Allysilane-imine cyclizations
by Jun Li

A thesis submitted in partial fulfillment of the requirement for the degree of Master of Science in Chemistry
Montana State University

Abstract:
Allylsilane chemistry has been widely used in organic synthesis. The intramolecular nucleophilic addition of allylsilane to imine allows the construction of many ring systems in a convenient pathway. After the preparation of appropriate allylsilane-imine substrates, various conditions were applied to furnish the formation of pyrrolidine derivatives. It was found triftuoroacetyl triflate could effect such cyclization to form N-trifluoroacetyl-pyrrolidine with reasonable diastereoselectivity. F-19 NMR was applied to determine the ratio of two possible diastereomers conveniently. The structures were determined with H-1 NMR NOE measurements and confirmed by X-ray crystallography.

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Bozeman, Montana

August 2001

APPROVAL

Of a thesis submitted by

Jun Li

This thesis has been read by each member of the thesis committee and had been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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Approved for the Department of Chemistry and Biochemistry

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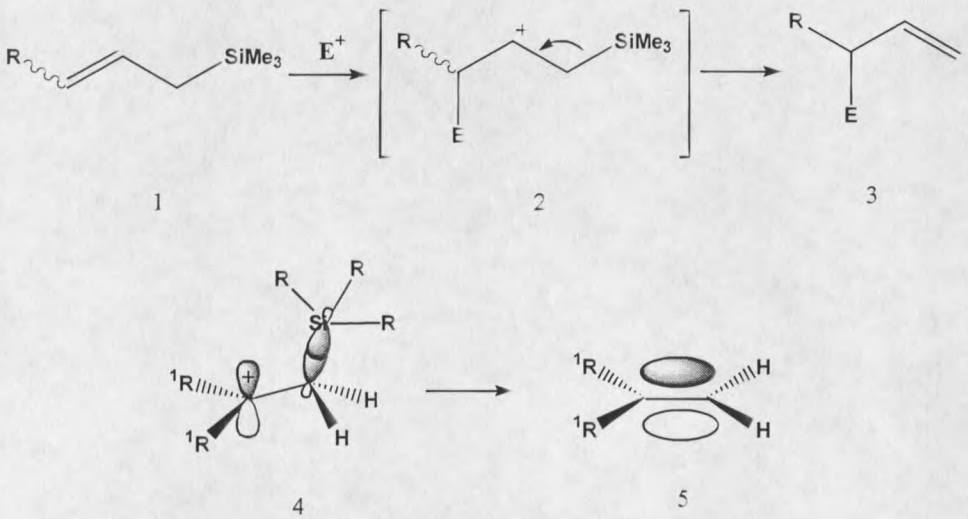
ABSTRACT

Allylsilane chemistry has been widely used in organic synthesis. The intramolecular nucleophilic addition of allylsilane to imine allows the construction of many ring systems in a convenient pathway. After the preparation of appropriate allylsilane-imine substrates, various conditions were applied to furnish the formation of pyrrolidine derivatives. It was found trifluoroacetyl triflate could effect such cyclization to form N-trifluoroacetyl-pyrrolidine with reasonable diastereoselectivity. F-19 NMR was applied to determine the ratio of two possible diastereomers conveniently. The structures were determined with H-1 NMR NOE measurements and confirmed by X-ray crystallography.

CHAPTER 1

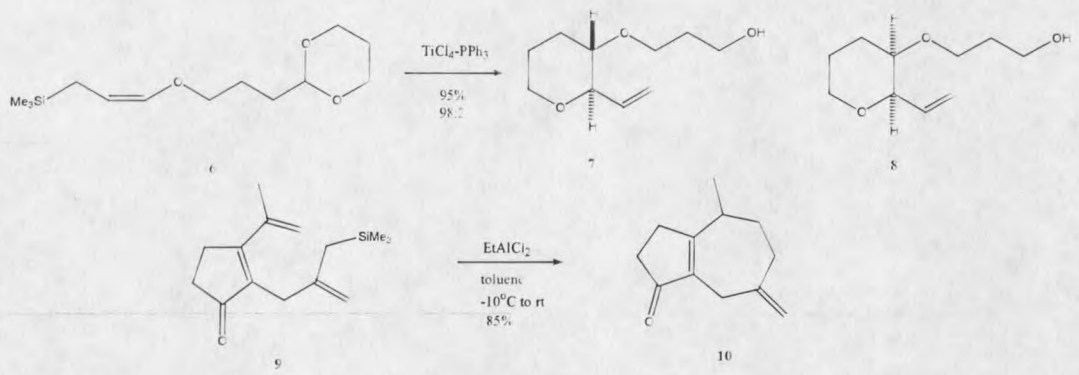
INTRODUCTION

Allylsilanes have proven to be among the most versatile of the silicon-containing carbon nucleophiles. The inter- or intramolecular addition of an allylsilane to carbon electrophiles has been widely used in organic synthesis, often with high level of stereocontrol.[1] A large majority of allylsilane chemistry is based on β-effect, the ability of silicon atom to stabilize the carbocation next to a C-Si bond. These systems tend to lose silyl group and form a double bond, thus give much higher regioselectivity than losing a proton in the analog without silyl group. (Scheme 1)



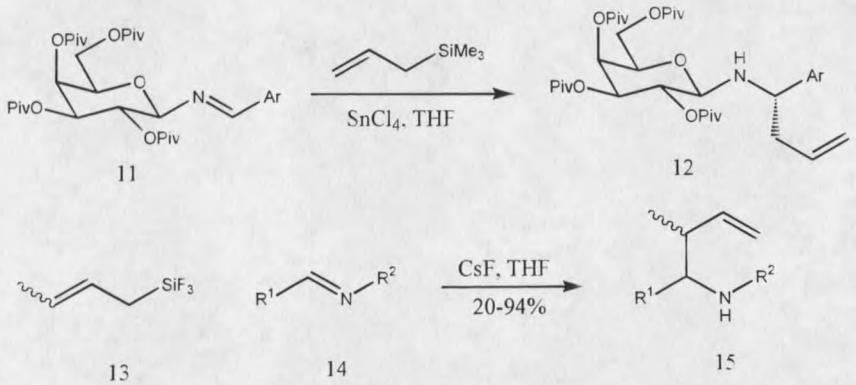
Scheme 1

The most commonly used substrates of allylsilane addition include aldehydes and ketones, acetals, α, β-unsaturated ketones. The intramolecular addition reactions have been widely used in construction of various ring systems. [2] (Scheme 2)



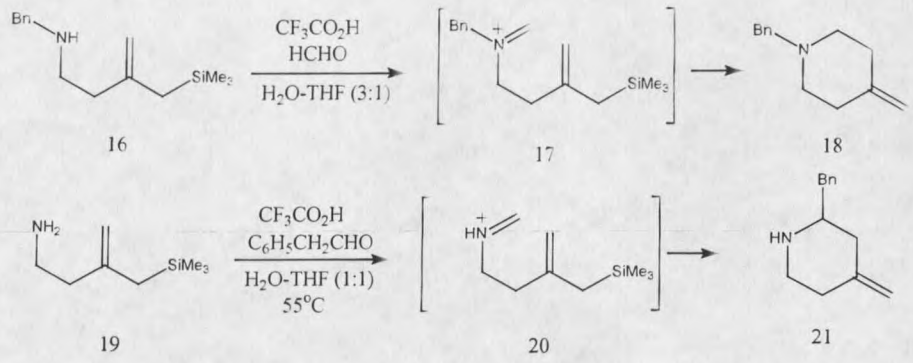
Scheme 2

Imines are also seen as substrates of allylsilane addition although not as widely used as the others. Compared to that of aldehydes, the reaction of imines with allylsilanes is sluggish even in the presence of Lewis acids. However, some examples have been reported.[3] (Scheme 3)



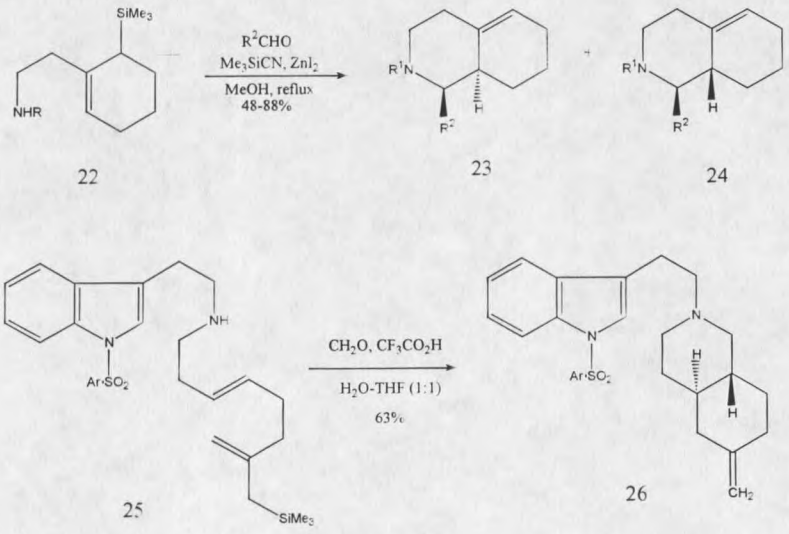
Scheme 3

It was reported that iminium salts, generated either from primary or secondary amine, are more reactive to the addition of allylsilane.[4] An intramolecular version gave rise to the adduct from simple phenylacetaldehyde. (Scheme 4)



Scheme 4

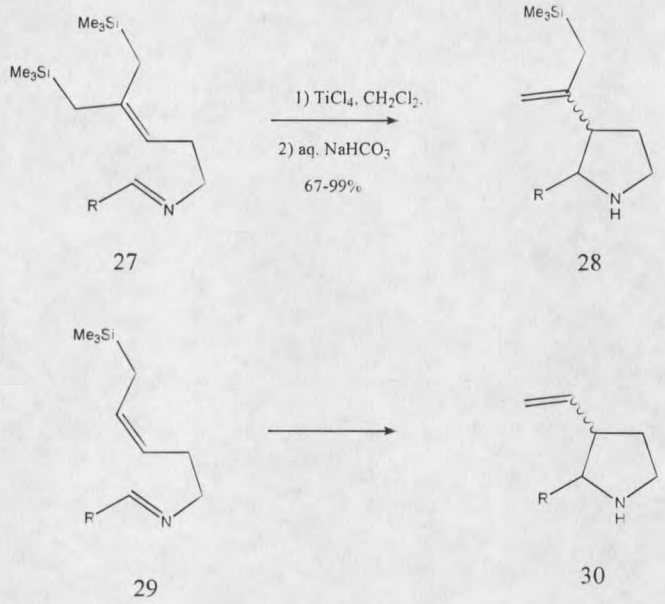
It was also reported that these reactions could be used in the construction of more complex ring system such as isoquinoline derivatives.[5] (Scheme 5)



Scheme 5

This project is directly related to what was done earlier in these laboratories. An intramolecular addition of allylbis(silane) was developed earlier, showing that the pyrrolidine ring can be constructed stereoselectively.[6] (Scheme 6) In most cases, these cyclizations showed interesting stereochemistry, with aromatic imines favoring *cis*-

pyrrolidines and aliphatic imines favoring *trans*- pyrrolidines. The goal of this project was to explore the appropriate conditions for similar cyclizations of the analogous allylsilane-imines and their stereochemistry.

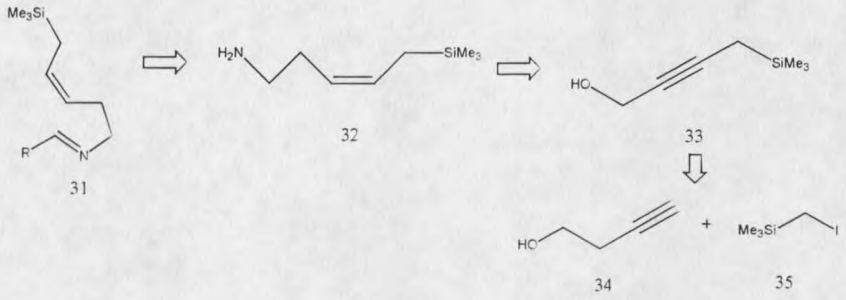


Scheme 6

CHAPTER 2

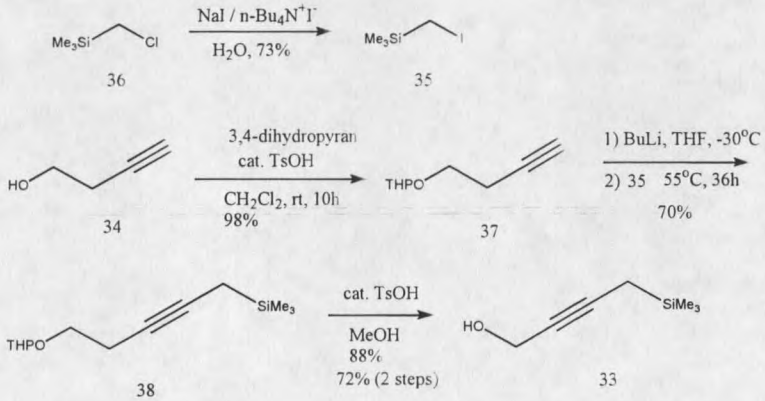
RESULTS AND DISCUSSION

The synthetic route to the allylsilane-imine precyclization substrates 31 is similar to the methods developed earlier in our laboratory and in the literature. [6,7] These imines can be conveniently prepared from amine 32 and a variety of aldehydes. (Scheme 7), while amine 32 can be prepared as shown below.



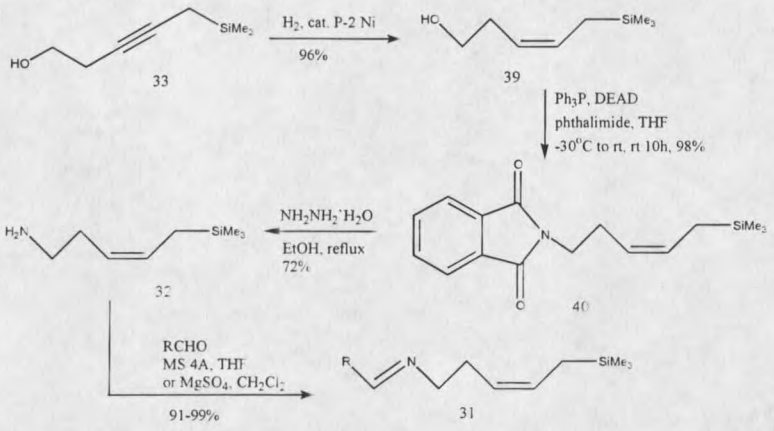
Scheme 7

The commercially available chloromethyltrimethylsilane 36 was converted to the corresponding iodide 35 by treatment with sodium iodide and tetrabutylammonium iodide in water. [8] Alkylation of the THP-protected 3-butyn-1-ol 37 [9] with iodomethyl-trimethylsilane 35 gave alkylated product 38. (Scheme 8)



Scheme 8

After acidic deprotection, 6-(trimethylsilyl)-4-hexyn-1-ol 33 was partially reduced to *cis* –alkenol 39 by P-2 nickel-catalyzed hydrogenation in high yield. A subsequent Mitsunobu reaction (modified from the literature. Initial temperature at –40□C) converted alcohol into *N*-substituted phthalimide 40, which generated unprotected amine 32 upon hydrazinolysis.[6] (Scheme 9)

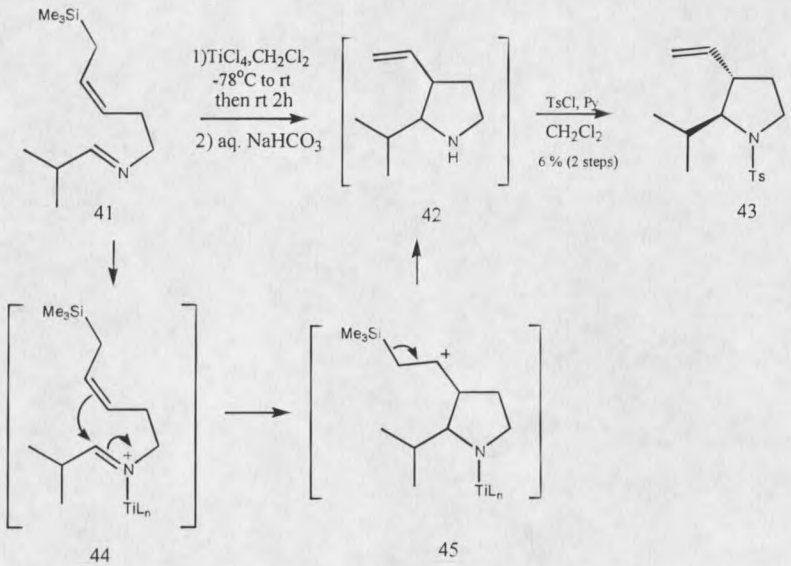


Scheme 9

The desired allylsilane-imines 31 for cyclizations were prepared from amine 32 and aldehyde under 4Å molecular sieves (THF, dichloromethane, or hexane) or anhydrous magnesium sulfate (dichloromethane) conditions. Condensations with molecular sieves were slower but gave cleaner products than those with magnesium sulfate. For imines that tend to form enamine, magnesium sulfate must be used to avoid tautomerization during prolonged reaction period. In most cases, condensations were complete within 12 hours, whereas sterically hindered aldehydes need much longer time to form imines.

Various methods were then explored to effect cyclization. The first attempt made was to use Lewis acid, following the existing model of bis(allylsilane)-imine substrates. [6]

Allylsilane-imine 41 (made from isobutyraldehyde) was treated with $TiCl_4$ at –78°C. The temperature was then allowed to rise gradually to room temperature and stay at room temperature for 2 hours. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate and worked up. After tosylated, cyclized product 43 was detected. However, the yield was only 6%. (Scheme 10)

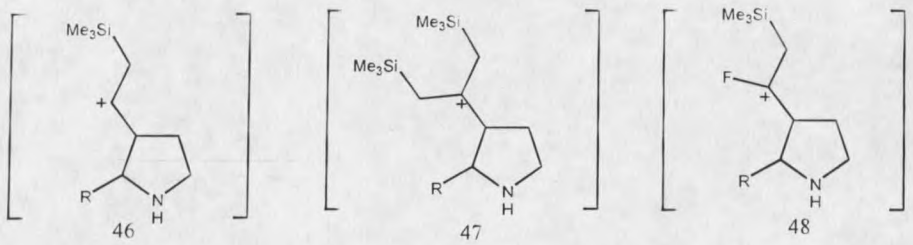


Scheme 10

Considering that pyrrolidine 42 with an isopropyl side-chain had a small molecular weight and might be volatile, which could cause loss in handling and workup, another allylsilane-imine (31, R=Ph) was made and tested for cyclization again (–78°C, then 0°C for 12 hours). However, it didn't give good yield either.

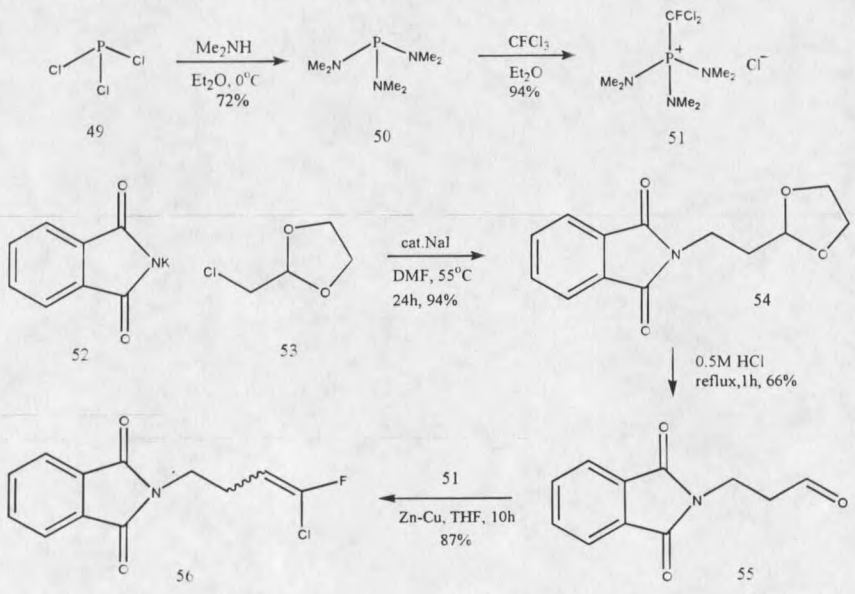
Other Lewis acids ($BF_3{\cdot}Et_2O$, TiF4, Et_2AlCl, $ZrCl_4$) as well as Bronsted acids (CF_3CO_2H, CF_3SO_3H) were tried in attempts to activate the imine moiety. They didn't give the cyclized product. The same conditions used for the allylbis(silane)-imine cyclization were not suitable in the new system. Presumably, the allylbis(silane) can

stabilize the cationic intermediate 47 much better and it is more effectively nucleophilic than the allylsilane (Scheme 11).



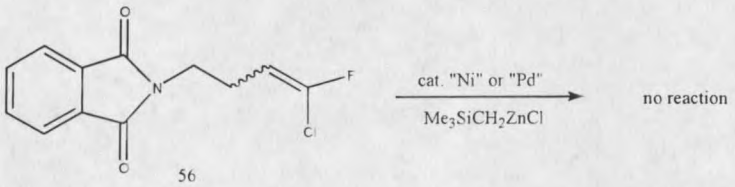
Scheme 11

To accomplish the proposed cyclization, we must increase the reactivity of the allylsilane-imine substrate, either the allylsilane moiety or the imine moiety. Fluorine was known to be able to stabilize its adjacent carbocation.[10] If a fluorinated allylsilane-imine substrate 48 was made, fluorine atom might help increase the reactivity of allylsilane moiety thus promote the cyclization. A route toward the desired fluoroallylsilane-imine substrate was explored. (Scheme 12)



Scheme 12

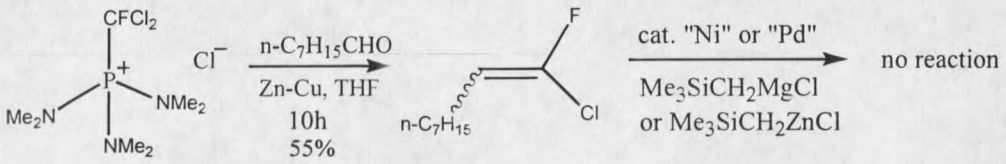
Following the preparation of phosphonamide 50 then ylide salt 51, a Wittig-type reaction was carried out. 1,1-Chlorofluoroalkene 56 was formed with no stereoselectivity between two possible isomers.[11] Unfortunately, catalyzed coupling reaction between chloroalkene 56 and trimethylsilylmethyl zinc reagent (generated from Grignard reagent and zinc chloride) could not be accomplished under various conditions. Neither Pd-based catalysts ($Pd(PPh_3)_2Cl_2$, $Pd(dppb)_2Cl_2$, $Pd(dppf)_2Cl_2$), nor Ni-based catalysts ($Ni(PPh_3)_2Cl_2$, $Ni(dppf)_2Cl_2$) could furnish the coupling. (Scheme 13)



56

Scheme 13

A structural analogue 57 with no other functionality was also made and tested. It didn't give coupling product, either. (Scheme 14) The adjacent fluorine atom could make the C-Cl bond more electron-deficient thus difficult for palladium insersion, which is crucial to the whole catalytic process. The exact reason remains unclear.

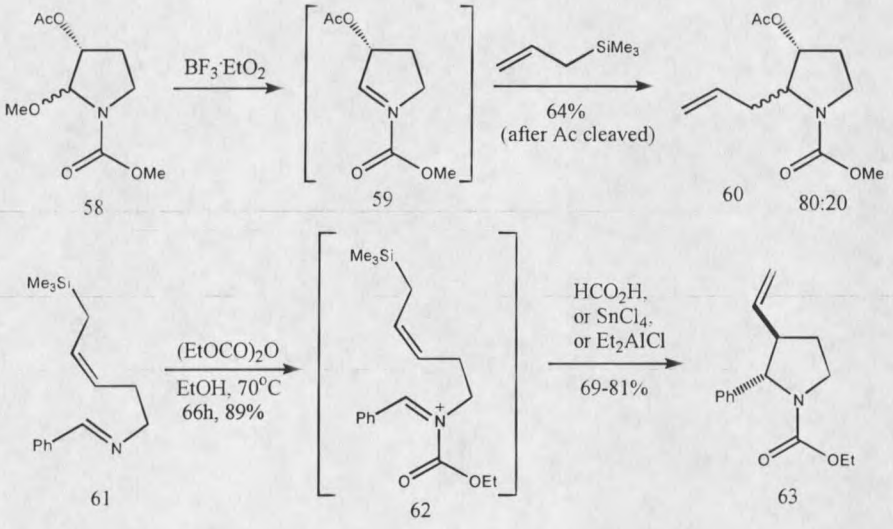


51 57

Scheme 14

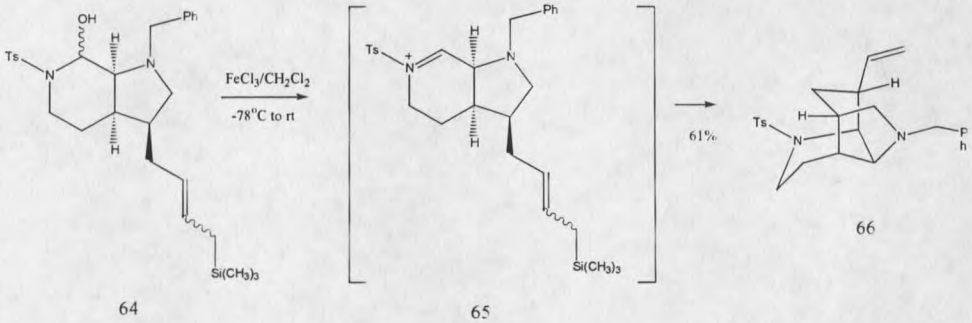
Besides activating the allylsilane moiety, the reactivity of the imine moiety also affects the desired cyclization. Several Lewis had been tested and failed to give satisfactory results. In order to increase the reactivity of iminium ion, another pathway to

the desired the pyrrolidine product was explored. It has been known that *N*-acyliminium ions are much more reactive than the corresponding imines. Allylsilane was added to the *N*-acyliminium ion intermediate 59 generated from the aminal 58.[12a] By converting imine 61 into an *N*-acyliminium ion 62, pyrrolidine 63 was formed by cyclization, although only aromatic imines were explored. [12b] (Scheme 15)



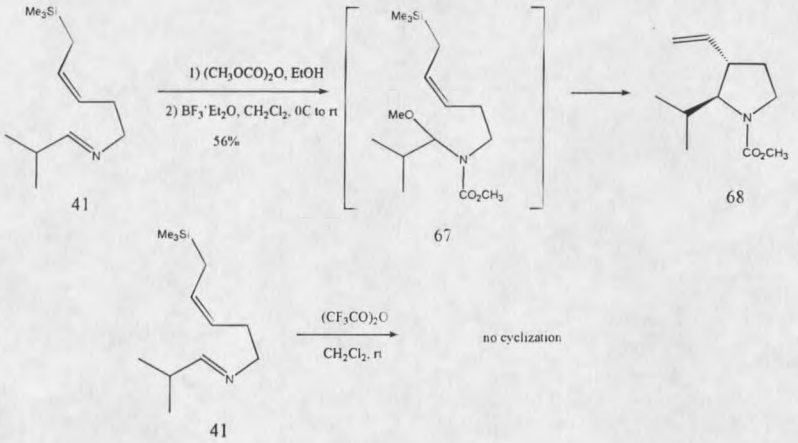
Scheme 15

Tosyliminium ions react in a similar manner. It was used in the contraction of a tricyclic system. (Scheme 16)



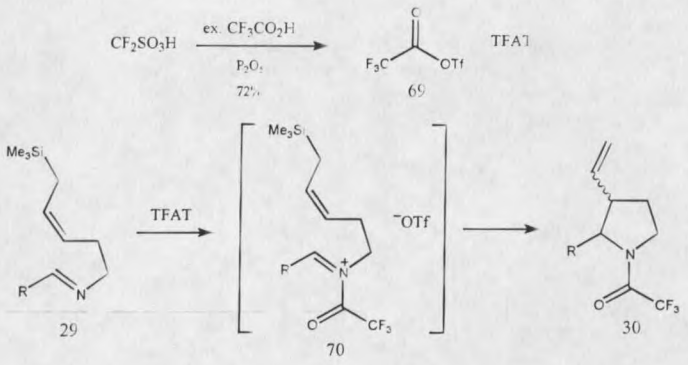
Scheme 16

Similar to a literature procedure.[12b] dimethylpyrocarbonate and Lewis acid were used consequently to convert an allylsilane-imine substrate 41 to iminium ion, cyclized product 68 was isolated as a single isomer. But an effort following the known procedure[6] toward a single-step conversion by using trifluoroacetic anhydride didn't generate the cyclized product. (Scheme 17)



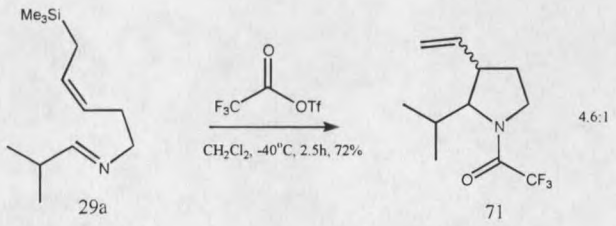
Scheme 17

Trifluoroacetyl triflate 69 (TFAT) was claimed an extremely reactive electrophile.[13] It can be made in the lab by condensation of triflic acid and trifluoroacetic acid with P_2O_5. Because of its high reactivity with electron-rich substrate, it was expected to form trifluoroacetyliminium ion with allylsilane-imine substrate 29, therefore promote the cyclization by activating the imine moiety. Since triflate is an excellent leaving group, it was possible to generate *N*-acyliminium ion 70 without further activation by Lewis acid, thus give rise to the cyclized product 30 in a single step. (Scheme 18)



Scheme 18

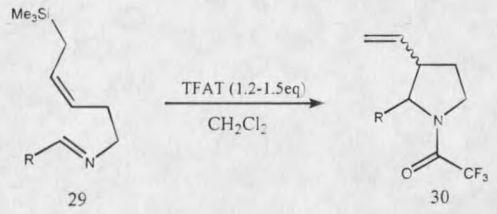
To that end, treatment of an allylsilane-imine 29a with TFAT at -78°C, followed by gradual warming to room temperature, gave the pyrrolidine derivative 30a in 54% yield in a single step (Scheme 19). With optimized conditions (-40°C), the yield was increased to 72%. The product was determined to be diastereomeric mixture of 4.6:1, with *trans*-isomer as the major product (see below). The lability of trifluoromethylacetamide to basic hydrolysis makes it a favorable amine-protecting group. Unprotected pyrrolidine for further conversion can be generated upon basic hydrolysis.



Scheme 19

After optimizing the experiment conditions, more imines were subjected to cyclizations. Most cyclizations were carried out at –40°C for 2-6 hours. For less reactive

substrates, longer reaction time was needed. The scope of this reaction has been evaluated with a variety of substrates. The results are collected in Table 1.

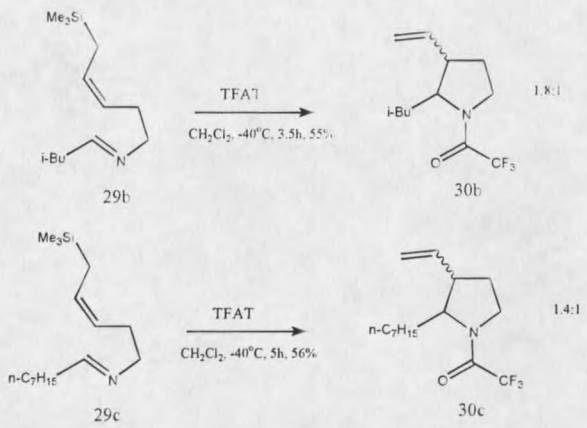


29 30

Table 1 Allylsilane-Imine Cyclizations

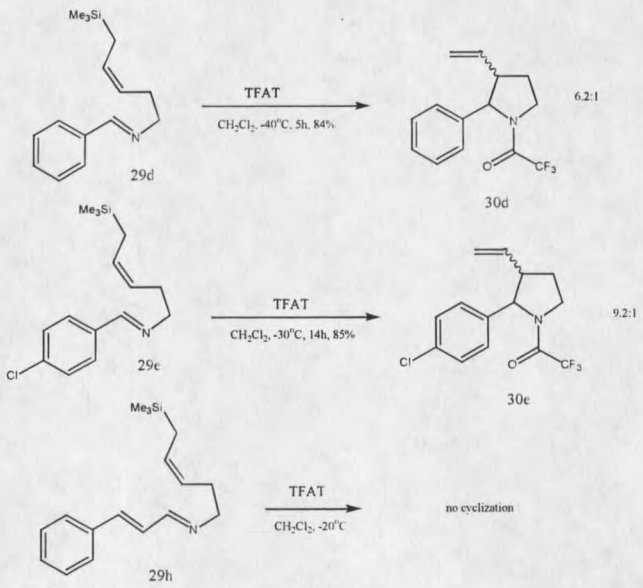
entry	R	Temp (^{o}C)	Time (h)	Yield (%)	Ratio
a	*i*-Pr	-40	2.5	72	1:4.6
b	*i*-Bu	-40	3.5	55	1:1.8
c	*n*-C_7H_{15}	-40	5	56	1:1.4
d	Ph	-40	2.5	84	1:6.2
e	*p*-ClPh	-30	14	85	1:9.2
f	*p*-MeOPh	-20	19	40	1:2.3
g	*o*-MeOPh	-30	14	61	1:1.5

Both aliphatic and aromatic imines undergo cyclization under these conditions. Aliphic imines 29a and 29b formed *trans*-predominant pyrrolidines. (Scheme 20)



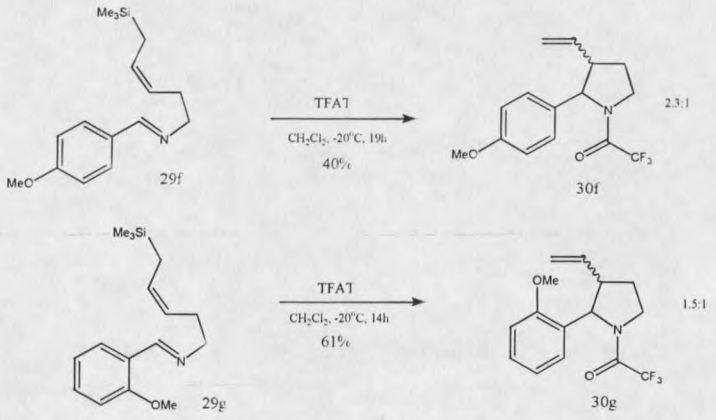
Scheme 20

It is interesting to observe the change of stereochemistry when aromatic imines were used for cyclization. When the side chain was changed to aromatic groups, the cyclization reaction formed pyrrolidines as expected, but with 2,3-*cis* predominant products, usually with higher selectivity. (Scheme 21)



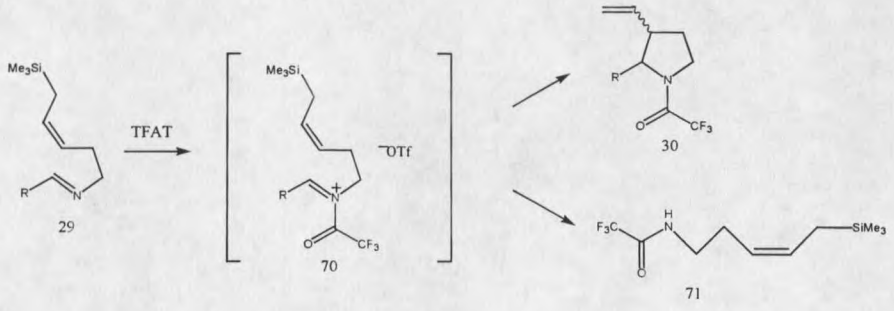
Scheme 21

When aromatic imines with electron-donating group were used, the yields were apparently lower than others. Presumably, an electron-donating group stabilizes the cationic intermediate and lowers its reactivity. (Scheme 22)



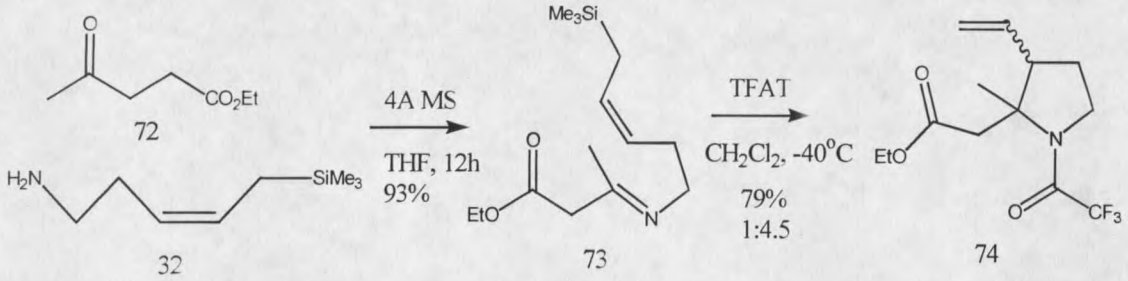
Scheme 22

In all cases, especially in 29f and 29g when imines had electron-donating groups, a considerable amount of byproduct 71 was detected, varying from 1% to 30%.[14] It was possibly generated from aqueous quenching of trifluoroactyliminium ion intermediate 70. When imine had electron-donating groups that help stabilize the carbocation, the highest amount of byproduct 71 was obtained. It could be seen as evidence that the cyclizations occur via a cationic pathway. (Scheme 23)



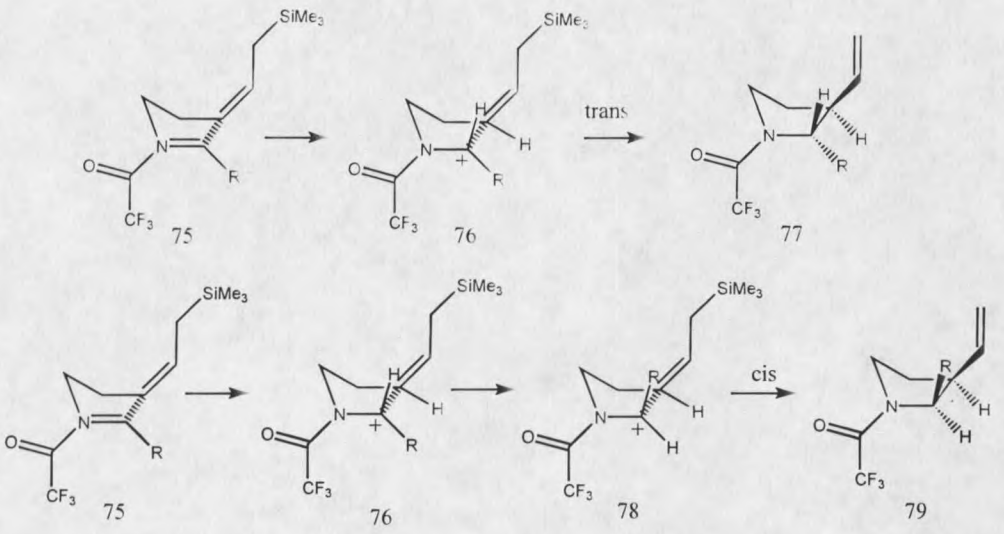
Scheme 23

There was one ketone tested for the cyclizaiton. Ethyl veluvinate was condensed with the precursor amine. The formed imine was subjected to the routine cyclization conditions. The product was formed in good yield and with reasonable diastereo-selectivity. The final stereochemistry has not been assigned yet. (Scheme 24)



Scheme 24

The reaction cyclization is 5-exo-trig for allylsilane moiety, while 5-endo-trig for imine moiety. Its transition state may be an envelop-shaped 5-member ring. (Scheme 25) To avoid higher steric hindrance, two groups prefer to stay at two faces (76). In the cases of aromatic imines, the aromatic substituent can stabilize the adjacent carbocation. Rotation around the C-N bond transforms *trans* orientation to *cis*. Moreover, LUMO of the imine moiety is delocalized through trifluoroactyl group and aromatic substituent. To reach the maximum overlapping with HOMO of allylsilane moiety, aromatic group prefers to be at the same face with allylsilane group (78).



Scheme 25

There was difficulty in the determination of exact ratio of two possible pyrrolidine stereoisomers. ^{1}H-NMR and GC are among the easiest methods used to determine the ratio of a pair of stereoisomers. In this case, the complicated signals of amide compounds hindered the direct reading of ratio from ^{1}H-NMR spectra. Their similar chromatographic property made it difficult to isolate enough pure sample for GC calibration. Quantitative ^{13}C-NMR were also tried but failed to give accurate integration due to the insufficient signal intensities.

^{19}F-NMR was finally chosen to determine the ratio of two stereoisomers. In most cases, however, four peaks representing two *N*-trifluoroactylpyrrolidine isomers, and two close peaks representing byproduct were observed. Analytically pure samples were isolated with preparative gas chromatography. When two isomers were too close to separate, a partial separated sample was subjected to ^{19}F-NMR measurement. The change in relative intensity of signals was used to assign the peaks in the original ^{19}F-NMR spectrum.

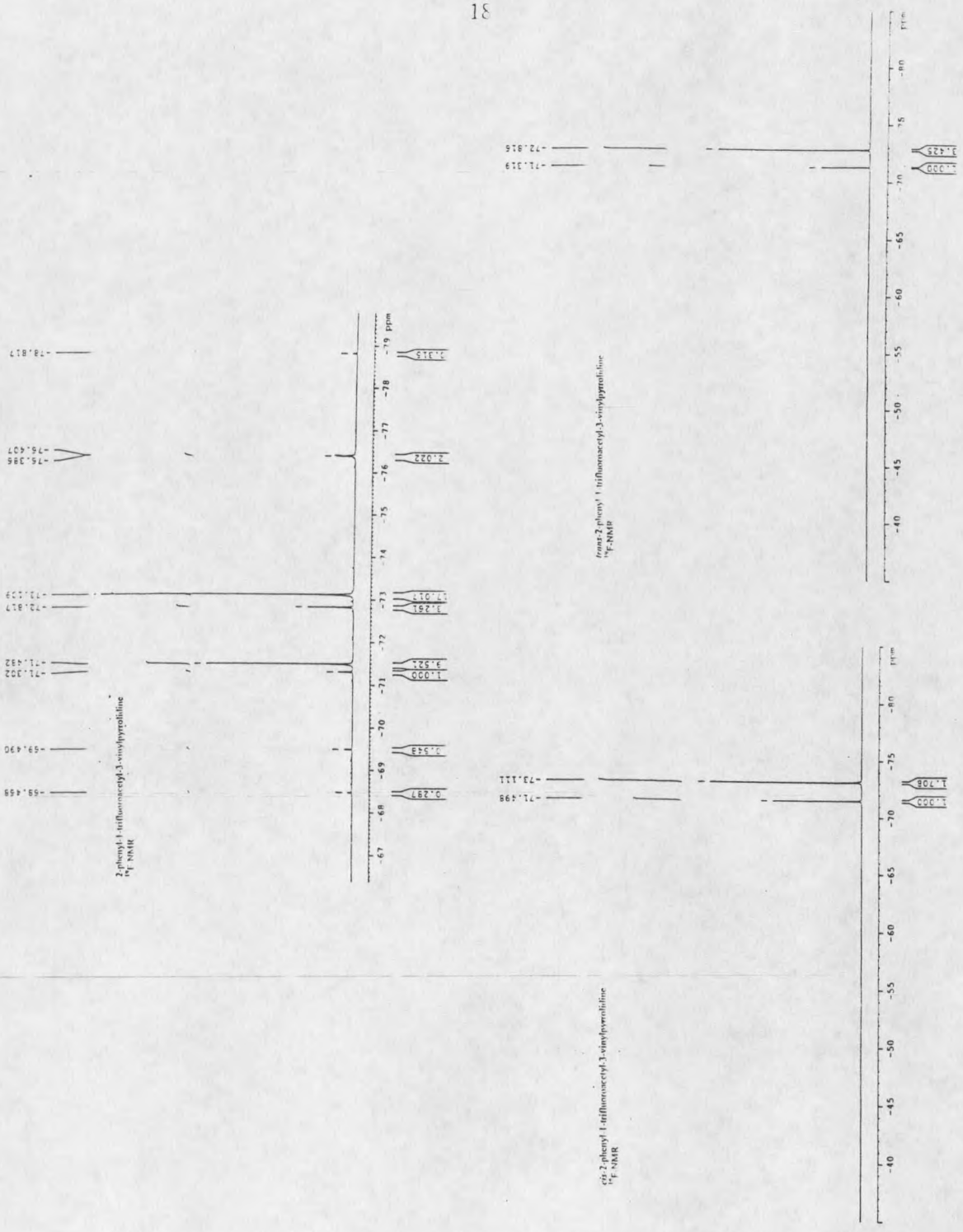
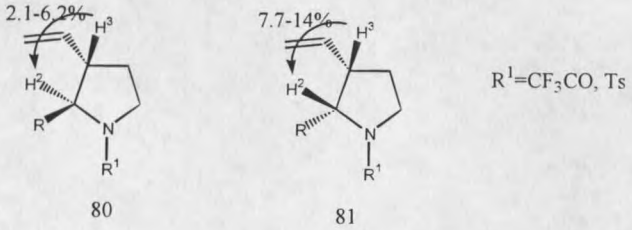


Figure 1. Determination of ratio of diastereomers using F-19 NMR

The stereochemistry at the 2- and 3-position of the pyrrolidine was determined to be *trans* in the cases of aliphatic side-chains, and *cis*- in the cases of aromatic side-chains by NOE experiments. (Scheme 26) The results are similar to those from bis(allylsilane)-imine cyclizations.

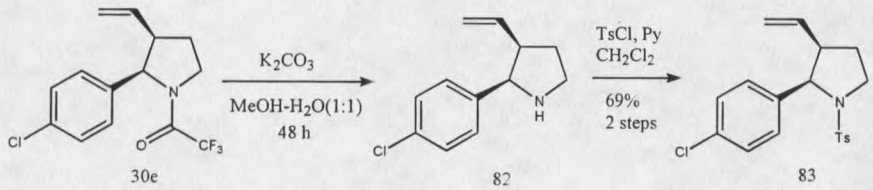


80 81

Scheme 26

In computer modeling experiment, 2-C and 3-C are closer in allylsilane-imine in *cis*- than in *trans*- orientation. In addition, coupling constant is consistent with structurally related compounds formed from allylbis(silane)-imines.[6]

NOE experiments showed similar results. In products of *cis*- orientation, significant NOE was observed between C2-H and C3-H. To confirm the structural assignment, one product was converted to the corresponding *N*-tosylpyrrolidine (Scheme 27). The result of NOE experiment of *N*-tosylpyrrolidine was consistent with that of *N*-trifluoroacetylpyrrolidine.



30e 82 83

Scheme 27

A single crystal of the resulting *N*-tosylpyrrolidine (grown in ethyl ether/hexane) was subjected to X-ray crystallography. The elucidated structure supported the proceeding stereochemistry assignment.

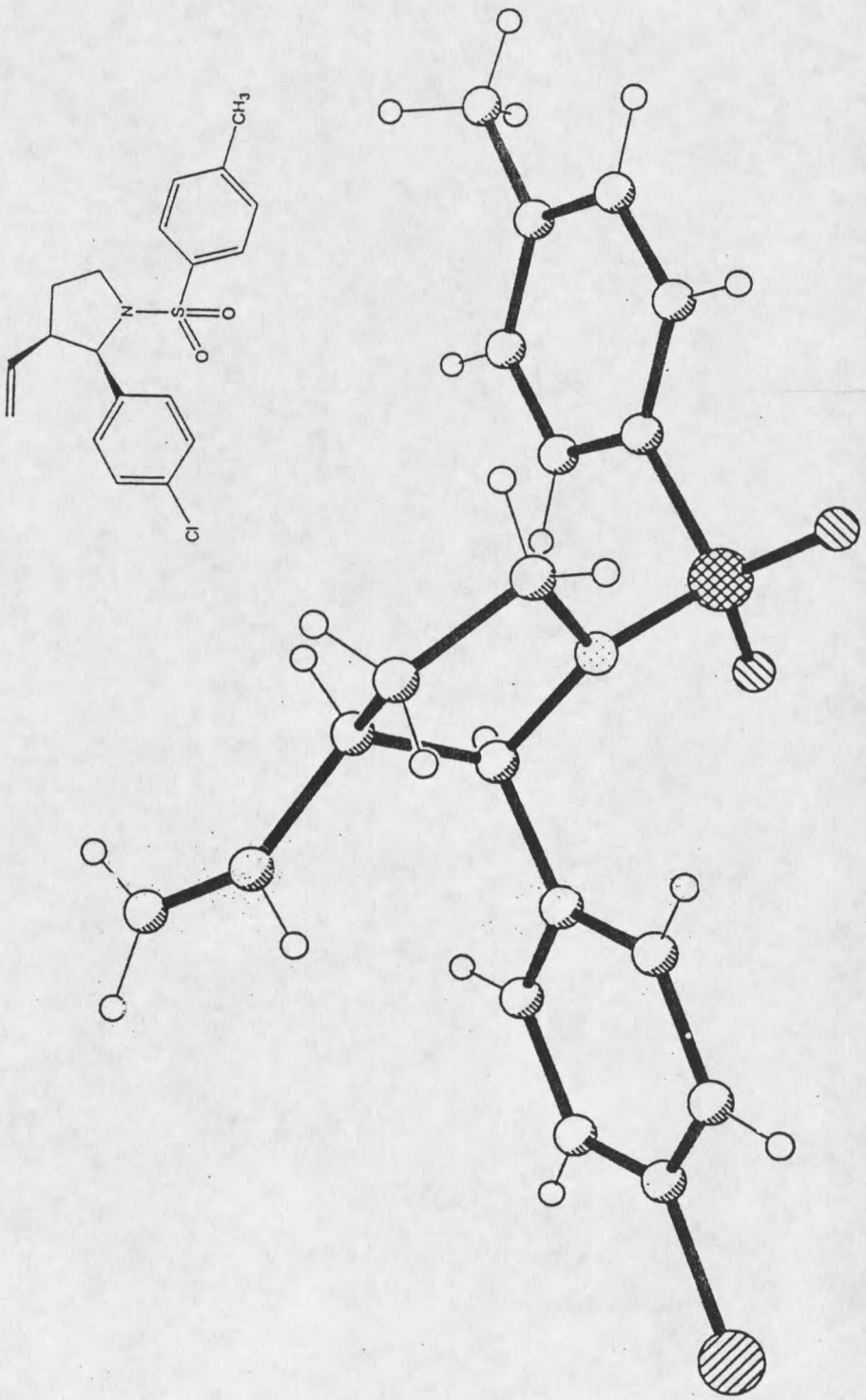


Figure 2. X-ray crystallography structure of *cis*-*N*-Tosyl-2-(4-chlorophenyl)-1-trifluoroacetyl-3-vinylpyrrolidine

CHAPTER 3

EXPERIMENTS

General Experimental Details: ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were measured at 300 MHz, 75 MHz, and 282.2 MHz respectively, with a Bruker AC-300 spectrometer. ^{1}H NMR NOE experiments were performed at 250MHz, with a Bruker AC-250 spectrometer. ^{1}H NMR, data were reported in δ value in ppm relative to residual proton signals in $CDCl_3$ or C_6D_6. ^{1}H NMR coupling constants are reported in Hz and refer to real or apparent multiplicities indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad); dd (doublet of doublet); dt (doublet of triplet); dq (doublet of quartet); etc. Infrared spectra were recorded on a Bruker IFS 25 IR. Electronic impact mass spectra (70 eV) were obtained with a Hewlett Packard 5970 series GC-masspec. High resolution mass spectra were recorded on a VG Instrument 70E-HF spectrometer. Melting points were obtained using a Mel-Temp II apparatus equipped with a Fluke 51 digital thermometer and are uncorrected.

Tetrahydrofuran, diethyl ether were distilled from sodium/benzophenone. Dichloromethane, toluene and dimethylformamide were distilled from CaH_2.

Unless otherwise noted, all reactions were carried out under an atmosphere of argon in flamed or oven-dried vessel with magnetic stir bar and stir plate. Unless otherwise stated, reagents were used without purification.

Iodomethyltrimethylsilane (35)

This procedure was slightly modified in separation from the literature procedure. A mixture of chloromethyltrimethylsilane (13.2 g, 107.5 mmol), sodium iodide (32.2 g, 215 mmol), tetrabutylammonium iodide (7.9 g, 21.5 mmol), and water (18 mL) was heated to reflux for 4 hours. After cooled to room temperature, the mixture was partitioned between water and pentane. The mixture settled into two phases with a thick interface of gray suspension. After filtration through a pad celite (washed with pentane), a clear two-phase solution was obtained. The organic phase was separated and washed with water (2x20 mL), then dried over magnesium sulfate. After filtration, pentane was evaporated under reduced pressure while the flask containing the product was cooled with an ice bath. The concentrated clear or lightly colored liquid was distilled (136 °C, 745 mmHg) to afford the product as a clear liquid (16.726g, 73%). The resulting iodide was used immediately. The compound shows pink color, a sign of decomposition, within 24 hours at 0 °C.

2-But-3-ynyloxy-tetrahydro-pyran (37)

To a mixture of 3--butyn-1-ol (2.9 mL, 38 mmol), dihydropyran (3.8 mL, 42 mmol) in CH_2Cl_2 (2 mL) cooled at 0# was added p-toluenesulfonic acid (10 mg; 20 mg) in one portion. Stirring was continued at that temperature for 30 minutes, followed by at room temperature for 16 hours. The solution was transferred to a separatory funnel, washed with saturated $NaHCO_3$ (15 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). The combined CH_2Cl_2 solution was dried over

Na_2SO_4. After filtration and evaporation, the residue was distilled (water aspirator, ~ 20 mmHg, 113-117 □C) to afford 2-but-3-ynyloxy-tetrahydro-pyran (THP-protected 3-butyn-1-ol) (4.78 g, 82 %) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (t, 1H, CH(OR)2), 3.8-4.0 (m, 2H, OCH_2), 3.4-3.6 (m, 2H, OCH_2), 2.5 (m, 2H, $C{=}CCH_2$), 2.0 (t, 1H, C=CH), 1.3-1.8 (m, 6H, $(CH_2)_3$)

6-(Trimethylsilyl)-4-hexyn-1-ol (33)

To a stirred solution of THP-protected 3-butyn-1-ol (30.84 g, 0.20 mol) in THF (200 mL) at –40 °C (bath) and under argon was added dropwise butyllithium (81.4 mL, 2.457 M in hexane, 0.20 mol), followed by stirring at –30 °C (bath) and 0 °C (bath) each for 15 min. Iodomethyltrimethylsilane (42.85 g, 0.20 mol) was added in one portion. The reaction flask was then cover with aluminum foil and heated with stirring at 55 °C for 36 hours. The reaction mixture was allowed to cool down to room temperature, then diluted with 500 mL of pentane. The resulting mixture was washed with water (3x300 mL), dried over $MgSO_4$, and concentrated in vacuo. Crude product was obtained as a yellowish oil which could be used without further purification (GC > 98 %). (It could be purified with Kugelrohr distillation to give a colorless oil in 70% yield).

To the solution of the crude from the previous step in methanol (300 mL) was added 2 drops of 98% sulfuric acid. The mixture was stirred at room temperature for 12 hours. The mixture was transferred to a 2 L separatory funnel. 300 mL of ethyl ether and 300 mL pentane were added. The resulting mixture was washed with half-saturated $NaHCO_3$ (400 mL), water (400 mL), and brine (400 mL), then dried over $MgSO_4$. After

filtration and evaporation of the solvent, fractional distillation (61-65°C, 2 mmHg) afforded the pure product as a clear liquid. (22.28g, 0.143 mol, 71.3% for 2 steps) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, 2H, J=6.2, OCH_2), 3.37 (s, 1H, OH), 2.40 (m, 2H, CH_2C=), 1.41 (t, J=2.6, 2H, CH_2Si), 0 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 129.1, 122.5, 62.5, 30.6, 18.7, -1.8;

(*Z*)-5-(Trimethylsilyl)-3-penten-1-ol (39)

To a stirred solution of nickel acetate hydrate (1.05 g, 4.2 mmol, 25% mol) in absolute ethanol (30 mL), under an atmosphere of argon, was added a solution of $NaBH_4$ in ethanol (4.2 mL, 4.2 mol, 1.0 M, 25% mol). The mixture turned black immediately upon addition. The flask was purged with hydrogen and ethylenediamine (0.56 mL, 8.4 mmol, 50% mol) was introduced. After 5 min, a solution of 6-(trimethylsilyl)-4-hexyn-1-ol (2.64g, 16.9 mmol) in absolute ethanol (4 mL) was added. The reaction mixture was stirred vigorously under hydrogen atmosphere for 5 hours (TLC). Significant absorption of hydrogen was observed. The reaction mixture was concentrated under reduced pressure and the residual was triturated with dichloromethane. Filtration through a short column of Florisil (CH_2Cl_2 as elutant), followed by evaporation of the solvents under reduced pressure gave the product which was pure enough (GC > 96%) for further transformation (2.53g, 16.0 mmol, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48-5.66 (m, 1H, CH=C), 5.16-5.33 (m, 1H, C=CH), 3.62 (q, 2H, OCH_2, J=6.4), 2.38 (q, 2H, J=7.2, CH_2C=), 1.50 (d, J=8.5, 2H, CH_2Si), 0 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 129.1, 122.5, 62.5, 30.6, 18.7, -1.8;

N-(*Z*)-(5-Trimethylsilylpent-3-enyl)phthalimide (40)

The preparation of phthalimide is modified from the literature. The reduction of the initial temperature (bath) to –40 °C greatly improved the yield. Presumably, the reaction of triphenylphosphine with diethyl diazocarboxylate is highly exothermic, which may cause certain side effect in Mitsunobu reaction. To a stirred mixture of (*Z*)-5-(trimethylsilyl)-3-penten-1-ol (6.62 g, 41.8 mmol), triphenylphosphine (12.06 g, 46.0 mmol, 1.1), phthalimide (9.23 g, 62.7 mmol), and THF (160 mL) at -40 °C (solids partially soluble) was added dropwise diethyl azodicarboxylate (7.25 mL, 46.0 mmol) over 30 min. The reaction mixture was allowed to warm to 0°C over 5 hours. The reaction mixture was then kept stirring at room temperature for 12 hours. Solvent was removed under reduced pressure. After most triphenylphosphine oxide was removed by recrystalization (ethyl acetate / hexane), the residue was subject to a short column of silica gel to remove the rest of triphenylphosphine oxide (10% ethyl acetate / hexane). Chromatography again on silica gel afforded the pure product as a colorless viscous oil (11.79 g, 41.0 mmol, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.82 (m, 2H, ArH), 7.58-7.68 (m, 2H, ArH), 5.35-5.55 (m, 1H, CH=C), 5.150-5.30 (m, 1H, C=CH), 3.65 (t, J=7.4, 2H, NCH_2), 2.32 (q, 2H, J=7.2, CH_2C=), 1.40 (d, 2H, J=8.7, CH_2Si), -0.08 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 168.8, 134.2, 132.6, 129.2, 123.5, 122.8, 38.1, 26.7, 19.0, -1.5;

(*Z*)-5-Trimethylsily-3-penten-1-amine (32)

To a 100 mL, single-necked, round-bottom flask containing a solution of phthalimide (4.22g, 14.7mmol) in degassed absolute ethanol (45 mL) was added hydrazine monohydrate (1.5 mL, 30 mmol) dropwise over 2 min via a syringe. The flask was then fitted with a condenser and the mixture was heated to reflux for 2.5 hours, during with a white solid precipitated. Upon cooling to room temperature, the solids was collected by filtration and washed thoroughly with hexane. The solvents were evaporated under reduce pressure and the residual was triturated with hexane. Filtration of the supernatant liquid followed by solvent removal *in vacuo* gave a cloudy liquid which was subject to Kugelrohr distillation (55 ^{o}C, 1.1 mmHg) to furnish the pure product (1.66g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.43-5.56 (m, 1H, CH=C), 5.16-5.29 (m, 1H, C=CH), 2.64-2.77 (t, 2H, NCH_2), 2.07-2.21 (q, 2H, CH_2C=), 1.68 (s, br, 2H, NH_2), 1.48 (d, 2H, CH_2Si), 0 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 128.0, 124.7, 42.4, 31.7, 19.0, -1.5; IR (film): 3338 (br), 2955, 1671, 1248, 856

(*S*)-Ethyl-(*O-tert*-butyldiphenylsilyl)lactate

To a 25 mL, single-necked , round-bottom flask containing a solution of *t*-butylchloro-diphenylsilane (2.6 mL, 10 mmol) and imidazole (1.63 g, 24 mmol) in DMF (5 mL) was added (S)-ethyl lactate (1.36 mL, 12 mmol) dropwise over a 30 min via a 5.0 mL addition funnel. During the course for the addition, mild exotherms and precipitation of a clear oil were observed. The reaction mixture was stirred at room temperature for 5 hours and let settle overnight into two layers. The bottom layer was removed with a separatory

funnel and extracted with hexane (3X5 mL). The combined product layer and extracts were washed with water (2X5 mL) the , dried over MgSO4, filtered and concentrated. The residual was eluted through a plug of silica gel and concentrated *in vacuo* to furnish the protected ester (3.27 g, 92%) as a colorless viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6-7.8 (m, 4H, ArH), 7.3-7.5 (m, 6H, ArH), 4.25 (q, 1H, J=6.8, OCH), 4.0 (q, 2H, J=7.1, OCH_2), 1.35 (d, 3H, J=6.7, $CHCH_3$), 1.13 (t, 3H, J=7.1, OCH_2CH_3), 1.08 (s, 9H, $SiC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 204.1, 136.1, 133.7,133.4, 130.4, 128.2, 74.9, 27.3, 19.6, 18.8;

(*S*)-Ethyl-(*O*-tert-butyldiphenylsilyl)lactaldehyde

A 50 mL, single-necked , round-bottom flask containing a solution of (*S*)-ethyl-(*O*-*t*-butyldiphenylsilyl)lactate (3.25g, 9.12 mmol) in toluene (18 mL) was cooled to -78 °C and diisobutylaluminum hydride (10 mL, 10 mmol, 1.0M in toluene) was added dropwise over 20 min via a 10 mL addition funnel. The reaction mixture was stirred for 2 hours and was carefully poured into half-saturated brine (50 mL). The biphasic mixture was extracted with ether (3X20 mL). The combined organic phase was washed with brine (40 mL), dried over $MgSO_4$, filtered and concentrated. The residual was eluted through a thin pad of silica gel (hexane as elutant) to provide the aldehyde. (2.30 g, 81%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.6 (s, 1H, CHO), 7.6-7.8 (m, 4H, ArH), 7.3-7.5 (m, 6H, ArH), 4.1 (q, 1H, J=6.8, OCH), 1.2 (d, 3H, J=6.7, $CHCH_3$), 1.13 (t, 3H, J=7.1, OCH_2CH_3), 1.08 (s, 9H, $SiC(CH_3)_3$);

Ethyl *O-t*-butylsimethylsilylactate

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (q, 1H, J=6.7, CHOTBS), 4.08-4.22 (m, 2H, OCH_2), 1.38 (d, 3H, J=6.7, CH_3CHOTBS), 1.26 (t, 3H, J=7.1, OCH_2CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.07 (d, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 174.5, 68.8, 61.1, 26.1, 21.7, 18.7, 14.6, -4.6, -4.9; IR (film) 2951, 2856, 1760, 1480, 1375, 1265, 1144, 1060, 830, 785;

O-t-Butylsimethylsilylactaldehyde

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (1H, N=CH), 4.06 (q, 1H, J=6.8, CHOTBS), 1.23 (d, J=6.8, CH3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.07 (d, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 204.5, 26.1, 18.9, 18.5, -4.4(d); IR (film) 2391, 1741, 1473, 1375, 1255, 1134, 1098, 1007, 837, 778

General procedure for the generation of allylsilane-imine: To a 10 mL single-necked round-bottom flask containing a solution of amine (1 mmol) in THF (3 mL) was added activated 4 Å molecular sieves followed by fleshly distilled isobutyraldehyde. The mixture was stirred at room temperature for appropriate time (mostly 12 hours) before diluted with diethyl ether (3 mL) and filtered through a plug of Celite. Evaporation of solvents and excessive aldehyde in vacuo afforded imine as colorless oil which was used immediately for further transformation without any purification.

Isobutylidene-(*Z*)-(5-trimethylsilylpent-3-enyl)amine (29a)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5 (1H, N=CH), 5.26-5.82 (m, 1H, CH=C), 5.0-5.2 (m, 1H, C=CH), 3.1-3.4 (m, 2H, NCH_2), 2.0-2.4 (m, .2H, CH_2C=), 1.3-1.5 (m, 2H, =CCH_2Si), 1.0 (dd, 6H, J=6.8), -0.05 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 170.2, 127.5, 124.6, 61.5, 34.4, 29.1, 19.8, 19.0, -1.4;

Benzylidene-(*Z*)-(5-trimethylsilylpent-3-enyl)amine (29d)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.3 (s, 1H, N=CH), 7.7 (m, 2H, ArH), 7.3 (m, 3H, ArH), 5.5 (m, 1H, CH=C), 5.3 (m, 1H, C=CH), 3.6 (m, 2H, NCH_2), 2.4(q, J=7.2, CH_2C=), 1.5 (d, J=8.5, 2H, CH_2Si), 0(s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 161.41, 136.72, 130.87, 128.95, 128.47, 127,68, 124.62, 62.03, 29.19, 19.05, -1.38; IR (film) 3007, 2952, 2834, 1646, 1580, 1450, 1310, 1247, 1149, 1052, 857, 753, 693

4-Chlorobenzylidene-(*Z*)-(5-trimethylsilylpent-3-enyl)amine (29e)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.2 (s, 1H, N=CH), 7.6 (m, 2H, ArH), 7.4 (m, 2H, ArH), 5.5 (m, 1H, CH=C), 5.3 (m, 1H, C=CH), 3.6 (m, 2H, NCH_2), 2.4(q, J=7.2, CH_2C=), 1.5 (d, J=8.5, 2H, CH_2Si), 0(s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 160.0, 129.7, 129.2, 127.8, 124.5, 62.0, 29.1, 19.1, -1.4;

4-Methoxybenzylidene-(Z)-(5-trimethylsilylpent-3-enyl)amine (29f)

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 1H, N=CH), 7.61-7.69 (m, 2H, ArH), 6.86-6.94 (m, 2H, ArH), 5.39-5.53 (m, 1H, CH=C), 5.22-5.35 (m, 1H, CH=C), 3.81 (s, 3H,

$ArOCH_3$), 3.19-3.61 (t, 2H, J=7.3, NCH_2), 2.31-2.42 (q, 2H, J=7.2, NCH_2CH_2), 1.48 (d, 2H, J=8.6, CH_2Si), -1.56 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 162.1, 131.4, 131.1, 128.9, 126.1, 116.1, 115.7, 63.3, 57.1, 30.7, 20.4, 0;

2-Methoxybenzylidene-(*Z*)-(5-trimethylsilylpent-3-enyl)amine (29g)

^1H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 1H, N=CH), 7.88-7.95 (m, 1H, ArH), 7.30-7.39 (m, 1H, ArH), 6.85-7.00 (m, 2H, ArH), 5.40-5.53 (m, 1H, CH=C), 5.24-5.35 (m, 1H, CH=C), 3.85 (s, 1H, OCH_3), 3.57-3.65 3.6 (td, 2H, J=7.4, 1.0, NCH_2), 2.32-2.43 (q, J=7.1, CH_2C=), 1.46-1.53 (d, J=8.4, 2H, CH_2Si), -0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 159.1, 157.4, 132.1, 127.7, 127.5, 125.2, 124.8, 121.2, 111.4, 62.3, 55.9, 29.4, 19.4, -1.4; IR (film) 3006, 2953, 2836, 1638, 1600, 1488, 1465, 1248, 1159, 1029, 856, 754;

2-*t*-Butyldimethylsiloxyethylidene-(*Z*)-(5-trimethylsilylpent-3-enyl)amine

^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 1H, J=5.0, N=CH), 5.26-5.82 (m, 1H, CH=C), 5.50-5.25 (m, 1H, C=CH), 4.28-4.31 (dq, 1H, J=6.5, 5.4, CHOTBS), 3.33-3.38 (t, 2H, J=7.2, NCH_2), 2.22-2.29 (ddd, J=6.9, 7.1, 2H, CH_2C=), 1.45 (d, 2H, J=8.6, $=CCH_2Si$), 1.24 (d, 3H, J=6.5, CH_3CHOTBS), 0.87 (s, 9H, $SiC(CH_3)_3$), 0.04 (d, 6H, $Si(CH_3)_2$), -0.03 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 168.2, 127,6, 124.5, 71.0, 61.1, 28.9, 26.2, 22.2, 19.1, 18.6, -1.4, -4.2; IR (film) 2951, 2856, 1676, 1473, 1362, 1252, 1148, 1091, 1005, 836, 777;

General procedure for allysilane-imine cyclizations: To a solution of allysilane-imine in dichloromethane (0.1-0.16M) at –78 °C was added 1.2-1.5 equivalent of TFAT over two minutes. The mixed solution was kept at the –78 °C for ten minutes, then at the setting temperature (ranging from - 40°C to -20 °C). After an appropriate reaction time, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The mixture was stirred at 0 °C for 1 hour. The organic phase was separated. The aqueous phase was extracted with dichloromethane for three times. The combined dichloromethane solution was dried over $MgSO_4$. After filtration of $MgSO_4$ followed by evaporation of dichloromethane, the residue was subjected to flash chromatography on silica gel and gave the cyclized product of *N*-trifluoromethylated pyrrolidine. An analytical sample of pure isomer was isolated by preparative gas chromatography.

trans-2-Isopropyl-1-trifluoroacetyl-3-vinylpyrrolidine (30a, *trans*)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.8-6.0 (m, 1H, C=CH), 5.1-5.2 (m, 2H, $C=CH_2$), 4.2 (t, 0.8H, J=6.7, C2-H), 3.3-3.9 (m, 2.2H, C5-H, C2-H), 2.7-2.9 (m, 1H, C3-H), 1.7-2.2 (m, 2H, C4-H); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 137.3, 129.1, 128.0, 127.9, 125.9, 125.3, 117.1, 116.5, 67.9, 52.7, 51.2, 47.9, 47.5, 31.1, 26.5; ^{19}F-NMR (82.2MHz $CDCl_3$) δ –71.4, -72.9; IR (film): 2960, 1693, 1557, 1455, 1204, 1146, 920, 854; HRMS: 235.1178 (calc 235.1184); NOE enhancement between C2-H and C3-H: 5.7%;

trans-2-Isobutyl-1-trifluoroacetyl-3-vinylpyrrolidine (30b, *trans*)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66-5.85 (m, 1H, C=CH), 5.02-5.24 (m, 2H, C=CH_2), 4.14-4.40 (m, 1H, C2-H), 3.30-3.80 (m, 2H, C5-H), 2.68-2.90 (m, 1H, C3-H), 1.85-2.33 (m, 2H, C4-H), 1.20-1.65 (m, 3H, C2-CH_2CH), 1.10-1.20 (m, 0.5H, CH(CH_3)$_2$), 0.75-1.14 (m, 5.5H, CH(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$, DEPT 135) δ 135.2, 117.5, 59.8, 45.0, 44.9, 38.7, 28.7, 25.5, 22.8, 22.7; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –70.6, -72.7; IR (film); 2958, 1692, 1592, 1447, 1245, 1200, 1141, 855; HRMS: 249.1343 (calc 249.1340); NOE enhancement between C2-H and C3-H: 6.2%;

trans-2-Heptyl-1-trifluoroacetyl-3-vinylpyrrolidine (30c, *trans*)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60-5.85 (m, 1H, C=CH), 4.92-5.24 (m, 2H, C=CH_2), 3.82-4.02 (m, 1H, C2-H), 3.82-4.02 (m, 1H, C5-H), 3.40-3.60 (m, 1H, C5-H), 2.55-2.80 (m, 1H, C3-H), 2.05-2.23 (m, 1H, C4-H), 1.41-1.90 (m, 3H, C4-H, C2-CH_2), 1.10-1.41 (s, br, 10H, C2-CH_2(CH_2)$_5$), 0.77-0.95 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 139.0, 116.0, 64.1, 46.2, 45.7, 32.2, 29.9, 29.6, 26.7, 25.7, 23.0, 14.5; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –71.0, -72.7; IR (film); 2928, 2857, 1691, 1452, 1240, 1200, 1141, 919; HRMS: 291.1804 (calc 291.1810); NOE enhancement between C2-H and C3-H: 2.1%;

cis-2-Heptyl-1-trifluoroacetyl-3-vinylpyrrolidine (30c, *cis*)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58-5.90 (m, 1H, C=CH), 5.00-5.28 (m, 2H, C=CH_2), 4.18-4.35 (m, 0.8H, C2-H), 3.98-4.10 (m, 0.2H, C2-H), 3.45-3.85 (m, 2H, C5-H), 2.70-

2.92 (m, 1H, C3-H), 1.88-2.15 (m, 2H, C4-H), 1.11-1.62 (m, 12H, C2-$(CH_2)_6$), 0.77-0.95 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 135.5, 117.9, 62.0, 45.5, 45.2, 32.2, 30.1, 30.0, 29.5, 29.2, 27.0, 23.0, 14.5; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –70.8, -72.7; IR (film); 2929, 2856, 1691, 1449, 1241, 1201, 1141, 919; HRMS: 291.1819 (calc 291.1810); NOE enhancement between C2-H and C3-H: 7.7%;

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cis-2-Phenyl-1-trifluoroacetyl-3-vinylpyrrolidine (30d, *cis*)

^1H NMR (300 MHz, $CDCl_3$) δ 7.18-7.36 (m, 3H, ArH), 6.94-7.08 (m, 2H, ArH), 5.15-5.28 (m, 1H, ArCHN), 4.88-5.14 (m, 3H, C=CH), 4.03-4.20 (m, 0.6H, NCH), 3.92-4.03 (m, 0.4H, NCH), 3.70-3.89 (m, 1H, NCH), 2.97-3.21(m, 1H, C3-H), 1.81-2.20 (m, 2H, C4-H); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 138.7, 137.6, 135.9, 135.8, 128.7, 128.1, 128.0, 127.1, 126.9, 122.4, 118.6, 118.3, 118.0, 117.8, 114.8, 65.9, 65.4, 49.7, 48.5, 47.1, 47.0, 46.9, 29.5, 26.2; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –71.5, -73.1; IR (film): 2980, 2903, 1695, 1448, 1347, 1240, 1200, 1139, 923, 756, 702; HRMS: 269.1028 (calc 269.1027); NOE enhancement between C2-H and C3-H: 9.4%

trans-2-Phenyl-1-trifluoroacetyl-3-vinylpyrrolidine (30d, *trans*)

^1H NMR (300 MHz, $CDCl_3$) δ 6.7-7.4 (m, 6H, ArH), 5.75-5.92 (m, 1H, C=CH), 5.0-5.2 (m, 2.2H, C=CH_2, C2-H), 4.8 (d, 0.8H, J=6.1, C2-H), 3.7-4.1 (m, 2H, C5-H), 2.7-2.9 (m, 1H, C33-H), 1.8-2.4 (m, 2H, C4-H) ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 137.3, 129.1, 128.0, 127.9, 125.9, 125.3, 117.1, 116.5, 67.9, 52.7, 51.2, 47.9, 47.5, 31.1, 26.5; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –71.3, -72.8; IR (film): 2932, 1692, 1448, 1239, 1195,

1140, 997, 754; HRMS: 269.1018 (calc 269.1027); NOE enhancement between C2-H and C3-H: 2.5%

cis-2-(4-Chlorophenyl)-1-trifluoroacetyl-3-vinylpyrrolidine (30e, *cis*)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.36 (m, 2H, ArH), 6.85-7.03 (m, 2H, ArH), 4.90-5.24 (m, 4H, ArCHN, $CH=CH_2$), 3.90-4.18 (m, 1H, C5-H), 3.70-3.89 (m, 2H, C5-H), 2.97-3.22 (m, 1H, C3-H), 1.75-2.20 (m, 2H, C4-H); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 137.3, 136.3, 135.4, 135.3, 134.0, 133.8, 129.0, 128.4, 128.2, 118.5, 118.3, 114.7, 65.4, 64.8, 49.5, 48.5, 47.0, 46.7, 29.5, 26.1; IR (film): 2936, 1692, 1491, 1448, 1239, 1202, 1145, 1091; HRMS: 361.0906 (calc 361.0903); NOE enhancement between C2-H and C3-H: 12%

cis-2-(4-Methoxyphenyl)-1-trifluoroacetyl-3-vinylpyrrolidine (30f, *cis*)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.77-7.0 (m, 3H, ArH), 4.90-5.22 (m, 4H, C2-H, $CH=CH_2$), 3.88-4.15 (m, 1H, C5-H), 3.7-3.8 (d, 3H, $ArOCH_3$), 2.95-3.14 (m, 1H, NCH), 1.8-2.2 (m, 2H, C4-H); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 136.0, 130.8, 129.7, 128.2, 128.0, 117.9, 117.7, 114.1, 114.0, 65.5, 65.0, 55.6; 50.0, 48.4, 47.0, 29.5, 26.2; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –71.6, -73.2; IR (film): 2958, 2838, 1694, 1612, 1586, 1612, 1514, 1450, 1248, 1199, 1143, 1071, 831; HRMS: 299.1132 (calc. 299.1133); NOE enhancement between C2-H and C3-H: 8.2%

2-(2-Methoxyphenyl)-1-trifluoroacetyl-3-vinylpyrrolidine (30g)

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1-7.3 (m, 1H, ArH), 6.8-7.0 (m, 3H, ArH), 5.6-6.0 (m, 1H, C=CH), 4.8-5.4 (m, 3H, C=CH_2, C2-H), 3.7-4.0 (m, 5H, CH_3, C3-H, C5-H), 2.8-3.2 (m, 1H, C5-H), 1.8-2.3 (m, 2H, C4-H); ; ^{19}F-NMR (282.2MHz $CDCl_3$) δ major: -71.9, -73.0; minor: -71.6, -72.8; ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 138.2, 129.0, 126.9, 125.9, 120.9, 116.1, 111.3, 64.5, 55.8, 48.1, 47.0, 30.3, 25.8; IR (film); 2922, 1694, 1492, 1454, 1237, 1195, 1142, 1108, 754; HRMS: major: 299.1132; minor: 299.1129 (calc 299.1133);

2-(2-Ethoxycarbonylethyl)-2-methyl-1-trifluoroacetyl-3-vinylpyrrolidine (74)

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66-5.90 (m, 1H, C=CH), 4.96-5.34 (m, 2H, C=CH_2), 4.14-4.40 (m, 1H, C2-H), 4.05-4.24 (q, 2H, J=7.1, OC$H_2$$CH_3$), 3.70-3.98 (m, 1H, C5-H), 3.36-3.58 (m, 1H, C5-H), 2.52-2.70 (m, 2H, CH_2COO), 1.83-2.36 (m, 5H, C3-H, C4-H, C2-CH_2), 1.18-1.35 (m, 6H, C2-CH_3, $OCH_2C$$H_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 173.5, 135.0, 119.2, 118.5, 69.1, 61.0, 49.1, 47.3, 30.7, 29.3, 28.6, 24.5, 19.6, 14.6; ^{19}F-NMR (282.2MHz $CDCl_3$) δ –67.5, -68.4, -72.9, -73.1; IR (film); 2981, 1735, 1690, 1440, 1247, 1202, 1142, 1110; HRMS: major 307.1395, minor 307.1395(calc 307.1386);

N-((*Z*)-5-Trimethylsilyl-3-enyl)trifluoroacetamide (71)

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.3(1H, s, br, NH), 5.6 (1H, m, C=CH), 5.2 (1H, m, C=CH), 3.3 (2H, q, J=6.5, NCH_2), 2.3 (2H, q, J=6.6, CH_2CH=), 1.5(2H, d, J=8.6,

CH_2Si), 0(9H, s, $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, ^1H decoupled) δ 130.5, 122.2, 39.9, 26.7, 19.2, -1.4; ^{19}F-NMR (282.2MHz $CDCl_3$) δ -76.41(1F, s), -76.46(3.7F, s); IR (film): 3310, 3107, 3013, 2955, 1704, 1560, 1445, 1369, 1250, 1207, 1184, 956, 723, 701, 644; HRMS: 253.1122 (calc 253.1110);

General procedure for converting *N*-trifluoroacetylpyrrolidine to *N*-tosylpyrrolidine: N-trifluoroacetylpyrrolidine (1mol) was dissolved in 10 mL of a solution of K_2CO_3 (1.5M) in MeOH/H_2O (1:1). The mixture was stirred at room temperature for 48 hours. TLC showed that starting material disappeared. The solution was diluted with water (10 mL) then extracted with dichloromethane (4X10 mL). The combined dichloromethane solution was dried over $MgSO_4$. After filtration and evaporation of solvent under reduced pressure, the residue was triturated with pentane. After filtration through a pad of Celite and evaporation of pentane under reduced pressure, the crude pyrrolidine was treated with tosyl chloride (1.5 mmol) and pyridine (3 mmol) in dichloromethane (2 mL) at 0 □C for 1 hour then at room temperature for 2 hours. Water (2 mL) was added to the reaction vessel and the resulting mixture was stirred vigorously for 1 hour. The organic phase was separated and the remaining aqueous phase was extracted with dichloromethane (3x5 mL). The combined dichloromethane solution was dried over $MgSO_4$. After filtration and evaporation of solvent under reduced pressure, the residue was subjected to column chromatography (silica gel).

cis-2-(4-Chlorophenyl)-1-tosyl-3-vinylpyrrolidine (83)

^{1}H NMR (300 MHz, C_6D_6) δ 7.7-7.8 (d, 2H, ArH), 7.1 (m, 2H, ArH), 6.8-6.9 (m, 4H, ArH), 4.58-4.90 (m, 4H, C2-H, CH=CH_2), 3.47-3.58 (m, 1H, C5-H), 3.17-3.32 (m, 1H, C5-H), 2.37-2.43 (m, 1H, C3-H), 2.0 (s, 3H, $ArCH_3$), 1.28-1.57 (m, 2H, C4-H); ^{13}C NMR (75 MHz, $CDCl_3$, ^{1}H decoupled) δ 143.9, 138.4, 136.1, 135.4, 133.4, 130.0, 129.3, 128.5, 127.8, 117.5, 65.9, 49.1, 48.4, 29.6, 21.9; IR (film): 2918, 2848, 1490, 1348, 1161, 1090, 1011, 922, 817, 665; HRMS: 361.0906 (calc 361.0903); m.p. 97.8-98.8°C; NOE enhancement between C2-H and C3-H (C_6D_6): 14.2%; A single crystal for X-ray crystallography experiment was obtained from ethyl ether/hexane.

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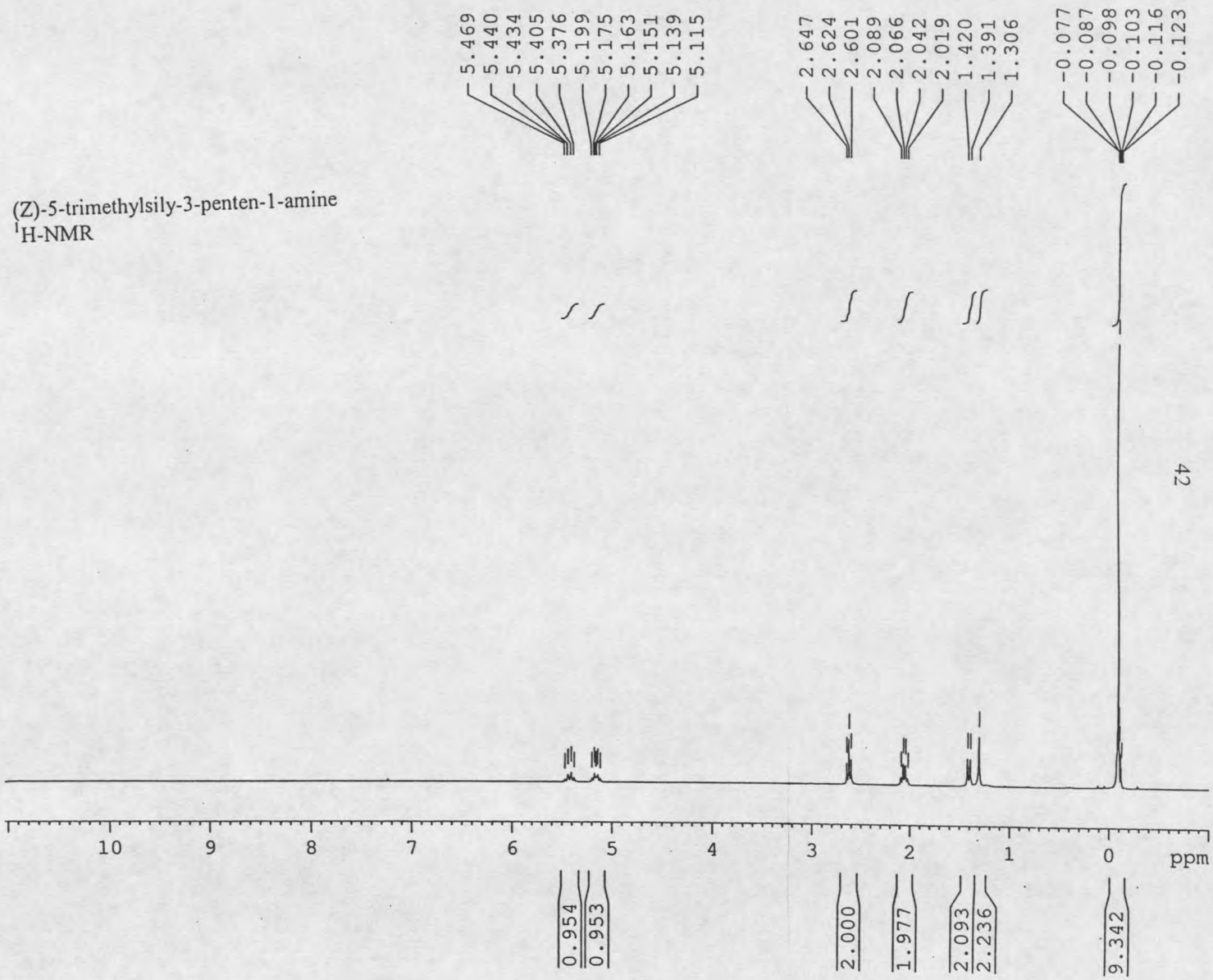
14. entry 6 had the highest amount of byproduct, 30% based on trifluoroacetamide (^{19}F-NMR)

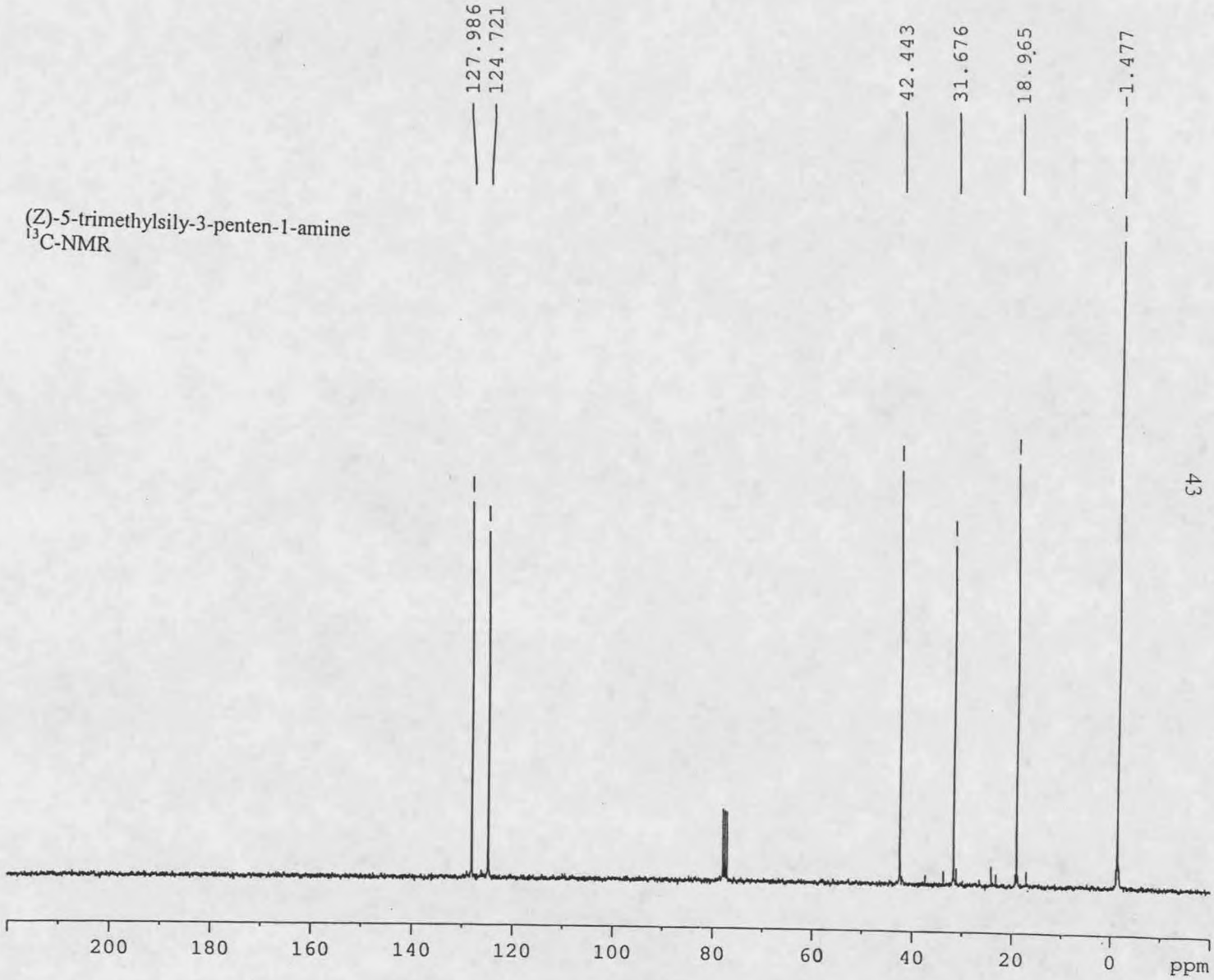
APPENDIX A

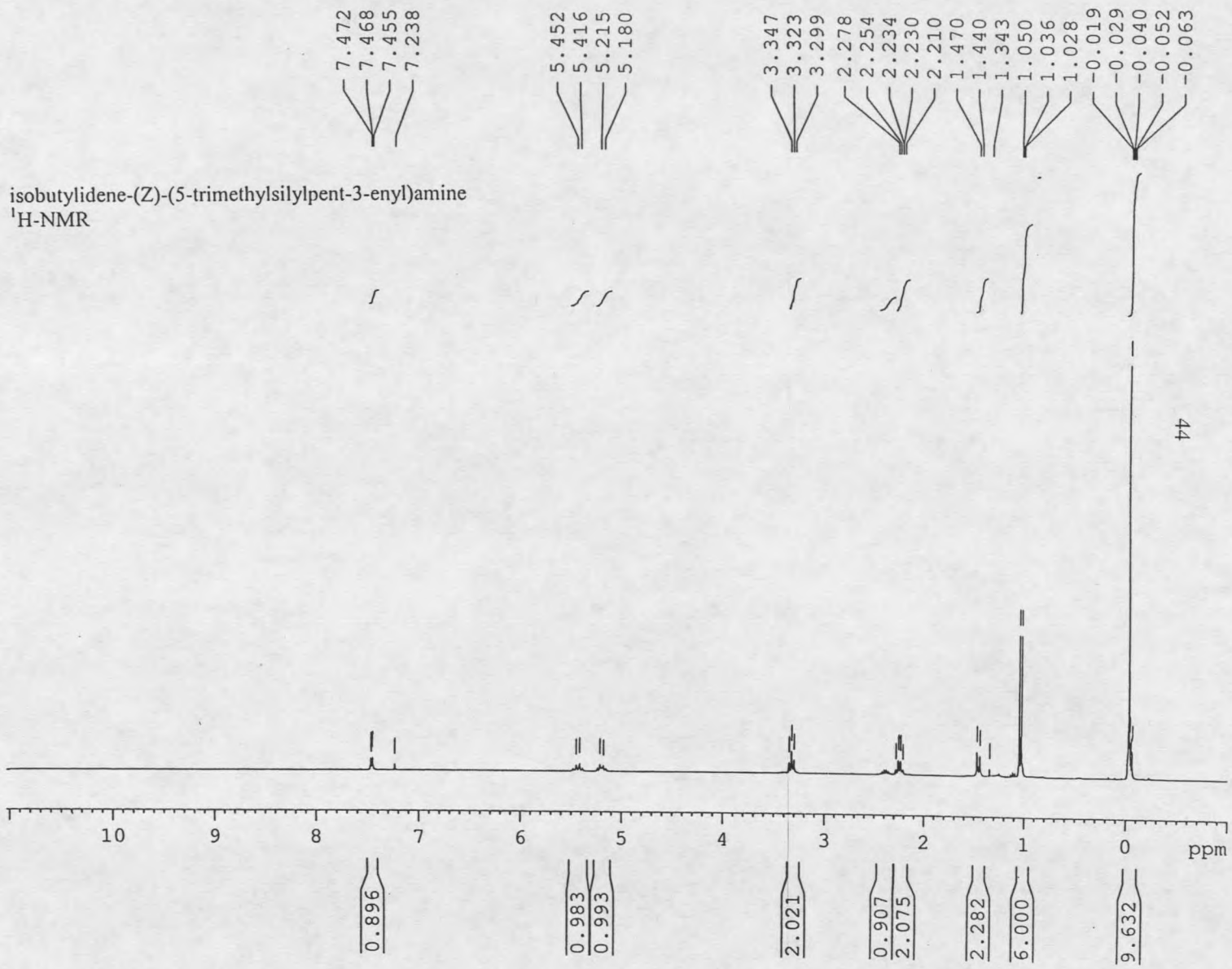
REPRESENTATIVE SPECTRA

(Z)-5-trimethylsily-3-penten-1-amine
^{1}H-NMR

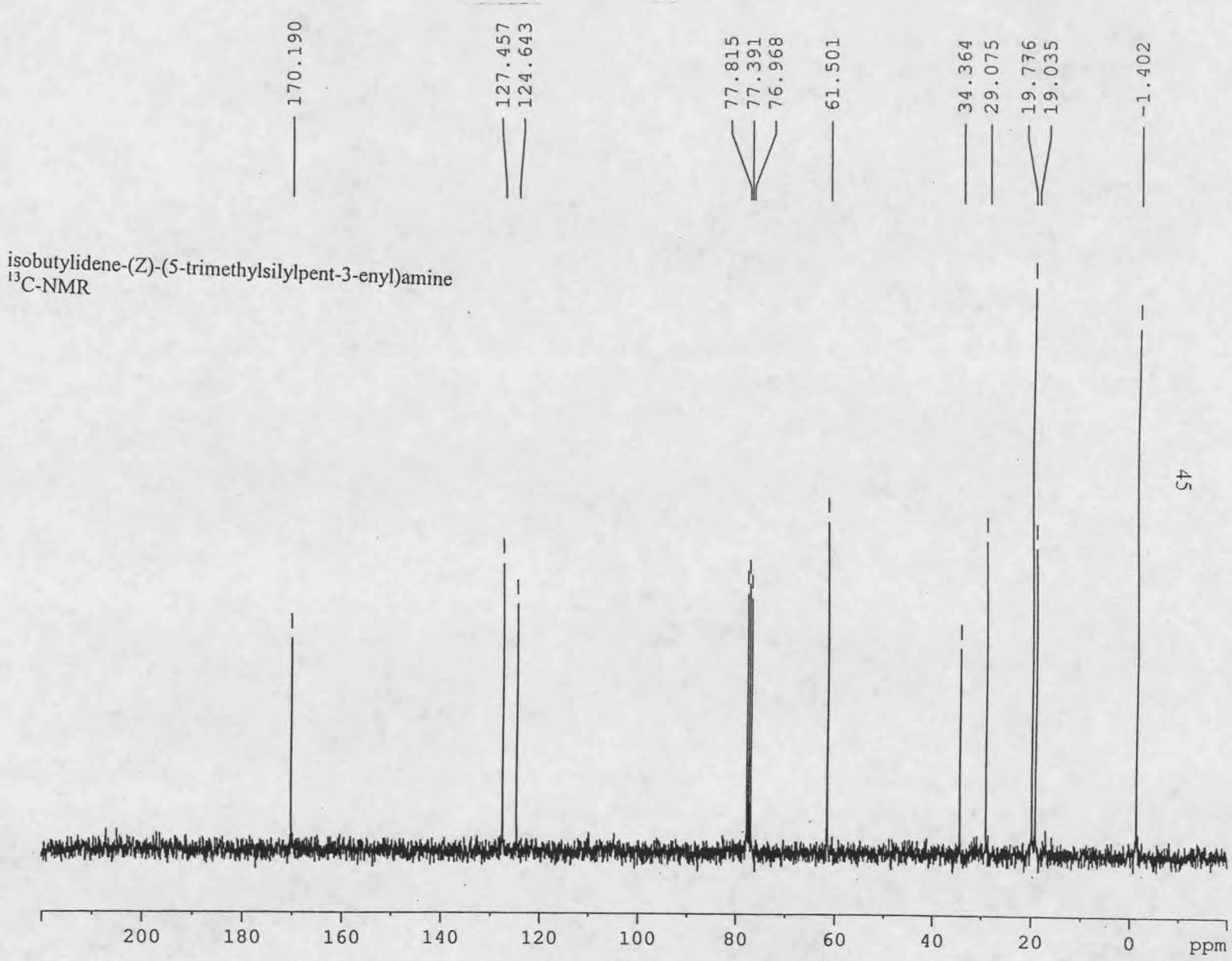


(Z)-5-trimethylsily-3-penten-1-amine
^{13}C-NMR





isobutylidene-(Z)-(5-trimethylsilylpent-3-enyl)amine
^{1}H-NMR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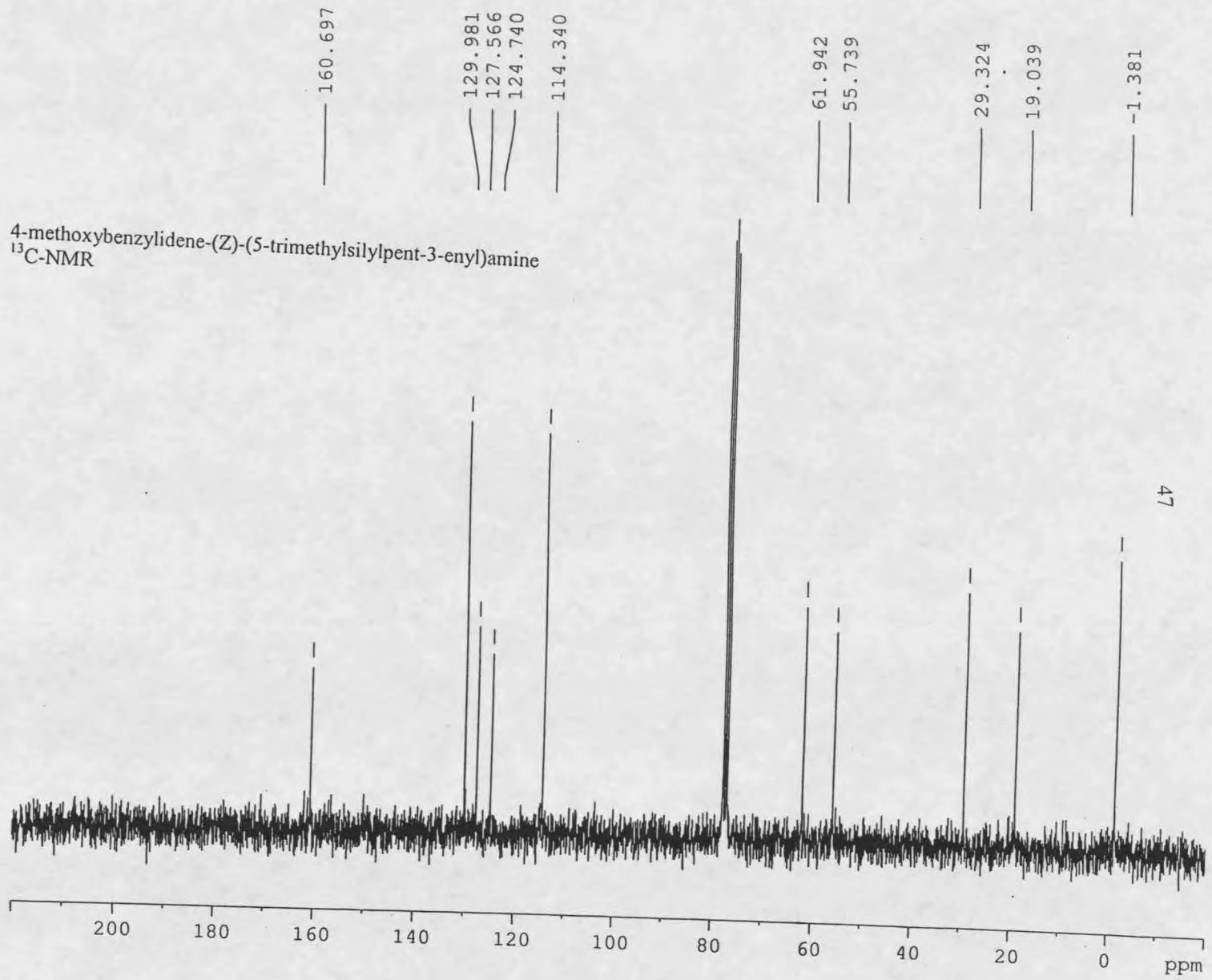
127.457
124.643
77.815
77.391
76.968
61.501
34.364
29.075
19.776
19.035
-1.402
isobutylidene-(Z)-(5-trimethylsilylpent-3-enyl)amine
13C-NMR
45
200
180
160
140
120
100
80
60
40
20
0
ppm

4-methoxybenzylidene-(Z)-(5-trimethylsilylpent-3-enyl)amine
^{1}H-NMR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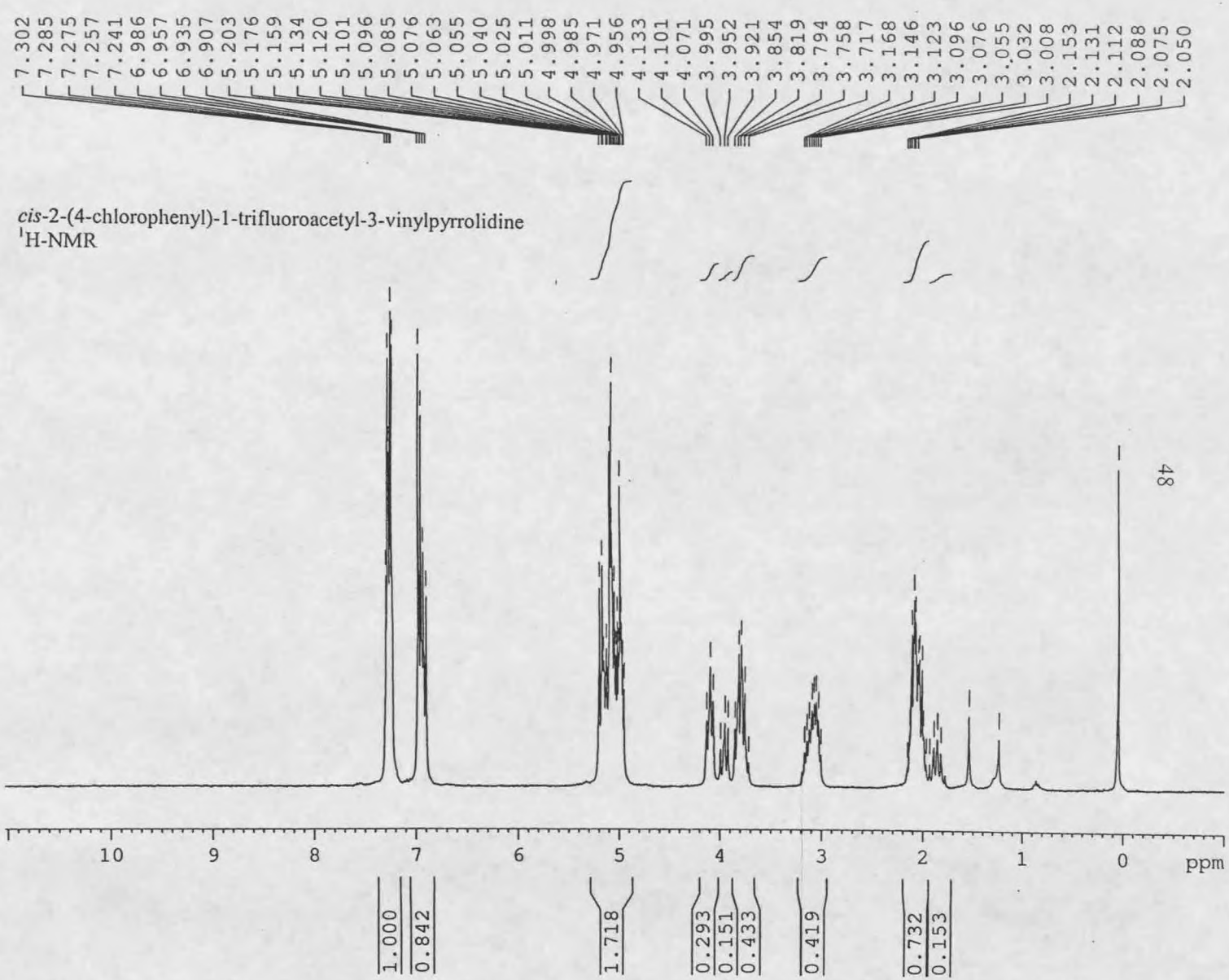
129.981
127.566
124.740
114.340
61.942
55.739
29.324
19.039
-1.381
4-methoxybenzylidene-(Z)-(5-trimethylsilylpent-3-enyl)amine
13C-NMR
200
180
160
140
120
100
80
60
40
20
0
ppm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5.203
5.176
5.159
5.134
5.120
5.101
5.096
5.085
5.076
5.063
5.055
5.040
5.025
5.011
4.998
4.985
4.971
4.956
4.133
4.101
4.071
3.995
3.952
3.921
3.854
3.819
3.794
3.758
3.717
3.168
3.146
3.123
3.096
3.076
3.055
3.032
3.008
2.153
2.131
2.112
2.088
2.075
2.050
cis-2-(4-chlorophenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
1H-NMR
48
10
9
8
7
6
5
4
3
2
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ppm
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1.718
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0.151
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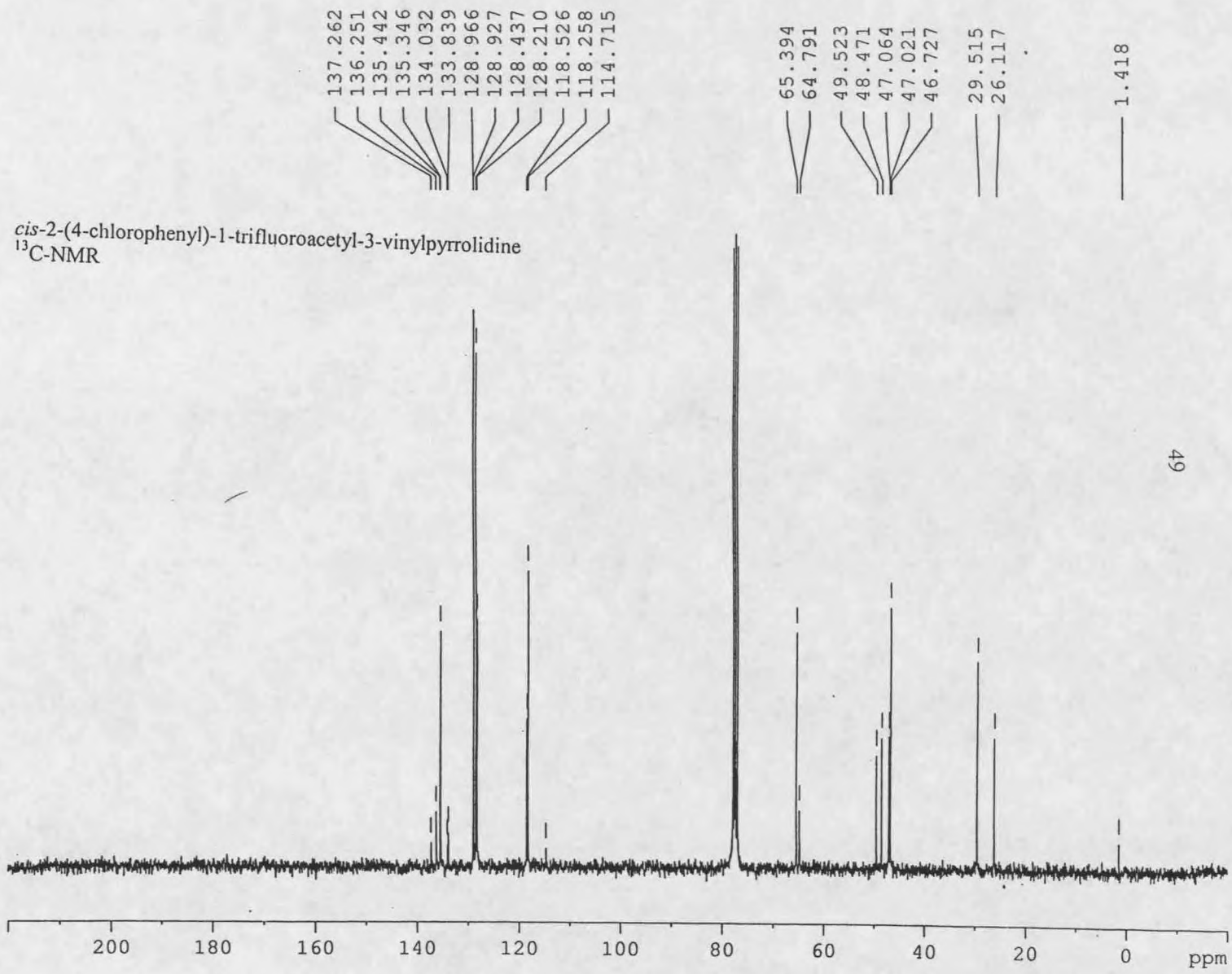
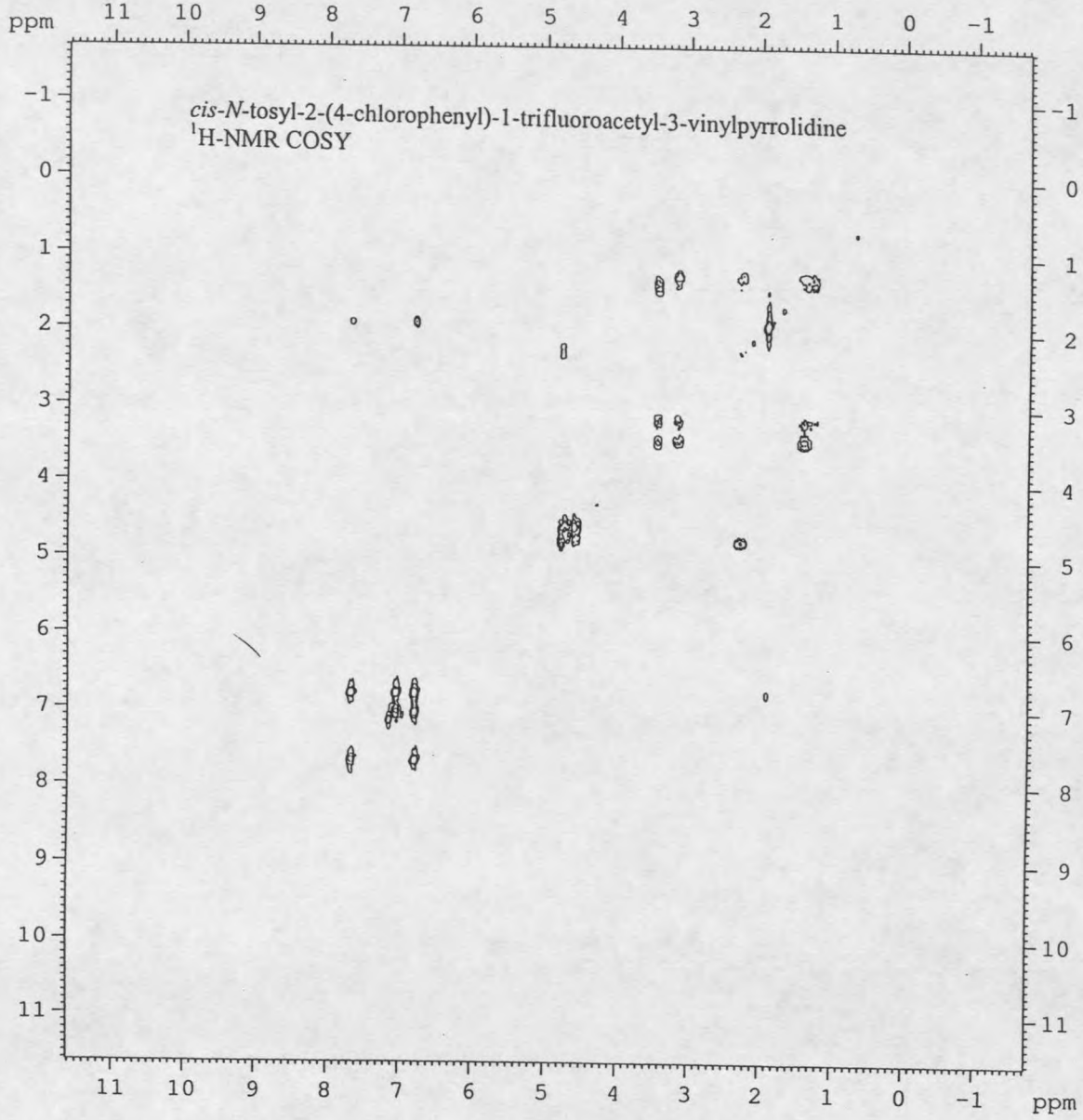
0.419
0.732
0.153



cis-2-(4-chlorophenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
^{13}C-NMR

cis-N-tosyl-2-(4-chlorophenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR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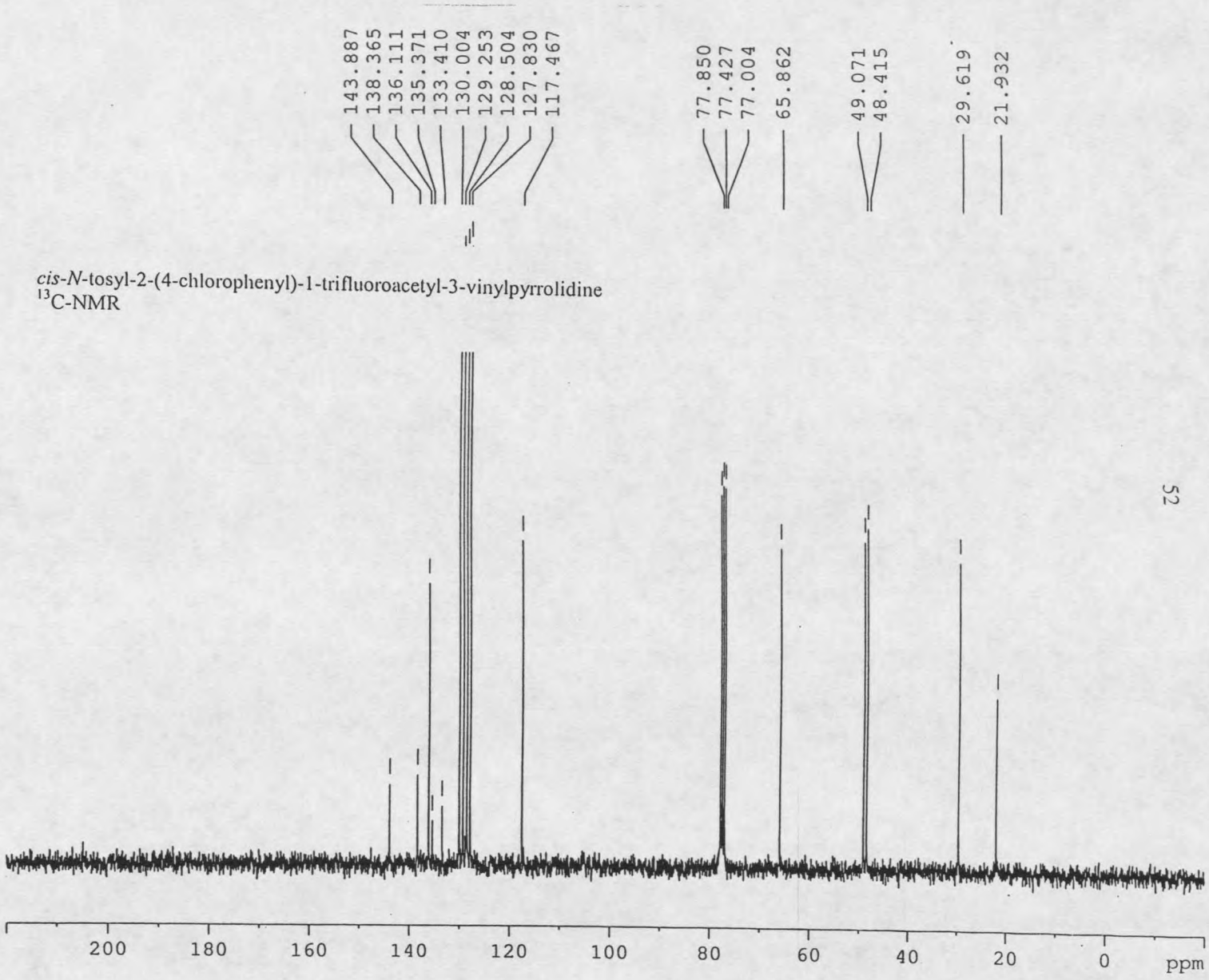
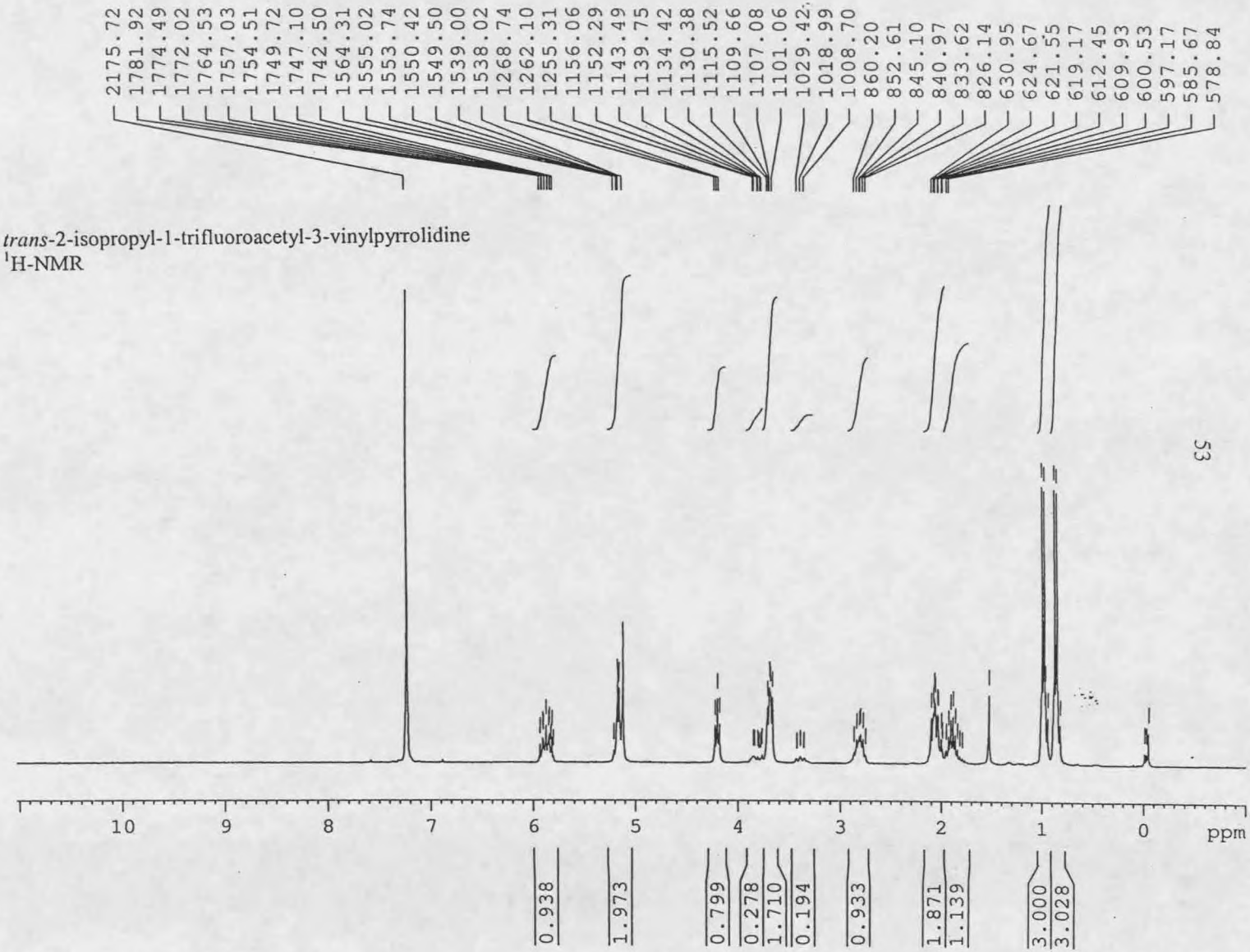
^{1}H-NMR COSY



cis-*N*-tosyl-2-(4-chlorophenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
^{13}C-NMR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1764.53
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1754.51
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1564.31
1555.02
1553.74
1550.42
1549.50
1539.00
1538.02
1268.74
1262.10
1255.31
1156.06
1152.29
1143.49
1139.75
1134.42
1130.38
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1107.08
1101.06
1029.42
1018.99
1008.70
860.20
852.61
845.10
840.97
833.62
826.14
630.95
624.67
621.55
619.17
612.45
609.93
600.53
597.17
585.67
578.84
trans-2-isopropyl-1-trifluoroacetyl-3-vinylpyrrolidine
1H-NMR
53
10
9
8
7
6
5
4
3
2
1
0
ppm
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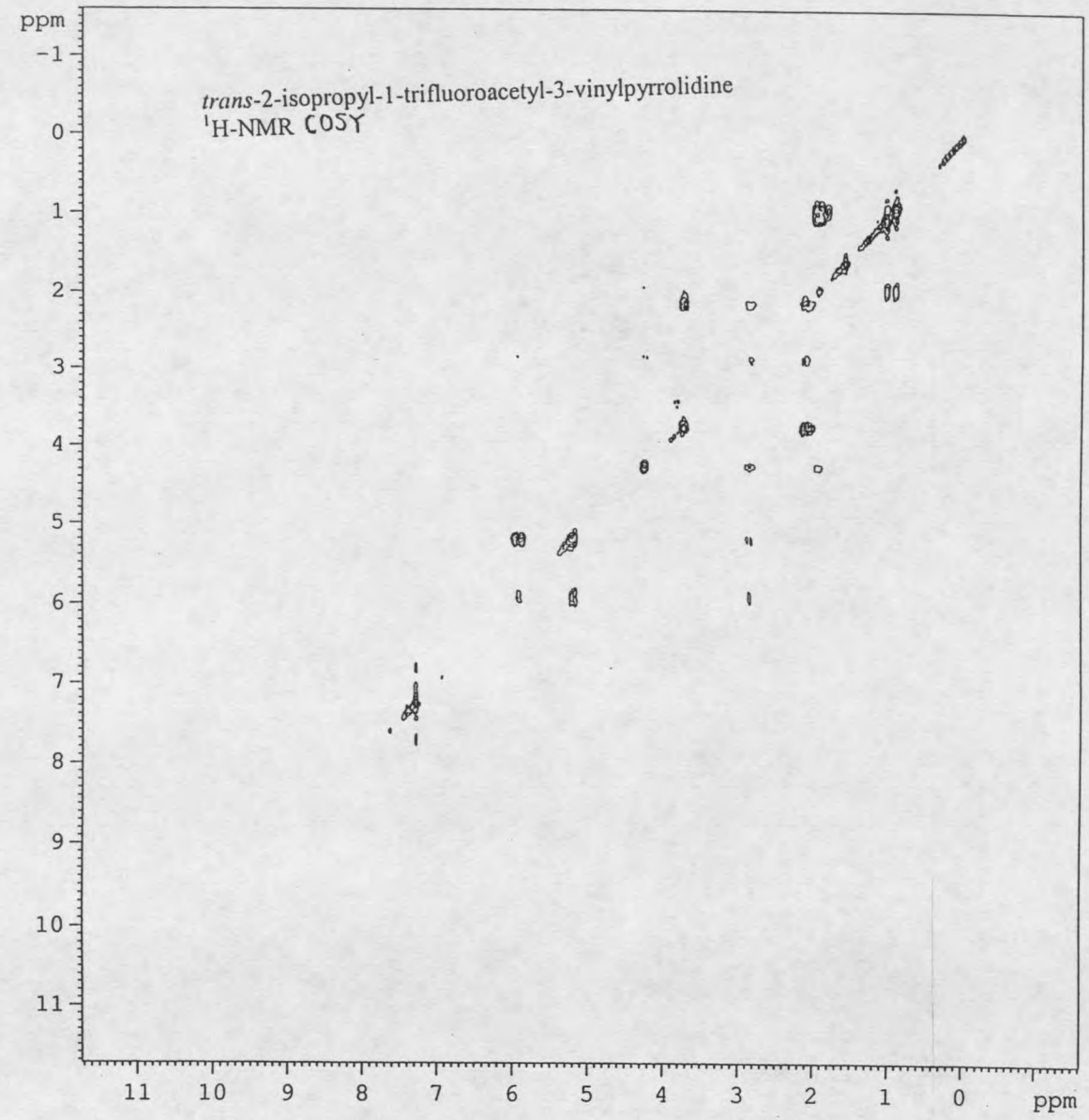
3.028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0
1
2
3
4
5
6
7
8
9
10
11
trans-2-isopropyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR COSY
11 10 9 8 7 6 5 4 3 2 1 0 ppm

1966.95
1958.79
1946.76
1938.55
1833.23
1793.31
1732.63
1718.65
1710.65
1699.65
1316.26
1307.95
1306.24
1298.92
1290.87
1289.19
1280.91
1184.98
1177.20
1167.28
896.04
891.11
886.16
875.74
870.43
868.53
864.03
859.15
857.31
851.97
794.13
787.64
786.18
782.87
779.72
776.43
774.95
768.46
621.74
614.87
608.01
602.61
601.33
594.50
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510.60
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trans-N-tosyl-2-isopropyl-1-trifluoroacetyl-3-vinylpyrrolidine
1H-NMR
55
11
10
9
8
7
6
5
4
3
2
1
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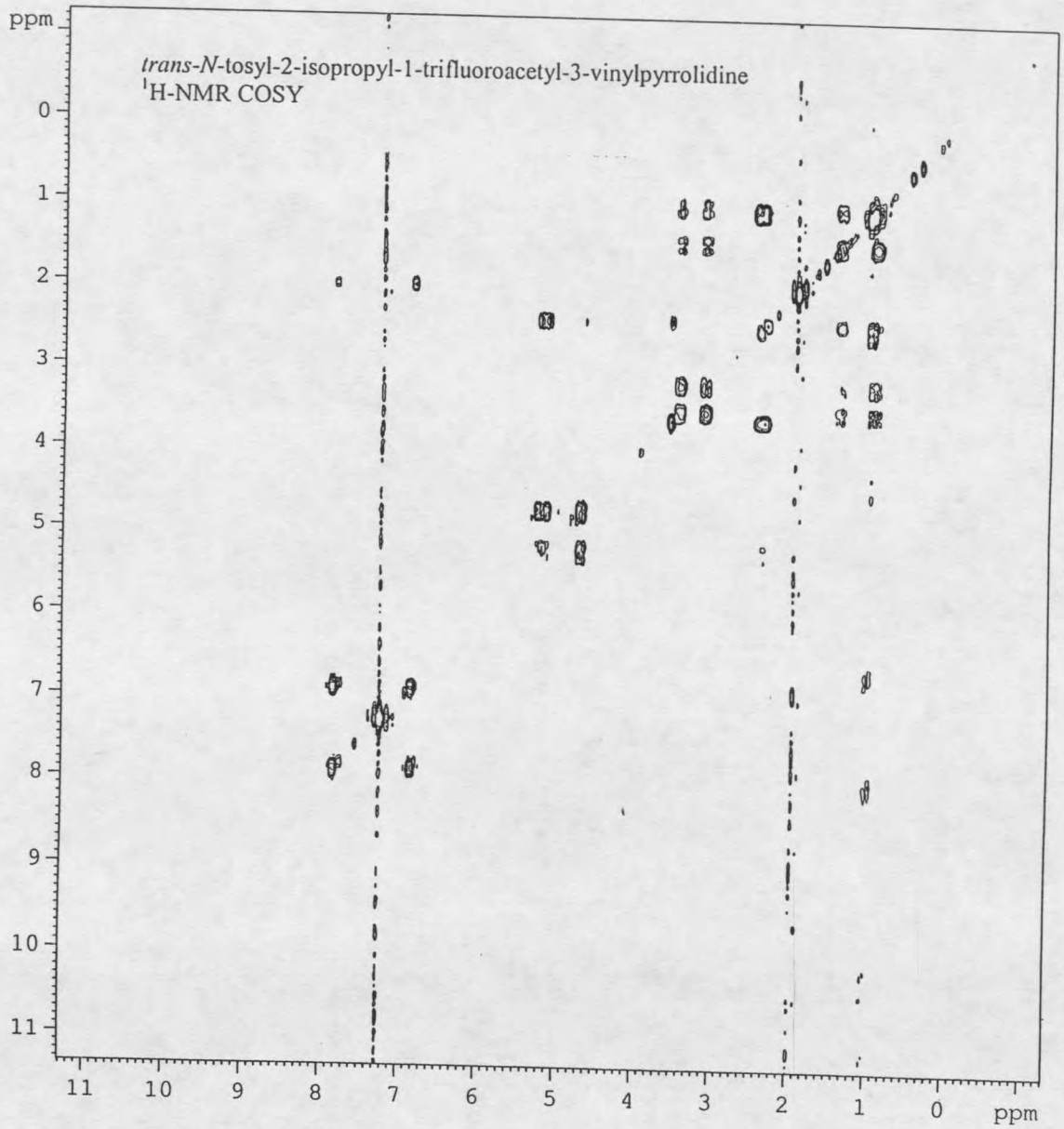
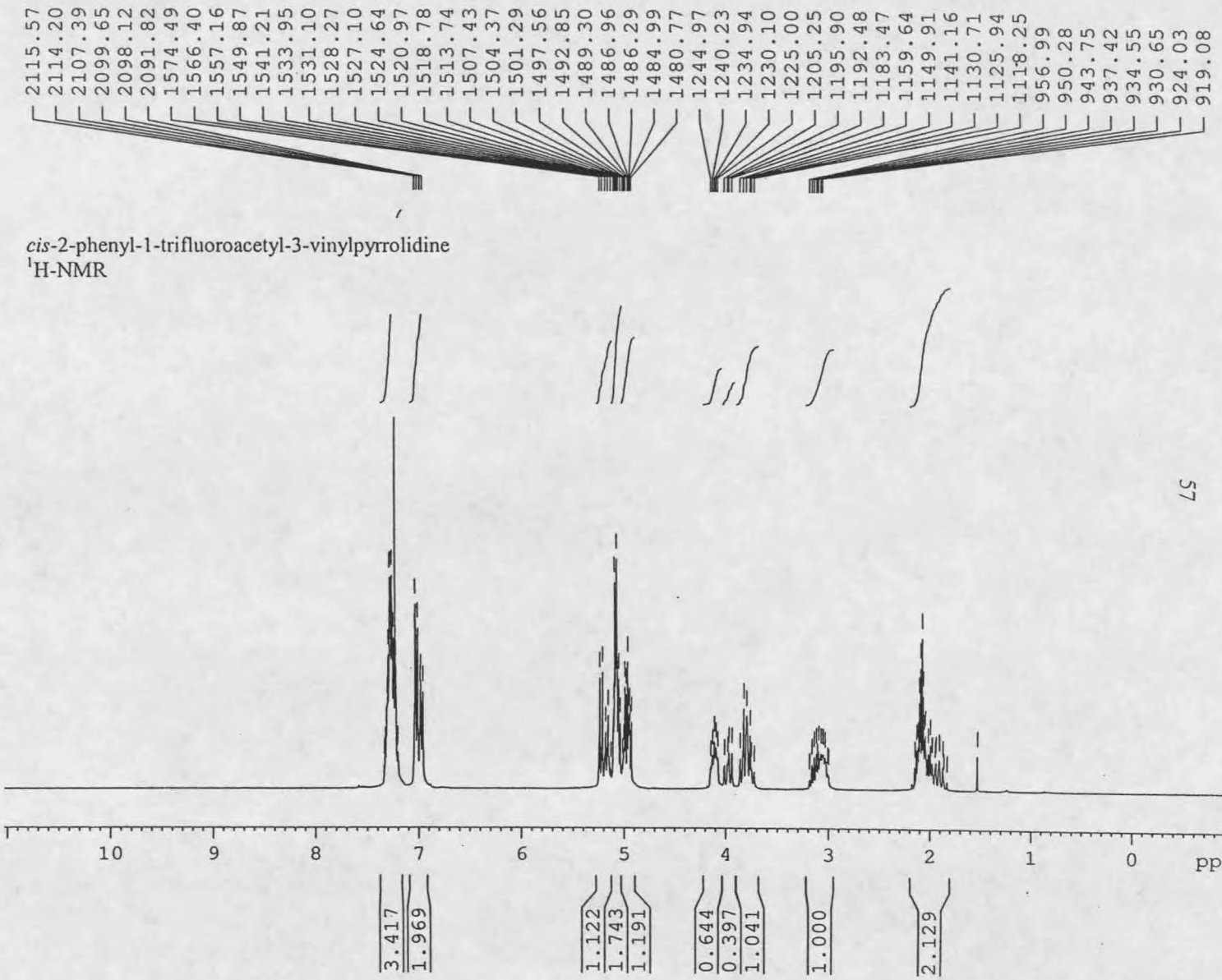
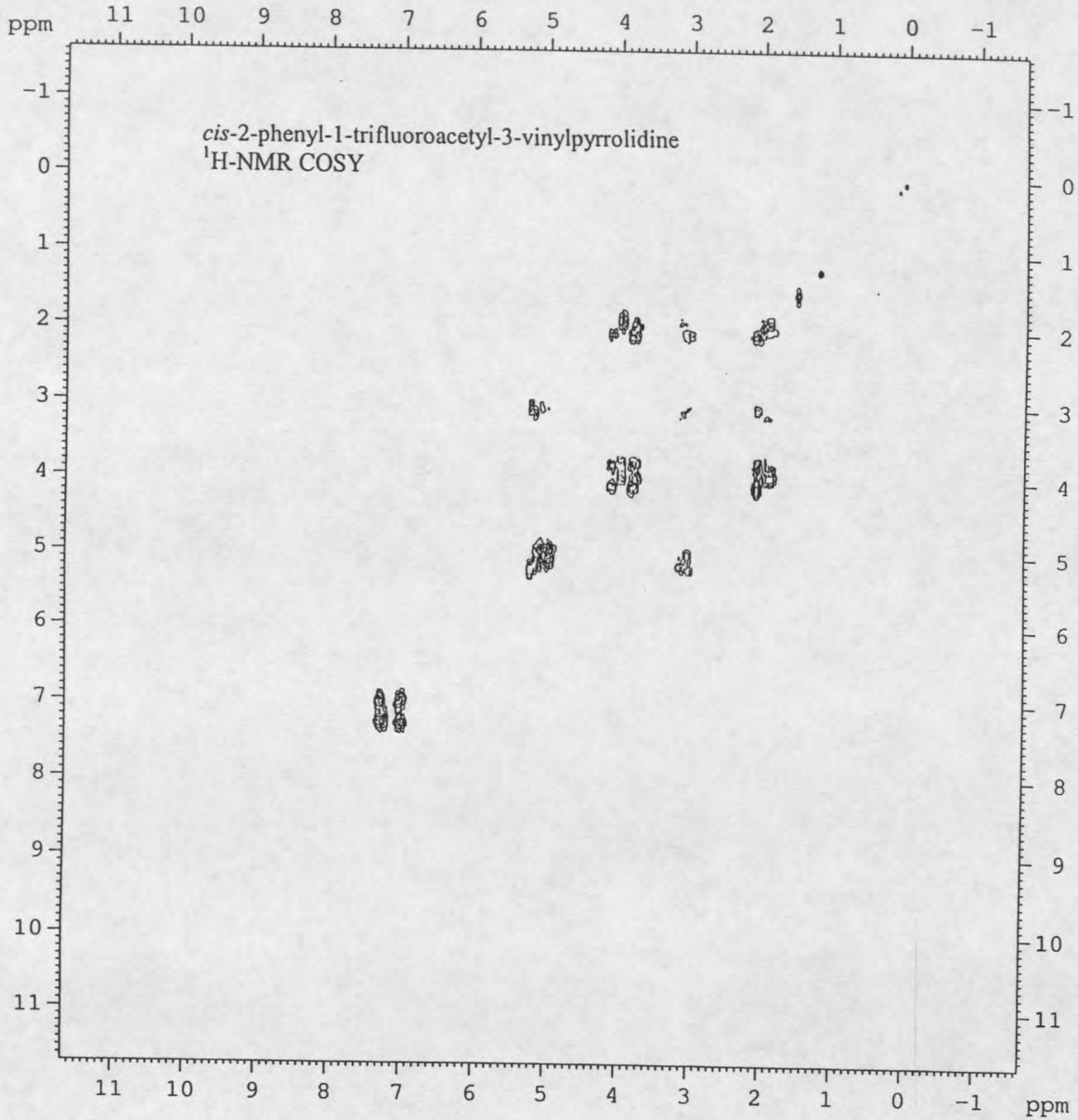
ppm
1.814
2.029
0.890
1.046
0.825
1.016
1.147
1.132
2.055
3.024
2.845
8.538

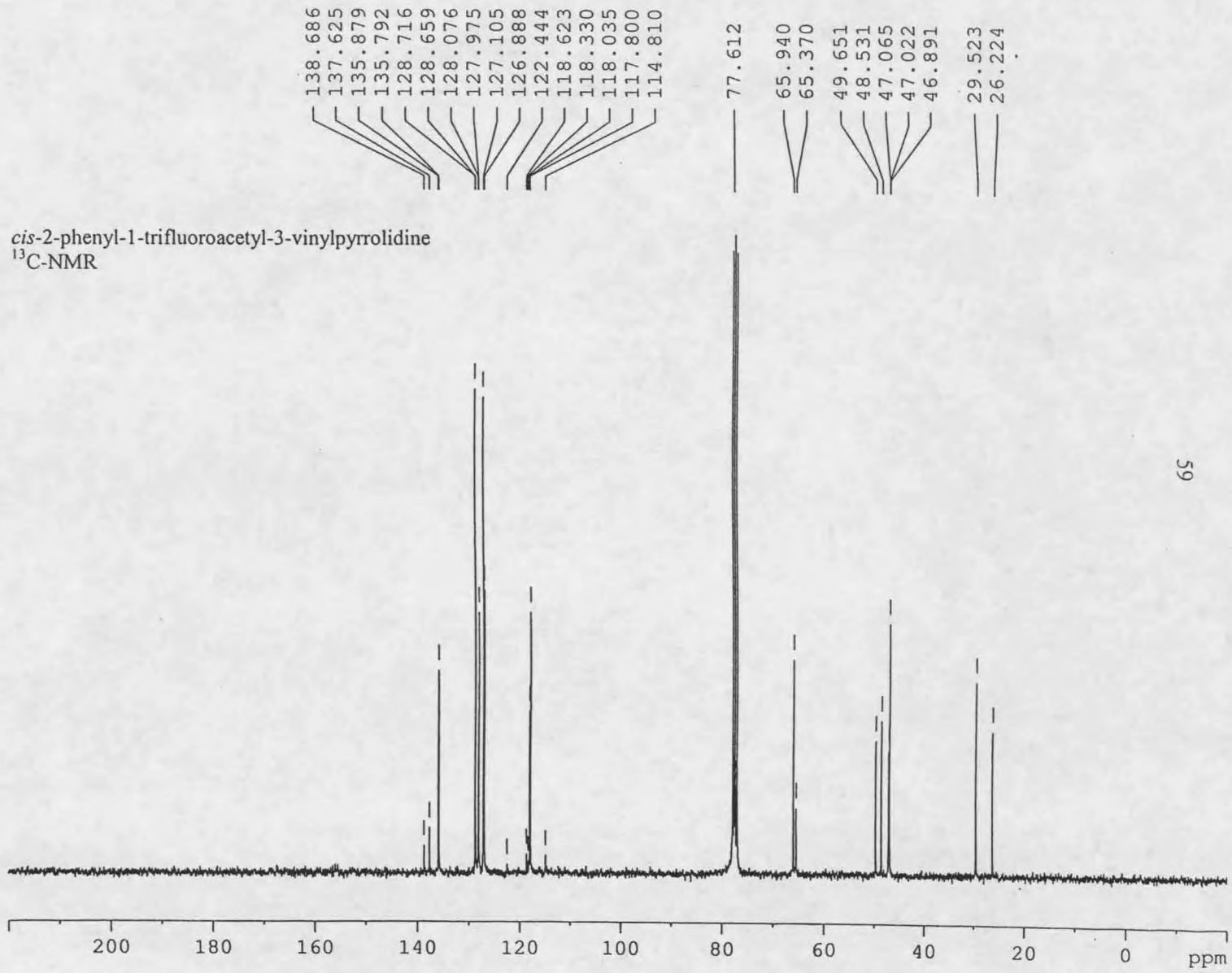


trans-N-tosyl-2-isopropyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR COSY

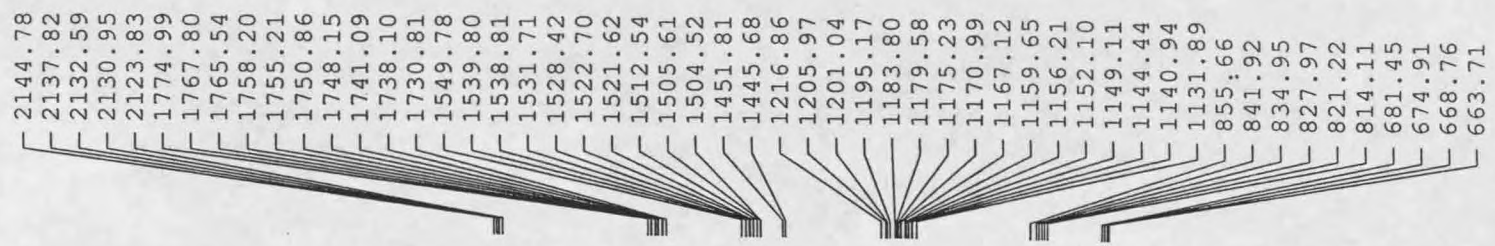


cis-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR

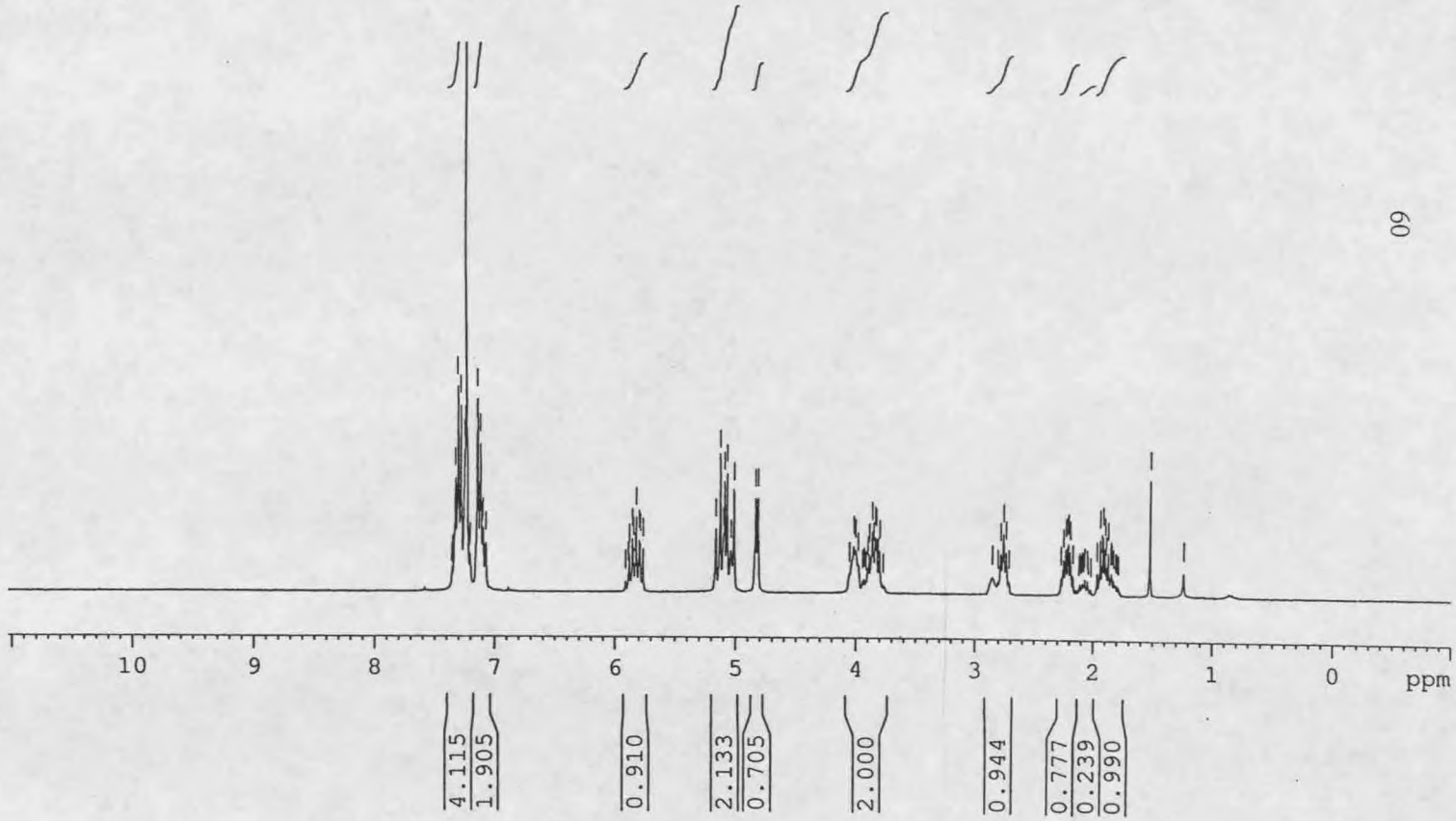

ppm
11 10 9 8 7 6 5 4 3 2 1 0 −1
−1 0 1 2 3 4 5 6 7 8 9 10 11
cis-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
1H-NMR COSY
ppm



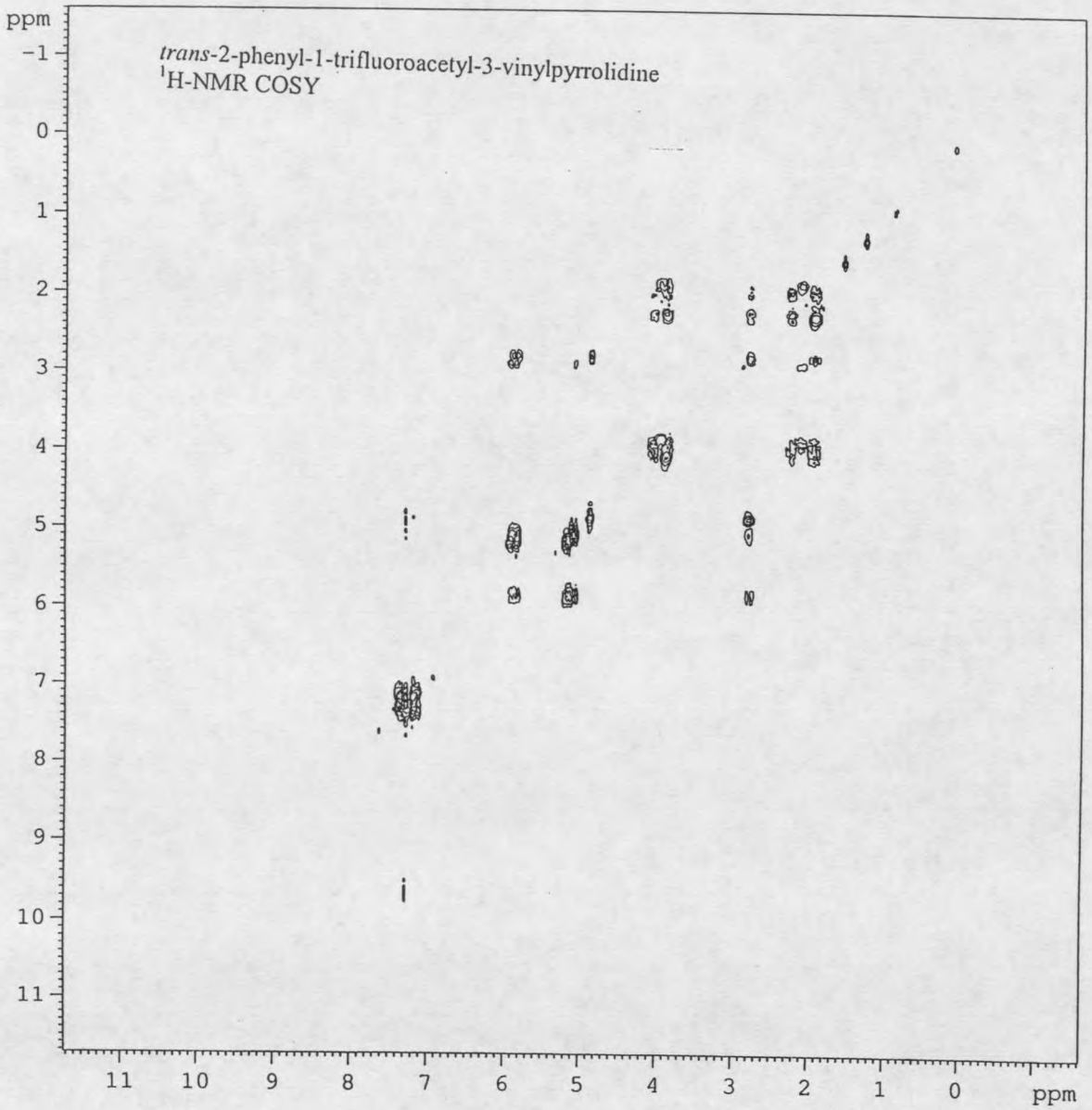
cis-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{13}C-NMR



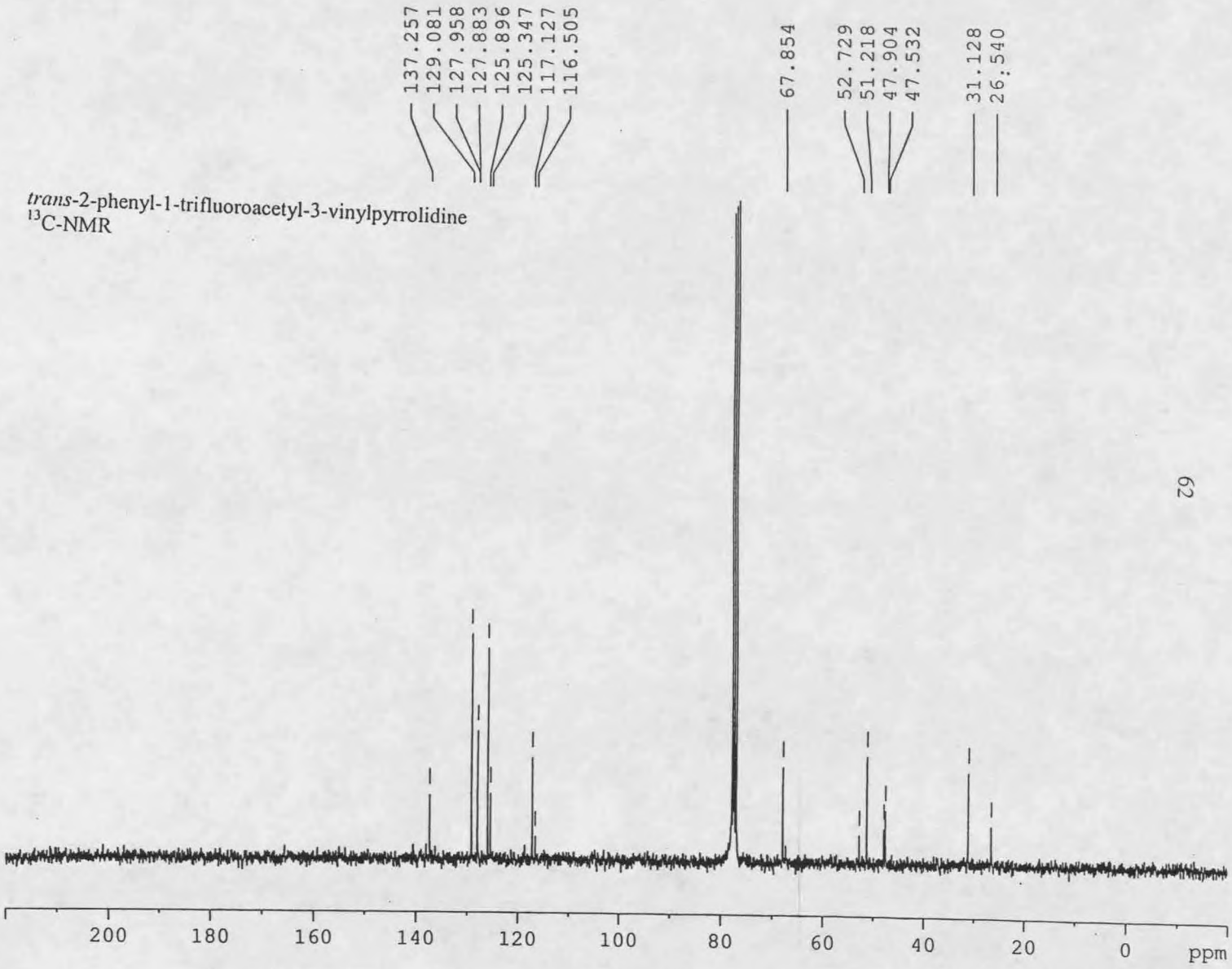
trans-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR

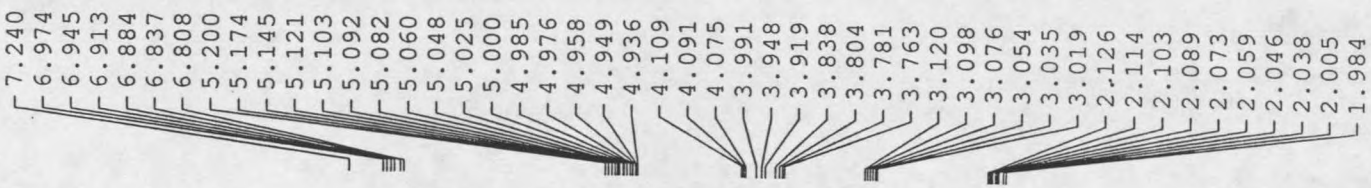


09

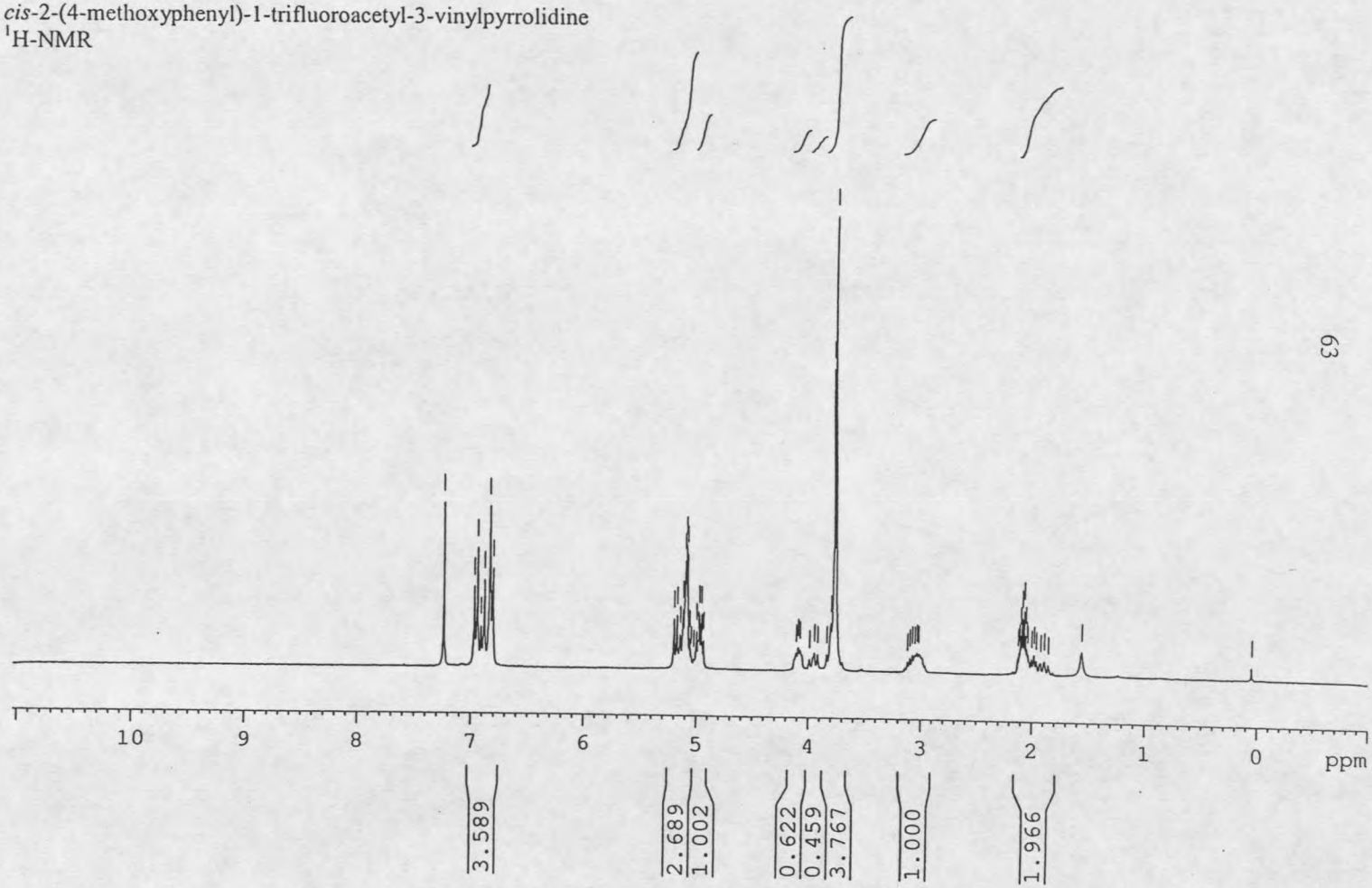


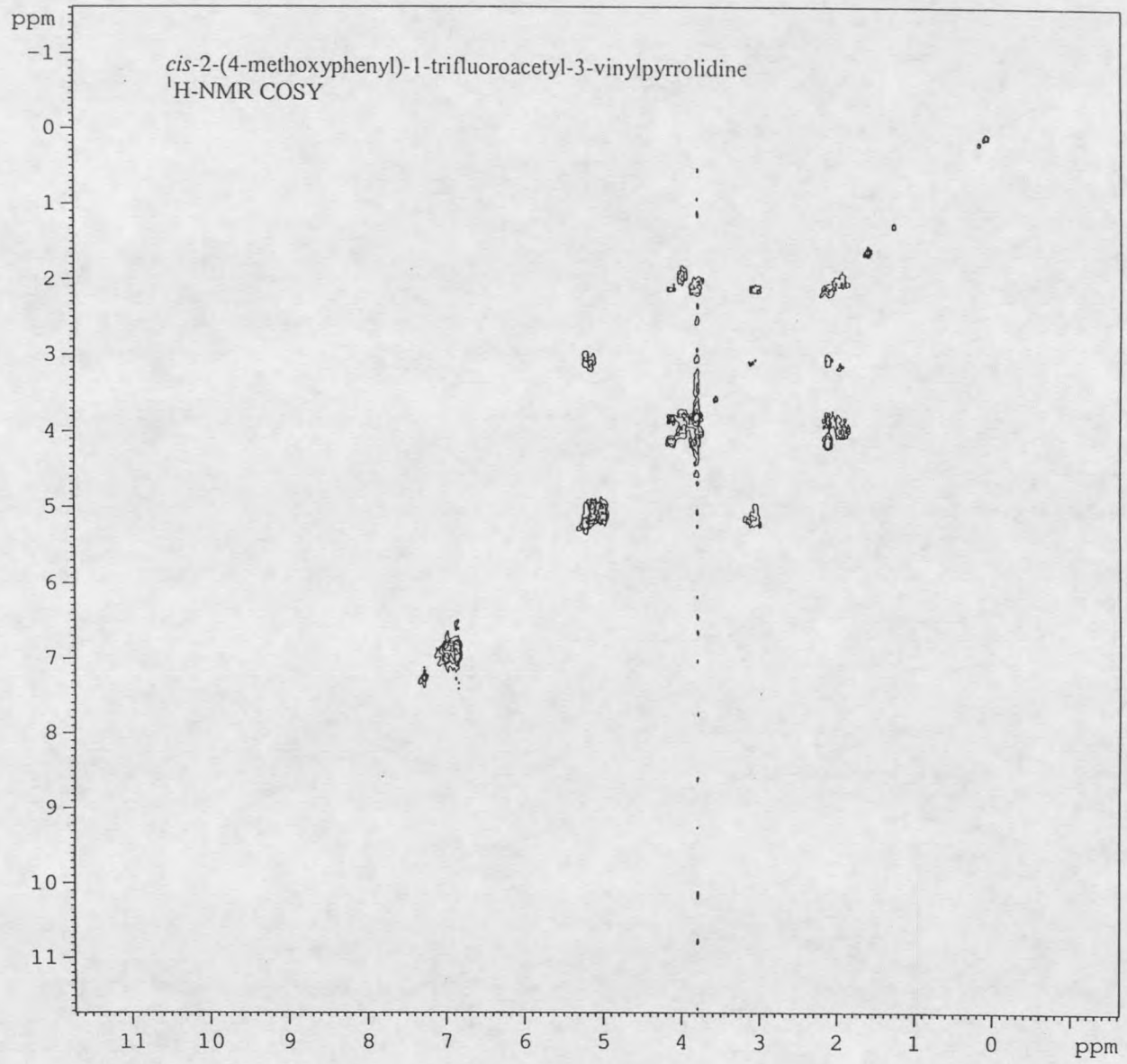
trans-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR COSY


137.257
129.081
127.958
127.883
125.896
125.347
117.127
116.505
67.854
52.729
51.218
47.904
47.532
31.128
26.540
trans-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
13C-NMR
200
180
160
140
120
100
80
60
40
20
0
ppm

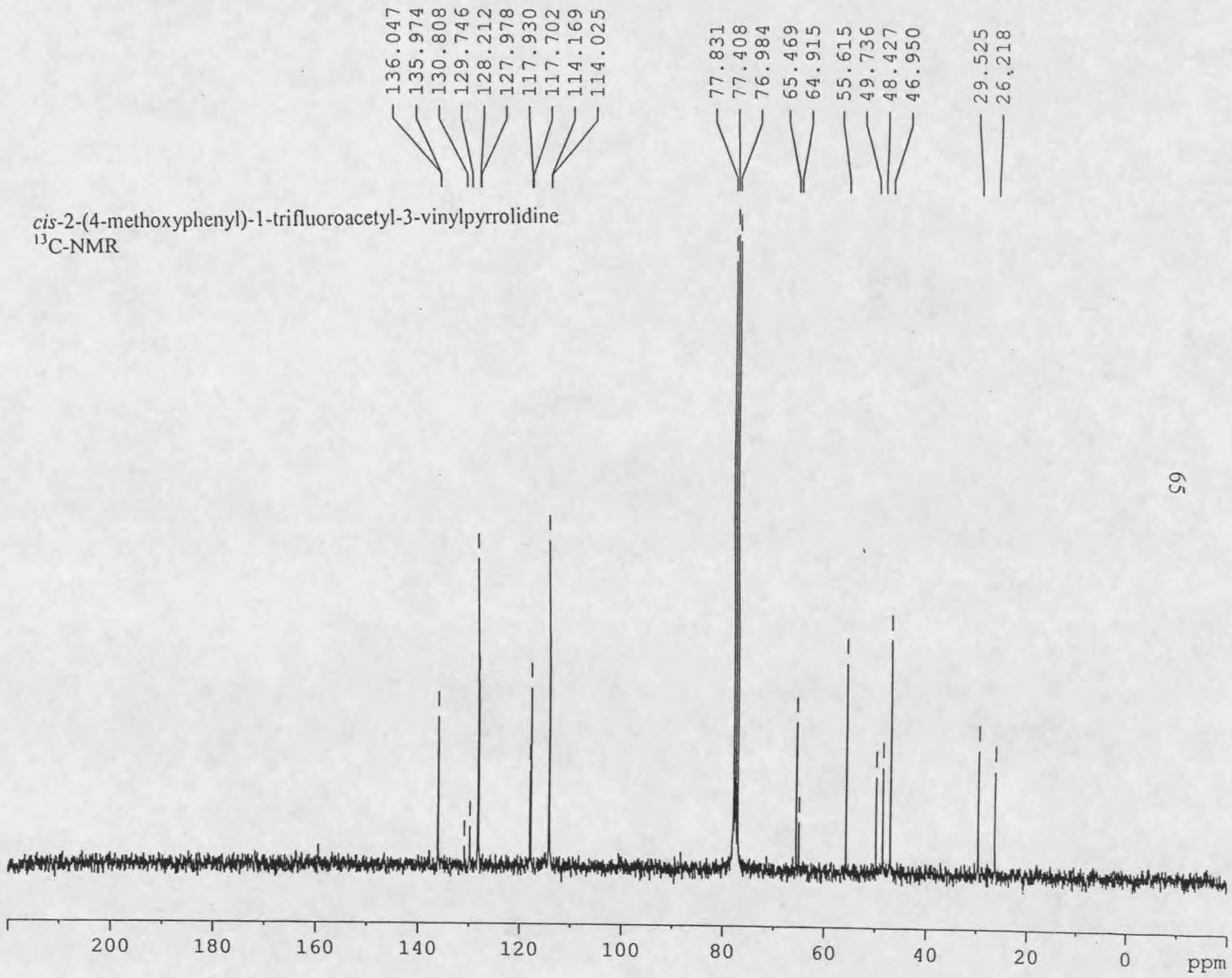


cis-2-(4-methoxyphenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR

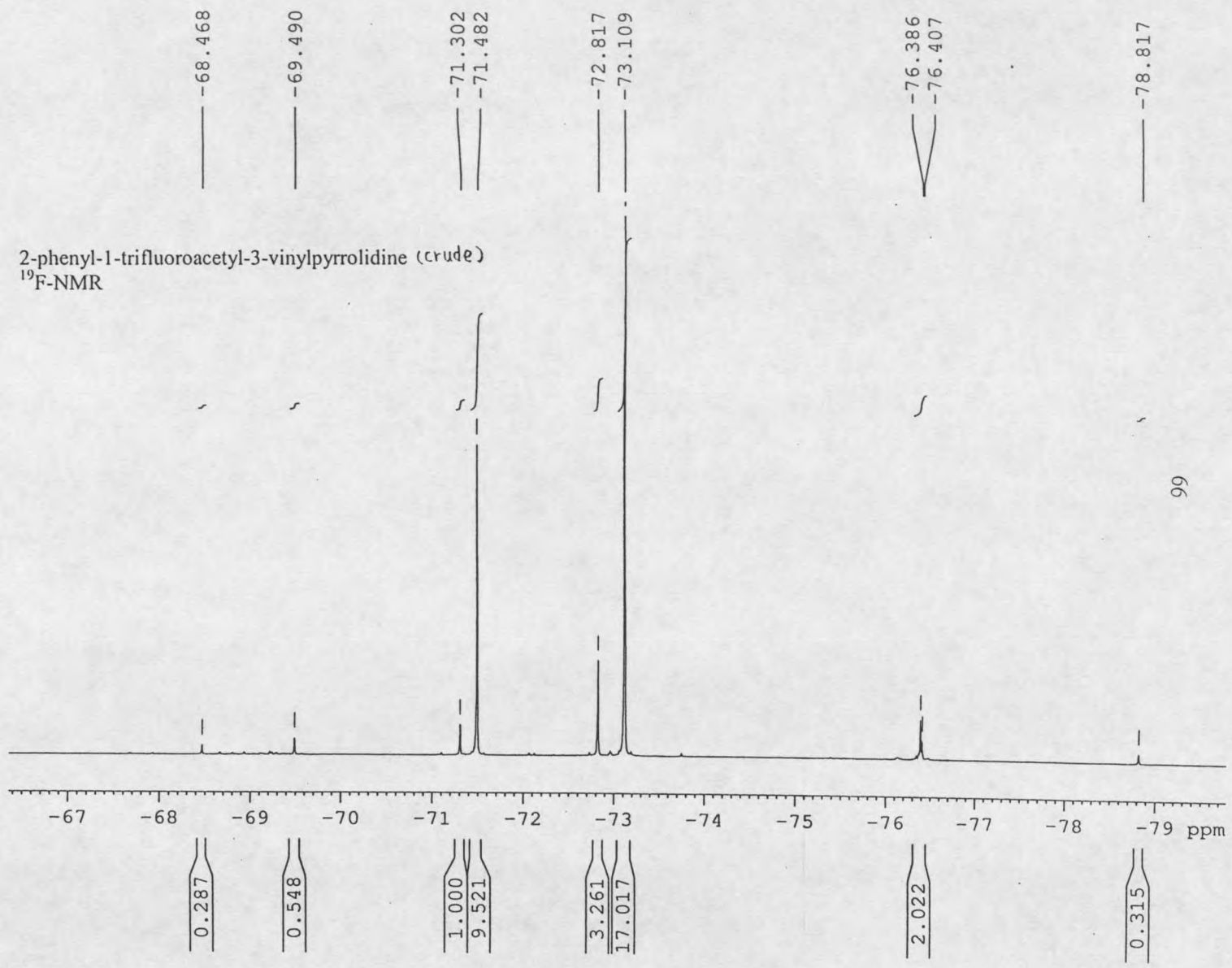




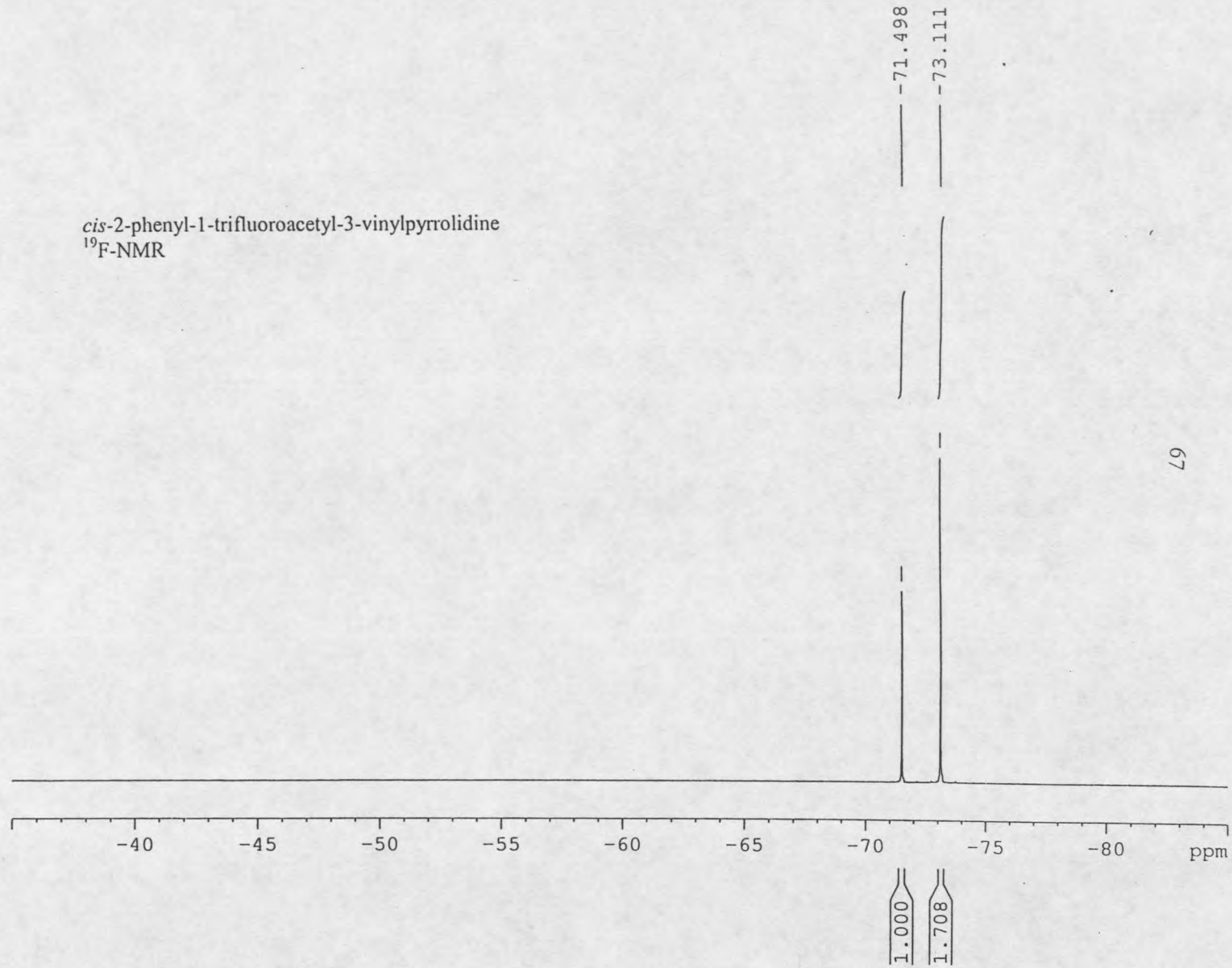
cis-2-(4-methoxyphenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
^{1}H-NMR COSY



cis-2-(4-methoxyphenyl)-1-trifluoroacetyl-3-vinylpyrrolidine
^{13}C-NMR


-68.468
-69.490
-71.302
-71.482
-72.817
-73.109
-76.386
-76.407
-78.817
2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine (crude)
19F-NMR
-67
-68
-69
-70
-71
-72
-73
-74
-75
-76
-77
-78
-79 ppm
0.287
0.548
1.000
9.521
3.261
17.017
2.022
0.315

cis-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{19}F-NMR



trans-2-phenyl-1-trifluoroacetyl-3-vinylpyrrolidine
^{19}F-NMR