LiHMDS was used to treat **36a**. In entry 3, $D_2O$ was used to quench the reaction to examine if the deprotonation of **36a** at C4 occurred.

The $^1$H-NMR showed only a trace amount of **30**, and the majority of the crude was thought to be the non-hydrolyzed imine. $^1$H-NMR showed the disappearance of H4, which suggested that deprotonation by LiHMDS occurred as expected. Interestingly, further study on the crude $^1$H-NMR coupling suggested the possibility of enamine formation. The structure of the non-hydrolyzed imine was expected to be **36a$_d$**, while the possible structure of the enamine was speculated to be **37** with no substitution of deuterium (**Figure 8**). If the imine was **36a$_d$**, one would expect a triplet for H5 and H3 each coupled to 4D. The $^1$H-NMR of the experimental result, however, showed a doublet for both H3 and H5. Moreover, a broad bump was observed at around 4.6 to 4.8 ppm which may also suggest the possible enamine formation.




**36a$_d$** **37**

**Figure 8:** The expected enamine (**36a$_d$**) and the speculated enamine structures (**37**)

Thus, it was suggested that upon an acid catalyzed hydrolysis of the enamine the epimerization may occur before the hydrolysis. The major step is the proton transfer between the two intermediates **A** and **B** which are in equilibrium after the treatment of acid. If the proton approaches from the back, the epimerization may occur and **36a** may be obtained after hydrolysis. Otherwise, the *cis* product (**30**) would be formed. In order to test this hypothesis, a second reaction was carried out quenching with $H_2O$ instead of $D_2O$. Unfortunately, crude $^1$H-NMR showed no formation of enamine. Crude $^1$H-NMR showed a ratio of 1:7 for compounds *cis* **30** and **36a**. No *trans*-product was observed at all. Seeing that the imine was stable even upon the treatment of strong base, acidic conditions were attempted. For the first acid-catalyzed reaction, 1 N HCl was used to catalyze the hydrolysis reaction (entry 5). The reaction afforded **30** to **36a** in a 4:1 ratio. No *trans*-product was observed at all. The FIA of the crude also showed the presence of imine.

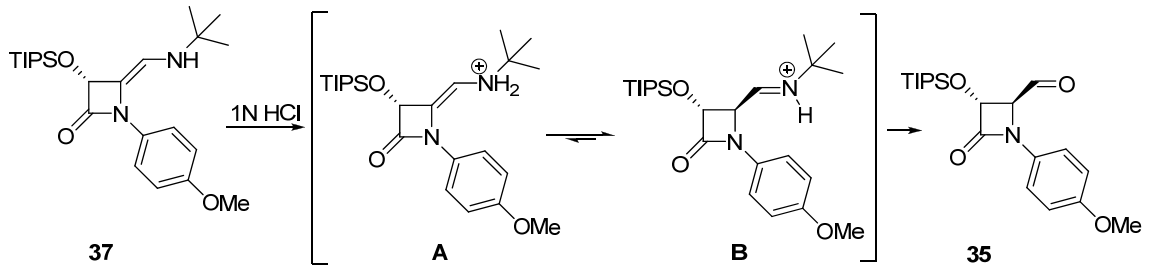



**Figure 9:** Proposed strategy for acid catalyzed hydrolysis of enamine (**37**)

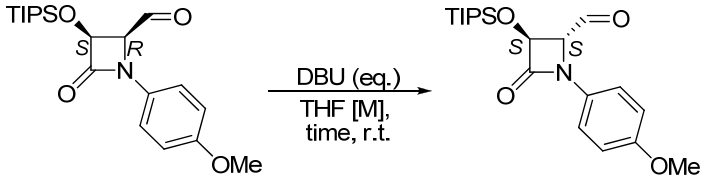
Since epimerization using Schiff base **36a** was unsuccessful, a new Schiff base was synthesized using aniline. Aniline is less bulky than the *t*-butyl amine thus it was used to help facilitate the hydrolysis of the imine, as the bulkiness from the *t*-butyl amine may have prevented hydrolysis. Unlike *t*-butyl amine, the equivalents of aniline were controlled to 1.1 equivalents since excess amount of aniline cannot be easily removed at this step. As shown in entry 6, after treating **36b** with DBU followed by saturated $NH_4Cl$, no reaction was observed. Therefore LiHMDS was used as base, the crude $^1$H-NMR showed to be messy and no *trans*- (**35**), **36b**, nor *cis*-*β*-lactam (**30**) was observed (entry 7). Finally, 2,4-dinitroaniline, a bulkier and more electron withdrawing moiety was used to synthesize **36c**. It was thought that 2,4-dinitroaniline may give better steric interaction with the TIPS moiety, thus forcing the imine into *trans* conformation and act as a better leaving group. Unfortunately, the reaction between 2,4-dinitroaniline and **30** did not proceed at all and no **36c** was obtained.

## § 1.2.3.3 Optimization of Epimerization Reactions using Treatment of Base

The use of DBU as a base gave optimal results for the epimerization of **30** into **35**, therefore other reaction conditions were optimized. The results are summarized in **Table 4**. For these reactions, *β*-lactam with low enantiomeric excess was used. Entries 1 to 3 showed that as the amount of DBU increases the ratio of **35** to **30** decreases. When comparing entries 1 and 4 to 6, the results showed that as the concentration increased the ratio of **35** to **30** increased. Due to the detection limit of the NMR, entries 6 and 7 were the reactions with the highest concentration 0.4 M and 1.0 M, respectively, gave essentially the same ratio. This may imply that the effect of high concentrations on the ratio of **35** to **30** eventually levels out. When the temperature effect was investigated, entries 1 and 8 showed that at higher temperature the ratio of **35** to **30** decreased significantly. It was hypothesized that the conditions in which the reaction was quenched could influence the epimerization. Thus, another reaction was carried out using

concentrated acetic acid as the quenching reagent (entry 9). This quenching procedure did not provide much difference as seen from entry 5 and entry 9. Finally, the reaction time was shortened to 8 hours (entry 10). Shortening the reaction time did not provide any improvement for the epimerization. In conclusion, as the amount of DBU increases the ratio of *trans* to *cis* product decreases. Moreover, high reaction concentration gave the highest ratio of **35** to **30**, whereas increasing the temperature decreased the ratio. Change of quenching reagent did not make much of a difference in the ratio. Whereas, shortening the time may increase the ratio slightly in a small scale, it may not be applicable to a larger scale reaction.

**Table 4:** Optimization for the epimerization reaction conditions of **30** using DBU

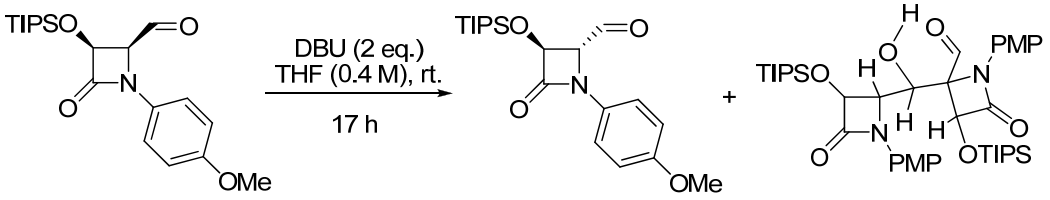



**30** (3*S*,4*R*) **35** (3*S*, 4*S*)

| Entry | 30 (mg) | DBU (eq.) | [M] | Time (h) | Work up[2] | 30[4] | 35[4] |
|---|---|---|---|---|---|---|---|
| a[1] | 50 | 2 | 0.44 | 16 | $NH_4Cl$ | 29 | 71 |
| 1 | 80 | 2 | 0.1 | 16 | $NH_4Cl$ | 22 | 78 |
| 2 | 25 | 4 | 0.1 | 16 | $NH_4Cl$ | 23 | 77 |
| 3 | 25 | 6 | 0.1 | 16 | $NH_4Cl$ | 29 | 71 |
| 4 | 25 | 2 | 0.025 | 18 | $NH_4Cl$ | 57 | 43 |
| 5 | 25 | 2 | 0.1 | 16 | $NH_4Cl$ | 43 | 57 |
| 6 | 25 | 2 | 0.4 | 16 | $NH_4Cl$ | 16 | 84 |
| 7 | 170 | 2 | 1 | 16 | $NH_4Cl$ | 20 | 80 |
| 8[3] | 80 | 2 | 0.1 | 16 | $NH_4Cl$ | 47 | 53 |
| 9 | 25 | 2 | 0.1 | 16 | Acetic acid (conc.) | 38 | 62 |
| 10 | 25 | 2 | 0.1 | 8 | $NH_4Cl$ | 38 | 62 |

[1]Entry a was the result obtained from **Table 2**
[2] Saturated $NH_4Cl$ was added dropwise to quench the reaction at 0 $^oC$
[3] The reaction was carried out at 60 $^oC$
[4]The ratio of **30** and **35** was determined by crude $^1$H-NMR based on H3, H4 or H5.

Purification was performed with column chromatography using alumina gel for the crude mixtures in **Table 4**. Despite several purification attempts, the reaction products were not isolated. In addition, a side product was observed for the epimerization of **30** made the isolation even more challenging. When comparing the peaks in $^{1}$H-NMR for collected crude of the three products, an extra aldehyde proton peak was observed near the aldehyde proton of both **30** and **35**. It was suspected that the side product may possess an aldehyde moiety. To characterize the structure of the side product, a reaction was carried out using **30(-)** (58 % *ee*) that would give predominantly the side product. This reaction was done in a 1g scale with higher concentration (0.4 M) in THF (**Scheme 22**). The purification of the products was performed and the isolation for **30**, **35** and the side product was again challenging. Fortunately, the side product did not decompose on silica gel, thus a mixture of the three products with predominantly the side product were purified using column chromatography on silica gel. An additional recrystallization from hexanes and ethyl acetate gave the side product (176 mg) in good purity. FIA, proton and carbon NMR all suggested a structure of **38**, the aldol product. The major formation of **38** could be explained because when the acidic H3 is deprotonated in the presence of base, an enolate is formed. In addition, under high concentration the intermolecular reaction with another aldehyde molecule is facilitated.



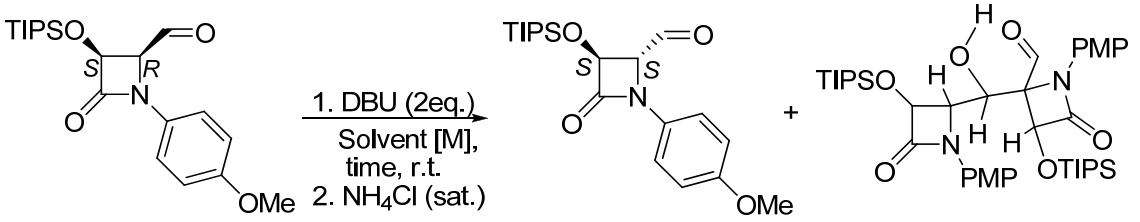

**30** (3*S*,4*R*) **35** (3*S*, 4*S*) **38**

**Scheme 22:** Epimerization reaction of **30** for the determination of side product

Since the side product was resolved, solvent effects of the epimerization reaction were examined to minimize side product formation (**Table 5**). The reaction with DMF gave a rather messy reaction although all three compounds were observed on the crude $^{1}$H-NMR (entry 1). Dichloromethane also gave the formation of **38**. The two repeating reactions in entries 3 and 4 with toluene showed no side product, although the ratio of *trans*- to *cis*-*β*-lactam was relatively low compared to THF. Furthermore, the reaction using THF and toluene in a 1:1 ratio was attempted to minimize side product formation while simultaneously improving the ratio of *cis*- to *trans*- (entry 5). As seen from the table, a higher ratio of **35** to **30** was observed along with a

trace amount of side product when THF and toluene were used as co-solvents. Therefore, it was decided that toluene should be used for the epimerization reaction. Remarkably, the side product formation is the highest when DMF was used in the reaction, and none for toluene. This result may be hypothesized due to the higher polarity of DMF compared to dichloromethane or toluene. Solvent with high polarity may drive the equilibrium towards deprotonation as compared to re-protonation because the solvent may better stabilize the enolate anion, thus facilitate the nucleophilic attack of another aldehyde.

**Table 5:** Solvent effect on the epimerization of **30**




**30** (3*S*,4*R*) | **35** (3*S*, 4*S*) | **38**

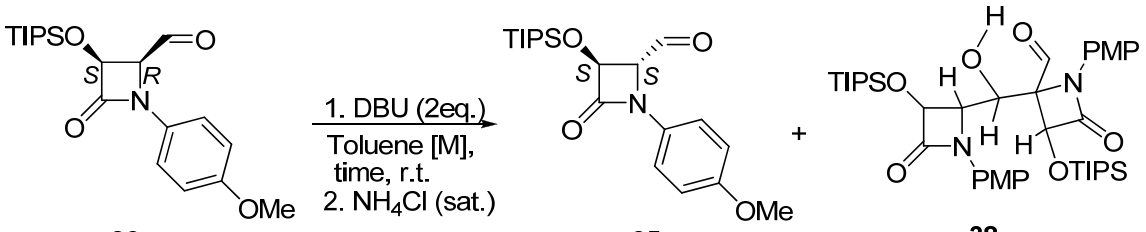
| Entry | 30(-) (mg) | Solv. | [M] | Time (h) | 30(-) (3*S*, 4*R*)[2] | 35 (3*S*, 4*S*)[2] | 38[2] |
|---|---|---|---|---|---|---|---|
| 1[1] | 25 | DMF | 0.1 | 16 | 40 | 46 | 14 |
| 2 | 25 | $CH_2Cl_2$ | 0.1 | 16 | 35 | 54 | 11 |
| 3 | 25 | Toluene | 0.1 | 16 | 52 | 48 | 0 |
| 4 | 25 | Toluene | 0.1 | 17 | 59 | 41 | 0 |
| 5 | 25 | THF:Toluene (1:1) | 0.1 | 18 | 38 | 62 | trace |

[1]Entry 1 has more than one side product formed, the crude $^1$H-NMR was messy
[2]The ratio of 30, 35 and 38 was determined by crude $^1$H-NMR based on H3, H4 or H5.

Furthermore, the concentration and reaction time of the epimerization reaction were investigated (**Table 6**). When comparing entries 1 to 2 and 6, the results shows that as the concentration increased, the ratio of **35** to **30** increased. At the same time, the side product also increased as with the case using THF. When the reaction time was prolonged, entries 1, 3 and 5 with 0.2 M showed a similar trend, however, with more side product formation. Entries 2 and 4 with only slightly higher concentration (0.25 M) showed more side product formation. Finally, when the reaction scale was increased with a decreased reaction time, side product formation was again observed (entry 7), but the ratio of **35** to **30** obtained is comparable to entry 1. In

conclusion, the optimized reaction condition using toluene at 0.2 M with careful control of reaction time should eliminate the formation of **38**. The resulting ratio of **35** to **30** might be low, however if a clean reaction could be carried out and if the products can be isolated successfully, the starting material can be recovered and be reused for another epimerization reaction.

**Table 6:** Optimization of epimerization reactions with toluene



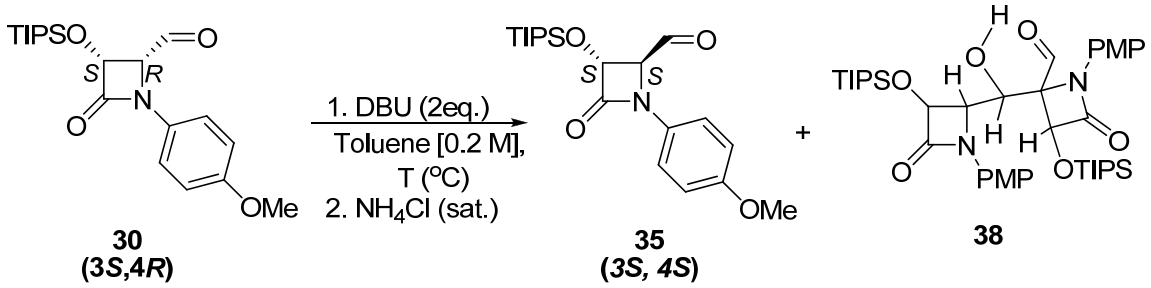

**30** (**3*S*,4*R***) **35** (***3S, 4S***) **38**

| Entry | 30(-) (mg) | [M] | Time (h) | 38[2] | 30(-) (3*S*, 4*R*)[2] | 35(-) (3*S*, 4*S*)[2] | *trans*/*cis* ratio |
|---|---|---|---|---|---|---|---|
| a[1] | 25 | 0.1 | 17 | 0 | 59 | 41 | 0.7 |
| 1 | 25 | 0.2 | 21.5 | 7 | 37 | 56 | 1.5 |
| 2 | 25 | 0.25 | 21.3 | 11 | 29 | 60 | 2.1 |
| 3 | 25 | 0.2 | 29 | 16 | 24 | 60 | 2.5 |
| 4 | 25 | 0.25 | 29 | 23 | 22 | 55 | 2.5 |
| 5 | 25 | 0.2 | 40 | 18 | 20 | 62 | 3.1 |
| 6 | 25 | 0.3 | 18 | 14 | 21 | 65 | 3.1 |
| 7 | 942.3 | 0.2 | 19.3 | 10 | 36 | 54 | 1.5 |

[1]Entry a was a result from **Table 5**
[2] The ratio of **30**, **35** and **38** was determined by crude $^1$H-NMR based on H3, H4 or H5.

The temperature effect of the epimerization reaction was also investigated. The results in table 7 showed that as the temperature increased the formation of the side product **38** increased, and the ratio of **35** to **30** decreased. The temperature at which the reaction was quenched was also critical to the ratio of **35** to **30**. The ratio of *trans* to *cis* is higher when the reaction was quenched at lower temperature as compared to at higher temperature. Further investigation on the temperature effect will be needed to draw further conclusion.

**Table 7:** Temperature effect of the epimerization reaction




**30** (**3*S*,4*R***) **35** (***3S, 4S***) **38**

| Entry | 30(-) (mg) | Temp. (°C) | Time (h) | Quenching Temp. (°C) | 38[2] | 30(-) (3*S*, 4*R*)[2] | 35(-) (3*S*, 4*S*)[2] | *trans*/*cis* ratio |
|---|---|---|---|---|---|---|---|---|
| 1 | 25 | 22 | 8 | 0 | 0 | 38 | 62 | 1.7 |
| 2 | 25 | 22 | 8 | 40 | 0 | 47 | 53 | 1.1 |
| 3 | 25 | 40 | 8 | 40 | 6 | 49 | 45 | 0.9 |

[1]Entry a was a result from Table 6
[2]The ratio of **30**, **35** and **38** was determined by crude $^1$H-NMR based on H3, H4 or H5.

## § 1.2.4 Isolation and Characterization of the *trans-β*-Lactams

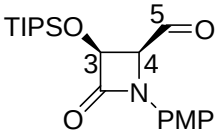
The epimerization reactions were done on a larger scale and isolations were performed to obtain the *trans-β*-lactams (**35**). However, the isolation still remained a challenge. Many epimerization reactions were carried out using **30** with low enantiopurity, however isolation of **35** with acceptable purity was unsuccessful. Interestingly, the $R_f$ for **30** is 0.66, while for **35** is 0.33. The big separation on alumina plate for the two spots was expected to provide easy separation for the two products; however the experimental results did not match this prediction. Somehow the **30** and **35** coeluted from the column. Several column chromatography conditions were examined. The speed of increment on the eluent, the eluent solvent, and the dimensions of the column were all investigated. Eventually some separation was achieved. The results are shown in **Table 8**. Unfortunately, the isolated yield did not reflect the amount of **35** that was formed. Several attempts on purifying **30(-)** to recover the starting material also failed due to the presence of the side product and impurities.

**Table 8:** Isolation of *cis*- and *trans*-*β*-lactams

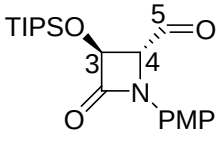
| Entry | 30(-) (mg) | ee % of 30(-) | [M] | Time (h) | 35(-) (3*S*, 4*S*) (mg)/ Isolated % yield | 30(-) (3*S*, 4*R*) (mg)/ Isolated % yield |
|---|---|---|---|---|---|---|
| 1 | 500 | 74 | 0.025 | 16 | 127/ 25 | 350 (crude) |
| 2 | 1000 | 74 | 0.2 | 17.5 | 344/34 | T/B |
| 3 | 659 | > 99.9 | 0.2 | 15.5 | 174/26 | 100/15 |

The $^{1}$H-NMR of the isolated *trans*-*β*-lactam (**35**) matched literature values.[20] The *J*-coupling of H3 and H4 is much larger in the *cis*-product (**30**) as compared to the **35**. Moreover, a rough calculation using Spartan showed that **35** is 5.9 kJ/mol more stable than **30**, thus it is the thermodynamically favorable product as expected.

**Table 9:** Characteristics of the *cis*- and *trans*-1-PMP-3-TIPSO-4-formylazetidin-2-one




**30 (-)**

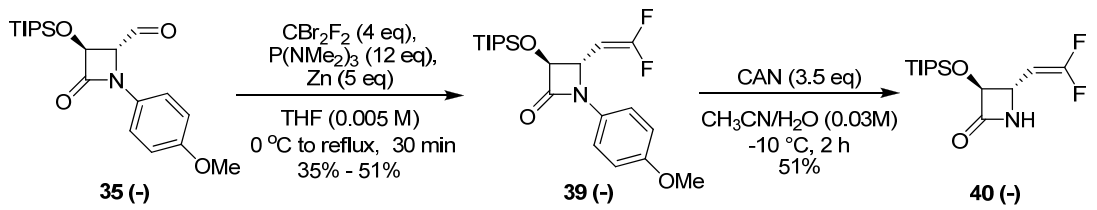



**35**

| Products | *J* H3-H4 (Hz) (Lit.)[20] | *J* H3-H4 (Hz) (Exp.) | H3 (ppm) | H4 (ppm) | H5 (ppm) | Heat of Formation[1] (kJ/mol) |
|---|---|---|---|---|---|---|
| *Cis* **30** | 5-6 Hz | 5.1 Hz | d (5.3) | dd (4.47) | d (9.77) | -135.051 |
| *Trans* **35** | 2 Hz | 2.1 Hz | d (5.04) | dd (4.37) | d (9.81) | -140.999 |

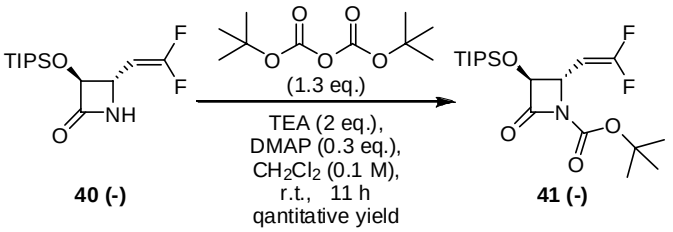
[1]The heat of formation was calculated by Spartan 08 V1.2.0: Energy, semi-empirical PM3

Once the *trans*-aldehyde **35** with high enantiopurity was isolated, it was subjected to the Wittig reaction to give **39** in moderate yield. A CAN-mediated deprotection gave **40(-)** in moderate yield (**Scheme 23**).




**Scheme 23:** Formation of (3*S*,3*S*)-3-Triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one (**40**)

Finally, the Boc-protection of **40(-)** gave **41(-)** in quantitative yield. **41** can be used as intermediate for the synthesis of *α*-hydroxy-*β*-amino acid.




**Scheme 24:** Formation of (3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one **41(-)**

## § 1.3 Conclusion

*β*-Lactams are very useful for the synthesis of various biologically relevant compounds. They can be used as intermediates for the facile syntheses of *α*-hydroxy-*β*-amino acids. As such, *β*-lactam **29(+)** with high enantiopurity was successfully synthesized. Since fluorine-containing molecules play an important role in biological system, fluorine-containing *β*-lactam **33(+)** with high enantiopurity was also synthesized. Unfortunately, it decomposed after the fifth purification on alumina gel. Two new protocols for the synthesis of *trans*- (**35**) from *cis*-*β*-lactams (**30**) were developed. The epimerization using Schiff base has failed. Hydrolysis of imine gave predominantly the *cis*-*β*-lactams (**30**). The epimerization using base, however, was successfully developed. DBU was found to be a promising base for the epimerization reaction. Toluene was also found to eliminate the formation of side product in small scale reaction. The reaction conditions were optimized. It was found that higher temperature decreased the ratio of **35** to **30** and at the same time increased the formation of the side product **38**. Higher reaction concentration, however, increased the ratio of **35** to **30** and also promoted the formation of the side product (**38**). Moreover, careful control of reaction time and reaction concentration should eliminate the formation of the side product. However, the isolation of **35** and **30** remained a challenge. Further investigation will be needed to allow a successful isolation of **35** and **30**. Remarkably, a novel fluoro-*β*-lactam was synthesized for (3*S*,4*S*)-1-(*tert*-butoxycarbonyl)-3-

triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one (**41)**, the enantiomeric excess can be determined after its enantiomer is also synthesized. This novel fluorine-containing *β*-lactam can be used for the synthesis of *α*-hydroxy-*β*-amino acids or be incorporated into other biologically active compounds to investigate its potency.

## § 1.4 Experimental Section

**General Information:**

All chemicals were obtained from either Sigma-Aldrich, Fisher Scientific or VWR International, and used as received unless otherwise noted. All reactions were carried out under nitrogen in oven dried glassware using standard Schlenk techniques unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using E. Merck 60F254 precoated silica gel plates and alumina plate depending on the compounds. Dry solvents were dried using the PURESOLV system (Inovatative Technologies, Newport, MA). Tetrahydrofuran was freshly distilled from sodium metal and benzophenone. Dichloromethane was also distilled immediately prior to use under nitrogen from calcium hydride. Toluene was also distilled immediately prior to use under nitrogen from calcium hydride. Yields refer to chromatographically and spectroscopically pure compounds. Flash chromatography was performed with the indicated solvents using Fisher silica gel (particle size 170-400 Mesh).$^{1}$H, $^{13}$C and $^{19}$F NMR data were obtained with either a 300 MHz Varian Gemni 2300 (75 MHz $^{13}$C, 121 MHz $^{19}$F) spectrometer, a 400 MHz Varian INOVA 400 (100 MHz $^{13}$C) spectrometer or a 500 MHz Varian INOVA 500 (125 MHz $^{13}$C) using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts (δ) are reported in ppm and standardized with solvent as internal standard based on literature reported values.[29] Normal phase analytical high performance liquid chromatography (HPLC) was performed with a Shimadzu LC-2010AHT system using a CHIRALCEL®OD-H column, employing isopropanol/hexanes (15/85 and 10/90 depending on the compounds) as the solvent system with a flow rate of 0.6 mL/min. Purity was determined by an Agilent 1100 series HPLC assembly. The analytical conditions was used and noted as a part of the characterization data for new compounds. HPLC: Kinetex C18, 2.6 μm, 100 A (pore size), 2 x 100 mm column, solvent A of $H_2O$/ACN, 95:5 (10 mM ammonium acetate, pH 6.5), solvent B of $H_2O$/ACN, 5:95 (10 mM ammonium acetate, pH 6.5), temperature of 35 $^{o}$C, flow rate of 0.4 mL/min, $t$ = 0-30 min, gradient of 5-95% solvent B. Melting points were measured on a Thomas

Hoover Capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. The ozonolysis reaction was performed using ozone generator from Ozone Services, A DIVISION OF YANCO INDUSTRIES LTD. (Ozone dial = 8, flow of oxygen = 1/8 lpm).

**Experimental Procedure:**

***N*-(4-Methoxyphenyl)-3-methyl-2-butenaldimine (23)** [26]

To a solution of recrystallized *p*-anisidine (9.5 g, 77 mmol) and excess anhydrous $Na_2SO_4$ (38 g, 269 mmol) dissolved in $CH_2Cl_2$ (150 mL) was added 3-methylbut-2-enal (7.8 g, 93 mmol). The reaction was monitored using TLC. After 3 h at room temperature the solvent was evaporated to yield **2-1**, as dark-red viscous oil, which was then used immediately in the subsequent step without further purification: $^1$H NMR (300 MHz, $CDCl_3$) δ 2.03 (d, 3H, *J* = 0.9 Hz), 2.09 (d, 3H, *J* = 0.9 Hz), 3.89 (s, 3H), 6.32 (d, 1H, *J* = 9.3 Hz), 6.93-6.99 (m, 2H), 7.19-7.22 (m, 2H), 8.46 (d, 1H, *J* = 9.6 Hz). All data are in agreement with literature values. [26]

**(±)-1-(4-Methoxyphenyl)-3-acetoxyl-4-(2-methylprop-1-enyl)azetidin-2-one (24)** [26]

To a solution of crude **23** in $CH_2Cl_2$ (260 mL), cooled to -78 ˚C and maintained for at least 30 min was added a cooled solution of TEA (16.0 g, 159 mmol) followed by the slow dropwise addition of acetoxyacetyl chloride (14.1 g, 103 mmol). The -78 ˚C temperature of the mixture was maintained for 7 h. Then, the mixture was allowed to warm to room temperature over a period of 9 h. The reaction was monitored using TLC. Upon completion, the reaction was quenched with saturated $NH_4Cl$. The organic layer was washed three times with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (5% to 8% to 10% to 13% to 20% to 28% ethyl acetate in hexanes). A brown solid was obtained (16.344 g). About half of the brown solid (8.150 g) was further purified by recrystallization using hexanes and ethyl acetate to yield racemic **24** (5.822 g, 20.12 mmol), as a light yellow-brown solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.79 (d, 3H, *J* = 1.5 Hz), 1.82 (d, 3H, *J* = 0.9 Hz), 2.11 (s, 3H), 4.97 (dd, 1H, *J* = 9.6, 4.8 Hz), 5.10-5.15 (m, 1H), 5.79 (d, 1H, *J* = 4.8 Hz), 6.83-6.88 (m, 2H), 7.29-7.24 (m, 2H). All data are in agreement with literature values. [26]

**Enantioselective Enzymatic Resolution of β-lactam 24** [27, 30]

To a solution of **24** (8.19 g, 28.3 mmol) in 0.2 M sodium phosphate buffer (pH = 7.5) (400 mL) with 10 volume % acetonitrile (40 mL) at 70 °C was added PS-Amano Lipase (1.67 g). After the addition, the mixture was stirred vigorously with a mechanical stirrer. The reaction was monitored using TLC and $^1$H-NMR, looking for 50% conversion of the acetate moiety to the hydroxyl moiety. Upon 50% conversion, the remaining Lipase was filtered off using vacuum filtration and washed with $CH_2Cl_2$. The organic layer was collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (hexanes to 40% ethyl acetate in hexanes). The same procedures were repeated, however, with much lower temperature (35 $^o$C) until **24(+)** was obtained. After 13 days, **24(+)** was obtained as a white solid (3.01 g, 15 % in three steps) with >99.9% ee: m.p. = 112-113 $^o$C (lit. 107-109 $^o$C).[30] The enantiomeric purity was determined by using normal phase analytical high performance liquid chromatography (HPLC) with a Shimadzu LC-2010AHT system using a CHIRALCEL®OD-H column, employing isopropanol/hexanes (15/85) as the solvent system with a flow rate of 0.6 mL/min. The alcohol **25(-)** (3.04 g, 43% in three steps) was also obtained in this reaction as a white solid: m.p. = 160-162 $^o$C; $[\alpha]^{22}_D$ -123 (*c* 0.22, $CH_2Cl_2$). For **24(+)**, $^1$H NMR (300 MHz, $CDCl_3$) δ 1.79 (d, 3H, *J* = 1.5 Hz), 1.82 (d, 3H, *J* = 0.9 Hz), 2.12 (s, 3H), 3.78 (s, 3H), 4.97 (dd, 1H, *J* = 9.6, 4.8 Hz), 5.11-5.15 (m, 1H), 5.80 (d, 1H, *J* = 4.8 Hz), 6.83-6.88 (m, 2H), 7.29-7.34 (m, 2H). All data are in agreement with literature values. [26]

**(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-hydroxy-4-(2-methylprop-1-enyl)azetidin-2-one [26(+)]**[26-27]

To a solution of **24(+)** (3.00 g, 10.4 mmol) in THF (104 mL) at 0°C was added 1 M NaOH (104 mL). The reaction mixture was stirred, allowed to warm to room temperature and monitored using TLC. The reaction was complete after 40 min. The reaction was quenched with saturated $NH_4Cl$ and extracted with $CH_2Cl_2$. The organic layer was collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to yield **26(+)** (2.49 g, 97%), as a white solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.86 (d, 6H, *J* = 0.9 Hz), 3.78 (s, 3H), 4.89 (dd, 1H, *J* = 9.0, 5.1 Hz), 5.03 (d, 1H, *J* = 5.4 Hz), 5.24-5.28 (m, 1H), 6.82-6.87 (m, 2H), 7.29-7.34 (m, 2H). All data are in agreement with literature values. [26] The enantiomeric purity was determined by using normal phase analytical high performance liquid chromatography (HPLC) with a Shimadzu LC-

2010AHT system using a CHIRALCEL®OD-H column, employing isopropanol/hexanes (15/85) as the solvent system with a flow rate of 0.6 mL/min.

**(3*R*,4*S*)-1-*p*-Methoxyphenyl-3-triisopropylsiloxy-4-(2-methylpropen-2-yl)azetidin-2-one [27(+)]** [28]

To a solution of **26(+)** (3.00 g, 12.1 mmol) and DMAP (0.445 g, 3.64 mmol) in $CH_2Cl_2$ (120 mL) at 0°C was added TEA (2.46 g, 24.2 mmol) followed by the dropwise addition of TIPSCl (3.50 g, 18.2 mmol). The reaction mixture was stirred at room temperature and monitored using TLC. The reaction was complete after 20 h and then it was quenched with saturated $NH_4Cl$ and extracted with $CH_2Cl_2$. The organic layer was collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (hexanes to 30% to 45% ethyl acetate in hexanes) to yield **27(+)** (3.81 g, 77%), as a white solid: m.p. = 94-95 $^oC$; $[\alpha]^{22}_D$ +63 (*c* 0.49, $CH_2Cl_2$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.03-1.20 (m, 21H), 1.79 (d, 3H, *J* = 1.5 Hz), 1.85 (d, 3H, *J* = 1.5 Hz), 3.77 (s, 3H), 4.81 (dd, 1H, *J* = 10.2, 4.8 Hz), 5.05 (d, 1H, *J* = 4.8 Hz), 5.31-5.35 (m, 1H), 6.81-6.86 (m, 2H), 7.29-7.34 (m, 2H). All data are in agreement with literature values. [26] The enantiomeric purity was determined by using normal phase analytical high performance liquid chromatography (HPLC) with a Shimadzu LC-2010AHT system using a CHIRALCEL®OD-H column, employing isopropanol/hexanes (10/90) as the solvent system with a flow rate of 0.6 mL/min.

**(3*R*,4*S*)-3-Triisopropylsilyloxy-4-(2-methylpropen-2-yl)azetidin-2-one [28(+)]** [28]

To a solution of **27(+)** (800 mg, 1.98 mmol) in acetonitrile (33 mL) at -10 °C was added a solution of cerium ammonium nitrate (3.80 g, 6.93 mmol) in $H_2O$ (35 mL) dropwise using an addition funnel. The reaction temperature of -10 °C was maintained throughout the reaction using dry ice and acetone. The reaction was monitored using TLC. After completion, the resulting solution was quenched with ethyl acetate. The resulting solution was washed with $H_2O$, then with sodium bisulfite. The organic layer was collected, dried over $MgSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (10% to 20% ethyl acetate in hexanes) to yield **28(+)** (471 mg, 80% yield), as a white solid: m.p. = 89-90 $^oC$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.02-1.15 (m, 21H), 1.69 (d, 3H, *J* =

1.5 Hz), 1.76 (d, 3H, *J* = 1.5 Hz), 4.44 (dd, 1H, *J* = 9.6, 4.8 Hz), 4.99 (dd, 1H, *J* = 4.8, 2.4 Hz), 5.29-5.35 (m, 1H), 5.34 (s, 1H). All data are in agreement with literature values.[26]

**(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-triisopropylsiloxy-4-(2-methylpropen-2-yl)azetidin-2-one [29(+)]**[28]

To a solution of **28(+)** (463 mg, 1.56 mmol), DMAP (57.5 mg, 0.467 mmol) and TEA (315 mg, 3.11 mmol) in $CH_2Cl_2$ (9.5 mL) at 0 °C was added di-*tert*-butyl dicarbonate.(339 mg, 1.56 mmol) in $CH_2Cl_2$ (9.5 mL). The reaction mixture was stirred at room temperature and monitored using TLC. After 8 h, the reaction was quenched with saturated $NH_4Cl$ and extracted with ethyl acetate. The organic layer was collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (hexanes to 5% to 8% ethyl acetate in hexanes) to yield **29(+)** (619 mg, quant. yield), as a colorless oil: $[\alpha]^{22}_D$ +35 (*c* 1.2, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.01-1.11 (m, 21H), 1.47 (s, 9H), 1.76 (d, 3H, *J* = 1.2 Hz), 1.79 (d, 3H, *J* = 1.2 Hz), 4.75 (dd, 1H, *J* = 9.9, 5.7 Hz), 4.97 (d, 1H, *J* = 5.7 Hz), 5.26-5.30 (m, 1H). All data are in agreement with literature values. [26]

**1-(4-Methoxyphenyl)-3-triisopropylsiloxyazetidine-2-one-4-carbaldehyde [(+) and (-) 30]** [21]

Nitrogen was bubbled into a solution of **27(-)** (5.33 g, 13.2 mmol) in $CH_2Cl_2$/MeOH (128 mL/64 mL) for 5 min. The solution was cooled to -78 $^o$C. Ozone was then bubbled into the solution for 2 h until the color of the solution turned blue. Nitrogen was bubbled into the reaction mixture again until the blue color disappears. Dimethylsulfide was added and the mixture was warmed to room temperature. The reaction mixture was stirred for another 4 h. The solvent was concentrated *in vacuo*. The resulting crude product was purified by column chromatography on alumina gel with increasing polarity of eluent (hexanes to 5% to 10% to 24% to 30% ethyl acetate in hexanes) to yield **30(-)** (2.20 g, 61% yield), as a white solid: m.p. = 72-81 $^o$C; $[\alpha]^{22}_D$ -152 (*c* 0.29, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.04-1.23 (m, 21H), 3.79 (s, 3H), 4.47 (dd, 1H, *J* = 5.4, 4.2 Hz), 5.30 (d, 1H, *J* = 5.1 Hz), 6.84-6.89 (m, 2H), 7.24-7.28 (m, 2H), 9.77 (d, 1H, *J* = 3.9 Hz). All data are in agreement with literature values.[21] The enantiomeric purity was determined by using normal phase analytical high performance liquid chromatography (HPLC)

with a Shimadzu LC-2010AHT system using a CHIRALCEL®OD-H column, employing isopropanol/hexanes (15/85) as the solvent system with a flow rate of 0.6 mL/min.

Using **27(+)** (950 mg, 2.35 mmol) following the same procedure as above, **30(+)** was obtained (539 mg, 61%, yield) as a white solid: m.p. = 82-85 $^{o}$C (lit. 78-80 $^{o}$C); $[\alpha]^{22}_{D}$ +159 (*c* 0.85, $CH_2Cl_2$); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.07-1.23 (m, 21H), 3.79 (s, 3H), 4.47 (dd, 1H, *J* = 5.1, 4.5 Hz), 5.30 (d, *J* = 5.1 Hz), 6.85-6.89 (m, 2H), 7.24-7.28 (m, 2H), 9.77 (d, 1H, *J* = 3.9 Hz). All data are in agreement with literature values except for the melting point.[21]

**(3*R*,4*S*)-1-*p*-Methoxyphenyl-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [31(+)][22]**

In a two-necked, round-bottomed flask, to a solution of **30(+)** (200 mg, 0.530 mmol) in THF (60 mL) was added Zn (173 mg, 2.65 mmol) at 0 $^{o}$C. In another flask, to a solution of dibromodifluoromethane (445 mg, 2.12 mmol) in THF (40 mL) at 0 $^{o}$C was added hexamethylphosphorous triamide (1.04 g, 6.36 mmol) to form a white precipitate. To the suspension in the two-necked, round-bottomed flask was added the white precipitate in a successive manner. The ice bath was removed immediately and the mixture was allowed to reflux for 30 min. After cooling to room temperature, the solution was filtered over celite and the precipitate was washed with ethyl acetate. The solution was washed with brine, dried over sodium sulfate and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (hexanes to 10% ethyl acetate in hexanes) to yield **31(+)** (171 mg, 78% yield), as a yellow solid: m.p. = 48-51 $^{o}$C; $[\alpha]^{21}_{D}$ +58 (*c* 0.40, $CH_2Cl_2$); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.05-1.25 (m, 21H), 3.79 (s, 3H), 4.54 (ddd, 1H, *J* = 9.9, 5.1, 2.1 Hz), 4.80-4.86 (m, 1H), 5.14 (d, 1H, *J* = 4.8 Hz), 6.85-6.89 (m, 2H), 7.29-7.35 (m, 2H). $^{19}$F (121 MHz, $CDCl_3$) δ 80.7 (d, 1F, 14.9 Hz), 86.3 (dd, 1F, 10.9, 14.0). All data are in agreement with literature values.[22]

**(3*R*,4*S*)-3-Triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [32(+)][22]**

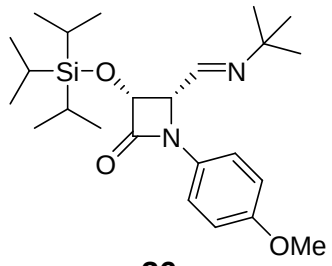
To a solution of **31(+)** (137 mg, 0.333 mmol) in acetonitrile (6.55 mL) at -10 °C was added cerium ammonium nitrate (809 mg, 1.17 mmol) in $H_2O$ (6.55 mL) dropwise using an addition funnel. The reaction temperature of -10 °C was maintained throughout the reaction. The reaction was monitored using TLC. After 4 h, the reaction mixture was extracted with ethyl

acetate. The resulting solution was washed with $H_2O$ followed by sodium bisulfite and then brine. The organic layer was collected, dried over $MgSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on silica gel with increasing polarity of eluent (hexanes to 5% to 10% ethyl acetate in hexanes) to yield **32(+)** (67.3 mg, 66% yield) as yellow oil: $[\alpha]^{21}_D$ +42 (*c* 1.2, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.05-1.25 (m, 21H), 4.44-4.57 (m, 2H), 5.04 (dd, 1H, *J* = 4.2, 2.4 Hz), 6.27 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 12.0, 17.8 (t, 2.3 Hz), 50.4 (d, 4.5 Hz), 79.3 (d, 13.7 Hz), 157.6 (t, 289.9 Hz), 169.3. $^{19}$F (121 MHz, $CDCl_3$) δ 82.3 (d, 1F, 14.9 Hz), 87.5 (m, 1F). All data are in agreement with literature values.[22]

**(3*R*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [33(+)][22]**

To a solution of **32(+)** (50 mg, 0.16 mmol), DMAP (58 mg, 0.05 mmol) and TEA (49.9 mg, 0.494 mmol) in $CH_2Cl_2$ (1.1 mL) at 0 °C was added di-*tert*-butyl dicarbonate (90 mg, 0.20 mmol) dissolved in $CH_2Cl_2$ (1.0 mL). The reaction mixture was stirred at room temperature and monitored using TLC. After 3 h the reaction was complete and it was quenched with saturated $NH_4Cl$ and extracted with ethyl acetate. The organic layer was collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo.* Purification was done using column chromatography on silica gel with increasing polarity of eluent (hexanes to 5% to 10% ethyl acetate in hexanes) to yield **33(+)** (76 mg, 114% yield) as light yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.04-1.20 (m, 21H), 1.50 (s, 9H), 4.51 (ddd, 1H, *J* = 23.7, 9.9, 1.5 Hz), 4.75 (dddd, 1H, *J* = 0.6, 2.1, 5.7, 9.9 Hz), 5.04 (d, 1H, *J* = 5.4 Hz). All data are in agreement with literature values.[22] Attempted purification on alumina gel caused decomposition of the compound.

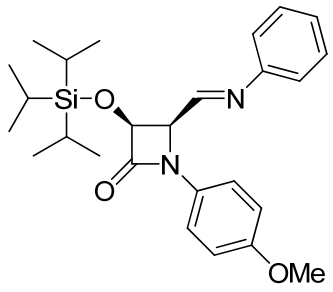
**(3*R*,4*S*)-4-(*tert*-Butyliminomethyl)-1-(4-methoxyphenyl)-3-triisopropylsilyoxyazetidin-2-one (36a)**




**36a**

To a solution of **30(+)** (174 mg, 0.462 mmol) and disodium sulfate (459 mg, 3.24 mmol) in $CH_2Cl_2$ (9.2 mL) was added dropwise *t*-butylamine (0.10 mL). After 10 h, excess amine was removed in *vacuo* to give **36a** (quantitative yield) as a waxy yellow solid: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.07-1.17 (m, 21 H), 1.21 (s, 9H), 3.77 (s, 3H), 4.62 (dd, 1H, *J* = 7.5, 4.8 Hz), 5.19 (d, 1H, *J* = 5.4 Hz), 6.81-6.85 (m, 2H), 7.33-7.37 (m, 2H), 7.67 (d, 1H, *J* = 7.2 Hz).

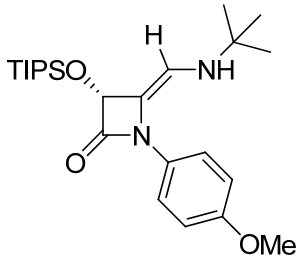
**(3*S*,4*R*)-1-(4-Methoxyphenyl)-4-(*N*-phenylcarboximidoyl)-3-triisopropylsilyoxyazetidin-2-one (36b)**




**36b**

The same procedure for **36a** was used to give **36b** (quantitative yield) as yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.08-1.26 (m, 21H), 3.78 (s, 3H), 4.83 (dd, 1H, *J* = 7,2, 4.8 Hz), 5.31 (d, 1H, *J* = 4.8 Hz), 6.84-6.89 (m, 2H), 7.09-7.13 (m, 2H), 7.21-7.24 (m, 1H), 7.33-7.45 (m, 4H).

**37 (reaction crude)**




**37**

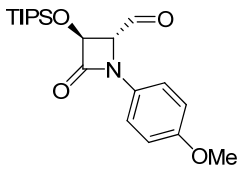
To a solution of **36a** (25 mg, 0.06 mmol) in THF (0.6 mL) was added LiHMDS (1 M) (0.08 mL), dropwise at -40 $^o$C. The reaction mixture was stirred for 1 h and allowed to warm up to -10 $^o$C. Then the reaction mixture was stirred for another 1.5 h at 0 $^o$C. LiHMDS (1M) (0.08 mL) was added dropwise to the solution at 0 $^o$C and stirred at room temperature for another 2 h. The reaction was quenched by dropwise addition of $D_2O$ and extracted with $CH_2Cl_2$. The organic

layer was collected, washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*.Crude $^1$H NMR (300 MHz, $CDCl_3$) δ 1.05-1.15 (m, 21H), 1.25 (s, 9H), 3.77 (s, 3H), 5.22 (d, 1H, *J* = 5.1 Hz), 6.82-6.86 (m, 2H), 7.34-7.39 (m, 2H), 7.70 (d, 1H, *J* = 7.7 Hz).

**General reaction procedure for the epimerization of 1-(4-methoxy-phenyl)-3-triisopropylsiloxyazetidin-2-one-4-carbaldehyde (30) using a base:**

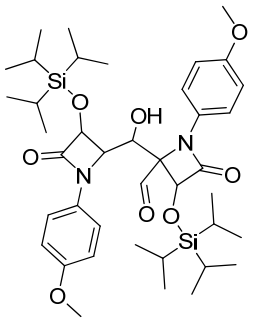
To a solution of **30** in toluene (0.2 M) was added 1,8-diazabicyclo[5.4.0]undec-7-ene in toluene, dropwise. The reaction mixture was stirred at room temperature. After the reaction was complete, the flask was cooled to 0 $^o$C, quenched by dropwise addition of saturated $NH_4Cl$, and extracted with ethyl acetate. The organic layer was collected, washed with brine, dried over anhydrous $NaSO_4$, and concentrated *in vacuo*. Purification was done using column chromatography on alumina gel.

**(3*S*,4*S*)-1-(4-Methoxyphenyl)-3-triisopropylsiloxy-4-formylazetidin-2-one [35(-)]**




Purification was done using column chromatography on alumina gel with increasing polarity of eluent (hexanes to 10% to 15% to 20% to 25% to 33% ethyl acetate in hexanes) to give **35** as yellow oil: $[\alpha]^{21}_D$ -13 (*c* 0.15, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.07-1.29 (m, 21H), 3.78 (s, 3H), 4.37 (dd, 1H, *J* = 4.2, 1.8 Hz), 5.04 (d, 1H, *J* = 1.8 Hz), 6.82-6.89 (m, 2H), 7.21-7.25 (m, 2H), 9.81 (d, 1H, *J* = 3.9 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 11.9, 17.7, 55.6, 68.7, 78.8, 114.7, 118.3, 130.7, 156.9, 163,8, 197.8. HPLC: 25.16 min.

**Aldol adduct [38]**




$C_{40}H_{62}N_2O_8Si_2$
Mol. Wt.: 755.1

White solid; m.p. = 165-167 $^{o}$C; $^{1}$H NMR (300 MHz, $CDCl_3$) δ 0.916-1.024 (m, 42H), 2.87 (d, 1H, *J* = 5.1 Hz), 3.77 (s, 3H), 3.79 (s, 3H), 4.21 (dd, 1H, *J* = 6.9, 1.2 Hz), 4.85 (d, 1H, *J* = 1.5 Hz), 4.95-5.00 (m, 1H), 5.10 (s, 1H), 6.82-6.88 (m, 4H), 7.20-7.23 (m, 2H), 7.49-7.52 (m, 2H), 9.83 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 11.8, 12.3, 17.7, 17.8, 17.9, 55.6 (t, 3.1 Hz), 63.9 (6.1 Hz), 68.9 (d, 8.3 Hz), 76.1, 79.8(d, 9.8 Hz), 81.2 (d, 9.9 Hz), 114.6 (d, 10.6 Hz), 120.5, 120.6, 130.3, 130.6, 157.2, 157.4, 164.2, 165.5, 200.4, 200.4; MS (ESI) *m*/*z* 755 $(M)^+$, 756 $(M+1)^+$. HPLC: 31.93 min, purity 77%; 32.99 min, 16%.

**(3*S*,4*S*)-1-4-Methoxyphenyl-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [39(-)]**

The same procedure for **31(+)** was employed. Compound **35** (154 mg, 0.408 mmol) was used to give **39(-)** (85 mg, 51% yield), as a white solid: m.p. = 75-78 $^{o}$C; $[\alpha]^{21}_{D}$ -27 (*c* 0.29, $CH_2Cl_2$); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.08-1.17 (m, 21H), 3.79 (s, 3H), 4.22-4.50 (m, 2H), 4.76 (d, 1H, *J* = 1.5 H), 6.87-6.89 (m, 2H), 7.27-7.31 (m, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 11.9, 17.6, 55.4, 57.1 (d, 6.1 Hz), 77.3 (dd, 22.9, 16.8 Hz), 82.3, 114.5, 118.6, 130.3, 156.5, 157.5 (t, 292.3 Hz), 164.2; $^{19}$F (121 MHz, $CDCl_3$) δ -80.9 (d, 1F, 13.4 Hz), -84.1 (ddd, 1F, 13.1, 9.8, 1.3 Hz). HPLC: 28.04 min, purity 78%.

**(3*S*,3*S*)-3-Triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [40(-)]**

The same procedure for **(+) 2-11** was employed. Compound **39(-)** (152 mg, 0.369 mmol) was used to give **40** (58 mg, 51% Yield), as a waxy yellow solid; $[\alpha]^{21}_{D}$ -18 (*c* 0.54, $CH_2Cl_2$); $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.05-1.16 (m, 21H), 4.15 (dd, 1H, *J* = 8.7, 1.2 Hz), 4.36 (ddd, 1H, *J*

= 23.4, 9.6, 1.5 Hz), 4.64 (t, 1H, *J* = 1.8 Hz), 6.37 (s, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 12.1, 17.8, 53.6 (d, 6.6 Hz), 78.6 (dd, 22.9 Hz, 16.8 Hz), 84.0, 157.3 (t, 290.9 Hz), 168.6; $^{19}$F (121 MHz, $CDCl_3$) δ -82.8 (d, 1F, 14.2 Hz), -85.4 (dd, 1F, 14.2 Hz, 10.2 Hz). HPLC: 22.22 min, purity 58%.

**(3*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-3-triisopropylsiloxy-4-(2,2-difluoroethenyl)azetidin-2-one [41(-)]**

The same procedure for **(+) 2-12** was employed. Compound **40(-)** (52 mg, 0.17 mmol) was used to give **41(-)** (69 mg, quantitative yield), as clear oil; $[\alpha]^{21}_{D}$ -11 (*c* 0.38, $CH_2Cl_2$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.04-1.15 (m, 21H), 1.49 (s, 9H), 4.29-4.39 (m, 2H), 4.63 (d, 2.1 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) 11.9, 17.7, 28.1, 56.8 (d, 7.1 Hz), 77.0 (dd, 16.6, 8.6 Hz), 82.1, 83.9, 147.9, 158.1 (dd, 290.3, 292.8 Hz), 165.2; $^{19}$F (121 MHz, $CDCl_3$) δ 84.1 (d, 1F, 5.4 Hz), 84.2 (m, 1F). HPLC: 28.39 min, purity 72%.

## References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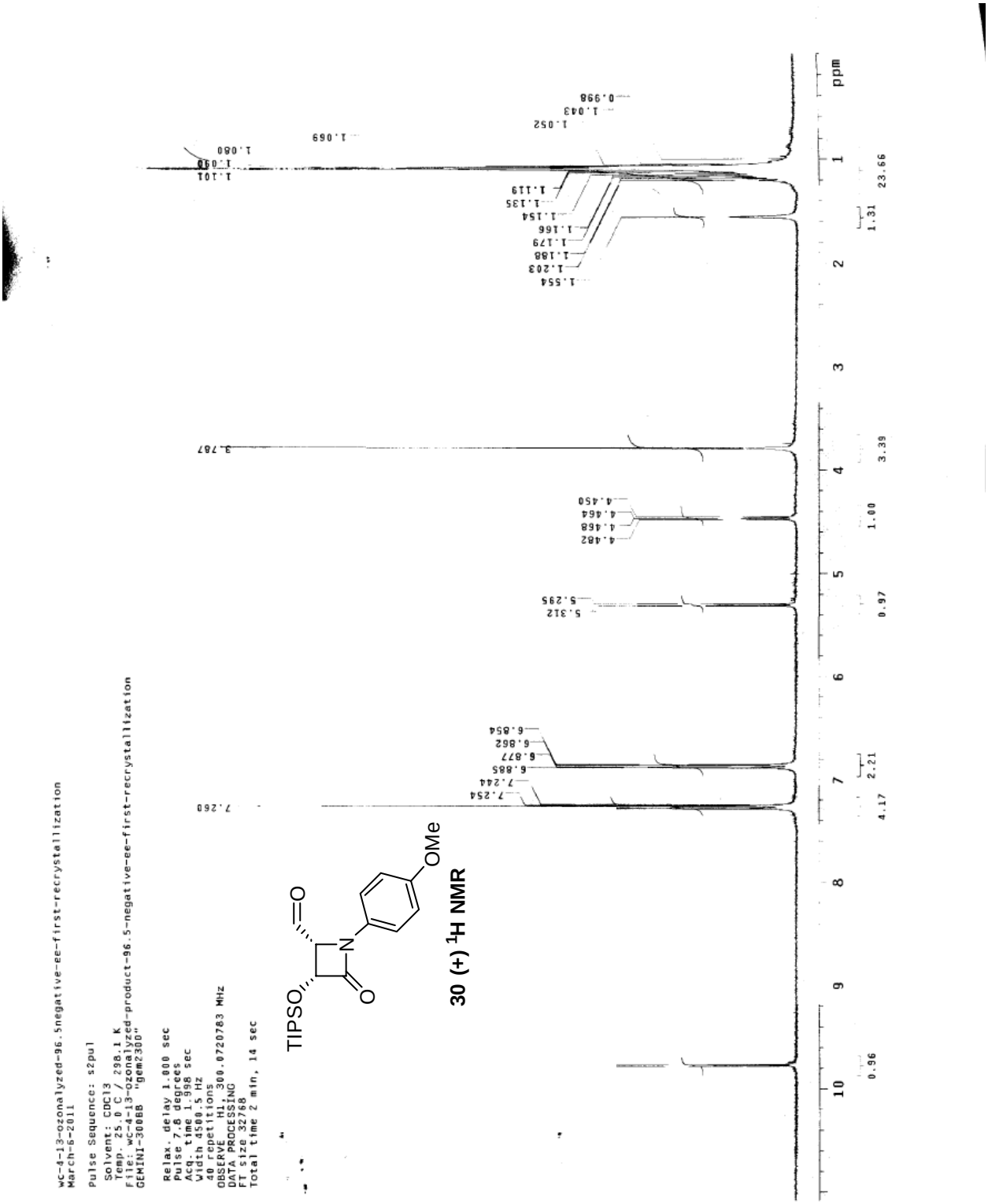
# Appendix

($^{1}H$, $^{13}C$, $^{19}F$ NMR, FIA)

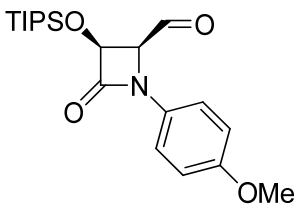


wc-4-51-plus-pure-aldehyde
April-20-2011

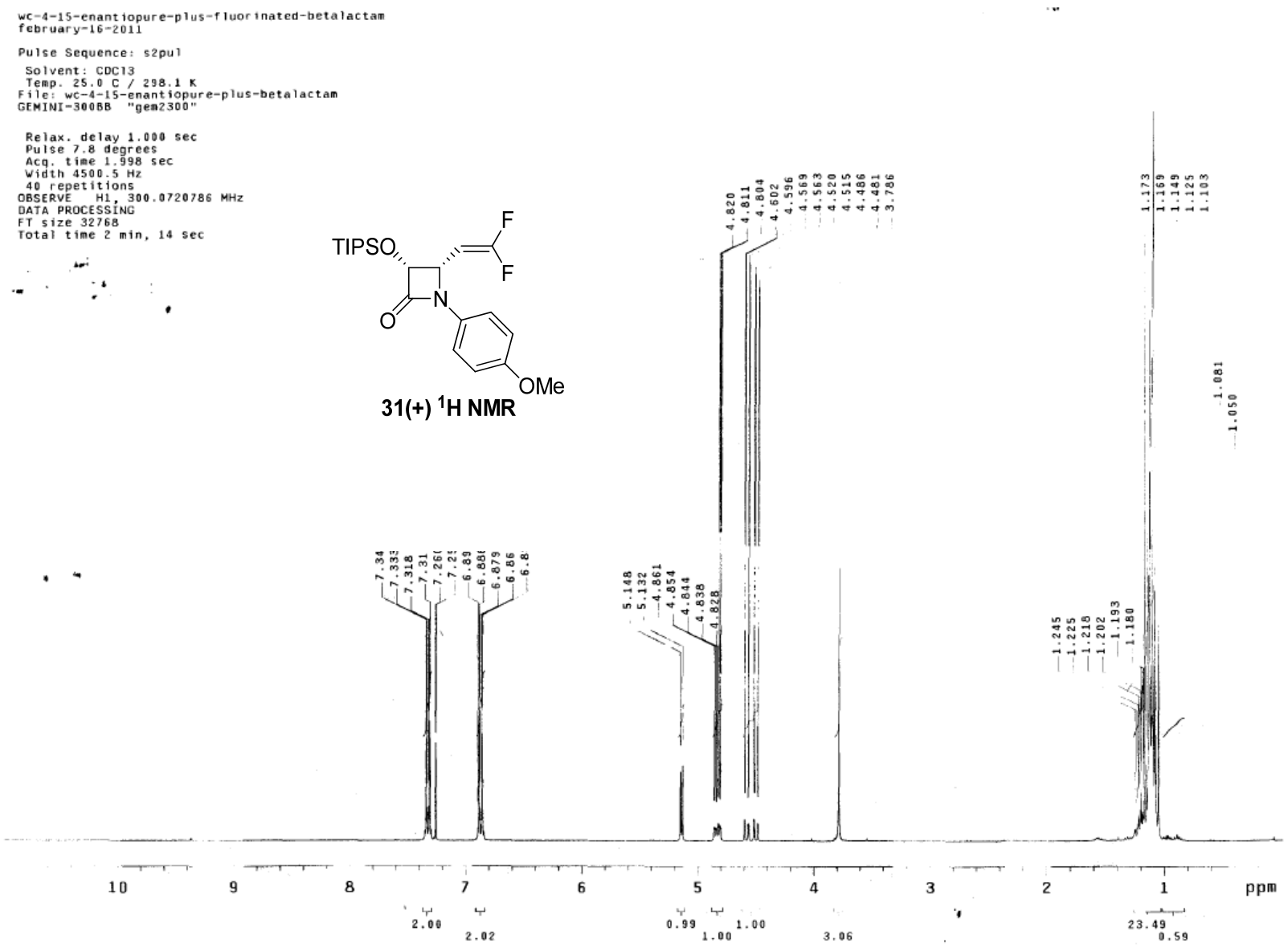
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-51-pure-plus-aldehyde
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0720576 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec




**30 (-) $^{1}$H NMR**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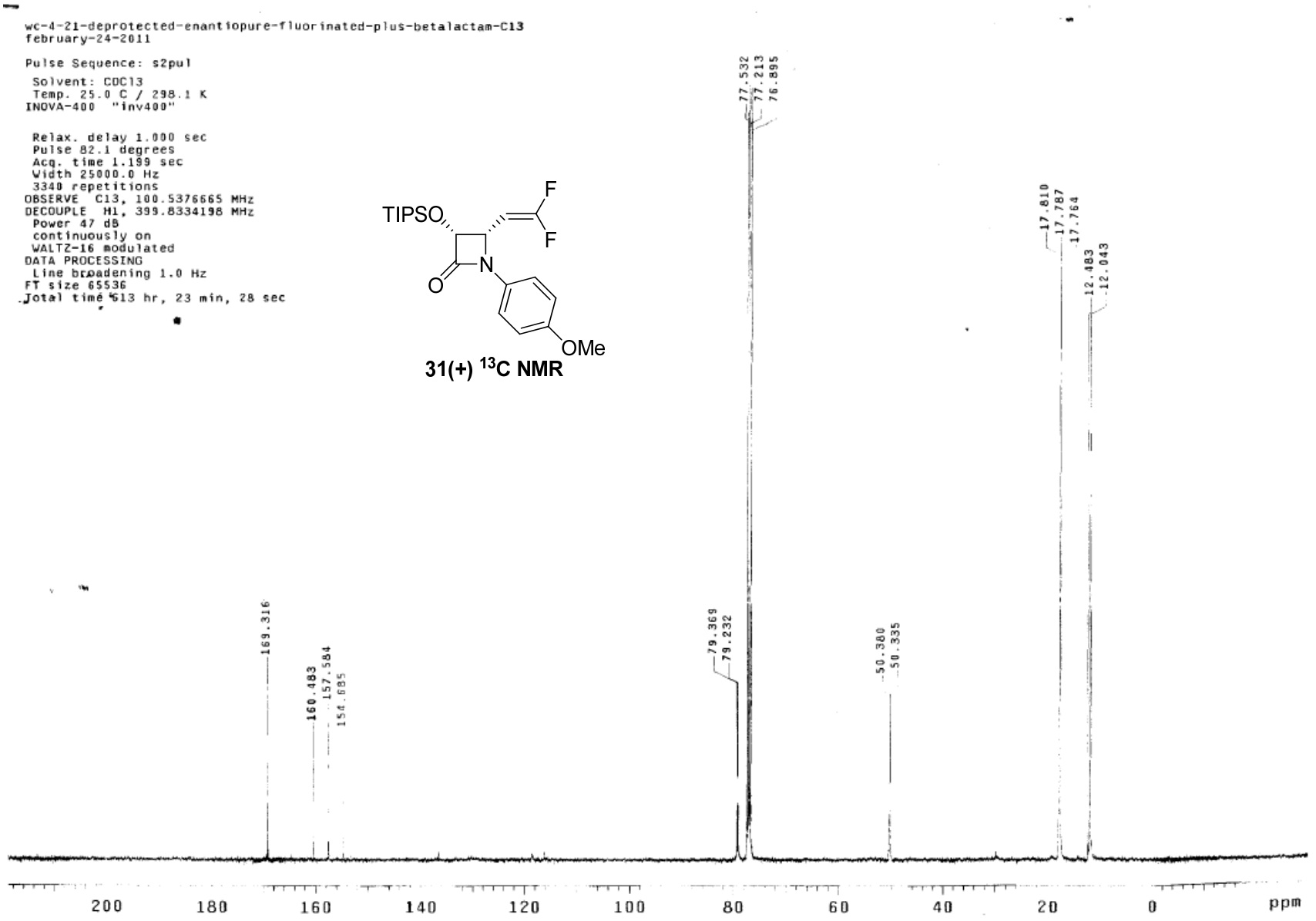
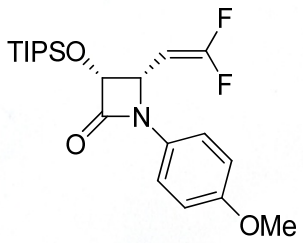
february-16-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-15-enantiopure-plus-betalactam
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec
TIPSO
F
F
N
O
OMe
31(+) 1H NMR
ppm


wc-4-21-deprotected-enantiopure-fluorinated-plus-betalactam-C13
february-24-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
3340 repetitions
OBSERVE C13, 100.5376665 MHz
DECOUPLE H1, 399.8334198 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 13 hr, 23 min, 28 sec
TIPSO
F
F
O
N
OMe
31(+) 13C NMR
77.532
77.213
76.895
169.316
160.483
157.584
154.685
79.369
79.232
50.380
50.335
17.810
17.787
17.764
12.483
12.043
200
180
160
140
120
100
80
60
40
20
0
ppm

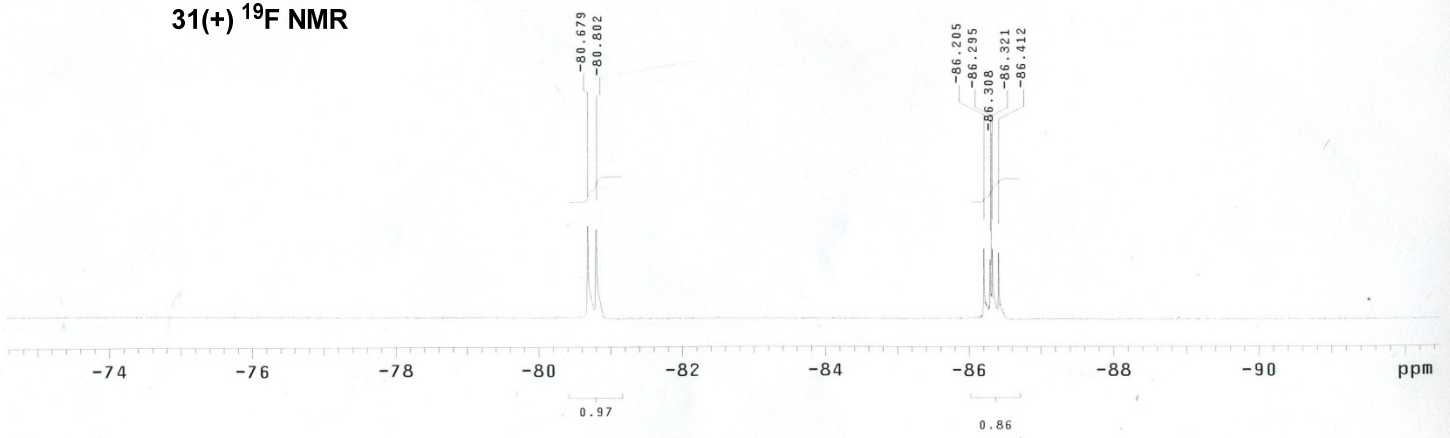
wc-4-15-fluorination-on-plus-cis-betalactam-enantiopure
May-18-2011

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 0.300 sec
Width 60000.0 Hz
260 repetitions
OBSERVE F19, 282.3499452 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 5 hr, 20 min, 36 sec



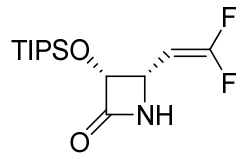

**31(+) $^{19}$F NMR**



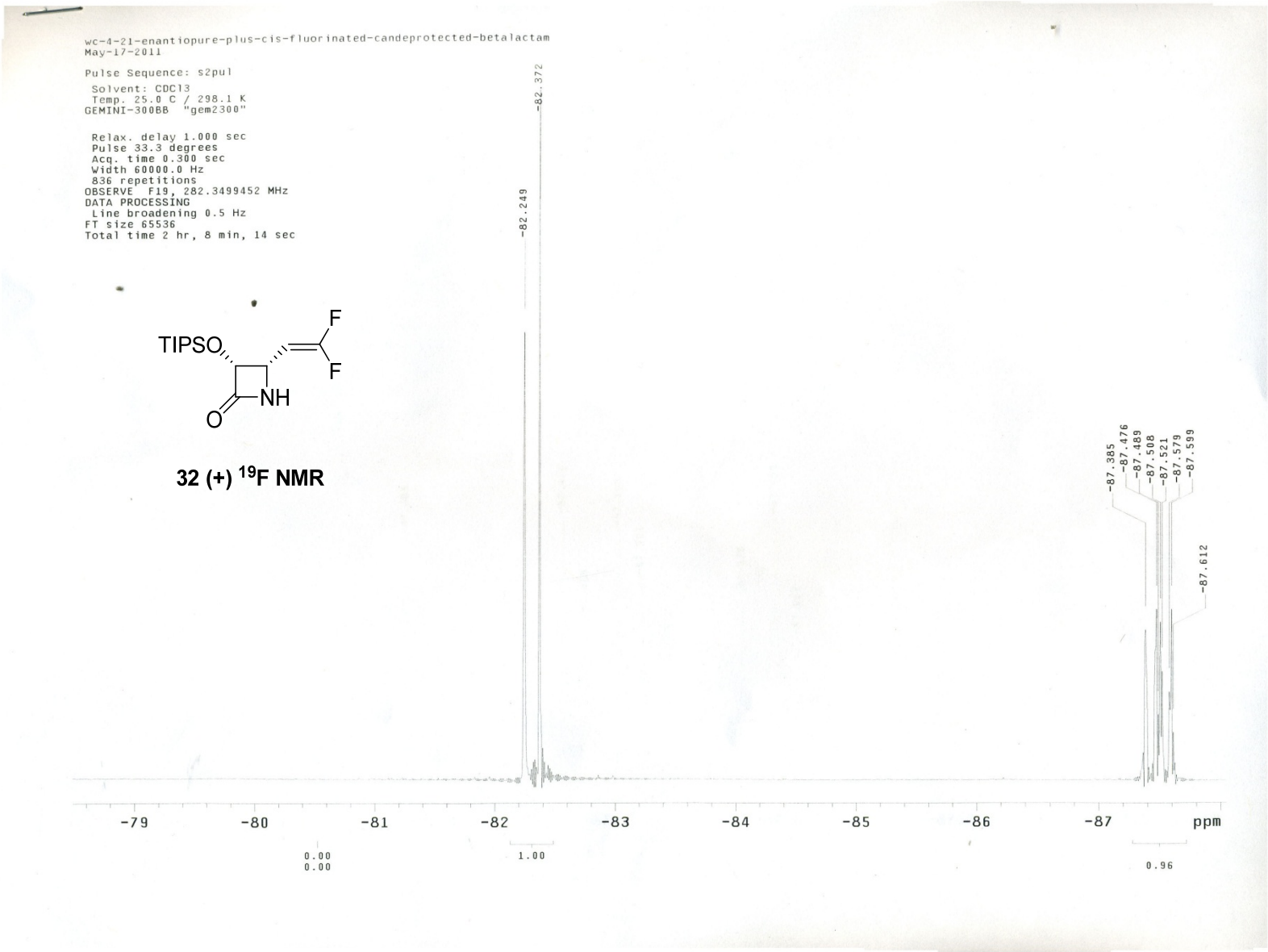
wc-4-21-CAN-deprotected-high-enantiopurity-plus-fluorinated-betalactam

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-21-candeprotected-enantiopure-plus-fluorinated-betalactam
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec




**32 (+) $^{1}$H NMR**

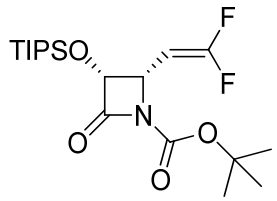

wc-4-21-enantiopure-plus-cis-fluorinated-candeprotected-betalactam
May-17-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 0.300 sec
Width 60000.0 Hz
836 repetitions
OBSERVE F19, 282.3499452 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 2 hr, 8 min, 14 sec
TIPSO
F
F
NH
O
-82.372
-82.249
-87.385
-87.476
-87.489
-87.508
-87.521
-87.579
-87.599
-87.612
-79
-80
-81
-82
-83
-84
-85
-86
-87
ppm
0.00
0.00
1.00
0.96

**32 (+) $^{19}$F NMR**

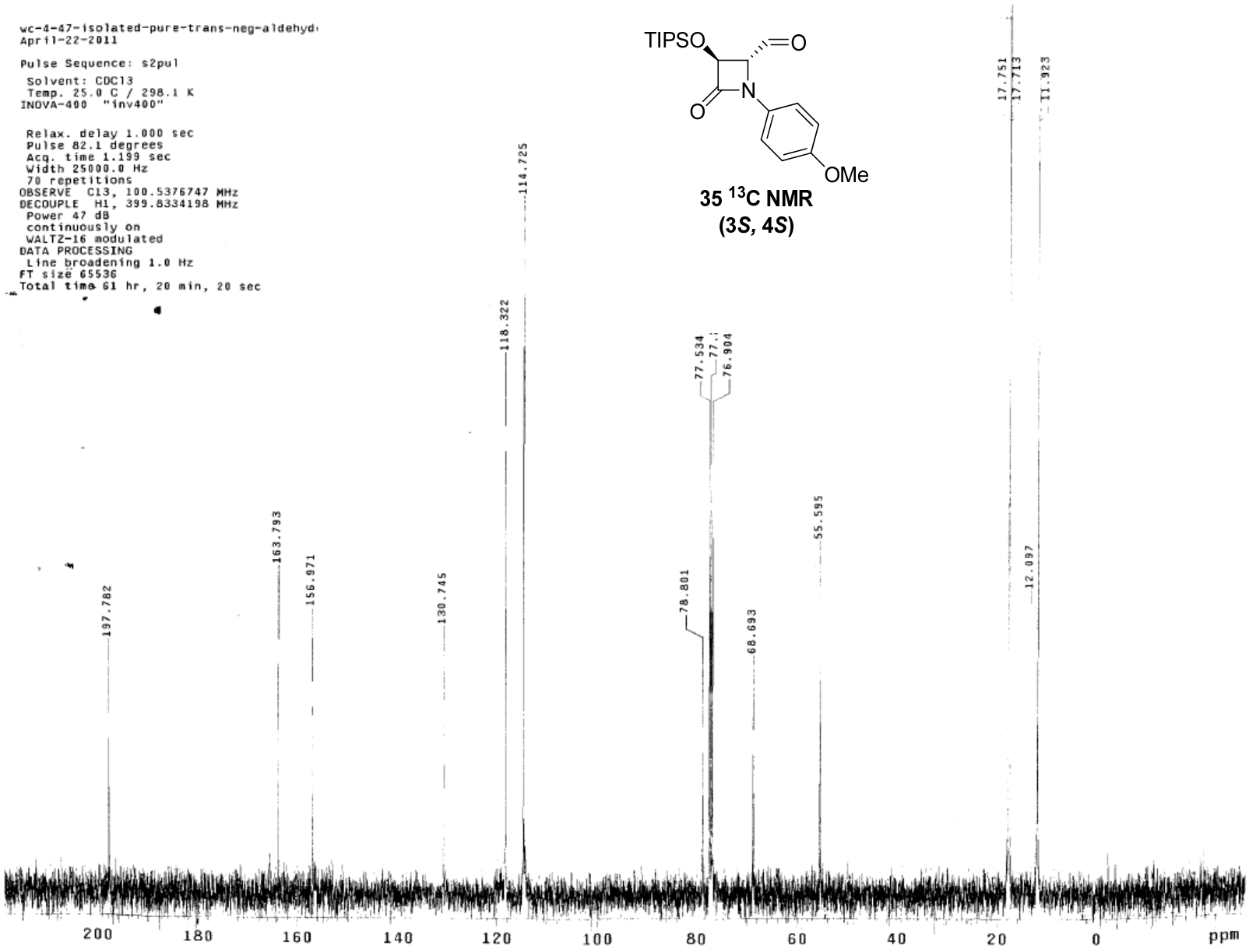
wc-3-33-plus-cis-boc-protected-betalactam

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-3-33-boc-protection
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720781 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 47 sec




**33 (+) $^{1}$H NMR**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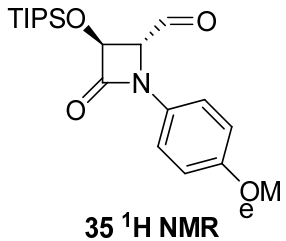
April-22-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
70 repetitions
OBSERVE C13, 100.5376747 MHz
DECOUPLE H1, 399.8334198 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 61 hr, 20 min, 20 sec
TIPSO
O
N
O
OMe
35 13C NMR
(3S, 4S)
197.782
163.793
156.971
130.745
118.322
114.725
78.801
77.534
76.904
68.693
55.595
17.751
17.713
12.097
11.923
200
180
160
140
120
100
80
60
40
20
0
ppm

wc-4-47-isolated-pure-trans-neg-betalactam
April-22-2011

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-47-isolated-pure-trans-neg-aldehyde
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec



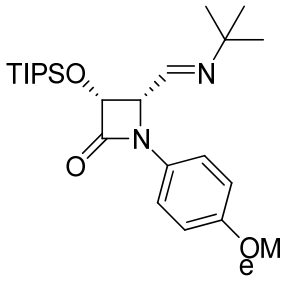

**35 $^{1}$H NMR**
**(3*S*, 4*S*)**

wc-3-43-t-butyl-imine

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-3-43-imine
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720786 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 47 sec



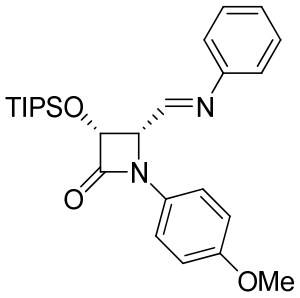

**36a $^{1}$H NMR**
**(3*R*,4*S*)**

wc-4-41-aniline-imine-formation
April-6-2011

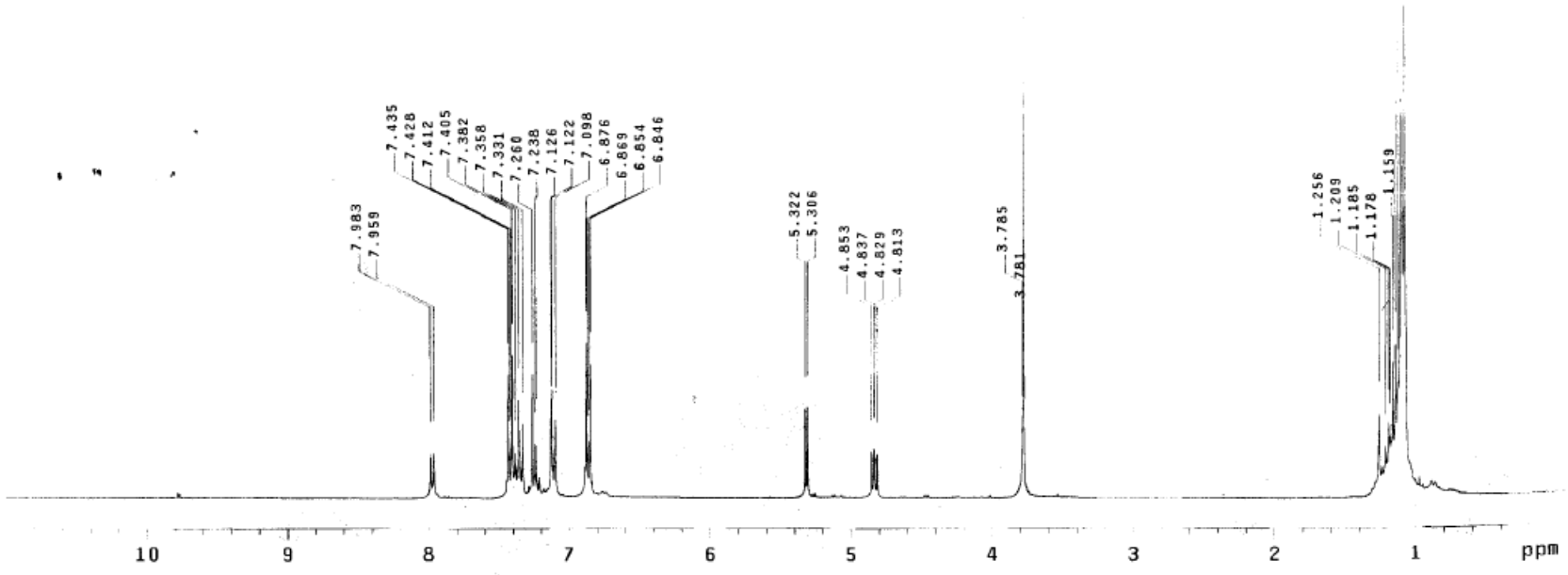
Pulse Sequence: s2pul

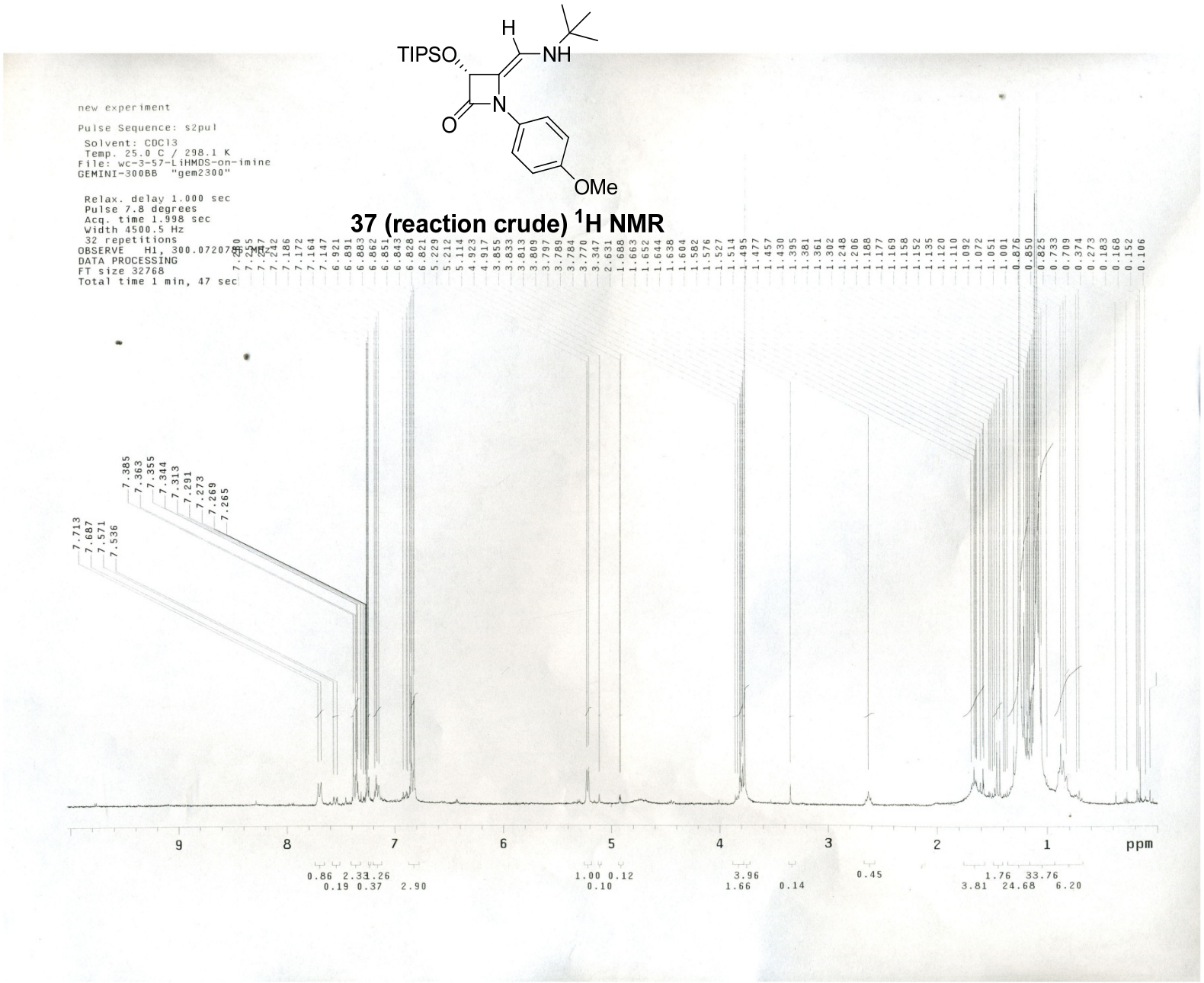
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-41-aniline-imine-formation
GEMINI-300BB "gem2300"

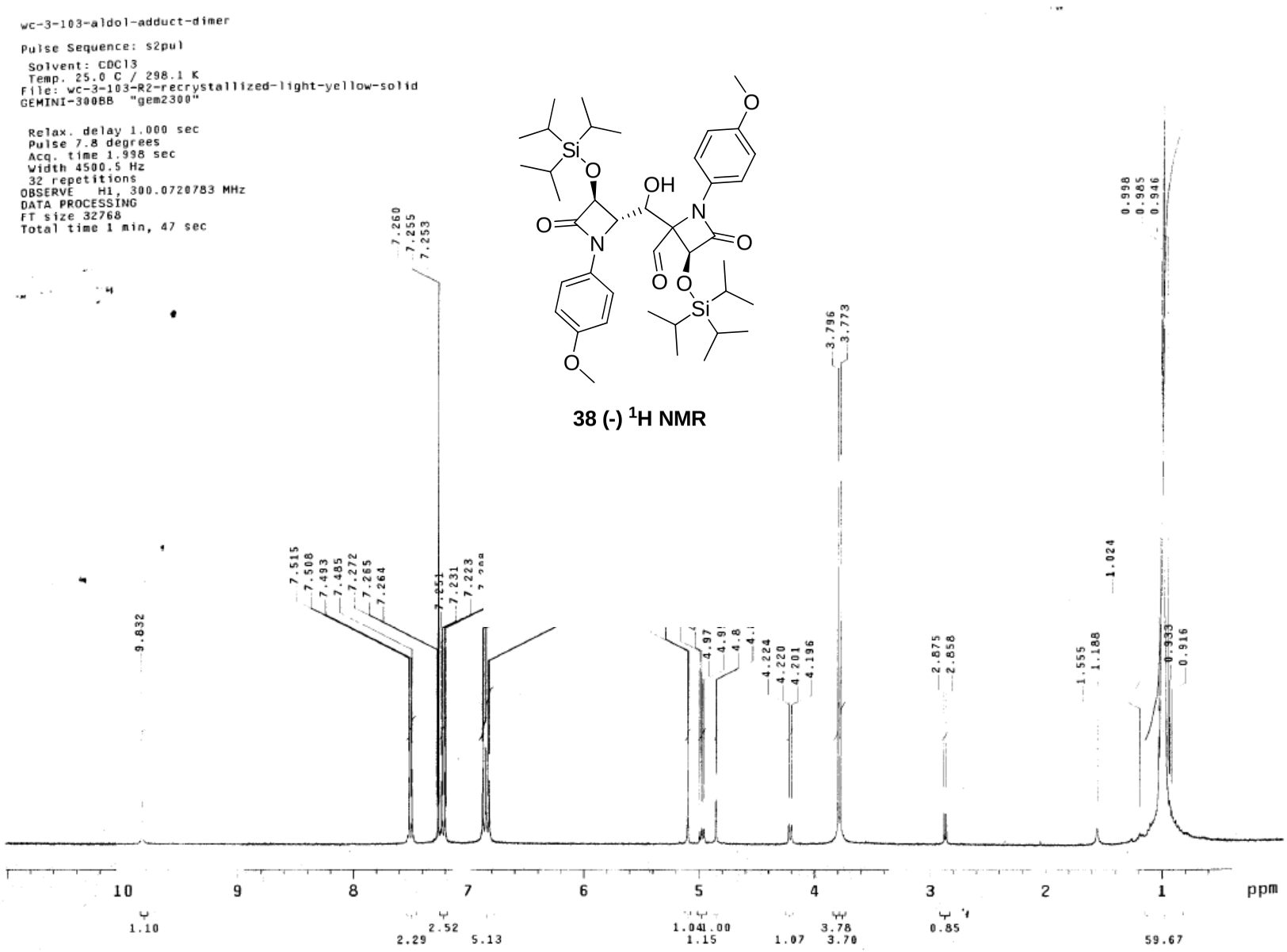
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
28 repetitions
OBSERVE H1, 300.0720781 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec

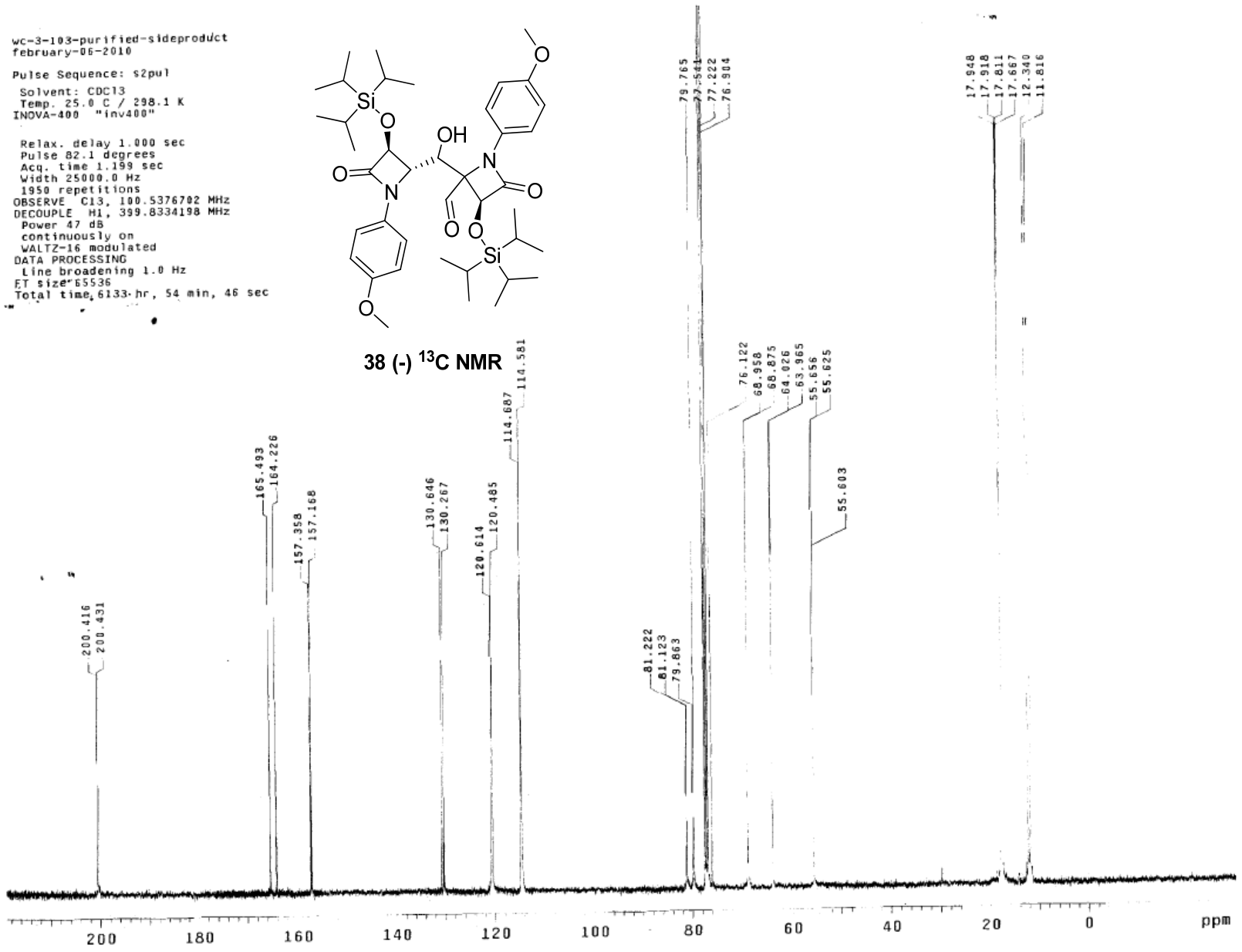



**36b $^{1}$H NMR**
**(3*S*,4*R*)**




TIPSO
H
NH
N
O
OMe
37 (reaction crude) 1H NMR
new experiment
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-3-57-LiHMDS-on-imine
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720786
DATA PROCESSING
FT size 32768
Total time 1 min, 47 sec
ppm


wc-3-103-aldol-adduct-dimer
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-3-103-R2-recrystallized-light-yellow-solid
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 47 sec
OH
Si
O
N
O
ppm
38 (-) 1H NMR


wc-3-103-purified-sideproduct
february-06-2010
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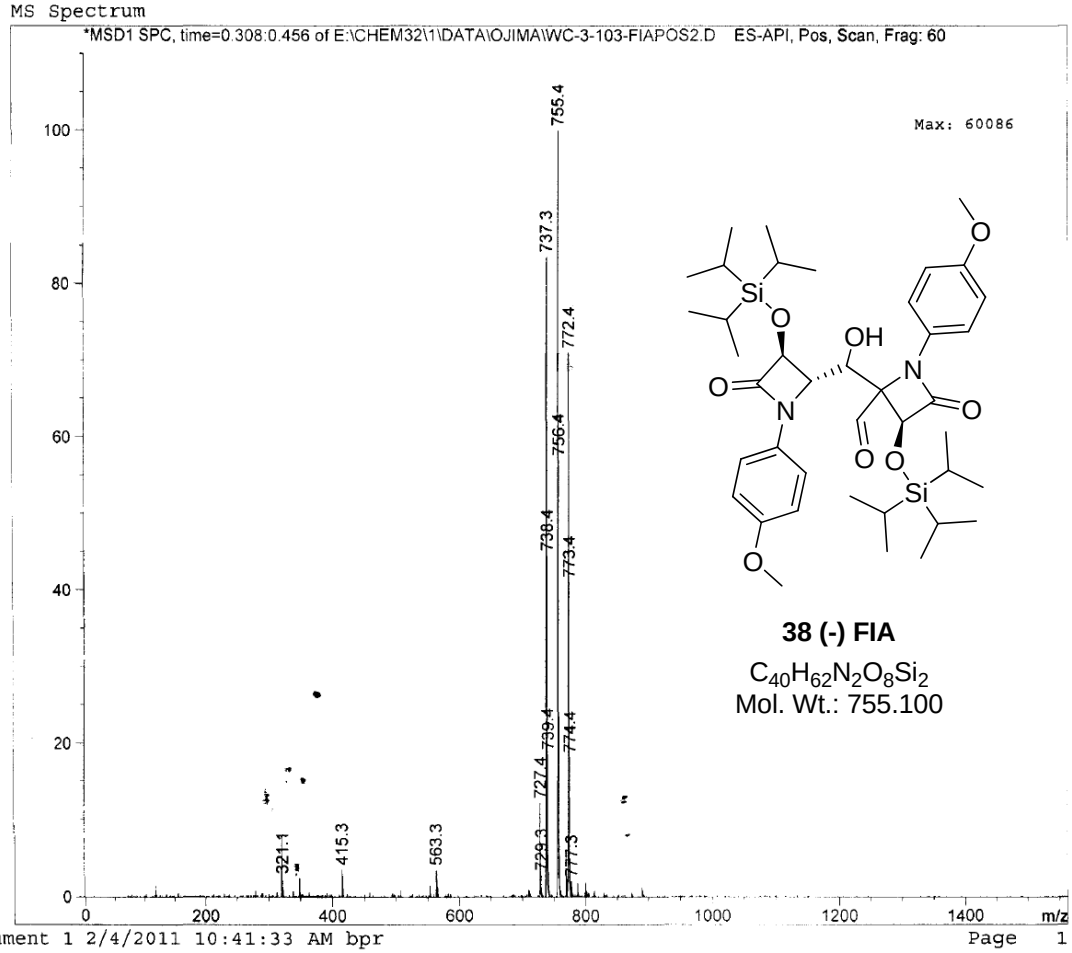
INOVA-400 "inv400"
Relax. delay 1.000 sec
Pulse 82.1 degrees
Acq. time 1.199 sec
Width 25000.0 Hz
1950 repetitions
OBSERVE C13, 100.5376702 MHz
DECOUPLE H1, 399.8334198 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time, 6133 hr, 54 min, 46 sec
38 (-) 13C NMR
200.416
200.431
165.493
164.226
157.358
157.168
130.646
130.267
120.614
120.485
114.687
114.581
81.222
81.123
79.863
79.765
77.541
77.222
76.904
76.122
68.958
68.875
64.026
63.965
55.656
55.625
55.603
17.948
17.918
17.811
17.667
12.340
11.816
200
180
160
140
120
100
80
60
40
20
0
ppm

```
Print of window 79: MS Spectrum
Data File  : E:\CHEM32\1\DATA\OJIMA\WC-3-103-FIAPOS2.D
Sample Name : WC-3-103
======================================================================
Acq. Operator   : bpr
Acq. Instrument : Instrument 1                    Location : FIA
Injection Date  : 2/4/2011 10:38:40 AM
Acq. Method     : E:\CHEM32\1\METHODS\FIA-PW.M
Last changed    : 2/4/2011 10:38:11 AM by bpr
                  (modified after loading)
Analysis Method : E:\CHEM32\1\DATA\OJIMA\WC-3-103-FIAPOS2.D\DA.M (FIA-PW.M)
Last changed    : 2/4/2011 10:41:23 AM by bpr
Method Info     : FIA positive ion mode
                  Solv A2- H2O (10mMAmAc,pH=6.5): MeOH; 90:10
                  Solv B2 - MeOH

Sample Info     : Wen Chen


Flow Injections :
          Inj. InjTime   Location   FIA Sample Name
                [min]
          ----|-------|-----------|--------------------|
             1   0.000   P1-F-09    WC-3-103
```

MS Spectrum






**38 (-) FIA**

$C_{40}H_{62}N_2O_8Si_2$

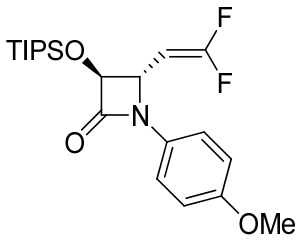
Mol. Wt.: 755.100

Instrument 1 2/4/2011 10:41:33 AM bpr  Page 1 of 1

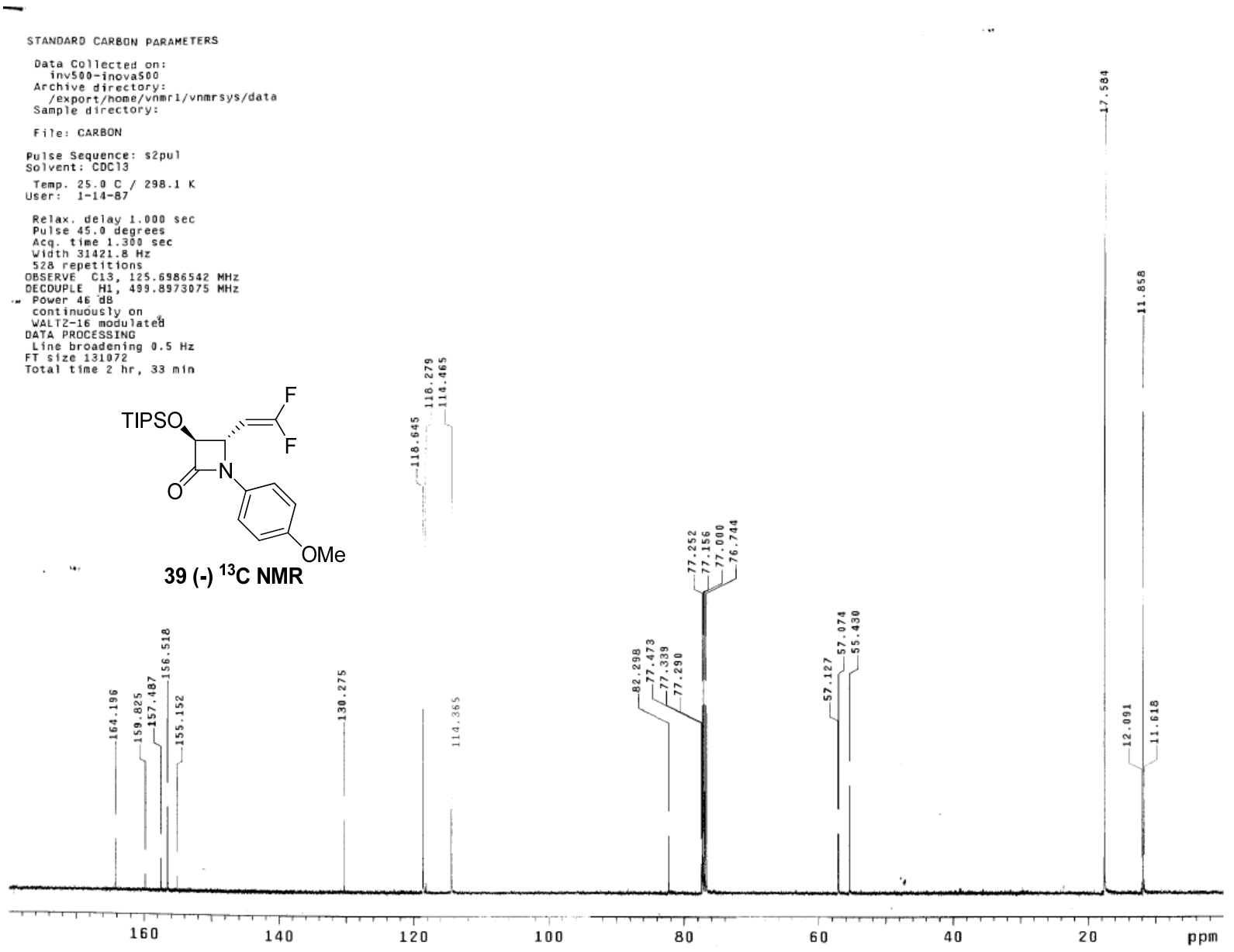
wc-4-31-fluorination-on-trans-96.5ee
April-10-2011

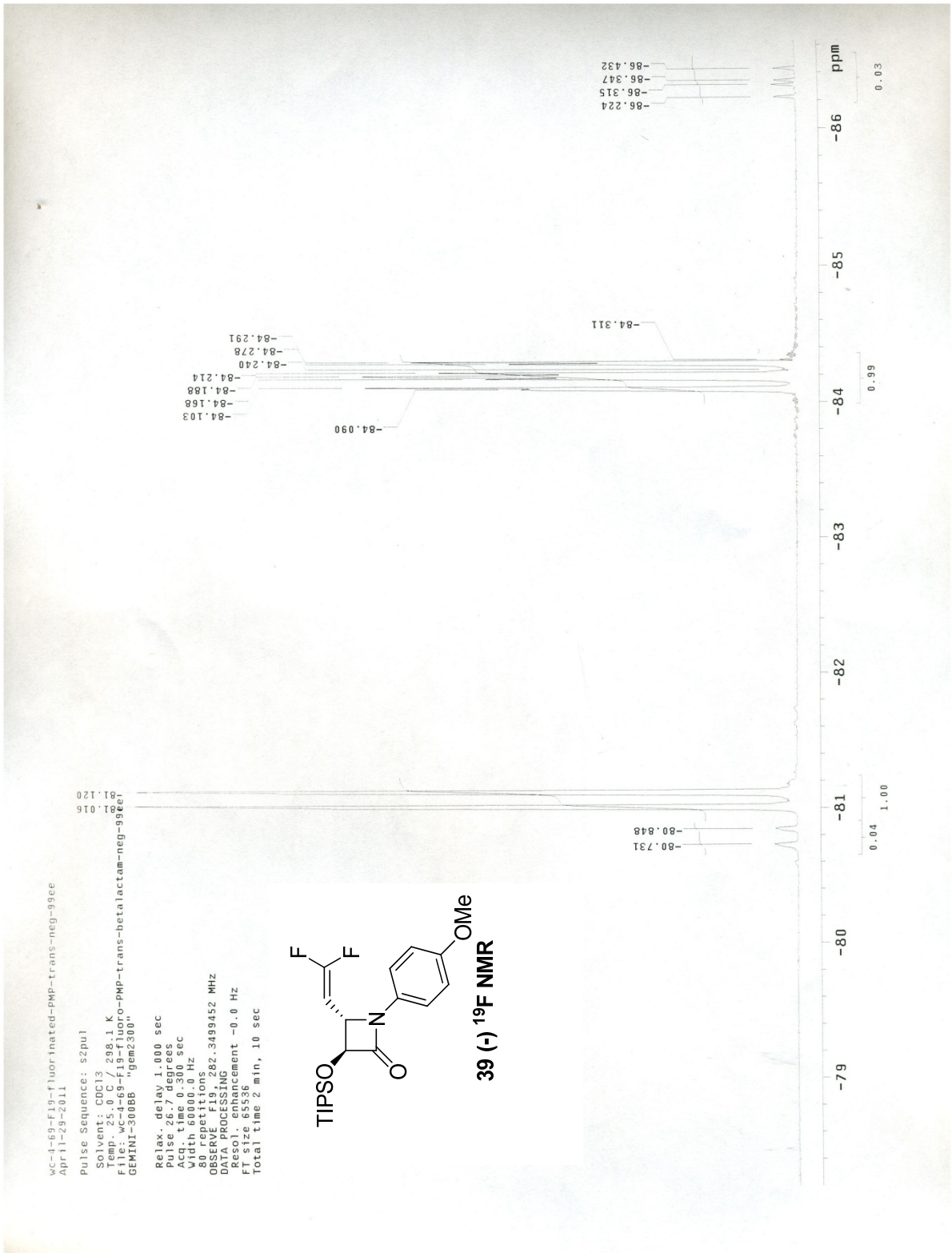
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-31-fluorination-on-trans-betalactam-96.5ee
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec




**39 (-) $^{1}$H NMR**

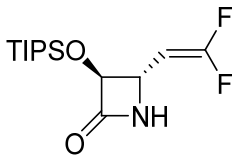

STANDARD CARBON PARAMETERS
Data Collected on:
inv500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31421.8 Hz
528 repetitions
OBSERVE C13, 125.6986542 MHz
DECOUPLE H1, 499.8973075 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 2 hr, 33 min
TIPSO
F
F
N
O
OMe
39 (-) 13C NMR
164.196
159.825
157.487
156.518
155.152
130.275
118.645
118.279
114.465
114.365
82.298
77.473
77.339
77.290
77.252
77.156
77.000
76.744
57.127
57.074
55.430
17.584
11.858
12.091
11.618
160
140
120
100
80
60
40
20
ppm


wc-4-69-F19-fluorinated-PMP-trans-neg-99ee
April-29-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-69-f19-fluoro-PMP-trans-betalactam-neg-99ee
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 26.7 degrees
Acq. time 0.300 sec
Width 60000.0 Hz
80 repetitions
OBSERVE F19, 282.3499452 MHz
DATA PROCESSING
FT size 65536
Total time 2 min, 10 sec
-81.016
-81.120
-80.731
-80.848
-84.090
-84.103
-84.168
-84.188
-84.214
-84.240
-84.278
-84.291
-84.311
-86.224
-86.315
-86.347
-86.432
F
F
TIPSO
N
O
OMe
39 (-) 19F NMR
-79
-80
-81
-82
-83
-84
-85
-86
ppm
0.04
1.00
0.99
0.03

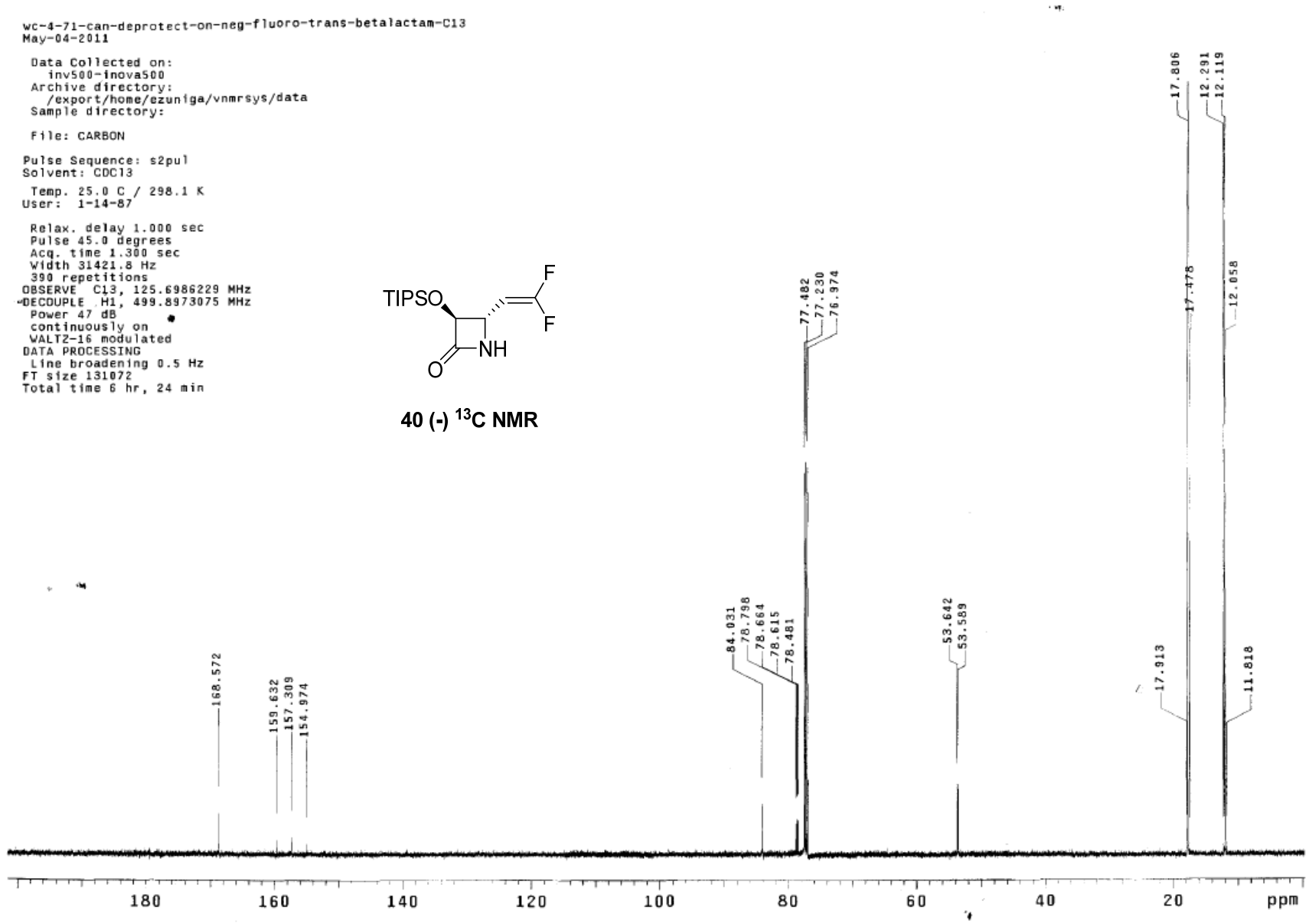
wc-4-71-Can-deprotect-of-neg-trans-fluoro-betalactam
May-03-2011

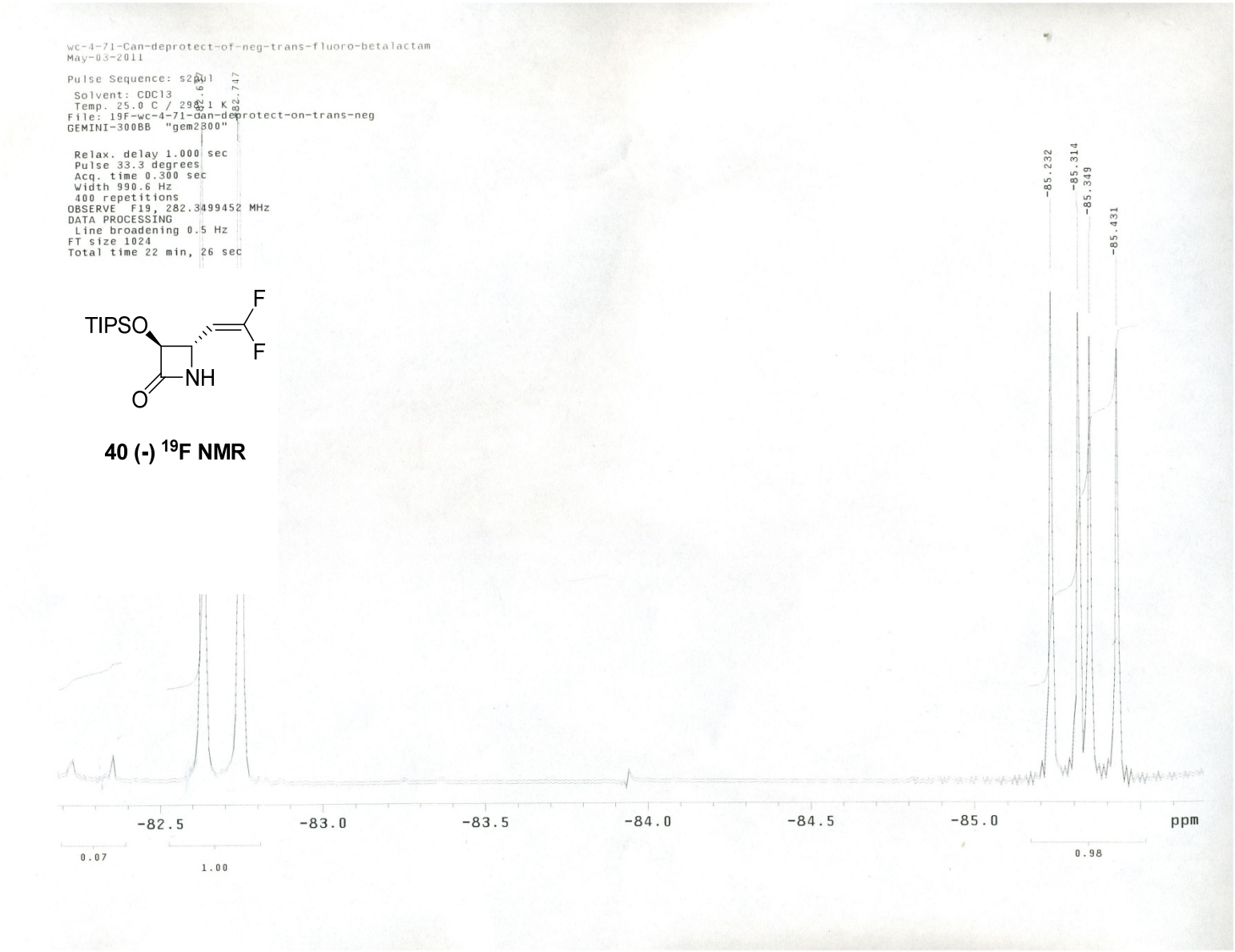
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"

Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720781 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 0 sec

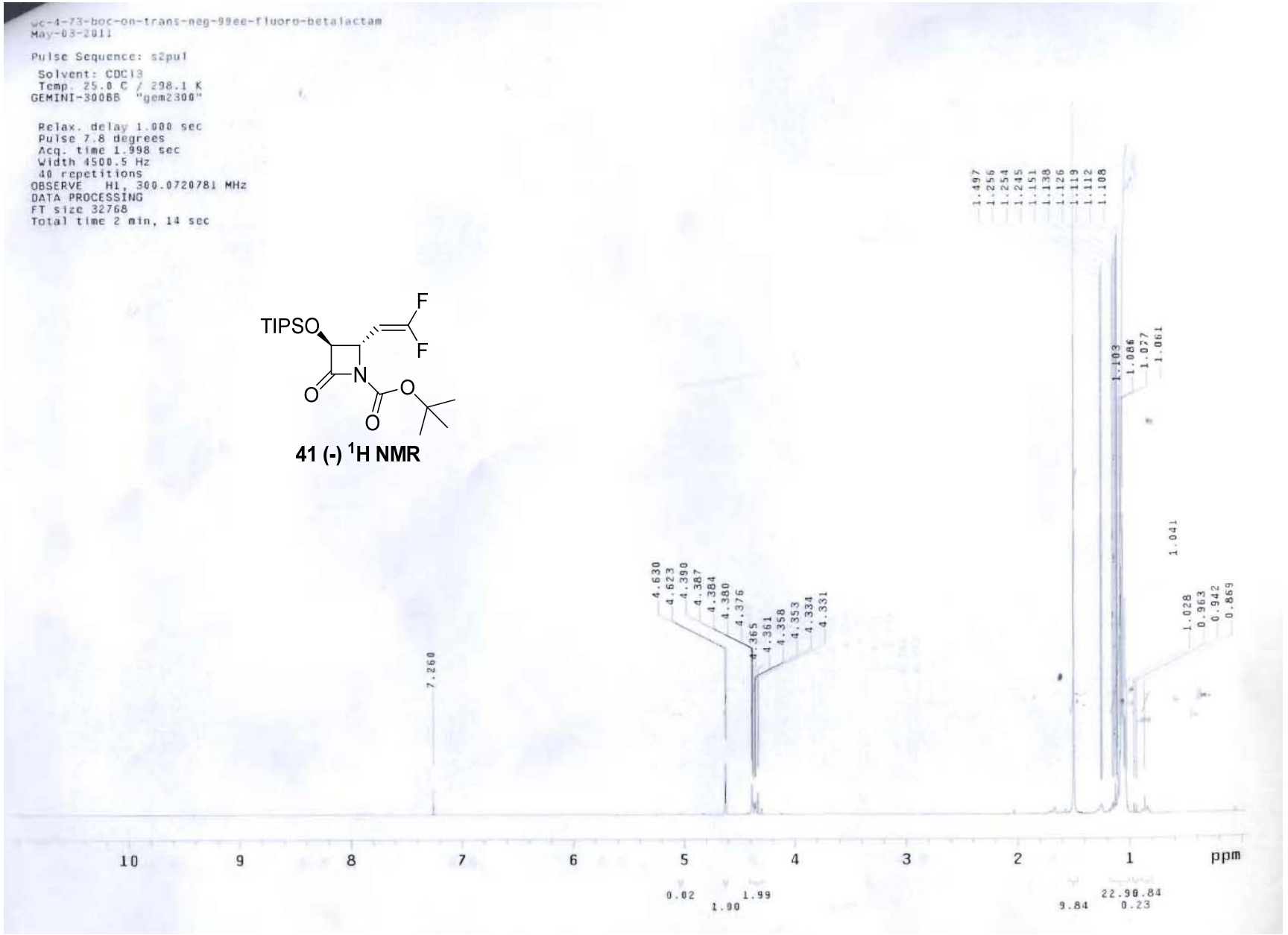


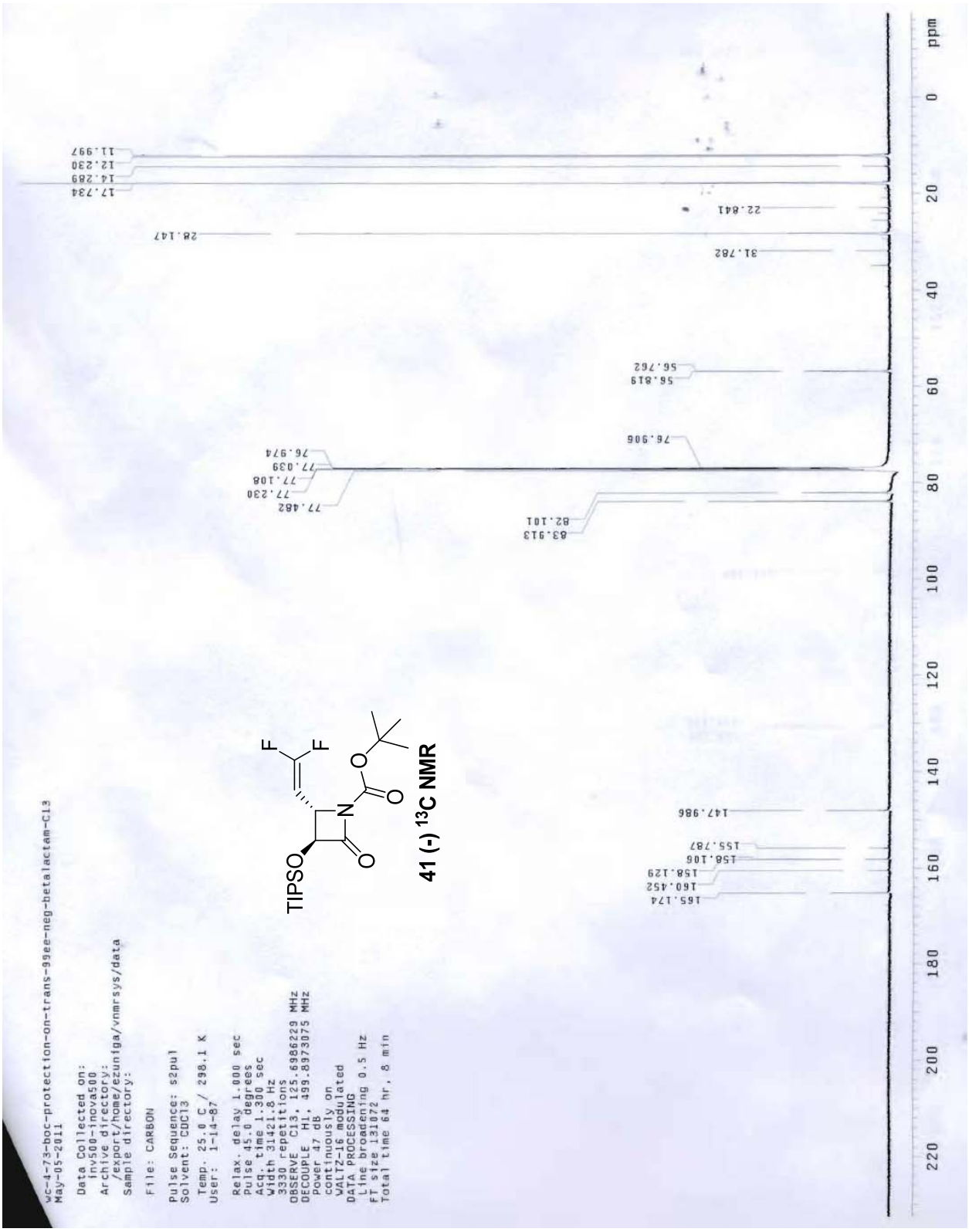

**40 (-) $^{1}$H NMR**

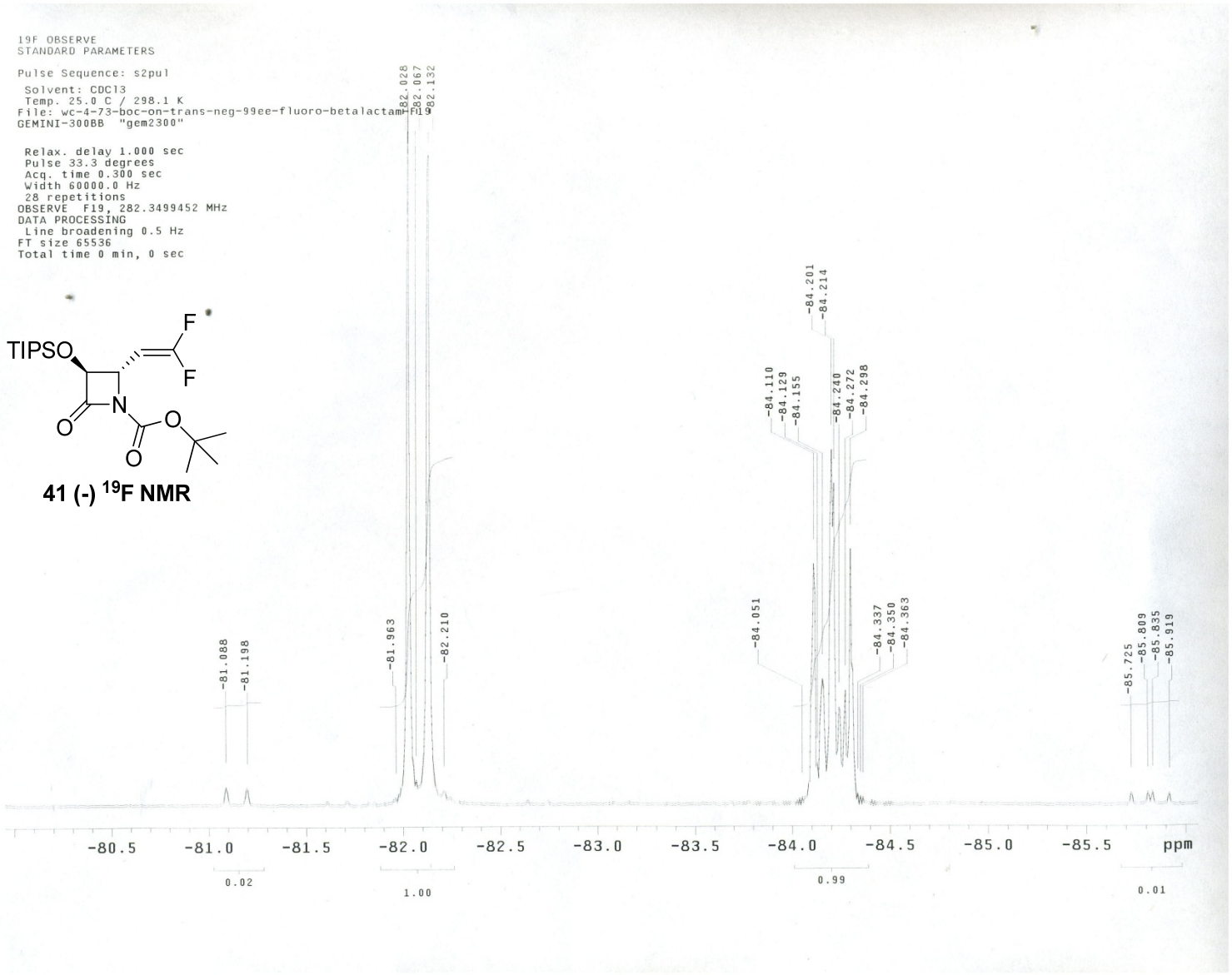

wc-4-71-can-deprotect-on-neg-fluoro-trans-betalactam-C13
May-04-2011
Data Collected on:
inv500-inova500
Archive directory:
/export/home/ezuniga/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31421.8 Hz
390 repetitions
OBSERVE C13, 125.6986229 MHz
DECOUPLE H1, 499.8973075 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 6 hr, 24 min
TIPSO
F
F
NH
O
40 (-) 13C NMR
168.572
159.632
157.309
154.974
84.031
78.798
78.664
78.615
78.481
77.482
77.230
76.974
53.642
53.589
17.913
17.806
17.478
12.291
12.119
12.058
11.818
180
160
140
120
100
80
60
40
20
ppm


wc-4-71-Can-deprotect-of-neg-trans-fluoro-betalactam
May-03-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: 19F-wc-4-71-can-deprotect-on-trans-neg
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 0.300 sec
Width 990.6 Hz
400 repetitions
OBSERVE F19, 282.3499452 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 1024
Total time 22 min, 26 sec
TIPSO
F
F
NH
O
-85.232
-85.314
-85.349
-85.431
-82.5
-83.0
-83.5
-84.0
-84.5
-85.0
ppm
0.07
1.00
0.98

**40 (-) $^{19}$F NMR**


wc-4-73-boc-on-trans-neg-99ee-fluoro-betalactam
May-03-2011
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 7.8 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
40 repetitions
OBSERVE H1, 300.0720781 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 14 sec
TIPSO
F
F
N
O
O
O
41 (-) 1H NMR
1.497
1.256
1.254
1.245
1.151
1.138
1.126
1.119
1.112
1.108
1.103
1.086
1.077
1.061
1.041
1.028
0.963
0.942
0.869
4.630
4.623
4.390
4.387
4.384
4.380
4.376
4.365
4.361
4.358
4.353
4.334
4.331
7.260
10
9
8
7
6
5
4
3
2
1
ppm
0.02
1.00
1.99
9.84
22.98
0.23
4.84


vc-4-73-boc-protection-on-trans-99ee-neg-betalactam-C13
May-05-2011
Data Collected on:
inv500-inova500
Archive directory:
/export/home/ezuniga/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.300 sec
Width 31421.8 Hz
3330 repetitions
OBSERVE C13, 125.6986229 MHz
DECOUPLE H1, 499.8973075 MHz
Power 47 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 131072
Total time 64 hr, 8 min
TIPSO
F
F
O
N
O
O
41 (-) 13C NMR
165.174
160.452
158.129
156.106
155.787
147.986
83.913
82.101
77.482
77.230
77.108
77.039
76.974
76.906
56.819
56.762
31.782
28.147
22.841
17.734
14.289
12.230
11.997
220
200
180
160
140
120
100
80
60
40
20
0
ppm


19F OBSERVE
STANDARD PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 25.0 C / 298.1 K
File: wc-4-73-boc-on-trans-neg-99ee-fluoro-betalactam-F1
GEMINI-300BB "gem2300"
Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 0.300 sec
Width 60000.0 Hz
28 repetitions
OBSERVE F19, 282.3499452 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 0 min, 0 sec
TIPSO
F
F
N
O
O
O
-82.028
-82.067
-82.132
-84.201
-84.214
-84.110
-84.129
-84.155
-84.240
-84.272
-84.298
-84.051
-84.337
-84.350
-84.363
-81.088
-81.198
-81.963
-82.210
-85.725
-85.809
-85.835
-85.919
-80.5
-81.0
-81.5
-82.0
-82.5
-83.0
-83.5
-84.0
-84.5
-85.0
-85.5
ppm
0.02
1.00
0.99
0.01

**41 (-) $^{19}$F NMR**