Direct Dehydrative *N*-Pyridinylation of Amides, the Interrupted Bischler–Napieralski Reaction, and the Enantioselective Total Synthesis and Arylative Dimerization of *Aspidosperma* Alkaloids

by

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A.B., Chemistry and Physics
Harvard University, 2007

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To my mother, Carol, and my father, Michael

To my brother, Patrick

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Preface

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ABSTRACT

I. Direct Dehydrative *N*-Pyridinylation of Amides

A method for the single-step *N*-pyridinylation of secondary amides is described. The process involves electrophilic activation of secondary amides with trifluoromethanesulfonic anhydride in the presence of 2-fluoropyridine followed by introduction of a pyridine *N*-oxide derivative and warming to afford the corresponding *N*-pyridinyl tertiary amide derivatives. The structure of activated amide intermediates is probed through in situ monitoring, and a mechanism supported by in situ monitoring and deuterium labeling experiments is discussed.

II. Synthesis of Spirocyclic Indolines by Interruption of the Bischler–Napieralski Reaction

The development of a versatile method for the synthesis of spirocyclic pyrrolidinoindolines is described. Treatment of *N*-acyltryptamines with trifluoromethanesulfonic anhydride–2-chloropyridine reagent combination affords highly persistent spiroindoleninium ions, which are selectively trapped intra- and intermolecularly by various nucleophiles.

III. A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Novel Arylative Dimerization of *Aspidosperma* Alkaloids

A strategy for the concise, stereoselective synthesis of *aspidosperma* alkaloids and related structures via a common putative diiminium ion intermediate is described. The approach enables the dimerization of *aspidosperma*-type structures at the sterically hindered C2-position. The diiminium intermediate is prepared in situ from an enantioenriched α-quaternary 2-chlorotryptamine lactam through a stereoselective electrophilic double-cyclization cascade. The key C5-quaternary stereocenter is secured via successive diastereoselective α-alkylations of pseudoephenamine crotonamide.

Thesis Supervisor: Professor Mohammad Movassaghi
Title: Associate Professor of Chemistry

Table of Contents

Abbreviations

Å	angstrom
[α]	specific rotation
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Anis	*para*-anisaldehyde
app	apparent
aq	aqueous
atm	atmosphere
Bn	benzyl
Br	broad
Bu	butyl
c	centi
c	concentration
°C	degree Celsius
CAM	ceric ammonium molybdate
cat.	catalyst
2-ClPyr	2-chloropyridine
cm	centimeter
3-CNPyr	3-cyanopyridine
CNS	central nervous system
d	doublet
d	deuterium
δ	parts per million
DART	direct analysis in real time
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
4-DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*'-dimethylpropylene urea
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
EDC•HCl	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrogen chloride
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
2-FPyr	2-fluoropyridine
FT	Fourier transform
g	gram
gCOSY	gradient correlation spectroscopy
gHMBC	gradient heteronuclear multiple bond correlation
h	hour

HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
Josiphos	(*R*)-1-[(S_P)-2-(di-*tert*-butylphosphino)ferrocenyl]ethylbis(2-methylphenyl)phosphine
L	liter
LDA	lithium *N*,*N*-diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	medium
m	multiplet
m	milli
m	meter
M	molar
μ	micro
Me	methyl
MHz	megahertz
min	minute
mol	mole
Ms	methanesulfonyl
MS	molecular sieves
MS	mass spectrometry
m/z	mass to charge ratio
n	normal
N	normal
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect correlation spectroscopy
Nuc	nucleophile
p	*para*
Ph	phenyl
PMA	phosphomolybdic acid
ppm	parts per million
Pr	propyl
psi	pounds per square inch
q	quartet
ref.	reference
R	rectus
R*f*	retention factor
ROESY	rotating-frame nuclear Overhauser effect correlation spectroscopy

s	singlet
s	strong
s	secondary
S	sinister
SFO	system fluidics organizer
str	stretch
t	triplet
t	tertiary
^{t}BuBrettPhos	[3,6-Dimethoxy-2′,4′,6′-tris(1-methylethyl)[1,1′-biphenyl]-2-yl]bis(1,1-dimethylethyl)phosphine
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	*para*-toluenesulfonyl
UV	ultraviolet
w	weak

Chapter I

Direct Dehydrative *N*-Pyridinylation of Amides

Introduction and Background

Pyridin-2-ylated amides are key structural motifs in a wide variety of pharmaceutical compounds and fine chemicals.[1] Propiram[2] (Figure 1) is a partial mu opioid receptor agonist and weak mu antagonist analgesic that has been shown to be more effective and potent than codeine. Eszopiclone[3] (Lunesta®), a CNS stimulant, is a short-acting, nonbenzodiazepine hypnotic agent widely used for the treatment of chronic insomnia. Piketoprofen[4] (Calmatel®) and piroxicam[5] (Feldene®) are non-steroidal anti-inflammatory drugs, the latter of which is prescribed for the relief of symptoms of rheumatoid and osteoarthritis. The pyridin-2-ylated amide structure is also present in topical retinoids used for the treatment of psoriasis.[6] Pirenzipine[7] (Gastrozepin®) is an M_1-selective antagonist used to treat peptic ulcers. The importance of pyridinylated amides continues to inspire new methods for their syntheses.

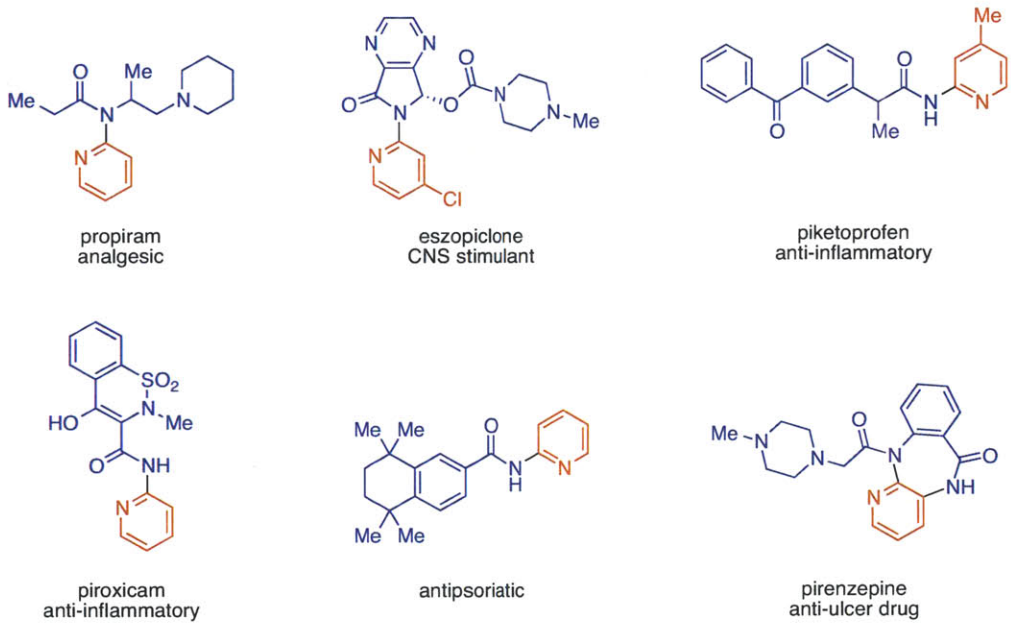
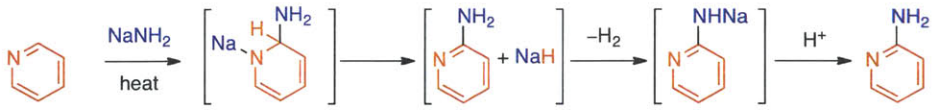


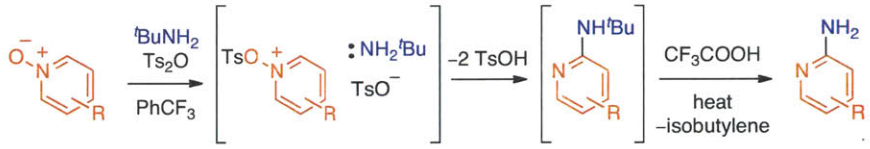
Figure 1. Representative compounds containing a pyridin-2-ylated amide substructure.

Among the earliest methods for the introduction of a pyridin-2-yl substituent onto a nitrogen atom was the reaction between sodamide and pyridine at elevated temperature reported by Chichibabin and co-workers (Scheme 1).[8] Addition of strongly basic sodamide into the weakly electrophilic 2-position of pyridine, followed by loss of hydrogen gas, affords 2-sodamidopyridine; acidification affords 2-aminopyridine. Recently, a milder set of conditions has been reported by Yin and co-workers[9] (Scheme 2), in which a pyridine *N*-oxide derivative[10] is activated with *para*-toluenesulfonic anhydride (Ts_2O) in the presence of excess *tert*-butyl

amine to effect in situ formation of a 2-*tert*-butylamino pyridine derivative. Addition of trifluoroacetic acid and heating affords the 2-aminopyridine product. While these methods provide efficient access to 2-aminopyridines,[11] they are not known to effect the *N*-pyridinylation of amide substrates.

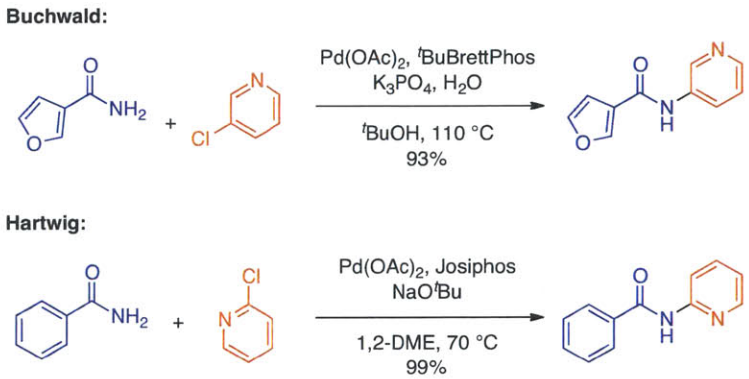


Scheme 1. The Chichibabin reaction.



Scheme 2. Synthesis of 2-aminopyridines from pyridine *N*-oxides.

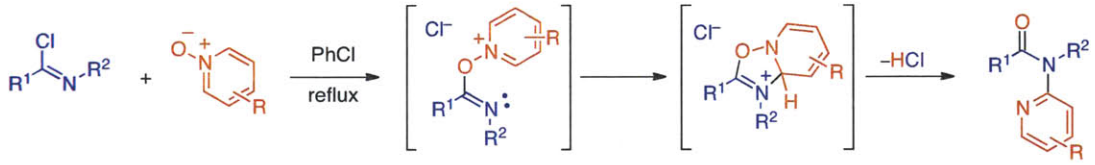
Metal-catalyzed cross-coupling reactions between nitrogen nucleophiles and aryl or heteroaryl halides or sulfonates,[12] such as the palladium- and copper-catalyzed methods reported by Buchwald[13] and the complementary palladium-catalyzed method reported by Hartwig,[14] have proven to highly efficient and mild means for the *N*-arylation and *N*-heteroarylation of a variety of nitrogen-containing compounds, including amines and amides (Scheme 3). Primary amide substrates, in general, are efficiently substituted with a wide range of aryl and heteroaryl groups, including pyridin-2-yl groups. Secondary lactams and sterically unhindered[15] acyclic secondary amides are also generally useful in these transformations, though sterically hindered acyclic secondary amides represent a challenging substrate class,[16] and to date, methods for the intermolecular cross-coupling of sterically hindered acyclic secondary amides and 2-



Scheme 3. *N*-pyridinylation of amides via the Buchwald–Hartwig reaction.

halopyridines has not been reported.

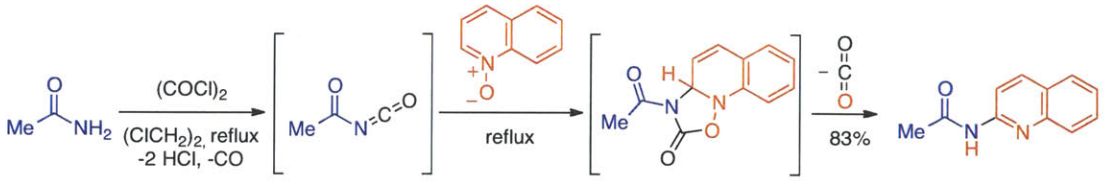
In 1969, R. A. Abramovitch and co-workers reported a fascinating methodology for the synthesis of *N*-pyridinyl amide derivatives via the nucleophilic addition of heteroaromatic *N*-oxides to *N*-aryl and *N*-alkyl imidoyl chlorides or nitrilium salts at elevated temperature followed by a thermal rearrangement (Scheme 4).[17] Abramovitch's proposed mechanism was supported by elegant mechanistic investigations, although the reversibility or irreversibility of the steps involved was not determined. The reactions in general give good regioselectivity with respect to site of substitution on the pyridine ring, typically affording the *N*-pyridin-2-yl amide product as the only regioisomer. The high temperatures required for the reaction, the need for the synthesis and isolation of sensitive imidoyl chlorides or nitrilium salts in a separate step, the failure of electron-deficient *N*-oxides to undergo reaction, and the tendency for undesired side-product formation represent drawbacks to the original methodology.



Scheme 4. The Abramovitch reaction.

Recently, more direct methods for the *N*-pyridinylation of amides through reaction with pyridine *N*-oxide derivatives have been developed. Couturier and co-workers[18] reported the *N*-quinolinylation and *N*-isoquinolinylation of primary amides by in situ activation of the amide with oxalyl chloride at elevated temperature to afford an *N*-acylisocyanate intermediate, which undergoes trapping by a quinoline or isoquinoline *N*-oxide and subsequent thermal rearrangement to afford a secondary *N*-quinolin-2-ylated or *N*-isoquinolin-1-ylated amide product as single regioisomers (Scheme 5). Also, Bilodeau and co-workers[19] reported a modification of the Abramovitch reaction for the *N*-pyridinylation of secondary amides via in situ activation of the amide substrate with oxalyl chloride in the presence of 2,6-lutidine (Scheme 6). Addition of a pyridine *N*-oxide derivative to the imidoyl chloride intermediate affords the *N*-pyridinylated amide product. While this method allows for the direct *N*-pyridinylation of sterically unhindered *N*-methyl and *N*-benzyl acetamides and benzamides, no successful examples of the *N*-pyridinylation of sterically hindered amides were reported, and *N*-aryl amides proved to be a highly recalcitrant substrate class. Given the importance of *N*-pyridinylated amide

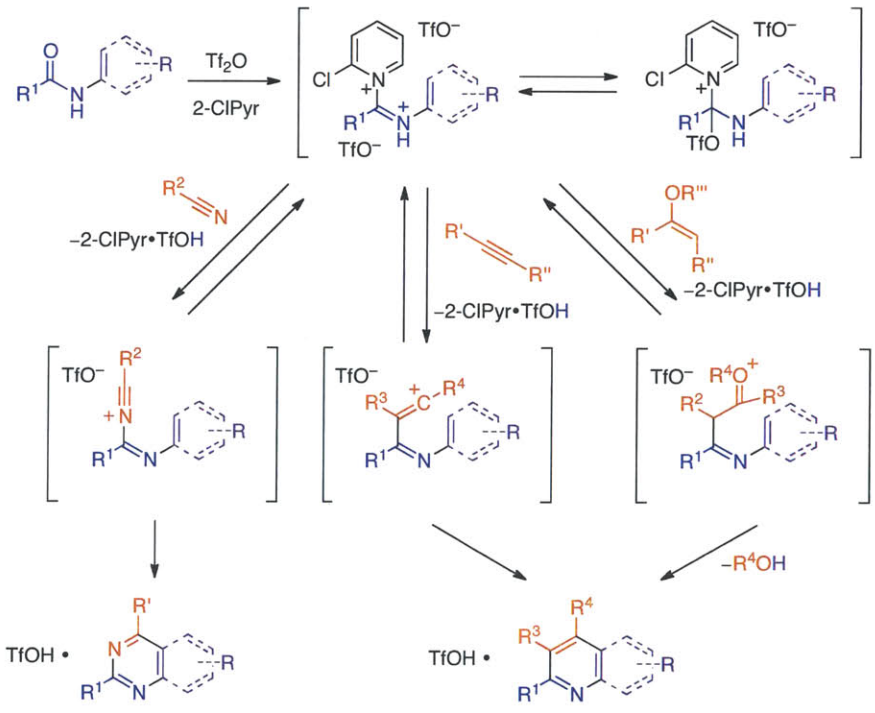
products, we sought to develop a mild protocol that would expand the substrate scope of the Abramovitch reaction.



Scheme 5. *N*-pyridinylation of primary amides via *N*-acylisocyanates.

Scheme 6. A modified Abramovitch reaction.

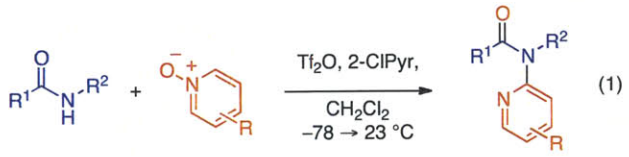
Our laboratory has previously reported the use of 2-chloropyridine (2-ClPyr) with trifluoromethanesulfonic anhydride[20] (Tf_2O) as a versatile reagent combination for the synthesis of pyrimidine[21] and pyridine derivatives (Scheme 7).[22] These methodologies provide the desired



Scheme 7. Previous condensative heterocycle syntheses by Movassaghi et al.

azaheterocycles via electrophilic activation of secondary *N*-aryl or *N*-vinyl amides to enable nucleophilic addition and annulation. Early spectroscopic studies indicated that activation of *N*-

aryl amides with our laboratory's reagent combination Tf_2O–2-ClPyr gives rise to 2-chloropyridinium adducts, which were proposed to potentially be highly electrophilic species that might enable reaction with the nucleophile. We envisioned that our laboratory's conditions would serve well for a modified Abramovitch reaction (eq 1). In this chapter, we describe the *N*-pyridinylation, *N*-isoquinolinylation and *N*-quinolinylation of various secondary amides and discuss a plausible mechanism supported by deuterium labeling and in situ monitoring experiments.



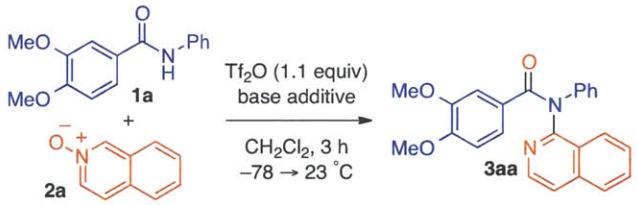
(1)

Results and Discussion

Based off of our laboratory's previous results in the context of azaheterocycle synthesis, we reasoned that *N*-aryl amide **1a** would be competent for in situ electrophilic activation with 2-ClPyr–Tf_2O and subsequent reaction with *N*-oxide nucleophiles. Thus, amide **1a** and isoquinoline *N*-oxide (**2a**) served as substrates for our early exploration of this chemistry (Table 1). Interestingly, the use of 2-fluoropyridine (2-FPyr, 1.2 equiv) as a base additive afforded a significant improvement in the reaction yield as compared to 2-ClPyr, furnishing amide **3aa** in 99% yield (compare entries 1 and 11, Table 1). More nucleophilic and stronger base additives generally gave poorer yields as compared to base additives with attenuated nucleophilicity and basicity. These observations suggest that optimal conditions provide a balance between the need for a base additive to promote electrophilic activation of the amide substrate while avoiding nucleophilic inhibition of this reaction. Consistent with our earlier findings,[21,22] both the presence of the optimal base additive in excess or its absence led to a marked decrease in the yield of the desired product (entries 3, 12 and 13, Table 1). The use of the Hendrickson reagent ($(Ph_3P^+)_2O{\bullet}2TfO^-$)[23] as the activating agent for this dehydrative *N*-pyridinylation reaction proved less effective as compared to the optimal conditions described above (entry 16, Table 1). The overall yield can be improved by use of excess **2a** due to competitive *N*-oxide decomposition (entry 2, Table 1).

We next examined the optimal conditions with a range of amide substrates with three representative heteroaromatic *N*-oxides (Table 2). Isoquinolinylation of amides under our conditions is highly efficient, giving good to excellent yields in all cases examined.

Table 1. Optimization of Reaction Conditions.[a]



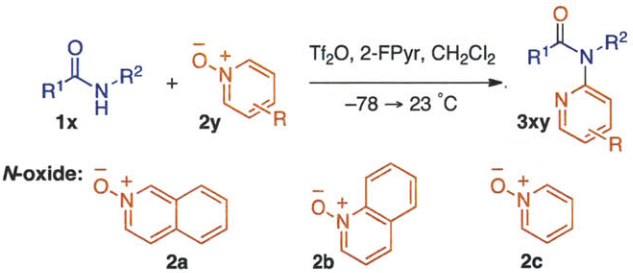
entry	base additive	base equiv	*N*-oxide X equiv	yield (%)[b]
1	2-Cl-pyridine	1.2	1.1	77
2	2-Cl-pyridine	1.2	2.0	81
3	None	-	1.1	16
4	pyridine	1.2	1.1	10
5	Et_3N	1.2	1.1	0
6	2-Br-pyridine	1.2	1.1	58
7	3-Cl-pyridine	1.2	1.1	74
8	Ethyl Nicotinate	1.2	1.1	73
9	3-Br-pyridine	1.2	1.1	72
10	2,6-lutidine	1.2	1.1	55
11	***2-F-pyridine***	***1.2***	***1.1***	***99***
12	2-F-pyridine	2.0	1.1	88
13	2-F-pyridine	5.0	1.1	76
14	DIPEA	1.2	1.1	48
15	2,6-dichloropyridine	1.2	1.1	15
16	Hendrickson Reagent[c]	1.5	1.1	72

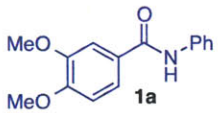
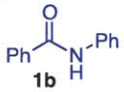
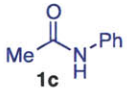
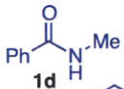
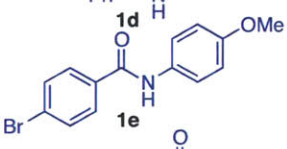
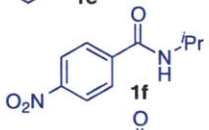
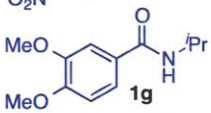
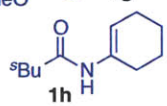
[a]Conditions: Amide **1a**, Tf_2O (1.1 equiv), base additive, CH_2Cl_2, −78 → 0 °C; isoquinoline *N*-oxide, 0 → 23 °C, 3 h. [b]Isolated yield. [c]Hendrickson reagent ($(Ph_3P^+)_2O{\bullet}2TfO^-$) was prepared (reference 23) and used in place of Tf_2O without base additive.

Isoquinolinylation of both *N*-alkyl benzamides (entries **3da**, **3fa**, and **3ga**, Table 2), in addition to *N*-aryl and *N*-vinyl amides (entries **3ca** and **3ha**, Table 2) were achieved in high yields under our standard reaction conditions. The high efficiency of our reaction with sterically hindered amide substrates (**3fa**, **3ga**, and **3ha**, Table 2) is notable. Electron rich benzamides notwithstanding (entry **3aa**, Table 2), the least efficient substrates in this series were *N*-aryl benzamides (entries **3ba** and **3ea**, Table 2). In all cases, completely regioselective isoquinolinylations proceeded at the 1-position of the isoquinoline ring.[17–19]

The use of quinoline *N*-oxide (**2b**, Table 2) and pyridine *N*-oxide (**2c**) as substrates also gave completely regioselective acylamination, however, with reduced overall efficiency for the formation of the desired products. This is due in part to the faster decomposition[17b,c,24] of *N*-oxides **2b** and **2c** (as compared to **2a**) under the electrophilic activation reaction conditions.[25] Interestingly, in reactions employing *N*-oxide **2c**, amides that exhibited high reactivity in

Table 2. Direct Dehydrative *N*-Pyridinylation of Amides.[a]



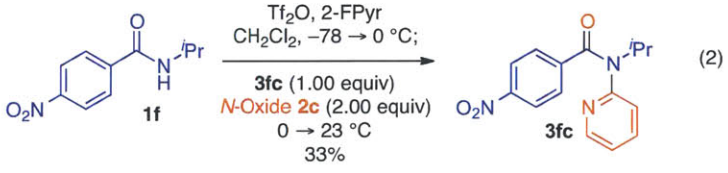
amide	*N*-(isoquinolin-1-yl) product **3**	*N*-(quinolin-2-yl) product **3**	*N*-(pyridin-2-yl) product **3**
 **1a**	**3aa**: 99%[b]	**3ab**: 0%[c]	**3ac**: 41%
 **1b**	**3ba**: 72%	**3bb**: 36%	**3bc**: 40%
 **1c**	**3ca**: 97%	**3cb**: 35%	**3cc**: 66%[d]
 **1d**	**3da**: 100%	**3db**: 60%	**3dc**: 67%[d]
 **1e**	**3ea**: 74%	**3eb**: 42%	**3ec**: 37%
 **1f**	**3fa**: 92%	**3fb**: 13%	**3fc**: 74%
 **1g**	**3ga**: 94%	**3gb**: 25%	**3gc**: 48%
 **1h**	**3ha**: 91%	**3hb**: 78%	**3hc**: 39%[d,e]

[a] Isolated yields of products **3xy**. Average of two experiments. Conditions: Amide **1x** (1 equiv), Tf_2O (1.1 equiv), 2-FPyr (1.2 equiv), CH_2Cl_2, –78 → 0 °C; *N*-oxide **2y** (2.0 equiv), 0 → 23 °C, 4 h. [b] *N*-oxide **2a** (1.1 equiv), 3 h. [c] Decomposition of **1a** observed over 4 h. [d] 2,6-lutidine used as base. [e] Low yield due to product decomposition.

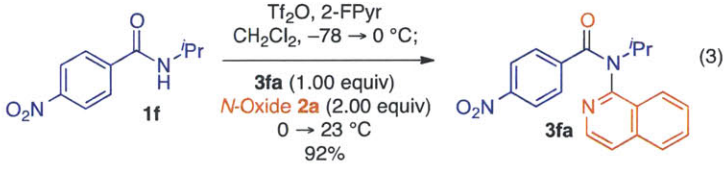
isoquinolinylation reactions gave higher yields when 2,6-lutidine[19] was used in place of 2-FPyr as the base additive (products **3cc**, **3dc** and **3hc** Table 2), likely owing to slight suppression of *N*-oxide decomposition. However, the use of 2,6-lutidine in place of 2-fluoropyridine with less

reactive *N*-aryl benzamides (**1b** and **1e**, Table 2) resulted in significantly lower yields of the desired products.

Attempts to *N*-quinolinylate amide **1a** under our standard conditions gave no detectable amount of the desired product **3ab**. This is consistent with poor nucleophilic addition of **2b** to the activated intermediate allowing a competitive decomposition of amide **1a**.[26] Given that nucleophilic base additives inhibit the desired reaction (Table 1), we conjectured that the *N*-pyridinylated products formed may also play an inhibitory role. Activation of amide **1f** followed by sequential addition of *N*-pyridinylated amide **3fc** (1.00 equiv) and pyridine *N*-oxide (**2c**) gave a low 33% yield of the desired amide **3fc** (eq 2),[27] which is less than half the expected yield. This suggests that product inhibition can be significant in these pyridinylation reactions. However, activation of amide **1f** under optimized conditions, followed by sequential addition of



(2)



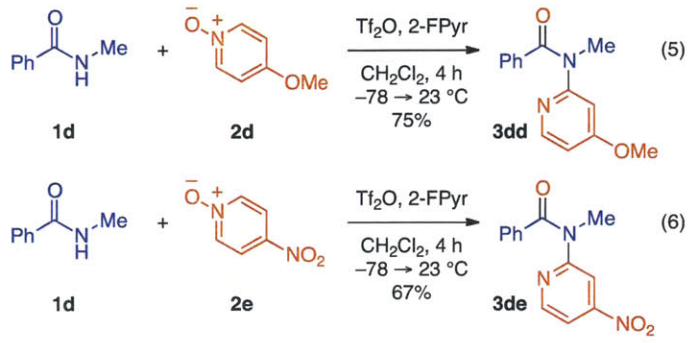
(3)

product **3fa** (1.00 equiv) and isoquinoline *N*-oxide (**2a**) gave 92% yield of the desired *N*-isoquinolinylated amide **3fa** (eq 3),[27] indicating no significant product inhibition in this reaction. Furthermore, sequential activation of an enantiomerically enriched amide **1h**[22] under optimized conditions followed by introduction of isoquinoline *N*-oxide (**2a**) provided the optically active *N*-isoquinolinylated amide (+)-**3ha** without erosion of optical activity (eq 4).

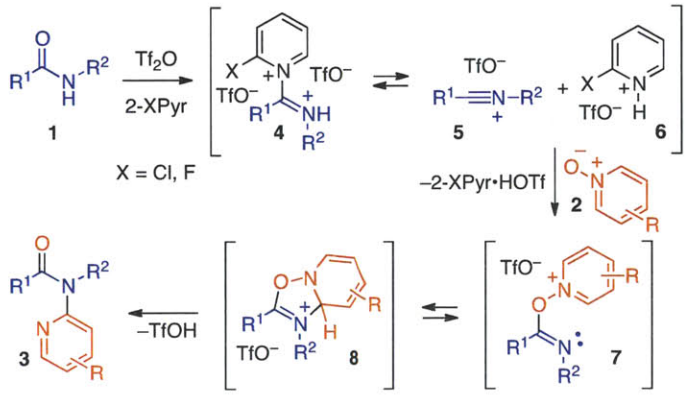
(4)

Interestingly, while *N*-pyridinylation of amides was generally less efficient as compared to *N*-isoquinolinylation, the use of both electron-rich and electron-poor 4-substituted pyridine *N*-oxides **2d** and **2e**, respectively, gave good yields of the desired products (eqs 5 and 6). The successful *N*-pyridinylation of amide **1d** with 4-nitropyridine *N*-oxide (**2e**) is notable, as its use

as a nucleophile for the Abramovitch reaction was previously reported to be unsuccessful,[17a,c] suggesting greater electrophilicity of the intermediate under the conditions described here.



To gain better understanding of the intermediates involved in this transformation, a series of in situ IR and NMR monitoring experiments were performed. The conversion of amide **1d** to *N*-isoquinolinylated amide **3da** under optimized conditions was monitored by in situ IR analysis. Addition of Tf_2O to a mixture of amide **1d** and 2-FPyr resulted in complete consumption of the amide absorption band (1668 cm^{-1}) and appearance of a persistent absorption at 2370 cm^{-1}, suggestive of a nitrilium ion intermediate.[17c,28] Addition of isoquinoline *N*-oxide (**2a**) resulted in immediate disappearance of the absorption at 2370 cm^{-1} and appearance of a persistent absorption at 1691 cm^{-1}, which was due to the protonated product **3da**. Interestingly, the activation of *N*-(4-methoxyphenyl)benzamide (**1i**) with the reagent combination of 2-ClPyr and Tf_2O did not lead to an observable absorption corresponding to a nitrilium ion, but instead gave rise to a persistent absorption at 1600 cm^{-1}, suggestive of an amidinium intermediate.[22] These observations suggest that while electrophilic activation of **1d** using 2-FPyr results in **5d** (Scheme 8), similar activation of **1i** using 2-ClPyr leads to predominant formation of **4i** rather than **5i**.

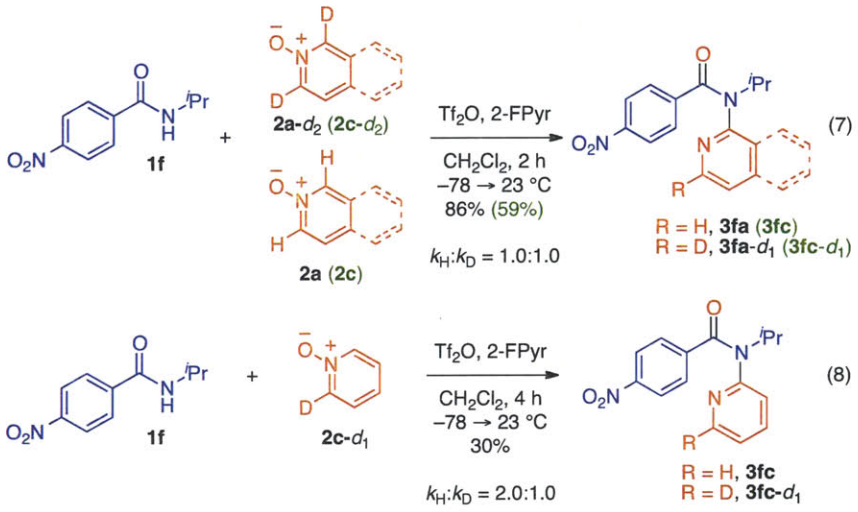


Scheme 8. Mechanism for direct dehydrative *N*-pyridinylation of amides.

To determine the degree to which the formation of a nitrilium ion depends on the nature of the base additive and the amide structure itself, a series of in situ IR monitoring experiments were carried out.[27] For comparison, while activation of *N*-alkyl benzamide **1d** under optimal conditions resulted in an absorption suggesting a nitrilium ion (2370 cm^{-1}),[29] the activation of *N*-aryl benzamides **1b** and **1i** under the same conditions led to no detection of an IR absorption consistent with a nitrilium ion, but instead resulted in the appearance of an IR absorption suggesting an amidinium ion (1621 cm^{-1} in both cases).[22] However, Tf_2O activation of the electron-rich *N*-aryl benzamide **1a** in the presence of either 2-FPyr or 2-ClPyr (1.2 equiv) indeed resulted in an absorption at 2312 cm^{-1}, suggesting a persistent nitrilium ion intermediate. Interestingly, addition of extra equivalents of 2-ClPyr resulted in complete disappearance of this absorption band and appearance of a persistent absorption at 1594 cm^{-1}, consistent with the formation of the previously observed amidinium ion.[22] Even the electron-poor *N*-alkyl benzamide **1f** resulted in a lasting nitrilium ion (2354 cm^{-1}) upon electrophilic activation in the presence of either 2-FPyr or 2-ClPyr (1.2 equiv), although the presence of excess 2-ClPyr resulted in disappearance of the absorption at 2354 cm^{-1} and the appearance of an absorption at 1609 cm^{-1}.[30] These observations suggest that activation of *N*-alkyl amides under these conditions more readily results in persistent nitrilium ion formation, while *N*-aryl amides show reluctance to form the corresponding nitrilium ion, likely owing to the inductive effect of the nitrogen substituent.[31] Only the particularly electron-rich *N*-aryl benzamide **1a** resulted in any observable nitrilium ion, perhaps due to greater stabilization by resonance contribution. These differences in amide reactivity were further substantiated by in situ ^1H NMR monitoring of the electrophilic activation step. Interestingly, amides that demonstrated the least propensity to form a nitrilium ion upon activation under the optimal reaction conditions also gave the lowest yields in reactions with isoquinoline *N*-oxide (e.g., entry **3ba**, Table 2). Furthermore, reduced yield of the desired product upon addition of excess base additive (or use of nucleophilic bases, Table 1) is consistent with the observed disappearance of the nitrilium species during in situ monitoring experiments.

Additional mechanistic insight was obtained using deuterated substrates **2a**-d_2, **2c**-d_2 and **2c**-d_1 (eqs 7 and 8). Electrophilic activation of *N*-alkyl benzamide **1f** under optimal conditions followed by introduction of excess[32] isoquinoline *N*-oxide (**2a**) and 1,3-dideuteroisoquinoline *N*-oxide (**2a**-d_2) provided a mixture of *N*-isoquinolinylated products **3fa** and **3fa**-d_1 corresponding

to k_H:k_D = 1.0:1.0 in 86% combined yield (eq 7).[27] The same outcome was observed in a similar experiment using excess **2c**-d_2 and **2c**, resulting in a mixture of the *N*-pyridinylated products **3fc** and **3fc**-d_1 corresponding to k_H:k_D = 1.0:1.0 in a combined yield of 59% (eq 7). As another mechanistic probe, activation of **1f** under optimal conditions and the use of excess 2-deuteropyridine *N*-oxide (**2a**-d_1) provided the expected *N*-pyridinylated amide **3fc** as a mixture of non-deuterated and monodeuterated derivatives (eq 8).[27] Importantly, the ratio of **3fc**-d_0 and **3fc**-d_1 was found to be 1.0:2.0, reflecting an observable primary kinetic isotope effect (k_H:k_D = 2.0:1.0).[33] These observations suggest that addition[34] of the imidate nitrogen onto the pyridinium ring is reversible, whereas nucleophilic addition of the *N*-oxide **2** to the nitrilium ion **5** (or another electrophilic variant) is irreversible (Scheme 8).



Conclusion

We have presented a direct method for the dehydrative *N*-pyridinylation of amides under electrophilic activation by the reagent combination of Tf_2O and 2-FPyr. This method allows for a highly effective activation of a variety of amide substrates, including sterically hindered and *N*-aryl amides,[19] without requiring the isolation of sensitive intermediates or the use of heavy metal Lewis acid additives, allows for the use of electron-deficient pyridine *N*-oxide derivatives, and proceeds in shortened reaction times without the need for elevated temperatures.[17] Our in situ monitoring experiments suggest greater propensity for the formation of persistent nitrilium ion intermediates when *N*-alkyl amide substrates are used as compared to *N*-aryl amides. Our studies with deuterated *N*-oxide substrates suggest an irreversible nucleophilic addition step and a plausible interconversion of intermediates **7** and **8** based on the observed kinetic isotope effect.

The activation conditions described here allow the trapping of highly electrophilic intermediates with weakly nucleophilic *N*-oxides.[35]

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[25] This observation is supported by control experiments involving the exposure of *N*-oxides **2a–c** to trifluoromethanesulfonic anhydride and 2-fluoropyridine under standard reaction conditions.

[26] Control experiments revealed that activation of amide **1a** in the absence of a competent nucleophile led to decomposition.

[27] Please see Experimental Section for details.

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[35] Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341.

Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks, modified Schlenk (Kjeldahl shape) flasks or glass pressure vessels. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel gas-tight syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60 Å pore size, 32–63 μm, standard grade) or non-activated alumina (80–325 mesh, chromatographic grade).[1] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel or neutral alumina impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic phosphomolybdic acid (PMA), an acidic solution of *p*-anisaldehyde (anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate ($KMnO_4$) or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C, then at ~1 Torr (vacuum pump) unless otherwise indicated.

Materials. Commercial reagents and solvents were used as received with the following exceptions: Dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.[2] 2-Chloropyridine was distilled from calcium hydride and stored sealed under an argon atmosphere. Secondary amides were prepared by acylation of the corresponding primary amines[3] or by previously reported copper–catalyzed C–N bond-forming reactions.[4]

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with 300 and 500 MHz spectrometers. Chemical shifts are recorded in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent ($CHCl_3$: δ 7.27, C_2D_5HSO: δ 2.50). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with 300 and 500 MHz spectrometers and are recorded in parts per million on the δ scale and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.2, $(D_3C)_2SO$: δ 39.5). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant(s) in Hertz, assignment]. Infrared data were obtained with an FTIR and are reported as follows: [frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad), assignment]. In situ IR reaction monitoring was performed with an in situ monitoring IR spectrometer.

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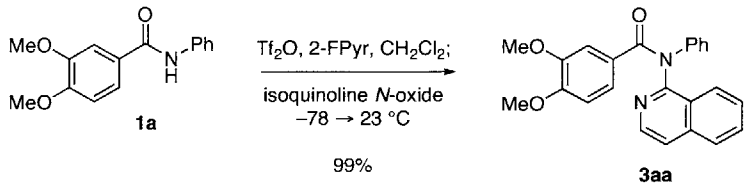
[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.
[3] For a general procedure, see: DeRuiter, J.; Swearingen, B. E.; Wandrekar, V.; Mayfield, C. A. *J. Med. Chem.* **1989**, *32*, 1033.
[4] For the general procedure used for the synthesis of *N*-vinyl amides, see: Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

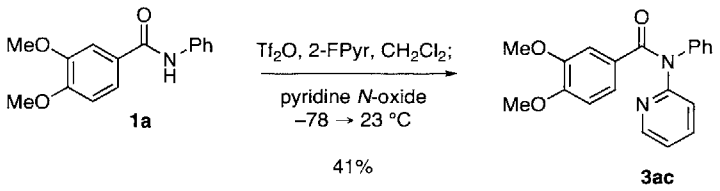


N-(Isoquinolin-1-yl)-3,4-dimethoxy-N-phenylbenzamide (3aa, Table 2):

Trifluoromethanesulfonic anhydride (46.0 μL, 0.270 mmol, 1.10 equiv) was added via syringe to a solution of 3,4-dimethoxy-*N*-phenylbenzamide[5] (**1a**, 63.0 mg, 0.245 mmol, 1 equiv) and 2-fluoropyridine (25.3 μL, 0.294 mmol, 1.20 equiv) in dichloromethane (1.0 mL) at –78 °C. After 2 min, the reaction mixture was warmed to 0 °C. After 5 min, isoquinoline *N*-oxide (39.2 mg, 0.270 mmol, 1.10 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 3 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (40 → 60% ethyl acetate in hexanes) to afford the amide **3aa** (93.1 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.37 (d, 1H, J = 5.6 Hz), 8.16 (dd, 1H, J = 8.5, 0.8 Hz), 7.86 (d, 1H, J = 8.3 Hz), 7.69–7.57 (m, 3H), 7.31 (t, 2H, J = 8.0 Hz), 7.24 (d, 2H, J = 7.5 Hz), 7.20 (m, 2H), 7.07 (s, 1H), 6.64 (s, 1H), 3.82 (s, 3H), 3.58 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.1, 155.4, 151.0, 148.1, 143.5, 141.9, 138.4, 130.7, 129.3, 128.5, 128.0, 127.3, 126.5, 126.3, 125.7, 125.0, 123.0, 121.1, 112.1, 110.1, 55.9, 55.7.
FTIR (neat) cm^{-1}:	3061 (w), 2936 (m), 1661 (s), 1516 (s), 1268 (s).
HRMS (ESI):	calc'd for $C_{24}H_{21}N_2O_3$ $[M+H]^+$: 385.1547, found: 385.1551.
TLC (50% EtOAc in hexanes), R_f:	0.21 (UV).

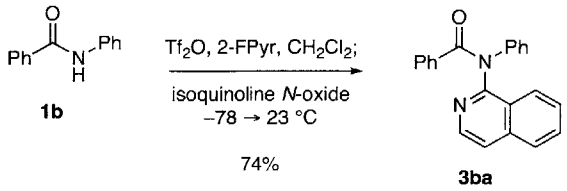
[5] Gore, V. G.; Narasimhan, N. S. *J. Chem. Soc., Perkin Trans. 1* **1988**, 481.



3,4-Dimethoxy-*N*-phenyl-*N*-(pyridin-2-yl)benzamide (3ac, Table 2):

Trifluoromethanesulfonic anhydride (38.2 μL, 0.227 mmol, 1.10 equiv) was added via syringe to a solution of 3,4-dimethoxy-*N*-phenylbenzamide[5] (**1a**, 52.7 mg, 0.206 mmol, 1 equiv) and 2-fluoropyridine (21.2 μL, 0.247 mmol, 1.20 equiv) in dichloromethane (1.0 mL) at –78 °C. After 2 min, the reaction mixture was warmed to 0 °C. After 5 min, pyridine *N*-oxide (39.2 mg, 0.412 mmol, 2.00 equiv) was added as a solid under an atmosphere of argon. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 3 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (40 → 60% ethyl acetate in hexanes) to afford the amide **3ac** (28.0 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.43-8.42 (m, 1H), 7.67–7.64 (m, 1H), 7.35–7.32 (m, 2H), 7.24–7.21 (m, 2H), 7.18–7.10 (m, 4H), 7.03 (d, 1H, J = 2.0 Hz), 6.70 (d, 1H, J = 8.0 Hz), 3.85 (s, 3H), 3.69 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ:	170.7, 157.0, 151.1, 149.3, 148.3, 143.4, 138.0, 129.5, 128.0, 127.8, 126.8, 123.6, 122.2, 121.4, 112.6, 110.2, 56.0, 55.9.
FTIR (neat) cm^{-1}:	3007 (w), 2936 (m), 1660 (s), 1585 (s), 1239 (s).
HRMS (ESI):	calc'd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$: 335.1390, found: 335.1381.
TLC (50% EtOAc in hexanes), R_f:	0.09 (UV).

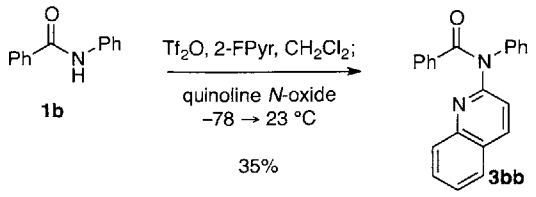


N-(Isoquinolin-1-yl)-N-phenylbenzamide[6] (3ba, Table 2):

Trifluoromethanesulfonic anhydride (49.2 μL, 0.292 mmol, 1.10 equiv) was added via syringe to a solution of *N*-phenylbenzamide (**1b**, 52.3 mg, 0.265 mmol, 1 equiv) and 2-fluoropyridine (27.3 μL, 0.318 mmol, 1.20 equiv) in dichloromethane (2.0 mL) at –78 °C. After 2 min, the resulting mixture was warmed to 0 °C. After 5 min, isoquinoline *N*-oxide (77.0 mg, 0.530 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 30% ethyl acetate in hexanes) to afford the amide **3ba**[6] (63.6 mg, 74%).

^{1}H NMR (500 MHz, $(D_3C)_2SO$, 20 °C) δ:	8.34–8.28 (m, 1H), 8.22 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 8.2 Hz), 7.84–7.74 (m, 2H), 7.73–7.67 (m, 1H), 7.47 (s, 2H), 7.34–7.27 (m, 3H), 7.26–7.16 (m, 5H).
^{13}C NMR (125 MHz, $(D_3C)_2SO$, 100 °C) δ:	170.2, 153.8, 142.3, 140.8, 137.4, 135.7, 130.1, 129.7, 128.4, 128.0, 127.6, 127.3, 126.6, 126.1, 125.7, 124.4, 124.1, 120.5.
FTIR (neat) cm^{-1}:	3059 (m), 1663 (s), 1584 (s), 1494 (s), 1386 (s).
HRMS (ESI):	calc'd for $C_{22}H_{17}N_2O$ $[M+H]^+$: 325.1335, found: 325.1345.
TLC (30% EtOAc in hexanes), R_f:	0.35 (UV).

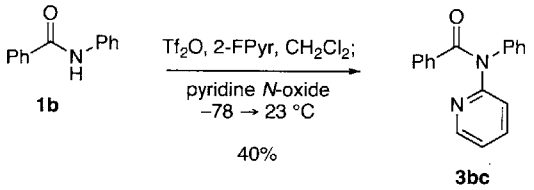
[6] Abramovitch, R. A.; Rogers, R. B.; Singer, G. M. *J. Org. Chem.* **1975**, *40*, 41.



***N*-(Quinolin-2-yl)-*N*-phenylbenzamide[6] (3bb, Table 2):**

Trifluoromethanesulfonic anhydride (46.3 μL, 0.275 mmol, 1.10 equiv) was added via syringe to a solution of *N*-phenylbenzamide (**1b**, 49.0 mg, 0.250 mmol, 1 equiv) and 2-fluoropyridine (25.8 μL, 0.300 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, quinoline *N*-oxide (72.6 mg, 0.500 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 30% ethyl acetate in hexanes) to afford the amide **3bb**[6] (28.2 mg, 35%).

^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ:	8.09 (d, 1H, J = 8.7 Hz), 7.81–7.74 (m, 2H), 7.66–7.59 (m, 1H), 7.58–7.45 (m, 3H), 7.39–7.17 (m, 9H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.7, 155.6, 147.3, 142.7, 138.1, 136.4, 130.7, 130.0, 129.4, 129.3, 129.0, 128.1, 128.1, 127.5, 127.0, 126.6, 126.5, 120.0.
FTIR (neat) cm^{-1}:	3062 (m), 1666 (s), 1594 (s), 1502 (s), 1301 (s).
HRMS (ESI):	calc'd for $C_{22}H_{17}N_2O$ $[M+H]^+$: 325.1335, found: 325.1343.
TLC (30% EtOAc in hexanes), R_f:	0.44 (UV).

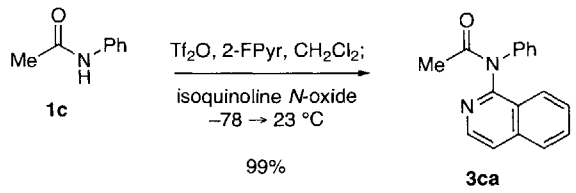


_N_-(Pyridin-2-yl)-_N_-phenylbenzamide[7] (3bc, Table 2):

Trifluoromethanesulfonic anhydride (48.1 μL, 0.286 mmol, 1.10 equiv) was added via syringe to a solution of _N_-phenylbenzamide (**1b**, 51.1 mg, 0.260 mmol, 1 equiv) and 2-fluoropyridine (26.8 μL, 0.312 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, pyridine _N_-oxide (49.5 mg, 0.520 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 50% ethyl acetate in hexanes) to afford the amide **3bc**[7] (28.4 mg, 40%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.40 (d, 1H, J = 4.5 Hz), 7.65 (dt, 1H, J = 7.5, 2.0 Hz), 7.49 (d, 2H, J = 6.0 Hz,), 7.36–7.29 (m, 3H), 7.28–7.20 (m, 4H), 7.18 (d, 2H, J = 7.5 Hz), 7.12–7.08 (m, 1H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.2, 156.6, 149.3, 142.9, 137.9, 136.2, 130.6, 129.4, 129.3, 128.2, 127.9, 127.0, 122.0, 121.5.
FTIR (neat) cm^{-1}:	3060 (w), 1660 (s), 1582 (s), 1435 (m), 1348 (m).
HRMS (ESI):	calc'd for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.1179, found: 275.1185.
TLC (30% EtOAc in hexanes), R_f:	0.24 (UV).

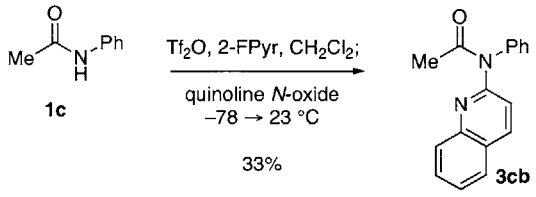
[7] Abramovitch, R. A.; Singer, G. M. *J. Org. Chem.* **1974**, *39*, 1795.



<u>*N*-(Isoquinolin-1-yl)-*N*-phenylacetamide (3ca, Table 2):</u>

Trifluoromethanesulfonic anhydride (54.0 μL, 0.321 mmol, 1.10 equiv) was added via syringe to a solution of *N*-phenylacetamide (**1c**, 39.5 mg, 0.292 mmol, 1 equiv) and 2-fluoropyridine (30.2 μL, 0.351 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, isoquinoline *N*-oxide (84.8 mg, 0.584 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 → 50% ethyl acetate in hexanes) to afford the amide **3ca** (73.6 mg, 96%).

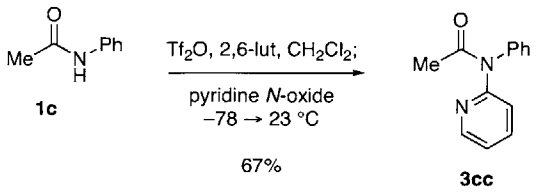
^{1}H NMR (500 MHz, $(D_3C)_2SO$, 80 °C)	8.47 (d, 1H, J = 5.7 Hz), 8.18 (d, 1H, J = 8.4 Hz), 8.05 (d, 1H, J = 8.3 Hz), 7.89 (d, 1H, J = 5.7 Hz), 7.84–7.79 (m, 1H), 7.74–7.70 (m, 1H), 7.46 (d, 2H, J = 7.8 Hz), 7.39–7.34 (m, 2H), 7.26–7.22 (m, 1H), 1.98 (s, 3H).
^{13}C NMR (125 MHz, $(D_3C)_2SO$, 100 °C) δ:	169.4, 153.4, 141.3, 141.0, 137.6, 130.3, 128.4, 128.1, 126.6, 126.2, 126.1, 124.6, 124.3, 120.9, 22.4.
FTIR (neat) cm^{-1}:	3059 (m), 2932 (w), 1680 (s), 1495 (s), 1370 (s).
HRMS (ESI):	calc'd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1179, found: 263.1172.
TLC (50% EtOAc in hexanes), R_f:	0.24 (UV).



N-(Quinolin-2-yl)-N-phenylacetamide (3cb, Table 2):

Trifluoromethanesulfonic anhydride (57.7 μL, 0.343 mmol, 1.10 equiv) was added via syringe to a solution of *N*-phenylacetamide (**1c**, 42.1 mg, 0.311 mmol, 1 equiv) and 2-fluoropyridine (32.1 μL, 0.374 mmol, 1.20 equiv) in dichloromethane (1.75 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, quinoline *N*-oxide (90.4 mg, 0.623 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 30% ethyl acetate in hexanes) to afford the amide **3cb** (26.7 mg, 33%).

^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ:	8.13 (d, 1H, 8.7 Hz), 7.98 (d, 1H, 8.4 Hz), 7.80 (d, 1H, *J* = 7.8 Hz), 7.73–7.65 (m, 1H), 7.56-7.50 (m, 1H), 7.46–7.29 (m, 6H), 2.27 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ:	171.6, 154.6, 147.1, 141.9, 138.2, 130.0, 129.6, 129.1, 128.6, 127.7, 127.5, 126.8, 126.7, 119.7, 24.7.
FTIR (neat) cm^{-1}:	3062 (m), 2927 (w), 1682 (s), 1593 (s), 1501 (s), 1292 (s).
HRMS (ESI):	calc'd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1179, found: 263.1168.
TLC (70% EtOAc in hexanes), R_f:	0.64 (UV).

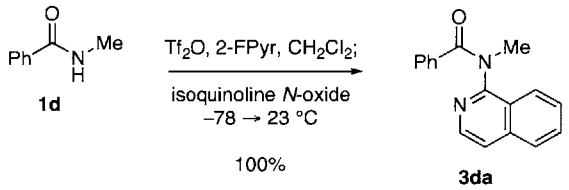


<u>*N*-(Pyridin-2-yl)-*N*-phenylacetamide[8] (3cc, Table 2):</u>

Trifluoromethanesulfonic anhydride (48.3 μL, 0.287 mmol, 1.10 equiv) was added via syringe to a solution of *N*-phenylacetamide (**1c**, 35.3 mg, 0.261 mmol, 1 equiv) and 2,6-lutidine (36.5 μL, 0.313 mmol, 1.20 equiv) in dichloromethane (1.75 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, pyridine *N*-oxide (49.7 mg, 0.522 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 50% ethyl acetate in hexanes) to afford the amide **3cc**[8] (42.1 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.44 (d, 1H, J = 5.0 Hz), 7.75–7.70 (m, 1H), 7.48 (d, 1H, J = 7.5 Hz), 7.45–7.40 (m, 2H), 7.35 (d, 1H, J = 7.5 Hz), 7.32–7.29 (m, 2H), 7.16–7.12 (m, 1H), 2.12 (s, 3H,).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.2, 155.4, 149.0, 142.2, 138.1, 129.7, 128.6, 127.8, 121.7, 121.4, 24.5.
FTIR (neat) cm^{-1}:	3058 (w), 2920 (w), 1678 (s), 1585 (s), 1433 (s).
HRMS (ESI):	calc'd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1022, found: 213.1023.
TLC (70% EtOAc in hexanes), R_f:	0.35 (UV).

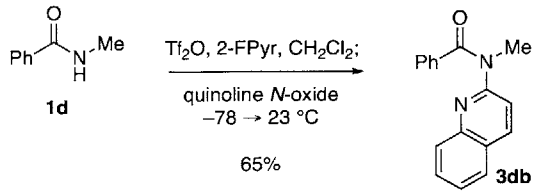
[8] Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2002**, *4*, 3127.



N-(Isoquinolin-1-yl)-N-methylbenzamide (3da, Table 2):

Trifluoromethanesulfonic anhydride (55.7 μL, 0.331 mmol, 1.10 equiv) was added via syringe to a solution of *N*-methylbenzamide (**1d**, 40.7 mg, 0.301 mmol, 1 equiv) and 2-fluoropyridine (31.0 μL, 0.361 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, isoquinoline *N*-oxide (87.4 mg, 0.602 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 → 50% ethyl acetate in hexanes) to afford the amide **3da** (79.0 mg, 100%).

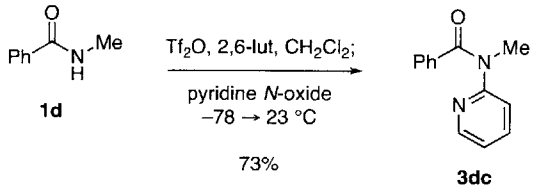
^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ:	8.31 (d, 1H, J = 5.5 Hz), 7.99 (d, 1H, J = 8.5 Hz), 7.78 (d, 1H, J = 8.5 Hz), 7.65–7.50 (m, 3H), 7.40–7.20 (m, 2 H), 7.15–6.90 (m, 3H), 3.63 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ:	171.8, 155.9, 141.5, 138.2, 136.2, 130.8, 130.0, 128.4, 128.1, 127.8, 127.3, 125.0, 124.5, 121.0, 37.2.
FTIR (neat) cm^{-1}:	3058 (m), 2936 (w), 1651 (s), 1560 (s), 1363 (s).
HRMS (ESI):	calc'd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1179, found: 263.1179.
TLC (50% EtOAc in hexanes), R_f:	0.33 (UV).



_N_-(Quinolin-2-yl)-_N_-methylbenzamide (3db, Table 2):

Trifluoromethanesulfonic anhydride (41.9 μL, 0.249 mmol, 1.10 equiv) was added via syringe to a solution of *N*-methylbenzamide (**1d**, 30.6 mg, 0.226 mmol, 1 equiv) and 2-fluoropyridine (23.4 μL, 0.272 mmol, 1.20 equiv) in dichloromethane (2.0 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, quinoline *N*-oxide (65.7 mg, 0.453 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 30% ethyl acetate in hexanes) to afford the amide **3db** (38.4 mg, 65%).

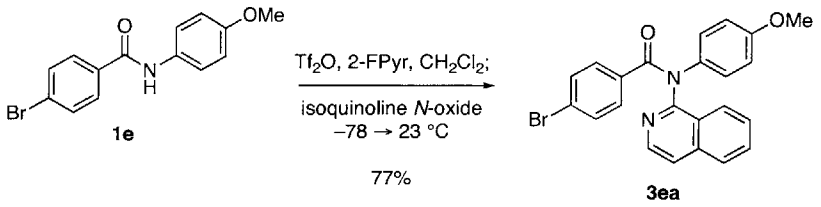
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	7.97 (d, 1H, J = 9.0 Hz), 7.84 (d, 1H, J = 9.0 Hz), 7.73–7.69 (m, 2H), 7.52–7.48 (m, 1H), 7.45-7.42 (m, 2H), 7.35–7.31 (m, 1H), 7.25–7.21 (m, 2H), 6.91 (d, 1H, J = 9.0 Hz), 3.74 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ:	171.6, 156.0, 147.1, 137.1, 136.3, 130.7, 130.2, 128.9, 128.7, 128.4, 127.6, 126.5, 126.0, 120.3, 36.4.
FTIR (neat) cm^{-1}:	3050 (m), 2918 (m), 1652 (s), 1595 (s), 1502 (m).
HRMS (ESI):	calc'd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1179, found: 263.1182.
TLC (70% EtOAc in hexanes), R_f:	0.71 (UV).



<u>*N*-(Pyridin-2-yl)-*N*-methylbenzamide[8] (3dc, Table 2):</u>

Trifluoromethanesulfonic anhydride (48.1 μL, 0.286 mmol, 1.10 equiv) was added via syringe to a solution of *N*-methylbenzamide (**1d**, 35.1 mg, 0.260 mmol, 1 equiv) and 2,6-lutidine (36.3 μL, 0.312 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, pyridine *N*-oxide (49.4 mg, 0.519 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 50% ethyl acetate in hexanes) to afford the amide **3dc**[8] (40.4 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.46–8.44 (m, 1H), 7.46–7.42 (m, 1H), 7.36–7.29 (m, 3H), 7.25–7.20 (m, 2H), 7.06–7.02 (m, 1H), 6.81 (d, 1H, J = 8.0 Hz), 3.60 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.2, 156.9, 148.9, 137.5, 136.2, 130.3, 128.7, 128.2, 121.8, 121.1, 36.2.
FTIR (neat) cm^{-1}:	3058 (w), 2931 (w), 1651 (s), 1587 (s), 1359 (s).
HRMS (ESI):	calc'd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1022, found: 213.1022.
TLC (70% EtOAc in hexanes), R_f:	0.45 (UV).

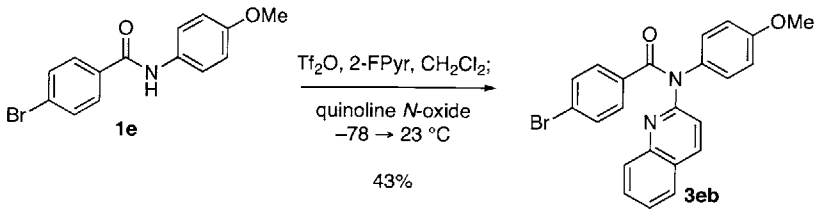


4-Bromo-*N*-(isoquinolin-1-yl)-*N*-(4-methoxyphenyl)benzamide (3ea, Table 2):

Trifluoromethanesulfonic anhydride (32.0 μL, 0.190 mmol, 1.10 equiv) was added via syringe to a solution of 4-bromo-*N*-(4-methoxyphenyl)benzamide[9] (**1e**, 52.9 mg, 0.173 mmol, 1 equiv) and 2-fluoropyridine (17.9 μL, 0.208 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, isoquinoline *N*-oxide (50.2 mg, 0.346 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 50% ethyl acetate in hexanes) to afford the amide **3ea** (57.7 mg, 77%).

^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ:	8.34 (d, 1H, J = 4.8 Hz), 8.15 (d, 1H, J = 8.1 Hz), 7.85 (d, 1H, J = 8.1 Hz), 7.72–7.56 (m, 3H), 7.46–7.24 (m, 4H), 7.20 (d, 2H, J = 7.8 Hz), 6.83 (d, 2H, J = 8.7 Hz), 3.76 (s, 3H).
^{13}C NMR (125 MHz, $(D_3C)_2SO$, 20 °C) δ:	169.3, 157.4, 153.7, 140.8, 137.5, 135.0, 134.8, 130.4, 130.2, 129.5, 128.0, 127.5, 126.6, 124.2, 124.2, 123.2, 120.5, 114.0, 54.9.
FTIR (neat) cm^{-1}:	3057 (m), 2933 (w), 1660 (s), 1509 (s), 1248 (s).
HRMS (ESI):	calc'd for $C_{23}H_{18}BrN_2O_2$ $[M+H]^+$: 433.0546, found: 433.0545.
TLC (50% EtOAc in hexanes), R_f:	0.45 (UV).

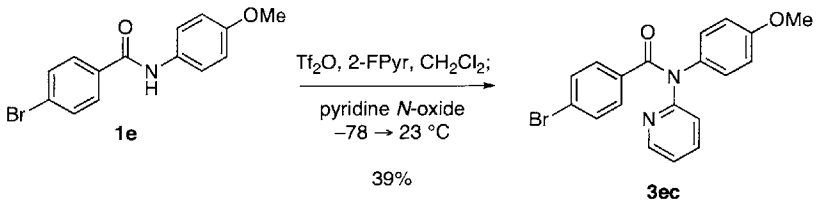
[9] Yang, K.; He, X.; Ha-soon, C.; Wang, Z.; Woodmansee, D. H.; Liu, H. *Tetrahedron Lett.* **2008**, *49*, 1725.



4-Bromo-*N*-(quinolin-2-yl)-*N*-(4-methoxyphenyl)benzamide (3eb, Table 2):

Trifluoromethanesulfonic anhydride (30.8 μL, 0.183 mmol, 1.10 equiv) was added via syringe to a solution of 4-bromo-*N*-(4-methoxyphenyl)benzamide[9] (**1e**, 51.0 mg, 0.167 mmol, 1 equiv) and 2-fluoropyridine (17.2 μL, 0.200 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, quinoline *N*-oxide (48.3 mg, 0.333 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5 → 30% ethyl acetate in hexanes) to afford the amide **3eb** (30.7 mg, 43%).

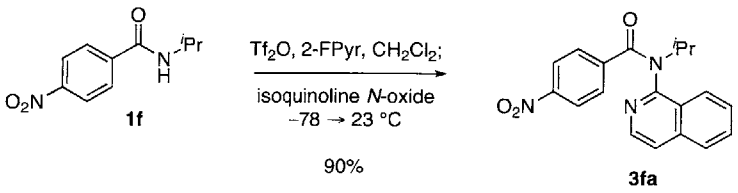
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.08 (d, 1H, *J* = Hz), 7.78–7.72 (m, 1H), 7.65–7.58 (m, 1H), 7.54–7.46 (m, 1H), 7.42–7.25 (m, 6H), 7.18–7.12 (m, 2H), 6.95–6.83 (m, 2H), 3.79 (s, 3H).
^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ:	170.7, 158.6, 155.3, 147.1, 138.3, 135.4, 135.1, 131.4, 130.8, 130.1, 129.2, 129.0, 127.5, 126.7, 126.5, 125.0, 119.5, 114.8, 55.6.
FTIR (neat) cm^{-1}:	3062 (w), 2956 (w), 1663 (s), 1509 (s), 1247 (s).
HRMS (ESI):	calc'd for $C_{23}H_{18}BrN_2O_2$ $[M+H]^+$: 433.0546, found: 433.0546.
TLC (30% EtOAc in hexanes), R_f:	0.39 (UV).



4-Bromo-*N*-(pyridin-2-yl)-*N*-(4-methoxyphenyl)benzamide (3ec, Table 2):

Trifluoromethanesulfonic anhydride (37.4 μL, 0.222 mmol, 1.10 equiv) was added via syringe to a solution of 4-bromo-*N*-(4-methoxyphenyl)benzamide[9] (**1e**, 61.8 mg, 0.202 mmol, 1 equiv) and 2-fluoropyridine (20.8 μL, 0.242 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, pyridine *N*-oxide (38.4 mg, 0.404 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 30% ethyl acetate in hexanes) to afford the amide **3ec** (29.9 mg, 39%).

^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ:	8.39 (dd, 1H, J = 4.8, 1.5 Hz), 7.67 (dt, 1H, J = 8.1, 2.1 Hz), 7.40–7.32 (m, 4H), 7.24 (d, 1H, J = 8.1 Hz), 7.14–7.07 (m, 3H), 6.85 (d, 2H, J = 8.7 Hz), 3.79 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	170.2, 158.5, 156.4, 149.2, 138.0, 135.3, 135.2, 131.4, 130.8, 129.1, 125.0, 121.5, 121.5, 114.8, 55.6.
FTIR (neat) cm^{-1}:	3055 (m), 2933 (m), 1662 (s), 1509 (s), 1247 (s).
HRMS (ESI):	calc'd for $C_{19}H_{16}BrN_2O_2$ $[M+H]^+$: 383.0390, found: 383.0391.
TLC (30% EtOAc in hexanes), R_f:	0.14 (UV).

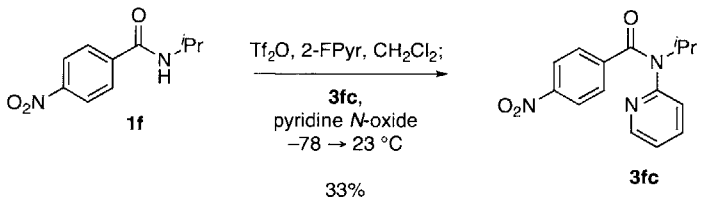


N-(Isoquinolin-1-yl)-N-isopropyl-4-nitrobenzamide (3fa, Table 2):

Trifluoromethanesulfonic anhydride (44.3 μL, 0.263 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-4-nitrobenzamide[10] (**1f**, 49.7 mg, 0.239 mmol, 1 equiv) and 2-fluoropyridine (24.6 μL, 0.286 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, isoquinoline *N*-oxide (69.2 mg, 0.477 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 20% ethyl acetate in hexanes) to afford the amide **3fa** (72.0 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.43 (d, 1H, J = 5.5 Hz), 7.92 (d, 1H, J = 8.5 Hz), 7.78 (d, 2H, J = 8.5 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.63–7.54 (m, 3H), 7.39 (d, 2H, J = 8.5 Hz), 5.15–5.05 (m, 1H), 1.65 (d, 3H, J = 6.5 Hz), 1.14 (d, 3H, J = 6.5 Hz).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	168.8, 152.9, 147.9, 143.5, 141.5, 138.1, 131.0, 128.9, 128.6, 127.4, 127.2, 124.6, 122.8, 121.7, 50.9, 22.2, 19.7.
FTIR (neat) cm^{-1}:	3057 (w), 2977 (m), 1651 (s), 1523 (s), 1346 (s).
HRMS (ESI):	calc'd for $C_{19}H_{18}N_3O_3$ $[M+H]^+$: 336.1343, found: 336.1353.
TLC (30% EtOAc in hexanes), R_f:	0.30 (UV).

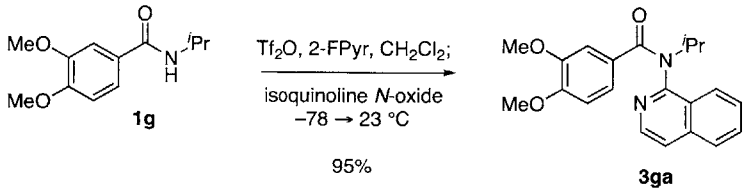
[10] Van den Hoven, B. G.; Alper, H. *J. Am. Chem. Soc.* **2001**, *123*, 10214.



_N_-(Pyridin-2-yl)-_N_-isopropyl-4-nitrobenzamide (3fc, Table 2):

Trifluoromethanesulfonic anhydride (45.1 μL, 0.268 mmol, 1.10 equiv) was added via syringe to a solution of _N_-isopropyl-4-nitrobenzamide[10] (**1f**, 50.7 mg, 0.244 mmol, 1 equiv) and 2-fluoropyridine (25.1 μL, 0.292 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, pyridine _N_-oxide (46.3 mg, 0.487 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 20% ethyl acetate in hexanes) to afford the amide **3fc** (51.6 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.47–8.43 (m, 1H), 8.01 (d, 2H, J = 8.4 Hz), 7.56–7.48 (m, 1H), 7.43 (d, 2H, J = 8.4 Hz), 7.16–7.10 (m, 1H), 6.86 (d, 1H, J = 8.1 Hz), 5.12–4.98 (m, 1H), 1.34 (d, 6H, J = 6.9 Hz).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	168.3, 153.7, 149.5, 148.0, 143.5, 138.0, 129.3, 124.8, 123.2, 122.9, 49.3, 21.1.
FTIR (neat) cm^{-1}:	3075 (w), 2976 (m), 1651 (s), 1522 (s), 1346 (s).
HRMS (ESI):	calc'd for $C_{15}H_{16}N_3O_3$ $[M+H]^+$: 286.1186, found: 286.1182.
TLC (30% EtOAc in hexanes), R_f:	0.21 (UV).

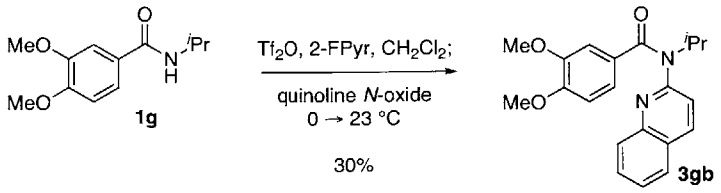


N-(Isoquinolin-1-yl)-N-isopropyl-3,4-dimethoxybenzamide (3ga, Table 2):

Trifluoromethanesulfonic anhydride (41.9 μL, 0.249 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-3,4-dimethoxybenzamide[11] (**1g**, 50.5 mg, 0.226 mmol, 1 equiv) and 2-fluoropyridine (23.3 μL, 0.271 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at 0 °C. After 7 min, isoquinoline *N*-oxide (65.7 mg, 0.452 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford the amide **3ga** (75.3 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.45 (d, 1H, J = 5.5 Hz), 7.93 (d, 1H, J = 8.5 Hz), 7.72 (d, 1H, J = 8.0 Hz), 7.59–7.53 (m, 2H), 7.51–7.46 (m, 1H), 6.91 (d, 1H, J = 8.5 Hz), 6.79 (s, 1H), 6.43 (d, 1H, J = 8.5 Hz), 5.19–5.07 (m, 1H), 3.65 (s, 3H), 3.56 (s, 3H), 1.63 (br s, 3H), 1.13 (br s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	170.5, 154.6, 150.0, 147.7, 141.3, 138.1, 130.6, 130.0, 128.1, 127.5, 127.1, 125.3, 122.1, 121.1, 111.6, 109.9, 55.8, 55.8, 50.8, 22.5, 19.8.
FTIR (neat) cm^{-1}:	3057 (w), 2971 (m), 2934 (m), 1640 (s), 1516 (s), 1264 (s).
HRMS (ESI):	calc'd for $C_{21}H_{23}N_2O_3$ $[M+H]^+$: 351.1703, found: 351.1703.
TLC (70% EtOAc in hexanes), R_f:	0.46 (UV).

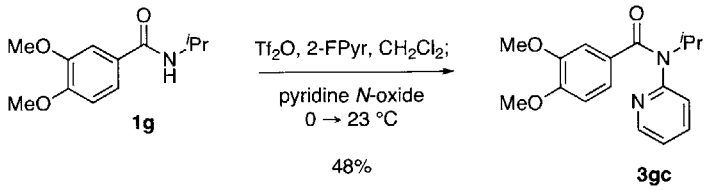
[11] Aljundi, F.; Hannig, E.; Boehm, R. *Pharmazie* **1973**, *28*, 362.



N-(Quinolin-2-yl)-N-isopropyl-3,4-dimethoxybenzamide (3gb, Table 2):

Trifluoromethanesulfonic anhydride (40.6 μL, 0.241 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-3,4-dimethoxybenzamide[11] (**1g**, 49.0 mg, 0.219 mmol, 1 equiv) and 2-fluoropyridine (22.6 μL, 0.263 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at 0 °C. After 7 min, quinoline *N*-oxide (63.7 mg, 0.439 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 50% ethyl acetate in hexanes) to afford the amide **3gb** (23.1 mg, 30%).

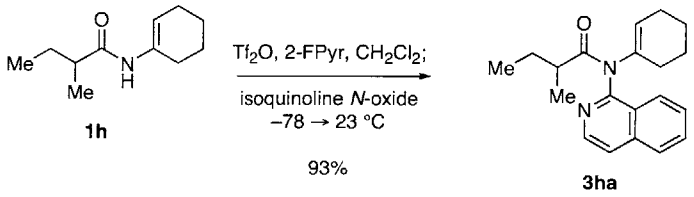
^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ:	8.03 (d, 1H, J = 9.0 Hz), 7.85 (d, 1H, J = 8.7 Hz), 7.76–7.68 (m, 2H), 7.52 (dt, 1H, J = 6.9, 1.2 Hz), 6.98–6.89 (m, 2H), 6.80 (d, 1H, J = 8.7 Hz), 6.54 (d, 1H, J = 8.4 Hz), 5.25–5.15 (m, 1H), 3.75 (s, 3H), 3.56 (s, 3H), 1.43 (d, 6H, J = 6.9 Hz).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	170.0, 155.2, 150.4, 148.2, 147.2, 137.2, 130.1, 129.6, 129.2, 127.5, 126.8, 126.3, 123.2, 122.8, 112.2, 110.1, 55.9, 55.8, 50.2, 21.3.
FTIR (neat) cm^{-1}:	3063 (w), 2969 (m), 2934 (m), 1647 (s), 1594 (s), 1264 (s).
HRMS (ESI):	calc'd for $C_{21}H_{23}N_2O_3$ $[M+H]^+$: 351.1703, found: 351.1702.
TLC (70% EtOAc in hexanes), R_f:	0.52 (UV).



N-(Pyridin-2-yl)-N-isopropyl-3,4-dimethoxybenzamide (3gc, Table 2):

Trifluoromethanesulfonic anhydride (40.9 μL, 0.243 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-3,4-dimethoxybenzamide[11] (**1g**, 49.3 mg, 0.221 mmol, 1 equiv) and 2-fluoropyridine (22.8 μL, 0.265 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at 0 °C. After 7 min, pyridine *N*-oxide (42.0 mg, 0.442 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (30 → 40% ethyl acetate in hexanes) to afford the amide **3gc** (31.8 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.54–8.47 (m, 1H), 7.51–7.44 (m, 1H), 7.13–7.07 (m, 1H), 6.91–6.83 (m, 2H), 6.75 (d, 1H, J = 8.4 Hz), 6.61 (d, 1H, J = 8.7 Hz), 5.13–5.00 (m, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 1.34 (d, 6H, J = 7.2 Hz).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	170.0, 155.7, 150.3, 149.0, 148.2, 137.7, 129.6, 125.2, 122.5, 121.9, 112.1, 110.1, 56.0, 55.9, 49.5, 21.2.
FTIR (neat) cm^{-1}:	2970 (m), 2934 (m), 1643 (s), 1585 (s), 1270 (s).
HRMS (ESI):	calc'd for $C_{17}H_{21}N_2O_3$ $[M+H]^+$: 301.1547, found: 301.1534.
TLC (70% EtOAc in hexanes), R_f:	0.27 (UV).

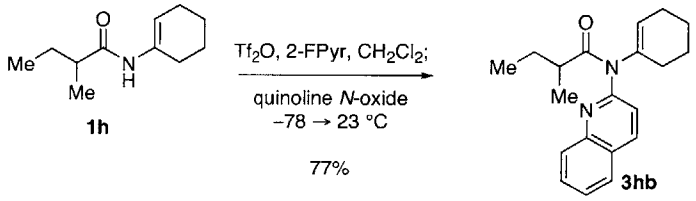


_N_-Cyclohexenyl-_N_-(isoquinolin-1-yl)-2-methylbutanamide (3ha, Table 2):

Trifluoromethanesulfonic anhydride (50.2 μL, 0.298 mmol, 1.10 equiv) was added via syringe to a solution of (±)-_N_-cyclohexenyl-2-methylbutanamide[12] (**1h**, 49.1 mg, 0.271 mmol, 1 equiv) and 2-fluoropyridine (27.9 μL, 0.325 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, isoquinoline _N_-oxide (78.7 mg, 0.542 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 50% ethyl acetate in hexanes) to afford the amide **3ha** (77.7 mg, 93%).

^{1}H NMR (500 MHz, $(D_3C)_2SO$, 100 °C) δ:	8.40 (d, 1H, J = 5.7 Hz), 8.06–7.96 (m, 2H), 7.85–7.76 (m, 2H), 7.74–7.67 (m, 1H), 5.67 (br s, 1H), 2.99 (br s, 1H), 2.51–2.20 (m, 3H), 2.12–1.83 (m, 2H), 1.75–1.25 (m, 5H), 1.06 (d, 3H, J = 6.4 Hz), 0.83 (t, 3H, J = 7.3 Hz).
^{13}C NMR (125 MHz, $(D_3C)_2SO$, 100 °C) δ:	175.7, 153.4, 140.8, 139.0, 137.3, 130.1, 128.7, 127.7, 126.6, 124.8, 124.2, 120.4, 27.9, 26.4, 24.8, 23.8, 22.0, 20.7, 17.0, 11.0.
FTIR (neat) cm^{-1}:	3055 (w), 2964 (s), 1673 (s), 1461 (m), 1384 (s).
HRMS (ESI):	calc'd for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found: 309.1949.
TLC (50% EtOAc in hexanes), R_f:	0.61 (UV).

[12] Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096.



N-Cyclohexenyl-2-methyl-N-(quinolin-2-yl)butanamide (3hb, Table 2):

Trifluoromethanesulfonic anhydride (51.3 μL, 0.305 mmol, 1.10 equiv) was added via syringe to a solution of *N*-cyclohexenyl-2-methylbutanamide[12] (**1h**, 50.2 mg, 0.277 mmol, 1 equiv) and 2-fluoropyridine (28.5 μL, 0.332 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, quinoline *N*-oxide (80.4 mg, 0.554 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (5 → 30% ethyl acetate in hexanes) to afford the amide **3hb** as an equal mixture of atropisomers (65.7 mg, 77%).

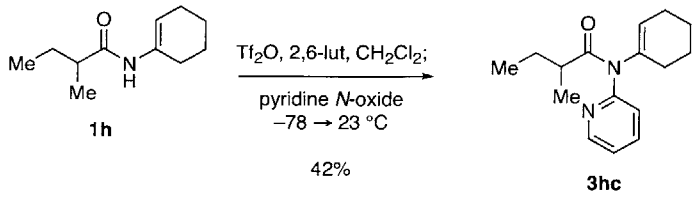
^{1}H NMR (300 MHz, $CDCl_3$, 20 °C, equal mixture of atropisomers) δ: 8.70 (d, 1H, J = 2.7 Hz), 8.12–8.03 (m, 2H), 7.98–7.93 (m, 1H), 7.85–7.81 (m, 1H), 7.80–7.74 (m, 2H), 7.70–7.59 (m, 2H), 7.54–7.45 (m, 3H), 5.78–5.73 (m, 1H), 4.85–4.80 (m, 1H), 2.97–2.73 (m, 2H), 2.37–2.26 (m, 2H), 2.23–2.14 (m, 2H), 2.09–2.00 (m, 2H), 1.97–1.40 (m, 14H), 1.33 (d, 3H, J = 6.9 Hz), 1.22 (d, 3H, J = 6.9 Hz), 1.03 (t, 3H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$, 20 °C, equal mixture of atropisomers) δ: 178.5, 164.8, 154.3, 147.4, 147.1, 146.9, 145.5, 142.7, 139.7, 137.6, 129.7, 129.2, 129.0, 128.7, 128.5, 127.7, 127.6, 127.4, 127.0, 126.5, 126.2, 126.0, 119.3, 108.4, 40.4, 35.8, 29.2, 29.1, 28.1, 27.2, 25.1, 24.3, 23.0, 22.8, 22.4, 21.8, 19.1, 18.3, 12.7, 12.4.

FTIR (neat) cm^{-1}: 3060 (w), 2963 (s), 1683 (s), 1597 (s), 1502 (s), 1225 (s).

HRMS (ESI): calc'd for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found: 309.1961.

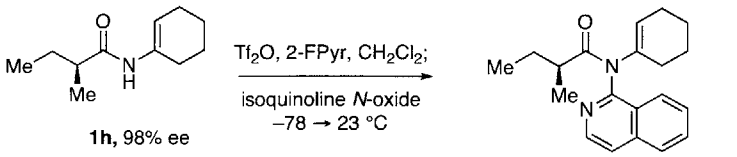
TLC (30% EtOAc in hexanes), R_f: 0.67 (UV).



<u>*N*-Cyclohexenyl-2-methyl-*N*-(pyridin-2-yl)butanamide (3hc, Table 2):</u>

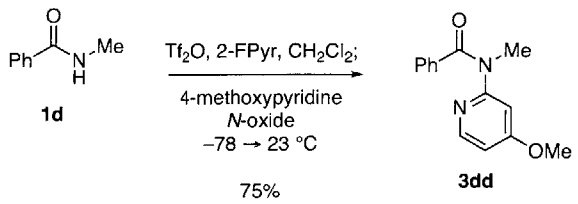
Trifluoromethanesulfonic anhydride (46.1 μL, 0.274 mmol, 1.10 equiv) was added via syringe to a solution of *N*-cyclohexenyl-2-methylbutanamide[12] (**1h**, 45.1 mg, 0.249 mmol, 1 equiv) and 2,6-lutidine (34.8 μL, 0.299 mmol, 1.20 equiv) in dichloromethane (1.75 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, pyridine *N*-oxide (47.3 mg, 0.498 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 30% ethyl acetate in hexanes) to afford the amide **3hc** (27.3 mg, 42%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.47–8.43 (m, 1H), 7.71–7.65 (m, 1H), 7.42 (d, 1H, J = 7.3 Hz), 7.14–7.09 (m, 1H), 5.77 (br s, 1H), 2.71 (br s, 1H), 2.19 (br s, 4H), 1.84–1.58 (m, 5H), 1.48–1.38 (m, 1H), 1.17 (d, 3H, J = 6.7 Hz), 0.92 (t, 3H, J = 7.4 Hz).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	177.8, 154.8, 148.9, 139.4, 137.7, 127.5, 121.3, 121.1, 40.0, 29.1, 28.1, 25.1, 23.0, 21.8, 18.4, 12.4.
FTIR (neat) cm^{-1}:	2933 (m), 2875 (w), 1667 (s), 1586 (s), 1432 (s).
HRMS (ESI):	calc'd for $C_{16}H_{23}N_2O$ $[M+H]^+$: 259.1805, found: 259.1812.
TLC (30% EtOAc in hexanes), R_f:	0.25 (UV).



(*S*)-(+)-*N*-Cyclohexenyl-*N*-(isoquinolin-1-yl)-2-methylbutanamide ((+)-3ha, Equation 1):

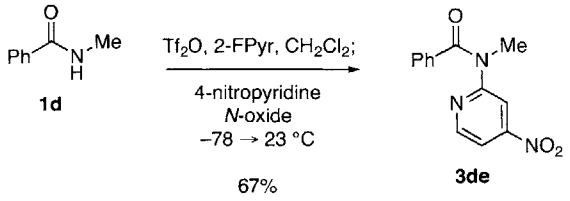
Trifluoromethanesulfonic anhydride (44.1 μL, 0.262 mmol, 1.10 equiv) was added via syringe to a solution of (*S*)-*N*-cyclohexenyl-2-methylbutanamide[12] (**1h**, 43.2 mg, 0.238 mmol, 1 equiv) and 2-fluoropyridine (24.6 μL, 0.286 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, isoquinoline *N*-oxide (69.2 mg, 0.477 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 50% ethyl acetate in hexanes) to afford the amide (+)-**3ha** (77.7 mg, 93%). The enantiomeric excess of the product amide was determined to be 98% by chiral HPLC analysis [Whelk-O (*R*,*R*); 0.5 mL/min; 3% ^{i}PrOH in hexanes; t_R (minor) = 69.3 min, t_R (major) = 74.5 min]. The enantiomeric excess of the starting material amide was determined to be 98% by chiral HPLC analysis [Whelk-O (*S*,*S*); 0.8 mL/min; 3% ^{i}PrOH in hexanes; t_R (major) = 37.7 min, t_R (minor) = 42.3 min]. (*S*)-(+)-**3ha**: $[a]^{20}_{D}$ = +98.3 (*c* 0.480, $CHCl_3$). See page 47 for complete characterization data for amide **3ha**.



_N_-(4-Methoxypyridin-2-yl)-_N_-methylbenzamide (3dd, Equation 2):

Trifluoromethanesulfonic anhydride (46.0 μL, 0.273 mmol, 1.10 equiv) was added via syringe to a solution of *N*-methylbenzamide (**1d**, 33.6 mg, 0.249 mmol, 1 equiv) and 2-fluoropyridine (25.6 μL, 0.298 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, 4-methoxypyridine *N*-oxide (62.2 mg, 0.497 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (10 → 20% ethyl acetate in hexanes) to afford the amide **3dd** (44.9 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.22 (d, 1H, J = 6.0 Hz), 7.38–7.28 (m, 3H), 7.26–7.20 (m, 2H), 6.57 (dd, 1H, J = 6.0, 2.5 Hz), 6.28 (d, 1H, J = 2.5 Hz), 3.56 (s, 3H), 3.55 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.2, 166.6, 158.4, 149.6, 136.3, 130.3, 128.5, 128.2, 108.4, 107.3, 55.4, 36.1.
FTIR (neat) cm^{-1}:	3061 (w), 2941 (w), 1652 (s), 1595 (s), 1362 (s).
HRMS (ESI):	calc'd for $C_{14}H_{15}N_2O_2$ $[M+H]^+$: 243.1128, found: 243.1133.
TLC (50% EtOAc in hexanes), R_f:	0.28 (UV).



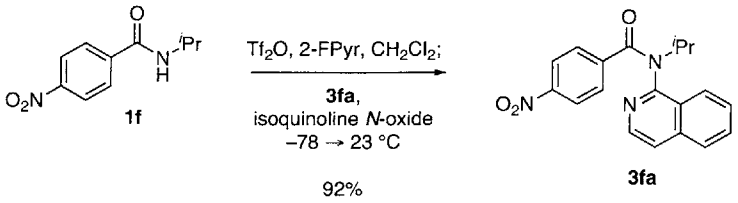
***N*-(4-Nitropyridin-2-yl)-*N*-methylbenzamide (3de, Equation 3):**

Trifluoromethanesulfonic anhydride (44.1 μL, 0.262 mmol, 1.10 equiv) was added via syringe to a solution of *N*-methylbenzamide (**1d**, 32.2 mg, 0.238 mmol, 1 equiv) and 2-fluoropyridine (24.6 μL, 0.286 mmol, 1.20 equiv) in dichloromethane (1.5 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, 4-nitropyridine *N*-oxide (66.7 mg, 0.476 mmol, 2.00 equiv) was added as a solid under an argon atmosphere. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the resulting mixture was concentrated under reduced pressure.[13] The residue was purified by flash column chromatography on silica gel (10 → 30% ethyl acetate in hexanes) to afford the amide **3de** (40.8 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C) δ:	8.66 (d, 1H, J = 5.0 Hz), 7.93 (d, 1H, J = 1.5 Hz), 7.75–7.71 (m, 1H), 7.46–7.40 (m, 3H), 7.38–7.33 (m, 2H), 3.62 (s, 3H).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C) δ:	171.9, 158.3, 154.5, 150.3, 135.6, 131.2, 128.8, 128.3, 113.2, 112.7, 36.6.
FTIR (neat) cm^{-1}:	3090 (w), 2923 (w), 1663 (s), 1534 (s), 1356 (s).
HRMS (ESI):	calc'd for $C_{13}H_{12}N_3O_3$ $[M+H]^+$: 258.0873, found: 258.0883.
TLC (30% EtOAc in hexanes), R_f:	0.38 (UV).

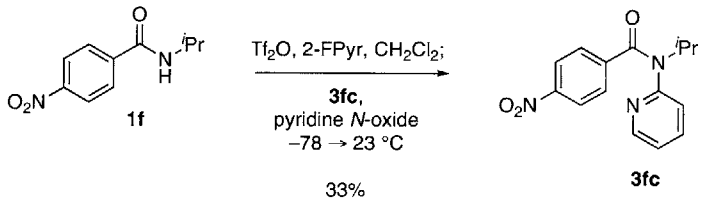
[13] In the case of amide **3de**, aqueous work-up resulted in a decreased isolated yield (60%).

Product Inhibition Studies:



***N*-(Isoquinolin-1-yl)-*N*-isopropyl-4-nitrobenzamide:**

Trifluoromethanesulfonic anhydride (22.6 μL, 0.134 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-4-nitrobenzamide[10] (**1f**, 25.4 mg, 0.122 mmol, 1 equiv) and 2-fluoropyridine (12.5 μL, 0.146 mmol, 1.20 equiv) in dichloromethane (0.75 mL) at –78 °C. After 2 min, the reaction mixture was warmed to 0 °C. After 5 minutes, a solution of amide **3fa** (38.2 mg, 0.114 mmol, 1.00 equiv) in dichloromethane (0.75 mL) was added via cannula followed by addition of isoquinoline *N*-oxide (35.4 mg, 0.244 mmol, 2.00 equiv) as a solid under an argon atmosphere. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 20% ethyl acetate in hexanes) to afford the amide **3fa** (75.7 mg). This corresponded to 37.5 mg (92%) of newly formed amide **3fa**. See page 42 for complete characterization data for amide **3fa**.

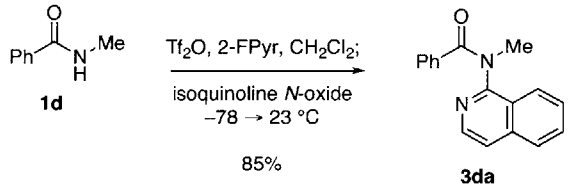


***N*-(Pyridin-2-yl)-*N*-isopropyl-4-nitrobenzamide:**

Trifluoromethanesulfonic anhydride (33.5 μL, 0.199 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-4-nitrobenzamide[10] (**1f**, 37.7 mg, 0.181 mmol, 1 equiv) and 2-fluoropyridine (18.6 μL, 0.217 mmol, 1.20 equiv) in dichloromethane (0.75 mL) at –78 °C. After 2 min, the reaction mixture was warmed to 0 °C. After 5 minutes, a solution of amide **3fc** (51.6 mg, 0.181 mmol, 1.00 equiv) in dichloromethane (1.0 mL) was added via cannula followed by addition of pyridine *N*-oxide (34.4 mg, 0.362 mmol, 2.00 equiv) as a solid under an argon atmosphere. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (15 → 20% ethyl acetate in hexanes) to afford the amide **3fc** (68.8 mg). This corresponded to 17.2 mg (33%) of newly formed amide **3fc**. See page 43 for complete characterization data for amide **3fc**.

React-IR Monitoring of Reactions:

All reactions were performed in a reaction vessel under an atmosphere of argon with the React-IR probe completely submerged in the reaction mixture.



In situ IR Analysis of the Conversion of Amide 1d to Amide 3da:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (70.0 μL, 0.416 mmol, 1.1 equiv) via syringe to a solution of *N*-methylbenzamide (**1d**, 51.1 mg, 0.378 mmol, 1 equiv) and 2-fluoropyridine (39.0 μL, 0.454 mmol, 1.2 equiv) in dichloromethane (4.5 mL) at 0 °C revealed within 1 min complete consumption of the starting material amide (cm^{-1}) and appearance of a persistent absorption at 2370 cm^{-1}, corresponding to an activated compound. After 5 min, isoquinoline *N*-oxide (109.8 mg, 0.756 mmol, 2.00 equiv) was added as a solid, resulting in immediate consumption of the activated compound and appearance of a persistent absorption at 1691 cm^{-1}, corresponding to a protonated amide **3da**. After 3 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 → 50% ethyl acetate in hexanes) to afford the amide **3da** (84.3 mg, 85%).

React-IR Control Experiments:

Assignment of the 2-fluoropyridine and the 2-fluoropyridinium trifluoromethanesulfonate characteristic stretches:

In situ IR monitoring of the addition of trifluoromethanesulfonic acid (26.8 μL, 0.303 mmol, 1.00 equiv) to a solution of 2-fluoropyridine (26.0 μL, 0.303 mmol, 1 equiv, 1598 cm^{-1}) in dichloromethane (3.5 mL) at 0 °C resulted in formation of the expected 2-fluoropyridinium trifluoromethanesulfonate salt (1632 cm^{-1}).

Assignment of the isoquinoline N-oxide and N-hydroxyisoquinolium trifluoromethanesulfonate characteristic stretches:

In situ IR monitoring of the addition of trifluoromethanesulfonic acid (36.2 μL, 0.409 mmol, 1.00 equiv) to a solution of isoquinoline *N*-oxide (59.3 mg, 0.409 mmol, 1 equiv, 1327 cm^{-1}) in dichloromethane (3.5 mL) at 0 °C resulted in formation of the expected *N*-hydroxyisoquinolium trifluoromethanesulfonate salt (1309 cm^{-1}).

*Assignment of Protonated, Trifluoromethanesulfonate Salt Derivatives of N-(isoquinolin-1-yl)-N-methylbenzamide **3da**:*

In situ IR monitoring of the addition of trifluoromethanesulfonic acid (28.1 μL, 0.317 mmol, 1.00 equiv) to a solution of *N*-(isoquinolin-1-yl)-*N*-methylbenzamide (**3da**, 83.1 mg, 0.317 mmol, 1 equiv, 1648 cm^{-1}) in dichloromethane (3.5 mL) at 0 °C resulted in consumption of the amide **3da** and formation of the expected trifluoromethanesulfonate salt (1649 cm^{-1}). Further addition of trifluoromethanesulfonic acid (28.1 μL, 0.317 mmol, 1.00 equiv) resulted in disappearance of the absorption at 1649 cm^{-1} and appearance of a strong absorption at 1691 cm^{-1}, corresponding to the doubly protonated amide ditrifluoromethanesulfonate salt.

React-IR Monitoring of Activated Amides:

Activation of *N*-methylbenzamide and addition of 2-fluoropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (52.0 μL, 0.309 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-methylbenzamide (38.0 mg, 0.281 mmol, 1 equiv, 1668 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material and appearance of a strong absorption consistent with a nitrilium trifluoromethanesulfonate salt (2370 cm^{-1}). Addition of 2-fluoropyridine (29.0 μL, 0.337 mmol, 1.20 equiv) resulted in a drastic increase in the intensity of this absorption. Further addition of 2-fluoropyridine (24.1 μL, 0.281 mmol, 1.00 equiv) had no significant effect on the intensity of this absorption. Subsequent addition of 2-fluoropyridine (67.6 μL, 0.787 mmol, 2.80 equiv) had no significant effect on the intensity of the absorption at 2370 cm^{-1}. Addition of triethylamine (47.0 μL, 0.337 mmol, 1.20 equiv) resulted in a significant decrease in intensity of this absorption.

Activation of *N*-methylbenzamide and addition of 2-chloropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (67.1 μL, 0.399 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-methylbenzamide (49.0 mg, 0.363 mmol, 1 equiv, 1668 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material and appearance of a strong absorption consistent with a nitrilium trifluoromethanesulfonate salt (2370 cm^{-1}). Addition of 2-chloropyridine (41.2 μL, 0.435 mmol, 1.20 equiv) resulted in a drastic increase in the intensity of this absorption. Further addition of 2-chloropyridine (34.3 μL, 0.363 mmol, 1.00 equiv) had no significant effect on the intensity of this absorption. Subsequent addition of 2-chloropyridine (96.0 μL, 1.01 mmol, 2.80 equiv) had no significant effect on the intensity of the absorption at 2370 cm^{-1}. Addition of triethylamine (60.6 μL, 0.435 mmol, 1.20 equiv) resulted in a significant decrease in intensity of this absorption.

Activation of *N*-phenylacetamide and addition of 2-fluoropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (55.6 μL, 0.330 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-phenylacetamide (40.6 mg, 0.300 mmol, 1 equiv, 1695 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material but did not result in appearance of an absorption consistent with a nitrilium trifluoromethanesulfonate salt. Addition of 2-fluoropyridine (30.9 μL, 0.360 mmol, 1.20 equiv) resulted in appearance of a strong absorption consistent with a nitrilium trifluoromethanesulfonate salt (2364 cm^{-1}). Further addition of 2-fluoropyridine (25.8 μL, 0.300 mmol, 1.00 equiv) had no significant effect on the intensity of this absorption. Subsequent addition of 2-fluoropyridine (72.3 μL, 0.841 mmol, 2.80 equiv) had no significant effect on the intensity of the absorption at 2364 cm^{-1}. Addition of triethylamine (50.2 μL, 0.360 mmol, 1.20 equiv) resulted in a significant decrease in intensity of this absorption.

Activation of *N*-isopropyl-4-nitrobenzamide[10] and addition of 2-fluoropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (66.7 μL, 0.396 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-isopropyl-4-nitrobenzamide[10] (75.0 mg, 0.360 mmol, 1 equiv, 1668 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material and appearance of a strong absorption consistent with a nitrilium trifluoromethanesulfonate salt (2354 cm^{-1}). Addition of 2-fluoropyridine (37.1 μL, 0.432 mmol, 1.20 equiv) resulted in a drastic increase in the intensity of this absorption. Further addition of 2-fluoropyridine (30.9 μL, 0.360 mmol, 1.00 equiv) had no significant effect on the intensity of this absorption. Subsequent addition of 2-fluoropyridine (86.6 μL, 1.01 mmol, 2.80 equiv) had no

significant effect on the intensity of the absorption at 2354 cm^{-1}. Addition of triethylamine (60.3 μL, 0.432 mmol, 1.20 equiv) resulted in a significant decrease in intensity of this absorption.

Activation of *N*-isopropyl-4-nitrobenzamide[10] and addition of 2-chloropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (66.7 μL, 0.396 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-isopropyl-4-nitrobenzamide[10] (75.0 mg, 0.360 mmol, 1 equiv, 1668 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material and appearance of a strong absorption consistent with a nitrilium trifluoromethanesulfonate salt (2354 cm^{-1}). Addition of 2-chloropyridine (40.9 μL, 0.432 mmol, 1.20 equiv) resulted in a drastic increase in the intensity of this absorption. Further addition of 2-chloropyridine (34.1 μL, 0.360 mmol, 1.00 equiv) resulted in a drastic decrease in the intensity of this absorption and the appearance of a strong absorption consistent with an amidinium trifluoromethanesulfonate salt (1609 cm^{-1}). Subsequent addition of 2-chloropyridine (95.5 μL, 1.01 mmol, 2.80 equiv) resulted in a further decrease in the intensity of the absorption at 2354 cm^{-1} and an increase in the intensity of the absorption at 1609 cm^{-1}. Addition of triethylamine (60.3 μL, 0.432 mmol, 1.20 equiv) resulted in a further decrease in intensity of the absorption at 2354 cm^{-1} and a drastic decrease in the absorption at 1609 cm^{-1}.

Activation of 3,4-dimethoxy-*N*-phenylbenzamide[5] and addition of 2-fluoropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (36.0 μL, 0.214 mmol, 1.10 equiv) to a vigorously stirred solution of 3,4-dimethoxy-*N*-phenylbenzamide[5] (50.1 mg, 0.195 mmol, 1 equiv, 1691 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material and appearance of a very weak absorption consistent with a nitrilium trifluoromethanesulfonate salt (2312 cm^{-1}). Addition of 2-fluoropyridine (20.1 μL, 0.234 mmol, 1.20 equiv) resulted in a drastic increase in the intensity of this absorption. Further addition of 2-fluoropyridine (16.8 μL, 0.195 mmol, 1.00 equiv) had no significant effect on the intensity of this absorption. Subsequent addition of 2-fluoropyridine (46.8 μL, 0.545 mmol, 2.80 equiv) resulted in a slight decrease in the intensity of the absorption at 2312 cm^{-1}. Addition of triethylamine (32.6 μL, 0.234 mmol, 1.20 equiv) resulted in a drastic decrease in intensity of this absorption.

Activation of 3,4-dimethoxy-*N*-phenylbenzamide[5] and addition of 2-chloropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (44.6 μL, 0.265 mmol, 1.10 equiv) to a vigorously stirred solution of 3,4-dimethoxy-*N*-phenylbenzamide[5] (62.0 mg, 0.241 mmol, 1 equiv, 1691 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material and appearance of a very weak absorption consistent with a nitrilium trifluoromethanesulfonate salt (2312 cm^{-1}). Addition of 2-chloropyridine (27.3 μL, 0.289 mmol, 1.20 equiv) resulted in a drastic increase in the intensity of this absorption and the appearance of a strong absorption consistent with an amidinium trifluoromethanesulfonate salt (1594 cm^{-1}). Further addition of 2-chloropyridine (22.8 μL, 0.241 mmol, 1.00 equiv) resulted in a significant decrease in the intensity of the absorption at 2312 cm^{-1} and an increase in the intensity of the absorption at 1594 cm^{-1}. Subsequent addition of 2-chloropyridine (63.9 μL, 0.675 mmol, 2.80 equiv) resulted in disappearance of the absorption at 2312 cm^{-1} and an increase in the intensity of the absorption at 1594 cm^{-1}. Addition of triethylamine (40.3 μL, 0.289 mmol, 1.20 equiv) resulted in disappearance of the absorption at 1594 cm^{-1}.

Activation of *N*-phenylbenzamide and addition of 2-fluoropyridine:

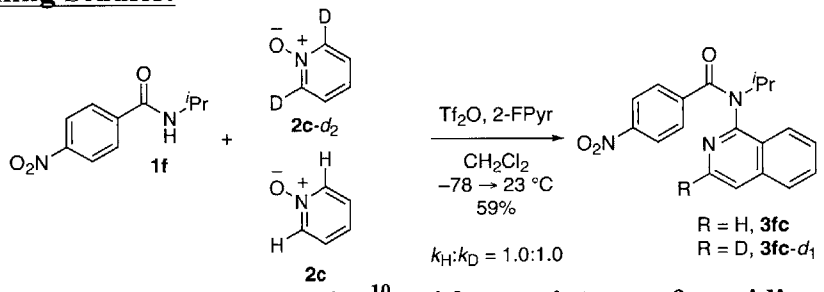
In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (44.1 μL, 0.262 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-phenylbenzamide (47.0 mg, 0.238 mmol, 1

equiv, 1679 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material but did not result in appearance of an absorption consistent with a nitrilium trifluoromethanesulfonate salt. Addition of 2-fluoropyridine (24.6 μL, 0.286 mmol, 1.20 equiv) resulted in appearance of a strong absorption consistent with an amidinium trifluoromethanesulfonate salt (1621 cm^{-1}). Further addition of 2-fluoropyridine (20.4 μL, 0.238 mmol, 1.00 equiv) resulted in a slight increase in the intensity of this absorption. Subsequent addition of 2-fluoropyridine (57.3 μL, 0.667 mmol, 2.80 equiv) resulted in an additional slight increase in the intensity of the absorption at 1621 cm^{-1}. Addition of triethylamine (39.9 μL, 0.286 mmol, 1.20 equiv) resulted in a drastic decrease in intensity of this absorption.

Activation of *N*-(4-methoxyphenyl)benzamide[14] and addition of 2-fluoropyridine:

In situ IR monitoring of the addition of trifluoromethanesulfonic anhydride (41.6 μL, 0.247 mmol, 1.10 equiv) to a vigorously stirred solution of *N*-(4-methoxyphenyl)benzamide[14] (51.0 mg, 0.224 mmol, 1 equiv, 1513 cm^{-1}) in dichloromethane (2.5 mL) at 0 °C resulted in immediate consumption of the starting material but did not result in appearance of an absorption consistent with a nitrilium trifluoromethanesulfonate salt. Addition of 2-fluoropyridine (23.1 μL, 0.269 mmol, 1.20 equiv) resulted in appearance of a strong absorption consistent with an amidinium trifluoromethanesulfonate salt (1621 cm^{-1}). Further addition of 2-fluoropyridine (19.2 μL, 0.224 mmol, 1.00 equiv) resulted in a slight increase in the intensity of this absorption. Subsequent addition of 2-fluoropyridine (54.0 μL, 0.628 mmol, 2.80 equiv) resulted in an additional slight increase in the intensity of the absorption at 1621 cm^{-1}. Addition of triethylamine (37.5 μL, 0.269 mmol, 1.20 equiv) resulted in a drastic decrease in intensity of this absorption.

Deuterium Labelling Studies:

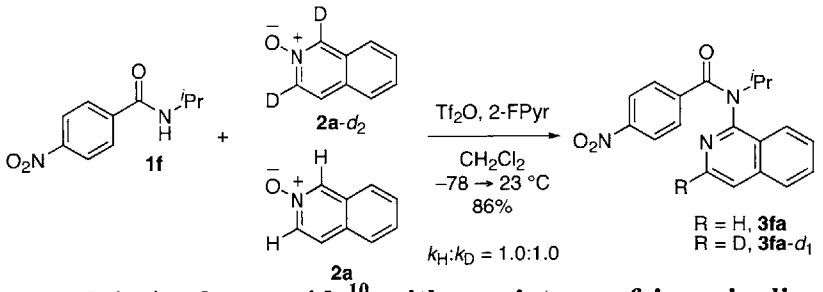


Reaction of *N*-isopropyl-4-nitrobenzamide[10] with a mixture of pyridine *N*-oxide and 2,6-dideuteropyridine *N*-oxide:

Trifluoromethanesulfonic anhydride (45.1 μL, 0.268 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-4-nitrobenzamide[10] (**1f**, 50.7 mg, 0.244 mmol, 1 equiv) and 2-fluoropyridine (25.1 μL, 0.292 mmol, 1.20 equiv) in dichloromethane (1.0 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, a solution of 2,6-dideuteropyridine *N*-oxide[15] (**2c**-d_2, 105 mg, 1.08 mmol, 4.42 equiv) and pyridine *N*-oxide (**2c**, 110 mg, 1.15 mmol, 4.73 equiv) in dichloromethane (1.0 mL) was added via cannula. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 2 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (15 →

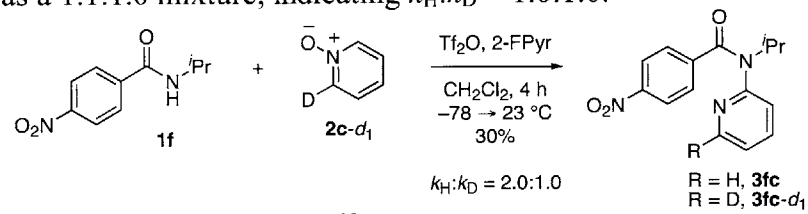
[14] Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254.
[15] Pavlik, J. W.; Laohhasurayotin, S. *J. Heterocyclic Chem.* **2007**, *44*, 1485.

20% ethyl acetate in hexanes) to afford the amide **3fc** (21.8 mg, 31%) and amide **3fc**-d_1 (19.4 mg, 28%) as a 1.1:1.0 mixture, indicating k_H:k_D = 1.0:1.0 based on the ratio of the respective starting materials.



Reaction of *N*-isopropyl-4-nitrobenzamide[10] with a mixture of isoquinoline *N*-oxide and 1,3-dideuteroisoquinoline *N*-oxide (equation 5):

Trifluoromethanesulfonic anhydride (24.9 μL, 0.148 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-4-nitrobenzamide[10] (**1f**, 28.1 mg, 0.135 mmol, 1 equiv) and 2-fluoropyridine (13.9 μL, 0.162 mmol, 1.20 equiv) in dichloromethane (0.8 mL) at 0 °C. After 7 min, a solution of 1,3-dideuteroisoquinoline *N*-oxide[16,17] (**2a**-d_2, 100 mg, 0.68 mmol, 5.0 equiv) and isoquinoline *N*-oxide (**2a**, 98 mg, 0.68 mmol, 5.0 equiv) in dichloromethane (0.8 mL) was added via cannula. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 2 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 20% ethyl acetate in hexanes) to afford the amide **3fa** (20.7 mg, 46%) and amide **3fa**-d_1 (18.3 mg, 40%) as a 1.1:1.0 mixture, indicating k_H:k_D = 1.0:1.0.



Reaction of *N*-isopropyl-4-nitrobenzamide[10] with 2-deuteropyridine *N*-oxide (Equation 6):

Trifluoromethanesulfonic anhydride (24.7 μL, 0.147 mmol, 1.10 equiv) was added via syringe to a solution of *N*-isopropyl-4-nitrobenzamide[10] (**1f**, 27.8 mg, 0.134 mmol, 1 equiv) and 2-fluoropyridine (13.7 μL, 0.160 mmol, 1.20 equiv) in dichloromethane (1.0 mL) at 0 °C. After 7 min, a solution of 2-deuteropyridine *N*-oxide (**2c**-d_1, 116 mg, 1.20 mmol, 9.00 equiv) in dichloromethane (0.7 mL) was added via cannula. After 5 min, the resulting mixture was allowed to warm to 23 °C. After 4 h, triethylamine (100 μL) was added to quench the trifluoromethanesulfonate salts, and the mixture was diluted by the addition of dichloromethane (10 mL). The reaction mixture was washed with brine (10 mL), and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 50% ethyl acetate in hexanes) to afford the amide **3fc** (3.81 mg, 10%) and amide **3fc**-d_1 (7.65 mg, 20%) as a 1.0:2.0 mixture, indicating k_H:k_D = 2.0:1.0.

[16] Pavlik, J. W.; Laohhasurayotin, S. *J. Heterocyclic Chem.* **2007**, *44*, 1485.
[17] The 1,3-dideuteroisoquinoline *N*-oxide employed contained 100% deuterium incorporation at the 1-position of the isoquinoline ring, and 91% deuterium incorporation at the 3-position by ^{1}H NMR. This incomplete isotopic enrichment was taken into account when calculating k_H:k_D.

Chapter II

Synthesis of Spirocyclic Indolines by Interruption of the Bischler–Napieralski Reaction

Introduction and Background

Spirocyclic pyrrolidinoindolines are a ubiquitous substructure in nature, representing the core of the *aspidosperma*, *kopsia,* and *strychnos* alkaloid families, and are prevalent also in pharmaceutically active compounds and other fine chemicals (Figure 1).[1] (–)-Vindoline[2] is a member of the *aspidosperma* alkaloid family with a complex pentacyclic core, while (–)-kopsinine[3] represents the *kopsia* alkaloids, a related family with a distinct cage substructure. (–)-Strychnine[4] is a potently poisonous glycine antagonist of the *strychnos* alkaloid family that blocks postsynaptic inhibition in the spinal cord.[5] The importance of the spiropyrrolidinoindoline structural motif has motivated the development of a number of elegant synthetic strategies in complex alkaloid synthesis.[6] Synthetic spiropyrrolidinoindolines display a range of useful properties and include insecticidal compounds[1d] and sky kinase inhibitors.[1h]

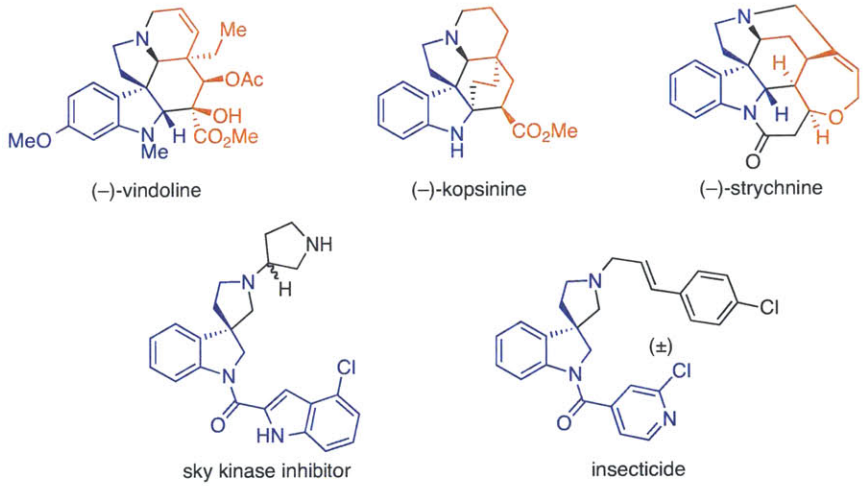
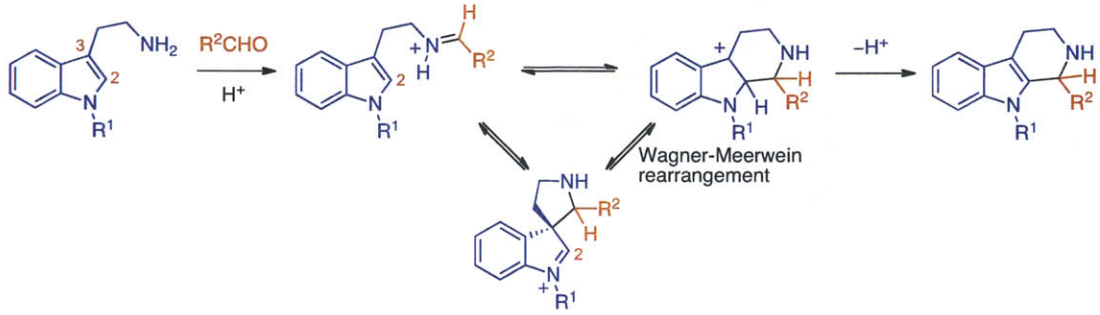


Figure 1. Representative spiropyrrolidinoindoline compounds.

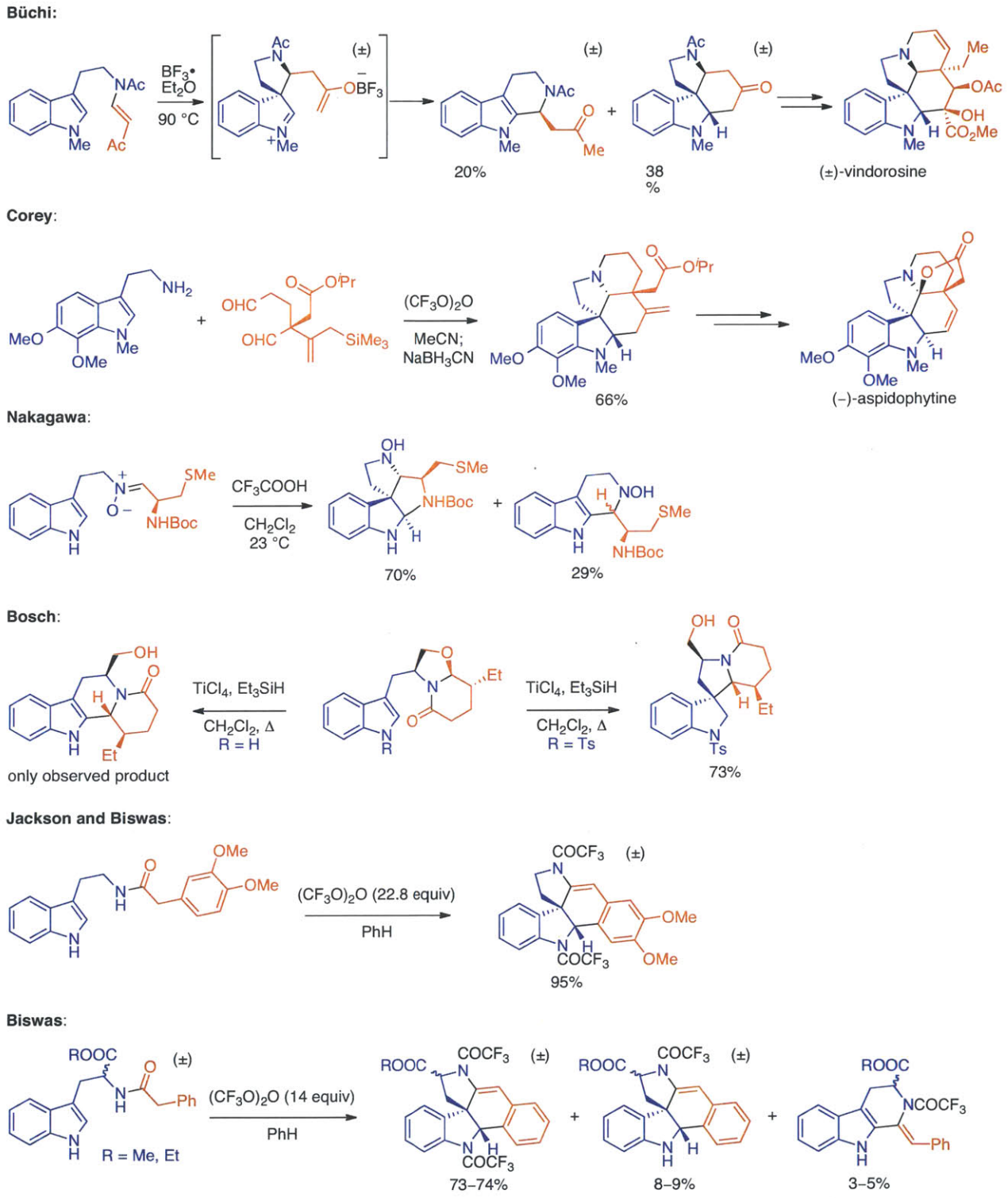
A direct route to the valuable spiropyrrolidinoindoline substructure would involve intramolecular electrophilic trapping of an appropriate tryptamine derivative at C3. Such an approach finds plausibility in the Pictet–Spengler reaction,[7] a common reaction in the synthesis and biosynthesis of tetrahydro-β-carbolines from tryptamines. Numerous studies into the mechanism of this reaction,[8] most notably Bailey's elegant isotope labelling study,[8c] have shown that the reaction proceeds by initial intramolecular electrophilic trapping of the 2*H*-indole nucleus at C3 by a pendant iminium ion to afford a spiroindoleninium intermediate (Scheme 1). Wagner–Meerwein rearrangement affords the C2-protonated tetrahydro-β-carboline, which undergoes deprotonation to afford the tetrahydro-β-carboline product. It is known, however, that the initial spirocyclization event is reversible, and it cannot be ruled out that the protonated

tetrahydro-β-carboline is formed by eventual direct attack of C2 onto the iminium ion.[9] Furthermore, kinetic isotope studies[8e] in a biological setting have shown the final deprotonation event to be rate-limiting, suggesting that all three of the aforementioned intermediates may be in or near equilibrium during the reaction.



Scheme 1. Mechanism of the Pictet-Spengler reaction.

The presence of spiroindoleninium ions during the course of the Pictet–Spengler reaction suggests the feasibility of intercepting such intermediates en route to spiropyrrolidinoindoline products; however, the inherent tendency of such 2*H*-indoleninium systems to undergo rapid Wagner–Meerwein rearrangement (Scheme 1) makes such an approach difficult. Previously reported methods[6d,6l,10] for such transformations overcome this problem by using strongly nucleophilic intramolecular traps or by employing electron-withdrawing groups on the indole or aliphatic nitrogen, or both, to minimize such rearrangements, which can still occur (Scheme 2). An early and illustrative example was reported in 1971 by Büchi[6d] in his seminal total synthesis of (±)-vindorosine: electrophilic activation of an *N*-acetyl vinylgous amide in boron trifluoride diethyl etherate resulted in electrophilic trapping of the indole nucleus at C3, followed by cyclizative trapping at C2 with a strongly nucleophilic boron trifluoride enolate to afford the desired spirocyclic product in 38% yield en route to the natural product. However, the isolation of the undesired tetrahydro-β-carboline side product in 20% yield demonstrates the difficulty of kinetically outcompeting the Wagner–Meerwein rearrangement. In Corey's enantioselective synthesis of (–)-aspidophytine,[6l] a similar strategy employing a chiral dialdehyde with a highly nucleophilic pendant allylic trimethylsilane allows for a remarkable condensative cascade reaction with a tryptamine derivative, affording the pentacyclic core of the natural product in 66% yield. Their use of an elaborate alkene reflects the need to outcompete rearrangement, as a simple vinyl group would have been an ideal synthon: manipulation of the exocyclic alkene in their pentacyclic product to the endocyclic alkene in the natural product requires four extra steps.



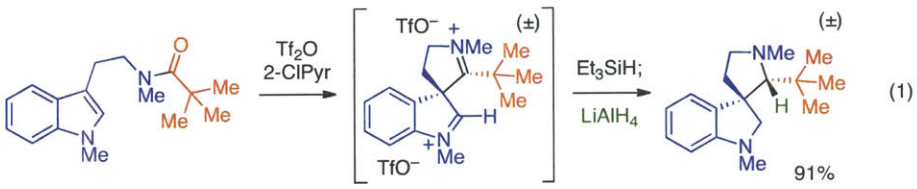
Scheme 2. Representative examples of trapping spiropyrrolodinoindoleninium ions.

Heteroatom nucleophiles have also been used as nucleophilic traps, as seen in an example reported by Nakagawa in which the nitrogen atom of a secondary carbamate serves as a trapping moiety to afford a spirocyclic product in 70% yield.[10h] Nonetheless, under their conditions, the

Wagner–Meerwein rearrangement competes with trapping of the spirocyclic indoleninium, as two diasteromeric tetrahydro-β-carboline products were isolated in a combined 29% yield. The use of an intermolecular nucleophilic trap present during iminium formation was employed by Bosch,[10j] who found that that the presence of an electron-withdrawing *para*-toluenesulfonyl group on the indole nitrogen was essential to reduce the rate of Wagner–Meerwein rearrangement relative to nucleophilic trapping by triethylsilane en route to their spirocyclic product. The absence of such an electon-withdrawing group gave the tetrahydro-β-carboline product under identical conditions.

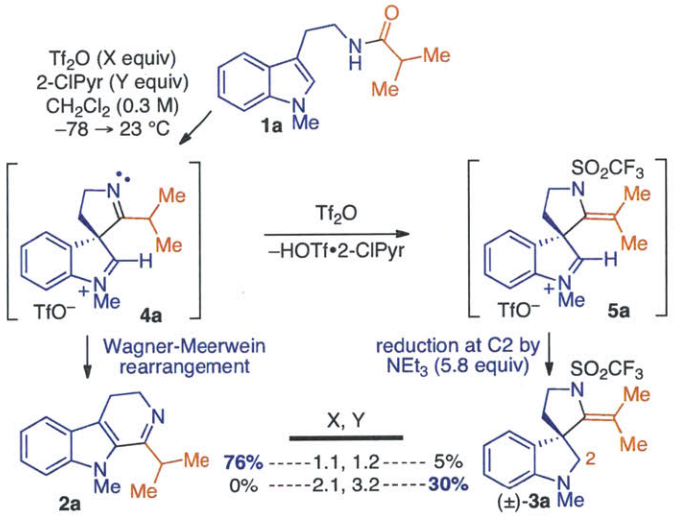
While the vast majority of examples of interception of spiropyrrolidinoindoleninium ions have been in the context of the Pictet–Spengler reaction, there have been reports[10a–d] on the use of carbon nucelophiles in such a strategy in the context of the related Bischler–Napieralski reaction,[11] which differs by employing electrophilically activated amide electrophiles in place of iminium ions. Jackson[10a,c] and Biswas reported an example of a tryptamine derived secondary amide bearing a highly nucleophilic dimethoxyphenyl group undergoing a spirocyclization/intramolecular trapping sequence when treated with a large excess of trifluoroacetic anhydride, affording the spirocyclic product in 95% yield. Notably, an electron-withdrawing trifluroacetyl group was installed on both nitrogen atoms during the reaction; the use of trichlorooxyphosphine as activating agent resulted in a mixture of spiroindoline and dihydro-β-carboline products. Later, Biswas[10d] reported two examples of a less nucleophilic phenyl group as a trap in a similar reaction. While doubly trifluoroacetylated spirocyclic products were isolated in yields of 73–74%, together with singly trifluoroacetylated 1*H*-spirocycles in yields of 8–9%, singly trifluoroacetylated products resulting from competetive Wagner–Meerwein rearrangement were also isolated in yields of 3–5%, consistent with a need for trifluoroacetylation of the indole nitrogen atom to enable trapping at C2 to sufficiently outcompete rearrangement when less powerful nucleophiles are used as intramolecular traps.

Due to the importance of spiropyrrolidinoindoline compounds, our group is interested in new methods for their synthesis. In this chapter, we report a method for the efficient synthesis of spiropyrrolidinoindolines by interruption of the Bischler–Napieralski reaction of 2*H*-*N*-acyltryptamines via spiroindoleninium intermediates with high resilience to Wagner–Meerwein rearrangements (eq 1).



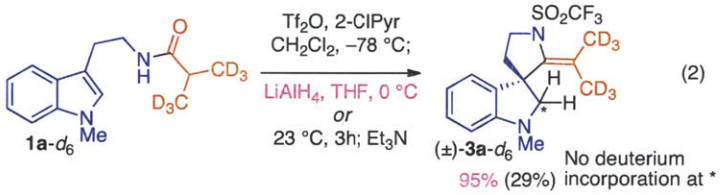
Results and Discussion

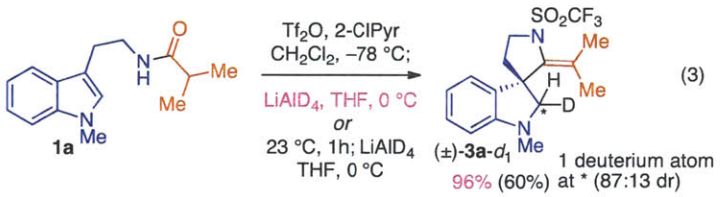
Earlier, our laboratory reported the use of the reagent combination trifluoromethanesulfonic anhydride (Tf_2O)–2-chloropyridine (2-ClPyr)[12] to effect the Bischler–Napieralski reaction of secondary amides.[13] Interestingly, exposure of amide **1a** to Tf_2O (1.1 equiv) in the presence of 2-ClPyr (1.2 equiv) followed by warming and addition of excess triethylamine[14] provided the expected Bischler–Napieralski product **2a** (76%) along with the unexpected spirocyclic side product (±)-**3a** in low yield (~5%, Scheme 3). The sulfonylation of the amide nitrogen was easily rationalized by sulfonylation of a spirocyclic indoleninium intermediate (±)-**4a** with the slight excess of Tf_2O used for amide activation to afford spiroindoleninium (±)-**5a**. Consistent with *N*-sulfonylation of intermediate (±)-**4a**, the use of 2.1 equivalents of Tf_2O and 3.2 equivalents of 2-ClPyr greatly increased the yield of (±)-**3a** to 30% together with a complex mixture of side products and none of the Bischler–Napieralski product **2a**. The reduction at C2 of the indoline nucleus prompted further investigation to better understand the reactivity of the intermediates. Given the propensity of spiropyrrolidinoindoleninium intermediates to undergo Wagner–Meerwein rearrangement unless a strongly nucleophilic trap present is prior to spirocyclization,[6d,l,10a–f,h–k] we hypothesized



Scheme 3. Mechanism of the Interrupted Bischler–Napieralski Reaction.

that the reduction at C2 may have been the result of a rapid hydride transfer reaction between two intermediates along the reaction pathway[15] (Scheme 3). This, however, was ruled out with a concise set of deuterium labeling studies. First, hexadeuterated amide **1a**-d_6 was subjected to the reaction conditions. Spirocycle (±)-**3a**-d_6 was isolated in 29% yield with complete deuterium retention on the alkenyl methyl groups and no deuterium enrichment at C2 (eq 2). Furthermore, when amide **1a** was exposed to the reaction conditions with lithium aluminum deuteride used in place of triethylamine as the quenching reagent, monodeuterated spirocycle (±)-**3a**-d_1 was isolated in 60% yield with incorporation of exactly one deuterium atom at C2 (eq 3, 6:1 dr at C2).[16] This showed unequivocally that reduction at C2 does not occur until an exogenous hydride source is introduced. We posited that triethylamine might be acting as a hydride source[17,18] and conjectured that the modest mass balance might be the result of spiroindoleninium (±)-**5a** undergoing competitive decompostion. Notably, when lithium aluminum hydride (eq 2) or lithium aluminum deuteride (eq 3, without warming to 23 °C) were introduced just 5 min after warming the respective reactions to 0 °C, products (±)-**3a**-d_6 and (±)-**3a**-d_1 were isolated in 95% and 96% yields, respectively.

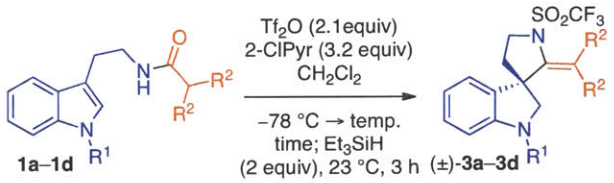




These results suggested that spirocyclic *N*-trifluoromethanesulfonyl indoleninium (±)-**5a** was electrophilic at C2 but recalcitrant to undergo a Wagner–Meerwein rearrangement due to deactivation of the trifluoromethanesulfonamide nitrogen lone pair. Electrophilic activation of **1a** followed by reduction with lithium aluminum hydride afforded spirocycle (±)-**3a** in excellent yield (Table 1, entry 1, 98% yield). When a less potent hydride source, triethylsilane, was introduced after activation and the resulting mixture warmed to ambient temperature, spirocycle (±)-**3a** was afforded in just 55% yield (Table 1, entry 2). On the other hand, 1-methyl-*N*-acetyltryptamine (**1b**), which bears no β-hydrogens, underwent highly efficient spirocyclization

and reduction to afford spirocycle (±)-**3b** using triethylsilane (Table 1, entry 3, 97% yield), lithium aluminum hydride (Table 1, entry 4, 92% yield), or triethylamine (Table 1, entry 5, 72% yield) as reducing agent. Spirocyclization followed by reduction with triethylsilane proceeded smoothly with 1-benzyl-*N*-acetyltryptamine (**1c**) and even with electron-deficient 1-*para*-toluenesulfonyl-*N*-acetyltryptamine (**1d**), providing the corresponding spirocycles (±)-**3c** (Table 1, entry 6, 100% yield) and (±)-**3d** (Table 1, entry 7, 94% yield), respectively. Trapping the spironindoleninium of amide **1b** at C2 with a carbon nucleophile, 1-methylindole, afforded the

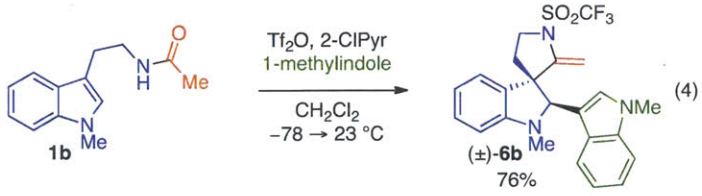
Table 1. Spirocyclization and Reduction.



entry	amide	R^1	R^2	temp.	time	yield[a]
1	**1a**	Me	Me	0 °C	5 min	98%[b]
2	**1a**	Me	Me	0 °C	30 min	55%
3	**1b**	Me	H	0 °C	30 min	97%
4	**1b**	Me	H	0 °C	5 min	92%[b]
5	**1b**	Me	H	23 °C	60 min	72%[c]
6	**1c**	Bn	H	0 °C	30 min	100%
7	**1d**	Ts	H	23 °C	30 min	94%

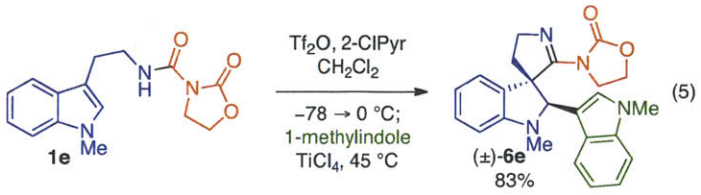
[a]Isolated yield. [b]$LiAlH_4$ (3.0 equiv) used as reducing agent at 0 °C. [c]Et_3N (5.0 equiv) used as reducing agent.

spirocyclic indole adduct (±)-**6b** in excellent overall yield (eq 4, 76%) as a single diastereomer.[16] The stereochemical outcome of the reaction is consistent with approach of the 1-methylindole nucleophile opposite the bulky and highly electronegative[19] trifluoromethanesulfonamide moiety.

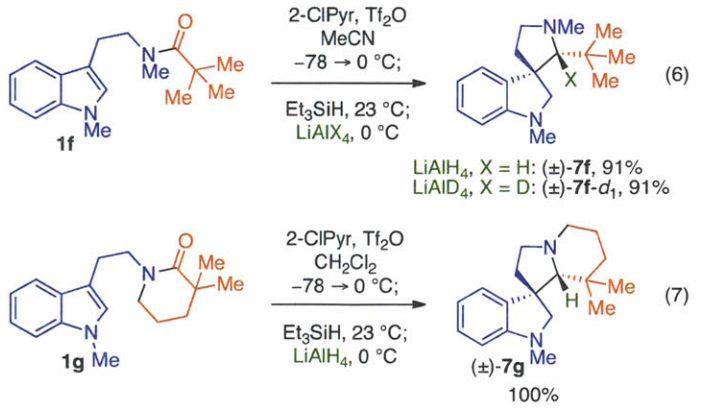


In order to avoid *N*-trifluoromethanesulfonylation, we hypothesized that a rapid, reversible nucleophilic trap at C2 with an oxygen nucleophile might give a persistent intermediate that could be further derivatized. Thus, 1-methyltryptamine oxazolidinone urea **1i** was activated with Tf_2O (1.1 equiv) and 2-ClPyr (2.2 equiv); introduction of 1-methyltryptamine

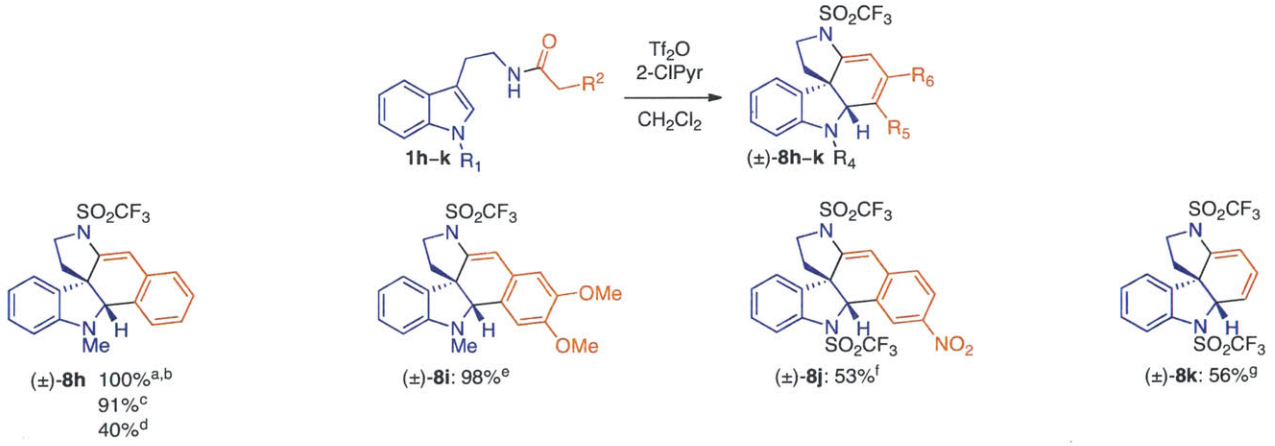
and titanium tetrachloride followed by heating to 45 °C afforded 1-methyltryptamine adduct (±)-**6e** in 83% yield as a single diastereomer[16] (eq 5) that was consistent with nucleophile approach from the same face of the spiroindoleninium as seen with amide **1b** (eq 4). The use of titanium tetrachloride was found to be essential to achieve C–C bond formation, consistent with competitive nucleophilic inibition at C2 by the oxazolidinone oxygen atom.



Motivated by a desire to extend the range of diastereoselective trappings of spiroindoleninium intermediates, we hypothesized that non-enolizable tertiary amides would, upon activation with Tf_2O–2-ClPyr, undergo rapid spirocyclization to afford a persistent diiminium dication resilient to Wagner–Meerwein rearrangement.[20] To our delight, treatment of tertiary pivalamide **1f** with 1.1 equivalents of Tf_2O–2-ClPyr at 0 °C in acetonitrile[21] and warming to 23 °C, followed by sequential trapping with triethylsilane and lithium aluminum hydride, afforded spirocyclic indoline (±)-**7f** as a single diastereomer[16] in 91% yield (eq 6), suggesting the in situ formation of a putative persistent diiminium dication intermediate. The diastereoselectivity is likely a result of the steric bulk of the arene, which blocks approach of lithium aluminum hydride. Use of lithium aluminum deuteride in place of lithium aluminum hydride afforded monodeuterated spirocyclic indoline (±)-**7f**-d_1, demonstrating the regioselective trapping at C2 with triethylsilane.[16] Similarly, activation of lactam **1g** followed by tandem reduction with triethylsilane–lithium aluminum hydride afforded tetracyclic indoline (±)-**7g** in quantitative yield as a single diastereomer[16] (eq 7).

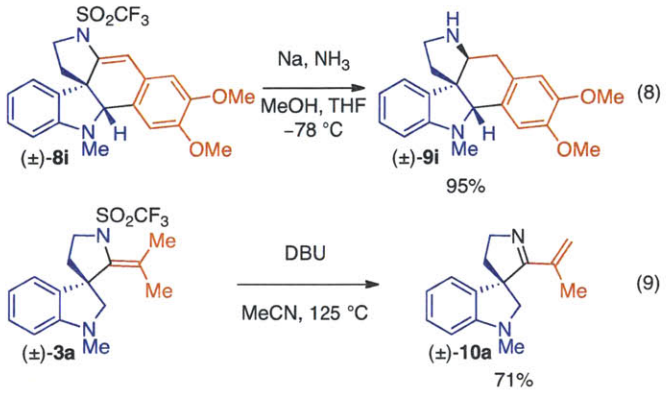


Encouraged by the efficiency of the spirocyclization/intermolecular nucleophilic trapping protocol, we envisaged a double-cyclization cascade making use of enolizable secondary amides with pendant nucleophiles. To explore and optimize this reaction, 1-methyltryptamine phenylacetamide (**1h**) was selected as substrate. Activation with a slight excess of Tf_2O (2.1 equiv) in the presence of 2-ClPyr (3.2 equiv) in CH_2Cl_2 followed by warming to 23 °C provided pentacycle (±)-**8h** in 40% yield (Scheme 4) accompanied with monocyclized side products and no recovered starting material or Bischler–Napieralski products. Heating the reaction to 45 °C in an oil bath afforded (±)-**8h** in excellent yield[22] (Scheme 2, 91% yield), while brief heating in a microwave[23] to 130 °C provided (±)-**8h** in quantitative yield. While similar cascades have been reported previously, the lack of any requirement of large excesses of activating agents[10a,c,d] or installation of an electron-withdwrawing group on N1[10a,c,d] and the ability to completely avoid Wagner–Meerwein rearrangement[10d] are specific advantages to our conditions, and highlight the importance of nitrogen lone pair deactivation by the highly electronegative trifluoromethanesulfonyl group. Not surprisingly, electron-rich 3,4-dimethoxyphenylacetamide **1i** provided pentacycle (±)-**8i** in 98% yield as a single regio- and diastereomer[16] under 45 °C conditions on half-gram scale (Scheme 4). Even highly electron-deficient 4-nitrophenylacetamide **1j** afforded pentacycle (±)-**8j** in moderate yield (53%) under microwave heating conditions (130 °C, 10 min), and vinylacetamide **1k** afforded tetracyclic spiroindoline (±)-**8k** in 56% yield under 45 °C conditions.



Scheme 4. Double-Cyclization Cascades. [a]Isolated yields of single diastereomers. [b]Tf_2O (2.1 equiv), 2-ClPyr (3.2 equiv), 130 °C (microwave), 5 min. [c]45 °C, 3 h. [d]23 °C, 3 h. [e]Tf_2O (2.1 equiv), 2-ClPyr (3.2 equiv), 45 °C, 3 h.

The trifluoromethanesulfonyl group present in the spirocyclic indolines derived from secondary amides is readily removed under reductive or eliminative conditions: desulfonylation of pentacycle (±)-**8i** with sodium and ammonia in the presence of methanol provided pentacyclic diamine (±)-**9i** in excellent yield (95%) as a single diastereomer[16] (eq 8), while dehydrosulfinylation of tricycle (±)-**3a** is effected with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile under microwave heating conditions (eq 9) to afford enimine (±)-**10a** in 71% yield.



Conclusion

We have presented a method for the efficient generation of distinctively persistent spiroindoleninium intermediates from secondary and tertiary *N*-acyl tryptamines. The exceptional resilience of these intermediates to Wagner–Meerwein rearrangement, determined through mechanistic studies, allows for efficient intra- and intermolecular trapping with nucleophiles, including weak nucleophiles such as deactivated arenes, which can be introduced even after[6d,l,10a–f,h–k] initial activation and spirocyclization. The use of oxazolidinone ureas and tertiary amides under our conditions allows for the direct and highly diastereoselective synthesis of spiropyrrolidinoindolines without competitive rearrangement[6d,10a,c–e,h,k] or the need for an electron-withdrawing group[6d,10a,c,d,g,j,k] on the aliphatic or indole nitrogen atoms.

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[14] The addition of triethylamine at the end of the reaction was carried out with the intention of neutralizing the trifluoromethanesulfonate salts prior to work-up.

[15] For a review on a classical redox disproportionation reaction, see Geissman, T. A. *Org. React.* **1944**, *2*, 94.

[16] Please see Experimental Section for details.

[17] When the quench was carried out by adding potassium carbonate or 1,4-diazabicyclo[2.2.2]octane, no trace of (±)-**3a** was detected.

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[21] Acetonitrile was used as solvent due to the poor solubility of the activated intermediates in dichloromethane in this case.

[22] 2-ClPyr was found to be the optimal base additive for this reaction; the use of 2-fluoropyridine or 2,6-lutidine gave yields of 90% and 66%, respectively, of (±)-**8h** under 45 °C conditions.

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Experimental Section

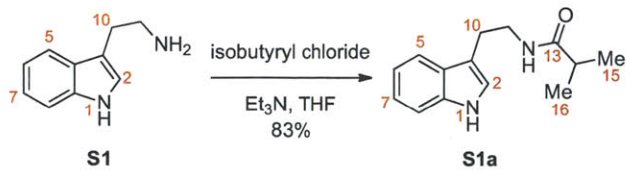
General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks, modified Schlenk (Kjeldahl shape) flasks or glass pressure vessels. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel gas-tight syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60 Å pore size, 32–63 μm, standard grade) or non-activated alumina (80–325 mesh, chromatographic grade).[1] Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel or neutral alumina impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an aqueous solution of ceric ammonium molybdate (CAM) or an aqueous solution of potassium permanganate ($KMnO_4$) followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C, then at ~1 Torr (vacuum pump) unless otherwise indicated.

Materials. Commercial reagents and solvents were used as received with the following exceptions: Dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer^{TM}) and were purified by the method of Grubbs et al. under positive argon pressure.[2] 2-Chloropyridine and *N*,*N*-diisopropylamine were distilled from calcium hydride and stored sealed under argon atmospheres. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid[3] (average of three titrations). Trifluoromethanesulfonic anhydride was purchased from Oakwood Products, Inc.; all other solvents and chemicals were purchased from Sigma–Aldrich.

Instrumentation. All reaction conducted at 130 °C were performed in a CEM Discover Lab Mate microwave reactor. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with Varian inverse probe INOVA-500 and Varian INOVA-500 spectrometers, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent ($CDCl_3$: δ 7.24 ($CHCl_3$), toluene-d_8: δ 2.09 ($C_6D_5CD_2H$)). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sp = septet, m = multiplet, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian INOVA-500 spectrometer, are reported in parts per million on the δ scale, and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.23, toluene-d_8: δ 20.4). Data are reported as follows: chemical shift (assignment). Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Mercury 300 spectrometer or a Varian INOVA-500 spectrometer, are reported in parts per million on the δ scale, and are referenced from the fluorine resonance of neat trichlorofluoromethane ($CFCl_3$: δ 0). Data are reported as follows: chemical shift (assignment). Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR, and are reported as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Optical rotations were measured on a Jasco-1010 polarimeter. We

[1] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
[2] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518.
[3] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879.

are grateful to Dr. Li Li for obtaining the mass spectrometric data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FTICR-MS using a direct analysis in real time (DART) ionization source.

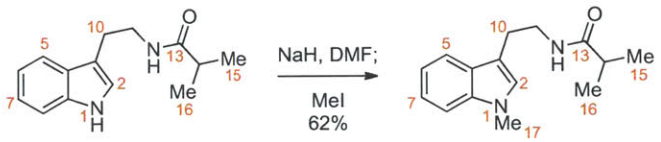


N-Isobutyryltryptamine (S1a):[4,5]

Isobutyryl chloride (1.96 mL, 18.7 mmol, 1.00 equiv) was added via syringe to a solution of tryptamine (**S1**, 3.00 g, 18.7 mmol, 1 equiv) and triethylamine (2.87 mL, 20.6 mmol, 1.10 equiv) in tetrahydrofuran (47.0 mL) at 23 °C. After 20 min, water was added, and the organic layer was diluted with ethyl acetate (250 mL). The layers were separated, and the organic layer was washed with aqueous hydrogen chloride solution (1N, 250 mL), saturated aqueous potassium carbonate solution (250 mL), and brine (250 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure to afford *N*-isobutyryltryptamine (**S1a**, 3.56 g, 82.6%) as a tan powder. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 8.32–8.18 (br-s, 1H, N_1**H**), 7.60 (dd, J = 1.0, 7.9, 1H, C_5**H**), 7.37 (d, J = 8.0, 1H, C_8**H**), 7.19 (app-dt, J = 1.1, 7.6, 1H, C_7**H**), 7.11 (app-dt, J = 1.1, 7.5, 1H, C_6**H**), 7.01 (d, J = 2.3, 1H, C_2**H**), 5.61–5.46 (br-s, 1H, N_{12}**H**), 3.58 (app-q, J = 6.7, 2H, C_{11}**H**$_2$), 2.96 (t, J = 6.7, 2H, C_{10}**H**$_2$), 2.24 (sp, J = 7.0, 1H, C_{14}**H**), 1.09 (d, J = 7.0, 6H, C_{15}**H**$_3$, C_{16}**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 177.4, 136.6, 127.5, 122.4, 122.1, 119.4, 118.7, 112.7, 111.6, 39.9, 35.7, 25.4, 19.7.
FTIR (neat) cm^{-1}:	3286 (br-s), 2969 (m), 1652 (s), 1529 (s), 1457 (m), 1229 (m), 743 (s).
HRMS (DART):	calc'd for $C_{14}H_{18}N_2NaO$ $[M+Na]^+$: 253.1311, found: 253.1314.
TLC (Al_2O_3, 30% EtOAc in hexanes), R_f:	0.08 (UV, CAM, $KMnO_4$).

[4] The C15,C16-hexadeuterated isotopomer **S1a**-d_6 was synthesized by dehydrative coupling of tryptamine (**S1**) with isobutyric acid-d_6 (ref. 5) in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrogen chloride (EDC•HCl) in dichloromethane.
[5] For a previous preparation of isobutyric acid-d_6, see Semmelhack, M. F.; Bargar, T. *J. Am. Chem. Soc.* **1980**, *102*, 7765.



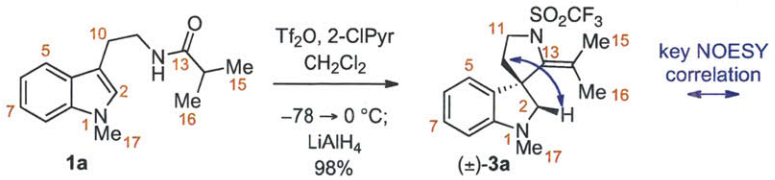
S1a **1a**

1-Methyl-*N*-isobutyryltryptamine (1a):[6]

Sodium hydride (60% dispersion in mineral oil, 564 mg, 14.1 mmol, 1.30 equiv) was added as a solid under an argon atmosphere to a solution of *N*-isobutyryltryptamine (**S1a**, 2.50 g, 10.9 mmol, 1 equiv) in *N*,*N*-dimethylformamide (27 mL) at 23 °C. After 55 min, iodomethane (901 µL, 14.4 mmol, 1.33 equiv) was added dropwise via syringe over 5 min. After 15 h, water (20 mL) was added to quench the excess base. The resulting mixture was diluted with diethyl ether (300 mL), and the organic layer was washed with brine (3 × 300 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 20% ethyl acetate in hexanes) to afford 1-methyl-*N*-isobutyryltryptamine (**1a**, 1.64 g, 61.8%) as a tan powder. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.59 (d, J = 7.9, 1H, C_5**H**), 7.29 (d, J = 8.2, 1H, C_8**H**), 7.23 (app-dt, J = 1.2, 7.7, 1H, C_7**H**), 7.10 (app-dt, J = 1.0, 7.5, 1H, C_6**H**), 6.86 (s, 1H, C_2**H**), 5.58–5.43 (br-s, 1H, N_{12}**H**), 3.74 (s, 3H, C_{17}**H**$_3$), 3.56 (app-q, J = 6.7, 2H, C_{11}**H**$_2$), 2.94 (t, J = 6.7, 2H, C_{10}**H**$_2$), 2.23 (sp, J = 6.9, 1H, C_{14}**H**), 1.09 (d, J = 6.9, 6H, C_{15}**H**$_3$, C_{16}**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 177.0, 137.2, 127.9, 126.9, 121.8, 119.0, 119.0, 111.7, 109.4, 39.9, 35.7, 32.7, 25.4, 19.7.
FTIR (neat) cm^{-1}:	3301 (br-s), 2967 (m), 1646 (m), 1548 (m), 1472 (m), 1236 (m), 740 (m).
HRMS (DART):	calc'd for $C_{15}H_{20}N_2NaO$ $[M+Na]^+$: 267.1468, found: 267.1465.
TLC (Al_2O_3, 30% EtOAc in hexanes):	R_f: 0.21 (UV, CAM, $KMnO_4$).

[6] The C15,C16-hexadeuterated isotopomer **1a**-d_6 was synthesized by an analogous procedure starting from **S1a**-d_6.

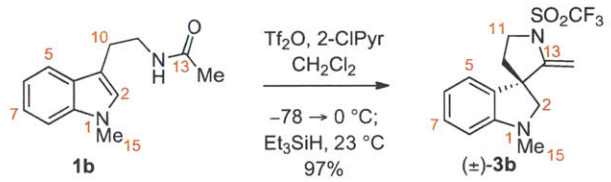


Spirocyclic indoline (±)-3a:

Trifluoromethanesulfonic anhydride (62.8 μL, 373 μmol, 2.10 equiv) was added via syringe to a solution of 1-methyl-*N*-isobutyryltryptamine (**1a**, 43.4 mg, 178 μmol, 1 equiv) and 2-chloropyridine (53.3 μL, 568 μmol, 3.20 equiv) in dichloromethane (1.8 mL) at −78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C.[7,8] After 5 min, tetrahydrofuran (1.0 mL) was added via syringe. After 30 sec, lithium aluminum hydride[9,10,11] (20.2 mg, 533 μmol, 3.00 equiv) was added as a solid under an argon atmophere. After 20 min, sodium sulfate decahydrate was added to quench the unreacted aluminum hydride salts. The resulting suspension was filtered, and the filter cake was extracted with ethyl acetate (20 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 10% ethyl acetate in hexanes) to afford spirocyclic indoline (±)-**3a** (62.7 mg, 97.9%) as a beige powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.11 (app-dt, J = 1.3, 7.7, 1H, C_7**H**), 6.95 (dd, J = 0.8, 7.4, 1H, C_5**H**), 6.68 (app-dt, J = 0.9, 7.4, 1H, C_6**H**), 6.51 (d, J = 7.9, 1H, C_8**H**), 3.75–3.60 (m, 2H, C_{11}**H**$_2$), 3.52 (d, J = 9.3, 1H, C_2**H**$_a$), 3.38 (d, J = 9.3, 1H, C_2**H**$_b$), 2.81 (s, 3H, C_{17}**H**$_3$), 2.38 (app-dt, J = 13.0, 6.5, 1H, C_{10}**H**$_a$), 2.13 (app-dt, J = 13.0, 6.7, 1H, C_{10}**H**$_b$), 1.86 (s, 3H, C_{15}**H**$_3$), 1.41 (s, 3H, C_{16}**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 151.8 (**C**$_9$), 135.6 (**C**$_4$), 134.7 (**C**$_{13}$), 130.1 (**C**$_{14}$), 128.4 (**C**$_7$), 122.4 (**C**$_5$), 120.0 (q, J = 323.4, SO_2**C**F_3), 118.6 (**C**$_6$), 107.6 (**C**$_8$), 68.8 (**C**$_2$), 53.0 (**C**$_3$), 50.5 (**C**$_{11}$), 43.9 (**C**$_{10}$), 35.7 (**C**$_{17}$), 23.5 (**C**$_{15}$), 21.2 (**C**$_{16}$).
^{19}F NMR (471 MHz, $CDCl_3$, 20 °C):	δ −75.1
FTIR (neat) cm^{-1}:	2860 (m), 1606 (m), 1493 (m), 1378 (s), 1223 (s), 1191 (s), 1024 (m), 738 (m).
HRMS (DART):	calc'd for $C_{16}H_{20}F_3N_2O_2S$ $[M+H]^+$: 361.1192, found: 361.1184.
TLC (30% EtOAc in hexanes), R_f:	0.67 (UV, CAM, $KMnO_4$).

[7] Warming to 23 °C followed by addition of triethylsilane affords spirocyclic indoline (±)-**3a** in 55% yield. Warming to 23 °C and keeping the mixture at 23 °C for 4.5 h followed by addition of triethylamine affords spirocyclic indoline (±)-**3a** in 30% yield.
[8] The use of C15,C16-hexadeuterated analog **1a**-d_6 as substrate and addition of triethylamine after warming to 23 °C for 4.5 h affords C15,C16-hexadeuterated spirocyclic indoline (±)-**3a**-d_6 in 29% yield (>99% deuterium incorporation at C15 and C16 by ^{1}H NMR analysis).
[9] The use of the C15,C16-hexadeuterated isotopomer **1a**-d_6 as substrate affords C15,C16-hexadeuterated spirocyclic indoline (±)-**3a**-d_6 in 95% yield (>99% deuterium incorporation at C15 and C16 by ^{1}H NMR analysis).
[10] The addition of lithium aluminum deuteride (98 atom% D) in place of lithium aluminum hydride affords C2-monodeuterated analog (±)-**3a**-d_1 in 96% yield (≥98% deuterium incorporation at C2 [d.r. = 6:1] by ^{1}H NMR analysis). The C2–deuterium bond in the major diastereomer is *syn* to the C3–C10 bond, as determined by ^{1}H NMR analysis and NOESY correlations for spirocyclic indoline (±)-**3a**.
[11] The addition of lithium aluminum deuteride (98 atom% D) 1 h after allowing the reaction mixture to warm to 23 °C affords C2-monodeuterated analog (±)-**3a**-d_1 in 60% yield (≥98% deuterium incorporation at C2 [dr = 6:1] by ^{1}H NMR analysis).

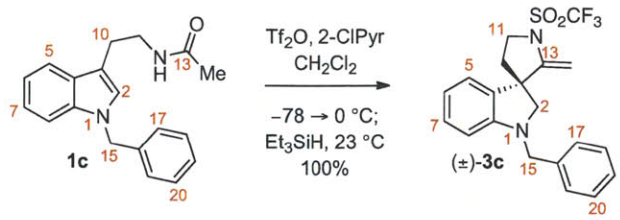


Spirocyclic indoline (±)-3b:

Trifluoromethanesulfonic anhydride (70.7 μL, 420 μmol, 2.10 equiv) was added via syringe to a solution of 1-methyl-*N*-acetyltryptamine[12] (**1b**, 43.3 mg, 200 μmol, 1 equiv) and 2-chloropyridine (60.1 μL , 640 μmol, 3.20 equiv) in dichloromethane (500 μL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 25 min, triethylsilane[13] (63.9 μL, 400 μmol, 2.00 equiv) was added via syringe. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 3 h, triethylamine (300 μL) was added to neutralize the trifluoromethanesulfonate salts. Brine (10 mL) was added, and the aqueous layer was extracted with dichloromethane (10 mL, 2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 20% ethyl acetate in hexanes) to afford spirocyclic indoline (±)-**3b** (64.7 mg, 97.3%) as an off-white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.17 (app-dt, J = 1.3, 7.7, 1H, C_7**H**), 6.99 (d, J = 7.4, 1H, C_5**H**), 6.75 (app-dt, J = 1.0, 7.5, 1H, C_6**H**), 6.56 (d, J = 7.9, 1H, C_8**H**), 5.25 (d, J = 2.4, 1H, $C_{14}\mathbf{H}_Z$), 4.42 (d, J = 2.4, 1H, $C_{14}\mathbf{H}_E$), 4.00 (app-dt, J = 2.5, 9.2, 1H, $C_{11}\mathbf{H}_a$), 3.78 (app-dt, J = 6.6, 10.2, 1H, $C_{11}\mathbf{H}_b$), 3.36 (d, J = 8.8, 1H, $C_2\mathbf{H}_a$), 3.21 (d, J = 8.8, 1H, $C_2\mathbf{H}_b$), 2.77 (s, 3H, $C_{15}\mathbf{H}_3$), 2.22 (ddd, J = 2.5, 6.6, 12.6, 1H, $C_{10}\mathbf{H}_a$), 2.07 (ddd, J = 8.2, 10.2, 12.6, 1H, $C_{10}\mathbf{H}_b$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 153.2 (**C**$_9$), 148.4 (**C**$_{13}$), 132.1 (**C**$_4$), 129.2 (**C**$_7$), 123.5 (**C**$_5$), 120.6 (q, J = 325.8, $SO_2\mathbf{C}F_3$), 118.8 (**C**$_6$), 108.1 (**C**$_8$), 94.8 (**C**$_{14}$), 68.4 (**C**$_2$), 55.6 (**C**$_{13}$), 49.8 (**C**$_{11}$), 35.9 (**C**$_{15}$), 35.1 (**C**$_{10}$).
^{19}F NMR (471 MHz, $CDCl_3$, 20 °C):	δ –74.0.
FTIR (neat) cm^{-1}:	2954 (w), 1657 (m), 1608 (m), 1492 (m), 1404 (m), 1383 (m), 1227 (s), 1198 (s), 1147 (s), 748 (m).
HRMS (DART):	calc'd for $C_{14}H_{16}F_3N_2O_2S$ $[M+H]^+$: 333.0879, found: 333.0872.
TLC (30% EtOAc in hexanes), R_f:	0.60 (UV, CAM, $KMnO_4$).

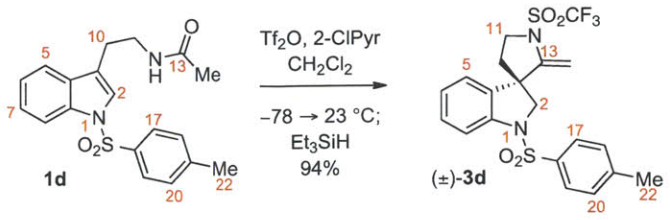
[12] For previous preparations of amides **1b**, **1c**, and **1d**, see Song, H.; Yang, J.; Chen, W.; Qin, Y. *Org. Lett.* **2006**, *8*, 6011.
[13] The addition of tetrahydrofuran and lithium aluminum hydride in place of triethylsilane affords spirocyclic indoline (±)-**3b** in 92% yield. The addition of triethylamine in place of triethylsilane affords spirocyclic indoline (±)-**3b** in 72% yield.



Spirocyclic indoline (±)-3c:

Trifluoromethanesulfonic anhydride (154 μL, 916 μmol, 2.10 equiv) was added via syringe to a solution of 1-benzyl-*N*-acetyltryptamine[12] (**1c**, 128 mg, 436 μmol, 1 equiv) and 2-chloropyridine (131 μL, 1.40 mmol, 3.20 equiv) in dichloromethane (1.5 mL) at −78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 25 min, triethylsilane (63.9 μL, 400 μmol, 2.00 equiv) was added via syringe. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 3 h, triethylamine (500 μL) was added to neutralize the trifluoromethanesulfonate salts. Brine (15 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 5% ethyl acetate in hexanes) to afford spirocyclic indoline (±)-**3c** (128 mg, 99.5%) as a viscous, colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

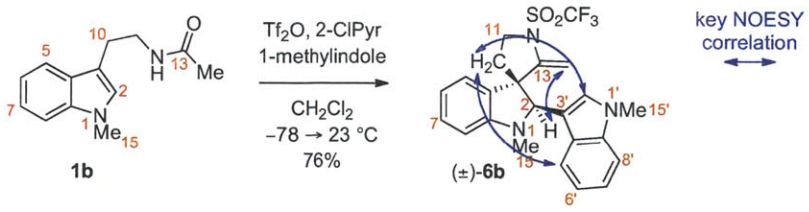
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.44–7.38 (m, 2H, C_{18}**H**, C_{20}**H**), 7.44–7.38 (m, 2H, C_{17}**H**, C_{21}**H**), 7.44–7.38 (m, 1H, C_{19}**H**), 7.20 (app-dt, J = 1.2, 7.7, 1H, C_7**H**), 7.07 (dd, J = 1.2, 7.5, 1H, C_5**H**), 6.81 (app-dt, J = 0.8, 7.4, 1H, C_6**H**), 6.65 (d, J = 7.9, 1H, C_8**H**), 5.30 (d, J = 2.3, 1H, C_{14}**H**$_Z$), 4.49 (d, J = 2.3, 1H, C_{14}**H**$_E$), 4.43 (d, J = 14.8, 1H, C_{15}**H**$_a$), 4.25 (d, J = 14.8, 1H, C_{15}**H**$_b$), 4.06–3.97 (m, 1H, C_{11}**H**$_a$), 3.82–3.70 (m, 1H, C_{11}**H**$_b$), 3.38 (d, J = 9.2, 1H, C_2**H**$_a$), 3.33 (d, J = 9.2, 1H, C_2**H**$_b$), 2.27–2.09 (m, 2H, C_{10}**H**$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 152.3 (**C**$_9$), 148.6 (**C**$_{13}$), 137.8 (**C**$_{16}$), 131.9 (**C**$_4$), 129.3 (**C**$_7$), 128.8 (**C**$_{18}$, **C**$_{20}$), 127.9 (**C**$_{17}$, **C**$_{21}$), 127.6 (**C**$_{19}$), 123.8 (**C**$_5$), 120.6 (q, J = 325.3, SO_2**C**F_3), 118.9 (**C**$_6$), 108.0 (**C**$_8$), 94.8 (**C**$_{14}$), 66.1 (**C**$_2$), 55.4 (**C**$_3$), 53.0 (**C**$_{15}$), 49.7 (**C**$_{11}$), 35.5 (**C**$_{10}$).
^{19}F NMR (282 MHz, $CDCl_3$, 20 °C):	δ −74.0.
FTIR (neat) cm^{-1}:	2831 (m), 1656 (m), 1606 (m), 1489 (s), 1404 (s), 1382 (s), 1228 (s), 1198 (s), 1029 (m), 742 (m).
HRMS (DART):	calc'd for $C_{20}H_{20}F_3N_2O_2S$ $[M+H]^+$: 409.1192, found: 409.1178.
TLC (20% EtOAc in hexanes), R_f:	0.67 (UV, CAM, $KMnO_4$).



Spirocyclic indoline (±)-3d:

Trifluoromethanesulfonic anhydride (64.9 μL, 386 μmol, 2.10 equiv) was added via syringe to a solution of 1-(*p*-toluenesulfonyl)-*N*-acetyltryptamine[12] (**1d**, 65.5 mg, 184 μmol, 1 equiv) and 2-chloropyridine (55.2 μL, 588 μmol, 3.20 equiv) in dichloromethane (1.0 mL) at –78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 30 min, triethylsilane (58.7 μL, 368 μmol, 2.00 equiv) was added via syringe. After 3 h, triethylamine (300 μL) was added to neutralize the trifluoromethanesulfonate salts. Brine (15 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 10% ethyl acetate in hexanes) to afford spirocyclic indoline (±)-**3d** (81.2 mg, 93.5%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

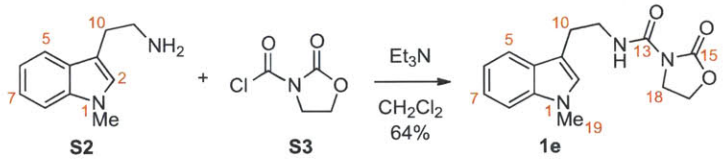
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.70 (d, J = 8.2, 1H, C_8**H**), 7.66 (d, J = 8.3, 2H, C_{17}**H**, C_{21}**H**), 7.30 (app-dt, J = 1.4, 7.8, 1H, C_7**H**), 7.23 (d, J = 8.3, 1H, C_{18}**H**, C_{20}**H**), 7.05 (app-dt, J = 0.9, 7.5, 1H, C_6**H**), 6.99 (d, J = 7.6, 1H, C_5**H**), 5.00 (d, J = 2.8, 1H, C_{14}**H**$_Z$), 3.99–3.95 (m, 1H, C_{11}**H**$_a$), 3.93 (d, J = 10.8, 1H, C_2**H**$_a$), 3.75 (d, J = 10.8, 1H, C_2**H**$_b$), 3.74 (d, J = 2.8, 1H, C_{14}**H**$_E$), 3.73–3.65 (m, 1H, C_{11}**H**$_b$), 2.36 (s, 3H, C_{22}**H**$_3$), 2.01 (ddd, J = 8.3, 10.9, 12.8, 1H, C_{10}**H**$_a$), 1.91 (ddd, J = 2.0, 6.2, 12.8, 1H, C_{10}**H**$_b$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 148.2 (**C**$_{13}$), 144.8 (**C**$_{19}$), 142.4 (**C**$_9$), 133.6 (**C**$_{15}$), 133.5 (**C**$_4$), 130.0 (**C**$_{18}$, **C**$_{20}$), 129.8 (**C**$_8$), 127.5 (**C**$_{17}$, **C**$_{21}$), 124.7 (**C**$_6$), 124.5 (**C**$_5$), 120.5 (q, J = 325.3, SO_2**C**F_3), 115.2 (**C**$_8$), 95.4 (**C**$_{14}$), 62.5 (**C**$_2$), 55.0 (**C**$_3$), 49.5 (**C**$_{11}$), 36.5 (**C**$_{10}$), 21.7 (**C**$_{22}$).
^{19}F NMR (282 MHz, $CDCl_3$, 20 °C):	δ –74.0.
FTIR (neat) cm^{-1}:	2919 (w), 1656 (m), 1599 (m), 1478 (m), 1405 (s), 1359 (s), 1229 (s), 1199 (s), 1169 (s), 1027 (m).
HRMS (DART):	calc'd for $C_{20}H_{20}F_3N_2O_4S_2$ $[M+H]^+$: 473.0811, found: 473.0807.
TLC (10% EtOAc in hexanes), R_f:	0.13 (UV, CAM, $KMnO_4$).



Spirocyclic 1-methyltryptamine adduct (±)-6b:

Trifluoromethanesulfonic anhydride (220 µL, 1.31 mmol, 2.10 equiv) was added via syringe to a solution of 1-methyl-*N*-acetyltryptamine[12] (**1b**, 135 mg, 622 µmol, 1 equiv), 2-chloropyridine (187 µL, 1.99 mmol, 3.20 equiv) and 1-methyltryptamine (85.5 µL, 685 µmol, 1.10 equiv) in dichloromethane (5.0 mL) at −78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 4 h, saturated aqueous potassium carbonate solution (5 mL) was added to neutralize the trifluoromethanesulfonate salts. Brine (10 mL) was added, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (25% dichloromethane in hexanes) to afford spirocyclic 1-methyltryptamine adduct (±)-**6b** (219 mg, 76.0%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, PhMe-d_8, 100 °C):	δ 7.69 (d, J = 8.1, 1H, $C_{5'}$**H**), 7.14–7.07 (m, 2H, $C_{7'}$**H**, C_7**H**), 7.02 (app-t, J = 7.7, 1H, $C_{6'}$**H**), 7.00 (d, J = 8.1, 1H, $C_{8'}$**H**), 6.91 (d, J = 7.4, 1H, C_5**H**), 6.72 (app-t, J = 7.5, 1H, C_6**H**), 6.70 (s, 1H, $C_{2'}$**H**), 6.47 (d, J = 7.9, 1H, C_8**H**), 5.48 (d, J = 1.7, 1H, C_{14}**H**$_Z$), 4.55 (d, J = 1.7, 1H, C_{14}**H**$_E$), 4.54 (s, 1H, C_2**H**), 3.19 (s, 3H, $C_{15'}$**H**$_3$), 3.15 (app-t, J = 9.1, 1H, C_{11}**H**$_a$), 2.52–2.43 (m, 1H, C_{11}**H**$_b$), 2.48 (s, 3H, C_{15}**H**$_3$), 2.26–2.16 (m, 1H, C_{10}**H**$_a$), 1.52–1.43 (m, 1H, C_{10}**H**$_b$).
^{13}C NMR (125 MHz, PhMe-d_8, 100 °C):	δ 153.3 (**C**$_9$), 151.2 (**C**$_{13}$), 138.5 (**C**$_{9'}$), 134.1 (**C**$_4$), 129.4 (**C**$_7$), 128.9 (**C**$_{2'}$), 128.4 (**C**$_{4'}$), 124.0 (**C**$_5$), 122.8 (**C**$_{7'}$), 121.4 (**C**$_{5'}$), 121.3 (q, J = 325.8, SO_2**C**F_3), 120.6 (**C**$_{6'}$), 119.7 (**C**$_6$), 110.5 (**C**$_{5'}$), 109.9 (**C**$_{8'}$), 108.5 (**C**$_8$), 95.5 (**C**$_{14}$), 77.9 (**C**$_2$), 61.4 (**C**$_3$), 50.3 (**C**$_{11}$), 34.1 (**C**$_{15}$), 33.2 (**C**$_{10}$), 32.2 (**C**$_{15'}$).
^{19}F NMR (471 MHz, PhMe-d_8, 100 °C):	δ −75.1.
FTIR (neat) cm^{-1}:	2915 (w), 1650 (m), 1605 (m), 1485 (s), 1402 (s), 1382 (s), 1228 (s), 1197 (s), 1146 (s), 1021 (m), 744 (m).
HRMS (DART):	calc'd for $C_{23}H_{23}F_3N_3O_2S$ $[M+H]^+$: 462.1458, found: 462.1477.
TLC (50% CH_2Cl_2 in hexanes), R_f:	0.42 (UV, CAM, $KMnO_4$).

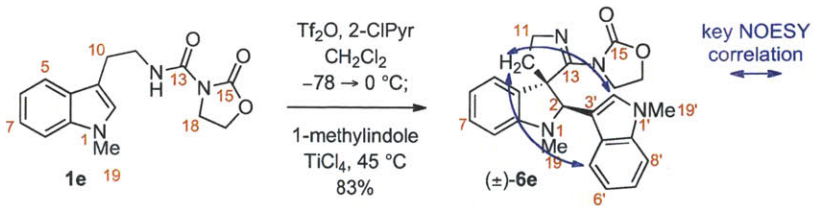


Oxazolidinone urea 1e:

A solution of 1-methyltryptamine[14] (**S2**, 1.66 g, 9.53 mmol, 1 equiv) in tetrahydrofuran (20 mL) was added via cannula to a solution of *N*-chlorocarbonyloxazolidin-2-one[15] (**S3**, 1.56 g, 10.4 mmol, 1.09 equiv) and triethylamine (3.33 mL, 23.9 mmol, 2.51 equiv) in tetrahydrofuran (40 mL) at 23 °C. After 12 h, the reaction mixture was diluted with ethyl acetate (250 mL). The organic layer was washed with saturated aqueous ammonium chloride solution (2 × 250 mL), aqueous sodium hydroxide solution (1N, 250 mL), saturated aqueous sodium bicarbonate solution (250 mL), and brine (250 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (50% ethyl acetate in hexanes) to afford oxazolidinone urea **1e** (1.76 g, 64.3%) as a beige powder. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.92–7.84 (br-m, 1H, N_{12}**H**), 7.63 (d, J = 7.9, 1H, C_5**H**), 7.30 (d, J = 8.2, 1H, C_8**H**), 7.24 (app-dt, J = 1.1, 7.6, 1H, C_7**H**), 7.13 (app-dt, J = 1.1, 7.4, 1H, C_6**H**), 6.92 (s, 1H, C_2**H**), 4.32 (t, J = 8.2, 2H, C_{18}**H**$_2$), 3.98 (t, J = 8.2, 2H, C_{19}**H**$_2$), 3.74 (s, 3H, C_{19}**H**$_3$), 3.58 (app-q, J = 7.1, 2H, C_{11}**H**$_2$), 3.02 (t, J = 7.1, 1H, C_{10}**H**$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 155.7, 151.6, 137.1, 127.6, 126.9, 121.6, 118.8, 118.8, 111.1, 109.3, 62.3, 42.4, 40.7, 32.6, 25.4.
FTIR (neat) cm^{-1}:	3349 (br-m), 2922 (m), 1755 (s), 1697 (s), 1540 (s), 1478 (s), 1400 (s), 1245 (s), 1104 (s), 1037 (m), 744 (s).
HRMS (DART):	calc'd for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1343, found: 288.1348.
TLC (50% EtOAc in hexanes), R_f:	0.19 (UV, CAM, $KMnO_4$).

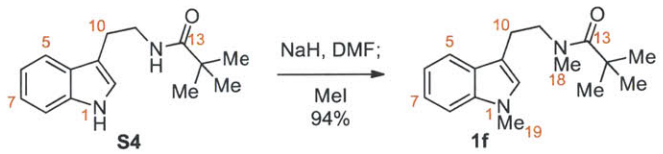
[14] For a previous preparation of 1-methyltryptamine (**S2**), see Lygin, A. V.; de Meijere, A. *Eur. J. Org. Chem.* **2009**, 5138.
[15] For a previous preparation of *N*-chlorocarbonyloxazolidin-2-one (**S3**), see Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595.



Spirocyclic 1-methyltryptamine adduct (±)-6e:

Trifluoromethanesulfonic anhydride (25.9 μL, 154 μmol, 1.10 equiv) was added via syringe to a solution of oxazolidinone urea **1e** (40.2 mg, 140 μmol, 1 equiv) and 2-chloropyridine (28.9 μL, 308 μmol, 2.20 equiv) in dichloromethane (1.8 mL) at −78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 30 min, 1-methylindole (19.2 μL, 154 μmol, 1.10 equiv) was added via syringe. After 1 min, titanium tetrachloride (1.0 M solution in dichloromethane, 154 μL, 154 μmol, 1.10 equiv) was added via syringe. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 5 min, the reaction vessel was placed into an oil bath and heated to 45 °C. After 3 h, the reaction vessel was removed from the oil bath and allowed to cool to 23 °C before saturated aqueous sodium bicarbonate solution (15 mL) was added to quench the titanium and trifluoromethanesulfonate salts. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 → 70% ethyl acetate in hexanes) to afford spirocyclic 1-methyltryptamine adduct (±)-**6e** (46.6 mg, 83.2%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, PhMe-d_8, 100 °C):	δ 7.83–7.60 (br-s, 1H, $C_{5'}$**H**), 7.13 (app-t, J = 7.6, 1H, $C_{7'}$**H**), 7.09 (app-t, J = 7.8, 1H, C_7**H**), 7.04 (app-t, J = 8.0, 1H, $C_{6'}$**H**), 7.01 (d, J = 8.2, 1H, $C_{8'}$**H**), 6.79 (d, J = 7.7, 1H, C_5**H**), 6.79–6.74 (br-s, 1H, $C_{2'}$**H**), 6.66 (app-t, J = 7.4, 1H, C_6**H**), 6.52 (d, J = 7.9, 1H, C_8**H**), 5.82–5.69 (br-s, 1H, C_2**H**), 3.78 (app-q, J = 9.0, 1H, C_{18}**H**$_a$), 3.71–3.57 (m, 1H, C_{18}**H**$_b$), 3.71–3.57 (m, 1H, C_{17}**H**$_a$), 3.53 (app-q, J = 8.3, 1H, C_{17}**H**$_b$), 3.39 (ddd, J = 3.5, 8.6, 14.8, 1H, C_{11}**H**$_a$), 3.17 (s, 3H, $C_{19'}$**H**$_3$), 2.83 (app-dt, J = 15.0, 7.5, 1H, C_{11}**H**$_b$), 2.72 (s, 3H, C_{19}**H**$_3$), 2.70–2.62 (m, 1H, C_{10}**H**$_a$), 1.86 (app-dt, J = 13.0, 7.9, 1H, C_{10}**H**$_b$).
^{13}C NMR (125 MHz, PhMe-d_8, 80 °C):	δ 163.9 (**C**$_{13}$), 154.0 (**C**$_9$), 153.0 (**C**$_{15}$), 138.4 (**C**$_{9'}$), 135.4 (**C**$_4$), 129.3 (**C**$_{4'}$), 128.9 (**C**$_{2'}$), 128.6 (**C**$_7$), 122.3 (**C**$_{7'}$), 121.6 (**C**$_5$), 120.7 (**C**$_{5'}$), 120.0 (**C**$_{6'}$), 118.4 (**C**$_6$), 113.2 (**C**$_{3'}$), 109.6 (**C**$_{8'}$), 108.2 (**C**$_8$), 69.7 (**C**$_2$), 64.4 (**C**$_3$), 62.1 (**C**$_{17}$), 54.9 (**C**$_{11}$), 46.8 (**C**$_{18}$), 40.4 (**C**$_{10}$), 34.7 (**C**$_{19}$), 32.2 (**C**$_{19'}$).
FTIR (neat) cm^{-1}:	2931 (m), 1770 (s), 1611 (s), 1488 (s), 1399 (s), 1121 (m), 1066 (m), 741 (s).
HRMS (DART):	calc'd for $C_{24}H_{25}N_4O_2$ $[M+H]^+$: 401.1972, found: 401.1972.
TLC (70% EtOAc in hexanes), R_f:	0.18 (UV, CAM, $KMnO_4$).

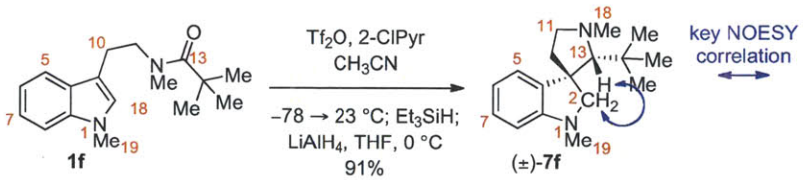


1,*N*-Dimethyl-*N*-pivalyltryptamine (1f):

Sodium hydride (60% dispersion in mineral oil, 1.24 g, 31.0 mmol, 8.00 equiv) was added slowly over 5 min as a solid under an argon atmosphere to a solution of *N*-pivalyltryptamine[16] (**S4**, 946 mg, 3.87 mmol, 1 equiv) in *N*,*N*-dimethylformamide (12.0 mL) at 0 °C, and the resulting mixture was allowed to warm to 23 °C. After 30 min, iodomethane (2.42 mL, 38.7 mmol, 10.0 equiv) was added slowly via syringe over 5 min. After 48 h, saturated aqueous ammonium chloride solution (20 mL) was added via syringe to quench the excess base, and the resulting biphasic mixture was concentrated under reduced pressure. The residue was diluted with diethyl ether (250 mL) and was washed with water (2 × 200 mL) and brine (200 mL). The organic layer was dried over anhydrous magnesium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 40% ethyl acetate in hexanes) to afford 1,*N*-dimethyl-*N*-pivalyltryptamine (**1f**, 993 mg, 94.1%) as a viscous yellow oil. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.63 (d, J = 7.7, 1H, C_5**H**), 7.28 (d, J = 8.2, 1H, C_8**H**), (d, J = 7.7, 1H, C_5**H**), 7.21 (app-t, J = 7.6, 1H, C_7**H**), 7.10 (app-t, J = 7.4, 1H, C_6**H**), 6.86 (s, 1H, C_2**H**), 3.73 (s, 3H, C_{19}**H**$_3$), 3.62 (t, J = 7.3, 2H, C_{11}**H**$_2$), 3.05 (s, 3H, C_{18}**H**$_3$), 2.99 (t, J = 7.3, 2H, C_{10}**H**$_2$), 1.28 (s, 9H, C(C**H**$_3$)$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 177.3, 137.1, 127.9, 126.7, 121.7, 119.0, 118.9, 111.7, 109.3, 51.6, 38.9, 36.9, 32.7, 28.4, 23.4.
FTIR (neat) cm^{-1}:	3054 (w), 2933 (m), 1623 (s), 1482 (s), 1403 (m), 1379 (m), 1328 (m), 1094 (m), 740 (s).
HRMS (DART):	calc'd for $C_{17}H_{24}N_2NaO$ $[M+Na]^+$: 295.1781, found: 295.1771.
TLC (30% EtOAc in hexanes), R_f:	0.20 (UV, CAM, $KMnO_4$).

[16] For a previous preparation of amide **S4**, see Eichele, O.; Mutschler, E. *Archiv der Pharmazie* **1967**, *300*, 1038.



Tricyclic indoline (±)-7f:

Trifluoromethanesulfonic anhydride (59.7 μL, 355 μmol, 1.10 equiv) was added via syringe to a solution of 1,*N*-dimethyl-*N*-pivalyltryptamine (**1f**, 87.8 mg, 322 μmol, 1 equiv) and 2-chloropyridine (36.3 μL, 387 μmol, 1.20 equiv) in acetonitrile (3.6 mL) at 0 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 20 min, triethylsilane (154 μL, 967 μmol, 3.00 equiv) was added via syringe. After 8 h, the reaction mixture was cooled to 0 °C, and tetrahydrofuran (3.0 mL) was added via syringe. After 30 sec, lithium aluminum hydride[17] (48.9 mg, 1.29 mmol, 4.00 equiv) was added as a solid under an argon atmosphere. After 10 min, sodium sulfate decahydrate was added to quench the unreacted aluminum hydride salts. The resulting suspension was filtered, and the filter cake was extracted with ethyl acetate (20 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 1.5% ethyl acetate in hexanes) to afford tricyclic indoline (±)-**7f** (76.1 mg, 91.4%) as a viscous, colorless oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 7.20 (d, J = 7.4, 1H, C_5**H**), 7.10 (app-t, J = 7.7, 1H, C_7**H**), 6.68 (app-t, J = 7.4, 1H, C_6**H**), 6.49 (d, J = 7.7, 1H, C_8**H**), 3.37–3.24 (m, 1H, C_{11}**H**$_a$), 3.18 (d, J = 7.9, 1H, C_2**H**$_a$), 2.72 (s, 1H, C_{13}**H**), 2.69 (s, 3H, C_{19}**H**$_3$), 2.64 (s, 3H, C_{18}**H**$_3$), 2.63 (d, J = 7.9, 1H, C_2**H**$_b$), 2.54 (app-dt, J = 7.5, 12.2, 1H, C_{10}**H**$_a$), 2.42 (ddd, J = 5.9, 8.7, 12.2, 1H, C_{11}**H**$_b$), 1.71 (app-dd, J = 5.9, 12.0, 1H, C_{10}**H**$_b$), 0.68 (s, 9H, C(C**H**$_3$)$_3$).

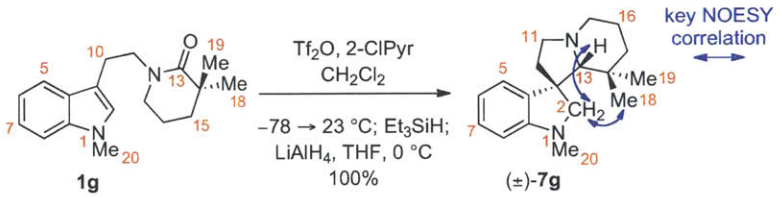
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 155.5 (**C**$_9$), 134.0 (**C**$_4$), 128.1 (**C**$_7$), 125.2 (**C**$_5$), 117.8 (**C**$_6$), 108.0 (**C**$_8$), 80.4 (**C**$_{13}$), 74.2 (**C**$_2$), 55.4 (**C**$_3$), 55.3 (**C**$_{11}$), 48.1 (**C**$_{18}$), 37.3 (**C**$_{14}$), 37.0 (**C**$_{19}$), 36.5 (**C**$_{10}$), 27.2 (C(**C**H$_3$)$_3$).

FTIR (neat) cm^{-1}: 2953 (s), 2797 (s), 1606 (s), 1484 (s), 1461 (m), 1365 (m), 1269 (m), 1154 (m), 1047 (m), 965 (m), 740 (s).

HRMS (DART): calc'd for $C_{17}H_{27}N_2$ $[M+H]^+$: 259.2169, found: 259.2164.

TLC (Al_2O_3, 10% EtOAc in hexanes), R_f: 0.76 (UV, CAM, $KMnO_4$).

[17] The use of lithium aluminum deuteride (98 atom% D) affords the C13-monodeuterated analog (±)-**7f**-d_1 (≥ 98% deuterium incorporation at C13 and <5% deuterium enrichment at C2 by ^{1}H NMR analysis).

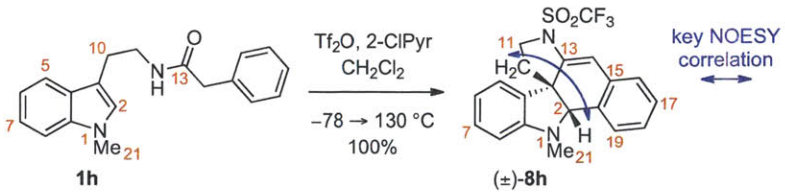


Tetracyclic indoline (±)-7g:

Trifluoromethanesulfonic anhydride (10.2 μL, 60.7 μmol, 1.10 equiv) was added via syringe to a solution of α-quaternary 1-methyltryptamine lactam **1g**[18] (15.7 mg, 55.2 μmol, 1 equiv) and 2-chloropyridine (11.4 μL, 121 μmol, 2.20 equiv) in dichloromethane (600 μL) at –78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 10 min, the reaction mixture was allowed to warm to 23 °C. After 20 min, triethylsilane (26.5 μL, 166 μmol, 3.00 equiv) was added via syringe. After 2 h, the reaction mixture was cooled to 0 °C, and tetrahydrofuran (2.0 mL) was added via syringe. After 30 sec, lithium aluminum hydride (8.4 mg, 221 μmol, 4.00 equiv) was added as a solid under an argon atmosphere. After 10 min, sodium sulfate decahydrate was added to quench the unreacted aluminum hydride salts. The resulting suspension was filtered, and the filter cake was extracted with ethyl acetate (20 mL). The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1% triethylamine, 10% ethyl acetate in hexanes) to afford tetracyclic indoline (±)-**7g** (14.9 mg, 99.8%) as an off-white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.15 (d, J = 7.3, 1H, C_5**H**), 7.06 (app-dt, J = 1.0, 7.6, 1H, C_7**H**), 6.61 (app-t, J = 7.3, 1H, C_6**H**), 6.39 (d, J = 7.8, 1H, C_8**H**), 3.50 (d, J = 9.3, 1H, C_2**H**$_a$), 3.29 (app-dt, J = 4.8, 9.1, 1H, C_{11}**H**$_a$), 3.17–3.11 (m, 1H, C_{17}**H**$_a$), 3.09 (d, J = 9.3, 1H, C_2**H**$_b$), 2.71 (s, 3H, C_{20}**H**$_3$), 2.20 (app-dt, J = 6.6, 9.9, 1H, C_{11}**H**$_b$), 2.09 (ddd, J = 6.6, 8.8, 12.7, 1H, C_{10}**H**$_a$), 1.92 (app-dt, J = 3.1, 11.7, 1H, C_{17}**H**$_b$), 1.87–1.79 (m, 1H, C_{10}**H**$_b$), 1.81 (s, 1H, C_{13}**H**), 1.69–1.56 (m, 1H, C_{16}**H**$_a$), 1.39–1.32 (m, 1H, C_{16}**H**$_b$), 1.20–1.13 (m, 1H, C_{15}**H**$_a$), 1.05 (app-dt, J = 3.7, 13.3, 1H, C_{15}**H**$_b$), 1.00 (s, 3H, C_{18}**H**$_3$), 0.28 (s, 3H, C_{19}**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 153.0 (**C**$_9$), 136.6 (**C**$_4$), 127.8 (**C**$_7$), 126.7 (**C**$_5$), 117.4 (**C**$_6$), 106.6 (**C**$_8$), 82.1 (**C**$_{13}$), 67.8 (**C**$_2$), 56.0 (**C**$_{17}$), 53.4 (**C**$_{11}$), 52.9 (**C**$_3$), 43.8 (**C**$_{15}$), 40.3 (**C**$_{10}$), 35.7 (**C**$_{20}$), 34.3 (**C**$_{14}$), 28.8 (**C**$_{18}$), 22.3 (**C**$_{16}$), 21.7 (**C**$_{19}$).
FTIR (neat) cm^{-1}:	2933 (s), 1605 (s), 1492 (s), 1386 (w), 1271 (m), 1163 (m), 1105 (w), 1023 (m), 740 (m).
HRMS (DART):	calc'd for $C_{18}H_{27}N_2$ $[M+H]^+$: 271.2169, found: 271.2170.
TLC (Al_2O_3, 10% EtOAc in hexanes), R_f:	0.60 (UV, CAM, $KMnO_4$).

[18] Lactam **1g** was prepared from the C14-didemethyl derivative by sequential treatment with excess lithium diisopropylamide and methyl iodide in tetrahydrofuran. For a previous preparation of the C14-didemethyl derivative of lactam **1g**, see Nagawa, M.; Kiuchi, M.; Obi, M.; Tonozuka, M.; Kobayashi, K.; Hino, T.; Ban, Y. *Chem. Pharm. Bull.* **1975**, *23*, 304.

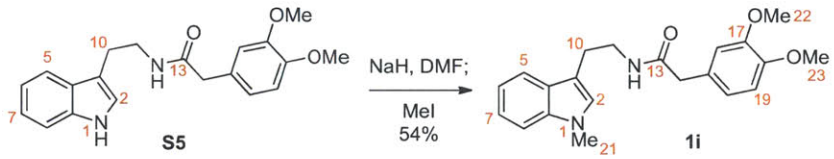


Pentacyclic indoline (±)-8h:

Trifluoromethanesulfonic anhydride (38.4 μL, 228 μmol, 2.10 equiv) was added via syringe to a solution of 1-methyl-*N*-phenylacetyltryptamine[19] (**1h**, 31.8 mg, 109 μmol, 1 equiv) and 2-chloropyridine (32.7 μL, 348 μmol, 3.20 equiv) in dichloromethane (1.0 mL) at –78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 5 min, the reaction vessel was placed into a microwave reactor and heated to 130 °C. After 5 min, the reaction vessel was removed from the microwave reactor and allowed to cool to 23 °C before triethylamine (500 μL) was added to neutralize the trifluoromethanesulfonate salts. Brine (10 mL) was added, and the aqueous layer was extracted with dichloromethane (10 mL, then 2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 20% ethyl acetate in hexanes) to afford spirocyclic indoline (±)-**8h** (44.1 mg, 99.8%) as an off-white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.43 (d, J = 6.7, 1H, C_{19}**H**), 7.14–7.05 (m, 1H, C_7**H**), 7.14–7.05 (m, 1H, C_{17}**H**), 7.14–7.05 (m, 1H, C_{18}**H**), 6.98–6.93 (m, 1H, C_5**H**), 6.98–6.93 (m, 1H, C_{16}**H**), 6.63 (app-dt, J = 0.9, 7.4, 1H, C_6**H**), 6.49 (d, J = 7.8, 1H, C_8**H**), 6.38 (s, 1H, C_{14}**H**), 4.80 (s, 1H, C_2**H**), 4.04 (app-t, J = 9.3, 1H, C_{11}**H**$_a$), 3.94 (app-dt, J = 5.7, 10.9, 1H, C_{11}**H**$_b$), 3.38 (s, 3H, C_{21}**H**$_3$), 2.23 (app-dt, J = 8.6, 11.8, 1H, C_{10}**H**$_a$), 2.12 (app-dd, J = 5.7, 11.8, 1H, C_{10}**H**$_b$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 149.6 (**C**$_9$), 137.4 (**C**$_{13}$), 133.7 (**C**$_{20}$), 133.4 (**C**$_4$), 133.0 (**C**$_{15}$), 129.4 (**C**$_7$), 128.2 (**C**$_{17}$), 127.6 (**C**$_{16}$), 127.1 (**C**$_{18}$), 126.8 (**C**$_{19}$), 121.7 (**C**$_5$), 120.4 (q, J = 324.8, SO_2**C**F_3), 118.1 (**C**$_6$), 108.1 (**C**$_8$), 106.1 (**C**$_{14}$), 73.4 (**C**$_2$), 55.0 (**C**$_3$), 49.1 (**C**$_{11}$), 38.7 (**C**$_{10}$), 37.2 (**C**$_{21}$).
^{19}F NMR (471 MHz, $CDCl_3$, 20 °C):	δ –75.0.
FTIR (neat) cm^{-1}:	2911 (w), 1671 (m), 1605 (m), 1485 (s), 1399 (s), 1227 (s), 1194 (s), 1147 (s), 1039 (m), 746 (m).
HRMS (DART):	calc'd for $C_{20}H_{18}F_3N_2O_2S$ $[M+H]^+$: 407.1036, found: 407.1026.
TLC (20% EtOAc in hexanes), R_f:	0.56 (UV, CAM, $KMnO_4$).

[19] For a previous preparation of amide **1h**, see Ho, B. T.; McIsaac, W. M.; Tansey, L. W.; Kralik, P. M. *J. Pharm. Sci.* **1968**, *57*, 1998.

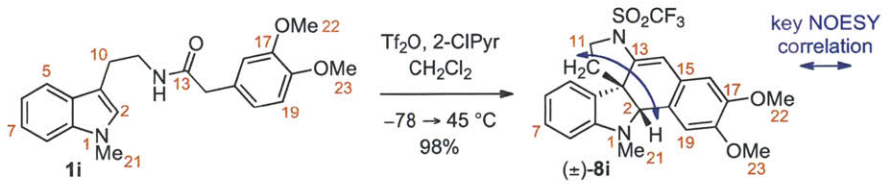


1-Methyl-*N*-(3,4-dimethoxyphenyl)acetyltryptamine (1i):

Sodium hydride (60% dispersion in mineral oil, 147 mg, 3.68 mmol, 1.30 equiv) was added slowly over 5 min as a solid under an argon atmosphere to a solution of *N*-(3,4-dimethoxyphenyl)acetyltryptamine[20] (**S5**, 958 mg, 2.83 mmol, 1 equiv) in *N*,*N*-dimethylformamide (25 mL) at 23 °C. After 30 min, iodomethane (230 μL, 3.68 mmol, 1.30 equiv) was added slowly via syringe over 5 min. After 18 h, the reaction mixture was concentrated under reduced pressure and then diluted with diethyl ether (125 mL). The organic layer was washed with water (2 × 125 mL), was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (50% ethyl acetate in hexanes) to afford 1-methyl-*N*-(3,4-dimethoxyphenyl)acetyltryptamine (**1i**, 536 mg, 53.7%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.50 (d, J = 7.9, 1H, C_5**H**), 7.26 (d, J = 8.2, 1H, C_8**H**), 7.21 (app-t, J = 7.6, 1H, C_7**H**), 7.07 (app-t, J = 7.4, 1H, C_6**H**), 6.74 (d, J = 8.1, 1H, C_{19}**H**), 6.65 (dd, J = 1.5, 8.1, 1H, C_{20}**H**), 6.62 (d, J = 1.5, 1H, C_{16}**H**), 6.57 (s, 1H, C_2**H**), 5.61-5.42 (br-s, 1H, N_{12}**H**), 3.85 (d, 3H, C_{23}**H**$_3$), 3.73 (s, 3H, C_{22}**H**$_3$), 3.66 (s, 3H, C_{21}**H**$_3$), 3.49 (app-q, J = 6.3, 2H, C_{11}**H**$_2$), 3.44 (s, 2H, C_{14}**H**$_2$), 2.86 (t, J = 6.6, 2H, C_{10}**H**$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 171.3 (**C**$_{13}$), 149.3 (**C**$_{17}$), 148.3 (**C**$_{18}$), 137.2 (**C**$_9$), 127.8 (**C**$_4$), 127.6 (**C**$_{15}$), 126.8 (**C**$_2$), 121.9 (**C**$_7$), 121.8 (**C**$_{20}$), 119.1 (**C**$_6$), 118.9 (**C**$_5$), 112.5 (**C**$_{16}$), 111.5 (**C**$_{19}$), 111.3 (**C**$_3$), 109.4 (**C**$_8$), 56.0 (**C**$_{23}$), 56.0 (**C**$_{22}$), 43.6 (**C**$_{14}$), 40.0 (**C**$_{11}$), 32.6 (**C**$_{21}$), 25.0 (**C**$_{10}$).
FTIR (neat) cm^{-1}:	3293 (br-m), 2934 (m), 1645 (s), 1514 (s), 1465 (m), 1328 (m), 1262 (s), 1235 (s), 1156 (m), 1027 (s), 742 (m).
HRMS (DART):	calc'd for $C_{21}H_{24}N_2NaO_3$ $[M+Na]^+$: 375.1679, found: 375.1687.
TLC (50% EtOAc in hexanes), R_f:	0.64 (UV, CAM, $KMnO_4$).

[20] For a previous preparation of amide **S5**, see Onda, M.; Kawanishi, M. *Yakugaku Zasshi* **1956**, *76*, 966.



Pentacyclic indoline (±)-8i:

Trifluoromethanesulfonic anhydride (417 μL, 2.48 mmol, 2.10 equiv) was added via syringe to a solution of 1-methyl-*N*-(3,4-dimethoxyphenyl)acetyltryptamine (**1i**, 416 mg, 1.18 mmol, 1 equiv) and 2-chloropyridine (355 μL, 3.78 mmol, 3.20 equiv) in dichloromethane (12.0 mL) at –78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 5 min, the reaction vessel was placed into an oil bath and heated to 45 °C. After 3 h, the reaction vessel was removed from the oil bath and allowed to cool to 23 °C before triethylamine (1.0 mL) was added to neutralize the trifluoromethanesulfonate salts. Brine (60 mL) was added, and the aqueous layer was extracted with dichloromethane (60 mL, then 2 × 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 30% ethyl acetate in hexanes) to afford pentacyclic indoline (±)-**8i** (540 mg, 98.1%) as a tan powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 7.11 (app-dt, J = 1.2, 7.7, 1H, C_7**H**), 6.96 (d, J = 7.3, 1H, C_5**H**), 6.94 (s, 1H, C_{19}**H**), 6.64 (app-dt, J = 1.0, 7.5, 1H, C_6**H**), 6.51 (d, J = 7.7, 1H, C_8**H**), 6.48 (s, 1H, C_{16}**H**), 6.29 (s, 1H, C_{14}**H**), 4.76 (s, 1H, C_2**H**), 4.03 (app-t, J = 9.2, 1H, C_{11}**H**$_a$), 3.93 (app-dt, J = 5.9, 11.0, 1H, C_{11}**H**$_b$), 3.84 (s, 3H, C_{22}**H**$_3$), 3.79 (s, 3H, C_{23}**H**$_3$), 3.37 (s, 3H, C_{21}**H**$_3$), 2.24 (app-dt, J = 8.4, 11.8, 1H, C_{10}**H**$_a$), 2.11 (app-dd, J = 5.6, 11.9, 1H, C_{10}**H**$_b$).

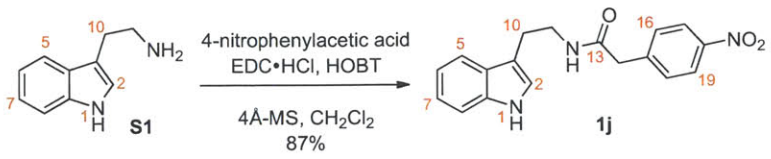
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 149.5 (**C**$_9$), 148.7 (**C**$_{17}$), 147.9 (**C**$_{18}$), 136.2 (**C**$_{13}$), 133.8 (**C**$_4$), 129.4 (**C**$_7$), 126.1 (**C**$_{15}$), 125.6 (**C**$_{20}$), 121.7 (**C**$_5$), 120.5 (q, J = 325.3, SO_2**C**F_3), 118.4 (**C**$_6$), 110.7 (**C**$_{16}$), 110.7 (**C**$_{19}$), 108.5 (**C**$_8$), 105.7 (**C**$_{14}$), 73.6 (**C**$_2$), 56.3 (**C**$_{22}$), 56.0 (**C**$_{23}$), 55.0 (**C**$_3$), 49.1 (**C**$_{11}$), 38.6 (**C**$_{10}$), 37.4 (**C**$_{21}$).

^{19}F NMR (282 MHz, $CDCl_3$, 20 °C): δ –75.0.

FTIR (neat) cm^{-1}: 2935 (m), 1670 (m), 1603 (m), 1516 (m), 1489 (m), 1396 (s), 1256 (s), 1225 (s), 1212 (s), 1148 (m), 1040 (m), 666 (s).

HRMS (DART): calc'd for $C_{22}H_{22}F_3N_2O_4S$ $[M+H]^+$: 467.1247, found: 467.1232.

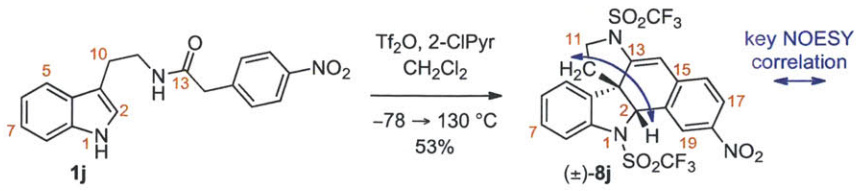
TLC (50% EtOAc in hexanes), R_f: 0.64 (UV, CAM, $KMnO_4$).



<u>*N*-(4-nitrophenyl)acetyltryptamine (1j):</u>

1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrogen chloride (EDC•HCl, 4.81 g, 25.1 mmol, 1.50 equiv) was added under an argon atmosphere to a solution of tryptamine (**S1**, 2.95 g, 18.4 mmol, 1.10 equiv), 4-nitrophenylacetic acid (3.03 g, 16.7 mmol, 1 equiv), *N*-hydroxybenzotriozole (HOBT, 3.39 g, 25.1 mmol, 1.50 equiv), and powdered 4 Å molecular sieves (3.0 g) in dichloromethane (100 mL) at 23 °C. After 48 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate (275 mL) and was washed with aqueous hydrogen chloride solution (1N, 250 mL), saturated aqueous ammonium chloride solution (250 mL), saturated aqueous sodium bicarbonate solution (2 × 250 mL), and brine (250 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure to afford *N*-(4-nitrophenyl)acetyltryptamine (**1j**, 4.71 g, 87.1%) as a tan powder. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 8.29–8.18 (br-s, 1H, N_1**H**), 8.05 (d, J = 8.6, 2H, C_{17}**H**, C_{19}**H**), 7.52 (d, J = 7.8, 1H, C_5**H**), 7.35 (d, J = 8.1, 1H, C_8**H**), 7.25 (d, J = 8.6, 2H, C_{16}**H**, C_{20}**H**), 7.21 (t, J = 7.6, 1H, C_7**H**), 7.10 (t, J = 7.5, 1H, C_6**H**), 6.89 (s, 1H, C_2**H**), 5.62–5.48 (br-s, 1H, N_{12}**H**), 3.59 (app-q, J = 6.3, 2H, C_{11}**H**$_2$), 3.53 (s, 2H, C_{14}**H**$_2$), 2.95 (t, J = 6.6, 2H, C_{10}**H**$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 169.3, 147.2, 142.5, 136.5, 130.3, 127.4, 124.0, 122.5, 122.3, 119.8, 118.7, 112.6, 111.6, 43.5, 40.3, 25.0.
FTIR (neat) cm^{-1}:	3403 (br-s), 3293 (br-s), 2929 (w), 1652 (s), 1517 (s), 1457 (m), 1346 (s), 1109 (w), 743 (m).
HRMS (DART):	calc'd for $C_{18}H_{17}N_3NaO_3$ $[M+Na]^+$: 346.1162, found : 346.1150.
TLC (70% EtOAc in hexanes), R_f:	0.25 (UV, CAM, $KMnO_4$).



Pentacyclic indoline (±)-8j:

Trifluoromethanesulfonic anhydride (110 μL, 652 μmol, 3.10 equiv) was added via syringe to a solution of *N*-(4-nitrophenyl)acetyltryptamine (**1j**, 68.0 mg, 210 μmol, 1 equiv) and 2-chloropyridine (82.9 μL, 883 μmol, 4.20 equiv) in dichloromethane (2.1 mL) at –78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 5 min, the reaction vessel was placed into a microwave reactor and heated to 130 °C. After 10 min, the reaction vessel was removed from the microwave reactor and allowed to cool to 23 °C before triethylamine (500 μL) was added to neutralize the trifluoromethanesulfonate salts. Brine (10 mL) was added, and the aqueous layer was extracted with dichloromethane (10 mL, then 2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 10% ethyl acetate in hexanes) to afford pentacyclic indoline (±)-**8j** (63.7 mg, 53.2%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 8.54 (s, 1H, C_{19}**H**), 8.05 (dd, J = 2.0, 8.2, 1H, C_{17}**H**), 7.59 (d, J = 8.1, 1H, C_8**H**), 7.33 (app-dt, J = 1.2, 7.8, 1H, C_7**H**), 7.22 (app-dt, J = 0.8, 7.6, 1H, C_6**H**), 7.18–7.10 (m, 1H, C_5**H**), 7.18–7.10 (m, 1H, C_{16}**H**), 6.55 (s, 1H, C_{14}**H**), 5.74 (s, 1H, C_2**H**), 4.20 (app-t, J = 9.5, 1H, C_{11}**H**$_a$), 4.01 (app-dt, J = 5.7, 11.1, 1H, C_{11}**H**$_b$), 2.51 (app-dt, J = 8.8, 11.9, 1H, C_{10}**H**$_a$), 2.22 (app-dd, J = 5.7, 12.1, 1H, C_{10}**H**$_b$).

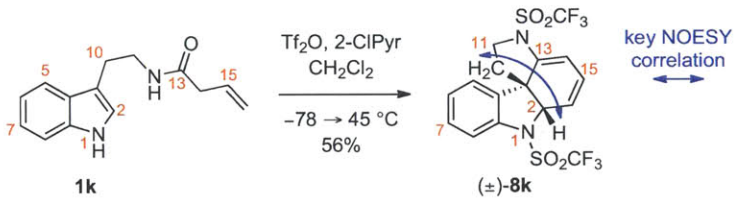
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 147.3 (**C**$_{18}$), 140.3 (**C**$_{13}$), 138.8 (**C**$_{15}$), 137.8 (**C**$_9$), 134.5 (**C**$_4$), 130.7 (**C**$_7$), 130.1 (**C**$_{20}$), 128.1 (**C**$_{16}$), 127.7 (**C**$_6$), 125.0 (**C**$_{17}$), 123.1 (**C**$_{19}$), 122.6 (**C**$_5$), 120.4 (q, J = 325.3, SO_2**C**F_3), 120.3 (q, J = 324.8, SO_2**C**F_3), 117.5 (**C**$_8$), 105.1 (**C**$_{14}$), 72.4 (**C**$_2$), 54.8 (**C**$_3$), 49.3 (**C**$_{11}$), 37.1 (**C**$_{10}$).

^{19}F NMR (282 MHz, $CDCl_3$, 20 °C): δ –73.9, –75.0.

FTIR (neat) cm^{-1}: 2918 (w), 1666 (m), 1582 (m), 1524 (s), 1404 (s), 1340 (s), 1229 (s), 1203 (s), 1145 (s), 1077 (m), 666 (m).

HRMS (DART): calc'd for $C_{20}H_{14}F_6N_3O_6S_2$ $[M+H]^+$: 570.0223, found: 570.0220.

TLC (10% EtOAc in hexanes), R_f: 0.15 (UV, CAM, $KMnO_4$).

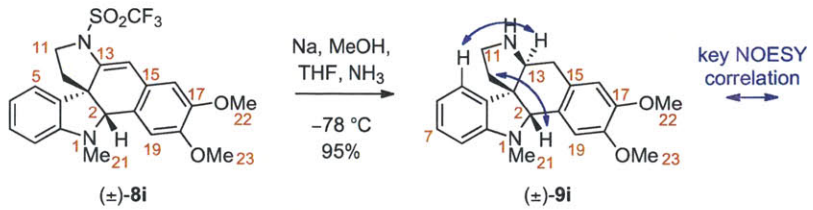


Tetracyclic indoline (±)-8k:

Trifluoromethanesulfonic anhydride (199 μL, 1.18 mmol, 3.10 equiv) was added via syringe to a solution of *N*-vinylacetyltryptamine[21] (**1k**, 87.0 mg, 381 μmol, 1 equiv) and 2-chloropyridine (150 μL, 1.21 mmol, 4.20 equiv) in dichloromethane (19.1 mL) at −78 °C. After 2 min, the reaction mixture was allowed to warm to 0 °C. After 5 min, the reaction mixture was allowed to warm to 23 °C. After 5 min, the reaction vessel was placed into an oil bath and heated to 45 °C. After 3 h, the reaction vessel was removed from the oil bath and allowed to cool to 23 °C before saturated aqueous sodium bicarbonate solution (30 mL) was added to neutralize the trifluoromethanesulfonate salts. Brine (40 mL) was added, and the aqueous layer was extracted with ethyl acetate (3 × 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 5% ethyl acetate in hexanes) to afford tetracyclic indoline (±)-**8k** (102 mg, 56.4%) as an off-white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 53 °C):	δ 7.55 (d, J = 8.1, 1H, C_8**H**), 7.34 (app-dt, J = 1.4, 7.8, 1H, C_7**H**), 7.20 (app-dt, J = 1.0, 7.5, 1H, C_6**H**), 7.14 (d, J = 7.5, 1H, C_5**H**), 5.97–5.91 (m, 1H, C_{15}**H**), 5.87 (d, J = 6.3, 1H, C_{14}**H**), 5.43 (dd, J = 2.2, 9.5, 1H, C_{16}**H**), 5.39 (s, 1H, C_2**H**), 4.06 (app-t, J = 9.6, 1H, C_{11}**H**$_a$), 3.92 (app-dt, J = 6.1, 10.8, 1H, C_{11}**H**$_b$), 2.33 (app-q, J = 10.9, 1H, C_{10}**H**$_a$), 2.11 (app-dd, J = 5.8, 12.2, 1H, C_{10}**H**$_b$).
^{13}C NMR (125 MHz, $CDCl_3$, 53 °C):	δ 137.9 (**C**$_{13}$), 137.7 (**C**$_9$), 135.3 (**C**$_4$), 130.2 (**C**$_7$), 126.7 (**C**$_6$), 125.8 (**C**$_{15}$), 122.8 (**C**$_5$), 121.1 (**C**$_{16}$), 120.5 (q, J = 324.8, SO_2**C**F_3), 120.4 (q, J = 324.3, SO_2**C**F_3), 116.2 (**C**$_8$), 101.6 (**C**$_{14}$), 72.4 (**C**$_2$), 53.6 (**C**$_3$), 48.7 (**C**$_{11}$), 37.3 (**C**$_{10}$).
^{19}F NMR (471 MHz, $CDCl_3$, 53 °C):	δ −75.0, −75.5.
FTIR (neat) cm^{-1}:	2918 (w), 1671 (m), 1603 (m), 1474 (m), 1463 (m), 1405 (s), 1229 (s), 1205 (s), 1146 (s), 1077 (m), 1048 (m), 666 (s).
HRMS (DART):	calc'd for $C_{16}H_{13}F_6N_2O_4S_2$ $[M+H]^+$: 475.0215, found: 475.0226.
TLC (20% EtOAc in hexanes), R_f:	0.51 (UV, CAM, $KMnO_4$).

[21] For a previous preparation of amide **1k**, see Airiau, E.; Spangenberg, T.; Girard, N.; Schoenfelder, A.; Salvadori, J.; Taddei, M.; Mann, A. *Chem. Eur. J.* **2008**, *14*, 10938.



Pentacyclic indoline (±)-9i:

Sodium metal ingot (25.0 mg, 1.09 mmol, 9.91 equiv) was added as a solid under an argon atmosphere to a solution of pentacyclic indoline (±)-**8i** (51.3 mg, 110 μmol, 1 equiv) and methanol (31.4 μL, 776 μmol, 7.05 equiv) in tetrahydrofuran (2.0 mL) and ammonia (2.5 mL) at −78 °C. After 4.25 h, ammonium chloride (150 mg) was added as a solid to quench the sodium salts, and the resulting mixture was allowed to warm to 23 °C over 1 h. Saturated aqueous potassium carbonate solution (60 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried over anhydrous potassium carbonate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1.4% ammonium hydroxide [40% aqueous solution], 12.6% methanol, 30% dichloromethane in chloroform) to afford pentacyclic indoline (±)-**9i** (35.0 mg, 94.6%) as a yellow powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

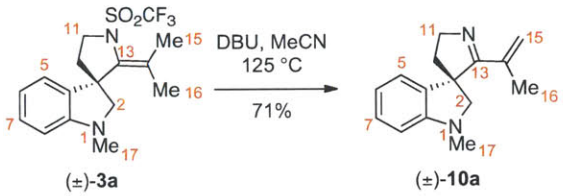
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 7.16 (d, J = 7.2, 1H, C_5**H**), 7.12 (app-t, J = 7.6, 1H, C_7**H**), 6.80–6.75 (m, 1H, C_6**H**), 6.79 (s, 1H, C_{19}**H**), 6.77 (s, 1H, C_{16}**H**), 6.47 (d, J = 7.6, 1H, C_8**H**), 3.91 (s, 3H, C_{22}**H**$_3$), 3.88 (s, 3H, C_{23}**H**$_3$), 3.81 (s, 1H, C_2**H**), 3.37 (br-s, 1H, C_{13}**H**), 3.07 (dd, J = 3.7, 14.7, 1H, C_{14}**H**$_a$), 3.03–2.87 (m, 2H, C_{11}**H**$_2$), 2.80 (d, J = 14.7, 1H, C_{14}**H**$_b$), 2.57–2.47 (m, 1H, C_{10}**H**$_a$), 2.53 (s, 3H, C_{21}**H**$_3$), 1.69 (app-dt, J = 12.8, 8.3, 1H, C_{10}**H**$_b$).

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 152.8 (**C**$_9$), 149.1 (**C**$_{18}$), 147.4 (**C**$_{17}$), 136.0 (**C**$_4$), 128.9 (**C**$_{20}$), 128.0 (**C**$_7$), 125.7 (**C**$_{15}$), 122.8 (**C**$_5$), 119.1 (**C**$_6$), 114.3 (**C**$_{19}$), 113.6 (**C**$_{16}$), 107.5 (**C**$_8$), 76.8 (**C**$_2$), 68.4 (**C**$_{13}$), 56.4 (**C**$_{22}$), 56.1 (**C**$_{23}$), 54.7 (**C**$_3$), 48.1 (**C**$_{11}$), 43.7 (**C**$_{10}$), 33.6 (**C**$_{21}$), 31.8 (**C**$_{14}$).

FTIR (neat) cm^{-1}: 3335 (br-w), 2952 (m), 1606 (m), 1515 (s), 1486 (s), 1294 (m), 1250 (m), 1119 (s), 1022 (m), 742 (m).

HRMS (DART): calc'd for $C_{21}H_{25}N_2O_2$ $[M+H]^+$: 337.1911, found: 337.1924.

TLC (2% NH_4OH [40% aqueous solution], 18% MeOH in $CHCl_3$), R_f: 0.59 (UV, CAM, $KMnO_4$).



Spirocyclic enimine (±)-10a:

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 257 μL, 1.72 mmol, 15.0 equiv) was added via syringe to a solution of spirocyclic indoline **3a** (41.3 mg, 115 μmol, 1 equiv) in acetonitrile (4.0 mL) at 23 °C. After 5 min, the reaction vessel was placed into a microwave reactor and heated to 125 °C. After 10 min, the reaction vessel was removed from the microwave reactor and allowed to cool to 23 °C and concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 10% ethyl acetate in hexanes) to afford spirocyclic enimine (±)-**10a** (18.3 mg, 70.6%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and ROESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.09 (app-dt, J = 1.3, 7.7, 1H, C_7**H**), 6.86 (dd, J = 1.3, 7.3, 1H, C_5**H**), 6.63 (app-dt, J = 0.9, 7.4, 1H, C_6**H**), 6.48 (d, J = 7.8, 1H, C_8**H**), 5.30 (s, 1H, C_{15}**H**$_E$), 5.19 (s, 1H, C_{15}**H**$_Z$), 4.05 (ddd, J = 4.5, 8.4, 16.6, 1H, C_{11}**H**$_a$), 3.86 (app-dt, J = 16.6, 7.4, 1H, C_{11}**H**$_b$), 3.61 (d, J = 9.4, 1H, C_2**H**$_a$), 3.35 (d, J = 9.4, 1H, C_2**H**$_b$), 2.80 (s, 3H, C_{17}**H**$_3$), 2.32 (ddd, J = 4.5, 7.8, 12.9, 1H, C_{10}**H**$_a$), 2.18 (ddd, J = 7.2, 8.4, 12.9, 1H, C_{10}**H**$_b$), 1.97 (s, 3H, C_{16}**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 176.0 (**C**$_{13}$), 151.8 (**C**$_9$), 137.7 (**C**$_{14}$), 135.4 (**C**$_4$), 128.5 (**C**$_7$), 123.2 (**C**$_5$), 122.5 (**C**$_{15}$), 118.3 (**C**$_6$), 107.3 (**C**$_8$), 65.1 (**C**$_3$), 61.1 (**C**$_2$), 57.9 (**C**$_{11}$), 43.3 (**C**$_{10}$), 35.7 (**C**$_{17}$), 21.6 (**C**$_{16}$).
FTIR (neat) cm^{-1}:	2918 (s), 2849 (s), 1679 (m), 1605 (s), 1493 (s), 1463 (s), 1377 (m), 744 (m), 666 (s).
HRMS (DART):	calc'd for $C_{15}H_{19}N_2$ $[M+H]^+$: 227.1543, found: 227.1554.
TLC (30% EtOAc in hexanes), R_f:	0.38 (UV, CAM, $KMnO_4$).

Chapter III

A Concise and Versatile Double-Cyclization Strategy for the Highly Stereoselective Synthesis and Novel Arylative Dimerization of *Aspidosperma* Alkaloids

Introduction and Background

The monoterpene–indole alkaloids represent the largest family of alkaloid natural products, whose more than 2,000 members display a broad range of chemical diversity and potent biological activity.[1] The structural challenges presented by this family have long been a source of interest, resulting in the development of a variety of inventive synthetic strategies to access various family members. The biogenetically related natural alkaloids *N*-methylaspidospermidine (**1**), *N*-methylquebrachamine (**2**), and tabernaebovine (**3**) represent the *aspidosperma* subfamily of indole–monoterpene alkaloids (Figure 1).[2,3,4,5,6,7,8,9] The desmethyl

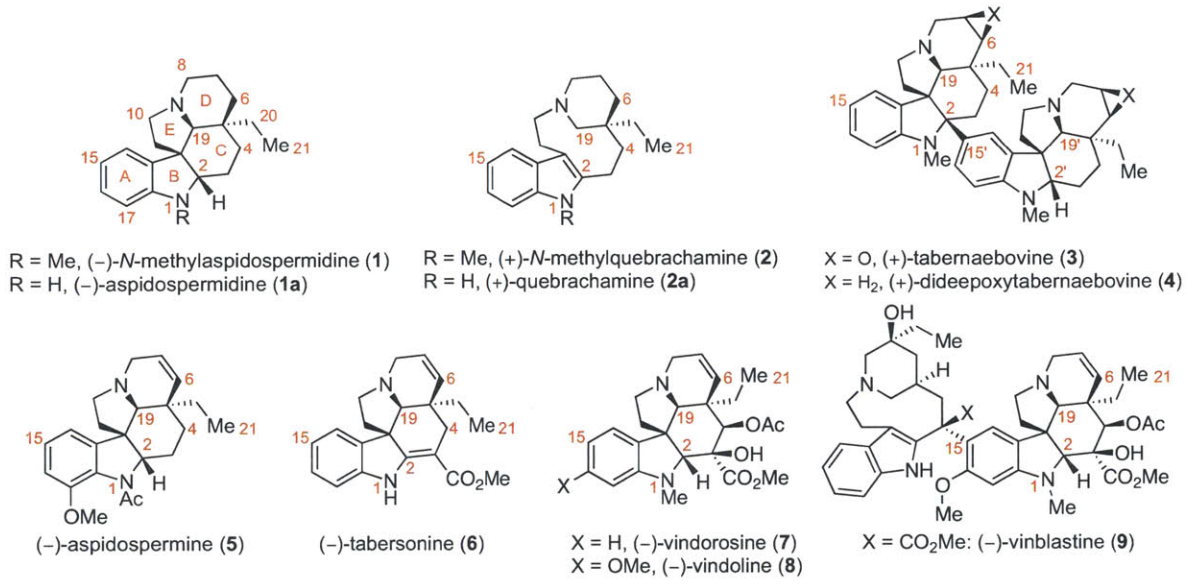
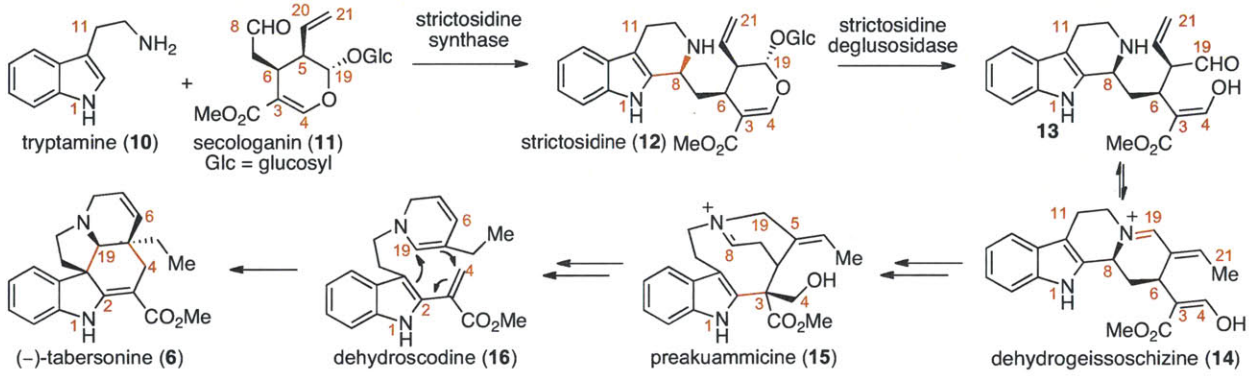


Figure 1. Representative *aspidosperma* alkaloids.

derivatives of **1** and **2**, aspidospermidine (**1a**) and quebrachamine (**2a**), are also natural products of the *aspidosperma* family. Aspidospermine (**5**) and tabersonine (**6**) represent further monomeric derivatives of **1**; tabersonine (**6**) is a key intermediate in the biosynthesis of the *aspidosperma* alkaloids (Scheme 1). Vindorosine (**7**) and vindoline (**8**) are skeletally functionalized derivatives of **1**, while dimeric alkaloid vinblastine (**9**), a potent oncolytic agent, is an dimeric natural product containing an *aspidosperma* alkaloid derived subunit. The dimeric alkaloid tabernaebovine (**3**), isolated from *Tabernaemontana bovina* in 1998,[2n] has a fascinating molecular constitution that exhibits a unique C2–C15' linkage between two pentacyclic *aspidosperma* skeletons. While elegant strategies for synthesis of other dimeric indole–monoterpene alkaloids have been reported,[9] no synthetic solution to the distinctive C2–C15' union present in **3** existed prior to our work. As an outgrowth of our laboratory's studies concerning electrophilic amide activation[10] and of our results discussed in chapter II, we were

inspired to develop a concise and convergent strategy for the enantioselective synthesis of alkaloids (–)-**1**, (+)-**2**, and dimeric (+)-dideepoxytabernaebovine (**4**).

The biosynthesis[1] of the *aspidosperma* alkaloids is known to begin from tryptamine (**10**) and geraniol derivative secologanin (**11**), and proceeds through the skeleton of the related *corynanthe* family of indole–monoterpene alkaloids followed by several structural rearrangements (Scheme 1). The first step in the biosynthetic route is the strictosidine synthase



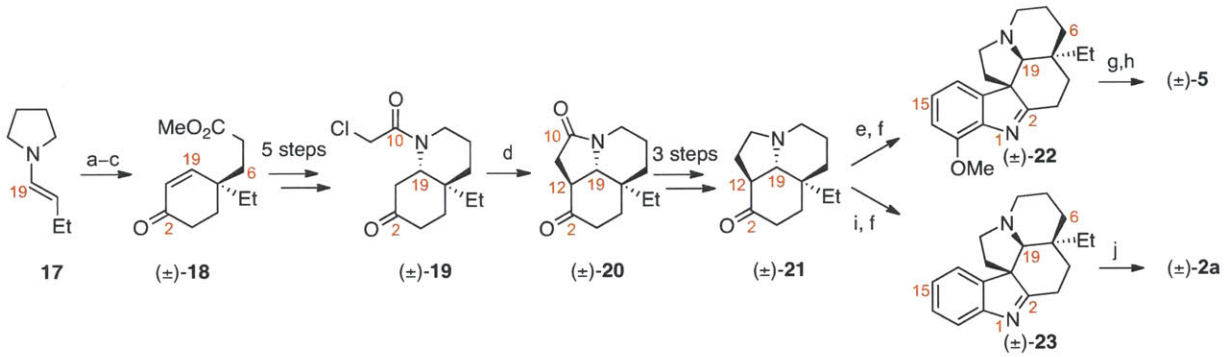
Scheme 1. Proposed biosynthesis of the *aspidosperma* alkaloids.

catalyzed Pictet–Spengler reaction between tryptamine (**10**) and secologanin (**11**), which affords strictosidine (**12**). Strictosidine deglucosidase acts on **12** to reveal an aldehyde intermediate **13**, which undergoes condensative N9–C19 double bond formation and isomerization of the C20–C21 olefin to give key intermediate dehydrogeissoschizine (**14**), an alkaloid of the *corynanthe* type. While the enzymes responsible for the remaining biosynthetic steps are not known, previous studies have allowed for a proposed sequence involving a retro-Pictet–Spengler reaction of **14** and subsequent C2–C3 bond formation to furnish preakuammicine (**15**), which undergoes a series of rearrangements to give dehydrosecodine (**16**). The final step is proposed to be an intramolecular Diels–Alder reaction to give tabersonine (**6**), which serves as a gateway into the biosynthesis of related *aspidosperma* alkaloids.

Review of Prior Total Syntheses of *Aspidosperma* Alkaloids

The first total synthesis of *aspidosperma* alkaloids related to **1** and **2** was the seminal collective syntheses of (±)-aspidospermine (**5**) and (±)-quebrachamine (**2a**) reported by Stork[6b] in 1963 (Scheme 2). The synthetic route exploits the potential for interconversion of the aspidospermidine- and quebrachamine-type skeletons, allowing for the collective syntheses of both targets through late-stage divergence. Michael addition of enamine **17** onto methyl acrylate and in situ enamine hydrolysis, followed by enamine formation and a subsequent Robinson

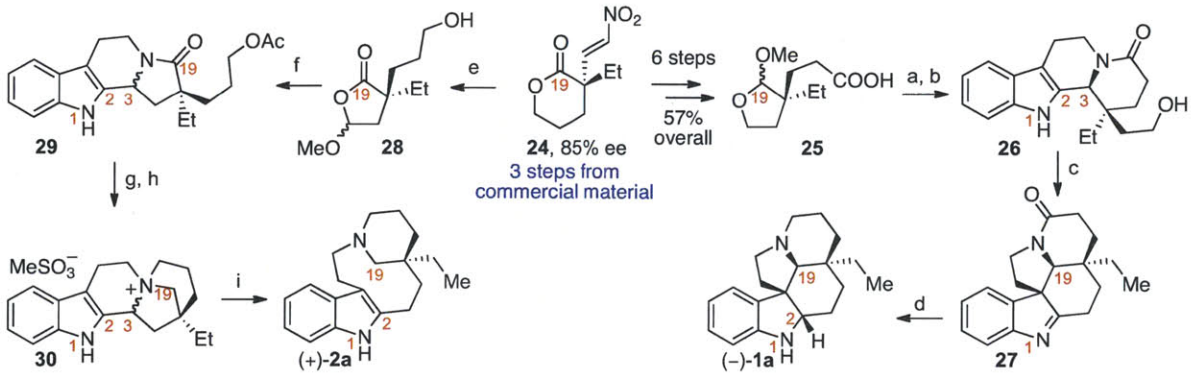
annulation with methyl vinyl ketone, afforded C-ring containing enone (±)-**18** in 32% yield over three steps. Enone (±)-**18** was converted to bicyclic chloroacetamide (±)-**19** in five steps. Treatment of (±)-**19** with potassium *tert*-butoxide in benzene effected smooth C11–C12 cyclization to afford tricycle (±)-**20**. Reduction of the C10-amide over 3 steps



Scheme 2. Stork's seminal syntheses of (±)-aspidospermine (**5**) and (±)-quebrachamine (**2a**): a) methyl acrylate, 67%. b) pyrrolidine. c) methyl vinyl ketone; AcOH, 48% (2 steps). d) KO^{t}Bu, PhH. e) 2-methoxyphenylhydrazine. f) AcOH, heat. g) $LiAlH_4$. h) Ac_2O. i) phenylhydrazine. j) KBH_4.

afforded key tricyclic ketone (±)-**21**. A two-step Fischer indoleninization sequence between (±)-**21** and 2-methoxyphenylhydrazine afforded pentacycle (±)-**22** with inversion of the C19-stereocenter to the more stable natural configuration via a reversible C12–C19 retro-Mannich reaction; reduction of (±)-**22** with lithium aluminum hydride and subsequent acetylation of N1 afforded (±)-aspidospermine (**5**). Alternatively, Fischer indoleninization of (±)-**21** with phenyl hydrazine afforded pentacycle (±)-**23**, which, upon treament with potassium borohydride, underwent C12–C19 bond cleavage and reduction of a putative C19-iminium ion to afford (±)-quebrachamine (**2a**). The judicious exploitation of late-stage divergence to form both natural products from a common intermediate highlights the strategic sophistication of Stork's synthetic route.

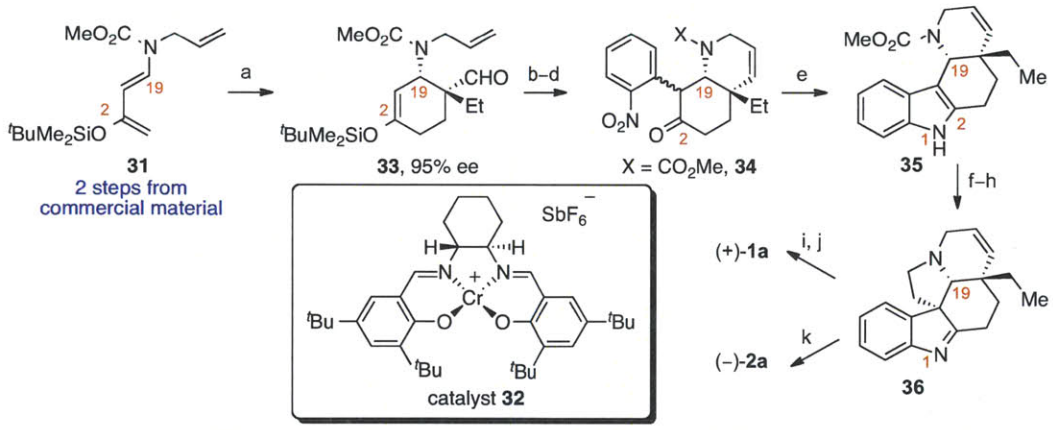
Following Stork's seminal work, over two decades would pass before the first enantioselective total synthesis of **1a**, the *aspidosperma* alkaloid most directly related to (–)-**1**, was achieved by Fuji in 1987 (Scheme 3).[5a] Enantioenriched chiral lactone **24**[11] was converted in six steps to key acetal **25** in 57% overall yield. An acetic acid mediated Picter–Spengler reaction of **25** with tryptamine (**10**) at elevated temperature and subsequent basic hydrolysis afforded *corynanthe* related tetracycle **26** in 42% overall yield. Trifluoromethanesulfonic acid mediated rearrangement of **26** afforded *aspidosperma* type pentacycle **27** in 60% yield, and subsequent reduction with lithium aluminum hydride afforded (–)-aspidospermidine (**1a**) in 81%



Scheme 3. Enantioselective total syntheses of (–)-**1a** and (+)-**2a** by Fuji: a) tryptamine (**10**), AcOH, Δ. b) NaOH, MeOH, 42% (2 steps). c) TfOH, 60%. d) $LiAlH_4$, Et_2O, 81%. e) $TiCl_3$, MeOH, pH 5. f) tryptamine (**10**), AcOH, Δ, 84% (2 steps). g) $LiAlH_4$, THF. h) MsCl, Et_3N, $CHCl_3$. i) Na, NH_3, EtOH, 53% (3 steps).

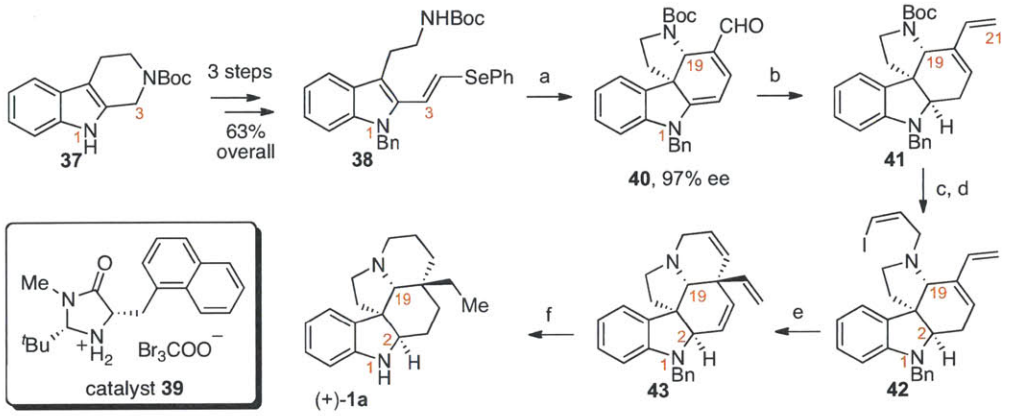
yield, completing the first enantioselective total synthesis of this alkaloid. Additionally, reduction of nitroolefin **24** with titanium trichloride afforded acetal **28**, which underwent a Pictet–Spengler reaction with tryptamine (**10**) to afford tetracycle **29** as a diastereomeric mixture in 84% yield. Conversion of **29** to quaternary ammonium salt **30** over two steps, followed by reductive cleavage of the C3–N9 bond under Birch conditions, afforded (+)-**2a** in 53% yield from **29**, thus completing the total synthesis. While Fuji's collective approach to (–)-**1a** and (+)-**2a** does not benefit from the strategic late-stage divergence employed by Stork, the completion of the first enantioselective synthesis of (–)-**1a** in biomimetic fashion was a substantial step forward in *aspidosperma* alkaloid synthesis.

Two more recent examples of *aspidosperma* alkaloid syntheses demonstrate efficient



Scheme 4. Rawal's enantioselective total syntheses of (+)-**1a** and (–)-**2a**: a) ethacrolein, catalyst **32** (5.0 mol %), 4Å-MS, CH_2Cl_2, 84%, 95% ee. b) Ph_3PCH_3I, ^{n}BuLi, THF. c) Grubbs' 1st generation catalyst (7.5 mol %), CH_2Cl_2, Δ. d) (2-nitrophenyl)(phenyl)iodonium fluoride, THF, DMSO, 57–62% (3 steps). e) $TiCl_3$, NH_4OAc, acetone, H_2O, 90%. f) Me_3SiI, CH_2Cl_2, Δ. g) $Br(CH_2)_2OH$, Na_2CO_3, EtOH, Δ. h) MsCl, NEt_3; KO^{t}Bu, 79% (3 steps). i) $NaBH_4$, EtOH. j) H_2, PtO_2, EtOH, 73% (2 steps). k) H_2, PtO_2, AcOH, 69%.

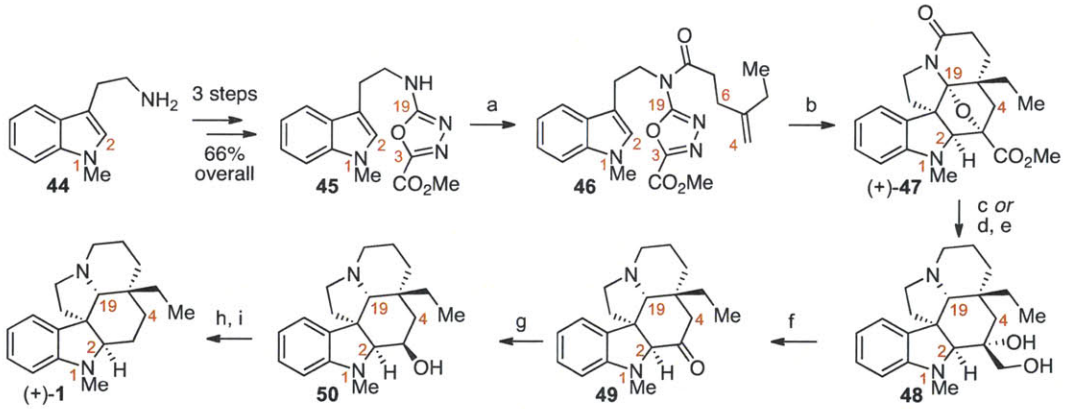
approaches for asymmetric synthesis. Rawal's[5f] 2002 collective syntheses of (+)-**1a** and (–)-**2a** (Scheme 4) commenced with a catalytic enantioselective Diels–Alder reaction between super-diene **31** and ethacrolein promoted by Jacobsen's[12] chiral chromium salen catalyst **32**, affording monocyclic compound **33** in 84% yield and 95% ee. Elaboration of **33** to nitroarene **34** through Wittig olefination, ring-closing olefin metathesis and arylation, followed by reductive



Scheme 5. MacMillan's enantioselective total synthesis of (+)-**1a**: a) propynal, catalyst **41** (20 mol %), PhMe, 83%, 97% ee. b) Ph_3PCH_3I, ^nBuLi, THF; $NaBH_3CN$, AcOH. c) TFA, CH_2Cl_2. d) (*Z*)-3-bromo-1-iodopropene, K_2CO_3, DMF, 73% (3 steps). e) $(Ph_3P)_4Pd$, Et_3N, PhMe, 80 °C, 65%. f) H_2 (200 psi), $Pd(OH)_2$, MeOH, EtOAc, 98%.

indolization of **34**, afforded tetracycle **35** in 51–56% overall yield. The C10–C11 ethylene group was installed in 79% yield over 3 steps in a sequence reminiscent of Stork's strategy to afford indolenine **36**. Reduction of indolenine **36** with sodium borohydride and subsequent catalytic hydrogenation afforded (–)-**1a** in 73% yield, completing a 12-step total synthesis. Catalytic hydrogenation of **36** in acetic acid afforded (+)-**2a** in 69% yield via a putative C19-iminium ion. Additionally, Rawal was able to access (+)-tabersonine (**6**) and other *aspidosperma* alkaloids via his route, highlighting the utility of late-stage synthetic divergence in a modern, asymmetric setting. MacMillan's[51] 2009 synthesis of (+)-**1a** (Scheme 5) centered on a key organocatalytic enantioselective Diels–Alder reaction/Michael addition cascade between 2-vinylindole **38** and propynal promoted by catalyst **39** afforded tetracycle **40** in 83% yield and 97% ee. Elaboration of **40** to vinyl iodide **42** and subsequent Heck cyclization afforded pentacyclic triene **43** in 47% yield over four steps. Exhaustive catalytic hydrogenation and hydrogenolysis afforded (+)-**1a** in 98% yield, completing a nine-step synthesis from tricycle **37**. Their strategy was also applied to the synthesis of related *kopsia* and *strychnos* alkaloids through a similar key Diels–Alder reaction/Michael addition cascade.

Despite numerous previous total syntheses of *aspidosperma* alkaloids, prior to our work, no total synthesis of *N*-methquebrachamine (**2**) had been reported, and no enantioselective synthesis of *N*-methylaspidospermidine (**1**) had been reported.[13] The only synthesis of **1** was reported by Boger[3] in 2006 in the context of his groups' total synthesis of (+)-vindoline (**8**). Oxadiazole **45**, synthesized in three steps from *N*-methyltryptamine (**44**), was acylated with 4-methylenehexanoic acid in the presence of EDC•HCl to afford achiral intermediate **46** in 87% yield. Heating of **46** in refluxing 1,2-dichlorobenzene effected a unique [4+2]/[3+2] cycloaddition cascade to secure hexacycle (±)-**47** in 74% yield; separation of the enantiomers by chiral HPLC afforded (+)-**47**, which was reduced in a single step or through a higher yielding two step sequence to pentacyclic diol **48**. Oxidative diol cleavage with sodium periodate, ketone reduction with sodium borohydride, and a two step Barton-McCombie deoxygenation afforded (+)-**1** in 68% yield over four steps, completing a nine or ten step synthesis from *N*-methyltryptamine (**44**).

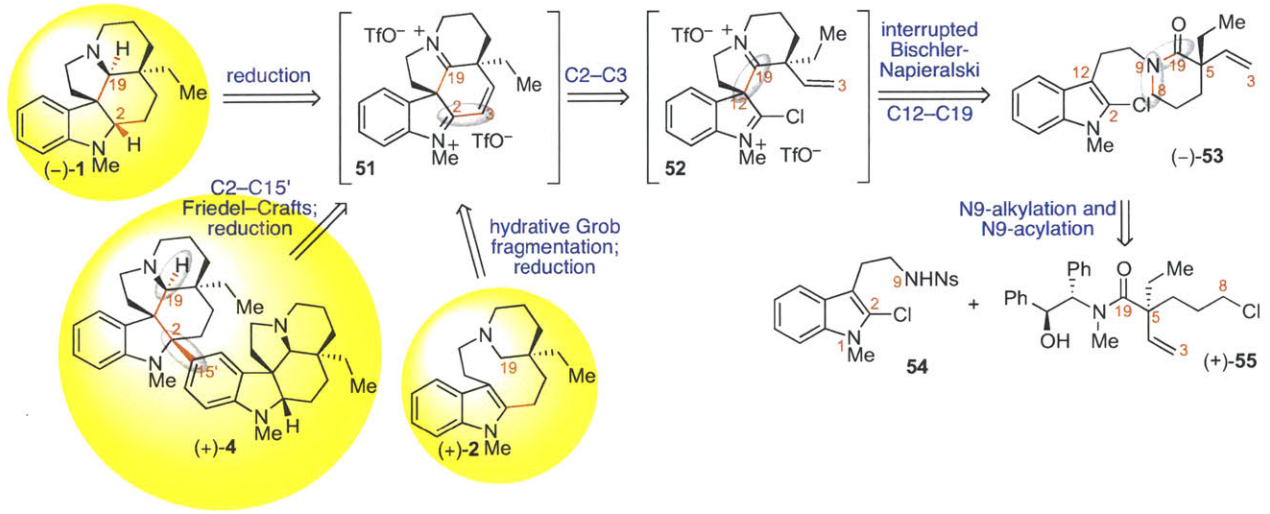


Scheme 6. Boger's total synthesis of (+)-*N*-methylaspidospermidine (**1**): a) 4-methylenehexanoic acid, 4-DMAP, EDC•HCl, CH_2Cl_2, 87%. b) 1,2-dichlorobenzene, 180 °C, 74% of (±)-**47**; 37% of (+)-**47** after chiral HPLC separation of enantiomers. c) $LiAlH_4$, 31%. d) $NaBH_3CN$, HCl, MeOH, 96%. e) $LiAlH_4$, 99%. f) $NaIO_4$, 93%. g) $NaBH_4$, 99%. h) LiHMDS, CS_2; MeI, 77%. i) AIBN, $^nBu_3SnH$, 96%.

In chapter II, we discussed the development of a methodology for the interruption of the Bischler–Napieralski reaction by intra- and intermolecular trapping of spirocyclic indoleninium ions. In this chapter, we discuss the development of a double-cyclization cascade based on our interrupted Bischler–Napieralski reaction methodology and its application to the previously unprecedented C2–C15' union of *aspidosperma* alkaloids in the enantioselective total synthesis of dimeric decacyclic product (+)-**4** in addition to enantioselective total syntheses of (–)-**1** and (+)-**2**.

Results and Discussion

Inspired by precedence in biogenetically relevant dimerizations of other monoterpene–indole alkaloids,[1,9] we posited the biogenesis of (+)-tabernaebovine (**3**) to involve late-stage

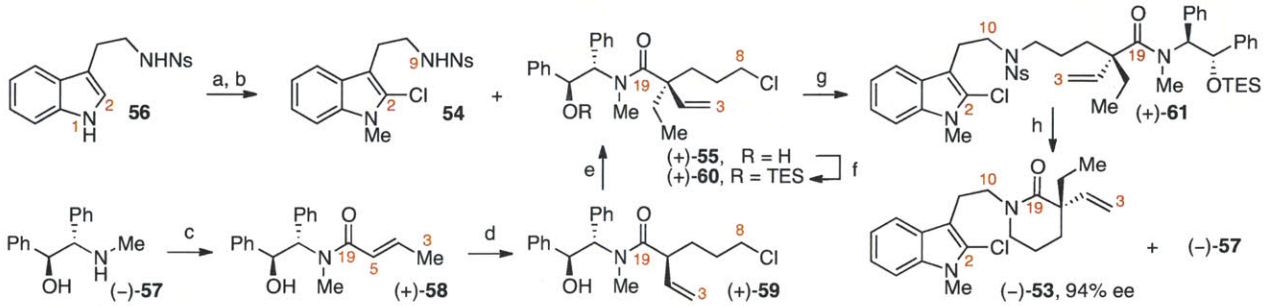


Scheme 7. Retrosynthetic analysis of the *aspidosperma* alkaloids.

union of two *aspidosperma* fragments at the C2–C15' linkage. This retrobiosynthetic analysis[14] prompted the development of a regio- and diastereoselective C2-arylation of pentacycle **51** (Scheme 7) en route to decacycle (+)-**4**. Based on our results discussed in chapter II, we envisioned that a highly electrophilic diiminium ion **51** would allow for stereo- and regioselective transformations that provide divergent access to dideepoxytabernaebovine (+)-**4** as well as monomeric *aspidosperma* alkaloids (–)-*N*-methylaspidospermidine (**1**) and (+)-*N*-methylquebrachamine (**2**) (Scheme 7). We expected reduction of the diiminium ion **51** would afford (–)-**1**, whereas hydrative Grob fragmentation followed by reduction would afford (+)-**2**. We hypothesized that the diiminium ion **51** could be generated from lactam (–)-**53** via a novel, stereoselective double-cyclization cascade. We envisioned a transformation involving spirocyclization of an electrophilically activated lactam intermediate onto the 2-chloroindole and subsequent interruption of the Bischler–Napieralski reaction by cyclization of an unactivated C3–C4 vinyl group onto the C2-position of the putative 2-chlorospiroindoleninium intermediate **52**, a bond formation uniquely favored by the relative stereochemistry in **52**. The overall stereochemical outcome of the process would be secured from the resident stereochemistry of the C5-quaternary center. The requisite lactam (–)-**53** could be simplified via *N*-acylation and *N*-alkylation transforms to 2-chlorotryptamine sulfonamide **54** and α-quaternary amide (+)-**55**, the

latter of which could be synthesized diastereoselectively via alkylative quaternization of an amide enolate.

The concise enantioselective synthesis of the key tryptamine–lactam (–)-**53** is illustrated in Scheme 8. Regioselective methylation of sulfonamide **56**[15] via its disodium dianion provided



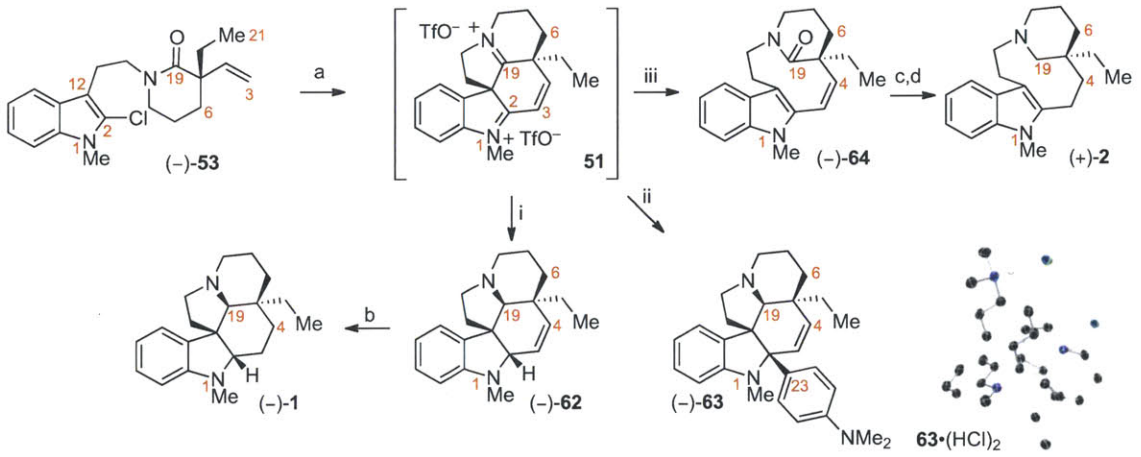
Scheme 8. Enantioselective synthesis of lactam (–)-**53**: a) NaH, DMF, 23 °C; MeI, 0 → 23 °C, 91%. b) *N*-chlorosuccinimide, MeCN, 23 °C, 76%. c) *E*-crotonyl chloride, Et_3N, THF, –30 → 23 °C, 97%. d) lithium 2,2,6,6-tetramethylpiperidide, LiCl, THF, 0 → –78 °C; 3-chloro-1-iodopropane, –78 → 0 °C, 83%. e) lithium diisopropylamide, LiCl, THF, –78 → 0 °C; *N*,*N*'-dimethylpropylene urea, –40 °C; EtI, –50 °C, 72%, >29:1 dr. f) triethylsilyl triflate, 2,6-lutidine, CH_2Cl_2, 23 °C, 100%. g) (+)-**60**, **54**, KH, $^nBu_4NI$, DMF, 100 °C, 86%. h) PhSH, K_2CO_3, DMSO, 23 °C; KOEt, $Et_3N{\bullet}3HF$, EtOH, 85 °C, 95%, 94% ee, 99% recovery of (–)-**57**. DMF = *N*,*N*'-dimethylformamide, Ns = 2-nitrobenzenesulfonyl, TES = triethylsilyl.

the requisite N1-methylated derivative in 91% yield.[16] Subsequent treatment with *N*-chlorosuccinimide afforded C2-chlorotryptamine **54** in 76% yield. The C5-quaternary stereogenic center that we envisioned would enable stereocontrolled introduction of all stereocenters found in alkaloids (–)-**1**, (+)-**2**, and (+)-**4** was secured by successive diastereoselective α-alkylations of crotonamide (+)-**58**. Acylation of (–)-pseudoephenamine (**57**)[17] with *E*-crotonyl chloride gave the enamide (+)-**58** in 97% yield. Chemoselective γ–deprotonation of enamide (+)-**58** with lithium 2,2,6,6-tetramethylpiperidide in the presence of lithium chloride,[18] followed by electrophilic trapping of the resulting enolate with 3-chloro-1-iodopropane afforded α-vinyl amide (+)-**59** as a single diastereomer in 83% yield. Inspired by Myers' alkylative quaternizations[19] of pseudoephedrine amides and precedent for α-alkylation of α-methyl crotonimides,[20] we reasoned that deprotonation of α-vinyl amide (+)-**59** would afford the corresponding enolate with the sterically less demanding vinyl group *cis* to the amide nitrogen. Alkylation from the less sterically shielded face of the enolate[17,18] would secure the desired C5-quaternary stereocenter. Gratifyingly, deprotonation of amide (+)-**59** with lithium diisopropylamide in the presence of lithium chloride, followed by electrophilic trapping with

iodoethane at –50 °C in the presence of *N,N'*-dimethylpropylene urea provided the α-quaternary amide (+)-**55** in 72% yield with an excellent level of stereoselection (>29:1 dr).[16,21,22]

Attempts to hydrolyze amide (+)-**55** to the corresponding carboxylic acid were unsatisfactory due to competitive lactone formation under either basic or acidic conditions. Initial efforts to couple α-quaternary amide (+)-**55** with sulfonamide **54** via nucleophilic displacement of the C8-chloride proved inefficient; fast N→O acyl transfer of amide (+)-**55** led to intramolecular *N*-alkylation. This propensity of amide (+)-**55**, however, could be used to our advantage for the synthesis of lactam (–)-**53** and recovery of the chiral auxiliary. Sequential treatment of sulfonamide **54** with potassium hydride and *O*-silyl derivative (+)-**60** in DMF in the presence of tetrabutylammonium iodide followed by heating to 100 °C afforded *N*-alkylated sulfonamide (+)-**61** in 86% yield. Desulfonylation[23] of (+)-**61** to the corresponding secondary amine and in situ desilylation and heating in ethanol afforded the key lactam (–)-**53** in 95% yield and 94% ee.[16] This single-step transformation, which occurs via a desilylation/N→O acyl transfer/lactam cyclization cascade, also leads to efficient recovery of the chiral auxiliary (–)-**57** in 99% yield (Scheme 8).[24]

We next focused on the development of a unified strategy to access a versatile intermediate en route to alkaloids (–)-**1**, (+)-**2**, and (+)-**4**. Electrophilic activation of lactam (–)-**53** with trifluoromethanesulfonic anhydride[10,25] initiated a double-cyclization cascade leading to the versatile diiminium ion **51** (Scheme 9). Guided by our methodology for the interrupted



Scheme 9. Synthesis of *aspidosperma* alkaloids by interception of diiminium ion **51**: a) Tf_2O, 3-cyanopyridine, MeCN, 85 °C. i) $NaBH_3CN$, THF, 50%. ii) 4-(Me_2N)-C_6H_4MgBr, –40 °C; Red-Al, 40%. iii) trifluoroacetic acid, sodium trifluoroacetate, H_2O, 70 °C, 57%. b) H_2, Pt/C, THF, 100%. c) H_2, Pt/C, THF. d) $LiAlH_4$, THF, 65 °C, 82% (two steps). Tf_2O = trifluoromethanesulfonic anhydride.

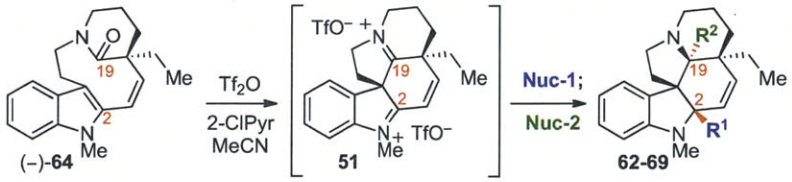
Bischler–Napieralski reaction discussed in chapter II and by our prior methodologies for azaheterocycle syntheses employing electrophilic amide activation,[10] we recognized the optimal conditions for conversion of lactam (–)-**53** to diiminium ion **51** involve the use of mildly basic additive 3-cyanopyridine in acetonitrile followed by warming. This transformation relies on C19-electrophilic activation of lactam (–)-**53** and rapid C12-nucleophilic spirocyclization affording the putative 2-chlorospiroindoleninium intermediate **52** (Scheme 7) that undergoes C2-addition by the vinyl group and loss of hydrogen chloride. The ability to employ an unactivated C3–C4 olefin as the nucleophile in the second cyclization is likely due to the enhanced C2-electrophilicity of intermediate **52** imparted by the chlorine atom,[26] together with a high resilience of **52** toward an undesired Wagner–Meerwein rearrangement.[27,28] Consistent with the sensitivity of this double-cyclization step, the use of less basic 2-chloropyridine or more nucleophilic pyridine as the additive gave the desired diiminium ion **51** with reduced efficiency as evidenced by the presence of singly cyclized side-products, recovered starting material, and significant decomposition.[29] The synthetic versatility of diiminium ion **51** is illustrated by its conversion to alkaloids (–)-**1**, (+)-**2**, and (–)-**63** (Scheme 9). In situ reduction of intermediate **51** with sodium cyanoborohydride furnished (–)-*N*-methyldehydroaspidospermidine (**62**) in 50% yield as a single diastereomer. Catalytic hydrogenation of *cis*-alkene (–)-**62** with a carbon-supported platinum catalyst afforded (–)-*N*-methylaspidospermidine (**1**) {$[\alpha]^{24}_{D}$ = –23 (*c* 0.17, $CHCl_3$); lit. $[\alpha]^{25}_{D}$ = –23 (*c* 1.1, $CHCl_3$);[3] for (+)-**1**, $[\alpha]^{20}_{D}$ = +24 (*c* 1.25, $CHCl_3$)[21]} in quantitative yield (Scheme 9). All spectroscopic data for our synthetic (–)-**1** was consistent with those reported in the literature.[3] The concise enantioselective synthesis of lactam (–)-**53** combined with the double-cyclization strategy described above enables rapid access to useful intermediates with highly reactive C2- and C19-iminium functions.

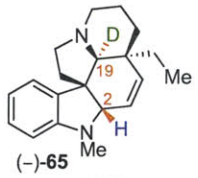
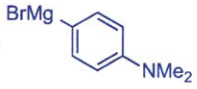
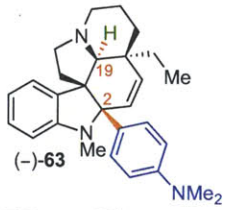
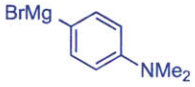
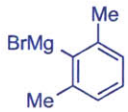
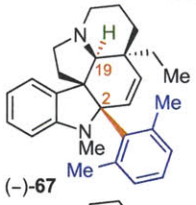
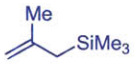
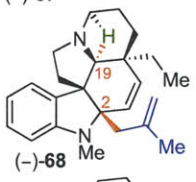
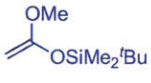
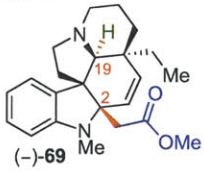
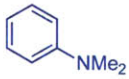
The unique reactivity of diiminium ion **51** is demonstrated by its utility in a C2-arylation reminiscent of the C2–C15' bond adjoining the two halves of the complex natural alkaloid (+)-tabernaebovine (**3**, Figure 1). We reasoned that the vicinal C19-iminium ion of intermediate **51** would enhance the electrophilicity of the C2-iminium ion both inductively and by reducing the steric environment through the flattening of the DE–ring system. Gratifyingly, treatment of in situ generated diiminium ion **51** with 4-(*N*,*N*-dimethylamino)phenylmagnesium bromide at –40 °C for 30 seconds followed by addition of Red-Al afforded hexacyclic C2-aniline adduct (–)-**63** in 40% yield as a single diastereomer (Scheme 9).[16] The steric congestion about C2 in adduct

(–)-**63** is evidenced by the ~20 kcal/mol barrier to rotation[16] about the C2–C23 σ-bond as measured through NMR coalescence temperature experiments. Also, heating an acidic aqueous solution of diiminium ion **51** to 70 °C effected Grob fragmentation to give the tetracyclic lactam (–)-**64**[30] in 57% yield in a single step from lactam (–)-**53**. Platinum catalyzed hydrogenation[31] of the C3–C4 olefin and subsequent C19-carbonyl reduction with lithium aluminium hydride at 60 °C provided (+)-*N*-methylquebrachamine (**2**) {$[\alpha]^{24}_{D}$ = +102 (*c* 0.22, $CHCl_3$); lit. $[\alpha]^{24}_{D}$ = +110 ($CHCl_3$)[2g]} in 82% yield over two steps.[16]

With particular interest in evaluating this chemistry as a general entry to the synthesis of complex *aspidosperma* alkaloids, we investigated a series of C2-addition reactions of relevance in synthetic planning. Importantly, lactam (–)-**64**, requiring mild activation conditions, proved to be an excellent precursor to diiminium ion **51**. Treatment of lactam (–)-**64** with Tf_2O–2-chloropyridine reagent combination[10] in acetonitrile (23 °C, 10 min) resulted in rapid stereo- and regioselective electrophilic transannular spirocyclization to **51** en route to various C2-adducts **62**–**69** (Table 1). Introduction of sodium cyanoborohydride afforded (–)-*N*-methyldehydroaspidospermidine (**62**) in 95% yield (Table 1, entry 1) consistent with efficient generation of the same electrophilic intermediate **51** accessed from lactam (–)-**53** (Scheme 9). The greater reactivity at C2 compared to C19 of diiminium ion **51** can be used for regioselective addition of the first nucleophile at the former.[32] For example, treatment of **51** with tributylstannane, followed by introduction of sodium borodeuteride, afforded C19-deuterated pentacycle (–)-**65** in 94% yield with no deuterium enrichment at C2 and 93% deuterium incorporation at C19 (Table 1, entry 2). Notably, the C2-arylated product (–)-**63** could be prepared efficiently from lactam (–)-**64** using 4-(*N*,*N*-dimethylamino)phenylmagnesium bromide as the first nucleophile followed by in situ C19 reduction (Table 1, entry 3, 76% yield). Alternatively, hexacyclic iminium triflate (–)-**66** could be isolated then reduced with sodium cyanoborohydride to (–)-**63** in a subsequent step (Table 1, entries 4 and 9). That this C19-reduction of pentacycle (–)-**66** occurs in the absence of an acidic additive is consistent with its spectroscopic data revealing its iminium ion structure.[16] It is notable that the ~12 kcal/mol barrier to rotation[16] about the C2–C23 σ-bond in iminium ion (–)-**66** is significantly lower than in the reduced product (–)-**63** (vide supra), consistent with the aforementioned structural flattening effect of the C19-iminium ion. The high electrophilicity of diiminium ion **51** allows

Table 1. Regio- and stereoselective transformations of lactam (–)-**64**.

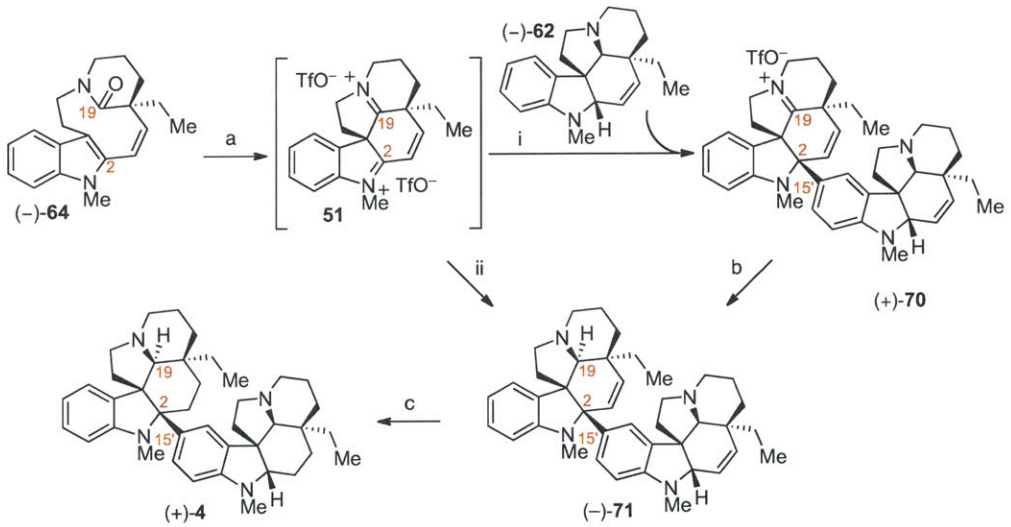


Entry	Nuc-1[a]	Nuc-2	Product	Yield[b]
1	$NaBH_3CN$	-	(–)-**62**	95%
2	$^nBu_3SnH$	$NaBD_4$	 (–)-**65**	94%
3		Red-Al	 (–)-**63**	76%
4		-	 (–)-**66**	76%
5		Red-Al	 (–)-**67**	59%
6		$NaHB(OMe)_3$	 (–)-**68**	92%
7		$NaHB(OMe)_3$	 (–)-**69**	79%
8		$NaHB(OHMe)_3$	(–)-**63**	74%
9		-	(–)-**66**	73%

[a]Grignard reagents at –40 °C. Other nucleophiles at 23 °C. [b]Isolated yield of single diastereomer. [c]93% Deuterium incorporation at C19. 2-ClPyr = 2-chloropyridine.

for C–C bond formation at C2 with highly hindered and mildly nucleophilic species. Treatment of intermediate **51** with 2,6-dimethylphenylmagnesium bromide followed by hydride reduction afforded the highly congested xylene adduct (–)-**67** in 59% yield (Table 1, entry 5). The high degree of steric congestion about C2 in (–)-**67** is evidenced by the complete lack of observable C2–C23 σ-bond rotation on the ^{1}H NMR timescale, even at 140 °C. Reaction of **51** with 2-methallyltrimethylsilane or 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene and subsequent hydride reduction afforded methallyl adduct (–)-**68** (Table 1, entry 6, 92% yield) or methyl acetate adduct (–)-**69** (Table 1, entry 7, 79% yield), respectively. The utility of this strategy to access C2-arylated derivatives is highlighted by a *Friedel–Crafts reaction* of **51** with *N*,*N*-dimethylaniline (23 °C, 90 min) and either in situ C19-reduction to provide C2-arylated amine (–)-**63** or isolation of the pentacyclic C19-iminium salt (–)-**66** (Table 1, entries 8 and 9, 74% and 73% yield, respectively).

With insight gained from these studies, *in particular entries 8 and 9 of Table 1*, we sought to implement this chemistry in effecting the dimerization of two pentacyclic *aspidosperma* type molecular frameworks at the challenging C2–C15' linkage (Scheme 10). In the event, electrophilic activation of tetracyclic lactam (–)-**64** followed by treatment with equimolar (–)-*N*-methyldehydroaspidospermidine (**62**) and heating to 85 °C afforded the decacyclic iminium triflate (+)-**70** in 80% yield. Subsequent C19-reduction of (+)-**70** gave (–)-didehydrodideepoxytabernaebovine (**71**), which upon hydrogenation provided (+)-



Scheme 10. Synthesis of (+)-dideepoxytabernaebovine (**4**): a) Tf_2O, 2-ClPyr, MeCN, 23 °C. i) (–)-**62** (1.0 equiv), 85 °C, 80%. ii) (–)-**62**, 85 °C; $NaHB(OMe)_3$, THF, 73%. b) Red-Al, THF, 0 °C, 73%. c) H_2, Pt/C, THF, 84%.

dideepoxytabernaebovine (**4**) in 64% yield over two steps. Alternatively, in situ C19-reduction of dimeric iminium ion (+)-**70**, formed through the union of lactam (–)-**64** with (–)-*N*-methyldehydroaspidospermidine (**62**) as described above, with sodium trimethoxyborohydride directly afforded product (–)-**71** from (–)-**64** in 73% yield. Apart from increasing the electrophilicity of the vicinal C2-iminium ion, the C19-iminium ion may be responsible for reducing the nucleophilicity of the dimeric intermediate (+)-**70**, as no oligomerized products could be observed even when only one equivalent of (–)-**62** was employed as nucleophile.

Conclusion

We have developed a concise synthetic strategy to access the *aspidosperma* type molecular framework employing a double-cyclization cascade that sets up to three contiguous stereogenic centers and forms up to three carbon–carbon bonds with complete regio- and stereochemical control in a single step. The use of the chiral auxiliary (–)-**57**[17] was critical in enabling our concise and enantioselective synthesis of the key intermediate (–)-**63**. The ability to use an unactivated olefin as a pendant nucleophile minimizes the need for functional group removal and allows for concise and convergent access to complex *aspidosperma* alkaloids. We have shown putative diiminium ion **51** to be a highly reactive and versatile intermediate, allowing the rapid enantioselective total syntheses of (–)-*N*-methylaspidospermidine (**1**) and (+)-*N*-methylquebrachamine (**2**) in 8 and 9 steps, respectively, from *E*-crotonyl chloride and (–)-pseudoephenamine (**57**), as well as previously unprecedented C–C bond formations onto the highly congested C2-position of the *aspidosperma* skeleton. The power of this synthetic strategy has been demonstrated in the first example of a C2–C15' dimerization of two *aspidosperma* type systems, a complex assembly drawing on biogenetic considerations of (+)-**3**, in the synthesis of (+)-dideepoxytabernaebovine (**4**).[33]

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Experimental Section

General Procedures. All reactions were performed in oven-dried or flame-dried round bottomed flasks, modified Schlenk (Kjeldahl shape) flasks or glass pressure vessels. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel gas-tight syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was performed as described by Still et al. using silica gel (60 Å pore size, 32–63 μm, standard grade) or non-activated alumina (80–325 mesh, chromatographic grade).[1] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel or neutral alumina impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to an ethanolic solution of phosphomolybdic acid (PMA), an acidic solution of *p*-anisaldehyde (anis), an aqueous solution of ceric ammonium molybdate (CAM), an aqueous solution of potassium permanganate ($KMnO_4$), or an ethanolic solution of ninhydrin followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C, then at ~1 Torr (vacuum pump) unless otherwise indicated.

Materials. Commercial reagents and solvents were used as received with the following exceptions: Dichloromethane, diethyl ether, tetrahydrofuran, acetonitrile, toluene, and triethylamine were purchased from J.T. Baker (Cycletainer™) and were purified by the method of Grubbs et al. under positive argon pressure.[2] 2-Chloropyridine, *N,N*-diisopropylamine and *N,N'*-dimethylpropylene urea were distilled from calcium hydride and stored sealed under argon atmospheres. Lithium chloride was dried by the method of Myers et al.[3] and stored in a chemical glovebox. The molarity of *n*-butyllithium solutions was determined by titration against diphenylacetic acid[4] (average of three titrations). Trifluoromethanesulfonic anhydride was purchased from Oakwood Products, Inc.; all other solvents and chemicals were purchased from Sigma–Aldrich.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded with Varian inverse probe INOVA-500 and Varian INOVA-500 spectrometers, are reported in parts per million on the δ scale, and are referenced from the residual protium in the NMR solvent ($CDCl_3$: δ 7.24 ($CHCl_3$), benzene-d_6: δ 7.16 (benzene-d_5), CD_3CN: δ 1.94 (CD_2HCN), toluene-d_8: δ 2.09 ($C_6D_5CD_2H$), DMSO-d_6: δ 2.50 (DMSO-d_5)). Data are reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constant(s) in Hertz, integration, assignment]. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded with a Varian INOVA-500 spectrometer, are reported in parts per million on the δ scale, and are referenced from the carbon resonances of the solvent ($CDCl_3$: δ 77.23, benzene-d_6: δ 128.39, CD_3CN: δ 1.39, toluene-d_8: δ 20.4, DMSO-d_6: δ 39.51). Data are reported as follows: chemical shift (assignment). Fluorine-19 nuclear magnetic resonance (^{19}F NMR) spectra were recorded with a Varian Mercury 300 spectrometer, are reported in parts per million on the δ scale, and are referenced from the fluorine resonance of neat trichlorofluoromethane ($CFCl_3$: δ 0). Data are reported as follows: chemical shift (assignment). Infrared data (IR) were obtained with a Perkin-Elmer 2000 FTIR, and are reported as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong,

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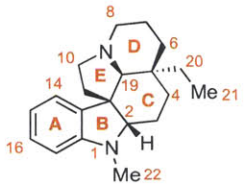
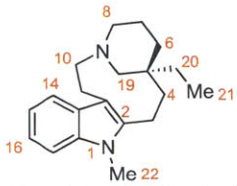
m = medium, w = weak, br = broad). Optical rotations were measured on a Jasco-1010 polarimeter. We are grateful to Dr. Li Li for obtaining the mass spectrometric data at the Department of Chemistry's Instrumentation Facility, Massachusetts Institute of Technology. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEXIV 4.7 Tesla FTICR-MS using a direct analysis in real time (DART) ionization source.

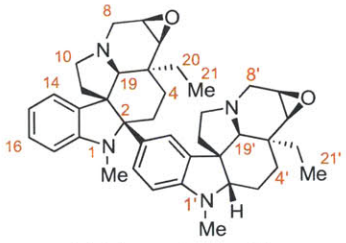
Positional Numbering System. At least two numbering systems exist in the literature for the *aspidosperma* alkaloids.[5] For direct comparison between structures, the system employed by Yates for (–)-aspidophytine is optimal and is used throughout this report. In the case of dimeric structures such as (+)-tabernaebovine (**3**), the subunit bearing C15' substitution is given primed numbers.



(–)-*N*-methylaspidospermidine (**1**)



(+)-*N*-methylquebrachamine (**2**)



(+)-tabernaebovine (**3**)

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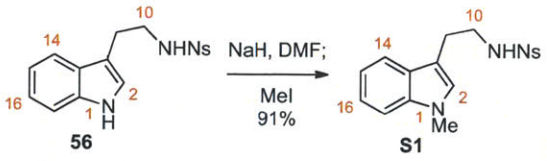
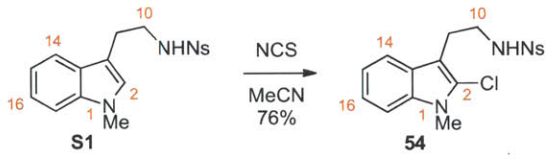


1-Methyltryptamine nosylamide (S1):

Sodium hydride (60% dispersion in mineral oil, 1.06 g, 26.5 mmol, 3.52 equiv) was added as a solid under an argon atmosphere to a solution of sulfonamide **56**[6] (2.60 g, 7.53 mmol, 1 equiv) in *N*,*N*-dimethylformamide (28 mL) at 23 °C. After 20 min, the reaction mixture was cooled to 0 °C. Iodomethane (470 μL, 7.53 mmol, 1.00 equiv) was added dropwise via syringe over 5 min. After 3 h, the reaction mixture was allowed to warm slowly to 23 °C. After 6 h, saturated aqueous ammonium chloride solution (20 mL) was added via syringe to quench the sodium salts. The resulting biphasic mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate (500 mL) and was washed with brine (2 × 500 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (30 → 40% ethyl acetate in hexanes) to afford sulfonamide **S1** (2.46 g, 90.9%) as a yellow powder. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 8.00–7.95 (m, 1H, Ph_{Ns}-**H**), 7.65–7.60 (m, 1H, Ph_{Ns}-**H**), 7.59–7.53 (m, 2H, Ph_{Ns}-**H**), 7.29 (d, J = 7.6, 1H, C_{14}-**H**), 7.20 (d, J = 8.2, 1H, C_{17}-**H**), 7.17–7.12 (m, 1H, C_{16}-**H**), 6.96–6.91 (m, 1H, C_{15}-**H**), 6.84 (s, 1H, C_2-**H**), 5.36–5.30 (br-m, 1H, N_9-**H**), 3.68 (s, 3H, C_{22}-**H**$_3$), 3.41 (app-q, J = 6.6, 2H, C_{10}-**H**$_2$), 2.97 (app-t, J = 6.6, 2H, C_{11}-**H**$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 147.5, 137.4, 133.4, 133.4, 132.7, 131.0, 127.8, 127.2, 125.5, 121.9, 119.1, 118.5, 109.7, 109.6, 44.0, 32.8, 25.5.
FTIR (neat) cm^{-1}:	3339 (br-m), 3095 (w), 2934 (m), 1538 (s), 1407 (s), 1344 (s), 1167 (s), 739 (s).
HRMS (DART):	calc'd for $C_{17}H_{18}N_3O_4S$ $[M+H]^+$: 360.1013, found: 360.1007.
TLC (50% EtOAc in hexanes),	R_f: 0.38 (UV, CAM).

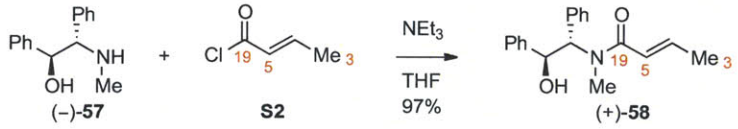
[6] The 2-nitrobenzenesulfonyl amide **56** was prepared in 1-step, see Matsuda, Y.; Kitajima, M.; Takayama, H. *Org. Lett.* **2008**, *10*, 125.



2-Chloro-1-methyltryptamine nosylamide (54):

N-Chlorosuccinimide (1.01 g, 7.57 mmol, 1.10 equiv) was added as a solid under an argon atmosphere to a solution of sulfonamide **S1** (2.47 g, 6.88 mmol, 1 equiv) in acetonitrile (120 mL) at 23 °C. After 1 h, saturated aqueous sodium thiosulfate solution (20 mL) was added to quench excess *N*-chlorosuccinimide. The mixture was diluted by addition of brine (125 mL) and dichloromethane (125 mL), and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 125 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20% ethyl acetate in hexanes) to afford sulfonamide **54** (2.06 g, 76.1%) as a yellow powder. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.96–7.91 (m, 1H, Ph_{Ns}-**H**), 7.67–7.64 (m, 1H, Ph_{Ns}-**H**), 7.59–7.53 (m, 2H, Ph_{Ns}-**H**), 7.29 (d, J = 7.9, 1H, C_{14}-**H**), 7.16–7.14 (m, 1H, C_{16}-**H**), 7.16–7.14 (m, 1H, C_{17}-**H**), 7.01–6.97 (m, 1H, C_{15}-**H**), 5.38–5.30 (br-m, 1H, N_9-**H**), 3.63 (s, 3H, C_{22}-**H**$_3$), 3.44 (app-q, J = 6.8, 2H, C_{10}-**H**$_2$), 2.98 (app-t, J = 6.8, 2H, C_{11}-**H**$_2$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 147.6, 135.8, 133.8, 133.3, 132.8, 130.9, 126.2, 125.5, 125.0, 122.2, 120.2, 117.9, 109.4, 106.5, 43.6, 30.1, 24.8.
FTIR (neat) cm^{-1}:	3354 (br-m), 2937 (m), 1537 (s), 1468 (s), 1332 (s), 1163 (s), 738 (s).
HRMS (DART):	calc'd for $C_{17}H_{17}ClN_3O_4S$ $[M+H]^+$: 394.0623, found: 394.0610.
TLC (30% EtOAc in hexanes), R_f:	0.35 (UV, CAM).



Crotonamide (+)-58:

An ice-cooled solution of *E*-crotonyl chloride (**S2**, 1.28 mL, 13.2 mmol, 1.00 equiv) in tetrahydrofuran (7.0 mL) was added slowly via cannula to a solution of amine (–)-**57** (3.00 g, 13.2 mmol, 1 equiv) and triethylamine (2.21 mL, 15.8 mmol, 1.20 equiv) in tetrahydrofuran (40 mL) at –30 °C. The resulting mixture was allowed to warm slowly to –10 °C over 80 min and then allowed to warm to 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (20 mL) was added to quench the amine hydrochloride salts. The mixture was diluted with ethyl acetate (600 mL), and the layers were separated. The organic layer was washed successively with aqueous hydrogen chloride solution (1N, 400 mL), saturated aqueous potassium carbonate solution (400 mL), and brine (400 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The residue was recrystallized from 40% ethyl acetate in hexanes to afford crotonamide (+)-**58** (3.78 g, 97.0%) as lustrous yellow needles.[7] Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, 6:1 atropisomer mixture, * denotes minor atropisomer): δ 7.43–7.15 (m, 10H, Ph-**H**), 7.43-7.15 (m, 10H, Ph-**H***), 6.92 (dq, *J* = 15.0, 6.9, 1H, C_4-**H**), 6.72–6.60 (m, 1H, C_4-**H***), 6.21 (d, *J* = 15.0, 1H, C_5-**H**), 6.20–6.13 (m, 1H, C_5-**H***), 5.70 (d, *J* = 8.4, 1H, NC-**H**), 5.41–5.35 (m, 1H, OC-**H***), 5.34 (app-t, *J* = 7.8, 1H, OC-**H**), 5.24–5.18 (m, 1H, NC-**H***), 4.45 (d, *J* = 6.9, 1H, O-**H**), 3.18–3.10 (m, 1H, O-**H***), 2.93 (s, 3H, NC-$\mathbf{H}_3$*), 2.91 (s, 3H, NC-$\mathbf{H}_3$), 1.87 (d, *J* = 6.9, 3H, C_3-$\mathbf{H}_3$), 1.82–1.76 (m, 3H, C_3-$\mathbf{H}_3$*).

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C, 6:1 atropisomer mixture, * denotes minor atropisomer): δ 168.9, 168.9*, 143.1, 142.1, 141.3*, 140.8*, 137.2, 136.6*, 128.7, 128.6, 128.5, 128.3*, 127.9*, 127.8*, 127.8, 127.7, 127.2*, 127.1, 127.0*, 126.8*, 122.7*, 122.3, 73.9, 73.4*, 66.0, 65.8*, 34.3, 30.1*, 18.5, 15.4*.

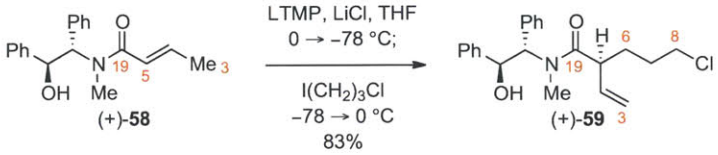
FTIR (neat) cm^{-1}: 3395 (br-s), 3031 (w), 1656 (s), 1597 (s), 1062 (m), 699 (m).

HRMS (DART): calc'd for $C_{19}H_{22}NO_2$ $[M+H]^+$: 296.1645, found: 296.1640.

$[\alpha]_D^{24}$: +199 (*c* = 0.41, $CHCl_3$).

TLC (50% EtOAc in hexanes), R_f: 0.20 (UV, $KMnO_4$).

[7] For a synthesis of a related unsaturated pseudoephedrine amide, see Yang, B. H. Ph.D. thesis, Harvard University, **1997**.



Vinyl tertiary amide (+)-59:

2,2,6,6-Tetramethylpiperidine (2.12 mL, 12.5 mmol, 2.30 equiv) was added via syringe to a suspension of lithium chloride (1.39 g, 32.7 mmol, 6.00 equiv) in tetrahydrofuran (6.0 mL) at –78 °C. A solution of *n*-butyllithium (2.01 M in hexanes, 5.56 mL, 11.2 mmol, 2.06 equiv) was added via syringe, and the resulting mixture was warmed to 0 °C. After 20 min, an ice-cooled solution of crotonamide (+)-**58** (1.61 g, 5.45 mmol, 1 equiv) in tetrahydrofuran (15 mL) was added via cannula. The transfer was quantitated with additional tetrahydrofuran (2 × 2.5 mL). After 10 min, the reaction mixture was cooled to –78 °C. After 10 min, 3-chloro-1-iodopropane (1.17 mL, 10.9 mmol, 2.00 equiv) was added via syringe. After 40 min, the reaction mixture was warmed to 0 °C. After 4.5 h, saturated aqueous ammonium chloride solution (40 mL) was added to quench the lithium alkoxide salts. Brine (85 mL) and ethyl acetate (125 mL) were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 125 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20 → 30% ethyl acetate in hexanes) to afford vinyl tertiary amide (+)-**59** (1.69 g, 83.4%) as a colorless gum.[8] Structural assignments were made with additional information from gCOSY data.

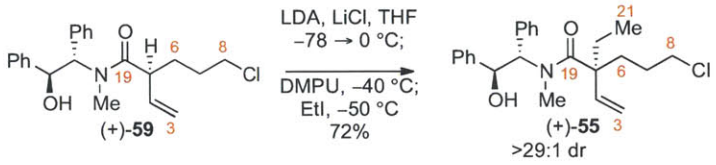
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, 4.6:1 atropisomer mixture, * denotes minor atropisomer): δ 7.47–7.22 (m, 10H, Ph-**H**), 7.47–7.22 (m, 10H, Ph-**H***), 5.88–5.79 (m, 1H, C_4-**H***), 5.79–5.72 (m, 1H, C_4-**H**), 5.65 (d, J = 7.4, 1H, NC-**H**), 5.49 (dd, J = 1.6, 6.5, 1H, OC-**H***), 5.40 (app-t, J = 7.2, 1H, OC-**H**), 5.34 (d, J = 6.5, 1H, NC-**H***), 5.19 (app-d, J = 10.3, 1H, C_3-$\mathbf{H}_E$), 5.15, (app-d, J = 17.2, 1H, C_3-$\mathbf{H}_Z$), 5.14–5.08 (m, 2H, C_3-$\mathbf{H}_2$*), 4.05 (br-s, 1H, O-**H**), 3.59–3.53 (m, 2H, C_8-$\mathbf{H}_2$), 3.51–3.44 (m, 2H, C_8-$\mathbf{H}_2$*), 3.22 (app-q, J = 7.1, 1H, C_5-**H**), 3.15 (app-q, J = 7.3, 1H, C_5-**H***), 2.94 (s, 3H, NC-$\mathbf{H}_3$), 2.90, (s, 3H, NC-$\mathbf{H}_3$*), 2.34 (br-d, J = 1.6, 1H, O-**H***), 1.96–1.82 (m, 2H, C_6-$\mathbf{H}_2$), 1.96–1.82 (m, 2H, C_7-$\mathbf{H}_2$), 1.77–1.59 (m, 2H, C_6-$\mathbf{H}_2$*), 1.77–1.59 (m, 2H, C_7-$\mathbf{H}_2$*).

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C, 4.6:1 atropisomer mixture, * denotes minor atropisomer): δ 174.9, 174.2*, 142.0, 141.8*, 137.8*, 137.1, 137.0*, 136.2, 129.0*, 128.8*, 128.7, 128.5, 128.4, 127.9, 127.8, 127.1*, 126.8, 117.8*, 117.7, 73.8, 73.5*, 66.1, 64.2*, 47.4, 47.2*, 45.1*, 44.9, 34.6, 31.0*, 30.4*, 30.3, 30.0*, 29.8.

FTIR (neat) cm^{-1}: 3382 (s), 3031 (w), 2958 (w), 1619 (s), 1451 (m), 1403 (m), 1063 (m), 700 (s).

[8] For α-alkylation of related pseudoephedrine amides, see Yang, B. H. Ph.D. thesis, Harvard University, **1997**.

HRMS (DART):	calc'd for $C_{22}H_{27}ClNO_2$ $[M+H]^+$: 372.1725, found: 372.1738.
$[\alpha]_D^{24}$:	+122 (c = 0.37, $CHCl_3$).
TLC (40% EtOAc in hexanes), R_f:	0.51 (UV, $KMnO_4$).



α-Quaternary amide (+)-55:

N,*N*-Diisopropylamine (531 μL, 3.79 mmol, 2.26 equiv) was added via syringe to a suspension of lithium chloride (428 mg, 10.1 mmol, 6.01 equiv) in tetrahydrofuran (3.0 mL) at −78 °C. A solution of *n*-butyllithium (2.25 M in hexanes, 1.55 mL, 3.48 mmol, 2.07 equiv) was added via syringe, and the resulting mixture was warmed to 0 °C. After 5 min, the resulting solution was cooled to −78 °C. An ice-cooled solution of vinyl tertiary amide (+)-**59** (625 mg, 1.68 mmol, 1 equiv) in tetrahydrofuran (5.0 mL) was added via cannula.[9] The transfer was quantitated with additional tetrahydrofuran (2 × 1.0 mL), and the resulting mixture was warmed to 0 °C. After 1 h, the reaction mixture was cooled to −40 °C, and *N*,*N*'-dimethylpropylene urea (507 μL, 4.21 mmol, 2.51 equiv) was added via syringe. After 10 min, the reaction mixture was cooled to −60 °C, and iodoethane (1.01 mL, 12.6 mmol, 7.50 equiv) was added slowly via syringe. After 5 min, the reaction mixture was warmed to −50 °C. After 42 h, saturated aqueous ammonium chloride solution (5 mL) was added to quench the lithium alkoxide salts, and the resulting biphasic mixture was allowed to warm to 23 °C. Brine (55 mL) and dichloromethane (60 mL) were added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (3 × 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 18% ethyl acetate in hexanes) to afford α-quaternary amide (+)-**55** (484 mg, 72.0%) as a colorless gum. Structural assignments were made with additional information from gCOSY data. The diastereomeric ratio of the purified α-quaternary amide (+)-**55** was determined to be >29:1 by ^{1}H NMR analysis of the oxazolinium trifluromethanesulfonate derivative **S3**.[10]

^{1}H NMR (500 MHz, C_6D_6, 73 °C): δ 7.32 (d, *J* = 7.6, 2H, Ph-**H**), 7.28 (d, *J* = 7.5, 2H, Ph-**H**), 7.10–7.02 (m, 4H, Ph-**H**), 7.02–6.95 (m, 2H, Ph-**H**),

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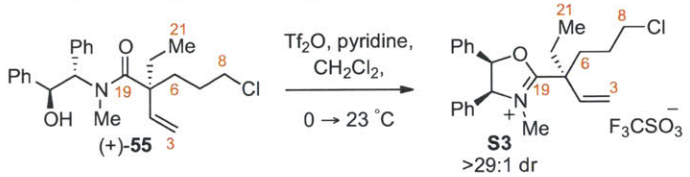
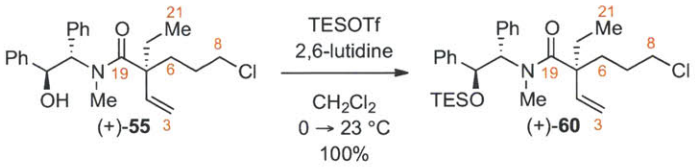
[9] We are grateful to professor Myers and co-workers for sharing their new asymmetric alkylation methodology in advance of publication: (a) *Personal communication*, Myers, A. G. **2011**. (b) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568.

[10] The diastereomeric ratio of the product (+)-**55** was determined by its conversion to the corresponding α-quaternary oxazolinium trifluoromethanesulfonate **S3**; see Chain, W. J.; Myers, A. G. *Org. Lett.* **2007**, *9*, 355.



A sample of **S3** was prepared as follows: Trifluoromethanesulfonic anhydride (2.3 μL, 14 μmol, 1.5 equiv) was added via syringe to a solution of α-quaternary amide (+)-**55** (3.7 mg, 9.3 μmol, 1 equiv) and pyridine (2.2 μL, 28 μmol, 3.0 equiv) in dichloromethane (1.0 mL) at 0 °C. After 10 min, the solution was allowed to warm to 23 °C. After 10 min the reaction mixture was concentrated under reduced pressure. The residue was dissolved in $CDCl_3$ for ^{1}H NMR analysis. Structural assignments were made with additional information from gCOSY experiments. ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, >29:1 diastereomer mixture, * denotes minor diastereomer): δ 7.21-7.10 (m, 6H, Ph-**H**), 7.21-7.10 (m, 6H, Ph-**H***), 6.98–6.92 (m, 2H, Ph-**H**), 6.98–6.92 (m, 2H, Ph-**H***), 6.98–6.92 (m, 1H, NC-**H**), 6.98–6.92 (m, 1H, NC-**H***), 6.88–6.83 (m, 2H, Ph-**H**), 6.88–6.83 (m, 2H, Ph-**H***), 6.32 (d, *J* = 11.9, 1H, OC-**H***), 6.24 (d, *J* = 10.9, 1H, OC-**H**), 6.18 (dd, *J* = 10.8, 17.7, 1H, C_4-**H**), 6.10 (dd, *J* = 10.9, 17.7, 1H, C_4-**H***), 5.69 (d, *J* = 10.8, 1H, C_3-$\mathbf{H}_E$), 5.68 (d, *J* = 10.9, 1H, C_3-$\mathbf{H}_E$*), 5.52 (d, *J* = 17.7, 1H, C_3-$\mathbf{H}_Z$), 5.50 (d, *J* = 17.7, 1H, C_3-$\mathbf{H}_Z$*), 3.76–3.68 (m, 1H, C_8-$\mathbf{H}_a$), 3.76–3.68 (m, 1H, C_8-$\mathbf{H}_a$*), 3.67–3.59 (m, 1H, C_8-$\mathbf{H}_b$), 3.67–3.59 (m, 1H, C_8-$\mathbf{H}_b$*), 3.39 (s, 3H, NC-$\mathbf{H}_3$), 3.37 (s, 3H, NC-$\mathbf{H}_3$*), 2.30–2.04 (m, 2H, C_6-$\mathbf{H}_2$), 2.30–2.04 (m, 2H, C_6-$\mathbf{H}_2$*), 2.30–2.04 (m, 2H, C_7-$\mathbf{H}_2$), 2.30–2.04 (m, 2H, C_7-$\mathbf{H}_2$*), 2.04–1.94 (m, 1H, C_2-$\mathbf{H}_a$), 2.04–1.94 (m, 1H, C_2-$\mathbf{H}_a$*), 1.92–1.82 (m, 1H, C_2-$\mathbf{H}_b$), 1.92–1.82 (m, 1H, C_2-$\mathbf{H}_b$*), 1.15 (t, *J* = 7.5, 3H, C_{21}-$\mathbf{H}_3$*), 1.06 (t, *J* = 7.5, 3H, C_{21}-$\mathbf{H}_3$).

	5.91 (d, J = 8.1, 1H, NC-**H**), 5.69 (dd, J = 10.9, 17.8, 1H, C_4-**H**), 5.22 (d, J = 8.1, 1H, OC-**H**), 4.92 (app-d, J = 10.9, 1H, C_3-$\mathbf{H}_E$), 4.84 (app-d, J = 17.8, 1H, C_3-$\mathbf{H}_Z$), 3.38-3.27 (br-s, 1H, O-**H**), 3.27–3.16 (m, 2H, C_8-$\mathbf{H}_2$), 2.74 (s, 3H, NC-$\mathbf{H}_3$), 1.89–1.79 (m, 1H, C_6-$\mathbf{H}_a$), 1.73–1.49 (m, 1H, C_6-$\mathbf{H}_b$), 1.73–1.49 (m, 2H, C_7-$\mathbf{H}_2$), 1.73–1.49 (m, 2H, C_{20}-$\mathbf{H}_2$), 0.76 (t, J = 7.4, 3H, C_{21}-$\mathbf{H}_3$).
^{13}C NMR (125 MHz, C_6D_6, 73 °C):	δ 175.8, 143.4, 142.6, 138.9, 129.6, 128.8, 128.7, 128.1, 128.0, 127.8, 114.2, 74.2, 66.4, 53.2, 46.1, 34.8, 34.2, 29.3, 28.5, 9.0.
FTIR (neat) cm^{-1}:	3407 (br-s), 2965 (m), 1607 (s), 1451 (m), 1391 (m), 1083 (m), 699 (s).
HRMS (DART):	calc'd for $C_{24}H_{31}ClNO_2$ $[M+H]^+$: 400.2038, found: 400.2056.
$[\alpha]_D^{24}$:	+92 (c = 0.44, CH_2Cl_2).
TLC (30% EtOAc in hexanes), R_f:	0.39 (UV, $KMnO_4$).



<u>*O*-Silylated α-quaternary amide (+)-60:</u>

Triethylsilyltrifluoromethanesulfonate (535 μL, 2.37 mmol, 2.00 equiv) was added via syringe to a solution of α-quaternary amide (+)-**55** (473 mg, 1.18 mmol, 1 equiv) and 2,6-lutidine (343 μL, 2.96 mmol, 2.50 equiv) in dichloromethane (8.0 mL) at 0 °C. After 5 min, the solution was allowed to warm to 23 °C. After 4.5 h, the reaction mixture was poured into saturated aqueous sodium bicarbonate solution (15 mL). Brine (25 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (4 × 40 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 5% ethyl acetate in hexanes) to afford *O*-silylated α-quaternary amide (+)-**60** (608 mg, 100%) as a viscous colorless oil. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, 4.5:1 atropisomer mixture, * denotes minor atropisomer): δ 7.46–7.04 (m, 10H, Ph-**H**), 7.46–7.04 (m, 8H, Ph-**H***), 6.94–6.77 (m, 2H, Ph-**H***), 6.24–6.03 (br-m, 1H, NC-**H**), 5.92–5.80 (m, 1H, C_4-**H***), 5.85 (dd, J = 10.7, 17.6, 1H, C_4-**H**), 5.66–5.56 (br-m, 1H, NC-**H***), 5.36 (d, J = 7.0, 1H, OC-**H**), 5.18–5.11 (m, 1H, C_3-$\mathbf{H}_a$*), 5.14 (d, J = 10.7, 1H, C_3-$\mathbf{H}_E$), 5.11–5.02 (br-m, 1H, OC-**H***), 5.00–4.92 (m, 1H, C_3-$\mathbf{H}_b$*), 4.96 (d, J = 17.6, 1H, C_3-$\mathbf{H}_Z$), 3.47–3.35 (m, 2H, C_8-$\mathbf{H}_2$), 3.30 (s, 3H, NC-$\mathbf{H}_3$*), 3.09 (s, 3H, NC-$\mathbf{H}_3$), 3.04–2.92 (m, 1H, C_8-$\mathbf{H}_a$*), 2.88–2.75 (m, 1H, C_8-$\mathbf{H}_b$*), 1.90–1.16 (m, 2H, C_6-$\mathbf{H}_2$), 1.90–1.16 (m, 2H, C_6-$\mathbf{H}_2$*), 1.90–1.16 (m, 2H, C_7-$\mathbf{H}_2$), 1.90–1.16 (m, 2H, C_7-$\mathbf{H}_2$*), 1.90–1.16 (m, 2H, C_{20}-$\mathbf{H}_2$), 1.90–1.16 (m, 2H, C_{20}-$\mathbf{H}_2$*), 0.86–0.71 (m, 9H, $Si(CH_2C\mathbf{H}_3)_3$*), 0.79 (t, J = 7.7, 9H, $Si(CH_2C\mathbf{H}_3)_3$), 0.78–0.73 (m, 3H, C_{21}-$\mathbf{H}_3$*), 0.64 (t, J = 7.1, 3H, C_{21}-$\mathbf{H}_3$), 0.46–0.32 (m, 6H, $Si(C\mathbf{H}_2CH_3)_3$*), 0.39 (q, J = 7.7, 6H, $Si(C\mathbf{H}_2CH_3)_3$).

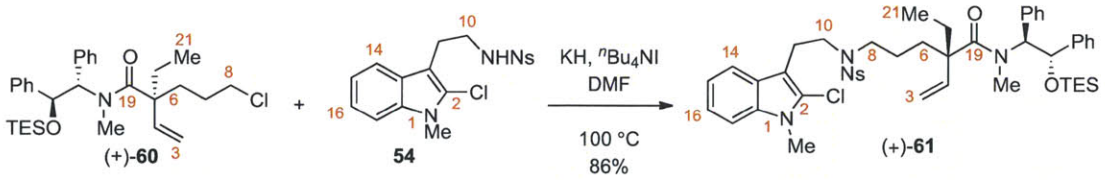
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C, 4.5:1 atropisomer mixture, * denotes minor atropisomer): δ 175.1*, 174.0, 143.4*, 142.3, 142.1, 141.9*, 139.3*, 138.6, 128.8, 128.6*, 128.2, 128.1, 128.0*, 127.7, 127.6*, 127.4, 127.2, 113.9, 113.3*, 78.0*, 75.3, 66.0*, 63.2, 52.2, 52.1*, 46.1, 45.2*, 33.8, 33.2, 31.3*, 29.9*, 28.4*, 27.7, 27.5, 8.5, 8.4*, 7.0, 6.9*, 5.1, 5.0*.

FTIR (neat) cm^{-1}: 3031 (w), 2957 (s), 2877 (m), 1624 (s), 1454 (m), 1384 (m), 1088 (m), 1005 (m), 699 (s).

HRMS (DART): calc'd for $C_{30}H_{44}ClNNaO_2Si$ $[M+Na]^+$: 536.2722, found: 536.2706.

$[\alpha]_D^{24}$: +72 (c = 0.52, $CHCl_3$).

TLC (20% EtOAc in hexanes), R_f: 0.61 (UV, $KMnO_4$).



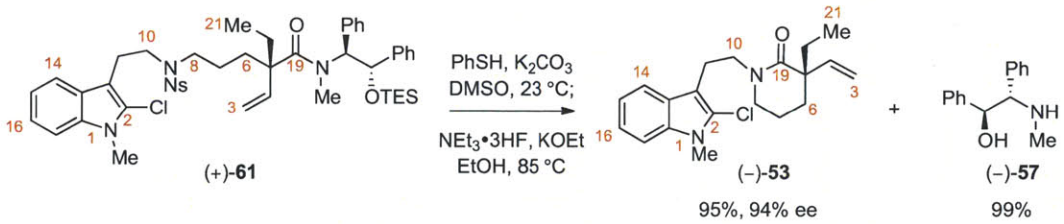
Tertiary sulfonamide (+)-61:

Potassium hydride (47.4 mg, 1.18 mmol, 1.10 equiv) was added as a solid under an argon atmosphere to a solution of *O*-silylated α-quaternary amide (+)-**60** (553 mg, 1.08 mmol, 1 equiv), sulfonamide **54** (466 mg, 1.18 mmol, 1.10 equiv), and tetrabutylammonium iodide (392 mg, 1.08 mmol, 1.00 equiv) in *N*,*N*-dimethylformamide (2.5 mL) at 23 °C. After 5 min, the solution was warmed to 100 °C. After 24 h, the solution was allowed to cool to 23 °C. Saturated aqueous ammonium chloride solution (20 mL) was added to quench the sulfonamide salts. Brine (40 mL) and dichloromethane (60 mL) were added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (80% dichloromethane in hexanes → 30% ethyl acetate in hexanes) to afford tertiary sulfonamide (+)-**61** (806 mg, 86.0%) as a beige foam. Structural assignments were made with additional information from gCOSY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, 4.4:1 atropisomer mixture, * denotes minor atropisomer): δ 7.93–7.85 (m, 1H, Ph_{Ns}-**H**), 7.85–7.75 (m, 1H, Ph_{Ns}-**H***), 7.65–7.53 (m, 3H, Ph_{Ns}-**H**), 7.65–7.53 (m, 3H, Ph_{Ns}-**H***), 7.53–7.05 (m, 14H, Ar-**H**), 7.53–7.05 (m, 12H, Ar-**H***), 6.96–6.84 (m, 2H, Ar-**H***), 6.21–6.07 (br-m, 1H, NC-**H**), 5.93–5.81 (m, 1H, C_4-**H***), 5.86 (dd, J = 11.0, 18.1, 1H, C_4-**H**), 5.66–5.56 (br-m, 1H, NC-**H***), 5.36 (d, J = 6.8, 1H, OC-**H**), 5.17–5.09 (m, 1H, C_3-$\mathbf{H}_a$*), 5.12 (d, J = 11.0, 1H, C_3-$\mathbf{H}_E$), 5.08–5.02 (br-m, 1H, OC-**H***), 4.98–4.88 (m, 1H, C_3-$\mathbf{H}_b$*), 4.93 (d, J = 18.1, 1H, C_3-$\mathbf{H}_Z$), 3.66 (s, 3H, C_{22}-$\mathbf{H}_3$), 3.66 (s, 3H, C_{22}-$\mathbf{H}_3$*), 3.45 (app-t, J = 7.3, 2H, C_{10}-$\mathbf{H}_2$), 3.45 (app-t, J = 7.3, 2H, C_{10}-$\mathbf{H}_2$*), 3.42–3.32 (m, 2H, C_8-$\mathbf{H}_2$), 3.30 (s, 3H, NC-$\mathbf{H}_3$*), 3.07 (s, 3H, NC-$\mathbf{H}_3$), 3.03–2.92 (m, 1H, C_8-$\mathbf{H}_a$*), 2.97 (app-t, J = 7.3, 2H, C_{11}-$\mathbf{H}_2$), 2.97 (app-t, J = 7.3, 2H, C_{11}-$\mathbf{H}_2$*), 2.93–2.75 (m, 1H, C_8-$\mathbf{H}_b$*), 1.88–1.06 (m, 2H, C_6-$\mathbf{H}_2$), 1.88–1.06 (m, 2H, C_6-$\mathbf{H}_2$*), 1.88–1.06 (m, 2H, C_7-$\mathbf{H}_2$), 1.88–1.06 (m, 2H, C_7-$\mathbf{H}_2$*), 1.88–1.06 (m, 2H, C_{20}-$\mathbf{H}_2$), 1.88–1.06 (m, 2H, C_{20}-$\mathbf{H}_2$*), 0.88–0.73 (m, 9H, $Si(CH_2C\mathbf{H}_3)_3$*), 0.80 (t, J = 7.8, 9H, $Si(CH_2C\mathbf{H}_3)_3$), 0.73–0.65 (m, 3H, C_{21}-$\mathbf{H}_3$*), 0.60 (t, J = 7.0, 3H, C_{21}-$\mathbf{H}_3$), 0.49–0.32 (m, 6H, $Si(C\mathbf{H}_2CH_3)_3$*), 0.40 (q, J = 7.8, 6H, Si $(C\mathbf{H}_2CH_3)_3$).

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 173.9, 147.9, 142.3, 142.1, 138.5, 135.7, 133.9, 133.1, 131.5, 130.8, 128.9, 128.2, 128.1, 127.7, 127.5, 127.2, 126.4, 124.4 124.1, 122.1, 120.2, 118.3, 114.0, 109.2, 107.5, 75.1, 63.2, 52.3, 48.3, 46.6, 34.0, 33.1, 30.0, 27.2, 23.8, 23.0, 8.7, 7.0, 5.1.

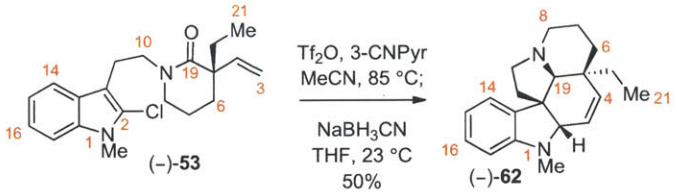
FTIR (neat) cm^{-1}:	2955 (m), 1622 (s), 1544 (s), 1468 (m), 1372 (s), 1091 (m), 741 (m).
HRMS (DART):	calc'd for $C_{47}H_{60}ClN_4O_6SSi$ $[M+H]^+$: 871.3686, found: 871.3678.
$[\alpha]_D^{24}$:	+49 (c = 0.38, CH_2Cl_2).
TLC (50% EtOAc in hexanes), R_f:	0.87 (UV).



Lactam (–)-53:

Thiophenol (203 μL, 1.98 mmol, 3.00 equiv) was added via syringe to a suspension of tertiary sulfonamide (+)-**61** (574 mg, 0.658 mmol, 1 equiv) and potassium carbonate (455 mg, 3.29 mmol, 5.00 equiv) in dimethylsulfoxide (3.6 mL) at 23 °C. After 3 h, triethylamine trihydrofluoride (716 μL, 4.39 mmol, 6.67 equiv) was added via syringe. After 1 min, potassium ethoxide (2.25 M solution in ethanol, 17.1 mL) was added via syringe. After 5 min, the solution was warmed to 85 °C. After 24 h, the solution was allowed to cool to 23 °C. Saturated aqueous ammonium chloride solution (20 mL) was added to quench the potassium ethoxide, and the resulting biphasic mixture was concentrated under reduced pressure. Saturated aqueous sodium bicarbonate (60 mL) and dichloromethane (60 mL) were added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 60 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 20% ethyl acetate in hexanes) to afford lactam (–)-**53** (216 mg, 95.1%) as a viscous light orange oil. Further elution (0.5% ammonium hydroxide, 4.5% methanol, 20% chloroform in dichloromethane) afforded amine (–)-**57** (148 mg, 98.9%) as a white powder. Structural assignments were made with additional information from gCOSY data. Lactam (–)-**7** was determined to be of 94% ee by chiral HPLC analysis (Chiralpak IC, 25% ^{i}PrOH / 75% hexanes, 0.5 ml/min, 230 nm, t_R (minor) = 19.8 min, t_R (major) = 22.7 min).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.64 (d, J = 7.8, 1H, C_{14}-**H**), 7.24–7.15 (m, 1H, C_{17}-**H**), 7.24–7.15 (m, 1H, C_{16}-**H**), 7.10 (app-t, J = 7.8, 1H, C_{15}-**H**), 5.90 (dd, J = 10.7, 17.6, 1H, C_4-**H**), 5.11 (dd, J = 1.0, 10.7, 1H, C_3-$\mathbf{H}_E$), 5.01 (dd, J = 1.0, 17.6, 1H, C_3-$\mathbf{H}_Z$), 3.69 (s, 3H, C_{22}-$\mathbf{H}_3$), 3.63–3.55 (m, 1H, C_{10}-$\mathbf{H}_a$), 3.54–3.46 (m, 1H, C_{10}-$\mathbf{H}_b$), 3.29–3.20 (m, 1H, C_8-$\mathbf{H}_a$), 3.20–3.13 (m, 1H, C_8-$\mathbf{H}_b$), 3.07–2.95 (m, 2H, C_{11}-$\mathbf{H}_2$), 1.96–1.56 (m, 2H, C_6-$\mathbf{H}_2$), 1.96–1.56 (m, 2H, C_7-$\mathbf{H}_2$), 1.96–1.56 (m, 2H, C_{20}-$\mathbf{H}_2$), 0.80 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 172.8, 142.7, 135.8, 126.9, 124.0, 122.0, 120.0, 118.8, 113.9, 109.1, 108.8, 49.3, 49.2, 48.3, 31.7, 30.0, 28.7, 22.4, 19.6, 8.6.
FTIR (neat) cm^{-1}:	2937 (m), 1629 (s), 1467 (s), 1328 (m), 1199 (m), 740 (m).
HRMS (DART):	calc'd for $C_{20}H_{26}ClN_2O$ $[M+H]^+$: 345.1728, found: 345.1721.
$[\alpha]_D^{24}$:	–5 (c = 0.19, $CHCl_3$).
TLC (30% EtOAc in hexanes), R_f:	0.70 (UV, CAM, $KMnO_4$).

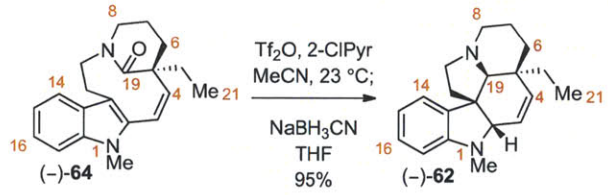


(–)-*N*-Methyldehydroaspidospermidine (62):

Trifluoromethanesulfonic anhydride (18.5 μL, 110 μmol, 1.10 equiv) was added via syringe to a solution of lactam (–)-**53** (34.6 mg, 100 μmol, 1 equiv) and 3-cyanopyridine (12.5 mg, 120 μmol, 1.20 equiv) in acetonitrile (6.5 mL) at 23 °C. After 5 min, the solution was warmed to 85 °C. After 3 h, the solution was allowed to cool to 0 °C. A solution of sodium cyanoborohydride (62.8 mg, 1.00 mmol, 10.0 equiv) in tetrahydrofuran (4 mL) was added via cannula, and the resulting mixture was allowed to warm to 23 °C. After 6 h, saturated aqueous sodium bicarbonate solution (15 mL) was added to quench the trifluoromethanesulfonate salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 3% ethyl acetate in hexanes) to afford (–)-*N*-methyldehydroaspidospermidine (**62**, 14.7 mg, 49.8%) as a light tan gum. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and ROESY data.

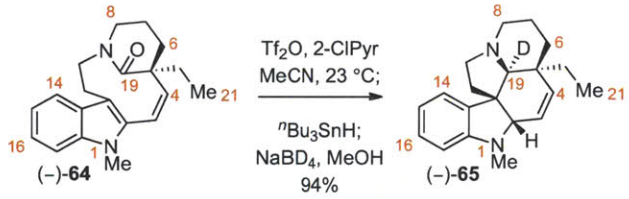
^{1}H NMR (500 MHz, C_6D_6, 20 °C):	δ 7.11 (app-t, J = 7.8, 1H, C_{16}-**H**), 7.02 (d, J = 7.8, 1H, C_{14}-**H**), 6.74 (app-t, J = 7.8, 1H, C_{15}-**H**), 6.25 (d, J = 7.8, 1H, C_{17}-**H**), 5.80 (dd, J = 4.0, 10.3, 1H, C_3-**H**), 5.59 (d, J = 10.3, 1H, C_4-**H**), 3.68 (d, J = 4.0, 1H, C_2-**H**), 2.97 (dt, J = 3.3, 8.5, 1H, C_{10}-$\mathbf{H_a}$), 2.88 (m, 1H, C_8-$\mathbf{H_a}$), 2.53 (s, 3H, C_{22}-$\mathbf{H_3}$), 2.25-2.18 (m, 1H, C_{10}-$\mathbf{H_b}$), 2.23 (s, 1H, C_{19}-**H**), 2.03 (dt, J = 12.2, 8.5, 1H, C_{11}-$\mathbf{H_a}$), 1.94–1.82 (m, 1H, C_8-$\mathbf{H_b}$), 1.94–1.82 (m, 1H, C_{11}-$\mathbf{H_b}$), 1.68–1.57 (m, 1H, C_7-$\mathbf{H_a}$), 1.57–1.49 (m, 1H, C_6-$\mathbf{H_a}$), 1.40–1.29 (m, 1H, C_7-$\mathbf{H_b}$), 1.40–1.29 (m, 1H, C_{20}-$\mathbf{H_a}$), 1.12–1.03 (m, 1H, C_{20}-$\mathbf{H_b}$), 1.03–0.95 (m, 1H, C_6-$\mathbf{H_b}$), 0.61 (t, J = 7.5, 3H, C_{21}-$\mathbf{H_3}$).
^{13}C NMR (125 MHz, C_6D_6, 20 °C):	δ 151.6 (**C**$_{18}$), 137.8 (**C**$_4$), 136.0 (**C**$_{13}$), 128.4 (**C**$_{16}$), 124.6 (**C**$_3$), 123.8 (**C**$_{14}$), 117.5 (**C**$_{15}$), 106.1 (**C**$_{17}$), 73.3 (**C**$_{19}$), 71.5 (**C**$_2$), 53.0 (**C**$_8$), 52.9 (**C**$_{10}$), 52.9 (**C**$_{12}$), 43.9 (**C**$_{11}$), 39.4 (**C**$_5$), 35.6 (**C**$_{20}$), 34.9 (**C**$_6$), 32.6 (**C**$_{22}$), 23.8 (**C**$_7$), 8.2 (**C**$_{21}$).
FTIR (neat) cm^{-1}:	2931 (s), 1605 (m), 1492 (m), 1264 (m), 1121 (m), 736 (s).
HRMS (DART):	calc'd for $C_{20}H_{27}N_2$ $[M+H]^+$: 295.2169, found: 295.2165.
$[\alpha]_D^{24}$:	–28 (c = 0.30, CH_2Cl_2).
TLC (Al_2O_3, 10% EtOAc in hexanes), R_f:	0.40 (UV, CAM, $KMnO_4$).

Alternate Synthesis:



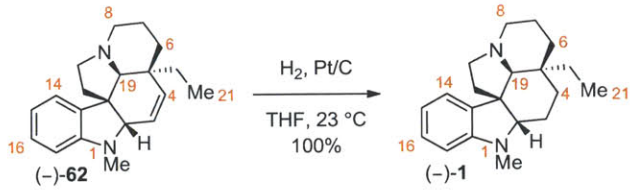
Synthesis of (–)-*N*-Methyldehydroaspidospermidine (16) from tetracyclic lactam (–)-64:

Trifluoromethanesulfonic anhydride (18.0 μL, 107 μmol, 1.10 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (29.9 mg, 96.9 μmol, 1 equiv) and 2-chloropyridine (10.9 μL, 116 μmol, 1.20 equiv) in acetonitrile (3.0 mL) at 23 °C. After 10 min, a solution of sodium cyanoborohydride (36.6 mg, 582 μmol, 6.00 equiv) in tetrahydrofuran (1.0 mL) was added via cannula. After 6 h, saturated aqueous sodium bicarbonate solution (15 mL) was added via syringe to quench the trifluoromethanesulfonate salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 3% ethyl acetate in hexanes) to afford (–)-*N*-methyldehydroaspidospermidine (**62**, 27.1 mg, 94.9%) as a light tan gum. See page 129 for characterization data for (–)-*N*-methyldehydroaspidospermidine (**62**).



Synthesis of C19-deuterated pentacycle (–)-65 from tetracyclic lactam (–)-64:

Trifluoromethanesulfonic anhydride (2.4 μL, 14 μmol, 1.1 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (4.0 mg, 13 μmol, 1 equiv) and 2-chloropyridine (1.5 μL, 16 μmol, 1.2 equiv) in acetonitrile (0.8 mL) at 23 °C. After 10 min, tributylstannane (5.2 μL, 20 μmol, 1.5 equiv) was added via syringe. After 30 min, a solution of sodium borodeuteride (98 atom% D, 2.2 mg, 52 μmol, 4.0 equiv) in methanol (0.8 mL) was added via cannula. After 30 min, saturated aqueous sodium bicarbonate solution (15 mL) was added via syringe to quench the trifluoromethanesulfonate salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 3% ethyl acetate in hexanes) to afford pentacycle (–)-**65** (3.6 mg, 94%) as a light tan gum. ^{1}H NMR analysis of the purified pentacycle (–)-**65** showed 0% deuterium incorporation at C2 and 93% deuterium incorporation at C19. See page 129 for characterization data for (–)-*N*-methyldehydroaspidospermidine (**62**).



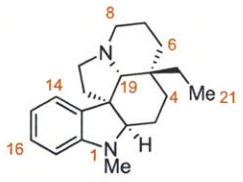
(–)-*N*-Methylaspidospermidine (1):

Platinum on charcoal (10% w/w, 10.0 mg, 5.13 μmol, 0.130 equiv) was added as a solid to a solution of (–)-*N*-methyldehydroaspidospermidine (**62**, 11.6 mg, 39.4 μmol, 1 equiv) in tetrahydrofuran (2.0 mL) at 23 °C. The opened reaction vessel was placed in a Fischer–Porter tube and sealed under an atmosphere of hydrogen gas (80 psi). After 48 h, the Fischer–Porter tube was opened in air, and the suspension was filtered over Celite. The solids were extracted with ethyl acetate, and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 3% ethyl acetate in hexanes) to afford (–)-*N*-methylaspidospermidine (**1**, 11.7 mg, 100%) as a pale off-white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

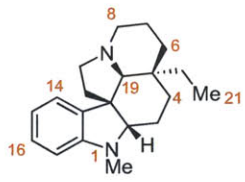
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.04 (app-t, J = 7.3, 1H, C_{16}-**H**), 7.00 (d, J = 7.1, 1H, C_{14}-**H**), 6.61 (app-t, J = 7.3, 1H, C_{15}-**H**), 6.35 (d, J = 7.7, 1H, C_{17}-**H**), 3.40 (dd, J = 5.8, 11.0, 1H, C_2-**H**), 3.15–3.06 (m, 1H, C_{10}-$\mathbf{H}_a$), 3.06-2.99 (m, 1H, C_8-$\mathbf{H}_a$), 2.72 (s, 3H, C_{22}-$\mathbf{H}_3$), 2.35–2.17 (m, 1H, C_{11}-$\mathbf{H}_a$), 2.35–2.17 (m, 1H, C_8-$\mathbf{H}_b$), 2.17 (s, 1H, C_{19}-**H**), 1.99–1.81 (m, 1H, C_{10}-$\mathbf{H}_b$), 1.99–1.81 (m, 1H, C_4-$\mathbf{H}_a$), 1.80–1.65 (m, 1H, C_3-$\mathbf{H}_a$), 1.80–1.65 (m, 1H, C_7-$\mathbf{H}_a$), 1.64–1.56 (m, 1H, C_6-$\mathbf{H}_a$), 1.53–1.37 (m, 1H, C_7-$\mathbf{H}_b$), 1.53–1.37 (m, 1H, C_{11}-$\mathbf{H}_b$), 1.53–1.37 (m, 1H, C_{20}-$\mathbf{H}_a$), 1.26–1.16 (m, 1H, C_3-$\mathbf{H}_b$), 1.15–1.03 (m, 1H, C_4-$\mathbf{H}_b$), 1.15–1.03 (m, 1H, C_6-$\mathbf{H}_b$), 0.90–0.80 (m, 1H, C_{20}-$\mathbf{H}_b$), 0.60 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 150.8 ($\mathbf{C}_{18}$), 137.1 ($\mathbf{C}_{13}$), 127.4 ($\mathbf{C}_{16}$), 122.4 ($\mathbf{C}_{14}$), 117.3 ($\mathbf{C}_{15}$), 106.6 ($\mathbf{C}_{17}$), 72.0 ($\mathbf{C}_2$), 71.4 ($\mathbf{C}_{19}$), 54.1 ($\mathbf{C}_8$), 53.3 ($\mathbf{C}_{10}$), 52.8 ($\mathbf{C}_{12}$), 39.3 ($\mathbf{C}_{11}$), 35.7 ($\mathbf{C}_5$), 34.7 ($\mathbf{C}_6$), 31.7 ($\mathbf{C}_{22}$), 30.3 ($\mathbf{C}_{20}$), 23.1 ($\mathbf{C}_4$), 22.2 ($\mathbf{C}_3$), 22.0 ($\mathbf{C}_7$), 7.0 ($\mathbf{C}_{21}$).
FTIR (neat) cm^{-1}:	2929 (s), 1606 (m), 1485 (m), 1446 (m), 1376 (m), 1265 (s), 1122 (m), 737 (m).
HRMS (DART):	calc'd for $C_{20}H_{29}N_2$ $[M+H]^+$: 297.2325. found: 297.2317.
$[\alpha]_D^{24}$:	–23 (c = 0.17, $CHCl_3$).[11]
TLC (Al_2O_3, 20% EtOAc in hexanes), R_f:	0.63 (UV, CAM, $KMnO_4$).

[11] Literature value: $[\alpha]_D^{25}$= –23 (c 1.1, $CHCl_3$) for (–)-**1**, Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596. $[\alpha]_D^{20}$= +24 (c 1.25, $CHCl_3$) for (+)-**1**, Mokry, J.; Kompis, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 2523.

Table S1. Comparison of our ^{1}H NMR data for (–)-*N*-methylaspidospermidine (1) with literature data for (+)-*N*-methylaspidospermidine (1):



(+)-*N*-methylaspidospermidine (**1**)

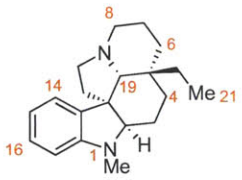


(–)-*N*-methylaspidospermidine (**1**)

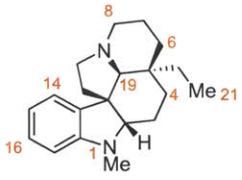
Assignment	Boger's Report[12] (+)-*N*-Methylaspidospermidine (**1**) ^{1}H NMR, 400 MHz, $CDCl_3$	This Work (–)-*N*-Methylaspidospermidine (**1**) ^{1}H NMR, 500 MHz, $CDCl_3$, 20 °C
C2	3.40 (dd, J = 5.8, 10.7, 1H)	3.40 (dd, J = 5.8, 11.0, 1H)
C3	1.80–1.65 (m, 1H) 1.29–1.20 (m, 1H)	1.80–1.65 (m, 1H) 1.26–1.16 (m, 1H)
C4	2.00–1.80 (m, 1H) 1.20–1.10 (m, 1H)	1.99–1.81 (m, 1H) 1.15–1.03 (m, 1H)
C5	-	-
C6	1.65–1.60 (m, 1H) 1.20–1.10 (m, 1H)	1.64–1.56 (m, 1H) 1.15–1.03 (m, 1H)
C7	1.80–1.65 (m, 1H) 1.55–1.40 (m, 1H)	1.80–1.65 (m, 1H) 1.53–1.37 (m, 1H)
C8	3.20–3.05 (m, 1H) 2.35–2.20 (m, 1H)	3.06–2.99 (m, 1H) 2.35–2.17 (m, 1H)
C10	3.20–3.05 (m, 1H) 2.00–1.80 (m, 1H)	3.15–3.06 (m, 1H) 1.99–1.81 (m, 1H)
C11	2.35–2.20 (m, 1H) 1.55–1.40 (m, 1H)	2.35–2.17 (m, 1H) 1.53–1.37 (m, 1H)
C12	-	-
C13	-	-
C14	7.02 (d, J = 7.7, 1H)	7.00 (d, J = 7.1, 1H)
C15	6.63 (t, J = 7.3, 1H)	6.61 (app-t, J = 7.3, 1H)
C16	7.05 (t, J = 7.7, 1H)	7.04 (app-t, J = 7.3, 1H)
C17	6.37 (d, J = 7.7, 1H)	6.35 (d, J = 7.7, 1H)
C18	-	-
C19	2.21 (s, 1H)	2.17 (s, 1H)
C20	1.55–1.40 (m, 1H) 0.90–0.80 (m, 1H)	1.53–1.37 (m, 1H) 0.90–0.80 (m, 1H)
C21	0.62 (t, J = 7.4, 3H)	0.60 (t, J = 7.5, 3H)
C22	2.74 (s, 3H)	2.72 (s, 3H)

[12] Ishikawa, H.; Elliott, G. I.; Velcicky, J.; Choi, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 10596.

Table S2. Comparison of our ^{13}C NMR data for (–)-*N*-methylaspidospermidine (1) with literature data for (+)-*N*-methylaspidospermidine (1):

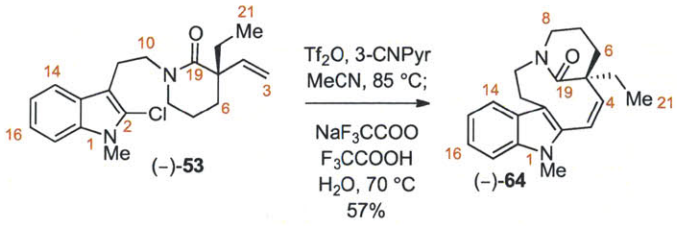


(+)-*N*-methylaspidospermidine (**1**)



(–)-*N*-methylaspidospermidine (**1**)

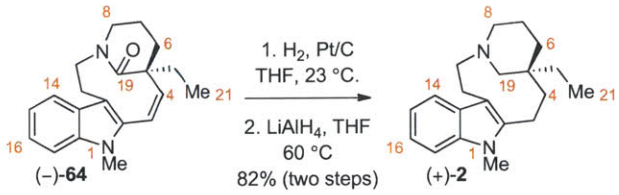
Assignment	**Boger's Report**[12] (+)-*N*-Methylaspidospermidine (**1**) ^{13}C NMR, 100 MHz, $CDCl_3$	**This Work** (–)-*N*-Methylaspidospermidine (**1**) ^{13}C NMR, 125 MHz, $CDCl_3$, 20 °C	**Chemical Shift Difference** $\Delta\delta$ = δ (this work) – δ (Ref. 12)
C2	71.7	72.0	0.3
C3	22.0	22.2	0.2
C4	22.9	23.1	0.2
C5	35.5	35.7	0.2
C6	34.5	34.7	0.2
C7	21.7	22.0	0.3
C8	53.8	54.1	0.3
C10	53.0	53.3	0.3
C11	39.0	39.3	0.3
C12	52.5	52.8	0.3
C13	136.9	137.1	0.2
C14	122.1	122.4	0.3
C15	117.0	117.3	0.3
C16	127.2	127.4	0.2
C17	106.4	106.6	0.2
C18	150.5	150.8	0.3
C19	71.2	71.4	0.2
C20	30.1	30.3	0.2
C21	6.8	7.0	0.2
C22	31.5	31.7	0.2



Tetracyclic lactam (–)-64:

Trifluoromethanesulfonic anhydride (115 μL, 686 μmol, 1.10 equiv) was added via syringe to a solution of lactam (–)-**53** (215 mg, 623 μmol, 1 equiv) and 3-cyanopyridine (77.9 mg, 748 μmol, 1.20 equiv) in acetonitrile (25 mL) at 23 °C. After 5 min, the solution was warmed to 85 °C. After 3 h, the solution was allowed to cool to 23 °C. Sodium trifluoroacetate (254 mg, 1.87 mmol, 3.00 equiv) was added as a solid under an argon atmosphere. After 2 min, water (12.5 mL) was added via syringe. After 5 min, trifluoroacetic acid (382 μL, 4.99 mmol, 8.00 equiv) was added via syringe, and the solution was warmed to 70 °C. After 12 h, the solution was allowed to cool to 23 °C. Saturated aqueous potassium carbonate solution (20 mL) was added to quench the trifluoroacetic acid. Brine (100 mL) and dichloromethane (120 mL) were added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 120 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (1.5% acetone in dichloromethane → 30% ethyl acetate in hexanes) to afford tetracyclic lactam (–)-**64** (110.4 mg, 57.4%) as a beige powder. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (500 MHz, CD_3CN, 73 °C):	δ 7.55 (d, J = 7.9, 1H, C_{14}-**H**), 7.30 (d, J = 7.9, 1H, C_{17}-**H**), 7.17 (app-t, J = 7.9, 1H, C_{16}-**H**), 7.06 (app-t, J = 7.9, 1H, C_{15}-**H**), 6.37 (d, J = 11.9, 1H, C_3-**H**), 6.21 (d, J = 11.9, 1H, C_4-**H**), 4.29–4.22 (m, 1H, C_{10}-$\mathbf{H}_a$), 3.59 (s, 3H, C_{22}-$\mathbf{H}_3$), 3.06–2.95 (m, 2H, C_8-$\mathbf{H}_2$), 3.06–2.95 (m, 1H, C_{11}-$\mathbf{H}_a$), 2.89 (ddd, J = 2.9, 6.0, 12.7, 1H, C_{10}-$\mathbf{H}_b$), 2.74–2.66 (m, 1H, C_{11}-$\mathbf{H}_b$), 1.92–1.58 (m, 2H, C_6-$\mathbf{H}_2$), 1.92–1.58 (m, 2H, C_7-$\mathbf{H}_2$), 1.92–1.58 (m, 2H, C_{20}-$\mathbf{H}_2$), 0.94 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).
^{13}C NMR (125 MHz, CD_3CN, 73 °C):	δ 176.1 ($\mathbf{C}_{19}$), 149.2 ($\mathbf{C}_4$), 138.4 ($\mathbf{C}_{18}$), 135.1 ($\mathbf{C}_2$), 129.1 ($\mathbf{C}_{13}$), 122.7 ($\mathbf{C}_{16}$), 121.2 ($\mathbf{C}_3$), 120.0 ($\mathbf{C}_{15}$), 119.2 ($\mathbf{C}_{14}$), 112.0 ($\mathbf{C}_{12}$), 110.3 ($\mathbf{C}_{17}$), 52.3 ($\mathbf{C}_{10}$), 49.8 ($\mathbf{C}_5$), 48.3 ($\mathbf{C}_8$), 32.5 ($\mathbf{C}_6$), 32.0 ($\mathbf{C}_{20}$), 31.0 ($\mathbf{C}_{22}$), 23.4 ($\mathbf{C}_{11}$), 21.6 ($\mathbf{C}_7$), 9.5 ($\mathbf{C}_{21}$).
FTIR (neat) cm^{-1}:	2926 (m), 1638 (s), 1469 (m), 1321 (m), 1245 (w), 742 (m).
HRMS (DART):	calc'd for $C_{20}H_{25}N_2O$ $[M+H]^+$: 309.1961, found: 309.1971.
$[\alpha]_D^{24}$:	–200 (c = 0.38, $CHCl_3$).
TLC (50% EtOAc in hexanes), R_f:	0.45 (UV, CAM, $KMnO_4$).



(+)-*N*-Methylquebrachamine (2):

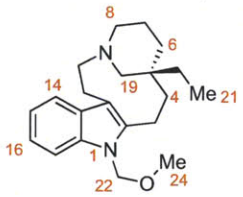
Platinum on charcoal (10% w/w, 10.0 mg, 5.13 μmol, 0.0806 equiv) was added as a solid to a solution of tetracyclic lactam (−)-**64** (19.6 mg, 63.6 μmol, 1 equiv) in tetrahydrofuran (2.0 mL) at 23 °C. The opened reaction vessel was placed in a Parr bomb and sealed under an atmosphere of hydrogen gas (400 psi). After 48 h, the Parr Bomb was opened in air, and the suspension was filtered over Celite. The solids were further extracted with ethyl acetate (30 mL), and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in tetrahydrofuran (1.5 mL) at 23 °C. Lithium aluminum hydride (2.0 M solution in tetrahydrofuran, 160 μL, 320 μmol, 5.0 equiv) was added via syringe. After 5 min, the reaction mixture was warmed to 60 °C. After 12 h, the reaction mixture was allowed to cool to 23 °C. Sodium sulfate decahydrate was added as a solid to quench the aluminum hydride salts. The resulting suspension was filtered over Celite. The solids were further extracted with ethyl acetate (30 mL), and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 5% ethyl acetate in hexanes) to afford (+)-*N*-methylquebrachamine (**2**, 15.3 mg, 81.7% over two steps) as a white gum. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.51 (d, J = 7.8, 1H, C_{14}-**H**), 7.28 (d, J = 7.8, 1H, C_{17}-**H**), 7.15 (app-t, J = 7.8, 1H, C_{16}-**H**), 7.07 (app-t, J = 7.8, 1H, C_{15}-**H**), 3.70 (s, 3H, C_{22}-$\mathbf{H}_3$), 3.36 (d, J = 11.9, 1H, C_{19}-$\mathbf{H}_a$), 3.03–2.82 (m, 1H, C_{11}-$\mathbf{H}_a$), 3.03–2.82 (m, 1H, C_{11}-$\mathbf{H}_b$), 2.79 (app-dd, J = 10.8, 15.3, 1H, C_3-$\mathbf{H}_a$), 2.65 (app-dd, J = 6.8, 15.6, 1H, C_3-$\mathbf{H}_b$), 2.51–2.40 (m, 1H, C_{10}-$\mathbf{H}_a$), 2.51–2.40 (m, 1H, C_8-$\mathbf{H}_a$), 2.34–2.21 (m, 1H, C_{10}-$\mathbf{H}_b$), 2.34–2.21 (m, 1H, C_8-$\mathbf{H}_b$), 1.81 (app-dd, J = 6.8, 13.7, 1H, C_4-$\mathbf{H}_a$), 1.64 (app-t, J = 12.1, 1H, C_4-$\mathbf{H}_b$), 1.61–1.54 (m, 1H, C_7-$\mathbf{H}_a$), 1.51 (d, J = 11.9, 1H, C_{19}-$\mathbf{H}_b$), 1.35–1.24 (m, 1H, C_7-$\mathbf{H}_b$), 1.35–1.24 (m, 1H, C_6-$\mathbf{H}_a$), 1.35–1.24 (m, 1H, C_{20}-$\mathbf{H}_a$), 1.24–1.10 (m, 1H, C_{20}-$\mathbf{H}_b$), 1.24–1.10 (m, 1H, C_6-$\mathbf{H}_b$), 0.90 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 142.2 ($\mathbf{C}_2$), 136.4 ($\mathbf{C}_{18}$), 127.9 ($\mathbf{C}_{13}$), 119.9 ($\mathbf{C}_{16}$), 118.4 ($\mathbf{C}_{15}$), 117.5 ($\mathbf{C}_{14}$), 108.7 ($\mathbf{C}_{17}$), 108.4 ($\mathbf{C}_{12}$), 56.8 ($\mathbf{C}_{19}$), 55.4 ($\mathbf{C}_8$), 53.7 ($\mathbf{C}_{10}$), 37.8 ($\mathbf{C}_5$), 35.0 ($\mathbf{C}_6$), 32.5 ($\mathbf{C}_4$), 32.2 ($\mathbf{C}_{20}$), 29.7 ($\mathbf{C}_{22}$), 22.8 ($\mathbf{C}_7$), 22.7 ($\mathbf{C}_{11}$), 19.2 ($\mathbf{C}_3$), 8.1 ($\mathbf{C}_{21}$).
FTIR (neat) cm^{-1}:	3051 (w), 2928 (s), 2782 (m), 1472 (s), 1371 (s), 1299 (m), 1191 (m), 1140 (m), 1012 (w), 736 (s).
HRMS (DART):	calc'd for $C_{20}H_{29}N_2$ $[M+H]^+$: 297.2325, found: 297.2329
$[\alpha]_D^{24}$:	+102 (c = 0.22, $CHCl_3$).[13]
TLC (Al_2O_3, 5% EtOAc in hexanes), R_f:	0.59 (UV, CAM, $KMnO_4$).

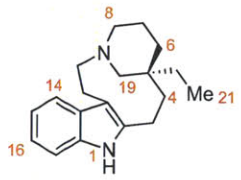
[13] Literature value: $[\alpha]_D^{24}$= +110 ($CHCl_3$), Mokry, J.; Kompis, I.; Dubravkova, L.; Sefcovic, P. *Tetrahedron Lett.* **1962**, *25*, 1185.

Table S3. Comparison of our ^{1}H NMR data for (+)-*N*-methylquebrachamine (2) with literature data for (–)-kopsiyunnanine D (S4) and (+)-quebrachamine (2a):

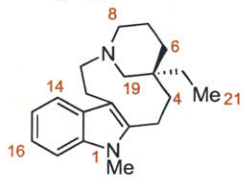
Though early reports concerning (+)-*N*-methylquebrachamine (**2**) have not reported ^{1}H or ^{13}C NMR spectra, later reports[14] have included ^{1}H and ^{13}C NMR data for the structural analog (–)-kopsiyunnanine D (**S4**) and have made assignments based on gCOSY, HSQC and gHMBC data. Furthermore, ^{1}H and ^{13}C NMR spectra have been reported for (+)-quebrachamine (**2a**), though assignments based upon 2D NMR data were not reported. A comparison of the ^{1}H data for the three compounds is presented below; a comparison of the ^{13}C NMR data is presented on page 137.



(–)-kopsiyunnanine D (**S4**)



(+)-quebrachamine (**S5**)



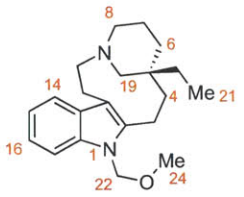
(+)-*N*-methylquebrachamine (**2**)

Assignment	**Takayama's Report**[14] (–)-Kopsiyunnanine D (**S4**) ^{1}H NMR, 500 MHz, $CDCl_3$	**Schrock's Report**[15] (+)-Quebrachamine (**2a**) ^{1}H NMR, 400 MHz, $CDCl_3$	**This Work** (+)-*N*-Methylquebrachamine (**2**) ^{1}H NMR, 500 MHz, $CDCl_3$, 20 °C
N1	-	7.70 (br-s, 1H)	-
C2	-	-	-
C3	2.79 (m, 1H) 2.55 (ddd, J = 1.5, 7.5, 7.5, 1H)	2.74 (ddd, J = 2.0, 10.4, 15.6, 1H) 2.67 (ddd, J = 2.0, 7.2, 15.2, 1H)	2.79 (app-dd, J = 10.8, 15.3, 1H) 2.65 (app-dd, J = 6.8, 15.6, 1H)
C4	1.74 (dd, J = 6.0, 13.0, 1H) 1.55 (m, 1H)	1.92 (ddd, J = 2.0, 6.8, 14.0, 1H) 1.65–1.53 (m, 1H)	1.81 (app-dd, J = 6.8, 13.7, 1H) 1.64 (app-t, J = 12.1, 1H)
C5	-	-	-
C6	1.18 (m, 1H) 1.09 (m, 1H)	1.33–1.08 (m, 2H)	1.35–1.24 (m, 1H) 1.24–1.10 (m, 1H)
C7	1.20 (m, 2H)	1.65–1.53 (m, 1H) 1.33–1.08 (m, 1H)	1.61–1.54 (m, 1H) 1.35–1.24 (m, 1H)
C8	2.32 (dd, J = 5.5, 13.0, 1H) 2.18 (ddd, J = 3.5, 13.0, 13.0, 1H)	2.41 (dd, J = 2.8, 4.4, 1H) 2.25 (dt, J = 2.8, 11.6, 1H)	2.51–2.40 (m, 1H) 2.34–2.21 (m, 1H)
C10	2.40 (ddd, J = 1.5, 4.5, 13.0, 1H)) 2.22 (ddd, J = 4.5, 13.0, 13.0, 1H)	2.48-2.43 (m, 1H)) 2.33 (dt, J = 4.4, 11.6, 1H)	2.51–2.40 (m, 1H) 2.34–2.21 (m, 1H)
C11	2.87 (ddd, J = 4.5, 13.0, 15.0, 1H) 2.77 (m, 1H)	2.94 (ddd, J = 4.8, 11.6, 14.8, 1H) 2.84 (ddd, J = 2.8, 4.4, 14.8, 1H)	3.03–2.82 (m, 1H) 3.03–2.82 (m, 1H)
C12	-	-	-
C13	-	-	-
C14	7.41 (d, J = 7.5, 1H)	7.49-7.47 (m, 1H)	7.51 (d, J = 7.8, 1H)
C15	7.03 (ddd, J = 1.5, 7.5, 7.5, 1H)	7.06 (dt, J = 1.6, 7.2, 1H)	7.07 (app-t, J = 7.8, 1H)
C16	7.08 (ddd, J = 1.5, 7.5, 7.5, 1H)	7.09 (dt, J = 1.6, 7.2, 1H)	7.15 (app-t, J = 7.8, 1H)
C17	7.33 (d, J = 7.5, 1H)	7.29-7.26 (m, 1H)	7.28 (d, J = 7.8, 1H)
C18	-	-	-
C19	3.28 (br-d, J = 12.0, 1H) 1.41 (m, 1H)	3.25 (br-d, J = 11.6, 1H) 1.50 (d, J = 11.6, 1H)	3.36 (d, J = 11.9, 1H) 1.51 (d, J = 11.9, 1H)
C20	1.21 (m, 1H) 1.05 (m, 1H)	1.33–1.08 (m, 2H)	1.35–1.24 (m, 1H) 1.24–1.10 (m, 1H)
C21	0.80 (t, J = 7.5, 3H)	0.85 (t, J = 7.2, 3H)	0.90 (t, J = 7.5, 3H)
C22	5.39 (d, J = 11.5, 1H) 5.35 (d, J = 11.5, 1H)	-	3.70 (s, 3H)
C24	3.19 (s, 3H)	-	-

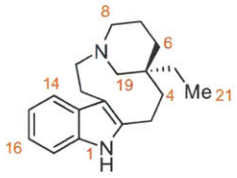
[14] Wu, Y.; Suehiro, M.; Kitajima, M.; Matsuzaki, T.; Hashimoto, S.; Nagaoka, M.; Zhang, R.; Takayama, H. *J. Nat. Prod.* **2009**, *72*, 204.

[15] Sattely, E. S.; Meek, S. J.; Malcolson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

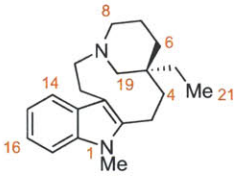
Table S4. Comparison of our ^{13}C NMR data for (+)-*N*-methylquebrachamine (2) with literature data for (–)-kopsiyunnanine D (S4) and (+)-quebrachamine (2a):



(–)-kopsiyunnanine D (**S4**)



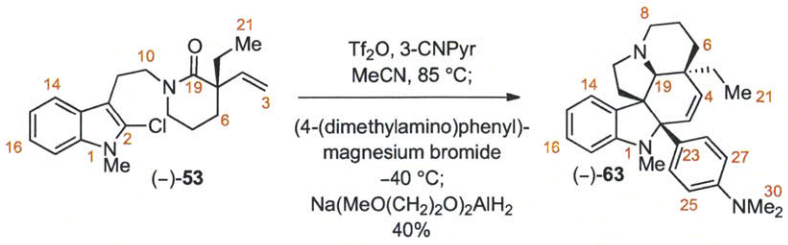
(+)-quebrachamine (**S5**)



(+)-*N*-methylquebrachamine (**2**)

Assignment	**Takayama's Report**[14] (–)-Kopsiyunnanine D (**S4**) ^{13}C NMR, 125 MHz, $CDCl_3$	**Schrock's Report**[15] (+)-Quebrachamine (**2a**) ^{13}C NMR, 100 MHz, $CDCl_3$	**This Work** (+)-*N*-Methyl quebrachamine (**2**) ^{13}C NMR, 125 MHz, $CDCl_3$, 20 °C	**Chemical Shift Difference** $\Delta\delta$ = δ (this work) – δ (Ref. 14)	**Chemical Shift Difference** $\Delta\delta$ = δ (this work) – δ (Ref. 15)
C2	141.8	140.0	142.2	0.4	2.2
C3	18.5	22.1	19.2	0.7	–2.9
C4	32.4	33.6	32.5	0.1	–1.1
C5	37.5	37.3	37.8	0.3	0.5
C6	34.7	34.9	35.0	0.3	0.1
C7	22.6	22.8	22.8	0.2	0.0
C8	55.2	55.2	55.4	0.2	0.2
C10	53.0	53.4	53.7	0.7	0.3
C11	22.3	22.6	22.7	0.4	0.1
C12	110.2	108.9	108.4	–1.8	–0.5
C13	128.3	129.1	127.9	–0.4	–1.2
C14	117.4	117.5	117.5	0.1	0.0
C15	119.2	118.8	118.4	–0.8	–0.4
C16	120.5	120.3	119.9	–0.6	–0.4
C17	108.8	110.1	108.7	–0.1	–1.4
C18	136.7	135.0	136.4	–0.3	1.4
C19	56.5	56.9	56.8	0.3	–0.1
C20	31.8	32.2	32.2	0.4	0.0
C21	7.9	7.9	8.1	0.2	0.2
C22	73.8	-	29.7	–44.1[16]	-[17]
C24	55.6	-	-	-[18]	-[19]

[16] Significant difference in chemical shift is due to oxygenation of C22 in (–)-kopsiyunnanine D (**S4**).
[17] No difference in chemical shift is reported due to absence of C22 in (+)-quebrachamine (**2a**).
[18] No difference in chemical shift is reported due to absence of C24 in (–)-*N*-methylquebrachamine (**2**).
[19] No difference in chemical shift is reported due to absence of C24 in (+)-*N*-methylquebrachamine (**2**) and (+)-quebrachamine (**2a**).



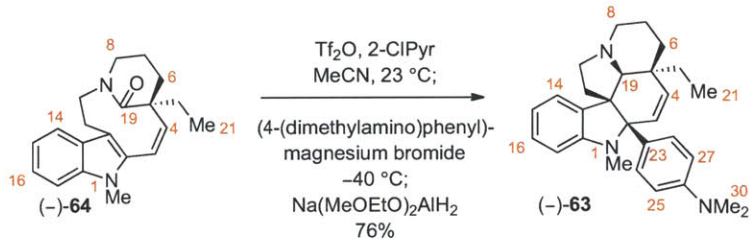
Hexacyclic aniline adduct (–)-63:

Trifluoromethanesulfonic anhydride (4.8 μL, 29 μmol, 1.1 equiv) was added via syringe to a solution of lactam (–)-**53** (9.0 mg, 26 μmol, 1 equiv) and 3-cyanopyridine (3.3 mg, 32 μmol, 1.2 equiv) in acetonitrile (1.0 mL) at 23 °C. After 5 min, the solution was warmed to 85 °C. After 3 h, the solution was cooled to –40 °C, and (4-(dimethylamino)phenyl)magnesium bromide (0.50 M solution in tetrahydrofuran, 130 μL, 65 μmol, 2.5 equiv) was added via syringe. After 30 sec, sodium bis(2-methoxyethoxy)aluminum hydride (65% w/v solution in toluene, 80 μL, 260 μmol, 10 equiv) was added via syringe. After 2 min, acetic acid (50 μL) was added via syringe to quench the aluminum hydride salts, and the solution was allowed warmed to 23 °C. Saturated aqueous potassium carbonate solution (15 mL) and ethyl acetate (15 mL) were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 1.5% ethyl acetate in hexanes) to afford hexacyclic aniline adduct (–)-**63** (4.3 mg, 40%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and ROESY data. The connectivity and relative stereochemistry of hexacyclic aniline adduct (–)-**63** were secured by X-Ray diffraction of a single crystal of its bis-(hydrogen chloride) salt (±)-**63**•2HCl[20] (page 164, vide infra).

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ 7.44 (dd, J = 2.2, 8.7, 1H, C_{28}-**H**), 7.27 (dd, J = 2.2, 8.6, 1H, C_{24}-**H**), 7.06 (app-t, J = 7.7, 1H, C_{16}-**H**), 6.97 (d, J = 7.7, 1H, C_{14}-**H**), 6.69 (dd, J = 2.7, 8.7, 1H, C_{27}-**H**), 6.64 (dd, J = 2.7, 8.6, 1H, C_{25}-**H**), 6.56 (app-t, J = 7.7, 1H, C_{15}-**H**), 6.30 (d, J = 7.7, 1H, C_{17}-**H**), 5.77 (d, J = 10.4, 1H, C_3-**H**), 5.70 (dd, J = 1.4, 10.4, 1H, C_4-**H**), 2.94 (s, 6H, C_{30}-($\mathbf{H}_3$)$_2$), 2.88–2.82 (m, 1H, C_8-$\mathbf{H}_a$), 2.66 (s, 3H, C_{22}-$\mathbf{H}_3$), 2.46 (s, 1H, C_{19}-**H**), 2.19–2.11 (m, 1H, C_{10}-$\mathbf{H}_a$), 2.07-2.00 (m, 1H, C_{10}-$\mathbf{H}_b$), 2.00–1.91 (m, 1H, C_8-$\mathbf{H}_b$), 1.81–1.72 (m, 1H, C_{11}-$\mathbf{H}_a$), 1.70–1.64 (m, 1H, C_6-$\mathbf{H}_a$), 1.64–1.56 (m, 1H, C_7-$\mathbf{H}_a$), 1.56–1.41 (m, 1H, C_7-$\mathbf{H}_b$), 1.56–1.41 (m, 1H, C_{11}-$\mathbf{H}_b$), 1.20 (app-dt, J = 4.2, 12.9, 1H, C_6-$\mathbf{H}_b$), 1.02–0.83 (m, 2H, C_{20}-$\mathbf{H}_2$), 0.65 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).

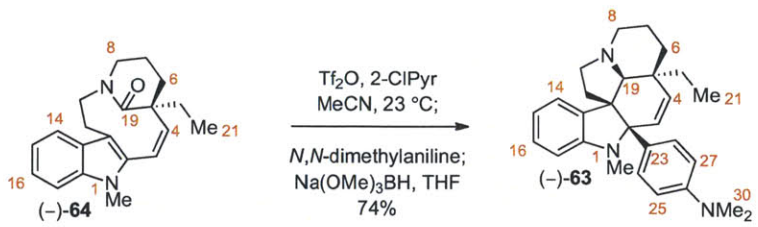
[20] A sample of the corresponding bis-(hydrogen chloride) salt (±)-**63**•2HCl was prepared from hexacyclic aniline adduct (±)-**63** as follows: Hydrogen chloride (2.0 M in diethyl ether, 9.6 μL, 19 μmol, 2.0 equiv) was added via syringe to a solution of hexacyclic aniline adduct (±)-**63** (4.0 mg, 9.7 μmol, 1 equiv) in diethyl ether–chloroform (3:1, 500 μL) at 23 °C. A white solid precipitated immediately. The resulting slurry was concentrated under reduced pressure, and the residue was dissolved in chloroform (200 μL). Vapor diffusion of diethyl ether into this solution provided crystals of hexacyclic aniline adduct bis-(hydrogen chloride) salt (±)-**63**•2HCl suitable for X-Ray diffraction. For a thermal ellipsoid representation of (±)-**63**•2HCl, see page 164.

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 150.7 ($\mathbf{C}_{18}$), 149.2 ($\mathbf{C}_{26}$), 136.1 ($\mathbf{C}_4$), 134.2 ($\mathbf{C}_{13}$), 132.1 ($\mathbf{C}_{28}$), 131.6 ($\mathbf{C}_{23}$), 128.9 ($\mathbf{C}_{24}$), 128.6 ($\mathbf{C}_3$), 127.8 ($\mathbf{C}_{16}$), 123.5 ($\mathbf{C}_{14}$), 116.0 ($\mathbf{C}_{15}$), 112.3 ($\mathbf{C}_{27}$), 111.1 ($\mathbf{C}_{25}$), 104.3 ($\mathbf{C}_{17}$), 73.8 ($\mathbf{C}_2$), 72.3 ($\mathbf{C}_{19}$), 57.4 ($\mathbf{C}_{12}$), 52.4 ($\mathbf{C}_8$), 51.5 ($\mathbf{C}_{10}$), 40.9 ($\mathbf{C}_{30}$), 38.6 ($\mathbf{C}_{11}$), 38.3 ($\mathbf{C}_5$), 35.6 ($\mathbf{C}_{20}$), 34.4 ($\mathbf{C}_6$), 29.8 ($\mathbf{C}_{22}$), 23.6 ($\mathbf{C}_7$), 7.8 ($\mathbf{C}_{21}$).
FTIR (neat) cm^{-1}:	2929 (s), 2791 (m), 1603 (s), 1517 (s), 1497 (s), 1315 (m), 1186 (m), 1121 (m), 734 (s).
HRMS (DART):	calc'd for $C_{28}H_{36}N_3$ $[M+H]^+$: 414.2904, found: 414.2912.
$[\alpha]_D^{24}$:	−186 (c = 0.16, CH_2Cl_2).
TLC (Al_2O_3, 5% EtOAc in hexanes), R_f:	0.65 (UV, CAM, $KMnO_4$).



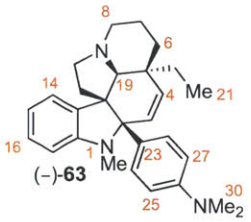
Synthesis of hexacyclic aniline adduct (−)-63 from tetracyclic lactam (−)-64 and (4-(dimethylamino)phenyl)magnesium bromide:

Trifluoromethanesulfonic anhydride (19.7 μL, 117 μmol, 1.10 equiv) was added via syringe to a solution of tetracyclic lactam (−)-**64** (32.7 mg, 106 μmol, 1 equiv) and 2-chloropyridine (11.9 μL, 127 μmol, 1.20 equiv) in acetonitrile (4 mL) at 23 °C. After 10 min, the reaction mixture was cooled to −40 °C, and (4-(dimethylamino)phenyl)magnesium bromide (0.50 M solution in tetrahydrofuran, 320 μL, 160 μmol, 1.5 equiv) was added via syringe. After 30 sec, sodium bis(2-methoxyethoxy)aluminum hydride (65% w/v solution in toluene, 323 μL, 1.06 mmol, 10.0 equiv) was added via syringe. After 2 min, acetic acid (500 μL) was added via syringe to quench the aluminum hydride salts, and the solution was allowed warmed to 23 °C. Saturated aqueous potassium carbonate solution (15 mL) and ethyl acetate (15 mL) were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 1.5% ethyl acetate in hexanes) to afford hexacyclic aniline adduct (−)-**63** (33.1 mg, 75.5%) as a white powder. See page 138 for characterization data for hexacyclic aniline adduct (−)-**63**.



Synthesis of hexacyclic aniline adduct (–)-63 from tetracyclic lactam (–)-64 and *N,N*-dimethylaniline:

Trifluoromethanesulfonic anhydride (5.6 μL, 34 μmol, 1.1 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (9.4 mg, 31 μmol, 1 equiv) and 2-chloropyridine (3.4 μL, 37 μmol, 1.2 equiv) in acetonitrile (0.7 mL) at 23 °C. After 10 min, *N,N*-dimethylaniline (4.6 μL, 37 μmol, 1.2 equiv) was added via syringe. After 90 min, a solution of sodium trimethoxyborohydride (39.0 mg, 305 μmol, 10.0 equiv) in tetrahydrofuran (1.0 mL) was added via cannula. After 2 h, saturated aqueous sodium bicarbonate solution (15 mL) was added to quench the trifluoromethanesulfonate salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 1.5% ethyl acetate in hexanes) to afford hexacyclic aniline adduct (–)-**63** (9.3 mg, 74%) as a white powder. See page 138 for characterization data for hexacyclic aniline adduct (–)-**63**.

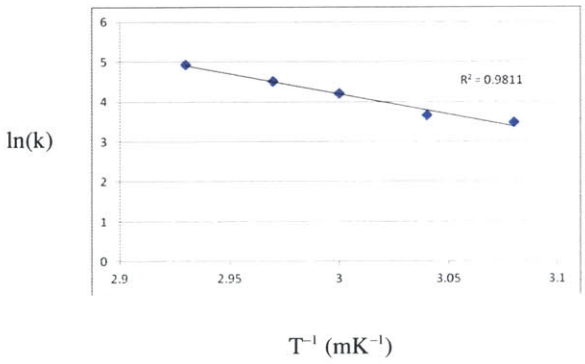


Activation energy calculation for hexacyclic aniline adduct (–)-63 C2–C23 bond rotation:

The rate constant for rotation about the C2–C23 bond of hexacyclic aniline adduct (–)-**63** in dimethyl sulfoxide-d_6 was approximated from changes in the ^{1}H NMR peak separation of the resonances corresponding to the C24 and C28 protons. Data were collected at temperatures sufficiently below the coalescence point of the two resonances. In this regime, defined by $k \approx \Delta\nu$ where k is the exchange rate constant and $\Delta\nu$ = 102.03 Hz is the peak separation of the resonances of the C24 and C28 protons at a temperature where negligible exchange is occurring, the rate constant for rotation can be approximated by $k = \frac{\pi}{\sqrt{2}}\sqrt{(\Delta\nu^2 - \Delta\nu_e{}^2)}$, where $\Delta\nu_e$ is the separation of the resonances of the C24 and C28 protons at the experimental temperature, T.[21]

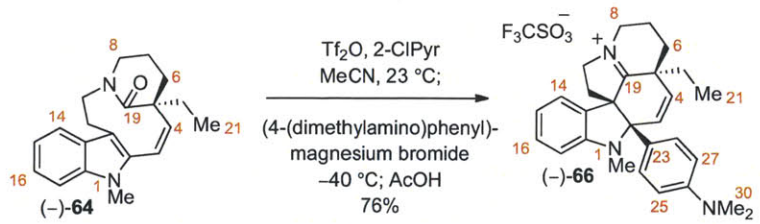
The activation energy E_a was calculated from the Arrhenius equation $k = Ae^{-\frac{E_a}{RT}}$, where R is the Boltzmann constant (1.98 cal/mol) and A is a constant factor. This can be written in form suitable for application of linear least squares regression: $\ln k = -\frac{E_a}{RT} + C$, where C is a constant.

T (°C)	$\Delta\nu_e$ (Hz)	T^{-1} (mK^{-1})	ln(k)
52.0	100.98	3.08	3.48
56.0	100.52	3.04	3.66
60.0	97.46	3.00	4.21
64.0	93.27	2.97	4.52
68.0	80.93	2.93	4.93



Linear least squares gives $\mathbf{E_a}$ = 20.1 ± 0.1 kcal/mol.

[21] (a) Gasparro, F. P.; Kolodny, N. H. *J. Chem. Ed.* **1977**, *54*, 258. (b) Johnson, E. S. In *Advances in Magnetic Resonance*, Waugh, J.S., Ed.; Academic Press: New York, 1956, Vol. 1, Chapter 2, pp. 64–68. (c) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.



Hexacyclic iminium trifluoromethanesulfonate (–)-66:

Trifluoromethanesulfonic anhydride (6.0 μL, 36 μmol, 1.1 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (10.0 mg, 32.4 μmol, 1 equiv) and 2-chloropyridine (3.7 μL, 39 μmol, 1.2 equiv) in acetonitrile (1.5 mL) at 23 °C. After 10 min, the reaction mixture was cooled to –40 °C, and (4-(dimethylamino)phenyl)magnesium bromide (0.50 M solution in tetrahydrofuran, 97 μL, 49 μmol, 1.5 equiv) was added via syringe. After 30 sec, acetic acid (20 μL) was added via syringe to quench the arylmagnesium bromide salts, and the solution was allowed warmed to 23 °C. Saturated aqueous sodium bicarbonate solution (15 mL) and dichloromethane (15 mL) were added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (20 → 80% acetone in hexanes) to afford hexacyclic iminium trifluoromethanesulfonate (–)-**66** (13.9 mg, 76.3%) as a yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, C_6D_6, 72 °C): δ 7.76 (d, J = 7.5, 1H, C_{14}-**H**), 7.06 (d, J = 7.5, 1H, C_{16}-**H**), 7.01 (br-d, J = 8.3, 2H, C_{24}-**H**, C_{28}-**H**), 6.80 (app-t, J =7.5, 1H, C_{15}-**H**), 6.74 (d, J = 8.3, 2H, C_{25}-**H**, C_{27}-**H**), 6.29 (d, J =7.5, 1H, C_{17}-**H**), 5.53 (d, 1H, J = 9.9, C_4-**H**), 5.43 (d, J = 9.9, 1H, C_3-**H**), 4.25 (app-dd, 1H, J = 5.6, 16.6, C_{10}-$\mathbf{H}_a$), 4.17–4.07 (m, 1H, C_8-$\mathbf{H}_a$), 3.57–3.44 (m, 2H, C_{10}-$\mathbf{H}_b$), 2.68 (s, 6H, C_{30}-$(\mathbf{H}_3)_2$), 2.68–2.55 (m, 1H, C_8-$\mathbf{H}_b$), 2.44 (s, 3H, C_{22}-$\mathbf{H}_3$), 2.20–2.10 (m, 1H, C_7-$\mathbf{H}_a$), 2.10–2.02 (m, 1H, C_{11}-$\mathbf{H}_a$), 2.10–2.02 (m, 1H, C_{20}-$\mathbf{H}_a$), 2.02–1.93 (m, 1H, C_{11}-$\mathbf{H}_b$), 1.86–1.73 (m, 1H, C_7-$\mathbf{H}_b$), 1.86–1.73 (m, 1H, C_6-$\mathbf{H}_a$), 1.67–1.55 (m, 1H, C_{20}-$\mathbf{H}_b$), 1.33–1.21 (m, 1H, C_6-$\mathbf{H}_b$), 0.52 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).

^{13}C NMR (125 MHz, C_6D_6, 72 °C): δ 192.0 ($\mathbf{C}_{19}$), 151.8 ($\mathbf{C}_{26}$), 150.6 ($\mathbf{C}_{18}$), 132.7 ($\mathbf{C}_4$), 130.9 ($\mathbf{C}_{13}$), 130.5 ($\mathbf{C}_{16}$), 129.2 ($\mathbf{C}_{24}$, $\mathbf{C}_{28}$), 127.5 ($\mathbf{C}_{14}$), 125.9 ($\mathbf{C}_3$), 123.2 ($\mathbf{C}_{23}$), 122.9 (q, J = 322.4, $F_3\mathbf{C}SO_3^-$), 120.1 ($\mathbf{C}_{15}$), 113.5 ($\mathbf{C}_{25}$, $\mathbf{C}_{27}$), 108.1 ($\mathbf{C}_{17}$), 82.8 ($\mathbf{C}_2$), 69.4 ($\mathbf{C}_{12}$), 59.3 ($\mathbf{C}_8$), 50.7 ($\mathbf{C}_{10}$), 43.5 ($\mathbf{C}_5$), 40.4 ($\mathbf{C}_{30}$), 32.8 ($\mathbf{C}_{11}$), 31.8 ($\mathbf{C}_{20}$), 30.2 ($\mathbf{C}_{22}$), 27.8 ($\mathbf{C}_6$), 17.7 ($\mathbf{C}_7$), 7.8 ($\mathbf{C}_{21}$).

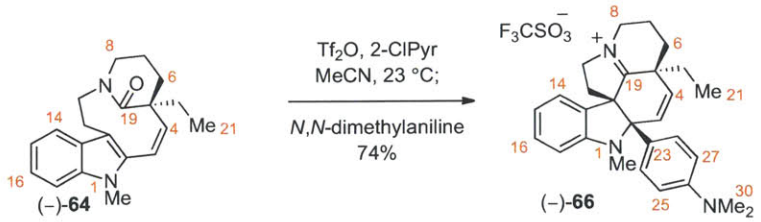
^{19}F NMR (300 MHz, C_6D_6, 20 °C): δ –78.6

FTIR (neat) cm^{-1}: 2925 (m), 1670 (m), 1609 (s), 1521 (m), 1489 (m), 1262 (s), 1157 (s), 1031 (s), 638 (s).

HRMS (DART): calc'd for $C_{28}H_{34}N_3$ [M–$CF_3O_3S^-$]$^+$: 412.2747, found: 412.2745.

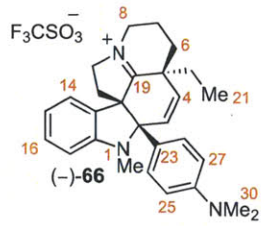
$[\alpha]_D^{24}$: –85 (c = 0.25, CH_2Cl_2).

TLC (Al_2O_3, 75% acetone in hexanes), R_f: 0.26 (UV, CAM, $KMnO_4$).



Synthesis of hexacyclic iminium trifluoromethanesulfonate (–)-66 from tetracyclic lactam (–)-64 and *N,N*-dimethylaniline:

Trifluoromethanesulfonic anhydride (17.2 μL, 102 μmol, 1.10 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (28.7 mg, 93.1 μmol, 1 equiv) and 2-chloropyridine (10.5 μL, 112 μmol, 1.20 equiv) in acetonitrile (3.5 mL) at 23 °C. After 10 min, *N,N*-dimethylaniline (14.2 μL, 112 μmol, 1.20 equiv) was added via syringe. After 90 min, a solution of sodium bicarbonate (150 mg) in water (15 mL) was added to quench the trifluoromethanesulfonic acid salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (20 → 80% acetone in hexanes) to afford hexacyclic iminium trifluoromethanesulfonate (–)-**66** (37.9 mg, 72.5%) as a yellow oil. See page 142 for characterization data for hexacyclic iminium trifluoromethanesulfonate (–)-**66**.

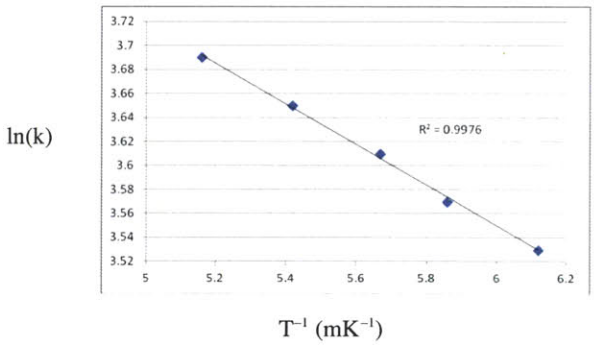


Activation energy calculation for hexacyclic iminium trifluoromethanesulfonate (–)-66 C2–C23 bond rotation:

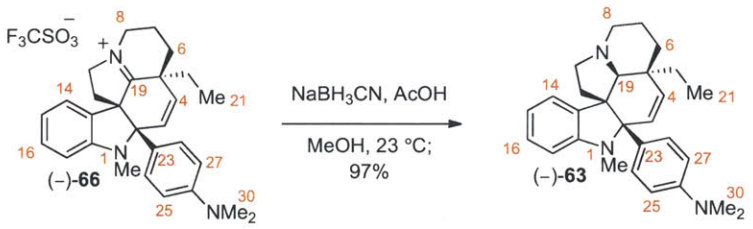
The rate constant for rotation about the C2–C23 bond of hexacyclic iminium trifluoromethanesulfonate (–)-**66** in acetonitrile-d_3 was approximated from changes in the ^{1}H NMR peak separation of the resonances corresponding to the C24 and C28 protons. Data were collected at temperatures sufficiently below the coalescence point of the two resonances. In this regime, defined by $k \approx \Delta\nu$ where k is the exchange rate constant and $\Delta\nu$ = 327.89 Hz is the peak separation of the resonances of the C24 and C28 protons at a temperature where negligible exchange is occurring, the rate constant for rotation can be approximated by $k = \frac{\pi}{\sqrt{2}}\sqrt{(\Delta\nu^2 - \Delta\nu_e{}^2)}$, where $\Delta\nu_e$ is the separation of the resonances of the C24 and C28 protons at the experimental temperature, T.

The activation energy E_a was calculated from the Arrhenius equation $k = Ae^{-\frac{E_a}{RT}}$, where R is the Boltzmann constant (1.98 cal/mol) and A is a constant factor. This can be written in form suitable for application of linear least squares regression: $\ln k = -\frac{E_a}{RT} + C$, where C is a constant.

T (°C)	$\Delta\nu_e$ (Hz)	T^{-1} (mK^{-1})	ln(k)
–2.0	318.41	3.69	5.16
1.0	311.86	3.65	5.42
4.0	300.67	3.61	5.67
7.0	287.73	3.57	5.86
10.0	256.17	3.53	6.12

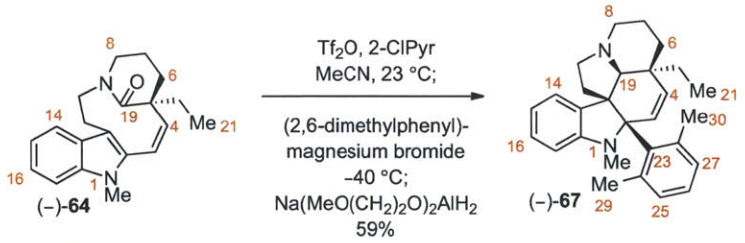


Linear least squares gives $\mathbf{E_a}$ = 11.7 ± 0.2 kcal/mol.



Reduction of hexacyclic iminium trifluoromethanesulfonate (–)-66:

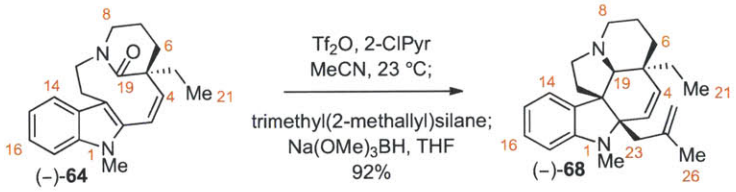
Sodium cyanoborohydride (10.1 mg, 161 μmol, 7.89 equiv) was added as a solid under an argon atmosphere to a solution of hexacyclic iminium trifluoromethanesulfonate (–)-**66** (11.5 mg, 20.4 μmol, 1 equiv) and acetic acid (42.9 μL, 533 μmol, 26.1 equiv) in methanol (2.0 mL) at 23 °C. After 2 h, saturated aqueous sodium bicarbonate solution (15 mL) was added via syringe to quench the trifluoromethanesulfonate salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 1.5% ethyl acetate in hexanes) to afford hexacyclic aniline adduct (–)-**63** (8.2 mg, 97%) as a white powder. See page 138 for characterization data for hexacyclic aniline adduct (–)-**63**. If the reaction is run in the absence of acetic acid, hexacyclic aniline adduct (–)-**63** is afforded in 92% yield.



Hexacyclic xylene adduct (–)-67:

Trifluoromethanesulfonic anhydride (10.5 μL, 62.4 μmol, 1.10 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (17.5 mg, 56.7 μmol, 1 equiv) and 2-chloropyridine (6.4 μL, 68 μmol, 1.2 equiv) in acetonitrile (1.5 mL) at 23 °C. After 10 min, the reaction mixture was cooled to –40 °C, and (2,6-dimethylphenyl)magnesium bromide (1.0 M solution in tetrahydrofuran, 85.1 μL, 85 μmol, 1.5 equiv) was added via syringe. After 10 min, sodium bis(2-methoxyethoxy)aluminum hydride (65% w/v solution in toluene, 104 μL, 340 μmol, 6.00 equiv) was added via syringe. After 2 min, acetic acid (100 μL) was added via syringe to quench the aluminum hydride salts, and the solution was allowed warmed to 23 °C. Saturated aqueous potassium carbonate solution (15 mL) and ethyl acetate (15 mL) were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0 → 2% ethyl acetate in hexanes) to afford hexacyclic xylene adduct (–)-**67** (13.4 mg, 59.2%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

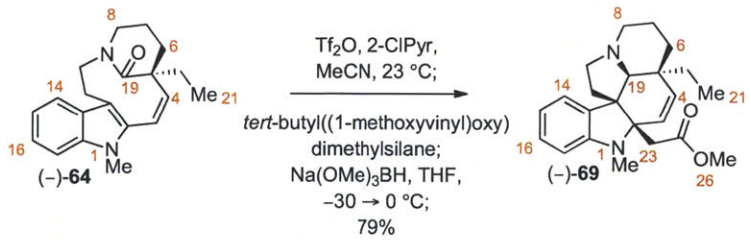
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.03 (t, J = 7.8, 1H, C_{16}-**H**), 7.01–6.95 (m, 1H, C_{25}-**H**), 7.01–6.95 (m, 1H, C_{26}-**H**), 7.01–6.95 (m, 1H, C_{14}-**H**), 6.91 (m, 1H, C_{27}-**H**), 6.50 (app-t, J = 7.8, 1H, C_{15}-**H**), 6.06 (d, J = 10.5, 1H, C_3-**H**), 6.03 (d, J = 7.8, 1H, C_{17}-**H**), 5.44 (dd, J = 1.5, 10.5, 1H, C_4-**H**), 2.89–2.83 (m, 1H, C_8-$\mathbf{H}_a$), 2.72 (s, 3H, C_{29}-$\mathbf{H}_3$), 2.56–2.50 (m, 1H, C_{10}-$\mathbf{H}_a$), 2.49 (s, 3H, C_{22}-$\mathbf{H}_3$), 2.27 (s, 1H, C_{19}-**H**), 2.17 (ddd, J = 5.7, 8.6, 10.5, 1H, C_{10}-$\mathbf{H}_b$), 2.02–1.95 (m, 1H, C_8-$\mathbf{H}_b$), 1.95–1.88 (m, 1H, C_{11}-$\mathbf{H}_a$), 1.92 (s, 3H, C_{30}-$\mathbf{H}_3$), 1.82 (ddd, J = 4.4, 10.5, 14.0, 1H, C_{11}-$\mathbf{H}_b$), 1.65–1.59 (m, 1H, C_6-$\mathbf{H}_a$), 1.57–1.42 (m, 2H, C_7-$\mathbf{H}_2$), 1.29–1.13 (m, 1H, C_6-$\mathbf{H}_b$), 0.81–0.66 (m, 2H, C_{20}-$\mathbf{H}_2$), 0.55 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 149.9 ($\mathbf{C}_{18}$), 142.0 ($\mathbf{C}_{23}$), 140.1 ($\mathbf{C}_{24}$), 139.7 ($\mathbf{C}_{28}$), 134.2 ($\mathbf{C}_{13}$), 132.5 ($\mathbf{C}_3$), 131.6 ($\mathbf{C}_4$), 131.5 ($\mathbf{C}_{25}$), 130.6 ($\mathbf{C}_{27}$), 128.5 ($\mathbf{C}_{16}$), 126.3 ($\mathbf{C}_{26}$), 123.0 ($\mathbf{C}_{14}$), 115.1 ($\mathbf{C}_{15}$), 103.0 ($\mathbf{C}_{17}$), 74.5 ($\mathbf{C}_2$), 74.0 ($\mathbf{C}_{19}$), 57.8 ($\mathbf{C}_{12}$), 52.3 ($\mathbf{C}_8$), 51.8 ($\mathbf{C}_{10}$), 38.4 ($\mathbf{C}_5$), 36.9 ($\mathbf{C}_{11}$), 34.9 ($\mathbf{C}_6$), 34.4 ($\mathbf{C}_{20}$), 28.7 ($\mathbf{C}_{22}$), 25.5 ($\mathbf{C}_{30}$), 23.6 ($\mathbf{C}_{29}$), 23.2 ($\mathbf{C}_7$), 7.9 ($\mathbf{C}_{21}$).
FTIR (neat) cm^{-1}:	2929 (s), 1603 (s), 1503 (s), 1457 (m), 1382 (m), 1188 (m), 666 (s).
HRMS (DART):	calc'd for $C_{28}H_{35}N_2$ $[M+H]^+$: 399.2795, found: 399.2790.
$[\alpha]_D^{24}$:	–145 (c = 0.14, CH_2Cl_2).
TLC (2% EtOAc in hexanes), R_f:	0.26 (UV, CAM, $KMnO_4$).



Pentacyclic methallyl adduct (–)-68:

Trifluoromethanesulfonic anhydride (6.0 μL, 36 μmol, 1.1 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (10.0 mg, 32.4 μmol, 1 equiv) and 2-chloropyridine (3.7 μL, 39 μmol, 1.2 equiv) in acetonitrile (1.3 mL) at 23 °C. After 10 min, trimethyl(2-methallyl)silane (8.5 μL, 49 μmol, 1.5 equiv) was added via syringe. After 90 min, a solution of sodium trimethoxyborohydride (24.9 mg, 195 μmol, 6.00 equiv) in tetrahydrofuran (1.0 mL) was added via cannula. After 2 h, saturated aqueous sodium bicarbonate solution (15 mL) was added to quench the trifluoromethanesulfonate salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (10 → 20% ethyl acetate in hexanes) to afford pentacyclic methallyl adduct (–)-**68** (10.4 mg, 92.0%) as a viscous yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

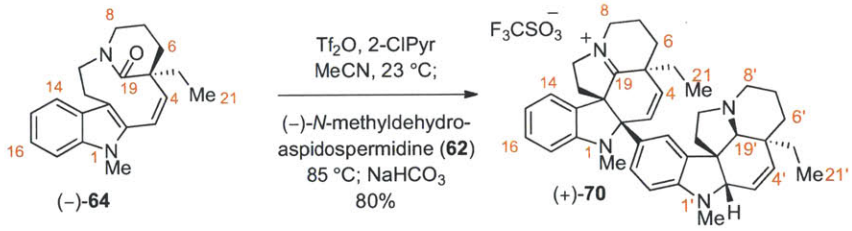
^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.03–6.93 (m, 1H, C_{16}-**H**), 7.03–6.93 (m, 1H, C_{14}-**H**), 6.51 (app-t, J = 7.8, 1H, C_{15}-**H**), 6.10 (d, J = 7.8, 1H, C_{17}-**H**), 5.80 (d, J = 10.3, 1H, C_3-**H**), 5.64 (d, J = 10.3, 1H, C_4-**H**), 4.87–4.76 (m, 2H, C_{25}-**H**$_2$), 3.03–2.94 (m, 1H, C_{10}-**H**$_a$), 3.03–2.94 (m, 1H, C_8-**H**$_a$), 2.69 (s, 3H, C_{22}-**H**$_3$), 2.65–2.55 (m, 1H, C_{11}-**H**$_a$), 2.47 (s, 2H, C_{23}-**H**$_2$), 2.28 (app-q, J = 8.5, 1H, C_{10}-**H**$_b$), 2.06 (s, 1H, C_{19}-**H**), 1.96–1.86 (m, 1H, C_8-**H**$_b$), 1.86–1.76 (m, 1H, C_{11}-**H**$_b$), 1.72 (s, 3H, C_{26}-**H**$_3$), 1.70–1.61 (m, 1H, C_6-**H**$_a$), 1.54–1.43 (m, 2H, C_7-**H**$_2$), 1.16–1.06 (m, 1H, C_6-**H**$_b$), 1.06–0.96 (m, 1H, C_{20}-**H**$_a$), 0.84–0.74 (m, 1H, C_{20}-**H**$_b$), 0.53 (t, J = 7.5, 3H, C_{21}-**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 150.3 (**C**$_{18}$), 143.2 (**C**$_{24}$), 137.2 (**C**$_4$), 136.3 (**C**$_{13}$), 129.5 (**C**$_3$), 128.0 (**C**$_{16}$), 123.2 (**C**$_{14}$), 115.8 (**C**$_{15}$), 114.4 (**C**$_{25}$), 104.1 (**C**$_{17}$), 77.4 (**C**$_{19}$), 68.4 (**C**$_2$), 57.4 (**C**$_{12}$), 53.9 (**C**$_{10}$), 53.0 (**C**$_8$), 45.6 (**C**$_{23}$), 39.0 (**C**$_5$), 36.3 (**C**$_{11}$), 34.7 (**C**$_6$), 33.7 (**C**$_{20}$), 30.0 (**C**$_{22}$), 25.4 (**C**$_{26}$), 23.2 (**C**$_7$), 7.7 (**C**$_{21}$).
FTIR (neat) cm^{-1}:	2927 (s), 1604 (s), 1501 (s), 1462 (s), 1376 (m), 736 (s).
HRMS (DART):	calc'd for $C_{24}H_{33}N_2$ $[M+H]^+$: 349.2638, found: 349.2645.
$[\alpha]_D^{24}$:	–130 (c = 0.15, CH_2Cl_2).
TLC (Al_2O_3, 5% EtOAc in hexanes), R_f:	0.63 (UV, CAM, $KMnO_4$).



Pentacyclic methyl acetate adduct (–)-69:

Trifluoromethanesulfonic anhydride (12.0 μL, 71.3 μmol, 1.10 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (20.0 mg, 64.8 μmol, 1 equiv) and 2-chloropyridine (7.3 μL, 78 μmol, 1.2 equiv) in acetonitrile (2.5 mL) at 23 °C. After 10 min, *tert*-butyl((1-methoxyvinyl)oxy)dimethylsilane (21.2 μL, 97.3 μmol, 1.50 equiv) was added via syringe. After 90 min, the reaction mixture was cooled to –30 °C, and a solution of sodium trimethoxyborohydride (49.8 mg, 389 μmol, 6.00 equiv) in tetrahydrofuran (1.0 mL) was added via cannula. After 30 min, the reaction mixture was allowed to warm slowly to 0 °C. After 30 min, saturated aqueous sodium bicarbonate solution (15 mL) was added to quench the trifluoromethanesulfonate salts, and the resulting biphasic mixture was allowed to warm to 23 °C. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (5 → 10% ethyl acetate in hexanes) to afford pentacyclic methyl acetate adduct (–)-**69** (18.8 mg, 79.1%) as a yellow oil. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C):	δ 7.04–6.93 (m, 1H, C_{14}-**H**), 7.04–6.93 (m, 1H, C_{16}-**H**), 6.54 (app-t, J = 7.8, 1H, C_{15}-**H**), 6.16 (d, J = 7.8, 1H, C_{17}-**H**), 5.84 (d, J = 10.3, 1H, C_3-**H**), 5.70 (d, J = 10.3, 1H, C_4-**H**), 3.46 (s, 3H, C_{26}-**H**$_3$), 3.07–2.99 (m, 1H, C_{10}-**H**$_a$), 2.99–2.90 (m, 1H, C_8-**H**$_a$), 2.80 (d, J = 14.1, 1H, C_{23}-**H**$_a$), 2.75 (d, J = 14.1, 1H, C_{23}-**H**$_b$), 2.72 (s, 3H, C_{22}-**H**$_3$), 2.55–2.45 (m, 1H, C_{11}-**H**$_a$), 2.30 (app-q, J = 8.4, 1H, C_{10}-**H**$_b$), 2.12 (s, 1H, C_{19}-**H**), 1.98–1.81 (m, 1H, C_8-**H**$_b$), 1.98–1.81 (m, 1H, C_{11}-**H**$_b$), 1.73–1.64 (m, 1H, C_6-**H**$_a$), 1.53–1.42 (m, 2H, C_7-**H**$_2$), 1.19–1.02 (m, 1H, C_6-**H**$_b$), 1.19–1.02 (m, 1H, C_{20}-**H**$_a$), 0.92–0.80 (m, 1H, C_{20}-**H**$_b$), 0.56 (t, J = 7.4, 3H, C_{21}-**H**$_3$).
^{13}C NMR (125 MHz, $CDCl_3$, 20 °C):	δ 171.7 (C_{24}), 149.9 (C_{18}), 138.3 (C_4), 135.7 (C_{13}), 127.9 (C_{14}), 127.8 (C_3), 123.0 (C_{16}), 116.6 (C_{15}), 104.8 (C_{27}), 76.3 (C_{19}), 68.9 (C_2), 57.1 (C_{12}), 53.4 (C_{10}), 52.7 (C_8), 51.5 (C_{26}), 42.1 (C_{23}), 39.0 (C_5), 36.6 (C_{11}), 34.8 (C_6), 33.8 (C_{20}), 29.6 (C_{22}), 23.0 (C_7), 7.8 (C_{21}).
FTIR (neat) cm^{-1}:	2934 (s), 1733 (s), 1603 (s), 1494 (s), 1304 (m), 1189 (m), 1156 (m), 737 (m).
HRMS (DART):	calc'd for $C_{23}H_{31}N_2O_2$ $[M+H]^+$: 367.2380, found: 367.2377.
$[\alpha]_D^{24}$:	–95 (c = 0.17, CH_2Cl_2).
TLC (Al_2O_3, 10% EtOAc in hexanes), R_f:	0.26 (UV, CAM, $KMnO_4$).



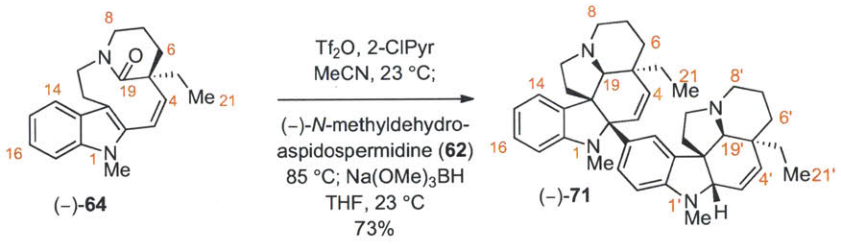
Decacyclic iminium trifluoromethanesulfonate (+)-70:

Trifluoromethanesulfonic anhydride (16.3 μL, 97.0 μmol, 1.10 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (27.2 mg, 88.2 μmol, 1 equiv) and 2-chloropyridine (10.0 μL, 106 μmol, 1.20 equiv) in acetonitrile (2.0 mL) at 23 °C. After 10 min, a solution of (–)-*N*-methyldehydroaspidospermidine (**62**, 26.0 mg, 88.2 μmol, 1.00 equiv) in acetonitrile (2.0 mL) was added via cannula. After 5 min, the reaction mixture was warmed to 85 °C. After 90 min, the reaction mixture was allowed to cool to 23 °C, and a solution of sodium bicarbonate (150 mg) in water (15 mL) was added to quench the trifluoromethanesulfonic acid salts. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (10 → 85% acetone in hexanes) to afford decacyclic iminium trifluoromethanesulfonate (+)-**70** (51.8 mg, 79.9%) as an amorphous orange solid. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, PhMe-d_8, 80 °C): δ 7.86 (d, J = 7.5, 1H, C_{14}-**H**), 7.01 (app-t, J = 7.5, 1H, C_{16}-**H**), 7.01–6.96 (br-s, 1H, $C_{14'}$-**H**), 6.78 (app-t, J = 7.5, 1H, C_{15}-**H**), 6.77–6.66 (br-m, 1H, $C_{16'}$-**H**), 6.30–6.21 (m, 1H, C_{17}-**H**), 6.30–6.21 (m, 1H, $C_{17'}$-**H**), 5.69 (dd, J = 3.8, 10.3, 1H, $C_{3'}$-**H**), 5.56 (d, J = 10.0, 1H, C_4-**H**), 5.51 (d, J = 10.3, 1H, $C_{4'}$-**H**), 5.46 (d, J = 10.0, 1H, C_3-**H**), 4.38–4.25 (m, 1H, C_8-$\mathbf{H_a}$), 4.38–4.25 (m, 1H, C_{10}-$\mathbf{H_a}$), 3.68 (d, J = 3.8, 1H, $C_{2'}$-**H**), 3.38–3.27 (m, 1H, C_8-$\mathbf{H_b}$), 3.07–2.98 (m, 1H, $C_{10'}$-$\mathbf{H_a}$), 2.86–2.79 (m, 1H, $C_{8'}$-$\mathbf{H_a}$), 2.72–2.64 (m, 1H, C_{10}-$\mathbf{H_b}$), 2.64 (s, 3H, $C_{22'}$-$\mathbf{H_3}$), 2.49 (s, 3H, C_{22}-$\mathbf{H_3}$), 2.35–2.26 (m, 1H, $C_{10'}$-$\mathbf{H_b}$), 2.26-2.15 (m, 1H, C_7-$\mathbf{H_a}$), 2.26–2.15 (m, 2H, C_{11}-$\mathbf{H_2}$), 2.15 (s, 1H, C_{19}-**H**), 2.14–2.04 (m, 1H, C_{20}-$\mathbf{H_a}$), 2.14–2.04 (m, 1H, $C_{11'}$-$\mathbf{H_a}$), 1.95–1.88 (m, 1H, C_6-$\mathbf{H_a}$), 1.88–1.74 (m, 1H, C_7-$\mathbf{H_b}$), 1.88–1.74 (m, 1H, $C_{8'}$-$\mathbf{H_b}$), 1.88–1.74 (m, 1H, $C_{11'}$-$\mathbf{H_b}$), 1.68 (dq, J = 6.3, 7.5, 1H, C_{20}-$\mathbf{H_b}$), 1.58–1.47 (m, 1H, $C_{7'}$-$\mathbf{H_a}$), 1.58–1.47 (m, 1H, $C_{6'}$-$\mathbf{H_a}$), 1.39–1.31 (m, 1H, $C_{7'}$-$\mathbf{H_b}$), 1.25–1.17 (m, 1H, C_6-$\mathbf{H_b}$), 1.13–1.04 (m, 1H, $C_{20'}$-$\mathbf{H_a}$), 1.01–0.91 (m, 1H, $C_{6'}$-$\mathbf{H_b}$), 1.01–0.91 (m, 1H, $C_{20'}$-$\mathbf{H_b}$), 0.59 (t, J = 7.5, 3H, C_{21}-$\mathbf{H_3}$), 0.56 (t, J = 7.5, 3H, $C_{21'}$-$\mathbf{H_3}$).

^{13}C NMR (125 MHz, PhMe-d_8, 80 °C): δ 192.2 ($\mathbf{C_{19}}$), 152.0 ($\mathbf{C_{18'}}$), 150.4 ($\mathbf{C_{18}}$), 137.4 ($\mathbf{C_{13'}}$), 136.9 ($\mathbf{C_{4'}}$), 132.7 ($\mathbf{C_4}$), 130.8 ($\mathbf{C_{13}}$), 130.3 ($\mathbf{C_{16}}$), 128.6 ($\mathbf{C_{16'}}$), 127.7 ($\mathbf{C_{14}}$), 125.9 ($\mathbf{C_3}$), 124.0 ($\mathbf{C_{3'}}$), 123.2 ($\mathbf{C_{15'}}$), 122.8 ($\mathbf{C_{14'}}$), 122.5 (q, J = 322.4, $F_3\mathbf{C}SO_3^-$), 120.0 ($\mathbf{C_{15}}$),

	107.9 ($\mathbf{C}_{17}$), 105.6 ($\mathbf{C}_{17'}$), 83.1 ($\mathbf{C}_{2}$), 73.0 ($\mathbf{C}_{19'}$), 71.5 ($\mathbf{C}_{2'}$), 69.6 ($\mathbf{C}_{12}$), 59.2 ($\mathbf{C}_{10}$), 52.9 ($\mathbf{C}_{12'}$), 52.6 ($\mathbf{C}_{8'}$), 52.4 ($\mathbf{C}_{10'}$), 50.7 ($\mathbf{C}_{8}$), 44.4 ($\mathbf{C}_{11'}$), 43.6 ($\mathbf{C}_{5}$), 39.3 ($\mathbf{C}_{5'}$), 36.2 ($\mathbf{C}_{20'}$), 34.6 ($\mathbf{C}_{6'}$), 32.4 ($\mathbf{C}_{11}$), 31.7 ($\mathbf{C}_{22'}$), 31.4 ($\mathbf{C}_{20}$), 29.9 ($\mathbf{C}_{22}$), 28.1 ($\mathbf{C}_{6}$), 23.5 ($\mathbf{C}_{7'}$), 17.6 ($\mathbf{C}_{7}$), 7.7 ($\mathbf{C}_{21}$), 7.6 ($\mathbf{C}_{21'}$).
^{19}F NMR (300 MHz, $CDCl_3$, 20 °C):	δ –78.9
FTIR (neat) cm^{-1}:	2933 (s), 1672 (m), 1608 (s), 1489 (s), 1454 (m), 1262 (s), 1155 (s), 1031 (s), 752 (m).
HRMS (DART):	calc'd for $C_{40}H_{49}N_4$ $[M–CF_3O_3S^-]^+$: 585.3952, found: 585.3941.
$[\alpha]_D^{24}$:	+9 (c = 0.076, CH_2Cl_2).
TLC (Al_2O_3, 75% acetone in hexanes), R_f:	0.48 (UV, CAM, $KMnO_4$).



Decacyclic dimer (–)-71:

Trifluoromethanesulfonic anhydride (7.2 μL, 42 μmol, 1.1 equiv) was added via syringe to a solution of tetracyclic lactam (–)-**64** (11.8 mg, 38.2 μmol, 1 equiv) and 2-chloropyridine (4.3 μL, 46 μmol, 1.2 equiv) in acetonitrile (0.6 mL) at 23 °C. After 10 min, a solution of (–)-*N*-methyldehydroaspidospermidine (**62**, 13.5 mg, 45.9 μmol, 1.20 equiv) in acetonitrile (1.2 mL) was added via cannula. After 5 min, the reaction mixture was warmed to 85 °C. After 90 min, the reaction mixture was allowed to cool to 23 °C, and a solution of sodium trimethoxyborohydride (29.3 mg, 229 μmol, 6.00 equiv) in tetrahydrofuran (1.8 mL) was added via cannula. After 3 h, saturated aqueous sodium bicarbonate solution (15 mL) was added to quench the trifluoromethanesulfonate salts, and the resulting biphasic mixture was allowed to warm to 23 °C. Dichloromethane (15 mL) was added, and the layers were separated. The aqueous layer was further extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (0.5% acetic acid, 20% methanol, 20% tetrahydrofuran in dichloromethane → 30% methanol in dichloromethane) to afford decacyclic dimer (–)-**71** as its acetic acid salt, which was dissolved in ethyl acetate (30 mL) and washed with saturated aqueous potassium carbonate solution (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure to afford decacyclic dimer (–)-**71** (16.3 mg, 72.6%) as a colorless gum. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 20 °C, 1.7:1 atropisomer mixture, * denotes minor atropisomer): δ 7.36 (d, J = 1.7, 1H, $C_{14'}$-**H***), 7.28 (d, J = 8.3, 1H, $C_{16'}$-**H**), 7.11–7.07 (m, 1H, $C_{16'}$-**H***), 7.09–7.06 (m, 1H, C_{16}-**H**), 7.08 (d, J = 1.8, 1H, $C_{14'}$-**H**), 7.04 (app-dt, J = 1.1, 7.5, 1H, C_{16}-**H***), 6.97 (d, J = 7.7, 1H, C_{14}-**H**), 6.97–6.94 (m, 1H, C_{14}-**H***), 6.58 (app-t, J = 7.2, 1H, C_{15}-**H**), 6.55 (app-t, J = 7.3, 1H, C_{15}-**H***), 6.33 (d, J = 7.7, 1H, C_{17}-**H**), 6.30 (d, J = 7.7, 1H, C_{17}-**H***), 6.23 (d, J = 8.3, 1H, $C_{17'}$-**H**), 6.17 (d, J = 8.2, 1H, $C_{17'}$-**H***), 5.98 (dd, J = 4.5, 10.2, 1H, $C_{3'}$-**H**), 5.98–5.95 (m, 1H, $C_{3'}$-**H***), 5.74 (d, J = 10.2, 1H, $C_{4'}$-**H**), 5.73–5.63 (m, 1H, $C_{4'}$-**H***), 5.73–5.63 (m, 1H, C_3-**H**), 5.73–5.63 (m, 1H, C_4-**H**), 5.73–5.63 (m, 1H, C_4-**H***), 5.73–5.63 (m, 1H, C_3-**H***), 3.76–3.71 (m, 1H, $C_{2'}$-**H**), 3.76–3.71 (m, 1H, $C_{2'}$-**H***), 3.16–3.00 (m, 1H, $C_{10'}$-$\mathbf{H}_a$*), 3.16–3.00 (m, 1H, $C_{10'}$-$\mathbf{H}_a$), 3.16–3.00 (m, 1H, $C_{8'}$-$\mathbf{H}_a$*), 3.16–3.00 (m, 1H, $C_{8'}$-$\mathbf{H}_a$), 2.84 (s, 3H, $C_{22'}$-$\mathbf{H}_3$), 2.82 (s, 3H, $C_{22'}$-$\mathbf{H}_3$*), 2.80–2.73 (m, 1H, C_8-$\mathbf{H}_a$), 2.80–2.73 (m, 1H, C_8-$\mathbf{H}_a$*), 2.62 (s, 3H, C_{22}-$\mathbf{H}_3$), 2.61 (s, 3H, C_{22}-$\mathbf{H}_3$*), 2.54 (s, 1H, C_{19}-**H***), 2.52 (s, 1H, C_{19}-**H**), 2.34–2.26 (m, 1H, $C_{10'}$-$\mathbf{H}_b$), 2.26–2.19 (m, 1H, $C_{10'}$-$\mathbf{H}_b$*), 2.17 (s, 1H, $C_{19'}$-**H***), 2.12 (s, 1H, $C_{19'}$-**H**), 2.15–1.83 (m,

1H, $C_{11'}$-$\mathbf{H}_a$), 2.15–1.83 (m, 1H, C_8-$\mathbf{H}_b$), 2.15–1.83 (m, 1H, C_{10}-$\mathbf{H}_2$*), 2.15–1.83 (m, 1H, $C_{8'}$-$\mathbf{H}_b$*), 2.15–1.83 (m, 1H, $C_{11'}$-$\mathbf{H}_a$*), 2.15–1.83 (m, 1H, $C_{11'}$-$\mathbf{H}_b$), 2.15–1.83 (m, 1H, C_{10}-$\mathbf{H}_2$), 2.15–1.83 (m, 1H, $C_{8'}$-$\mathbf{H}_b$), 2.15–1.83 (m, 1H, C_8-$\mathbf{H}_b$*), 2.15–1.83 (m, 1H, $C_{11'}$-$\mathbf{H}_b$*), 2.15–1.83 (m, 1H, C_{11}-$\mathbf{H}_a$), 2.15–1.83 (m, 1H, C_{11}-$\mathbf{H}_a$*), 1.77–1.60 (m, 1H, $C_{6'}$-$\mathbf{H}_a$*), 1.77–1.60 (m, 1H, C_6-$\mathbf{H}_a$*), 1.77–1.60 (m, 1H, C_6-$\mathbf{H}_a$), 1.77–1.60 (m, 1H, $C_{6'}$-$\mathbf{H}_a$), 1.67–1.48 (m, 2H, $C_{7'}$-$\mathbf{H}_2$*), 1.67–1.48 (m, 1H, C_7-$\mathbf{H}_a$*), 1.67–1.48 (m, 1H, C_7-$\mathbf{H}_a$), 1.67–1.48 (m, 1H, $C_{7'}$-$\mathbf{H}_a$), 1.67–1.48 (m, 1H, C_7-$\mathbf{H}_b$), 1.67–1.48 (m, 1H, C_7-$\mathbf{H}_b$*), 1.67–1.48 (m, 1H, $C_{7'}$-$\mathbf{H}_b$), 1.53–1.39 (m, 1H, C_{11}-$\mathbf{H}_b$), 1.53–1.39 (m, 1H, C_{11}-$\mathbf{H}_b$*), 1.32–1.15 (m, 1H, C_6-$\mathbf{H}_b$*), 1.32–1.15 (m, 1H, C_6-$\mathbf{H}_b$), 1.32–1.15 (m, 1H, $C_{6'}$-$\mathbf{H}_b$), 1.32–1.15 (m, 1H, $C_{6'}$-$\mathbf{H}_b$*), 1.15–0.83 (m, 2H, C_{20}-$\mathbf{H}_2$*), 1.15–0.83 (m, 1H, $C_{20'}$-$\mathbf{H}_a$), 1.15–0.83 (m, 2H, $C_{20'}$-$\mathbf{H}_2$*), 1.15–0.83 (m, 1H, C_{20}-$\mathbf{H}_2$), 1.15–0.83 (m, 1H, $C_{20'}$-$\mathbf{H}_b$), 0.66 (t, J = 7.4, 3H, $C_{21'}$-$\mathbf{H}_3$*), 0.65 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$), 0.62 (t, J = 7.4, 3H, C_{21}-$\mathbf{H}_3$*), 0.50 (t, J = 7.5, 3H, $C_{21'}$-$\mathbf{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C, 1.7:1 atropisomer mixture, * denotes minor atropisomer): δ 150.8 ($\mathbf{C}_{18}$), 150.8 ($\mathbf{C}_{18}$*), 149.4 ($\mathbf{C}_{18'}$), 149.3 ($\mathbf{C}_{18'}$*), 139.1 ($\mathbf{C}_{4'}$*), 137.9 ($\mathbf{C}_{4'}$), 135.5 ($\mathbf{C}_4$), 135.4 ($\mathbf{C}_4$*), 134.8 ($\mathbf{C}_{13'}$*), 134.6 ($\mathbf{C}_{13'}$), 134.0 ($\mathbf{C}_{13}$), 133.9 ($\mathbf{C}_{13}$*), 131.8 ($\mathbf{C}_{16'}$), 131.5 ($\mathbf{C}_{15'}$), 131.2 ($\mathbf{C}_{15'}$*), 128.7 ($\mathbf{C}_3$*), 128.4 ($\mathbf{C}_3$), 127.7 ($\mathbf{C}_{16}$), 127.7 ($\mathbf{C}_{16}$*), 127.7 ($\mathbf{C}_{16'}$*), 127.1 ($\mathbf{C}_{14'}$*), 125.1 ($\mathbf{C}_{3'}$), 124.6 ($\mathbf{C}_{3'}$*), 123.5 ($\mathbf{C}_{14}$), 123.5 ($\mathbf{C}_{14}$*), 123.2 ($\mathbf{C}_{14'}$), 116.2 ($\mathbf{C}_{15}$*), 116.1 ($\mathbf{C}_{15}$), 104.7 ($\mathbf{C}_{17'}$), 104.7 ($\mathbf{C}_{17}$*), 104.6 ($\mathbf{C}_{17}$), 103.4 ($\mathbf{C}_{17'}$*), 75.3 ($\mathbf{C}_{19'}$), 74.4 ($\mathbf{C}_2$*), 74.3 ($\mathbf{C}_2$), 74.0 ($\mathbf{C}_{19'}$*), 71.7 ($\mathbf{C}_{2'}$), 71.5 ($\mathbf{C}_{2'}$*), 71.3 ($\mathbf{C}_{19}$), 71.2 ($\mathbf{C}_{19}$*), 57.0 ($\mathbf{C}_{12}$*), 57.0 ($\mathbf{C}_{12}$), 53.3 ($\mathbf{C}_{10'}$*), 53.0 ($\mathbf{C}_{10'}$), 52.9 ($\mathbf{C}_{8'}$*), 52.8 ($\mathbf{C}_{8'}$), 52.3 ($\mathbf{C}_8$*), 52.3 ($\mathbf{C}_{12'}$), 52.1 ($\mathbf{C}_8$), 52.1 ($\mathbf{C}_{12'}$*), 51.2 ($\mathbf{C}_{10}$*), 50.7 ($\mathbf{C}_{10}$), 45.4 ($\mathbf{C}_{11'}$), 44.5 ($\mathbf{C}_{11'}$*), 39.1 ($\mathbf{C}_{5'}$), 39.1 ($\mathbf{C}_{5'}$*), 38.5 ($\mathbf{C}_5$), 38.4 ($\mathbf{C}_5$*), 38.2 ($\mathbf{C}_{11}$*), 38.1 ($\mathbf{C}_{11}$), 36.1 ($\mathbf{C}_{20}$), 36.0 ($\mathbf{C}_{20}$*), 35.4 ($\mathbf{C}_{20'}$), 34.4 ($\mathbf{C}_{6'}$*), 34.3 ($\mathbf{C}_{6'}$), 34.3 ($\mathbf{C}_6$), 34.2 ($\mathbf{C}_6$*), 34.1 ($\mathbf{C}_{20'}$*), 33.4 ($\mathbf{C}_{22'}$), 33.2 ($\mathbf{C}_{22'}$*), 29.9 ($\mathbf{C}_{22}$*), 29.5 ($\mathbf{C}_{22}$), 23.7 ($\mathbf{C}_7$*), 23.6 ($\mathbf{C}_7$), 23.3 ($\mathbf{C}_{7'}$), 23.3 ($\mathbf{C}_{7'}$*), 8.0 ($\mathbf{C}_{21'}$*), 7.9 ($\mathbf{C}_{21}$), 7.9 ($\mathbf{C}_{21}$*), 7.7 ($\mathbf{C}_{21'}$).

FTIR (neat) cm^{-1}: 2928 (s), 2781 (m), 1603 (s), 1494 (s), 1373 (m), 1263 (m), 1190 (m), 1122 (m), 736 (m), 666 (m).

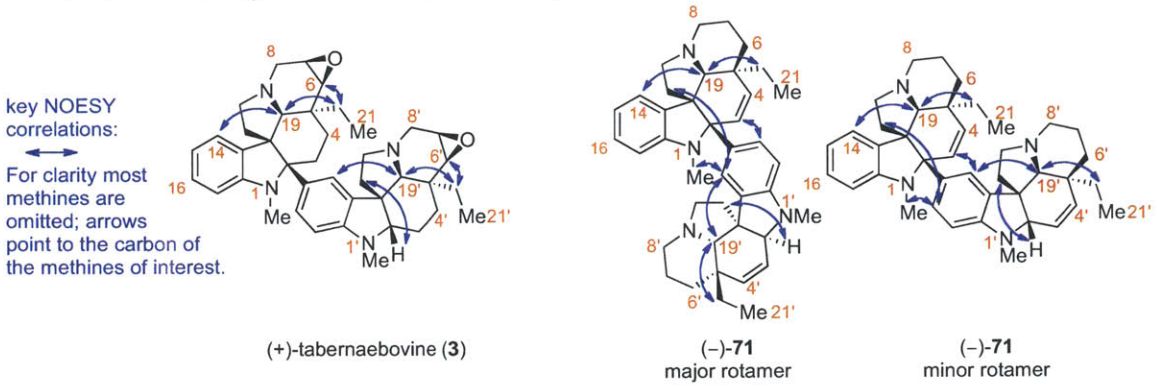
HRMS (DART): calc'd for $C_{40}H_{51}N_4$ $[M+H]^+$: 587.4108, found: 587.4111.

$[\alpha]_D^{24}$: –240, (c = 0.10, CH_2Cl_2).

TLC (Al_2O_3, 10% EtOAc in hexanes), R_f: 0.40 (UV, CAM, $KMnO_4$).

Table S5. Comparison of our ^{1}H NMR data for decacyclic dimer (–)-71 with literature data for (+)-tabernaebovine (3):[22,23]

Blue arrows in the figure below represent key NOESY correlations:



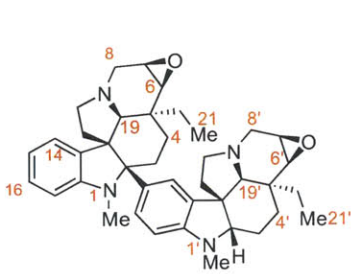
(+)-tabernaebovine (**3**) (–)-**71** major rotamer (–)-**71** minor rotamer

Assignment	Ripperger's Report[22] (+)-Tabernaebovine (**3**) ^{1}H NMR, 500 MHz, $CDCl_3$	This Work (–)-**71** ^{1}H NMR, 500 MHz, $CDCl_3$, 20 °C * denotes minor atropisomer resonance
C2	-	-
C3	2.83 (dd, J = 3.7, 13.4, 1H) 1.83 (m, 1H)	5.73–5.63 (m, 1H) 5.73–5.63* (m, 1H)
C4	2.08 (m, 1H) 1.43 (m, 1H)	5.73–5.63 (m, 1H) 5.73–5.63* (m, 1H)
C5	-	-
C6	2.98 (d, J = 3.9, 1H)	1.77–1.60 (m, 1H) 1.32–1.15 (m, 1H) 1.77–1.60* (m, 1H) 1.32–1.15* (m, 1H)
C7	3.30 (m, 1H)	1.67–1.48 (m, 2H) 1.67–1.48* (m, 2H)
C8	3.49 (dd, J = 13.0, 1.5, 1H) 2.27 (d, J = 12.8, 1H)	2.80–2.73 (m, 1H) 2.15–1.83 (m, 1H) 2.80–2.73* (m, 1H) 2.15–1.83* (m, 1H)
C10	2.78 (dt, J = 3.4, 8.5, 1H) 2.07 (m, 1H)	2.15–1.83 (m, 2H) 2.15–1.83* (m, 2H)
C11	1.59 (m, 1H) 1.50 (m, 1H)	2.15–1.83 (m, 1H) 1.53–1.39 (m, 1H) 2.15–1.83* (m, 1H) 1.53–1.39* (m, 1H)
C12	-	-
C13	-	-
C14	6.90 (d, J = 6.7, 1H)	6.97 (d, J = 7.7, 1H) 6.97-6.94* (m, 1H)
C15	6.54 (dt, J = 0.7, 7.3, 1H)	6.58 (app-t, J = 7.2, 1H) 6.55* (app-t, J = 7.3, 1H)
C16	7.09 (dt, J = 1.2, 7.6, 1H)	7.09-7.06 (m, 1H) 7.04* (app-dt, J = 1.1, 7.5, 1H)
C17	6.27 (d, J = 7.9, 1H)	6.33 (d, J = 7.7, 1H) 6.30* (d, J = 7.7, 1H)
C18	-	-
C19	2.04 (s, 1H)	2.52 (s, 1H) 2.54* (s, 1H)
C20	1.07 (m, 2H)	1.15–0.83 (m, 2H) 1.15–0.83* (m, 2H)

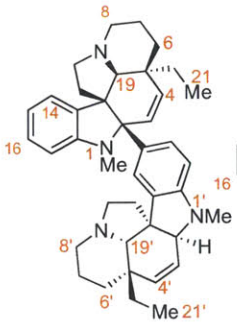
[22] Lim, T. P.; Kamperdick, C.; Sung, T. V.; Adam, G.; Ripperger, H. *Phytochemistry* **1998**, *49*, 1797.

C21	0.68 (t, J = 7.4, 3H)	0.65 (t, J = 7.5, 3H) 0.62* (t, J = 7.4, 3H)
C22	2.46 (s, 3H)	2.62 (s, 3H) 2.61* (s, 3H)
C2'	3.34 (br-d, J = 5.2, 1H)	3.76–3.71 (m, 1H) 3.76–3.71* (m, 1H)
C3'	1.74 (m, 1H) 1.10 (m, 1H)	5.98 (dd, J = 4.5, 10.2, 1H) 5.98–5.95* (m, 1H)
C4'	1.76 (m, 1H) 1.37 (m, 1H)	5.74 (d, J = 10.2, 1H) 5.73–5.63* (m, 1H)
C5'	-	-
C6'	2.88 (br-s, 1H)	1.77–1.60 (m, 1H) 1.32–1.15 (m, 1H) 1.77–1.60* (m, 1H) 1.32–1.15* (m, 1H)
C7'	3.30 (m, 1H)	1.67–1.48 (m, 2H) 1.67–1.48* (m, 2H)
C8'	3.53 (br-d, J = 12.8, 1H) *ca.* 2.30 (m, 1H)	3.16–3.00 (m, 1H) 2.15–1.83 (m, 1H) 3.16–3.00* (m, 1H) 2.15–1.83* (m, 1H)
C10'	3.15 (t, J = 7.6, 1H) 2.07 (m, 1H)	3.16–3.00 (m, 1H) 2.34–2.26 (m, 1H) 3.16–3.00* (m, 1H) 2.26–2.19* (m, 1H)
C11'	2.23 (m, 1H) 1.50 (m, 1H)	2.15–1.83 (m, 2H) 2.15–1.83* (m, 2H)
C12'	-	-
C13'	-	-
C14'	not observed	7.08 (d, J = 1.8, 1H) 7.36* (d, J = 1.7, 1H)
C15'	-	-
C16'	6.93 (br, 1H)	7.28 (d, J = 8.3, 1H) 7.11–7.07* (m, 1H)
C17'	6.24 (br-d, J = 7.0, 1H)	6.23 (d, J = 8.3, 1H) 6.17* (d, J = 8.2, 1H)
C18'	-	-
C19'	2.05	2.12 (s, 1H) 2.17* (s, 1H)
C20'	1.11 (m, 2H)	1.15–0.83 (m, 2H) 1.15–0.83* (m, 2H)
C21'	0.68 (t, J = 7.4, 3H)	0.50 (t, J = 7.5, 3H) 0.66* (t, J = 7.4, 3H)
C22'	2.70 (s, 3H)	2.84 (s, 3H) 2.82* (s, 3H)

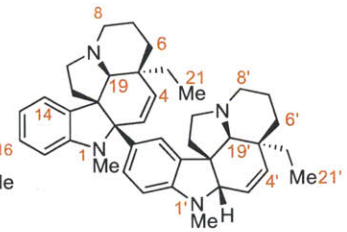
Table S6. Comparison of our ^{13}C NMR data for decacyclic dimer (–)-71 with literature data for (+)-tabernaebovine (3):[23]



(+)-tabernaebovine (**3**)



(–)-**71**
major rotamer



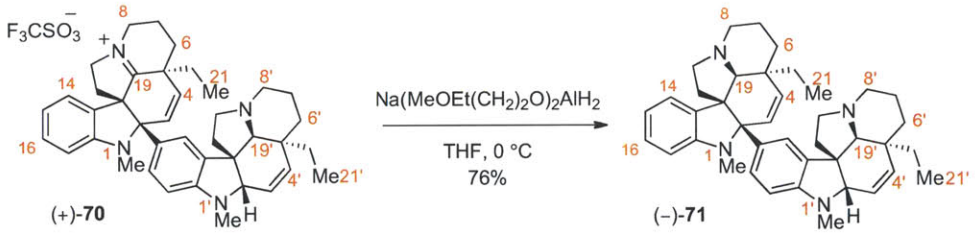
(–)-**71**
minor rotamer

	Ripperger's Report[22] (+)-tabernaebovine (**3**) ^{13}C NMR, 125 MHz, $CDCl_3$	**This Work** (–)-**71** ^{13}C NMR, 125 MHz, $CDCl_3$, 20 °C * denotes minor atropisomer resonance		**Chemical Shift Difference** $\Delta\delta$ = δ (this work) – δ (Ref. 22)
Assign -ment	Chemical Shift	Chemical Shift	Key gHMBC Correlations	
C2	74.8	74.3 74.4*	C3, C4, C11, C19, C22, C14', C16' C3*, C4*, C11*, C19*, C22*, C14'*, C16'*	–0.5 –0.4*
C3	26.0	128.4 128.7*	- -	102.4[24] 102.7*[24]
C4	28.4	135.5 135.4*	C6, C19, C20 C6*, C19*, C20*	107.1[24] 107.0*[24]
C5	32.8	38.5 38.4*	C3, C4, C7, C19, C20, C21 C3*, C4*, C7*, C19*, C20*, C21*	5.7 5.6*
C6	60.2	34.3 34.2*	C4, C7, C8, C19, C20 C4*, C7*, C8*, C19*, C20*	–25.9[25] –26.0*[25]
C7	53.12	23.6 23.7*	C6, C8 C6*, C8*	–29.52[25] –29.42[25]
C8	52.2	52.1 52.3*	C6, C7, C10, C19 C6*, C7*, C10*, C19*	–0.1 0.1*
C10	53.6	50.7 51.2*	C8, C11, C19 C8*, C11*, C19*	–2.9 –2.4*
C11	36.2	38.1 38.2*	C10, C19 C10*, C19*	1.9 2.0*
C12	56.8	57.0 57.0*	C3, C10, C11, C14, C19 C3*, C10*, C11*, C14*, C19*	0.2 0.2*
C13	135.1	134.0 133.9*	C11, C15, C17, C19 C11*, C15*, C17*, C19*	–1.1 –1.2*
C14	123.0	123.5 123.5*	C15, C16 C15*, C16*	0.5 0.5*
C15	115.6	116.1 116.2*	C16, C17 C16*, C17*	0.5 0.6*
C16	128.1	127.7 127.7*	C14, C15 C14*, C15*	–0.4 –0.4*
C17	102.7	104.6 104.7*	C15, C16 C15*, C16*	1.9 2.0*
C18	152.4	150.8 150.8*	C14, C16, C22 C14*, C16*, C22*	–1.6 –1.6*

[23] The lack of epoxides and the presence of alkenes in dimer (–)-**71** results in greater C2–C15' atropisomerism compared to (+)-tabernaebovine (**3**).

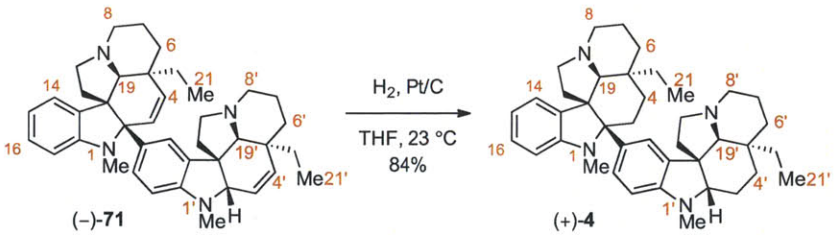
C19	72.8	71.3 71.2*	C4, C6, C8, C10, C11, C20 C4*, C6*, C8*, C10*, C11*, C20*	–1.5 –1.6*
C20	32.9	36.1 36.0*	C4, C6, C19, C21 C4*, C6*, C19*, C21*	3.2 3.1*
C21	8.1	7.9 7.9*	C20 C20*	–0.2 –0.2*
C22	29.0	29.5 29.9*	- -	0.5 0.9*
C2'	73.3	71.7 71.5*	C3', C4', C11', C19', C22' C3'*, C4'*, C11'*, C19'*, C22'*	–1.6 –1.8*
C3'	20.1	125.1 124.6*	C2' C2'*	105.0[26] 104.5*[26]
C4'	24.3	137.9 139.1*	C2', C6', C19', C20' C2'*, C6'*, C19'*, C20'*	113.6[26] 114.8*[26]
C5'	34.5	39.1 39.1*	C3', C4', C7', C19', C20', C21' C3'*, C4'*, C7'*, C19'*, C20'*, C21'*	4.6 4.6*
C6'	57.6	34.3 34.4*	C4', C7', C8', C19', C20' C4'*, C7'*, C8'*, C19'*, C20'*	–23.3[27] –23.2*[27]
C7'	53.1	23.3 23.3*	C6', C8' C6'*, C8'*	–29.8[27] –29.8*[27]
C8'	53.06	52.8 52.9*	C6', C7', C10', C19' C6'*, C7'*, C10'*, C19'*	–0.26 –0.16*
C10'	53.6	53.0 53.3*	C8', C11', C19' C8'*, C11'*, C19'*	–0.6 –0.3*
C11'	41.1	45.4 44.5*	C2', C10', C19' C2'*, C10'*, C19'*	4.3 3.4*
C12'	51.2	52.3 52.1*	C2', C3', C10', C11', C14', C19' C2'*, C3'*, C10'*, C11'*, C14'*, C19'*	1.1 0.9*
C13'	136.4	134.6 134.8*	C11', C17', C19' C11'*, C17'*, C19'*	–1.8 –1.6*
C14'	120.7	123.2 127.1*	C16' C16'*	2.5 6.4*
C15'	132.2	131.5 131.2*	C3, C17' C3*, C17'*	–0.7 –1.0*
C16'	126.9	131.8 127.7*	C14' C14'*	4.9 0.8*
C17'	105.9	104.7 103.4*	C16' C16'*	–1.2 –2.5*
C18'	148.8	149.4 149.3*	C14', C16', C22' C14'*, C16'*, C22'*	0.6 0.5*
C19'	66.7	75.3 74.0*	C2', C4', C6', C8', C10', C11', C20' C2'*, C4'*, C6'*, C8'*, C10'*, C11'*, C20'*	8.6 7.3*
C20'	27.9	35.4 34.1*	C4', C6', C19', C21' C4'*, C6'*, C19'*, C21'*	7.5 6.2*
C21'	7.5	7.7 8.0*	C20' C20'*	0.2 0.5*
C22'	31.5	33.4 33.2*	C2' C2'*	1.9 1.7*

[24] Difference in chemical shift is due to presence and absence of C3–C4 double bond in (–)-**71** and (+)-tabernaebovine (**3**), respectively.
[25] Difference in chemical shift is due to absence and presence of C6–C7 epoxide in (–)-**71** and (+)-tabernaebovine (**3**), respectively.
[26] Difference in chemical shift is due to presence and absence of C3'–C4' double bond in (–)-**71** and (+)-tabernaebovine (**3**), respectively.
[27] Difference in chemical shift is due to absence and presence of C6'–C7' epoxide in (–)-**71** and (+)-tabernaebovine (**3**), respectively.



Synthesis of decacylic dimer (–)-71 by reduction of decacyclic iminium trifluoromethanesulfonate (+)-70:

Sodium bis(2-methoxyethoxy)aluminum hydride (65% w/v solution in toluene, 91.2 μL, 299 μmol, 5.00 equiv) was added via syringe to a solution of decacyclic iminium trifluoromethanesulfonate (+)-**70** (43.9 mg, 59.7 μmol, 1 equiv) in tetrahydrofuran (4.0 mL) at 0 °C. After 30 min, aqueous hydrogen chloride solution (2.0 mL) was added to quench the aluminum hydride salts, and the reaction mixture was allowed to warm to 23 °C. Saturated aqueous potassium carbonate solution (15 mL) and ethyl acetate (15 mL) were added, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (3 → 7% ethyl acetate in hexanes) to afford decacyclic dimer (–)-**71** (26.6 mg, 75.9%) as a colorless gum. See page 151 for characterization data for decacyclic dimer (–)-**71**.



(+)-Dideepoxytabernaebovine (4):

Platinum on charcoal (10% w/w, 50.0 mg, 25.6 μmol, 2.00 equiv) was added as a solid to a solution of decacyclic dimer (–)-**71** (7.5 mg, 13 μmol, 1 equiv) in tetrahydrofuran (1.4 mL) at 23 °C. The opened reaction vessel was placed in a Parr bomb and sealed under an atmosphere of hydrogen gas (900 psi). After 72 h, the Parr Bomb was opened in air, and the suspension was filtered over Celite. The solids were further extracted with ethyl acetate, and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on alumina (0 → 2% ethyl acetate in hexanes) to afford (+)-dideepoxytabernaebovine (**4**, 6.3 mg, 84%) as a colorless gum. Structural assignments were made with additional information from gCOSY, HSQC, gHMBC, and NOESY data.

^{1}H NMR (500 MHz, $CDCl_3$, 53 °C): δ 7.19 (br-d, J = 8.2, 1H, $C_{16'}$-**H**), 7.16 (br-s, 1H, $C_{14'}$-**H**), 7.08 (app-t, J = 7.5, 1H, C_{16}-**H**), 6.94 (d, J = 7.1, 1H, C_{14}-**H**), 6.57 (app-t, J = 7.4, 1H, C_{15}-**H**), 6.30 (d, J = 7.6, 1H, C_{17}-**H**), 6.24 (d, J = 8.2, 1H, $C_{17'}$-**H**), 3.37 (dd, J = 6.0, 10.6, 1H, $C_{2'}$-**H**), 3.07 (app-dt, J = 2.9, 8.9, 1H, $C_{10'}$-$\mathbf{H}_a$), 2.99 (app-d, J = 10.8, 1H, $C_{8'}$-$\mathbf{H}_a$), 2.86 (app-d, J = 9.5, 1H, C_8-$\mathbf{H}_a$), 2.73 (s, 3H, $C_{22'}$-$\mathbf{H}_3$), 2.60–2.51 (m, 1H, C_3-$\mathbf{H}_a$), 2.50 (s, 3H, C_{22}-$\mathbf{H}_3$), 2.32–2.20 (m, 1H, $C_{11'}$-$\mathbf{H}_a$), 2.32–2.20 (m, 1H, C_{10}-$\mathbf{H}_a$), 2.17 (s, 1H, C_{19}-**H**), 2.17–2.06 (m, 1H, $C_{10'}$-$\mathbf{H}_b$), 2.17–2.06 (m, 1H, C_4-$\mathbf{H}_a$), 2.03 (s, 1H, $C_{19'}$-**H**), 1.98–1.82 (m, 1H, C_{10}-$\mathbf{H}_b$), 1.98–1.82 (m, 1H, $C_{8'}$-$\mathbf{H}_b$), 1.98–1.82 (m, 1H, C_8-$\mathbf{H}_b$), 1.98–1.82 (m, 1H, $C_{4'}$-$\mathbf{H}_a$), 1.98–1.82 (m, 1H, C_{11}-$\mathbf{H}_a$), 1.82–1.64 (m, 1H C_3-$\mathbf{H}_b$), 1.82–1.64 (m, 1H, $C_{3'}$-$\mathbf{H}_a$), 1.82–1.64 (m, 1H, C_7-$\mathbf{H}_a$), 1.82–1.64 (m, 1H, $C_{7'}$-$\mathbf{H}_a$), 1.63–1.28 (m, 1H, $C_{6'}$-$\mathbf{H}_a$), 1.63–1.28 (m, 1H, C_6-$\mathbf{H}_a$), 1.63–1.28 (m, 1H, C_7-$\mathbf{H}_b$), 1.63–1.28 (m, 1H, $C_{7'}$-$\mathbf{H}_b$), 1.63–1.28 (m, 1H, $C_{11'}$-$\mathbf{H}_b$), 1.63–1.28 (m, 1H, C_{11}-$\mathbf{H}_b$), 1.63–1.28 (m, 1H, C_4-$\mathbf{H}_b$), 1.63–1.28 (m, 1H, $C_{20'}$-$\mathbf{H}_a$), 1.28–1.17 (m, 1H, C_{20}-$\mathbf{H}_a$), 1.28–1.17 (m, 1H, $C_{3'}$-$\mathbf{H}_b$), 1.16–0.98 (m, 1H, C_6-$\mathbf{H}_b$), 1.16–0.98 (m, 1H, $C_{4'}$-$\mathbf{H}_b$), 1.16–0.98 (m, 1H, $C_{6'}$-$\mathbf{H}_b$), 0.98–0.82 (m, 1H, C_{20}-$\mathbf{H}_b$), 0.78–0.65 (m, 1H, $C_{20'}$-$\mathbf{H}_b$), 0.57 (t, J = 7.5, 3H, C_{21}-$\mathbf{H}_3$), 0.53 (t, J = 7.3, 3H, $C_{21'}$-$\mathbf{H}_3$).

^{13}C NMR (125 MHz, $CDCl_3$, 20 °C): δ 151.4 ($\mathbf{C}_{18}$), 149.1 ($\mathbf{C}_{18'}$), 135.9 ($\mathbf{C}_{13}$), 135.8 ($\mathbf{C}_{13'}$), 133.4 ($\mathbf{C}_{15'}$), 127.8 ($\mathbf{C}_{16}$), 127.7 ($\mathbf{C}_{16'}$), 123.4 ($\mathbf{C}_{14}$), 123.3 ($\mathbf{C}_{14'}$), 116.5 ($\mathbf{C}_{15}$), 105.4 ($\mathbf{C}_{17'}$), 105.1 ($\mathbf{C}_{17}$), 74.5 ($\mathbf{C}_{19}$), 74.1 ($\mathbf{C}_2$), 72.0 ($\mathbf{C}_{2'}$), 71.6 ($\mathbf{C}_{19'}$), 57.1 ($\mathbf{C}_{12}$), 54.1 ($\mathbf{C}_{8'}$), 53.5 ($\mathbf{C}_8$), 53.3 ($\mathbf{C}_{10'}$), 52.7 ($\mathbf{C}_{10}$), 51.9 ($\mathbf{C}_{12'}$), 39.5 ($\mathbf{C}_{11'}$), 37.3 ($\mathbf{C}_{11}$), 35.6 ($\mathbf{C}_6$), 35.3 ($\mathbf{C}_{5'}$), 34.6 ($\mathbf{C}_{6'}$), 31.8 ($\mathbf{C}_{20}$),

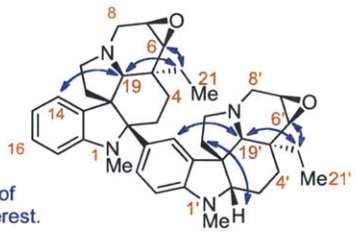
	31.8 ($\mathbf{C}_5$), 31.7 ($\mathbf{C}_{22'}$), 30.3 ($\mathbf{C}_{20'}$), 29.3 ($\mathbf{C}_{22}$), 28.8 ($\mathbf{C}_3$), 26.4 ($\mathbf{C}_4$), 23.2 ($\mathbf{C}_{4'}$), 22.4 ($\mathbf{C}_{3'}$), 22.3 ($\mathbf{C}_7$), 22.0 ($\mathbf{C}_{7'}$), 7.6 ($\mathbf{C}_{21}$), 6.8 ($\mathbf{C}_{21'}$).
FTIR (neat) cm^{-1}:	2929 (s), 1604 (s), 1490 (s), 1375 (m), 1262 (m), 1181 (m), 1122 (m), 801 (m), 737 (m), 666 (m).
HRMS (DART):	calc'd for $C_{40}H_{55}N_4$ $[M+H]^+$: 591.4421, found: 591.4420.
$[\alpha]_D^{24}$:	+144, (c = 0.10, $CHCl_3$).
TLC (Al_2O_3, 10% EtOAc in hexanes), R_f:	0.48 (UV, CAM, $KMnO_4$).

Table S7. Comparison of our ^{1}H NMR data for (+)-dideepoxytabernaebovine (4) with literature data for (+)-tabernaebovine (3):[28]

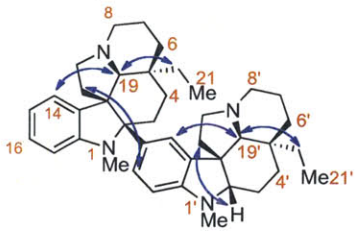
Blue arrows in the figure below represent key reported NOESY correlations:

key NOESY correlations: ⟷

For clarity most methines are omitted; arrows point to the carbon of the methines of interest.



(+)-tabernaebovine (**3**)



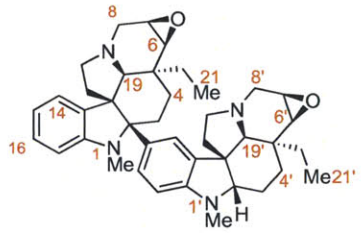
(+)-dideepoxytabernaebovine (**4**)

Assignment	Ripperger's Report[22] (+)-Tabernaebovine (**3**) ^{1}H NMR, 500 MHz, $CDCl_3$	This Work (+)-Dideepoxytabernaebovine (**4**) ^{1}H NMR, 500 MHz, $CDCl_3$, 53 °C
C2	-	-
C3	2.83 (dd, J = 3.7, 13.4, 1H) 1.83 (m, 1H)	2.60–2.51 (m, 1H) 1.82–1.64 (m, 1H)
C4	2.08 (m, 1H) 1.43 (m, 1H)	2.17–2.06 (m, 1H) 1.63–1.28 (m, 1H)
C5	-	-
C6	2.98 (d, J = 3.9, 1H)	1.63–1.28 (m, 1H) 1.16–0.98 (m, 1H)
C7	3.30 (m, 1H)	1.82–1.64 (m, 1H) 1.63–1.28 (m, 1H)
C8	3.49 (dd, J = 13.0, 1.5, 1H) 2.27 (d, J = 12.8, 1H)	2.86 (app-d, J = 9.5, 1H) 1.98–1.82 (m, 1H)
C10	2.78 (dt, J = 3.4, 8.5, 1H) 2.07 (m, 1H)	2.32–2.20 (m, 1H) 1.98–1.82 (m, 1H)
C11	1.59 (m, 1H) 1.50 (m, 1H)	1.98–1.82 (m, 1H) 1.63–1.28 (m, 1H)
C12	-	-
C13	-	-
C14	6.90 (d, J = 6.7, 1H)	6.94 (d, J = 7.1, 1H)
C15	6.54 (dt, J = 0.7, 7.3, 1H)	6.57 (app-t, J = 7.4, 1H)
C16	7.09 (dt, J = 1.2, 7.6, 1H)	7.08 (app-t, J = 7.5, 1H)
C17	6.27 (d, J = 7.9, 1H)	6.30 (d, J = 7.6, 1H)
C18	-	-
C19	2.04 (s, 1H)	2.17 (s, 1H)
C20	1.07 (m, 2H)	1.28–1.17 (m, 1H) 0.98–0.82 (m, 1H)
C21	0.68 (t, J = 7.4, 3H)	0.57 (t, J = 7.5, 3H)
C22	2.46 (s, 3H)	2.50 (s, 3H)
C2'	3.34 (br-d, J = 5.2, 1H)	3.37 (dd, J = 6.0, 10.6, 1H)
C3'	1.74 (m, 1H) 1.10 (m, 1H)	1.82–1.64 (m, 1H) 1.28–1.17 (m, 1H)
C4'	1.76 (m, 1H) 1.37 (m, 1H)	1.98–1.82 (m, 1H) 1.16–0.98 (m, 1H)
C5'	-	-
C6'	2.88 (br-s, 1H)	1.63–1.28 (m, 1H) 1.16–0.98 (m, 1H)
C7'	3.30 (m, 1H)	1.82–1.64 (m, 1H) 1.63–1.28 (m, 1H)
C8'	3.53 (br-d, J = 12.8, 1H) *ca.* 2.30 (m, 1H)	2.99 (app-d, J = 10.8, 1H) 1.98–1.82 (m, 1H)

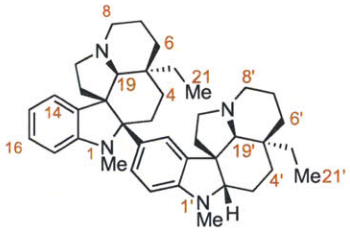
[28] The lack of epoxides in (+)-dideepoxytabernaebovine (**4**) results in local variation compared to (+)-tabernaebovine (**3**).

C10'	3.15 (t, J = 7.6, 1H) 2.07 (m, 1H)	3.07 (app-dt, J = 2.9, 8.9, 1H) 2.17–2.06 (m, 1H)
C11'	2.23 (m, 1H) 1.50 (m, 1H)	2.32–2.20 (m, 1H) 1.63–1.28 (m, 1H)
C12'	-	-
C13'	-	-
C14'	not observed	7.16 (br-s, 1H)
C15'	-	-
C16'	6.93 (br, 1H)	7.19 (br-d, J = 8.2, 1H)
C17'	6.24 (br-d, J = 7.0, 1H)	6.24 (d, J = 8.2, 1H)
C18'	-	-
C19'	2.05	2.03 (s, 1H)
C20'	1.11 (m, 2H)	1.63–1.28 (m, 1H) 0.78–0.65 (m, 1H)
C21'	0.68 (t, J = 7.4, 3H)	0.53 (t, J = 7.3, 3H)
C22'	2.70 (s, 3H)	2.73 (s, 3H)

Table S8. Comparison of our ^{13}C NMR data for (+)-dideepoxytabernaebovine (4) with literature data for (+)-tabernaebovine (3):[29]



(+)-tabernaebovine (**3**)



(+)-dideepoxytabernaebovine (**4**)

	Ripperger's Report[22] (+)-Tabernaebovine (**3**) ^{13}C NMR, 125 MHz, $CDCl_3$	**This Work** (+)-Dideepoxytabernaebovine (**4**) ^{13}C NMR, 125 MHz, $CDCl_3$, 20 °C		**Chemical Shift Difference** $\Delta\delta$ = δ (this work) – δ (Ref. 22)
Assign-ment	Chemical Shift	Chemical Shift	Key gHMBC Correlations	
C2	74.8	74.1	C4, C11, C22, C19, C14', C16'	–0.7
C3	26.0	28.8	-	2.8
C4	28.4	26.4	C6, C19, C20	–2.0
C5	32.8	31.8	C3, C7, C19, C21	–1.0
C6	60.2	35.6	C4, C8, C19, C20	–24.6[30]
C7	53.12	22.3	-	–30.82[30]
C8	52.2	53.5	C6, C10, C19	1.3
C10	53.6	52.7	C8, C19	–0.9
C11	36.2	37.3	C19	1.1
C12	56.8	57.1	C3, C10, C14	0.3
C13	135.1	135.9	C11, C15, C17, C19	0.8
C14	123.0	123.4	C16	0.4
C15	115.6	116.5	C17	0.9
C16	128.1	127.8	C14	–0.3
C17	102.7	105.1	C15	2.4
C18	152.4	151.4	C14, C16, C22	–1.0
C19	72.8	74.5	C4, C6, C8, C10, C11, C20	1.7
C20	32.9	31.8	C4, C6, C19, C21	–1.1
C21	8.1	7.6	-	–0.5
C22	29.0	29.3	-	0.3
C2'	73.3	72.0	C4', C11', C19', C22'	–1.3
C3'	20.1	22.4	-	2.3
C4'	24.3	23.2	C2', C6', C19', C20'	–1.1
C5'	34.5	35.3	C3', C7', C19', C21'	0.8
C6'	57.6	34.6	C4', C8', C19', C20'	–23.0[31]
C7'	53.1	22.0	-	–31.1[31]
C8'	53.06	54.1	C6', C10', C19'	1.04
C10'	53.6	53.3	C8', C19'	–0.3
C11'	41.1	39.5	C2', C19'	–0.6
C12'	51.2	51.9	C3', C10', C14', C19'	0.7
C13'	136.4	135.8	C11', C17', C19'	–0.6
C14'	120.7	123.3	C16'	2.6
C15'	132.2	133.4	C3, C17'	1.2
C16'	126.9	127.7	C14'	0.8
C17'	105.9	105.4	-	–0.5

[29] The lack of epoxides in (+)-dideepoxytabernaebovine (**4**) results in local variation compared to (+)-tabernaebovine (**3**).

C18'	148.8	149.1	C14', C16', C22'	0.3
C19'	66.7	71.6	C2', C4', C6', C8', C10', C11', C20'	4.9
C20'	27.9	30.3	C4', C6', C19', C21'	2.4
C21'	7.5	6.8	-	–0.7
C22'	31.5	31.7	C2'	0.2

[30] Difference in chemical shift is due to absence and presence of C6–C7 epoxide in (+)-dideepoxytabernaebovine (**4**) and (+)-tabernaebovine (**3**), respectively.

[31] Difference in chemical shift is due to absence and presence of C6'–C7' epoxide in (+)-dideepoxytabernaebovine (**4**) and (+)-tabernaebovine (**3**), respectively.

Crystal structure of diammonium dichloride (±)-63•2HCl.

Structural parameters for diammonium dichloride (±)-**63**•2HCl are freely available from the Cambridge Crystallographic Data Center under CCDC 862060.

View 1:

View 2:

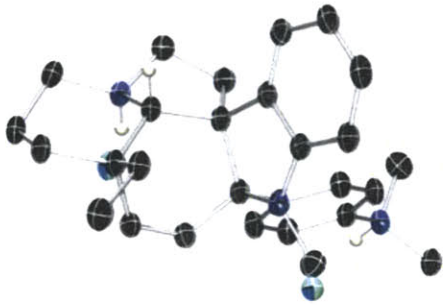


Table S9. Crystal data and structure refinement for (±)-**63**•2HCl.

Identification code	x8_11133	
Empirical formula	C28 H38.66 Cl2 N3 O1.33	
Formula weight	509.50	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 12.4338(15) Å	α= 90°.
	b = 12.6833(16) Å	β= 105.660(2)°.
	c = 17.824(2) Å	γ = 90°.
Volume	2706.6(6) $Å^3$	
Z	4	
Density (calculated)	1.250 Mg/m^3	
Absorption coefficient	0.267 mm^{-1}	
F(000)	1089	
Crystal size	0.30 x 0.09 x 0.02 mm^3	
Theta range for data collection	1.79 to 28.91°.	
Index ranges	-16<=h<=16, -17<=k<=17, -24<=l<=24	
Reflections collected	57036	
Independent reflections	7129 [R(int) = 0.0547]	
Completeness to theta = 28.91°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9947 and 0.9243	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7129 / 29 / 356	
Goodness-of-fit on F^2	1.017	
Final R indices [I>2sigma(I)]	R1 = 0.0413, wR2 = 0.0954	
R indices (all data)	R1 = 0.0706, wR2 = 0.1113	
Largest diff. peak and hole	0.530 and -0.242 $e.Å^{-3}$	

Table S10. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for (±)-**63**•2HCl. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	-1713(1)	8982(1)	-1123(1)	29(1)
Cl(2)	-1102(1)	7643(1)	-4549(1)	30(1)
N(1)	3463(1)	9333(1)	-3315(1)	23(1)
C(2)	2326(1)	8847(2)	-3539(1)	22(1)
C(3)	1564(1)	9560(2)	-4134(1)	24(1)
C(4)	1454(1)	9523(2)	-4896(1)	23(1)
C(5)	2043(1)	8717(2)	-5265(1)	23(1)
C(6)	1396(1)	8504(2)	-6125(1)	25(1)
C(7)	318(1)	7880(2)	-6225(1)	27(1)
C(8)	553(1)	6844(2)	-5791(1)	26(1)
N(9)	1053(1)	7108(1)	-4951(1)	23(1)
C(10)	1318(2)	6207(2)	-4396(1)	27(1)
C(11)	1920(2)	6774(2)	-3645(1)	26(1)
C(12)	2550(1)	7728(1)	-3886(1)	22(1)
C(13)	3812(1)	7622(2)	-3586(1)	23(1)
C(14)	4484(2)	6756(2)	-3593(1)	28(1)
C(15)	5641(2)	6844(2)	-3281(1)	31(1)
C(16)	6097(2)	7794(2)	-2965(1)	30(1)
C(17)	5431(1)	8674(2)	-2934(1)	27(1)
C(18)	4278(1)	8572(2)	-3255(1)	23(1)
C(19)	2155(1)	7688(1)	-4798(1)	22(1)
C(20)	3235(1)	9104(2)	-5248(1)	26(1)
C(21)	3260(2)	10052(2)	-5772(1)	33(1)
C(22)	3675(2)	10317(2)	-2890(1)	31(1)
C(23)	1891(1)	8722(2)	-2813(1)	23(1)
C(24)	2624(1)	8446(2)	-2099(1)	25(1)
C(25)	2253(1)	8296(2)	-1437(1)	26(1)
C(26)	1124(1)	8430(2)	-1497(1)	24(1)
C(27)	376(1)	8705(2)	-2194(1)	28(1)
C(28)	759(1)	8845(2)	-2855(1)	28(1)
N(29)	708(1)	8276(1)	-803(1)	25(1)
C(30)	843(2)	7166(2)	-513(1)	34(1)
C(31)	1230(2)	9023(2)	-157(1)	30(1)
O(1S)	-1326(5)	5786(5)	-3361(3)	72(2)
O(1T)	-1036(8)	5537(9)	-3607(8)	63(3)
O(2T)	-1118(4)	6723(4)	-1925(2)	35(1)

Table S11. Bond lengths [Å] and angles [°] for (±)-**63**•2HCl.

N(1)-C(18)	1.383(2)
N(1)-C(22)	1.447(2)
N(1)-C(2)	1.494(2)
C(2)-C(3)	1.517(2)
C(2)-C(23)	1.539(2)
C(2)-C(12)	1.602(2)
C(3)-C(4)	1.327(2)
C(4)-C(5)	1.510(2)
C(5)-C(19)	1.533(2)
C(5)-C(6)	1.549(2)
C(5)-C(20)	1.554(2)
C(6)-C(7)	1.525(2)
C(7)-C(8)	1.513(3)
C(8)-N(9)	1.497(2)
N(9)-C(10)	1.489(2)
N(9)-C(19)	1.514(2)
C(10)-C(11)	1.526(2)
C(11)-C(12)	1.564(2)
C(12)-C(13)	1.521(2)
C(12)-C(19)	1.567(2)
C(13)-C(14)	1.382(3)
C(13)-C(18)	1.396(3)
C(14)-C(15)	1.400(3)
C(15)-C(16)	1.384(3)
C(16)-C(17)	1.400(3)
C(17)-C(18)	1.399(2)
C(20)-C(21)	1.528(3)
C(23)-C(24)	1.395(2)
C(23)-C(28)	1.397(2)
C(24)-C(25)	1.392(2)
C(25)-C(26)	1.388(2)
C(26)-C(27)	1.380(2)
C(26)-N(29)	1.478(2)
C(27)-C(28)	1.397(2)
N(29)-C(30)	1.493(3)
N(29)-C(31)	1.496(2)
C(18)-N(1)-C(22)	122.32(15)
C(18)-N(1)-C(2)	110.73(14)
C(22)-N(1)-C(2)	121.41(14)
N(1)-C(2)-C(3)	107.90(14)
N(1)-C(2)-C(23)	109.91(13)
C(3)-C(2)-C(23)	110.77(13)
N(1)-C(2)-C(12)	102.59(12)
C(3)-C(2)-C(12)	113.51(13)
C(23)-C(2)-C(12)	111.76(14)
C(4)-C(3)-C(2)	124.57(16)
C(3)-C(4)-C(5)	122.78(16)
C(4)-C(5)-C(19)	108.87(13)
C(4)-C(5)-C(6)	111.43(14)
C(19)-C(5)-C(6)	109.62(15)
C(4)-C(5)-C(20)	110.45(15)
C(19)-C(5)-C(20)	108.16(14)
C(6)-C(5)-C(20)	108.24(12)
C(7)-C(6)-C(5)	114.33(13)
C(8)-C(7)-C(6)	110.41(14)
N(9)-C(8)-C(7)	106.72(15)
C(10)-N(9)-C(8)	116.73(15)
C(10)-N(9)-C(19)	103.14(13)
C(8)-N(9)-C(19)	113.58(13)
N(9)-C(10)-C(11)	100.84(14)
C(10)-C(11)-C(12)	106.73(13)
C(13)-C(12)-C(11)	112.40(14)
C(13)-C(12)-C(19)	111.49(12)
C(11)-C(12)-C(19)	102.70(13)
C(13)-C(12)-C(2)	102.28(13)
C(11)-C(12)-C(2)	115.30(13)
C(19)-C(12)-C(2)	113.03(14)
C(14)-C(13)-C(18)	120.44(16)
C(14)-C(13)-C(12)	129.47(17)
C(18)-C(13)-C(12)	110.07(15)
C(13)-C(14)-C(15)	119.44(18)
C(16)-C(15)-C(14)	119.71(18)
C(15)-C(16)-C(17)	121.84(17)
C(18)-C(17)-C(16)	117.56(18)
N(1)-C(18)-C(13)	110.92(15)
N(1)-C(18)-C(17)	128.08(17)
C(13)-C(18)-C(17)	120.98(17)
N(9)-C(19)-C(5)	111.76(13)
N(9)-C(19)-C(12)	102.52(12)
C(5)-C(19)-C(12)	119.53(14)
C(21)-C(20)-C(5)	114.44(15)
C(24)-C(23)-C(28)	118.46(15)
C(24)-C(23)-C(2)	120.07(15)
C(28)-C(23)-C(2)	121.44(14)
C(25)-C(24)-C(23)	121.59(16)
C(26)-C(25)-C(24)	118.45(15)
C(27)-C(26)-C(25)	121.55(15)
C(27)-C(26)-N(29)	118.90(15)
C(25)-C(26)-N(29)	119.55(15)
C(26)-C(27)-C(28)	119.29(16)
C(27)-C(28)-C(23)	120.65(16)
C(26)-N(29)-C(30)	112.52(14)
C(26)-N(29)-C(31)	112.56(14)
C(30)-N(29)-C(31)	110.23(14)

Symmetry transformations used to generate equivalent atoms.

Table S12. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (±)-**63**•2HCl. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	21(1)	39(1)	28(1)	1(1)	10(1)	1(1)
Cl(2)	21(1)	47(1)	24(1)	-2(1)	8(1)	-3(1)
N(1)	21(1)	31(1)	19(1)	-2(1)	7(1)	1(1)
C(2)	20(1)	33(1)	14(1)	-1(1)	6(1)	2(1)
C(3)	22(1)	33(1)	19(1)	0(1)	8(1)	4(1)
C(4)	19(1)	32(1)	18(1)	2(1)	5(1)	2(1)
C(5)	19(1)	35(1)	15(1)	0(1)	7(1)	0(1)
C(6)	21(1)	40(1)	15(1)	0(1)	5(1)	0(1)
C(7)	19(1)	42(1)	18(1)	-2(1)	4(1)	-1(1)
C(8)	21(1)	38(1)	20(1)	-7(1)	5(1)	-3(1)
N(9)	20(1)	31(1)	19(1)	-1(1)	7(1)	-1(1)
C(10)	25(1)	31(1)	25(1)	0(1)	7(1)	-1(1)
C(11)	26(1)	32(1)	20(1)	2(1)	8(1)	-1(1)
C(12)	20(1)	31(1)	16(1)	0(1)	7(1)	0(1)
C(13)	19(1)	36(1)	14(1)	1(1)	6(1)	3(1)
C(14)	27(1)	38(1)	19(1)	-3(1)	5(1)	6(1)
C(15)	26(1)	49(1)	18(1)	0(1)	7(1)	13(1)
C(16)	19(1)	55(1)	18(1)	3(1)	8(1)	4(1)
C(17)	22(1)	42(1)	17(1)	2(1)	7(1)	-3(1)
C(18)	23(1)	34(1)	13(1)	2(1)	9(1)	1(1)
C(19)	16(1)	32(1)	17(1)	-1(1)	5(1)	-1(1)
C(20)	21(1)	39(1)	19(1)	-2(1)	7(1)	-4(1)
C(21)	31(1)	45(1)	25(1)	1(1)	10(1)	-8(1)
C(22)	32(1)	34(1)	28(1)	-4(1)	9(1)	0(1)
C(23)	22(1)	33(1)	15(1)	-1(1)	7(1)	2(1)
C(24)	19(1)	40(1)	19(1)	1(1)	8(1)	3(1)
C(25)	21(1)	41(1)	16(1)	2(1)	4(1)	3(1)
C(26)	22(1)	36(1)	16(1)	-1(1)	9(1)	0(1)
C(27)	19(1)	46(1)	21(1)	-1(1)	8(1)	4(1)
C(28)	21(1)	45(1)	16(1)	2(1)	5(1)	7(1)
N(29)	20(1)	38(1)	17(1)	1(1)	8(1)	1(1)
C(30)	32(1)	39(1)	35(1)	7(1)	16(1)	0(1)
C(31)	30(1)	43(1)	18(1)	-1(1)	10(1)	-2(1)
O(1S)	58(3)	64(3)	72(3)	27(2)	-19(2)	-18(2)
O(1T)	25(3)	47(5)	105(8)	29(5)	-1(4)	-7(3)
O(2T)	31(2)	45(3)	27(2)	3(2)	6(2)	3(2)

Table S13. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for (±)-**63**•2HCl.

	x	y	z	U(eq)
H(3)	1137	10069	-3949	29
H(4)	983	10026	-5222	27
H(6A)	1214	9189	-6396	30
H(6B)	1889	8114	-6380	30
H(7A)	-217	8297	-6024	32
H(7B)	-25	7743	-6786	32
H(8A)	-147	6439	-5856	32
H(8B)	1080	6414	-5992	32
H(9N)	536(15)	7531(15)	-4792(11)	28
H(10A)	1809	5685	-4553	32
H(10B)	631	5850	-4347	32
H(11A)	2455	6293	-3296	31
H(11B)	1376	7024	-3369	31
H(14)	4163	6106	-3807	34
H(15)	6111	6256	-3287	37
H(16)	6885	7849	-2763	36
H(17)	5750	9316	-2704	32
H(19)	2687	7223	-4977	26
H(20A)	3634	9293	-4705	31
H(20B)	3646	8515	-5408	31
H(21A)	2989	9839	-6319	50
H(21B)	4028	10313	-5670	50
H(21C)	2781	10611	-5662	50
H(22A)	3791	10179	-2333	47
H(22B)	3033	10788	-3075	47
H(22C)	4344	10649	-2974	47
H(24)	3394	8360	-2064	31
H(25)	2760	8105	-954	31
H(27)	-393	8799	-2223	34
H(28)	246	9025	-3337	33
H(29N)	-42(13)	8455(16)	-941(12)	30
H(30A)	1636	6976	-368	51
H(30B)	429	6692	-924	51
H(30C)	550	7102	-56	51
H(31A)	2032	8879	30	44
H(31B)	884	8929	272	44
H(31C)	1114	9749	-349	44
H(1SA)	-1270(60)	6270(40)	-3660(30)	108
H(1SB)	-1900(40)	5400(40)	-3510(40)	108
H(1TA)	-1110(90)	6130(50)	-3820(70)	94
H(1TB)	-1620(60)	5180(70)	-3690(70)	94
H(2TA)	-1400(70)	7330(30)	-1900(40)	70(30)
H(2TB)	-1300(40)	6470(40)	-2386(17)	18(14)

Appendix A

Spectra for Chapter I

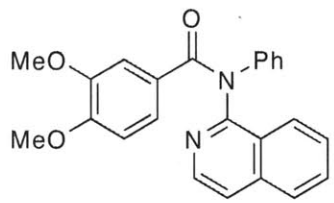
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

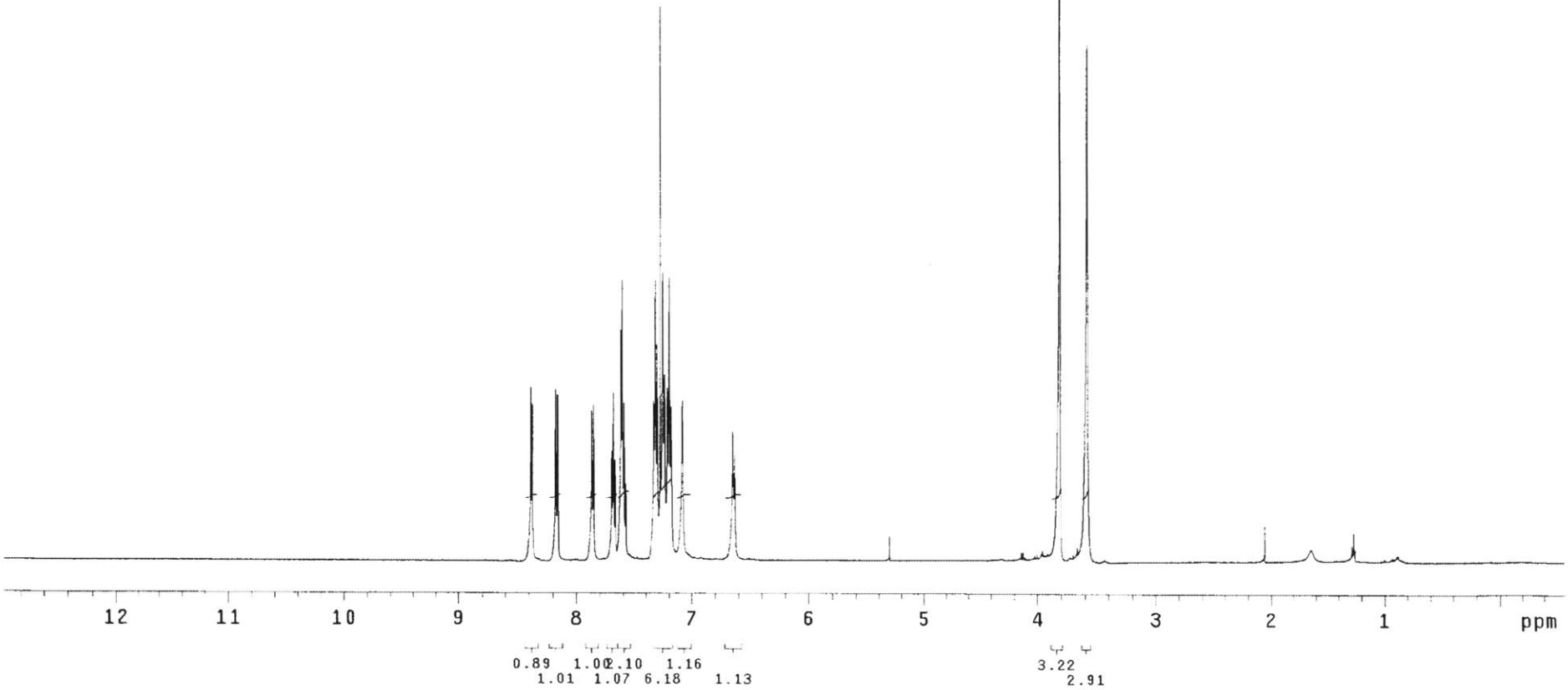
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.100 sec
Pulse 73.1 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4294973 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 21 sec



3aa

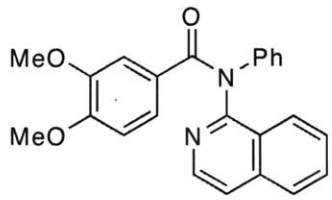


STANDARD CARBON PARAMETERS

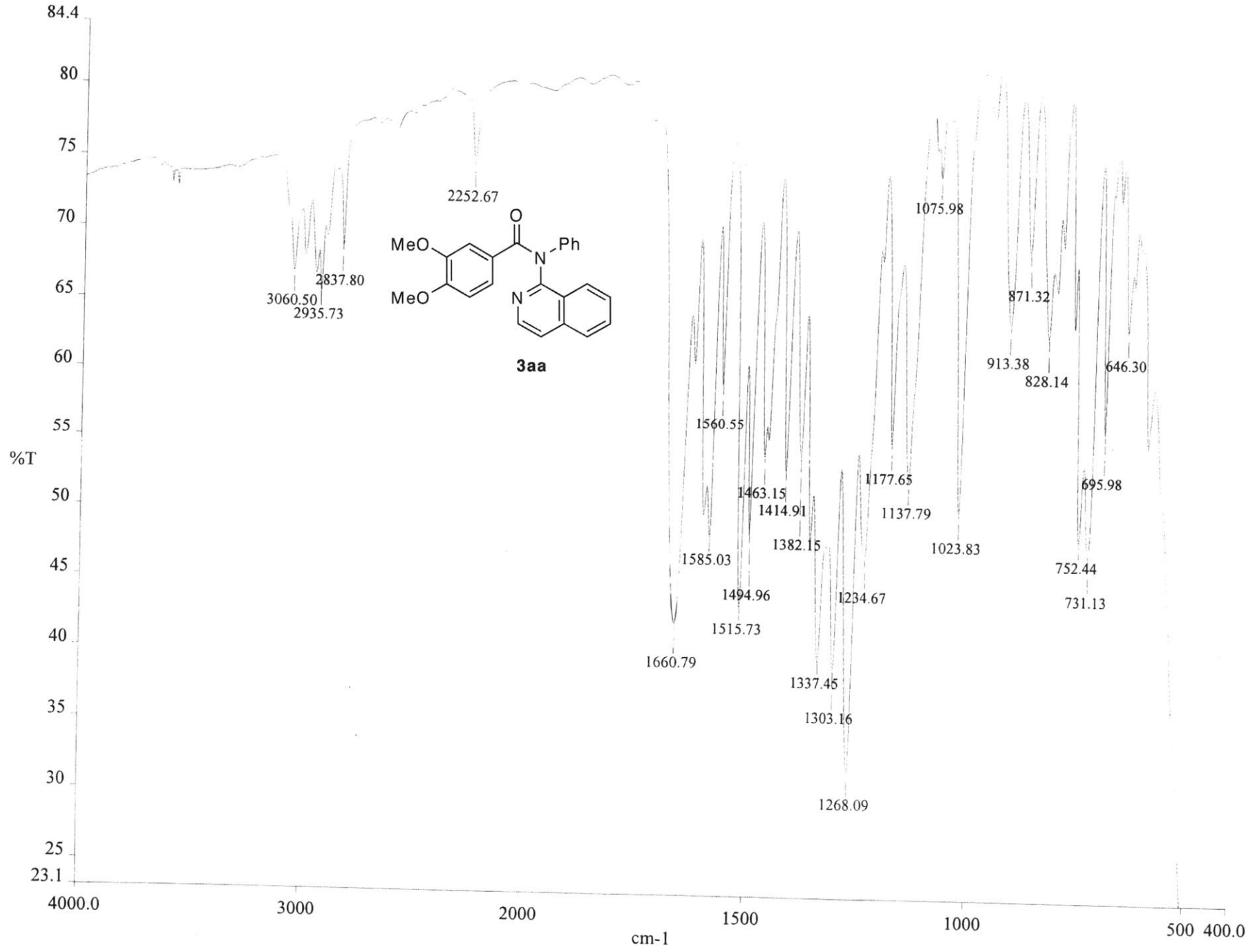
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
221 repetitions
OBSERVE C13, 125.7822234 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 45 hr, 39 min, 31 sec



3aa

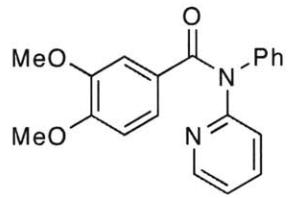

84.4
80
75
70
65
60
55
50
45
40
35
30
25
23.1
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2252.67
3060.50
2935.73
2837.80
1660.79
1585.03
1560.55
1515.73
1494.96
1463.15
1414.91
1382.15
1337.45
1303.16
1268.09
1234.67
1177.65
1137.79
1075.98
1023.83
913.38
871.32
828.14
752.44
731.13
695.98
646.30
MeO
MeO
N
O
N
Ph
3aa

STANDARD PROTON PARAMETERS

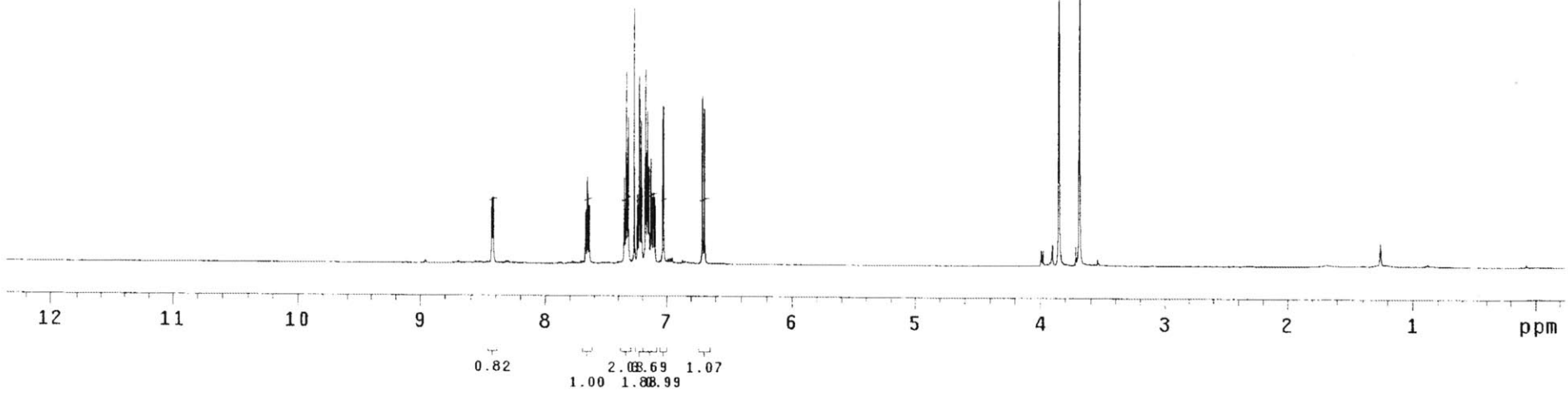
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.100 sec
Pulse 78.7 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4294975 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 21 sec



3ac

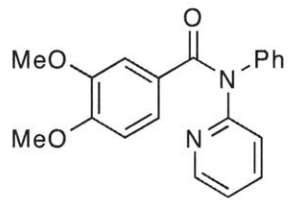


13C OBSERVE

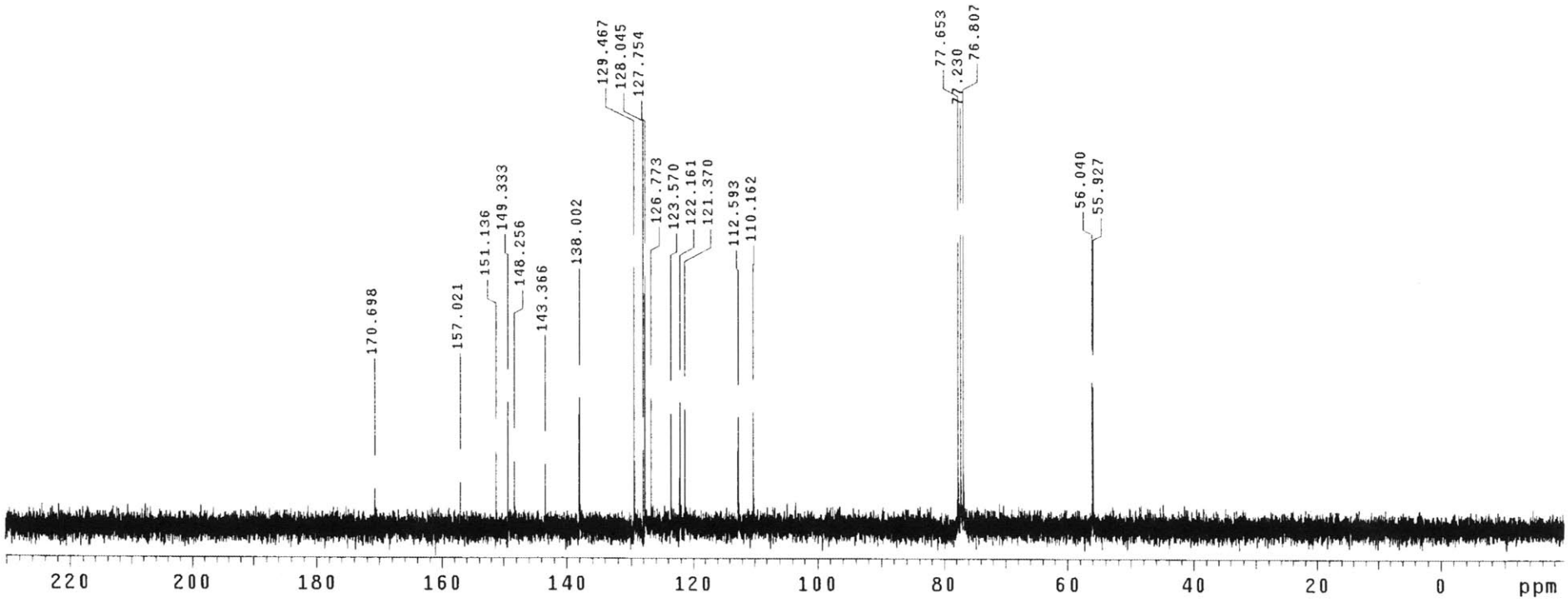
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

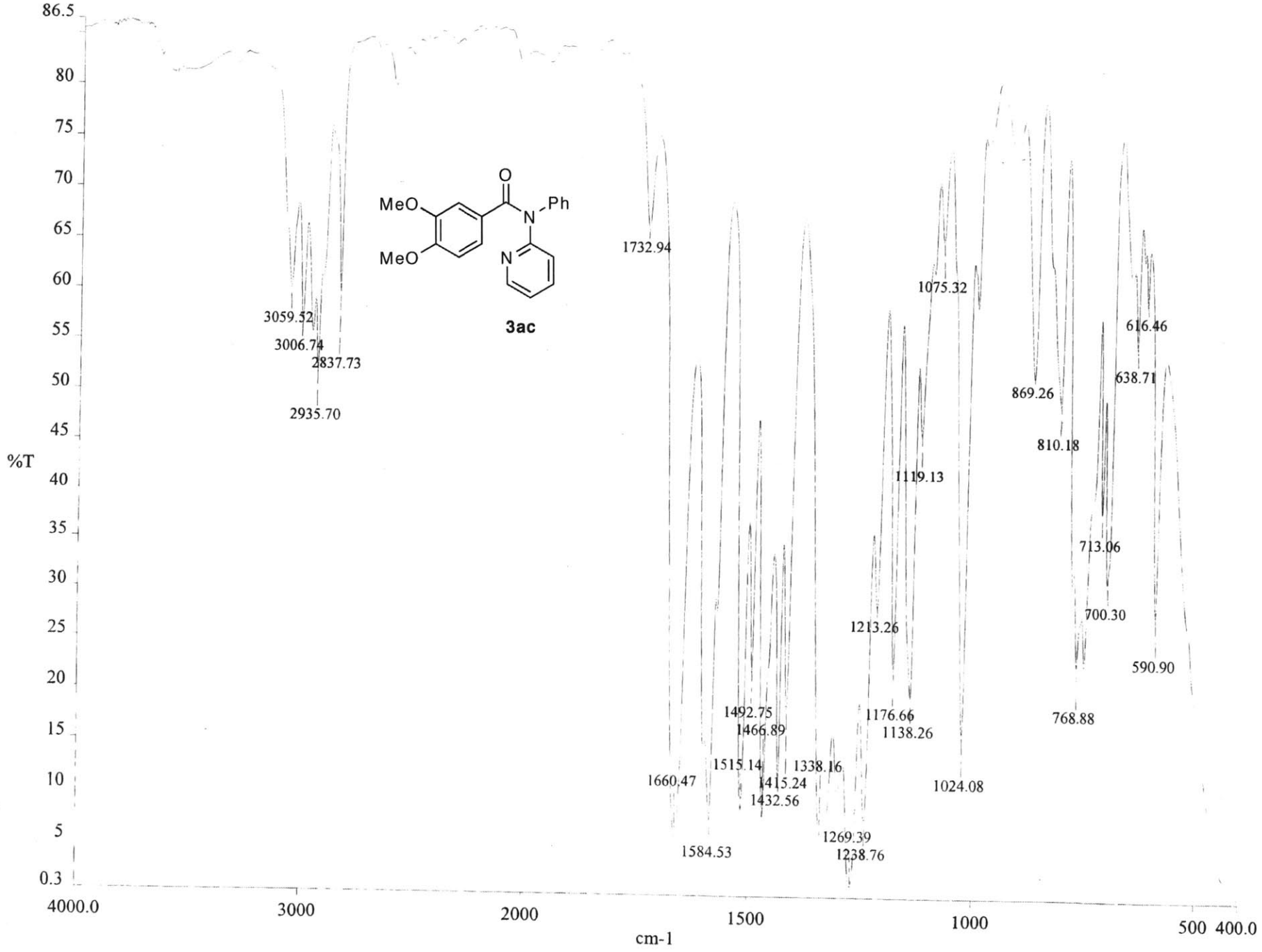
INOVA-500 "zippy"

Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
512 repetitions
OBSERVE C13, 75.4615184 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 17 min, 8 sec



3ac



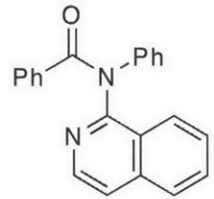

86.5
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.3
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
MeO
MeO
O
N
Ph
N
3ac
3059.52
3006.74
2837.73
2935.70
1732.94
1075.32
616.46
638.71
869.26
810.18
1119.13
713.06
700.30
1213.26
590.90
1492.75
1466.89
1176.66
1138.26
768.88
1515.14
1338.16
1660.47
1415.24
1432.56
1024.08
1269.39
1584.53
1238.76

STANDARD PROTON PARAMETERS

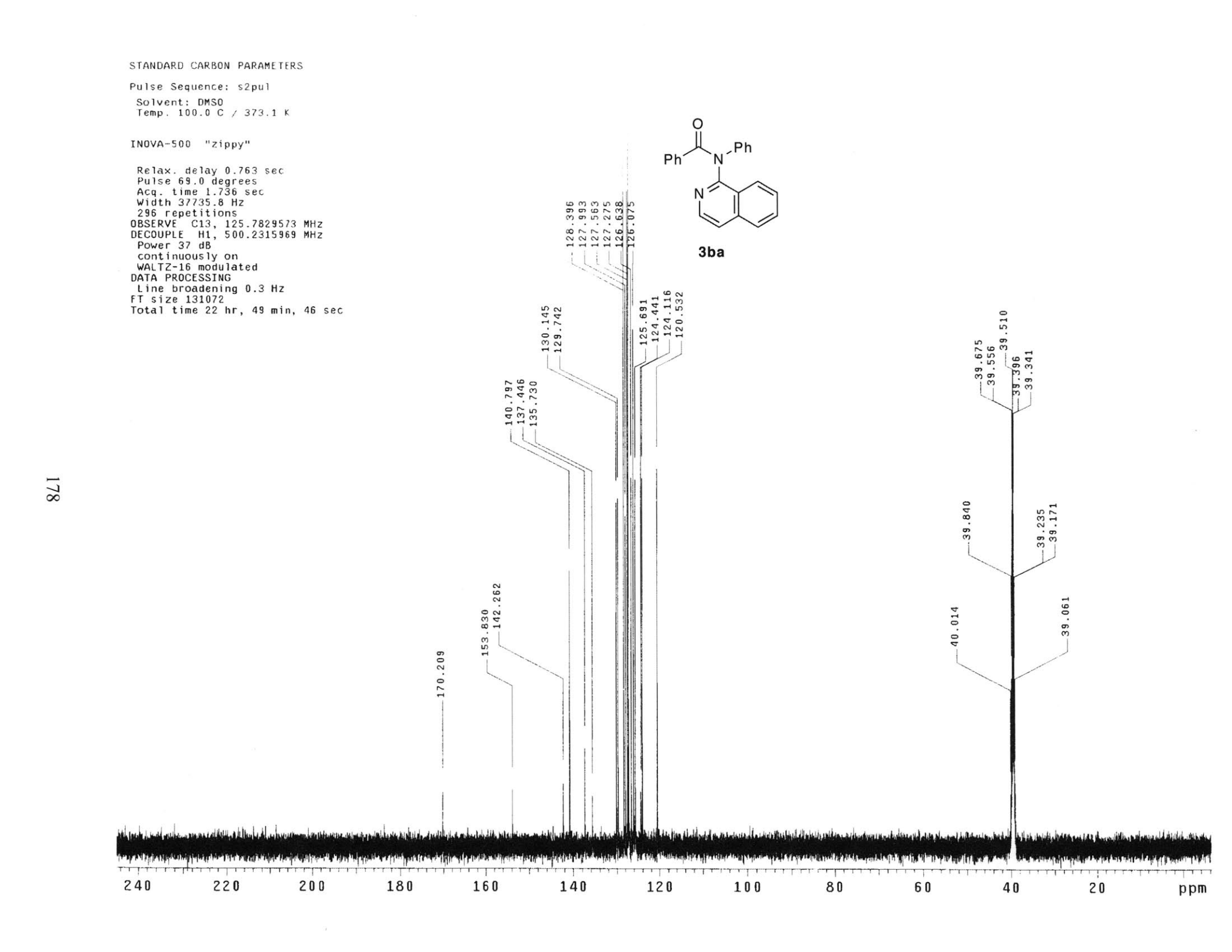
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature

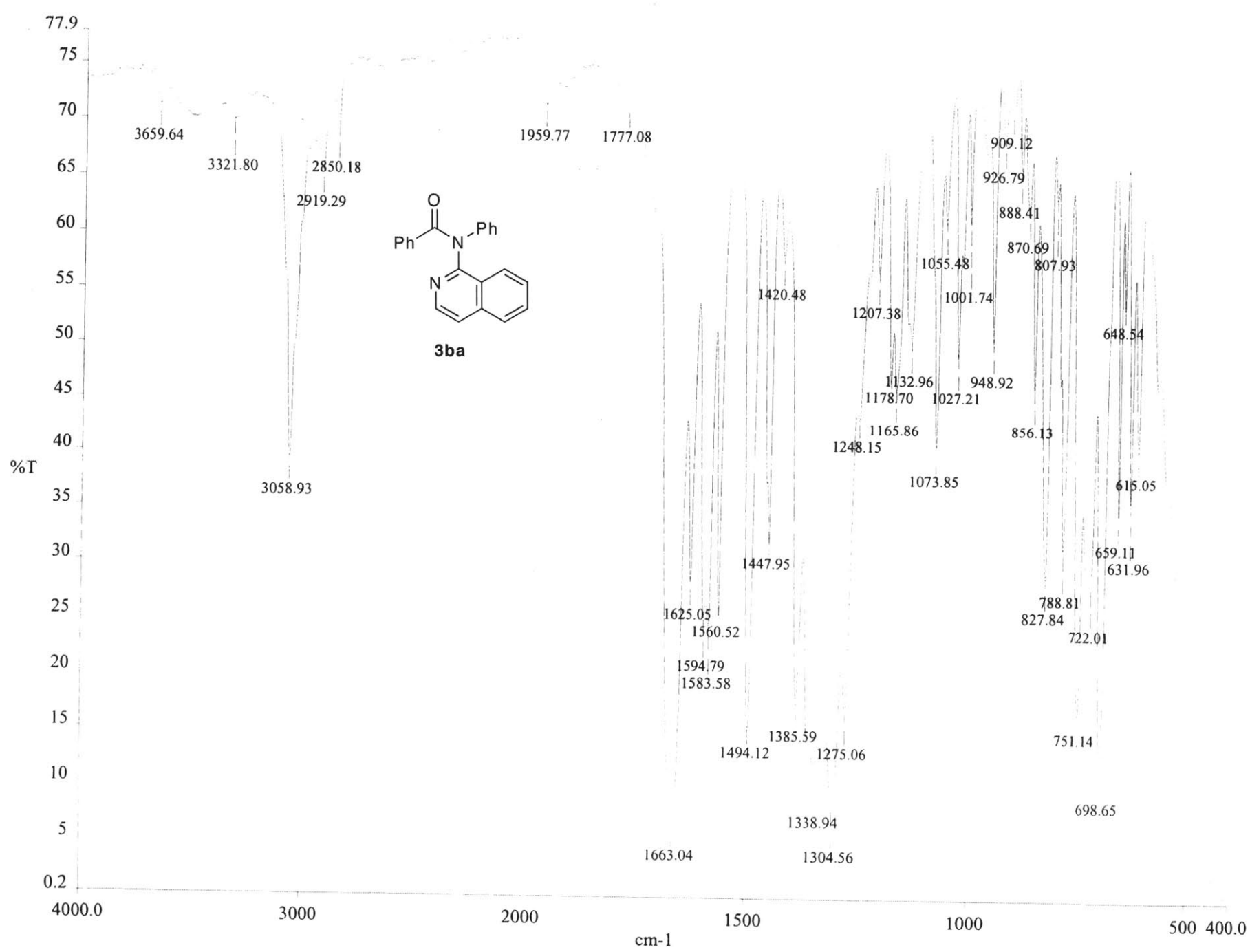
INOVA-500 "zippy"

Relax. delay 0.100 sec
Pulse 78.7 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4318716 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 21 sec



3ba


STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 100.0 C / 373.1 K
INOVA-500 "zippy"
Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
296 repetitions
OBSERVE C13, 125.7829573 MHz
DECOUPLE H1, 500.2315969 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 22 hr, 49 min, 46 sec
O
Ph
N
Ph
N
3ba
128.396
127.993
127.563
127.275
126.638
126.075
130.145
129.742
125.691
124.441
124.116
120.532
140.797
137.446
135.730
153.830
142.262
170.209
39.675
39.556
39.510
39.396
39.341
39.840
39.235
39.171
40.014
39.061
240
220
200
180
160
140
120
100
80
60
40
20
ppm

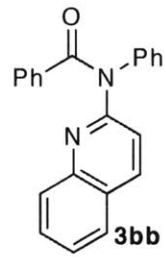

77.9
75
70
65
60
55
50
45
40
%T
35
30
25
20
15
10
5
0.2
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3659.64
3321.80
2850.18
2919.29
3058.93
1959.77
1777.08
1420.48
1447.95
1625.05
1560.52
1594.79
1583.58
1385.59
1494.12
1275.06
1338.94
1663.04
1304.56
909.12
926.79
888.41
870.69
807.93
1055.48
1001.74
1207.38
648.54
1132.96
948.92
1178.70
1027.21
1165.86
856.13
1248.15
1073.85
615.05
659.11
631.96
788.81
827.84
722.01
751.14
698.65
O
Ph
N
Ph
N
3ba

STANDARD 1H OBSERVE

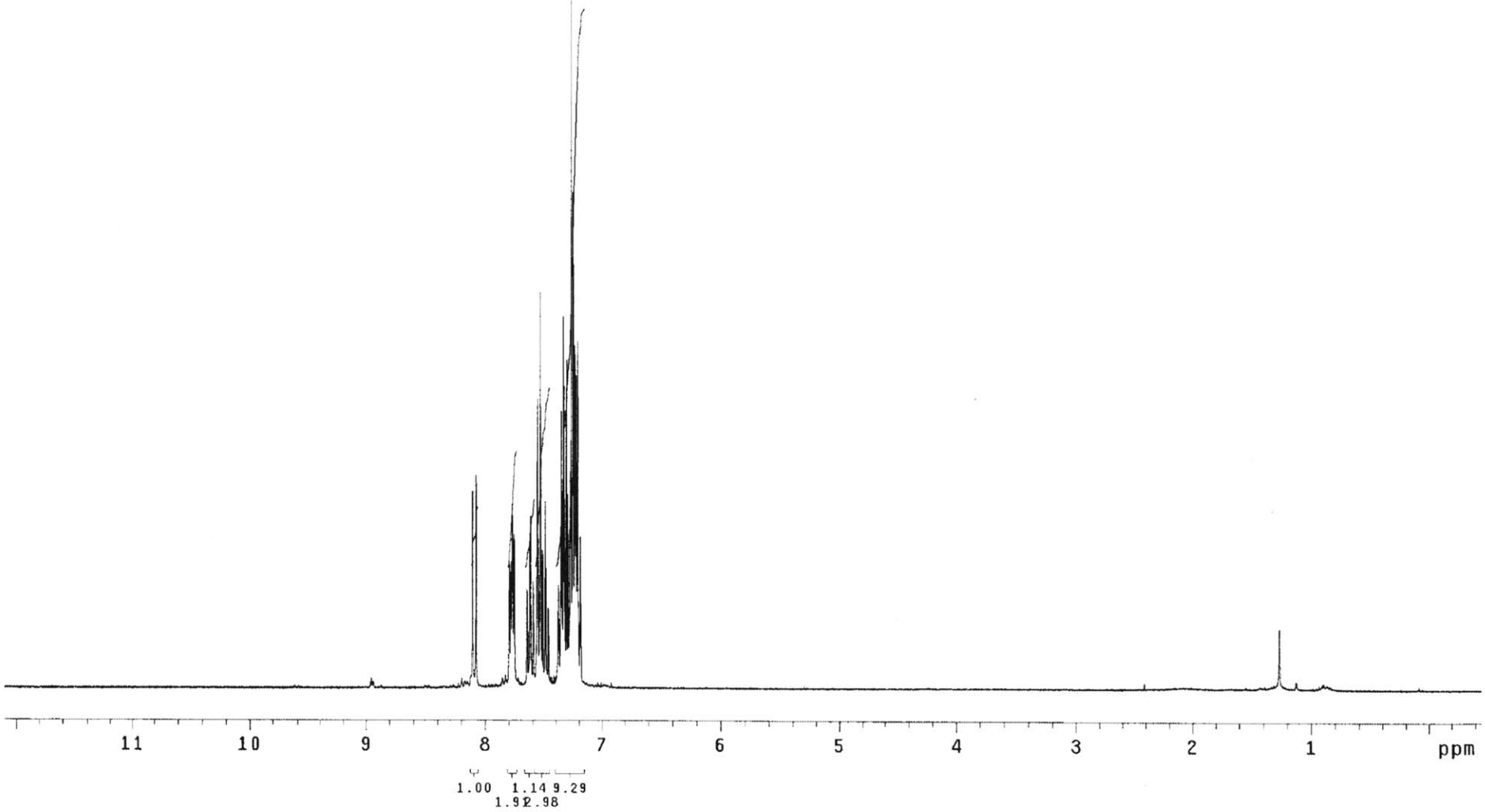
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

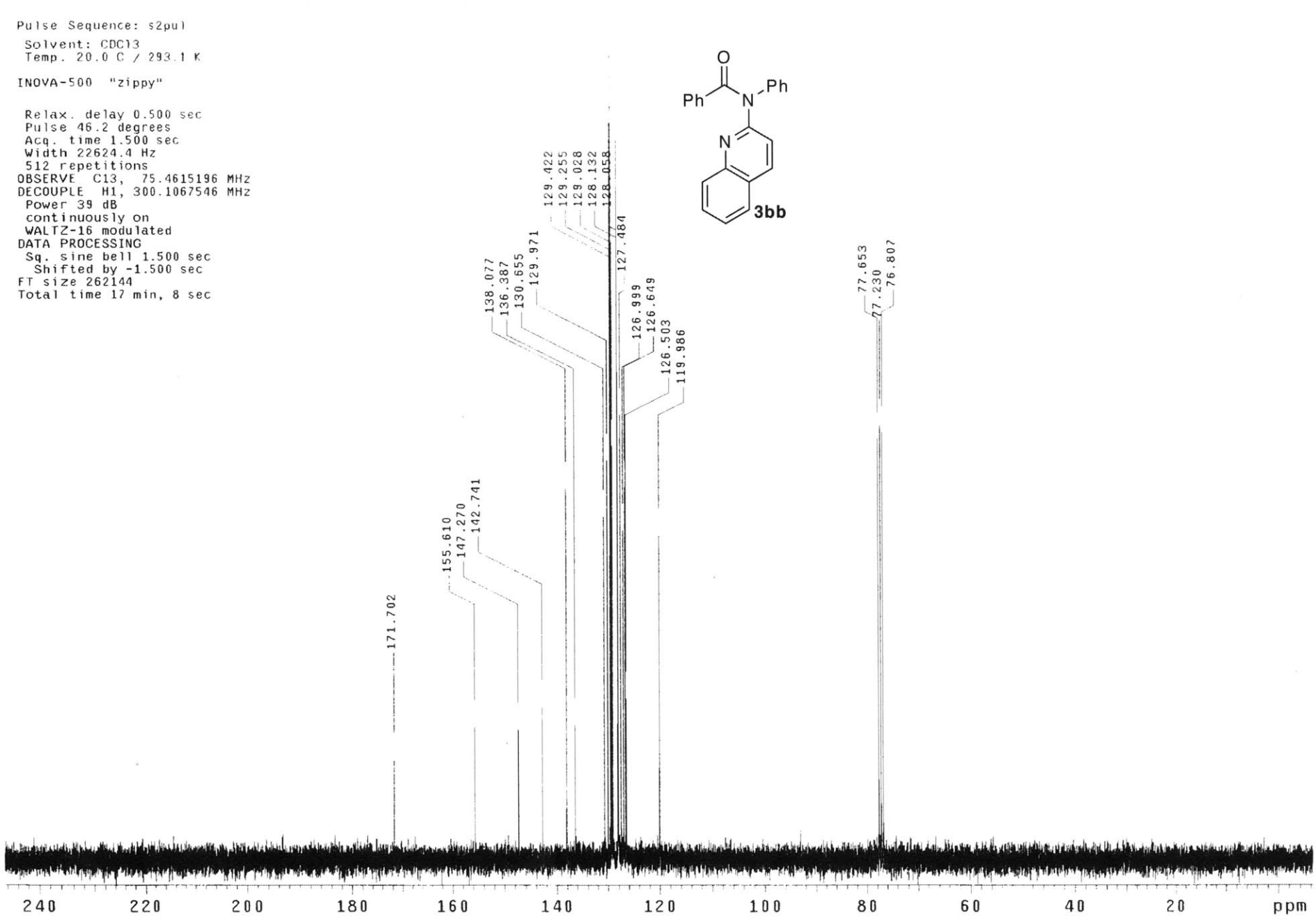
INOVA-500 "zippy"

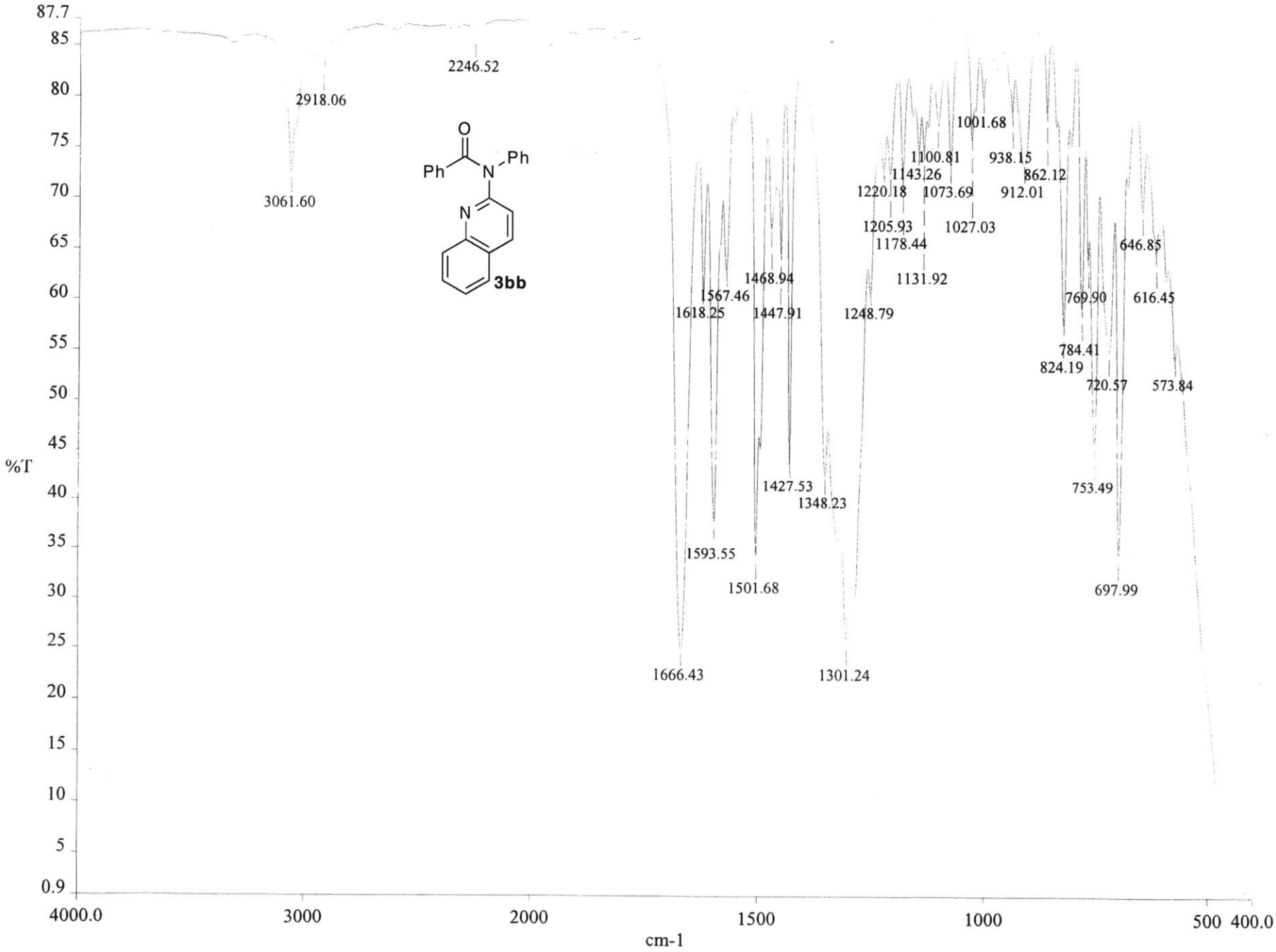
Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052783 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



3bb




13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K
INOVA-500 "zippy"
Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
512 repetitions
OBSERVE C13, 75.4615196 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 17 min, 8 sec
O
Ph
N
Ph
N
3bb
171.702
155.610
147.270
142.741
138.077
136.387
130.655
129.971
129.422
129.255
129.028
128.132
128.058
127.484
126.999
126.649
126.503
119.986
77.653
77.230
76.807
240
220
200
180
160
140
120
100
80
60
40
20
ppm

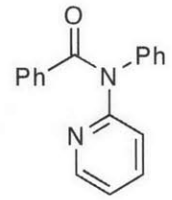

87.7
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.9
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2246.52
2918.06
3061.60
1666.43
1618.25
1593.55
1567.46
1501.68
1468.94
1447.91
1427.53
1348.23
1301.24
1248.79
1220.18
1205.93
1178.44
1143.26
1131.92
1100.81
1073.69
1027.03
1001.68
938.15
912.01
862.12
824.19
784.41
769.90
753.49
720.57
697.99
646.85
616.45
573.84
Ph
N
Ph
O
N
3bb

STANDARD PROTON PARAMETERS

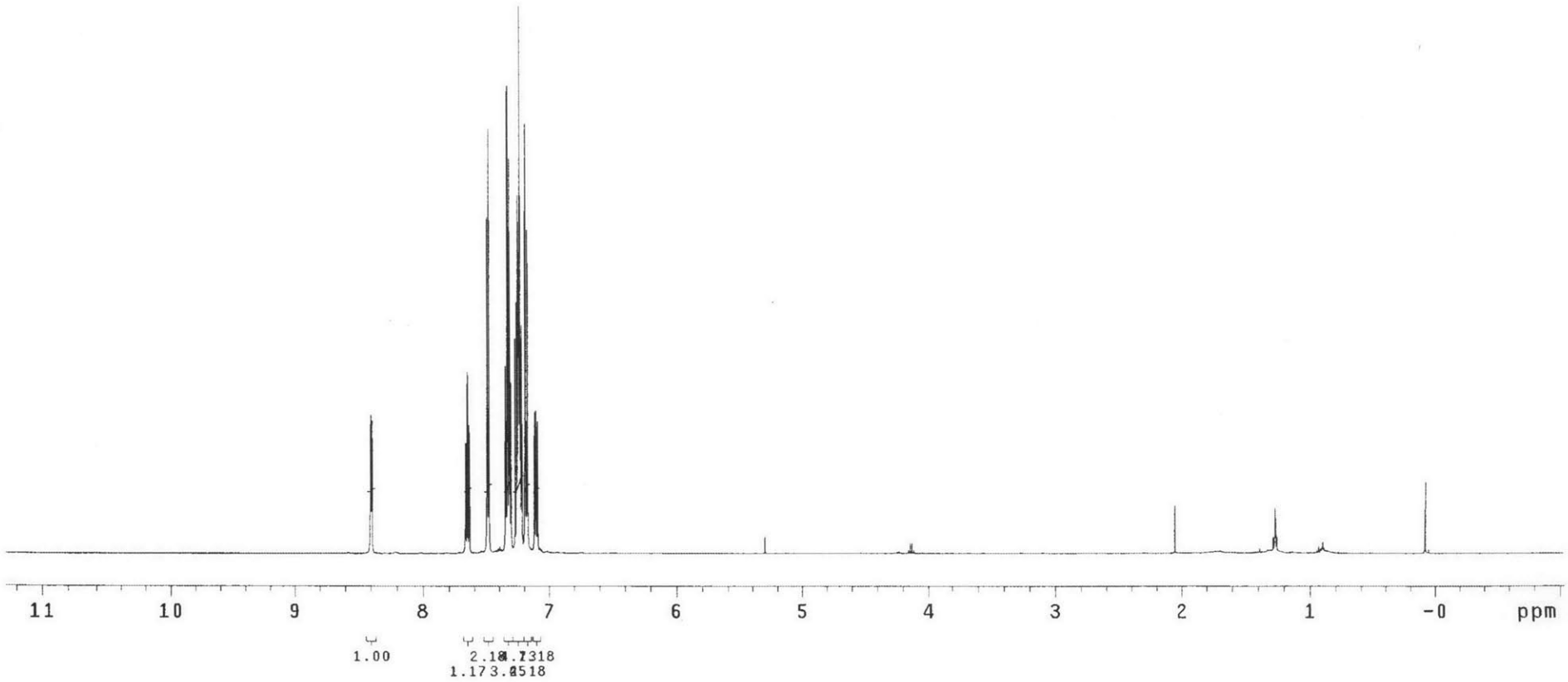
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

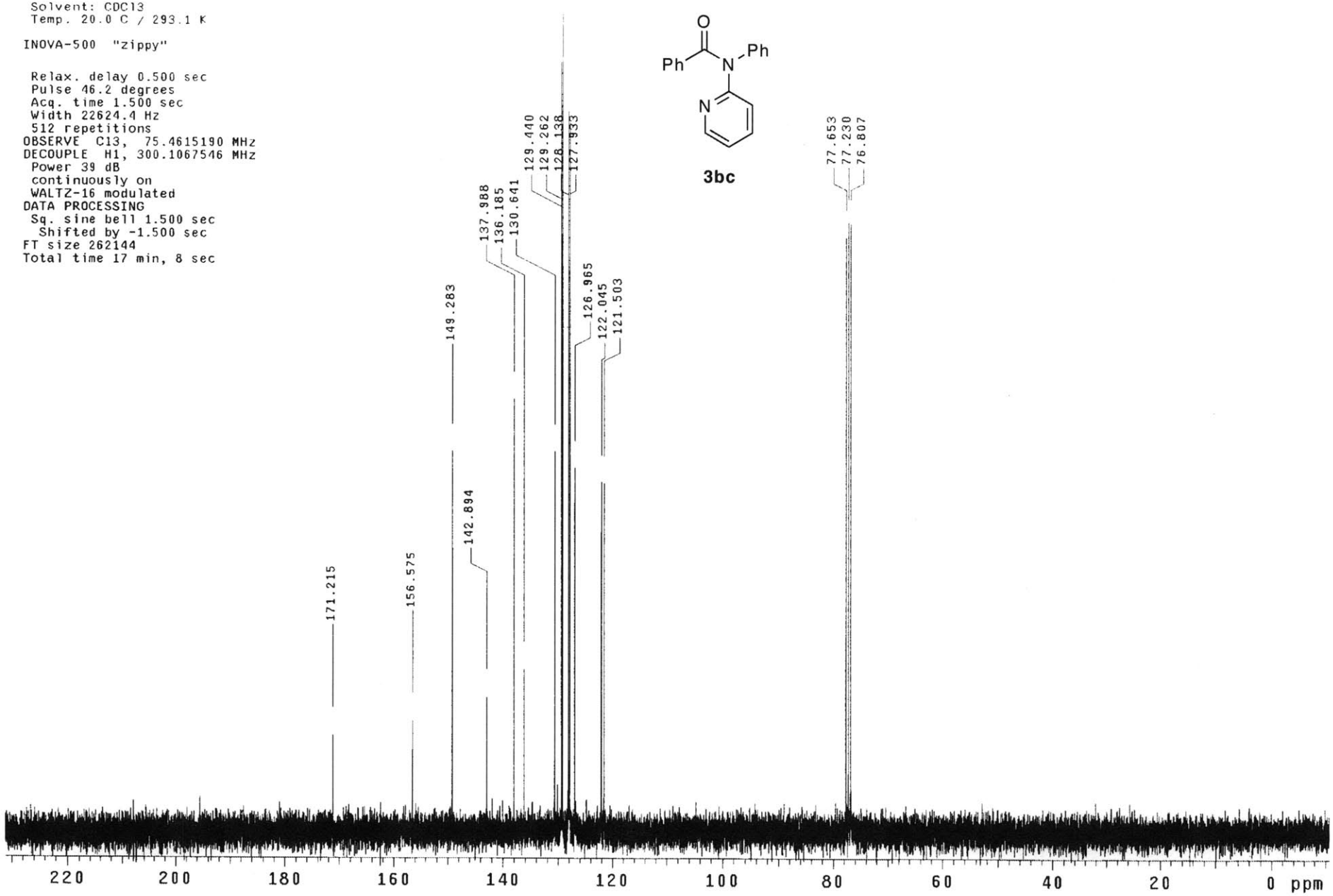
INOVA-500 "zippy"

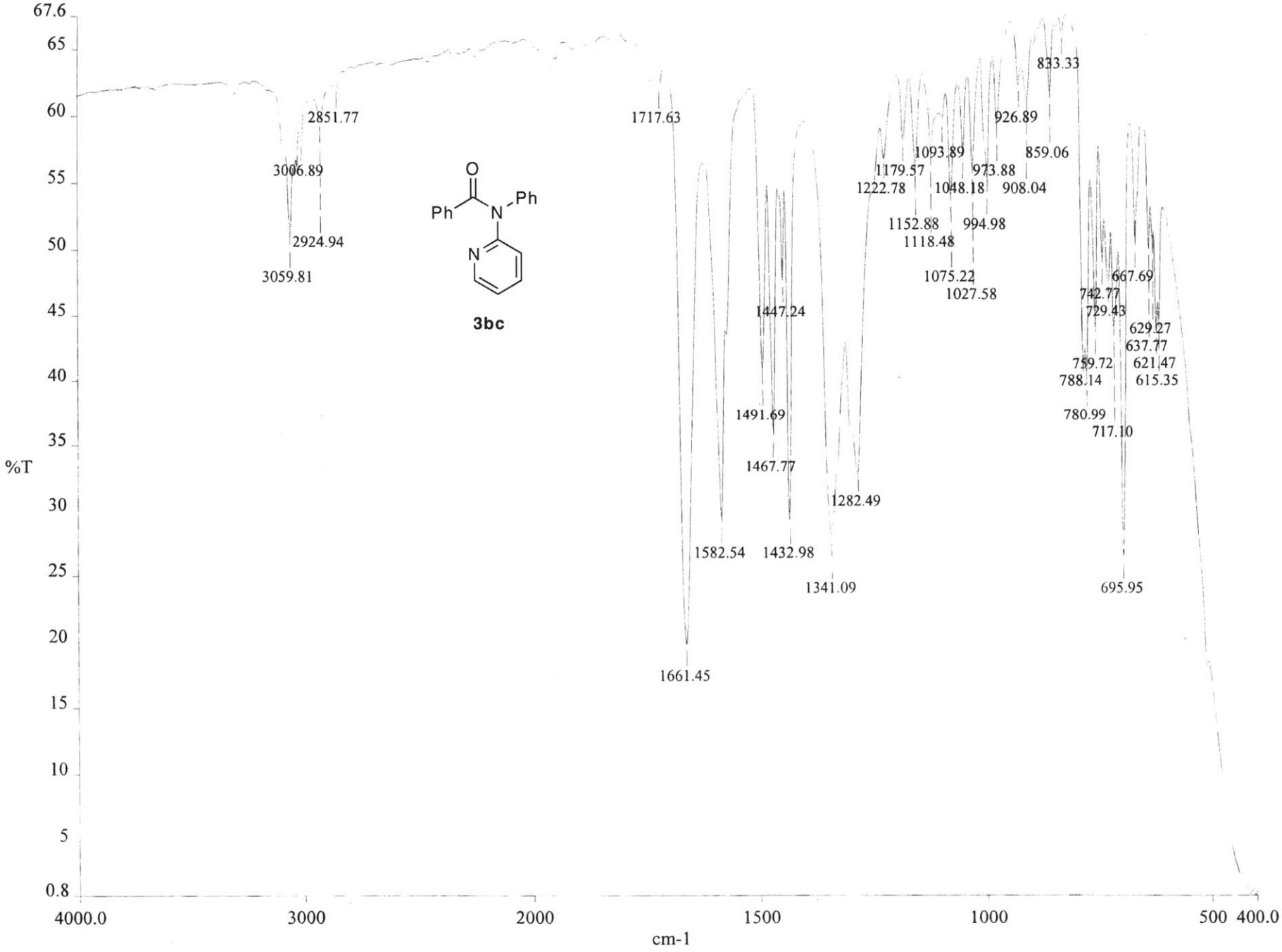
Relax. delay 2.000 sec
Pulse 94.4 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417199 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 20 sec



3bc




13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K
INOVA-500 "zippy"
Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
512 repetitions
OBSERVE C13, 75.4615190 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 17 min, 8 sec
O
Ph
N
Ph
N
3bc
171.215
156.575
149.283
142.894
137.988
136.185
130.641
129.440
129.262
128.138
127.933
126.965
122.045
121.503
77.653
77.230
76.807
220
200
180
160
140
120
100
80
60
40
20
0 ppm


67.6
65
60
55
50
45
40
35
30
25
20
15
10
5
0.8
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2851.77
3006.89
2924.94
3059.81
1717.63
1447.24
1491.69
1467.77
1582.54
1432.98
1282.49
1341.09
1661.45
833.33
926.89
859.06
1093.89
1179.57
973.88
1222.78
1048.18
908.04
1152.88
994.98
1118.48
1075.22
1027.58
667.69
742.77
729.43
629.27
637.77
759.72
621.47
788.14
615.35
780.99
717.10
695.95
O
Ph
N
Ph
N
3bc

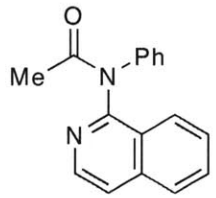
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

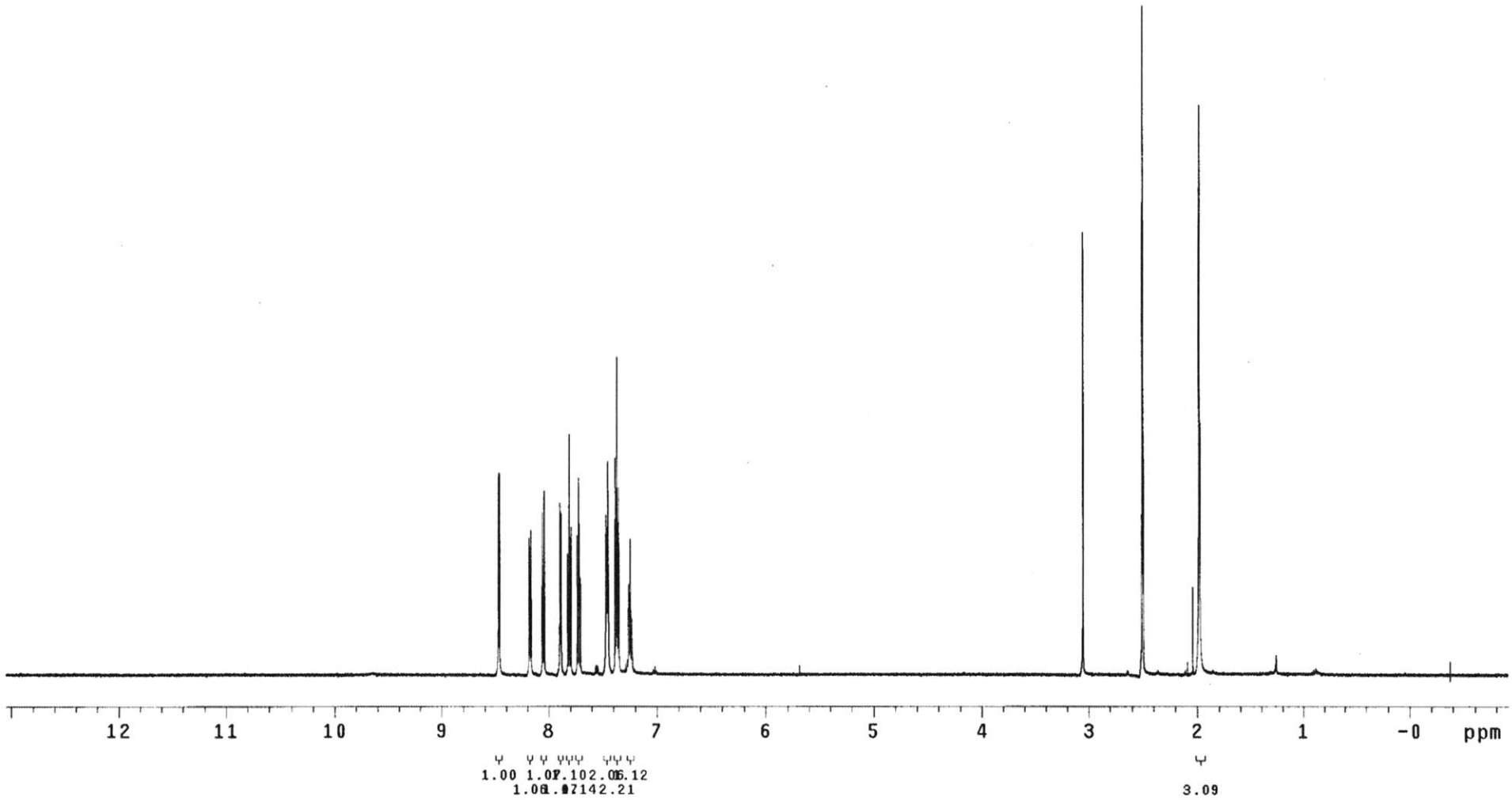
Solvent: DMSO
Temp. 80.0 C / 353.1 K

INOVA-500 "zippy"

Relax. delay 0.100 sec
Pulse 73.1 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
32 repetitions
OBSERVE H1, 500.4318712 MHz
DATA PROCESSING
FT size 262144
Total time 2 min, 43 sec



3ca

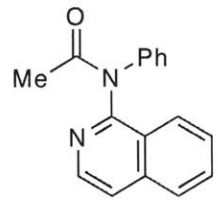


STANDARD CARBON PARAMETERS

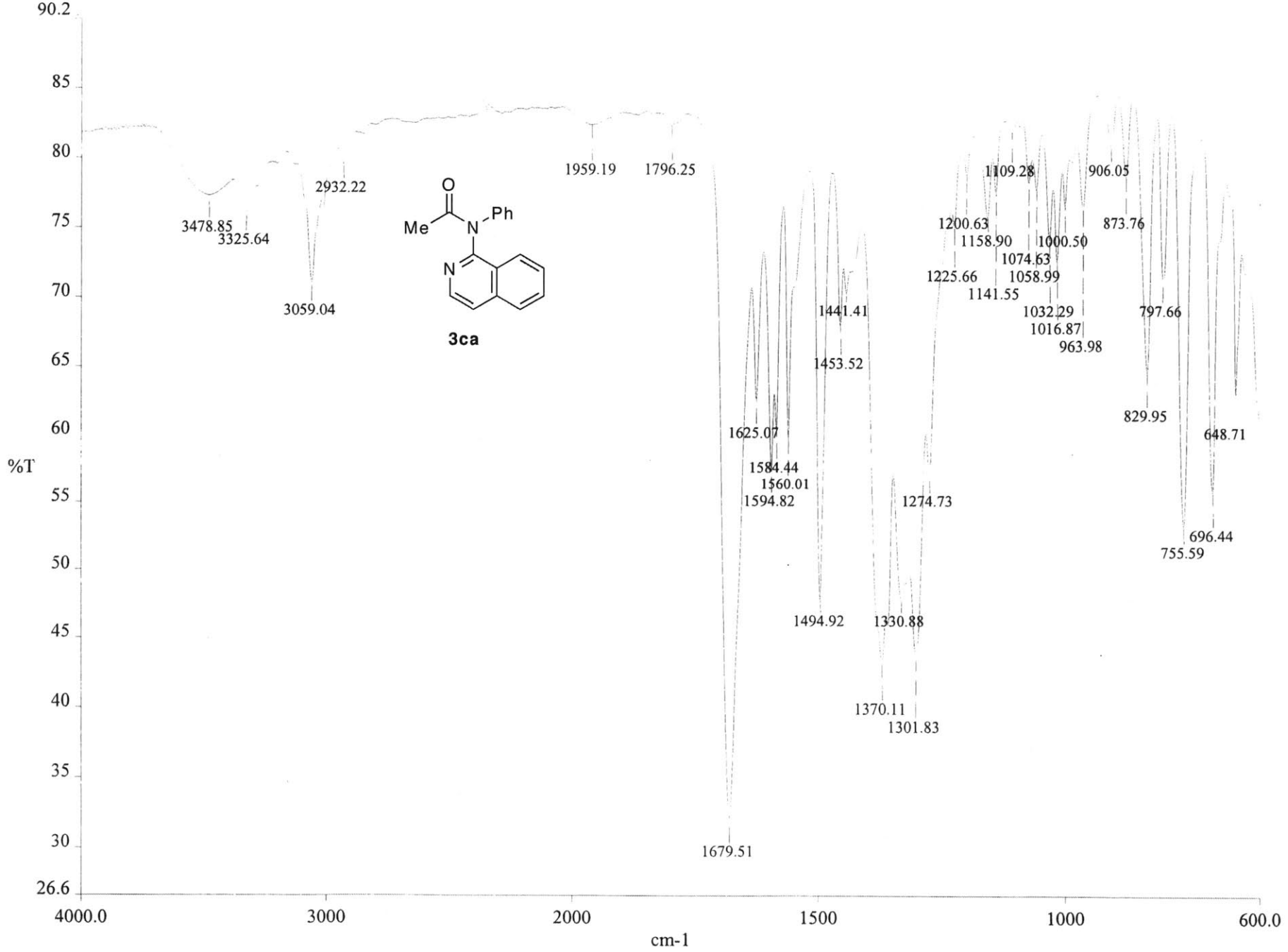
Pulse Sequence: s2pul
Solvent: DMSO
Temp 100.0 C / 373.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
168 repetitions
OBSERVE C13, 125.7829567 MHz
DECOUPLE H1, 500.2315969 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 22 hr, 49 min, 46 sec



3ca

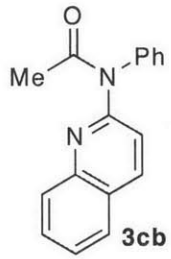

90.2
85
80
75
70
65
60
55
50
45
40
35
30
26.6
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3478.85
3325.64
2932.22
3059.04
1959.19
1796.25
1679.51
1625.07
1594.82
1584.44
1560.01
1494.92
1453.52
1441.41
1370.11
1330.88
1301.83
1274.73
1225.66
1200.63
1158.90
1141.55
1109.28
1074.63
1058.99
1032.29
1016.87
1000.50
963.98
906.05
873.76
829.95
797.66
755.59
696.44
648.71
O
Me
N
Ph
N
3ca

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052818 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



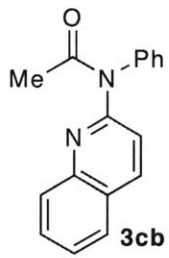
3cb

13C OBSERVE

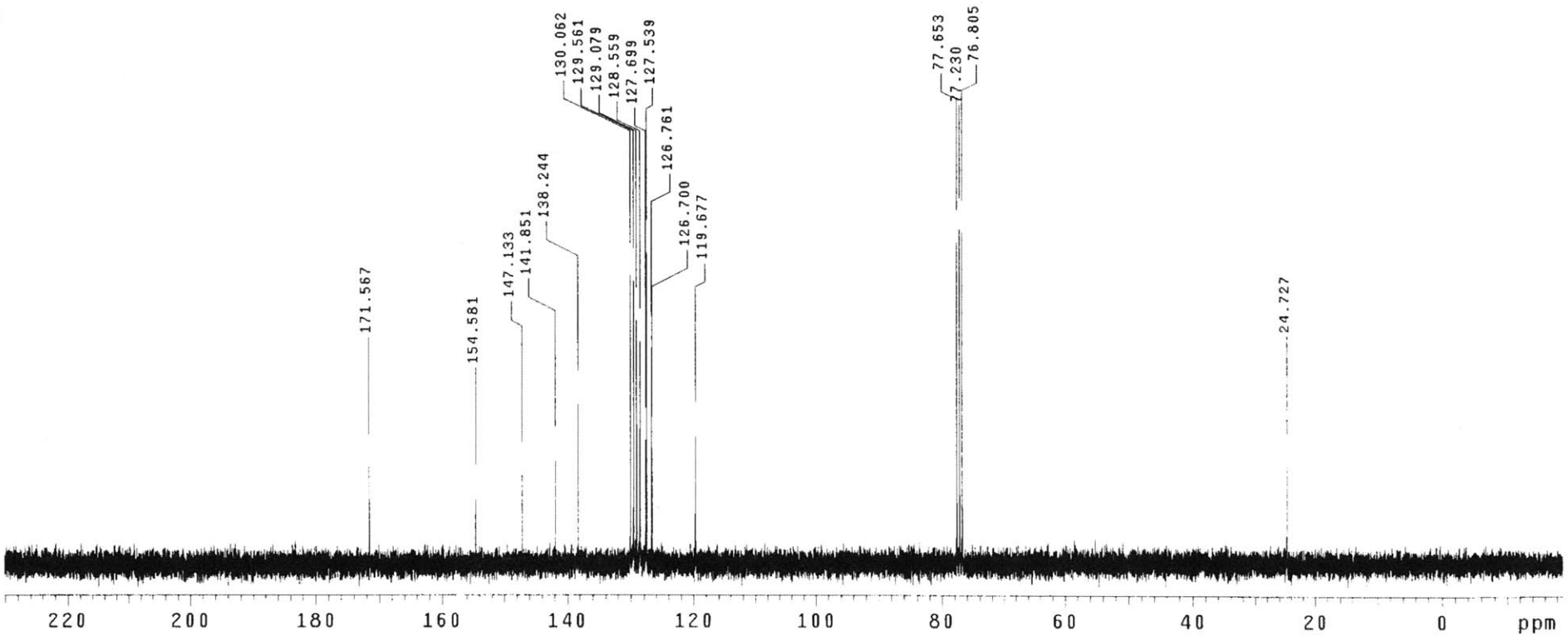
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

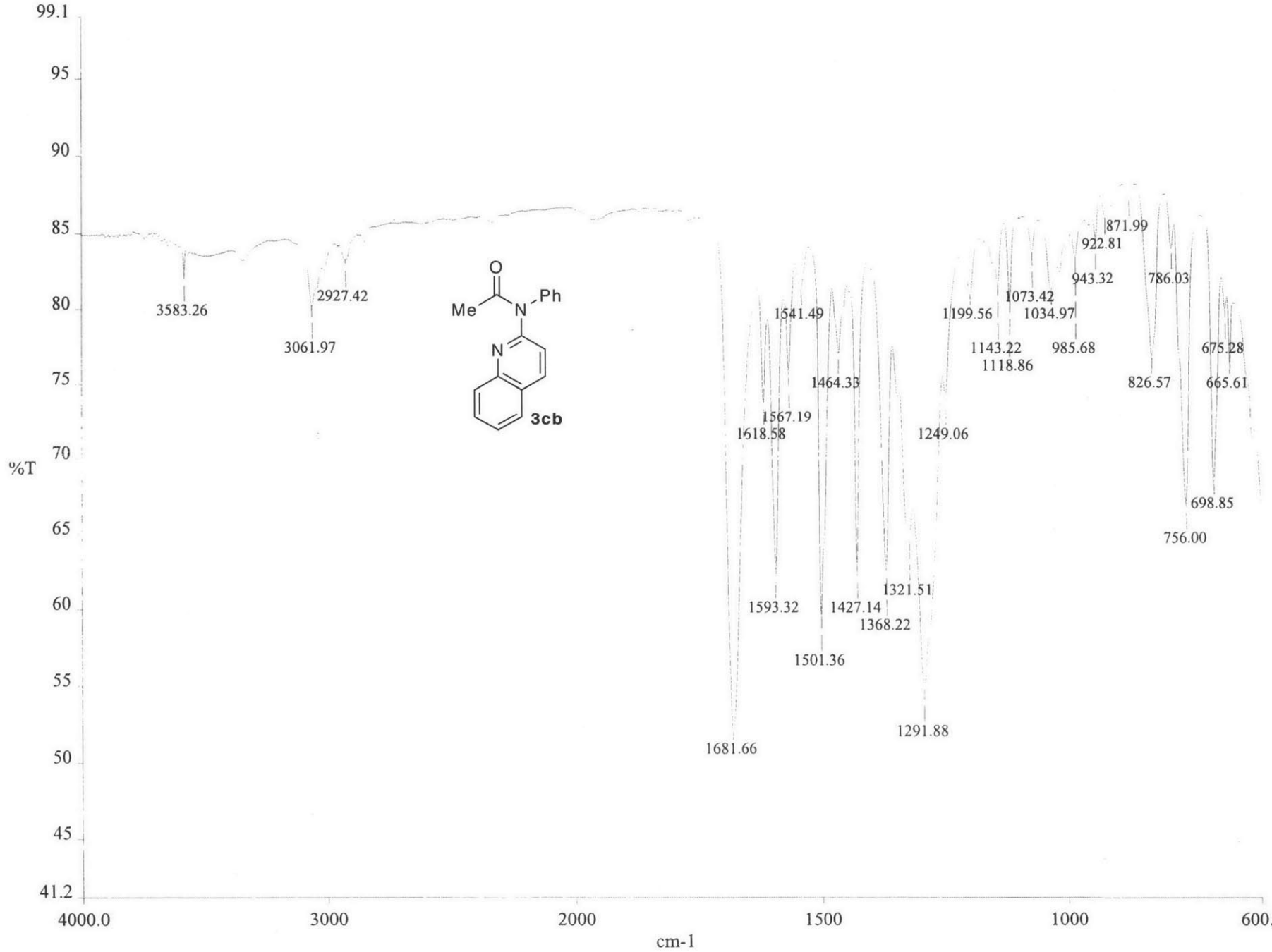
INOVA-500 "zippy"

Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
256 repetitions
OBSERVE C13, 75.4615215 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 8 min, 34 sec



3cb



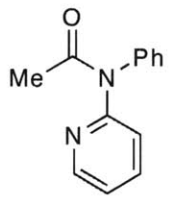

99.1
95
90
85
80
75
70
65
60
55
50
45
41.2
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3583.26
2927.42
3061.97
1681.66
1618.58
1593.32
1567.19
1541.49
1501.36
1464.33
1427.14
1368.22
1321.51
1291.88
1249.06
1199.56
1143.22
1118.86
1073.42
1034.97
985.68
943.32
922.81
871.99
826.57
786.03
756.00
698.85
675.28
665.61
Me
N
Ph
O
N
3cb

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 2.000 sec
Pulse 59.1 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417203 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 20 sec



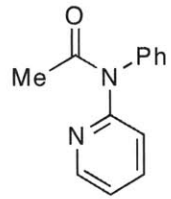
3cc

STANDARD CARBON PARAMETERS

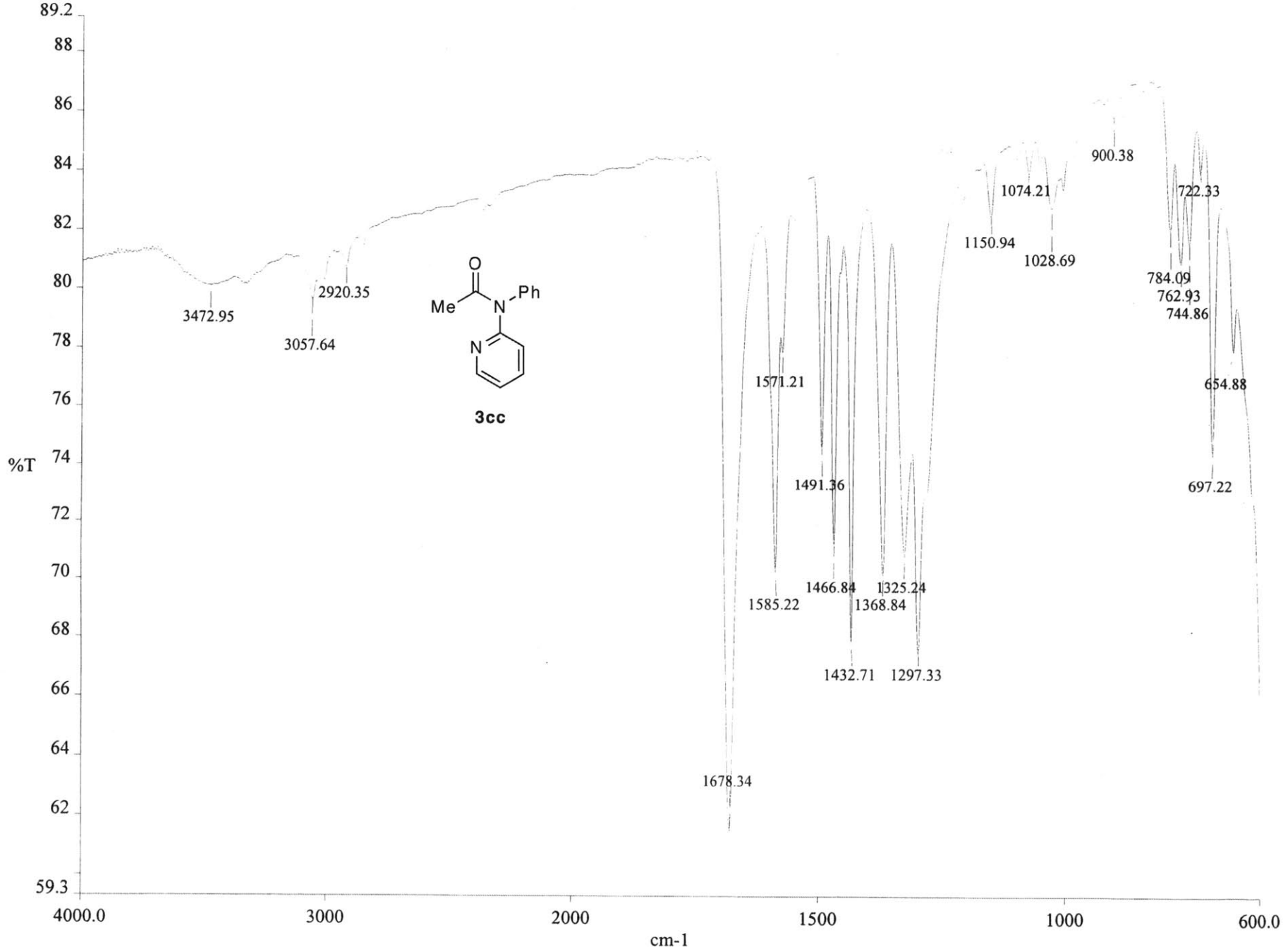
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
4096 repetitions
OBSERVE C13, 125.7822090 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 2 hr, 51 min, 15 sec



3cc

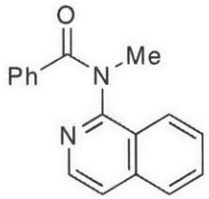

89.2
88
86
84
82
80
78
76
74
72
70
68
66
64
62
59.3
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3472.95
2920.35
3057.64
1678.34
1571.21
1585.22
1491.36
1466.84
1432.71
1368.84
1325.24
1297.33
1150.94
1074.21
1028.69
900.38
784.09
762.93
744.86
722.33
697.22
654.88
Me
N
Ph
O
N
3cc

STANDARD PROTON PARAMETERS

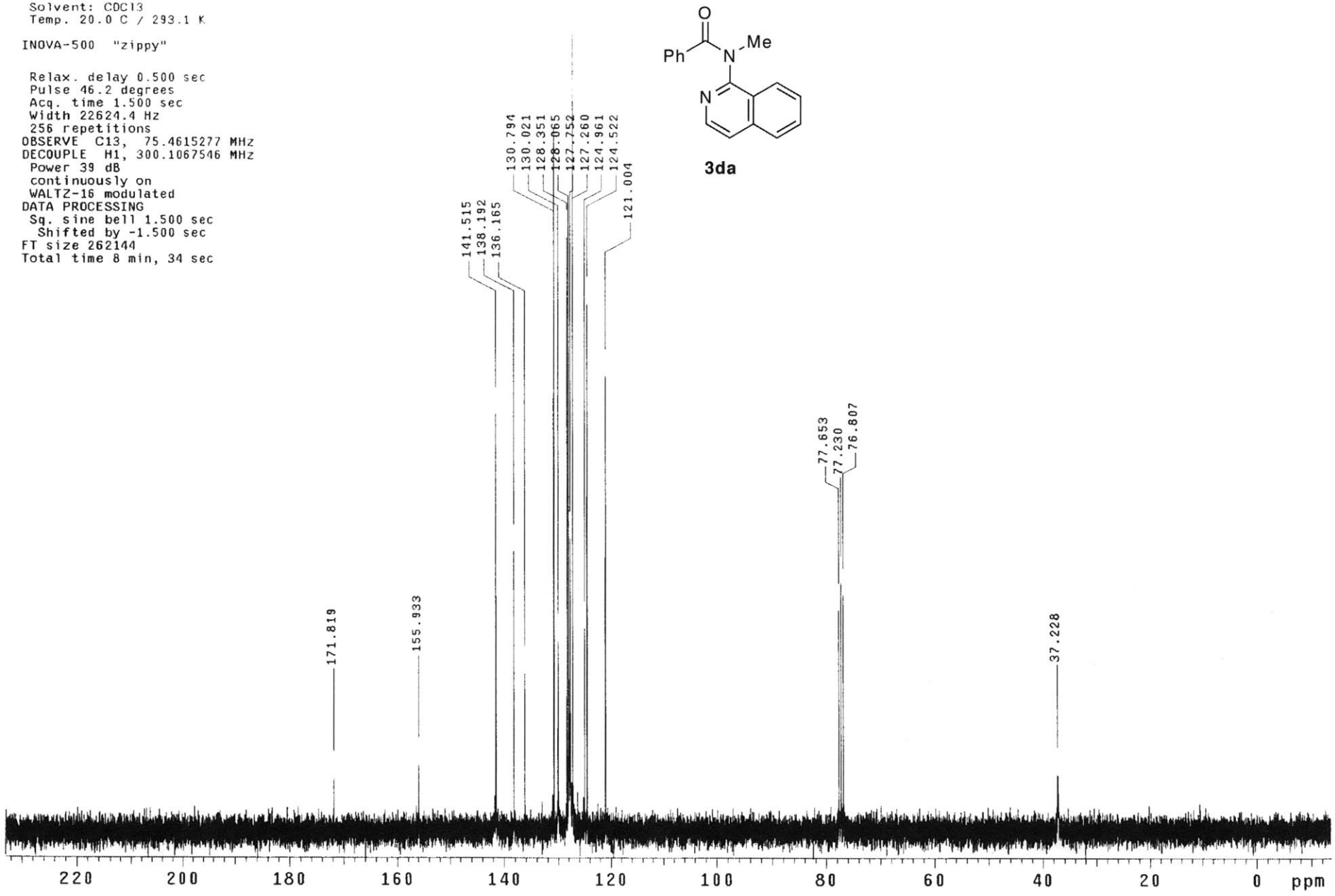
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

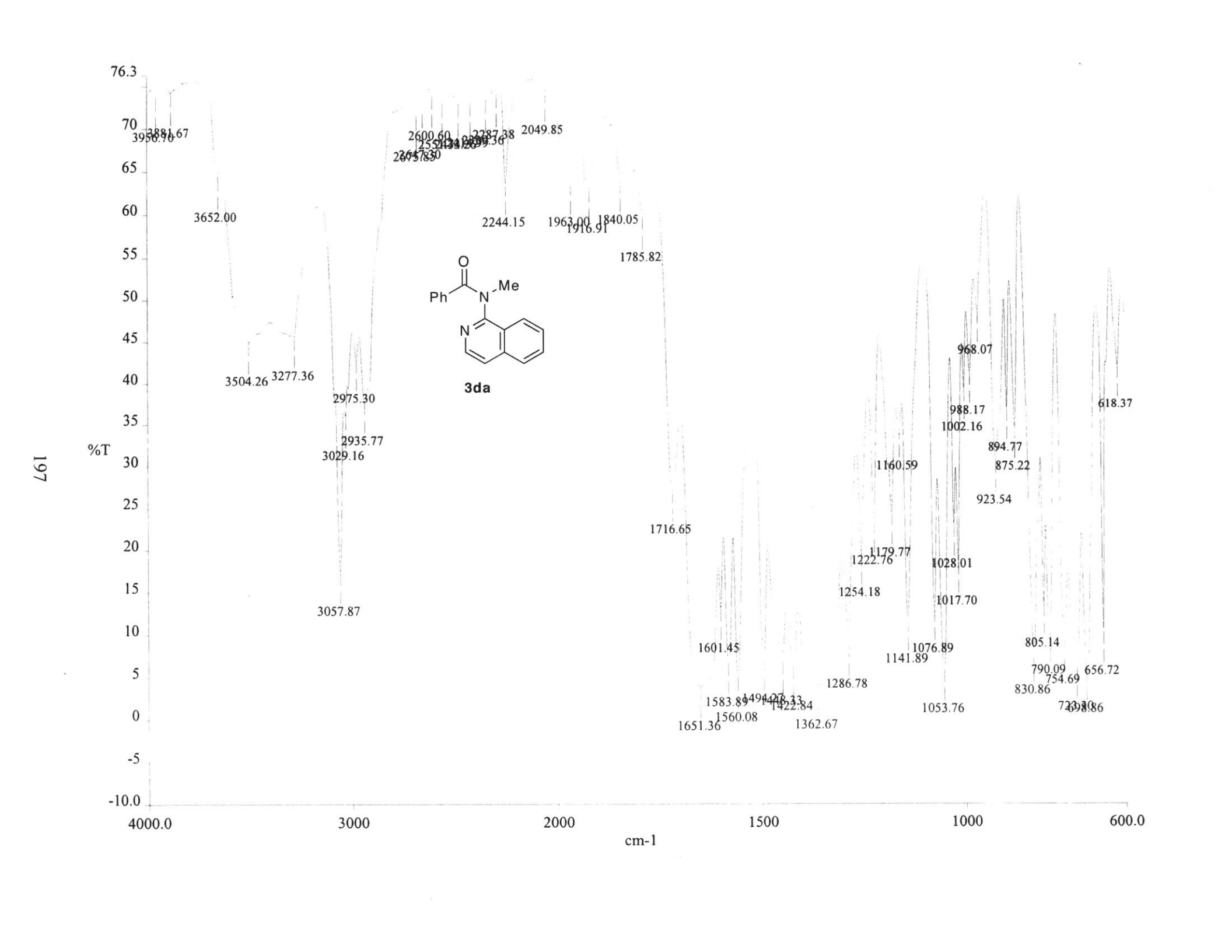
INOVA-500 "zippy"

Relax. delay 0.100 sec
Pulse 78.7 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
Single scan
OBSERVE H1, 500.4294965 MHz
DATA PROCESSING
FT size 262144
Total time 0 min, 5 sec



3da

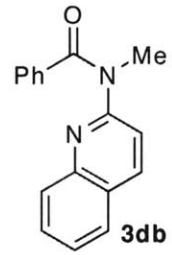

13C OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K
INOVA-500 "zippy"
Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
256 repetitions
OBSERVE C13, 75.4615277 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 8 min, 34 sec
O
Ph
N
Me
N
3da
171.819
155.933
141.515
138.192
136.165
130.794
130.021
128.351
128.065
127.752
127.260
124.961
124.522
121.004
77.653
77.230
76.807
37.228
220
200
180
160
140
120
100
80
60
40
20
0
ppm


76.3
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
-10.0
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3881.67
3956.70
3652.00
3504.26
3277.36
2975.30
2935.77
3029.16
3057.87
2600.60
2287.38
2049.85
2244.15
1963.00
1916.91
1840.05
1785.82
1716.65
1601.45
1583.89
1560.08
1651.36
1494.27
1422.84
1362.67
1286.78
1254.18
1222.76
1179.77
1160.59
1141.89
1076.89
1053.76
1028.01
1017.70
1002.16
988.17
968.07
923.54
894.77
875.22
805.14
790.09
754.69
656.72
830.86
618.37
O
Ph
N
Me
N
3da
197

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.100 sec
Pulse 78.7 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4294963 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 21 sec



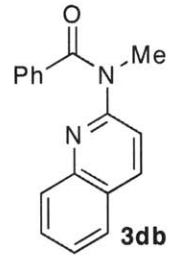
3db

13C OBSERVE

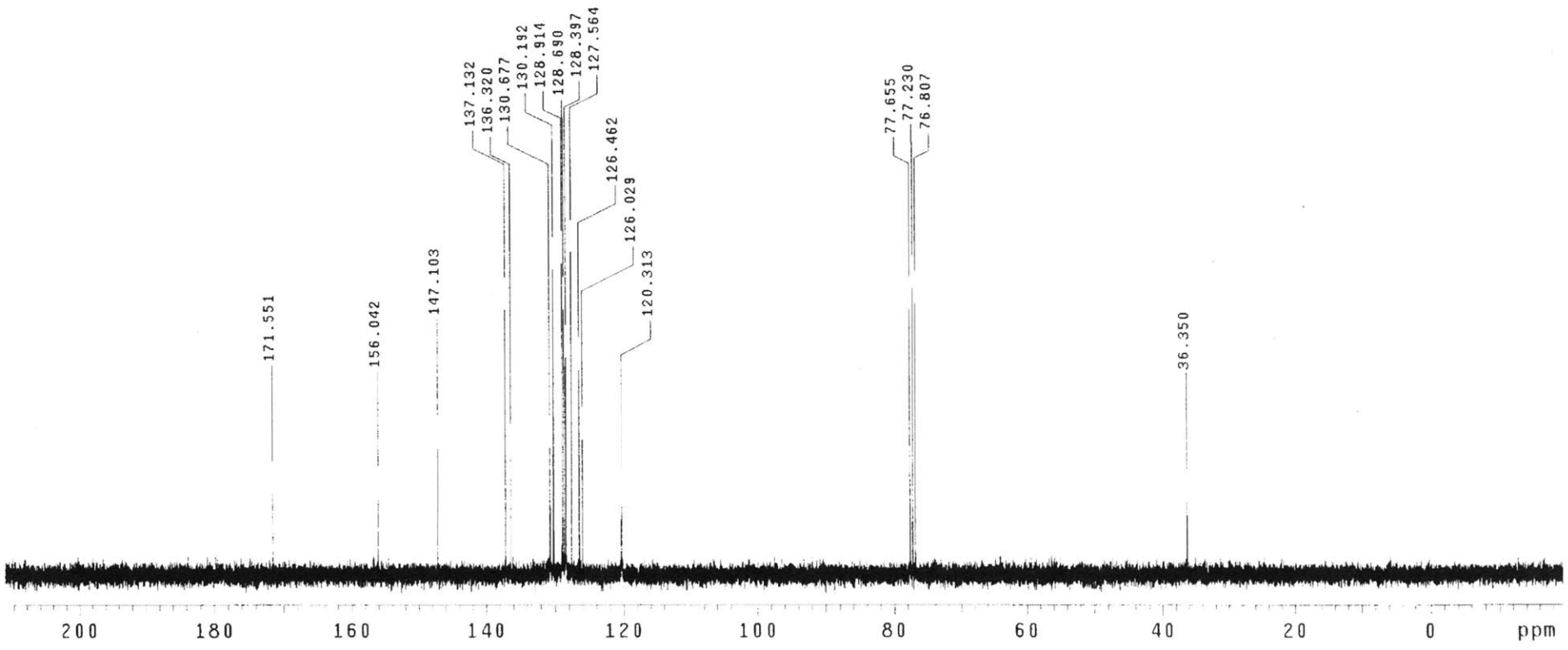
Pulse Sequence: s2pul
 Solvent: CDCl3
 Temp. 20.0 C / 293.1 K

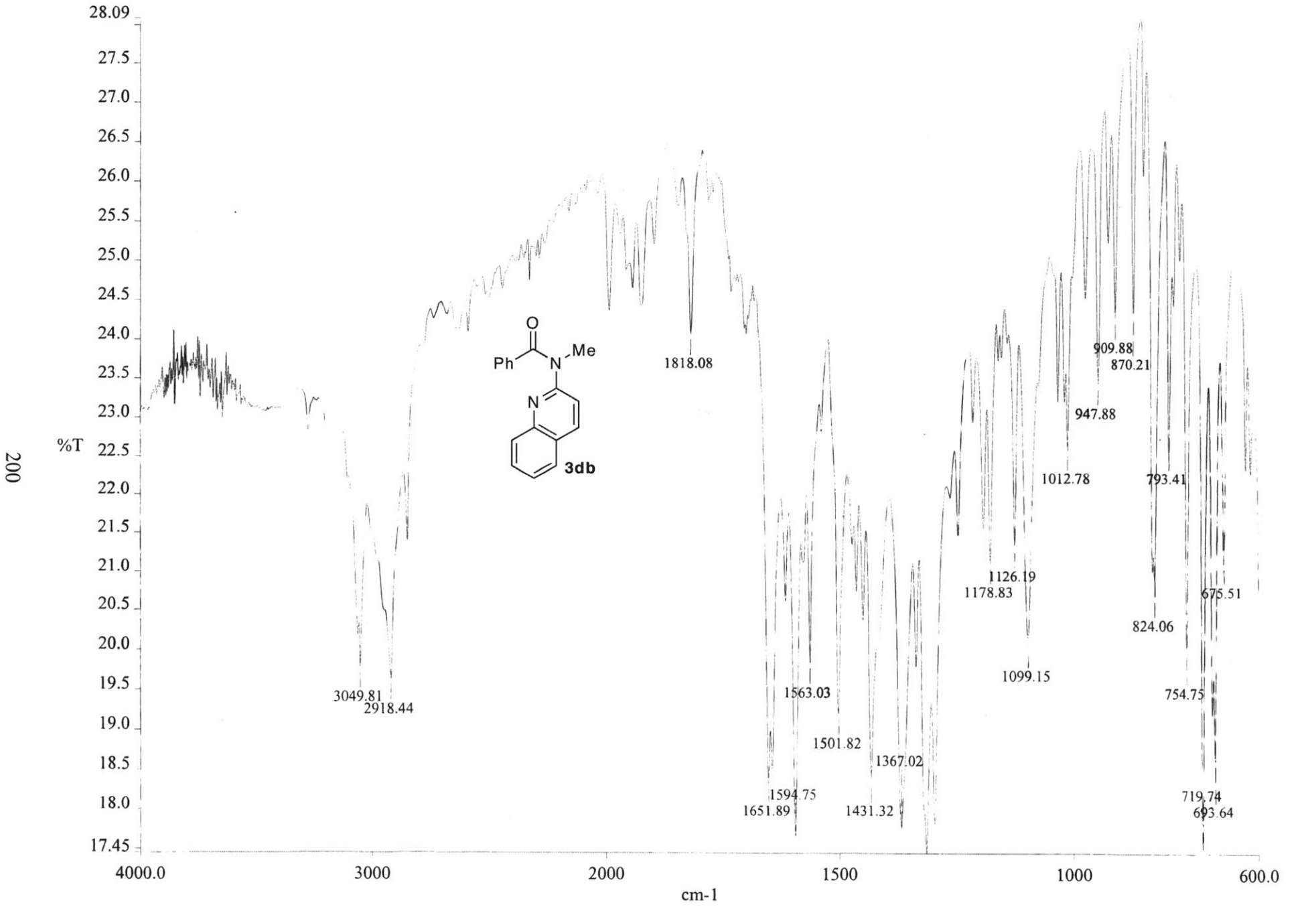
INOVA-500 "zippy"

 Relax. delay 0.500 sec
 Pulse 46.2 degrees
 Acq. time 1.500 sec
 Width 22624.4 Hz
 256 repetitions
OBSERVE C13, 75.4615208 MHz
DECOUPLE H1, 300.1067546 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Sq. sine bell 1.500 sec
  Shifted by -1.500 sec
FT size 262144
Total time 8 min, 34 sec



3db

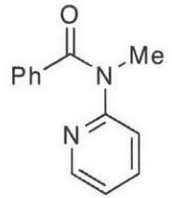



28.09
27.5
27.0
26.5
26.0
25.5
25.0
24.5
24.0
23.5
23.0
22.5
22.0
21.5
21.0
20.5
20.0
19.5
19.0
18.5
18.0
17.45
%T
200
4000.0
3000
2000
1500
1000
600.0
cm-1
O
Ph
N
Me
N
3db
3049.81
2918.44
1818.08
1651.89
1594.75
1563.03
1501.82
1431.32
1367.02
1178.83
1126.19
1099.15
1012.78
947.88
909.88
870.21
824.06
793.41
754.75
719.74
693.64
675.51

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Pulse 88.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272164 MHz
DATA PROCESSING
FT size 131072
Total time 0 min, 54 sec



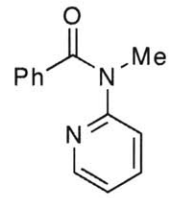
3dc

STANDARD CARBON PARAMETERS

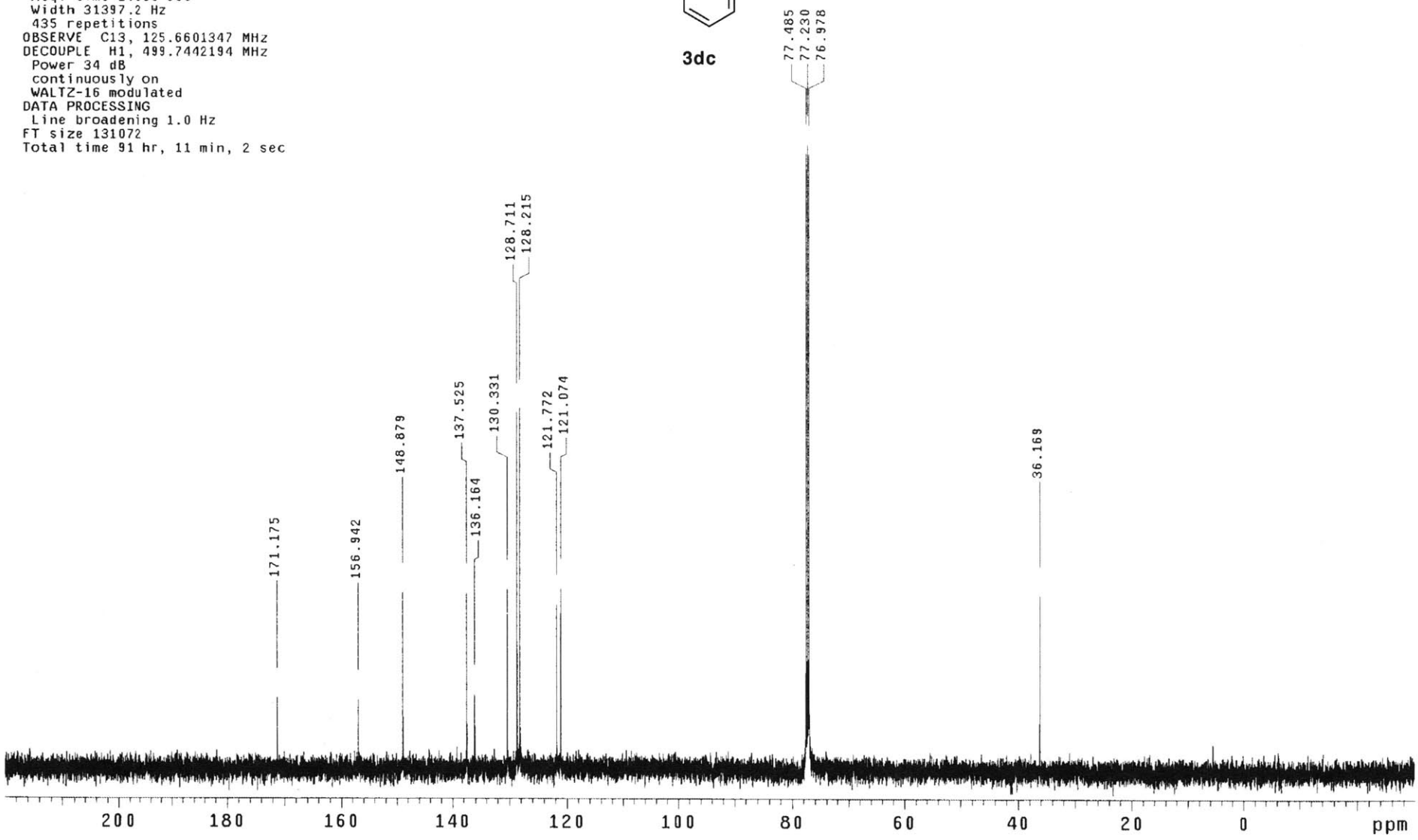
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

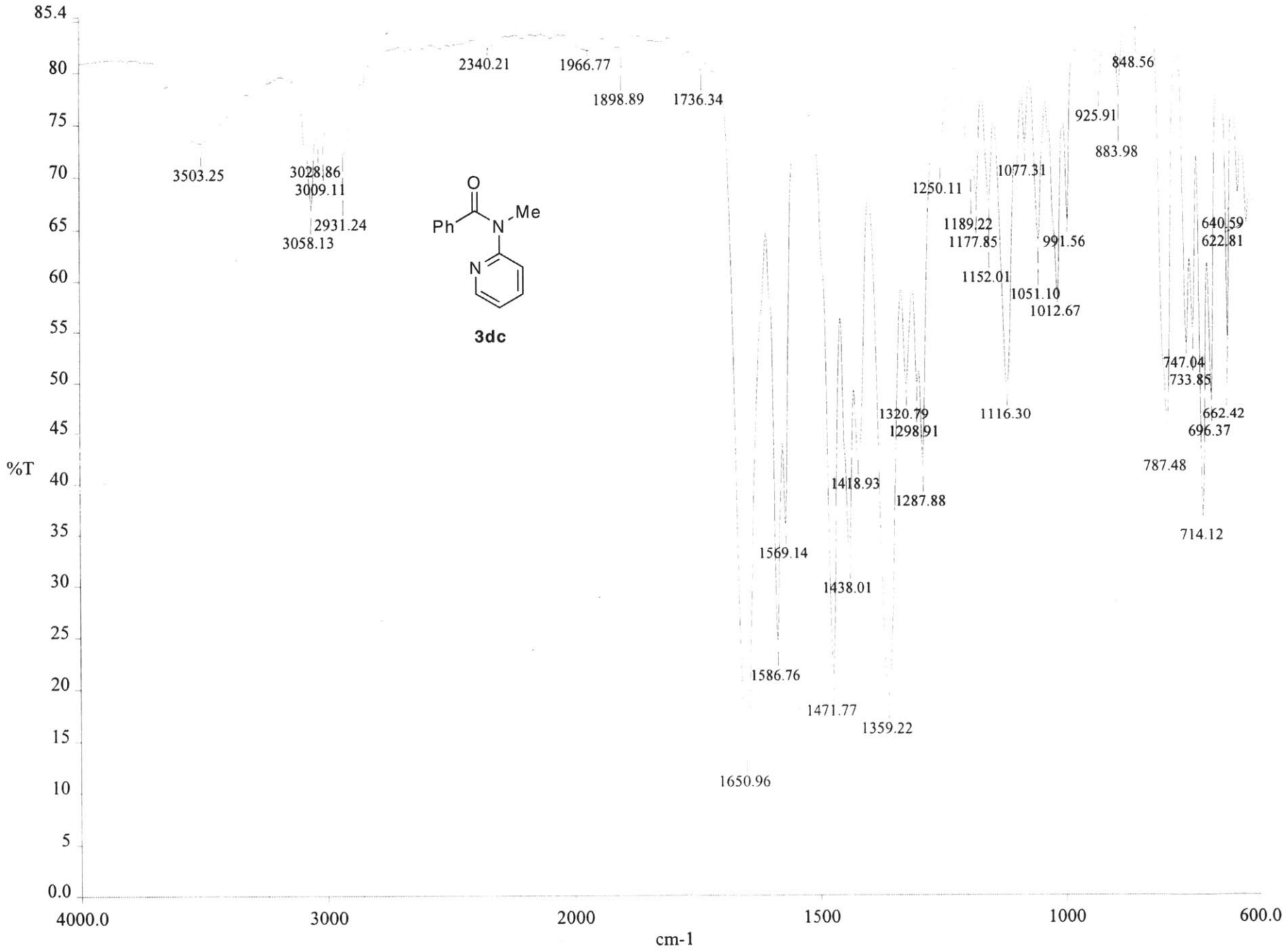
INOVA-500 "zippy"

Relax. delay 3.000 sec
Pulse 33.6 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
435 repetitions
OBSERVE C13, 125.6601347 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 91 hr, 11 min, 2 sec



3dc



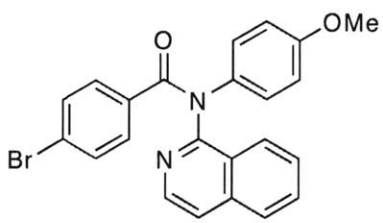

85.4
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3503.25
3028.86
3009.11
2931.24
3058.13
2340.21
1966.77
1898.89
1736.34
848.56
925.91
883.98
1077.31
1250.11
1189.22
1177.85
991.56
640.59
622.81
1152.01
1051.10
1012.67
747.04
733.85
1320.79
1298.91
1116.30
662.42
696.37
787.48
1418.93
1287.88
714.12
1569.14
1438.01
1586.76
1471.77
1359.22
1650.96
O
Ph
N
Me
N
3dc
203

STANDARD 1H OBSERVE

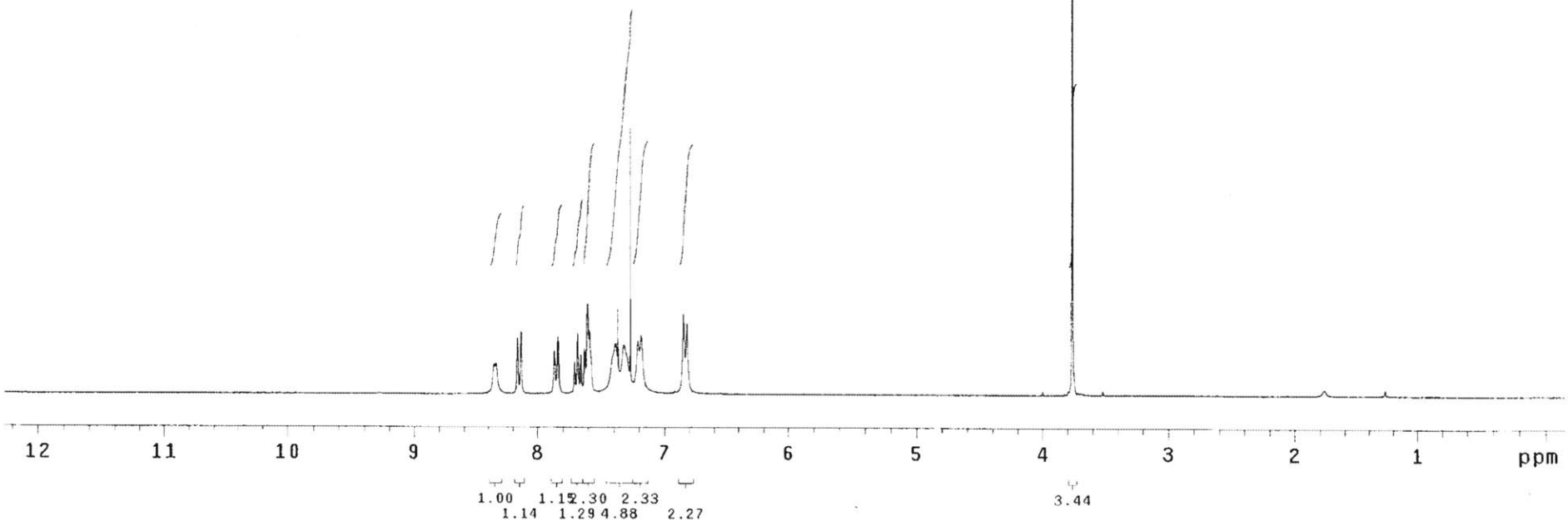
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052785 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



3ea

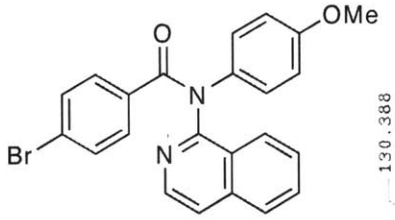


STANDARD CARBON PARAMETERS

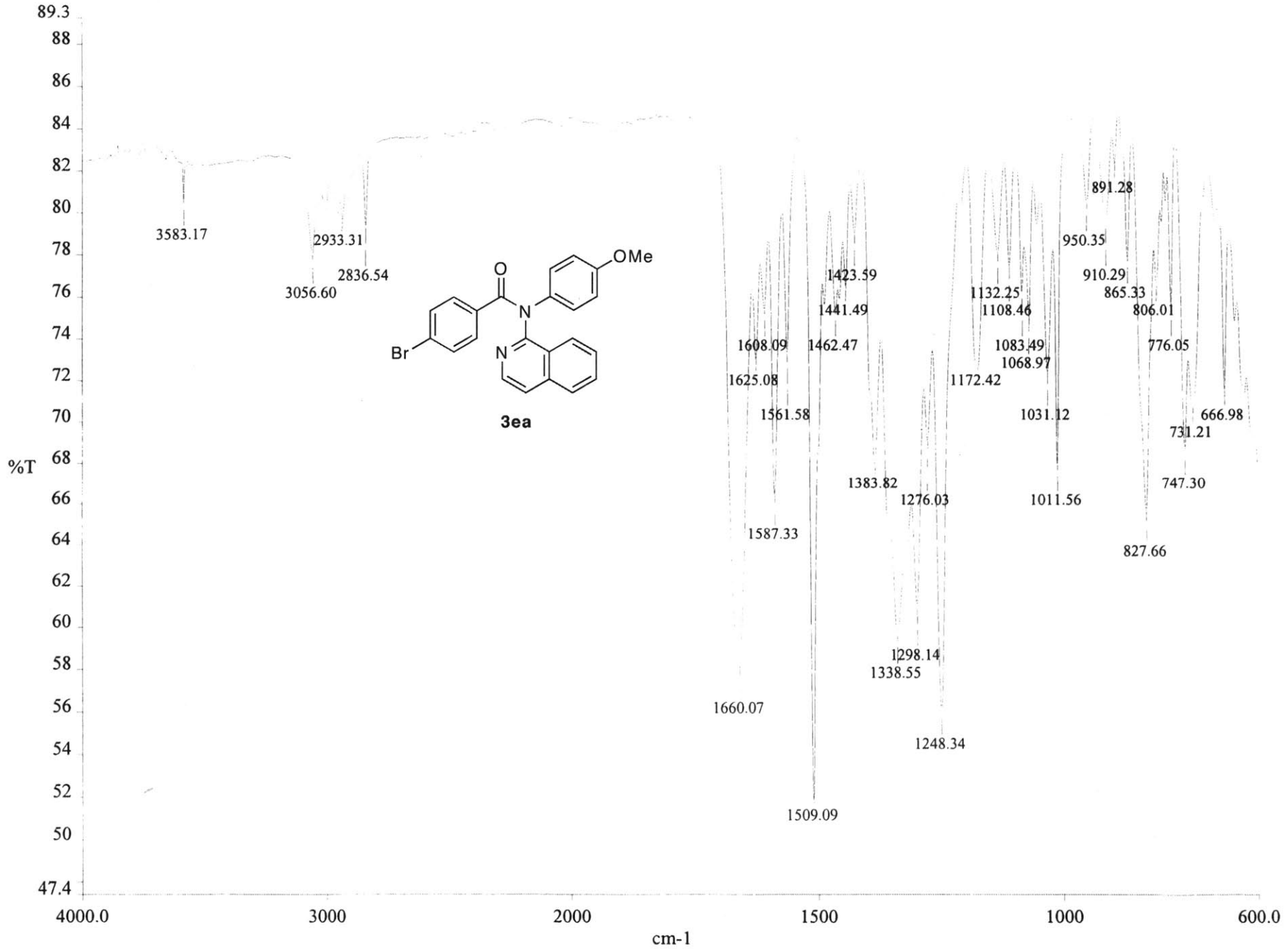
Pulse Sequence: s2pul
Solvent: DMSO
Temp. 100.0 C / 373.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
271 repetitions
OBSERVE C13, 125.7829573 MHz
DECOUPLE H1, 500.2315969 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 22 hr, 49 min, 46 sec



3ea

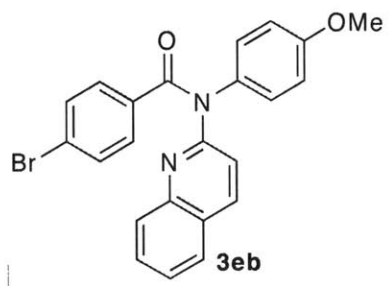

89.3
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
47.4
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3583.17
3056.60
2933.31
2836.54
1660.07
1625.08
1608.09
1587.33
1561.58
1509.09
1462.47
1441.49
1423.59
1383.82
1338.55
1298.14
1276.03
1248.34
1172.42
1132.25
1108.46
1083.49
1068.97
1031.12
1011.56
950.35
910.29
891.28
865.33
827.66
806.01
776.05
747.30
731.21
666.98
O
N
N
Br
OMe
3ea

STANDARD 1H OBSERVE

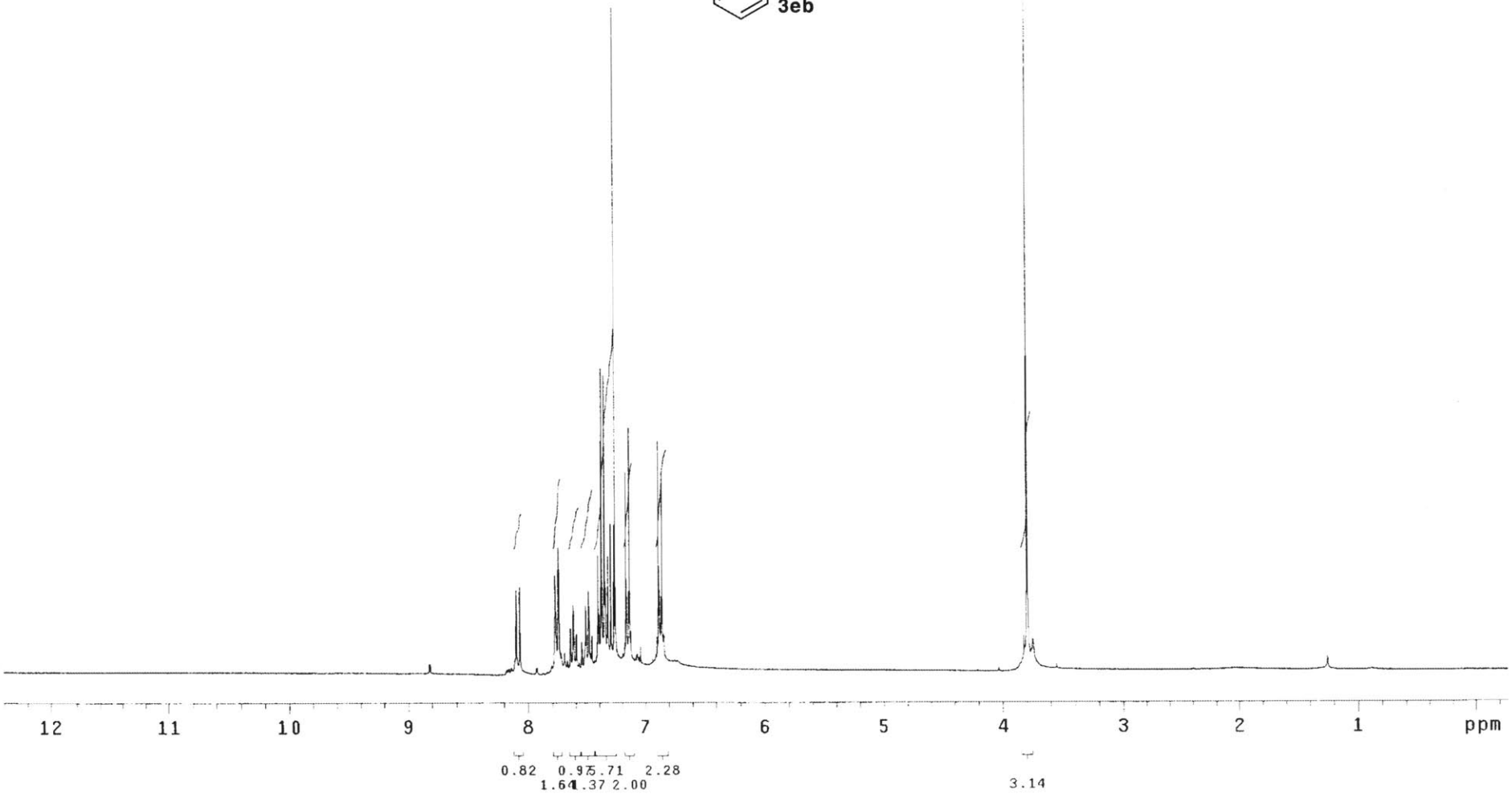
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052821 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



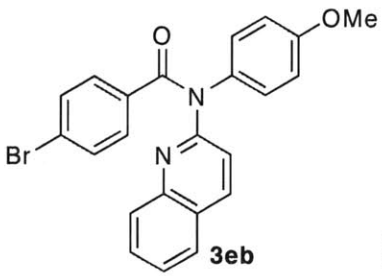
3eb



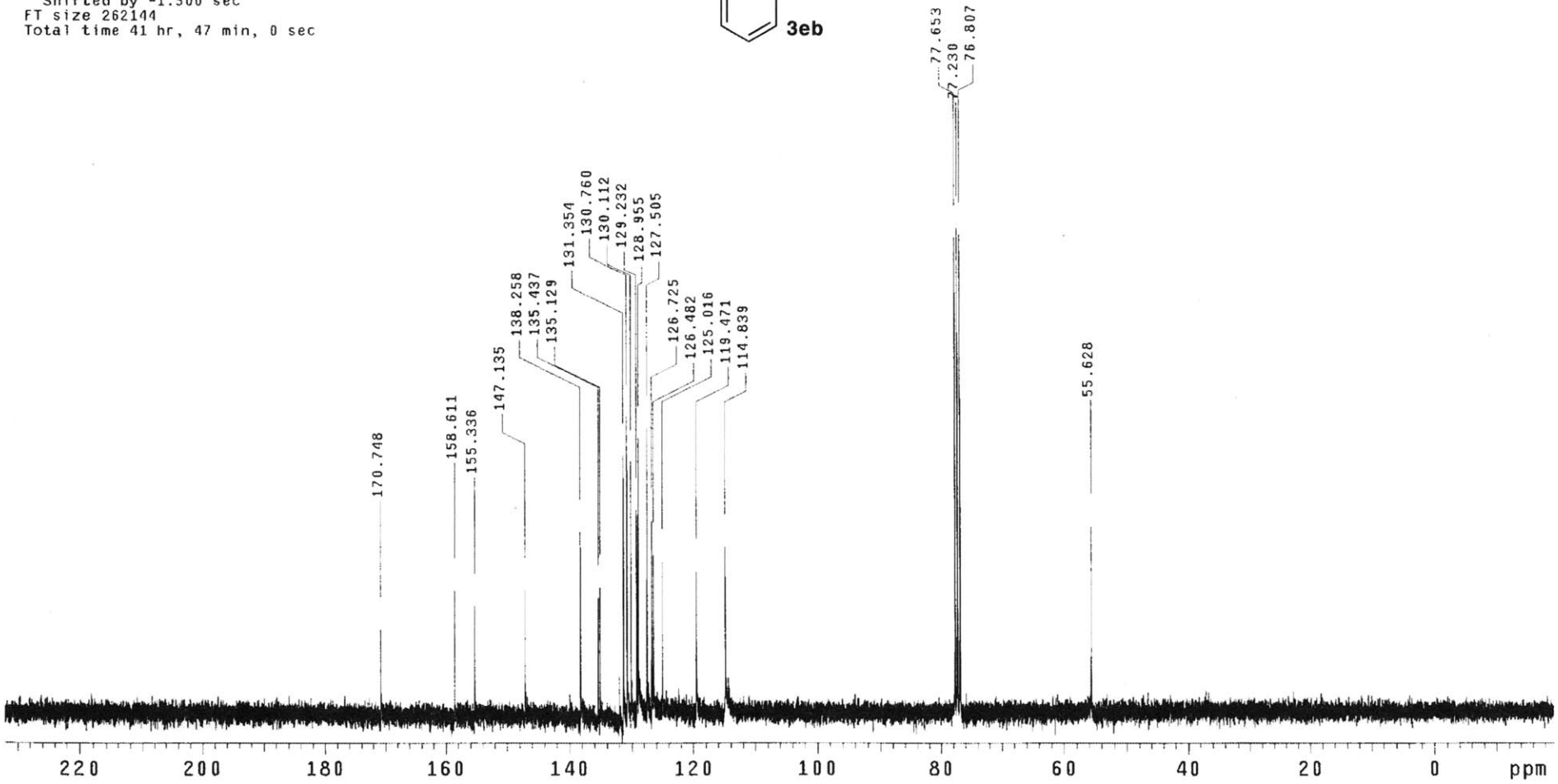
13C OBSERVE

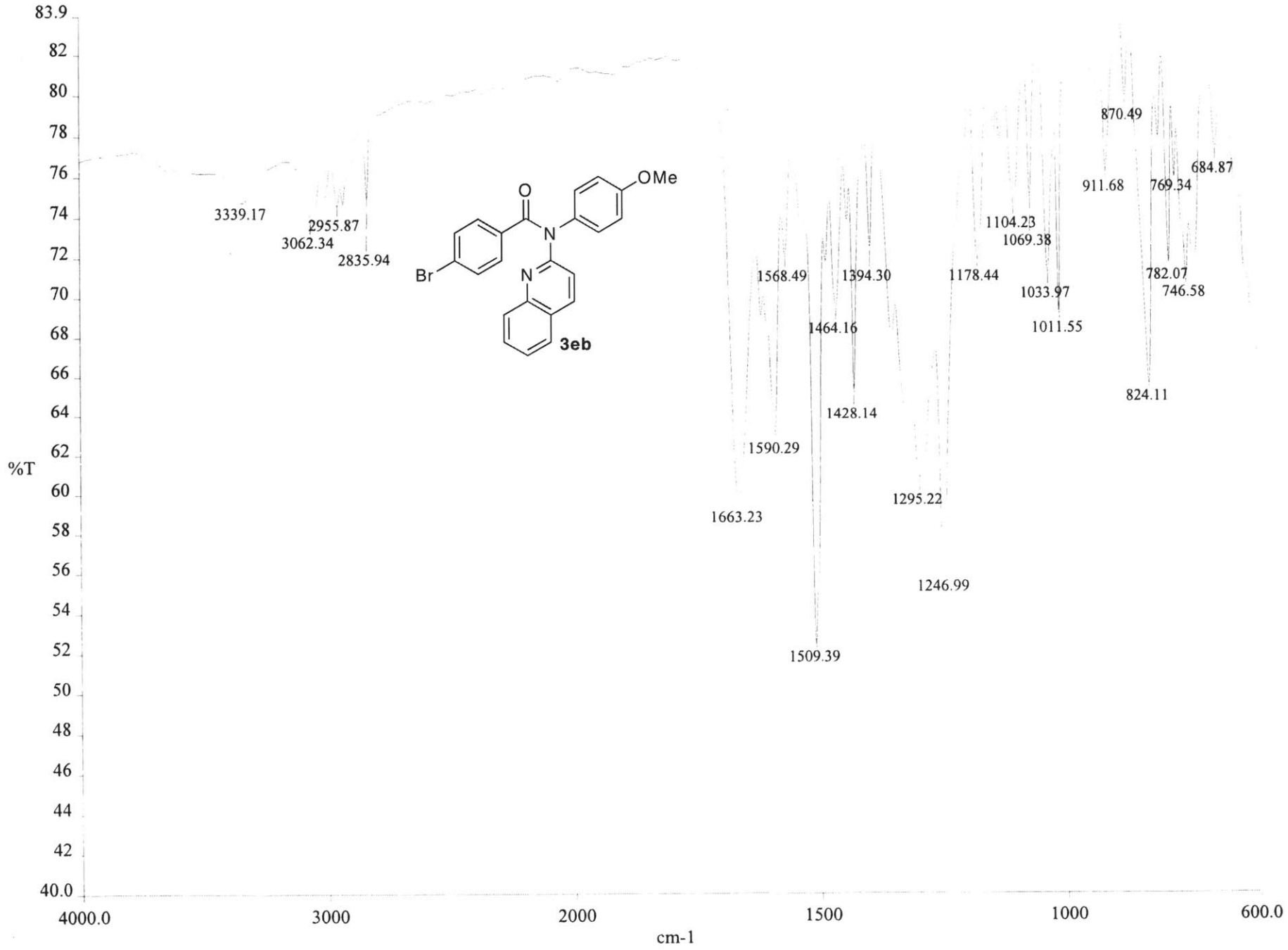
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K
Mercury-300 "mrhat"

Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
1756 repetitions
OBSERVE C13, 75.4615196 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 41 hr, 47 min, 0 sec



3eb



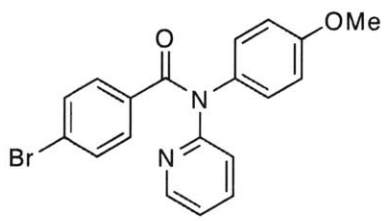

83.9
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48
46
44
42
40.0
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3339.17
3062.34
2955.87
2835.94
1663.23
1590.29
1568.49
1509.39
1464.16
1428.14
1394.30
1295.22
1246.99
1178.44
1104.23
1069.38
1033.97
1011.55
911.68
870.49
824.11
782.07
769.34
746.58
684.87
Br
N
O
N
OMe
3eb

STANDARD 1H OBSERVE

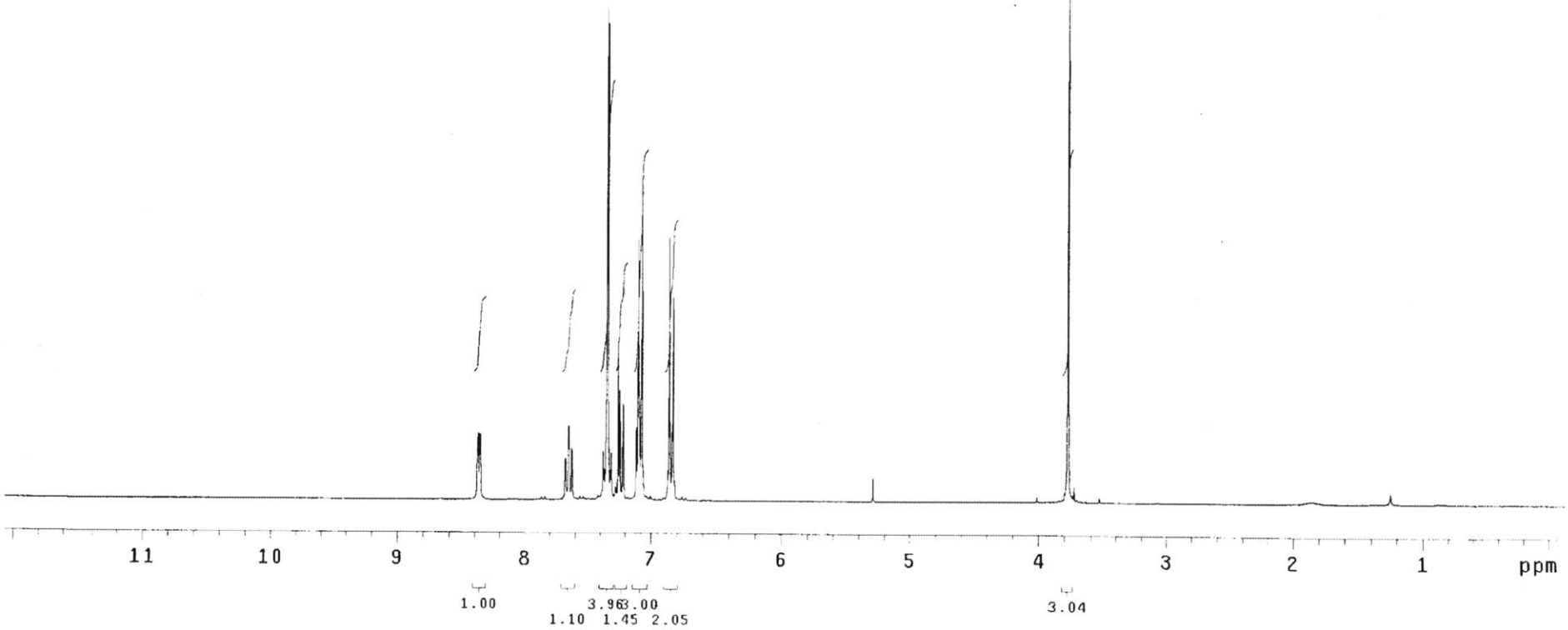
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052821 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



3ec

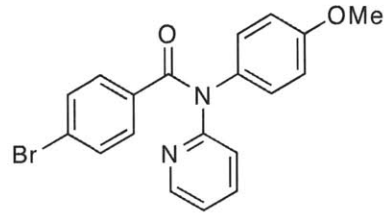


STANDARD CARBON PARAMETERS

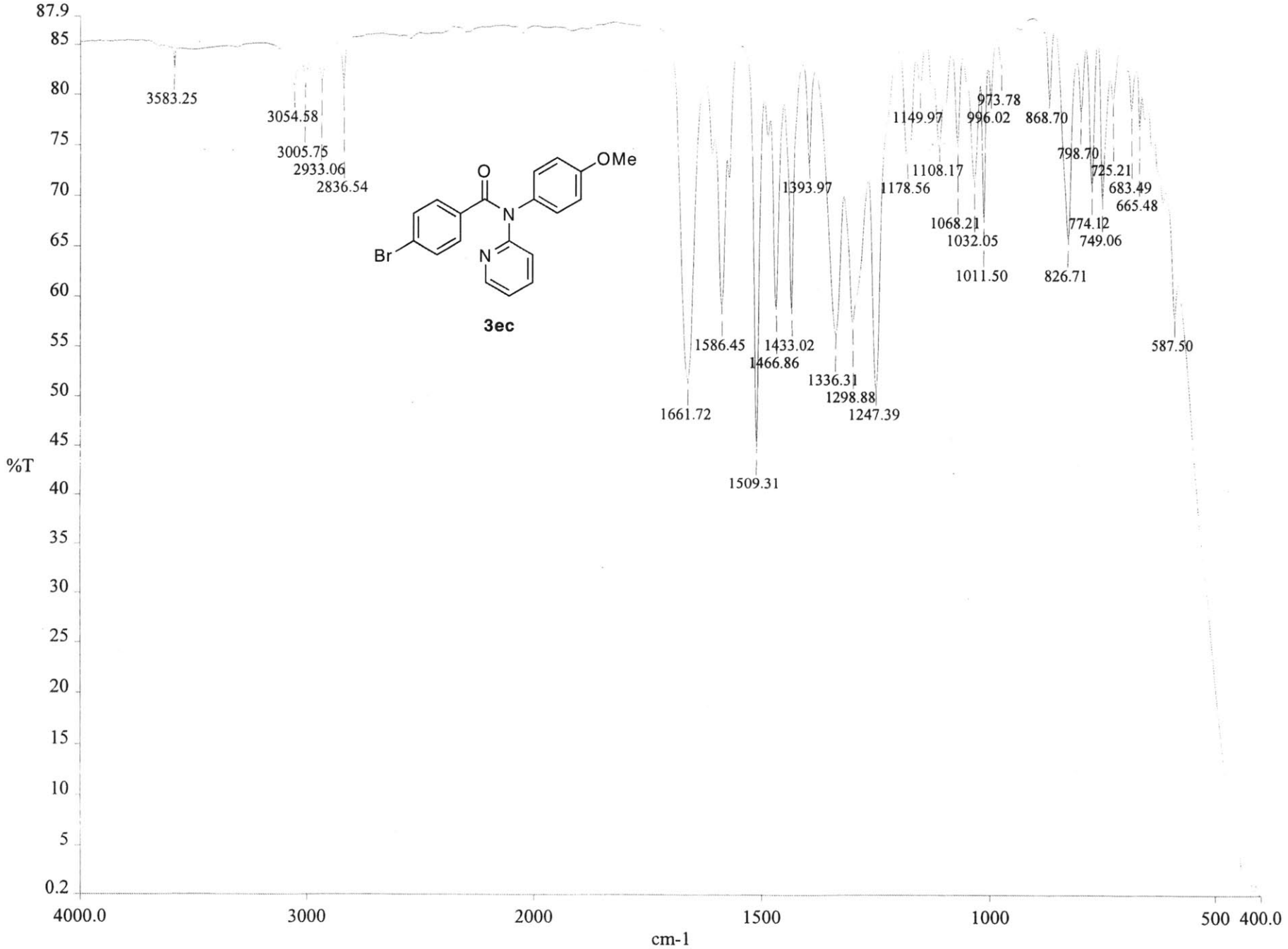
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
512 repetitions
OBSERVE C13, 125.7822136 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 21 min, 26 sec



3ec

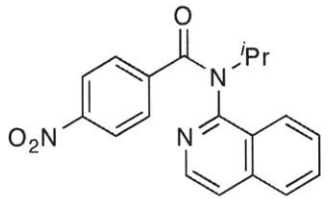

87.9
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.2
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.25
3054.58
3005.75
2933.06
2836.54
1661.72
1586.45
1509.31
1466.86
1433.02
1393.97
1336.31
1298.88
1247.39
1178.56
1149.97
1108.17
1068.21
1032.05
1011.50
996.02
973.78
868.70
826.71
798.70
774.12
749.06
725.21
683.49
665.48
587.50
Br
N
O
N
OMe
3ec

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 2.000 sec
Pulse 94.4 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417185 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 20 sec



3fa

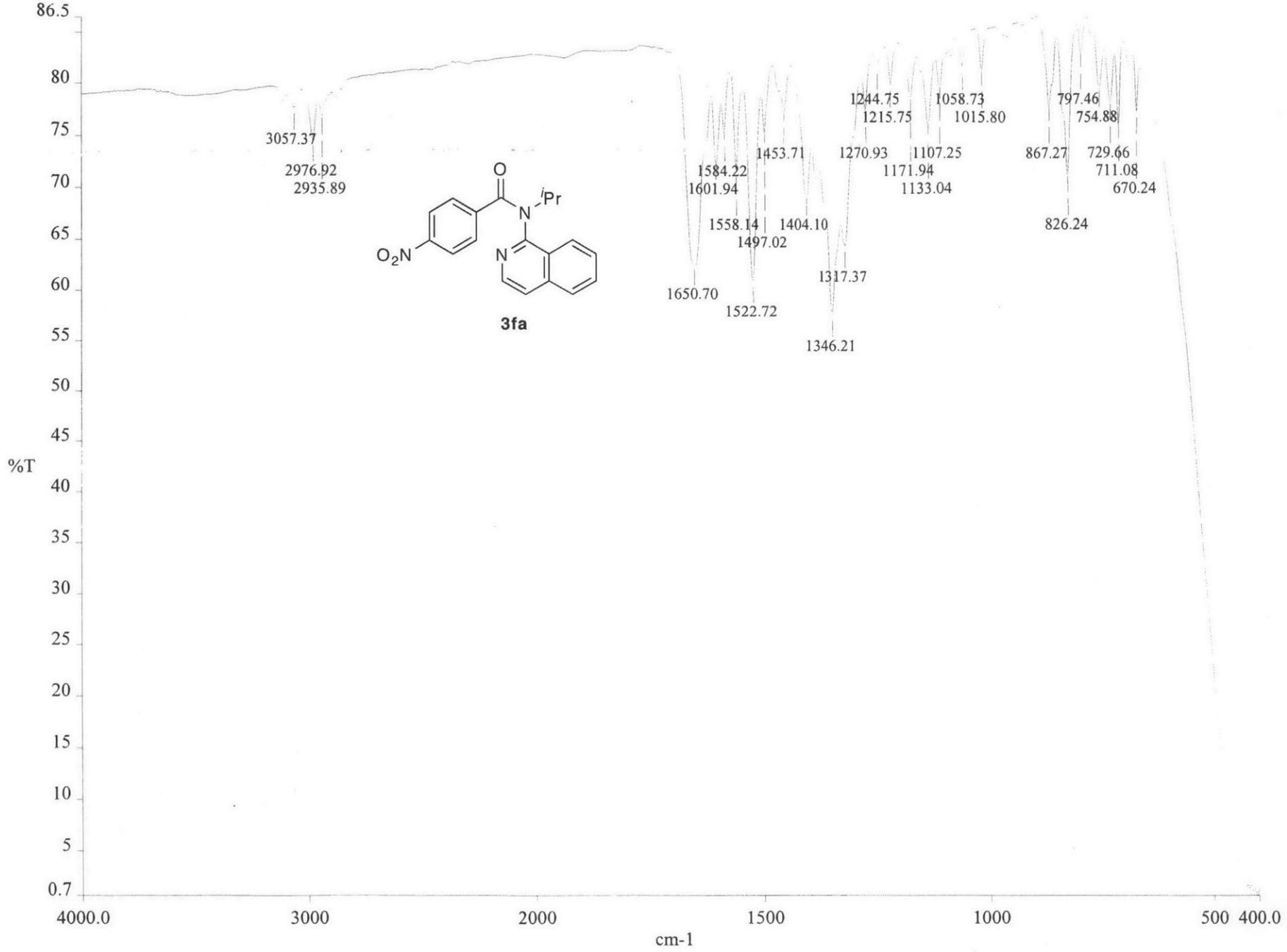
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
256 repetitions
OBSERVE C13, 125.7822113 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 10 min, 44 sec

3fa

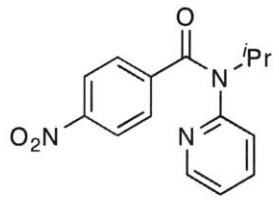

86.5
80
75
70
65
60
55
50
45
%T
40
35
30
25
20
15
10
5
0.7
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3057.37
2976.92
2935.89
1650.70
1601.94
1584.22
1558.14
1522.72
1497.02
1453.71
1404.10
1346.21
1317.37
1270.93
1244.75
1215.75
1171.94
1133.04
1107.25
1058.73
1015.80
867.27
826.24
797.46
754.88
729.66
711.08
670.24
O
N
iPr
O2N
N
3fa

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052786 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



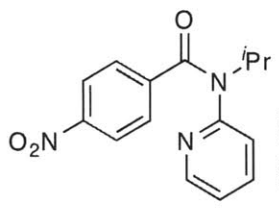
3fc

STANDARD CARBON PARAMETERS

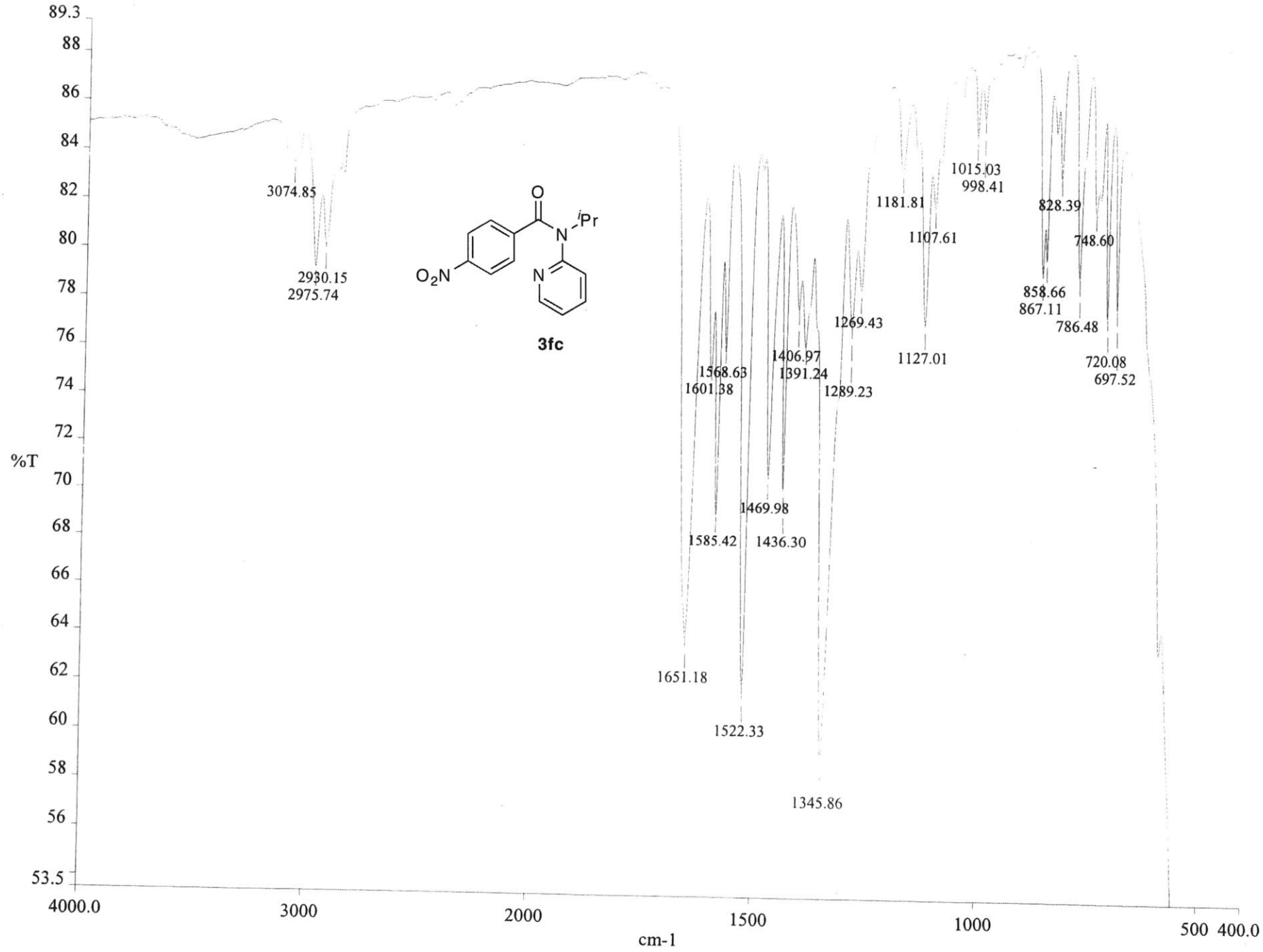
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
2124 repetitions
OBSERVE C13, 125.7822072 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 44 hr, 8 min, 23 sec



3fc

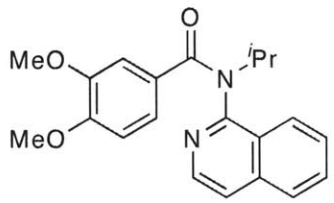

89.3
88
86
84
82
80
78
76
74
72
%T
70
68
66
64
62
60
58
56
53.5
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3074.85
2930.15
2975.74
1651.18
1601.38
1568.63
1585.42
1522.33
1469.98
1436.30
1406.97
1391.24
1345.86
1289.23
1269.43
1181.81
1127.01
1107.61
1015.03
998.41
858.66
867.11
828.39
786.48
748.60
720.08
697.52
O
N
iPr
O2N
N
3fc

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 2.000 sec
Pulse 94.4 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417206 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 20 sec



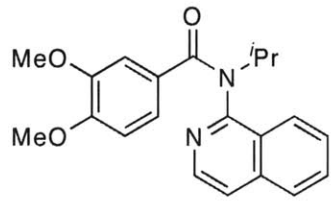
3ga

STANDARD CARBON PARAMETERS

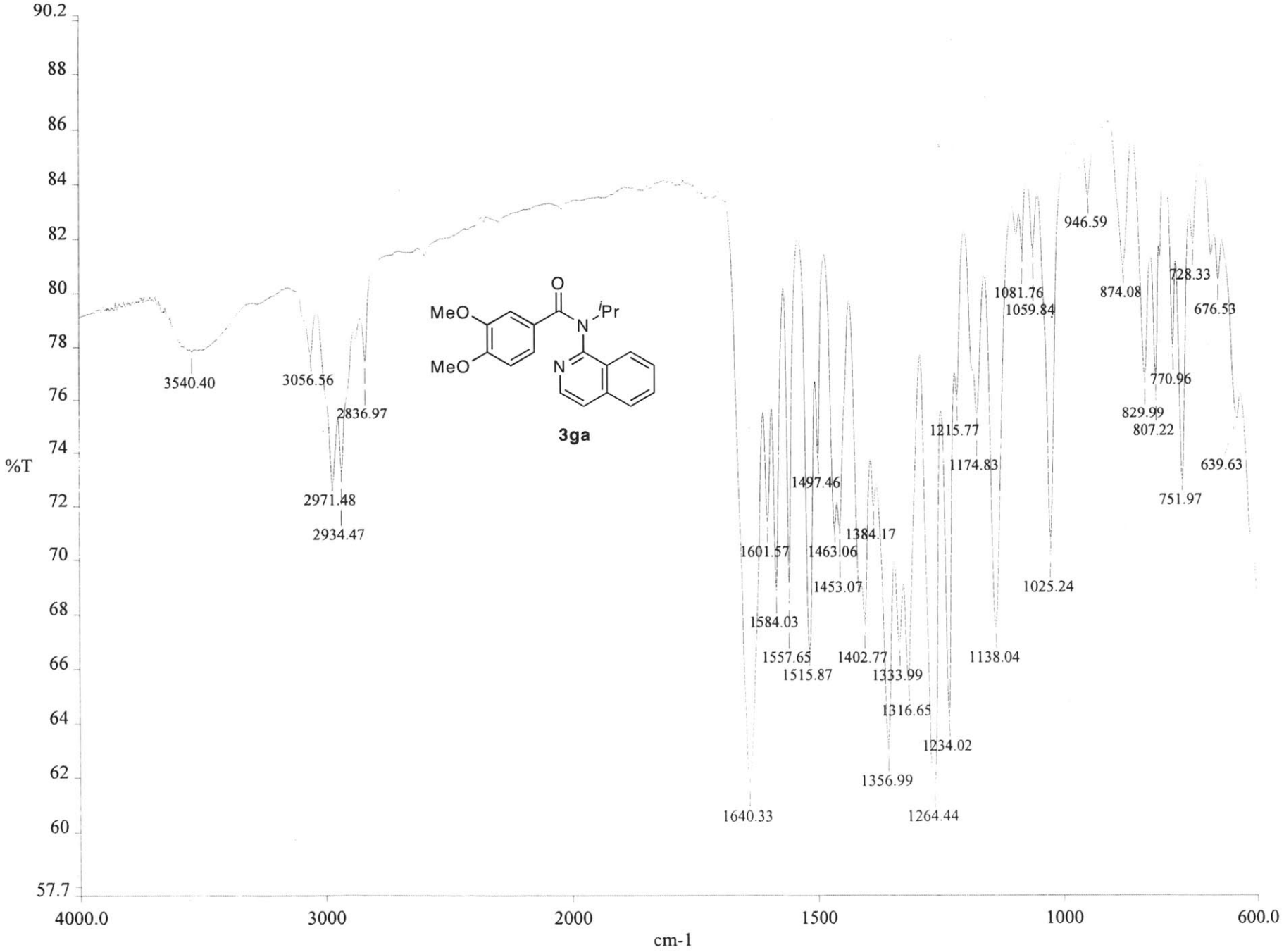
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
4719 repetitions
OBSERVE C13, 125.7822078 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 22 hr, 49 min, 46 sec



3ga


90.2
88
86
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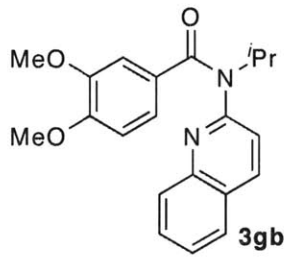
82
80
78
76
74
72
70
68
66
64
62
60
57.7
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
MeO
MeO
O
N
iPr
N
3ga
3540.40
3056.56
2836.97
2971.48
2934.47
1601.57
1584.03
1557.65
1515.87
1497.46
1463.06
1453.07
1384.17
1402.77
1333.99
1316.65
1356.99
1640.33
1264.44
1234.02
1215.77
1174.83
1138.04
1081.76
1059.84
1025.24
946.59
874.08
829.99
807.22
770.96
751.97
728.33
676.53
639.63

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052782 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



3gb

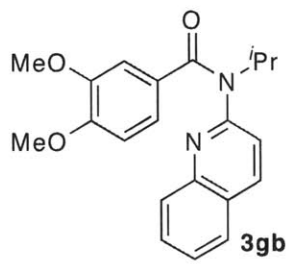
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

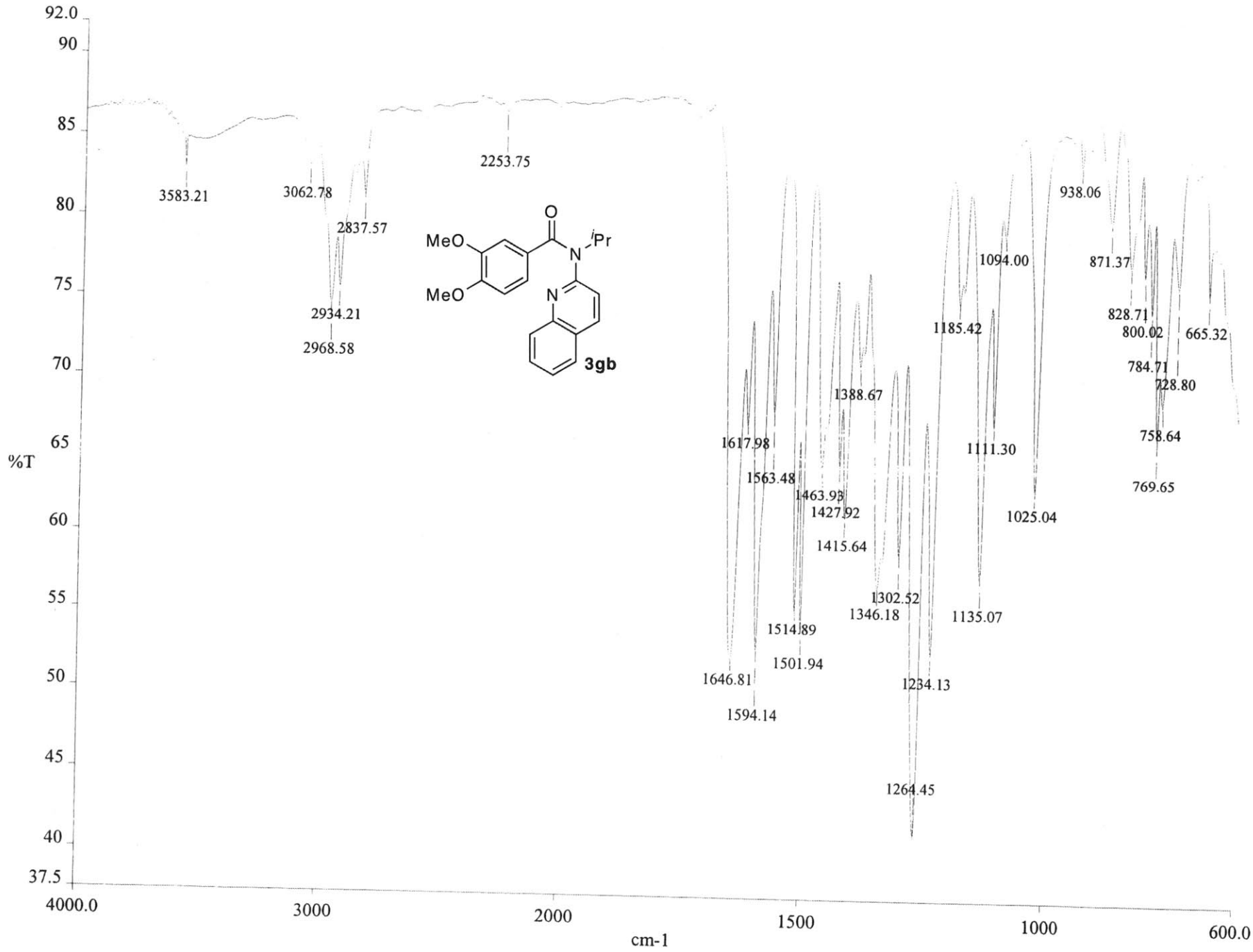
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
480 repetitions
OBSERVE C13, 125.7822130 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 22 hr, 49 min, 46 sec



3gb


92.0
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85
80
75
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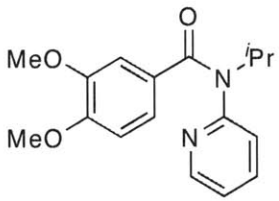
65
60
55
50
45
40
37.5
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3583.21
3062.78
2837.57
2253.75
2934.21
2968.58
MeO
MeO
N
O
N
iPr
3gb
938.06
871.37
1094.00
828.71
800.02
665.32
1185.42
784.71
728.80
1388.67
758.64
1617.98
1111.30
1563.48
769.65
1463.93
1427.92
1025.04
1415.64
1302.52
1346.18
1135.07
1514.89
1501.94
1646.81
1234.13
1594.14
1264.45

STANDARD 1H OBSERVE

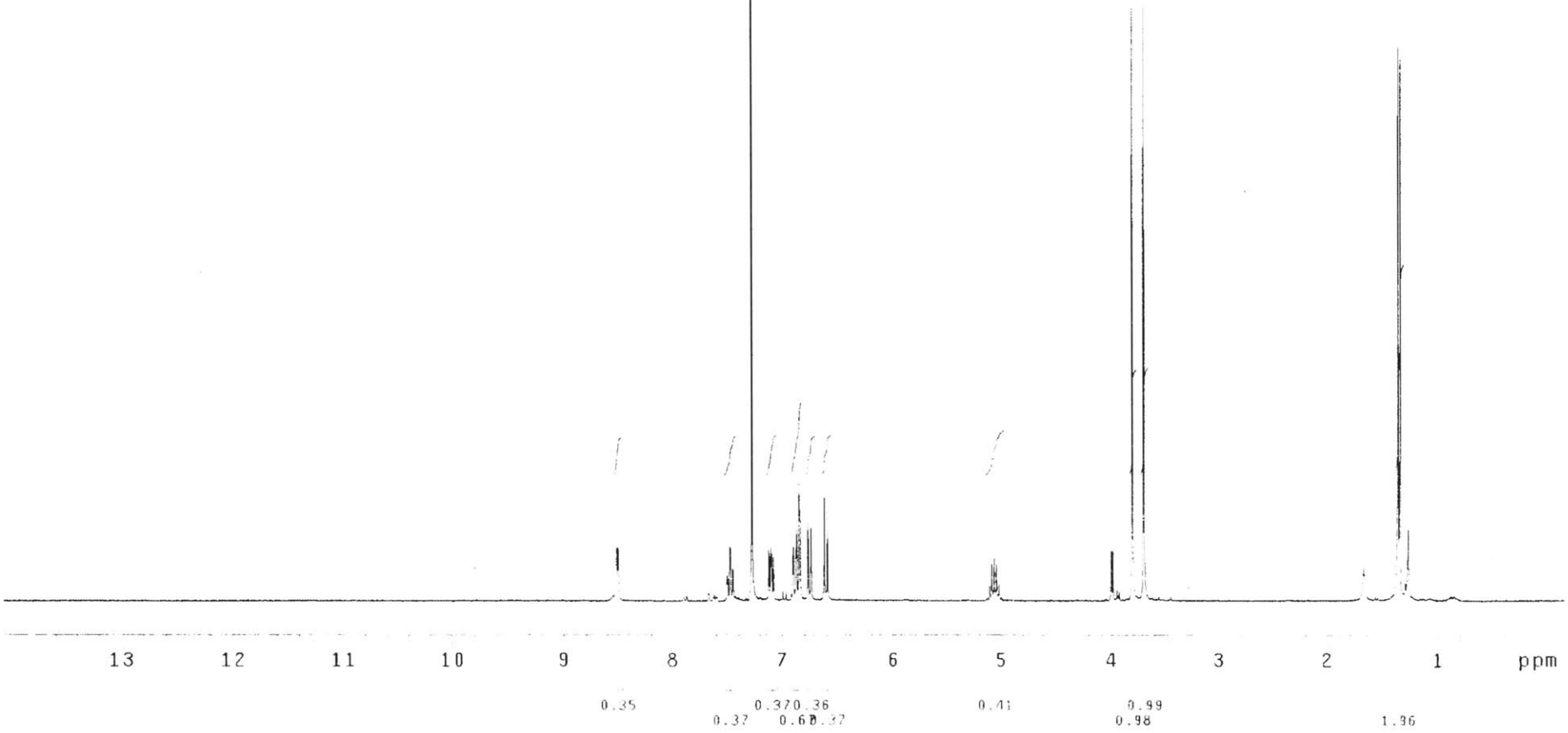
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052789 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



3gc

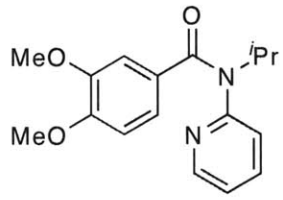


STANDARD CARBON PARAMETERS

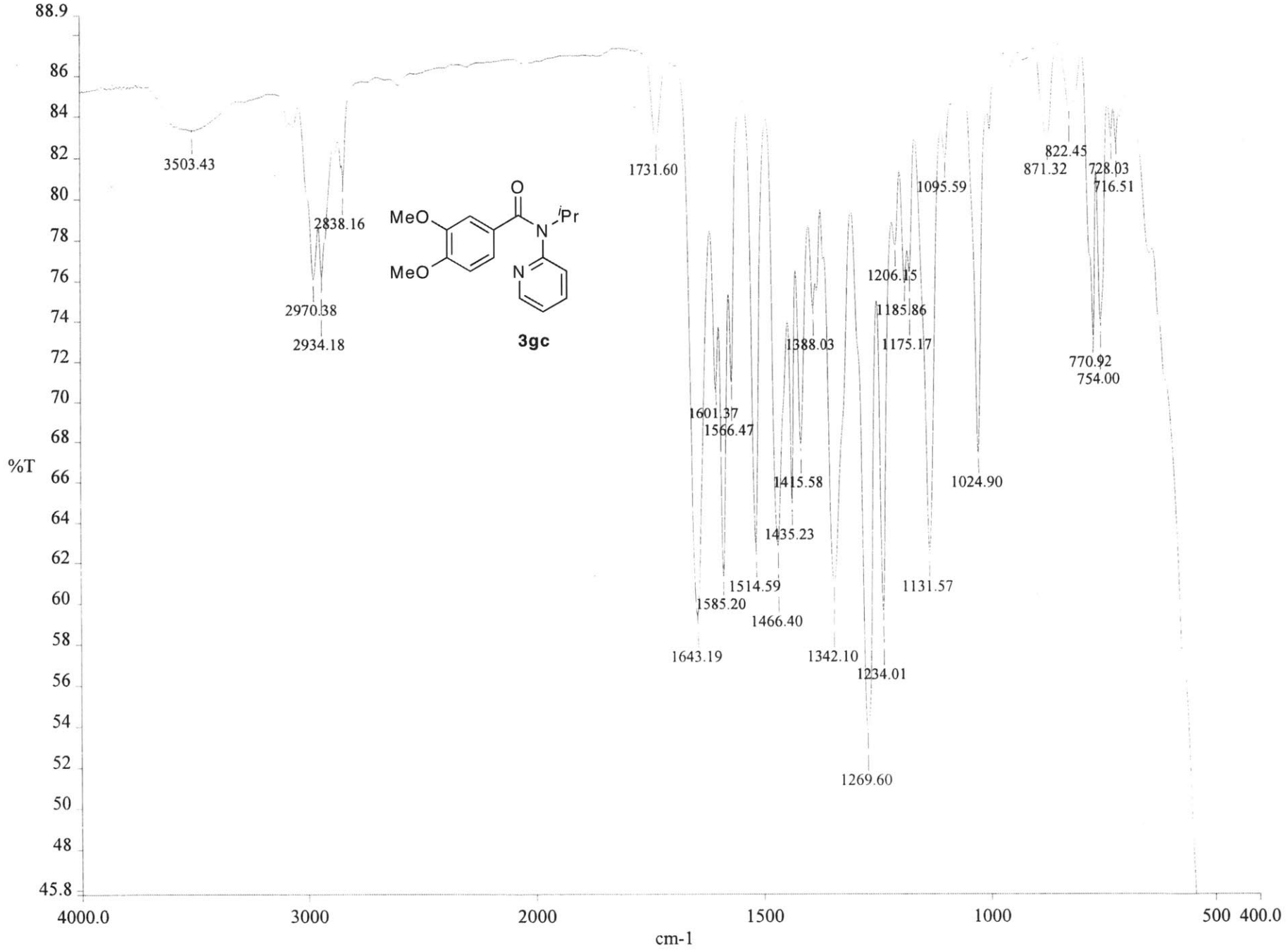
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
644 repetitions
OBSERVE C13, 125.7822084 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 45 hr, 39 min, 31 sec



3gc


88.9
86
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68
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64
62
60
58
56
54
52
50
48
45.8
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3503.43
2838.16
2970.38
2934.18
1731.60
1601.37
1566.47
1514.59
1585.20
1466.40
1643.19
1435.23
1415.58
1388.03
1342.10
1269.60
1234.01
1206.15
1185.86
1175.17
1131.57
1095.59
1024.90
822.45
871.32
728.03
716.51
770.92
754.00
MeO
MeO
O
N
iPr
N
3gc

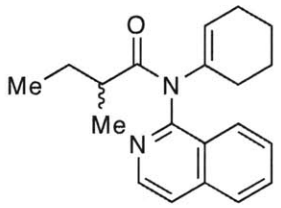
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: DMSO
Temp. 100.0 C / 373.1 K

INOVA-500 "zippy"

Pulse 79.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2295896 MHz
DATA PROCESSING
FT size 131072
Total time 0 min, 54 sec



3ha

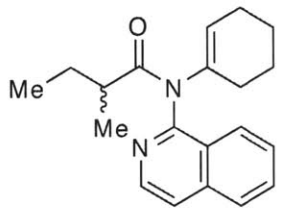
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

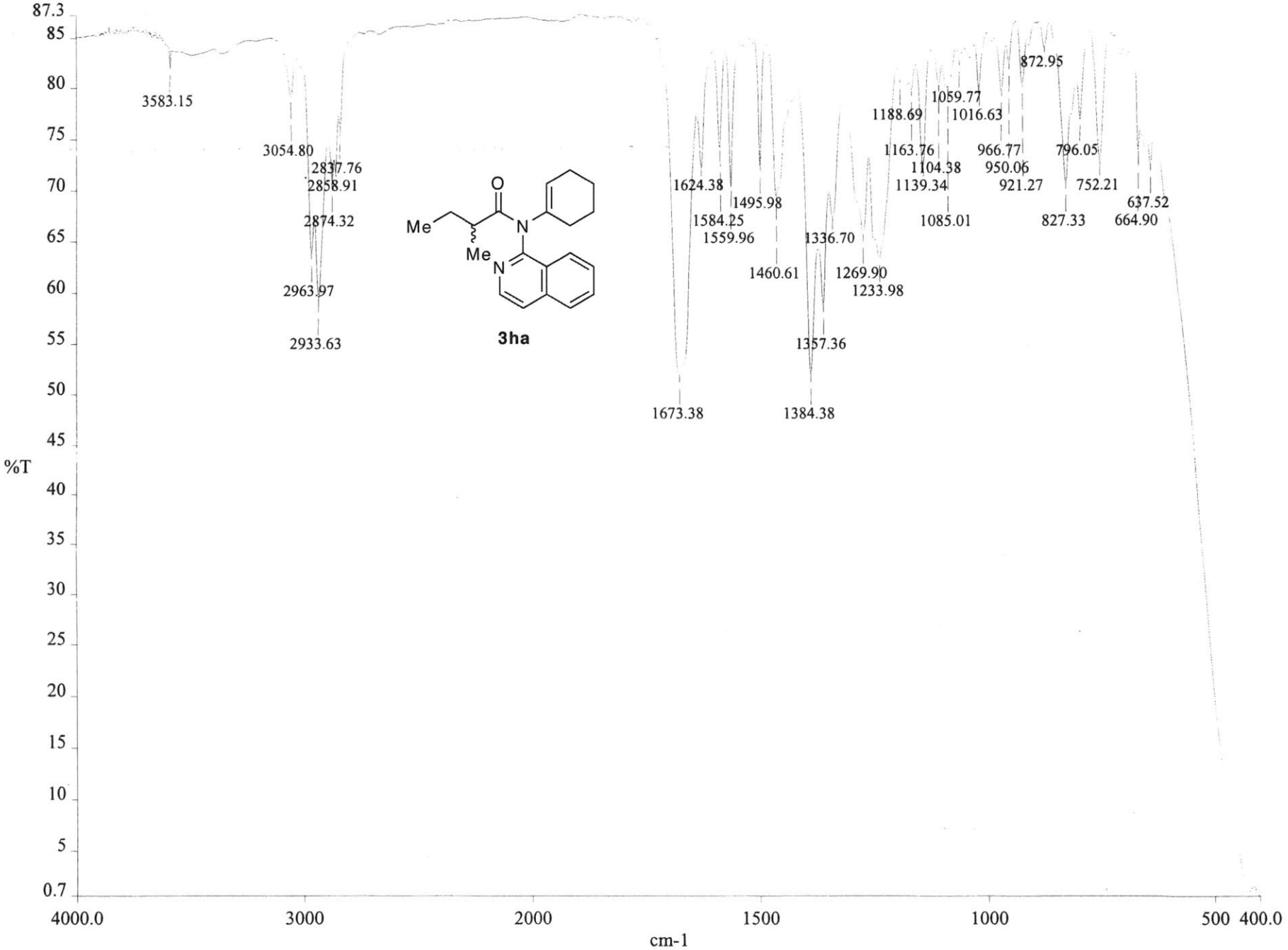
Solvent: DMSO
Temp. 100.0 C / 373.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
1272 repetitions
OBSERVE C13, 125.7829550 MHz
DECOUPLE H1, 500.2315969 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 22 hr, 49 min, 46 sec



3ha


87.3
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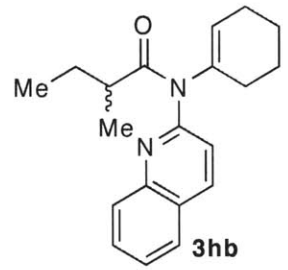
25
20
15
10
5
0.7
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.15
3054.80
2837.76
2858.91
2874.32
2963.97
2933.63
1673.38
1624.38
1584.25
1559.96
1495.98
1460.61
1384.38
1357.36
1336.70
1269.90
1233.98
1188.69
1163.76
1139.34
1104.38
1085.01
1059.77
1016.63
966.77
950.06
921.27
872.95
827.33
796.05
752.21
664.90
637.52
Me
Me
N
O
N
3ha

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.050 sec
Pulse 34.3 degrees
Acq. time 4.003 sec
Width 6002.4 Hz
16 repetitions
OBSERVE H1, 300.1052790 MHz
DATA PROCESSING
FT size 131072
Total time 1 min, 4 sec



3hb

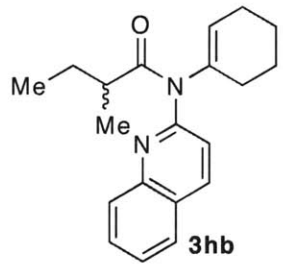
1:1 mixture of atropisomers

13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

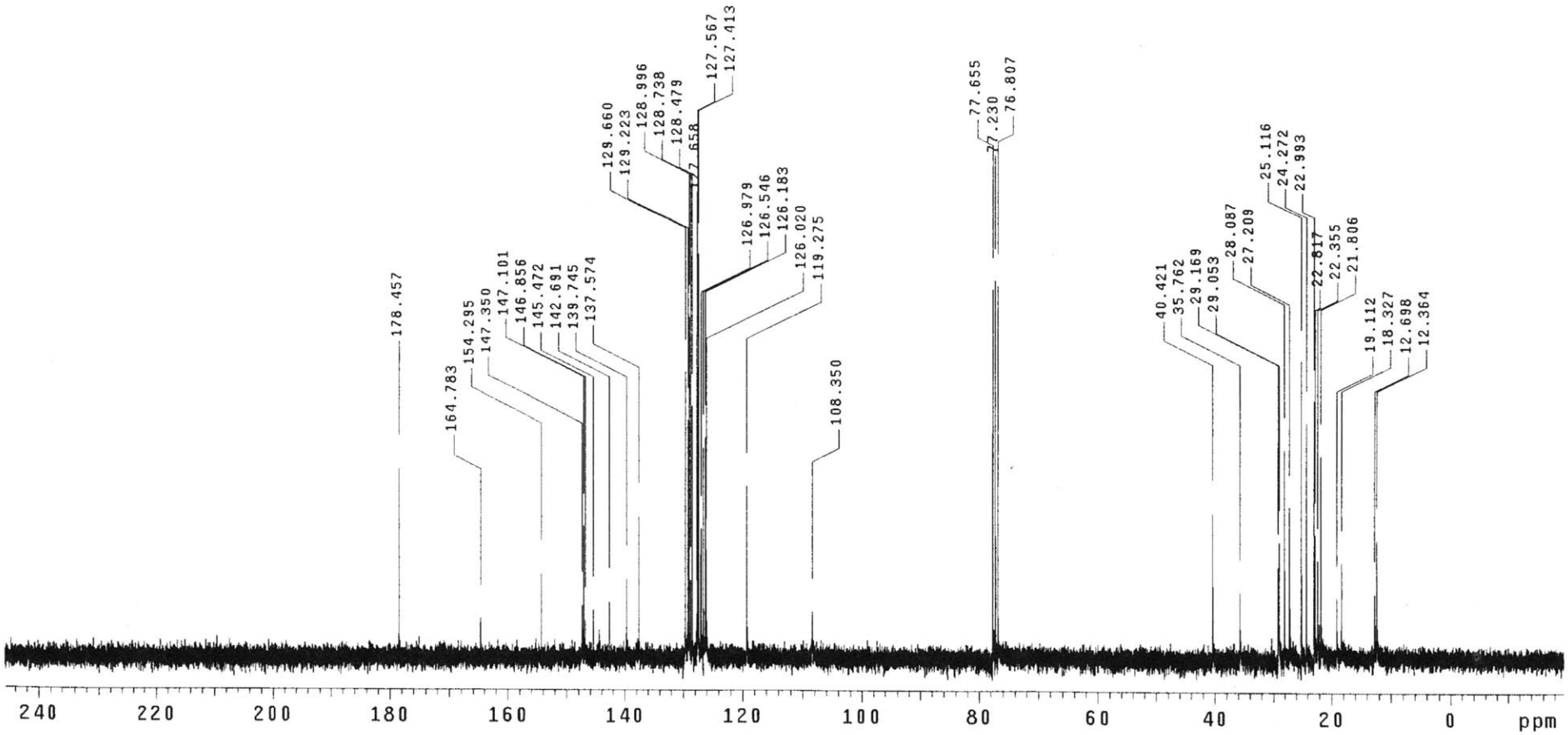
INOVA-500 "zippy"

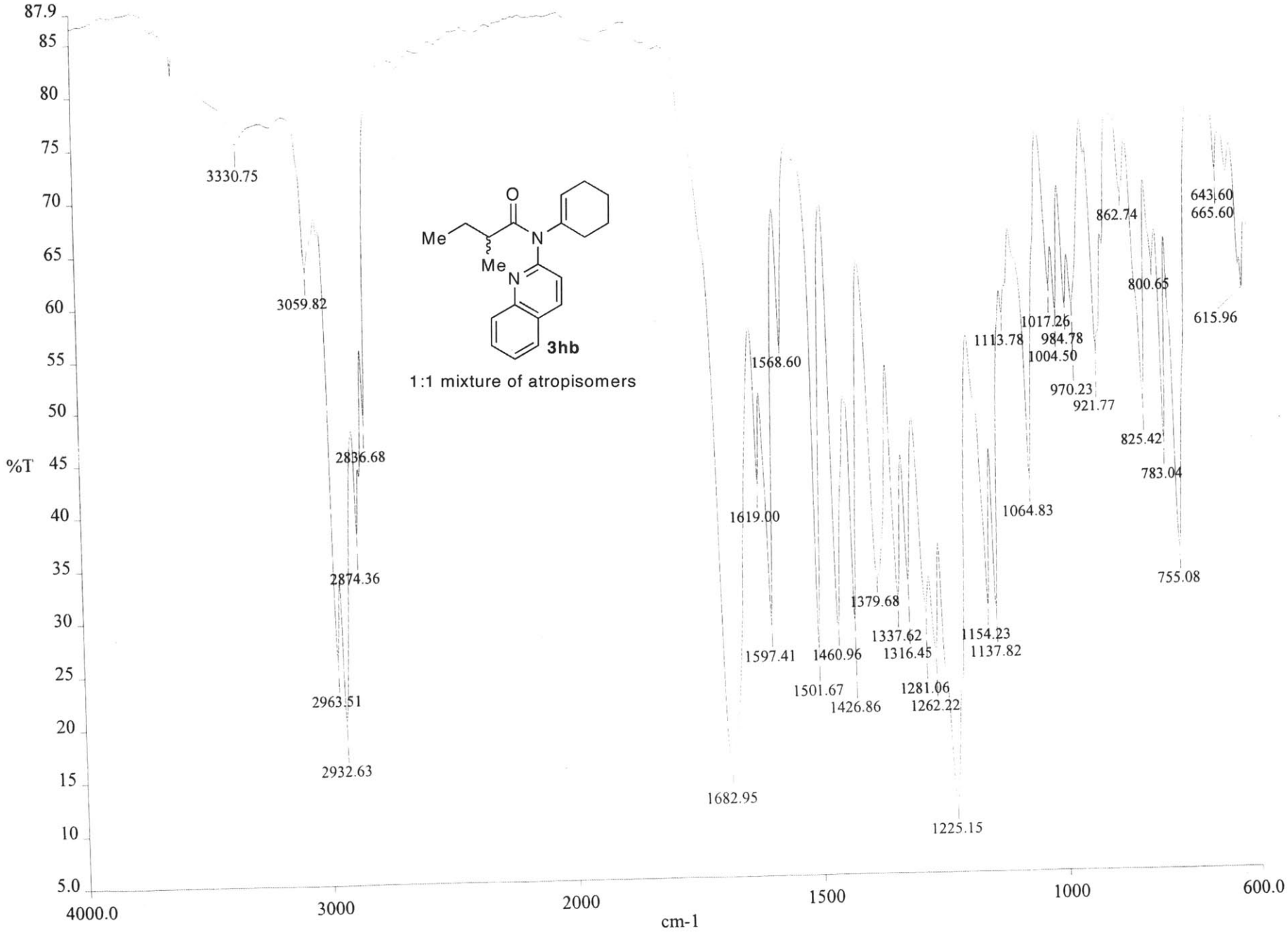
Relax. delay 0.500 sec
Pulse 46.2 degrees
Acq. time 1.500 sec
Width 22624.4 Hz
512 repetitions
OBSERVE C13, 75.4615227 MHz
DECOUPLE H1, 300.1067546 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Sq. sine bell 1.500 sec
Shifted by -1.500 sec
FT size 262144
Total time 17 min, 8 sec



3hb

1:1 mixture of atropisomers




87.9
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%T 45
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25
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15
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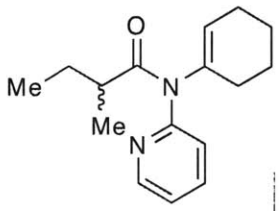
5.0
4000.0
3000
2000
1500
1000
600.0
cm-1
3330.75
3059.82
2836.68
2874.36
2963.51
2932.63
1682.95
1619.00
1568.60
1597.41
1460.96
1501.67
1426.86
1379.68
1337.62
1316.45
1281.06
1262.22
1225.15
1154.23
1137.82
1113.78
1064.83
1017.26
984.78
1004.50
970.23
921.77
862.74
800.65
825.42
783.04
755.08
643.60
665.60
615.96
Me
Me
N
O
N
3hb
1:1 mixture of atropisomers

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Pulse 79.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272157 MHz
DATA PROCESSING
FT size 131072
Total time 0 min, 54 sec



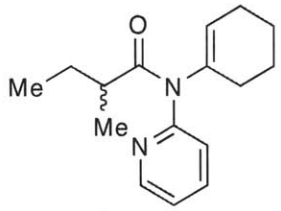
3hc

STANDARD CARBON PARAMETERS

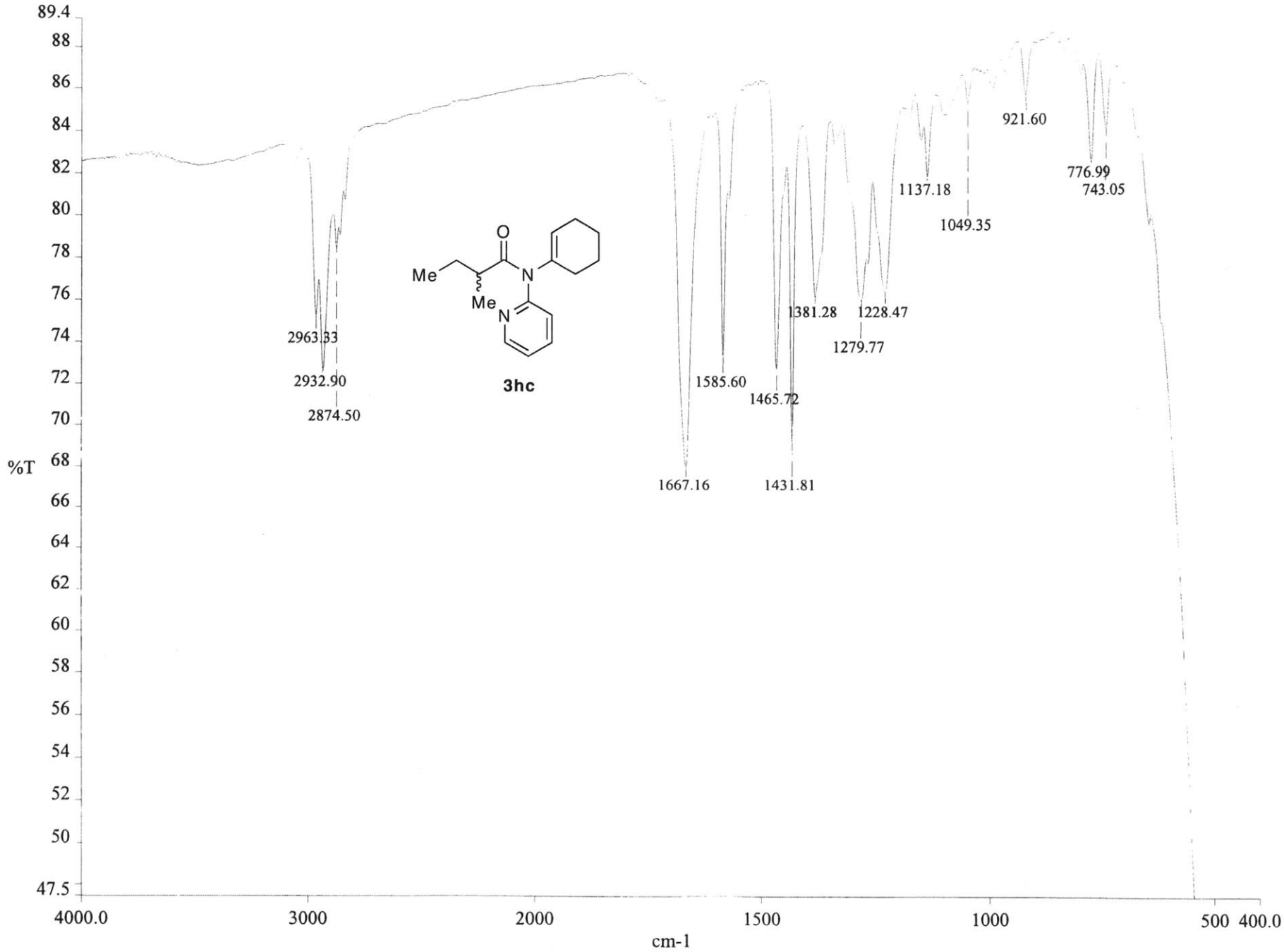
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
12712 repetitions
OBSERVE C13, 125.7821446 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 45 hr, 39 min, 31 sec



3hc


89.4
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52
50
47.5
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2963.33
2932.90
2874.50
1667.16
1585.60
1465.72
1431.81
1381.28
1279.77
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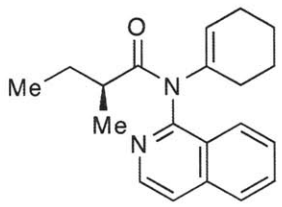
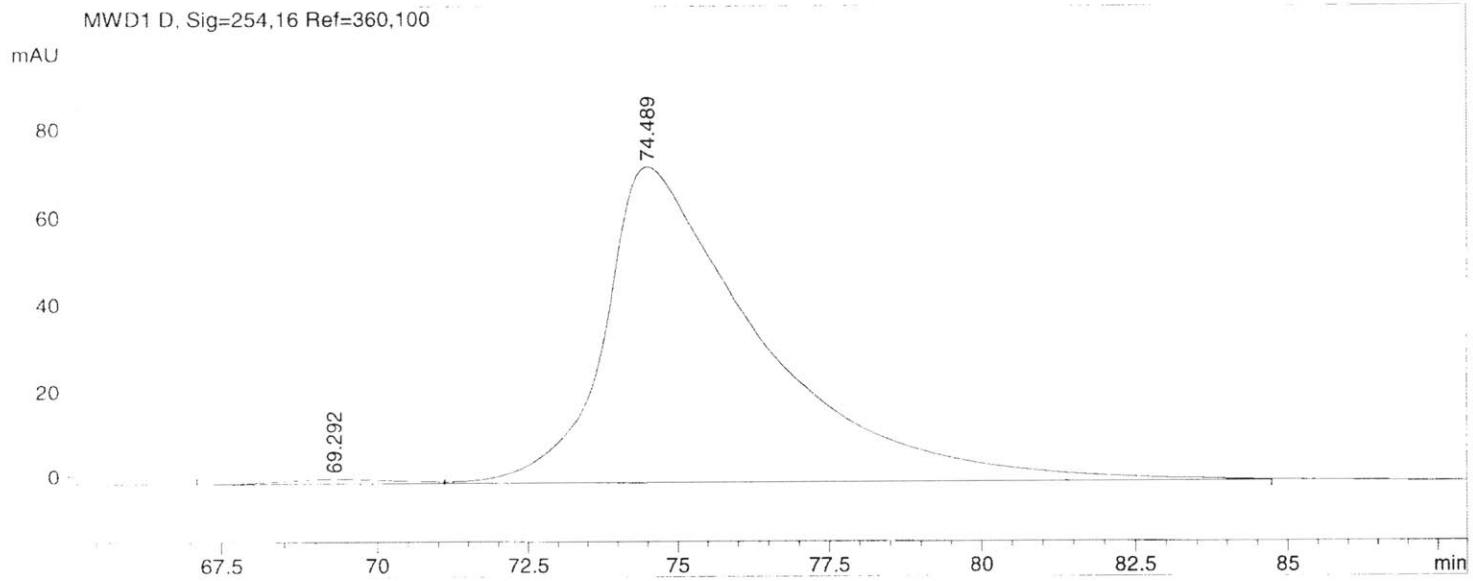
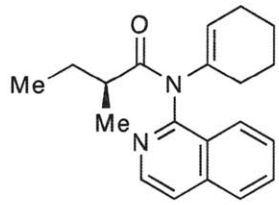
1137.18
1049.35
921.60
776.99
743.05
Me
Me
N
O
N
3hc



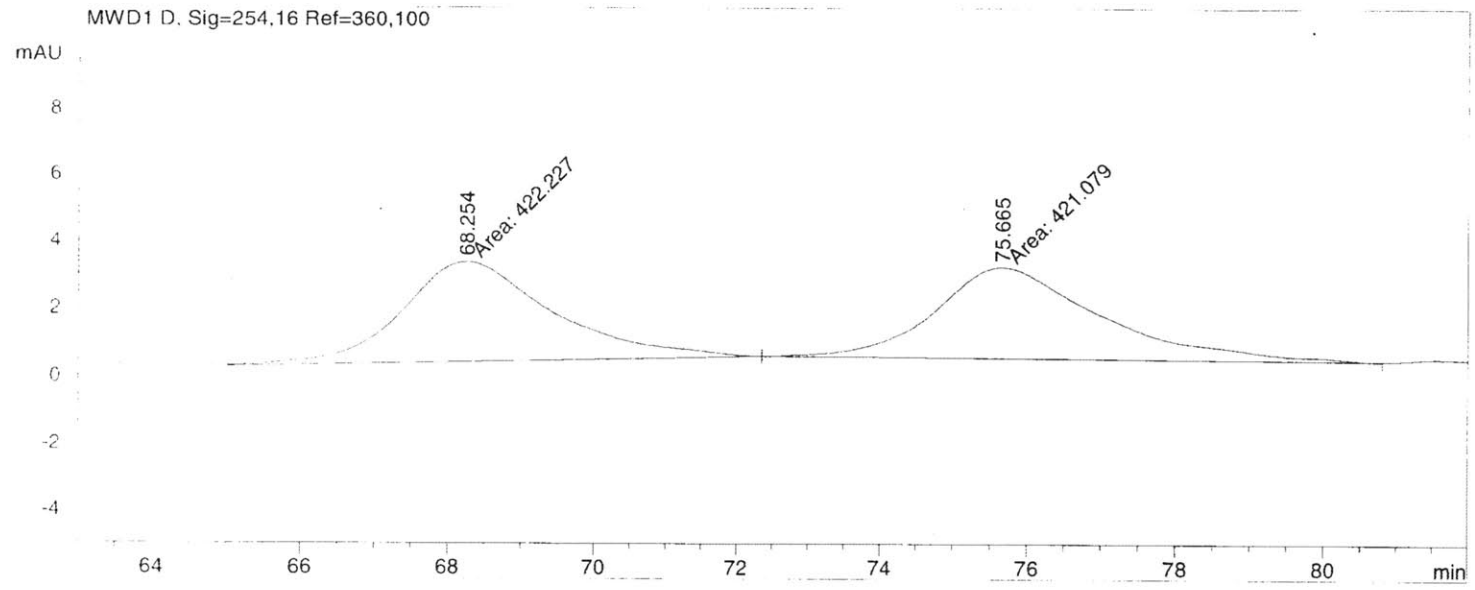
(+)-3ha



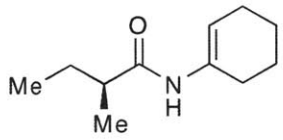

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]      [min]    [mAU*s]     [mAU]       %
----|--------|----|-------|----------|----------|--------|
   1  69.292 PV    1.4743  143.10532    1.15119   1.0655
   2  74.489 VB    2.4760 1.32871e4    72.98418  98.9345

Totals :                  1.34302e4    74.13538

 Results obtained with enhanced integrator!
=====================================================================
                        *** End of Report ***
```



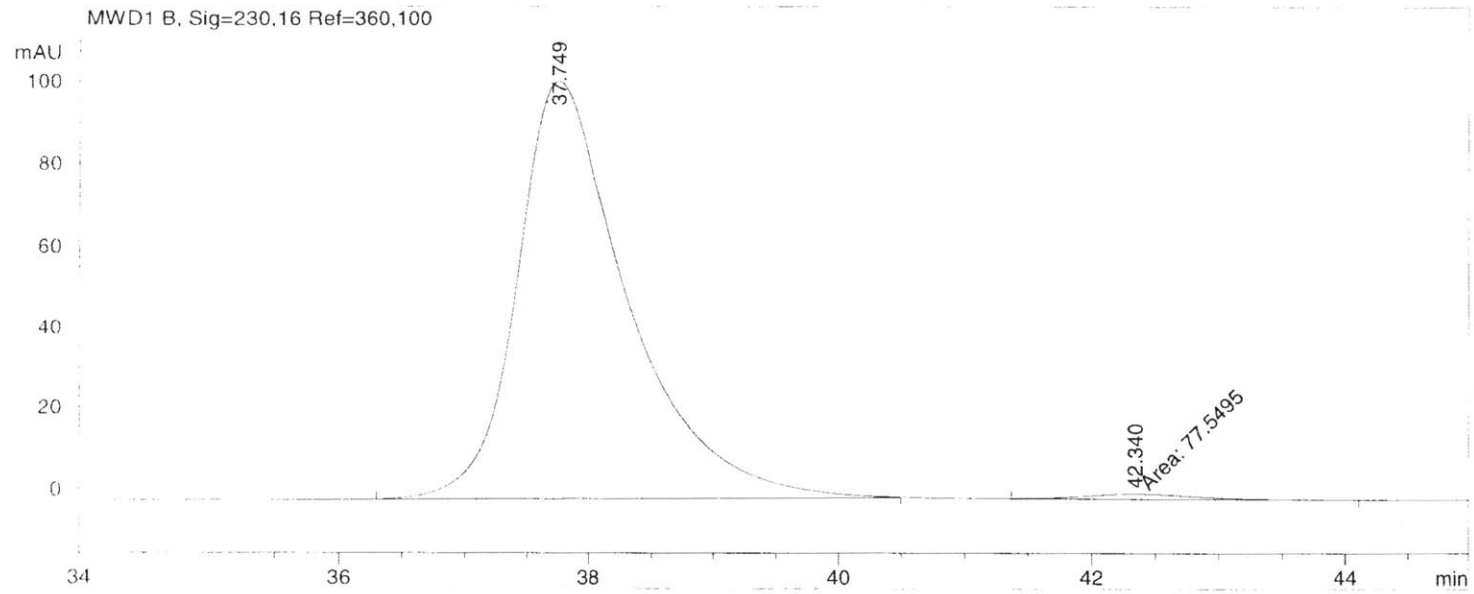
(+)-3ha



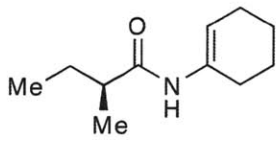

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 D, Sig=254,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|--------|----|-------|----------|----------|--------|
   1  68.254 MM    2.3878  422.22662    2.94713  50.0681
   2  75.665 MM    2.6063  421.07855    2.69268  49.9319

Totals :                   843.30518    5.63980

 Results obtained with enhanced integrator!
=====================================================================
                        *** End of Report ***
```



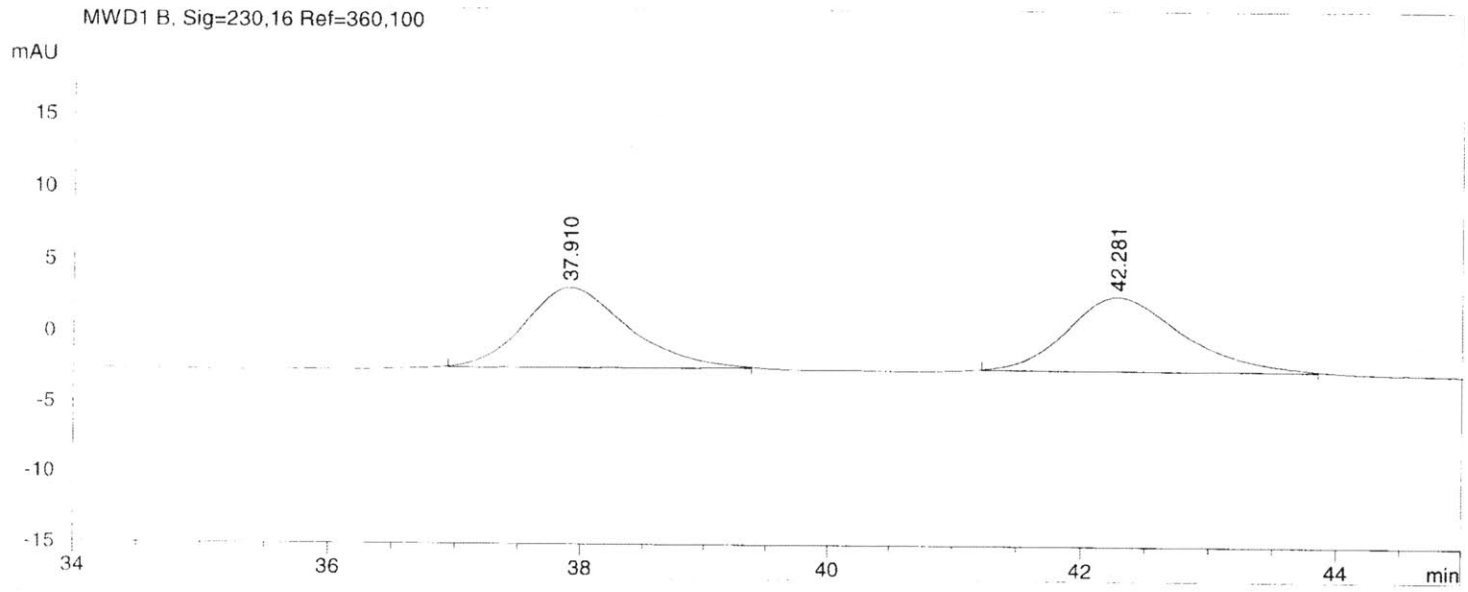
1h




```
================================================================================
                              Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]      %
----|-------|----|-------|----------|----------|--------|
   1  37.749 BB    0.9076 6347.98145  102.34804  98.7931
   2  42.340 MM    0.9913   77.54951    1.30385   1.2069

Totals :                  6425.53096  103.65188

 Results obtained with enhanced integrator!
================================================================================
                              *** End of Report ***
```



1h



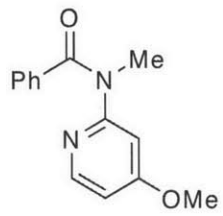

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 B, Sig=230,16 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  37.910 BB    0.7657  323.57190    5.65401  49.6895
   2  42.281 BB    0.7854  327.61554    5.28346  50.3105

Totals :                   651.18744   10.93746

 Results obtained with enhanced integrator!
=====================================================================
                          *** End of Report ***
```

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 2.000 sec
Pulse 89.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417195 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 20 sec



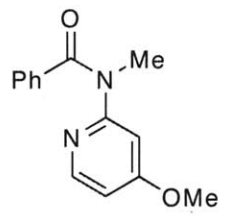
3dd

STANDARD CARBON PARAMETERS

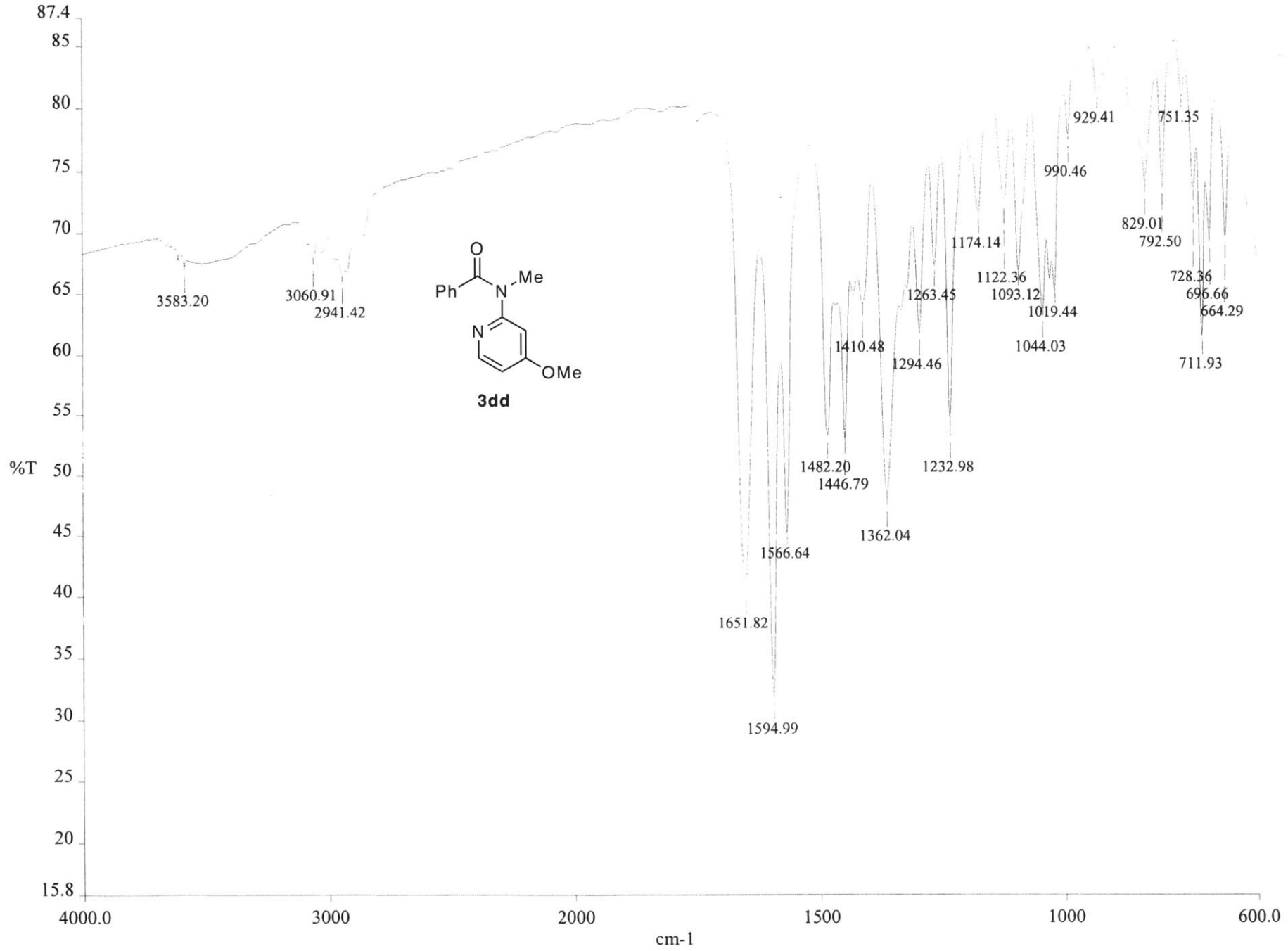
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
52 repetitions
OBSERVE C13, 125.7822142 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 45 hr, 39 min, 31 sec



3dd

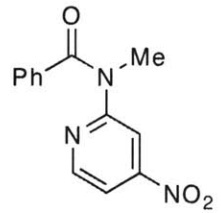

87.4
85
80
75
70
65
60
55
%T 50
45
40
35
30
25
20
15.8
4000.0
3000
2000
1500
1000
600.0
cm-1
3583.20
3060.91
2941.42
1651.82
1594.99
1566.64
1482.20
1446.79
1410.48
1362.04
1294.46
1263.45
1232.98
1174.14
1122.36
1093.12
1044.03
1019.44
990.46
929.41
829.01
792.50
751.35
728.36
696.66
664.29
711.93
O
Ph
N
Me
N
OMe
3dd

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 2.000 sec
Pulse 89.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417195 MHz
DATA PROCESSING
FT size 262144
Total time 1 min, 20 sec



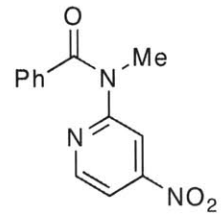
3de

STANDARD CARBON PARAMETERS

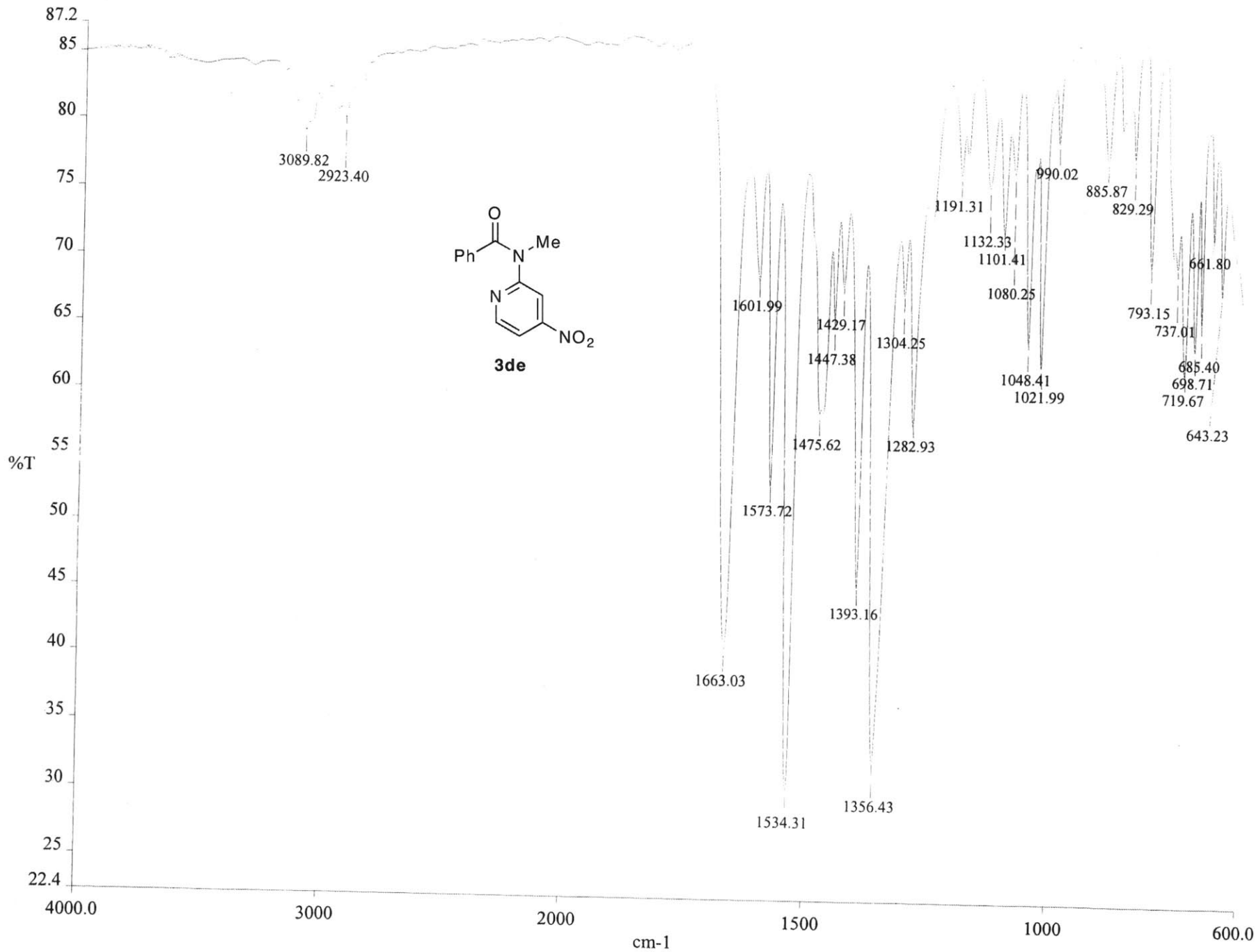
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

INOVA-500 "zippy"

Relax. delay 0.763 sec
Pulse 69.0 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
255 repetitions
OBSERVE C13, 125.7822118 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072
Total time 45 hr, 39 min, 31 sec



3de


87.2
85
80
75
70
65
60
55
50
45
40
35
30
25
22.4
%T
4000.0
3000
2000
1500
1000
600.0
cm-1
3089.82
2923.40
1663.03
1601.99
1573.72
1534.31
1475.62
1447.38
1429.17
1393.16
1356.43
1304.25
1282.93
1191.31
1132.33
1101.41
1080.25
1048.41
1021.99
990.02
885.87
829.29
793.15
737.01
719.67
698.71
685.40
661.80
643.23
O
Ph
N
Me
N
NO2
3de

Appendix B

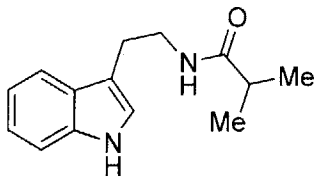
Spectra for Chapter II

STANDARD PROTON PARAMETERS

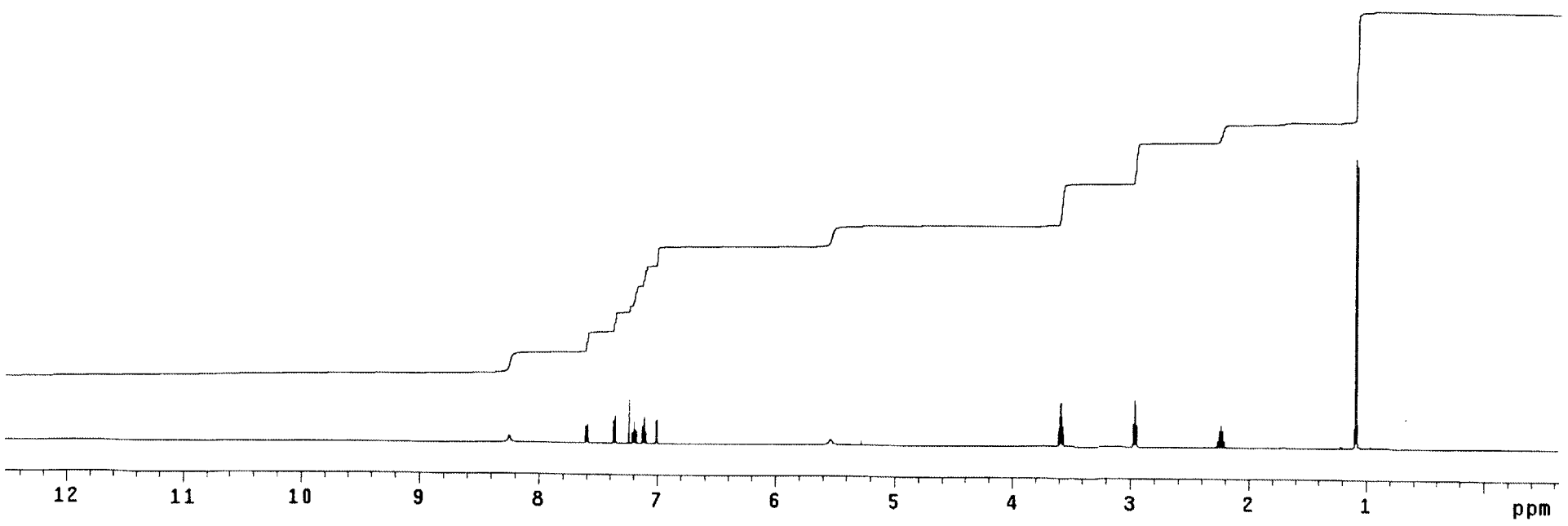
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 72.4 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252875 MHz
DATA PROCESSING
FT size 262144



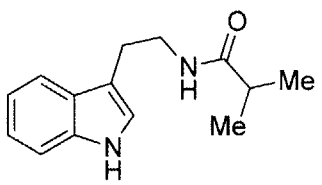
S1a



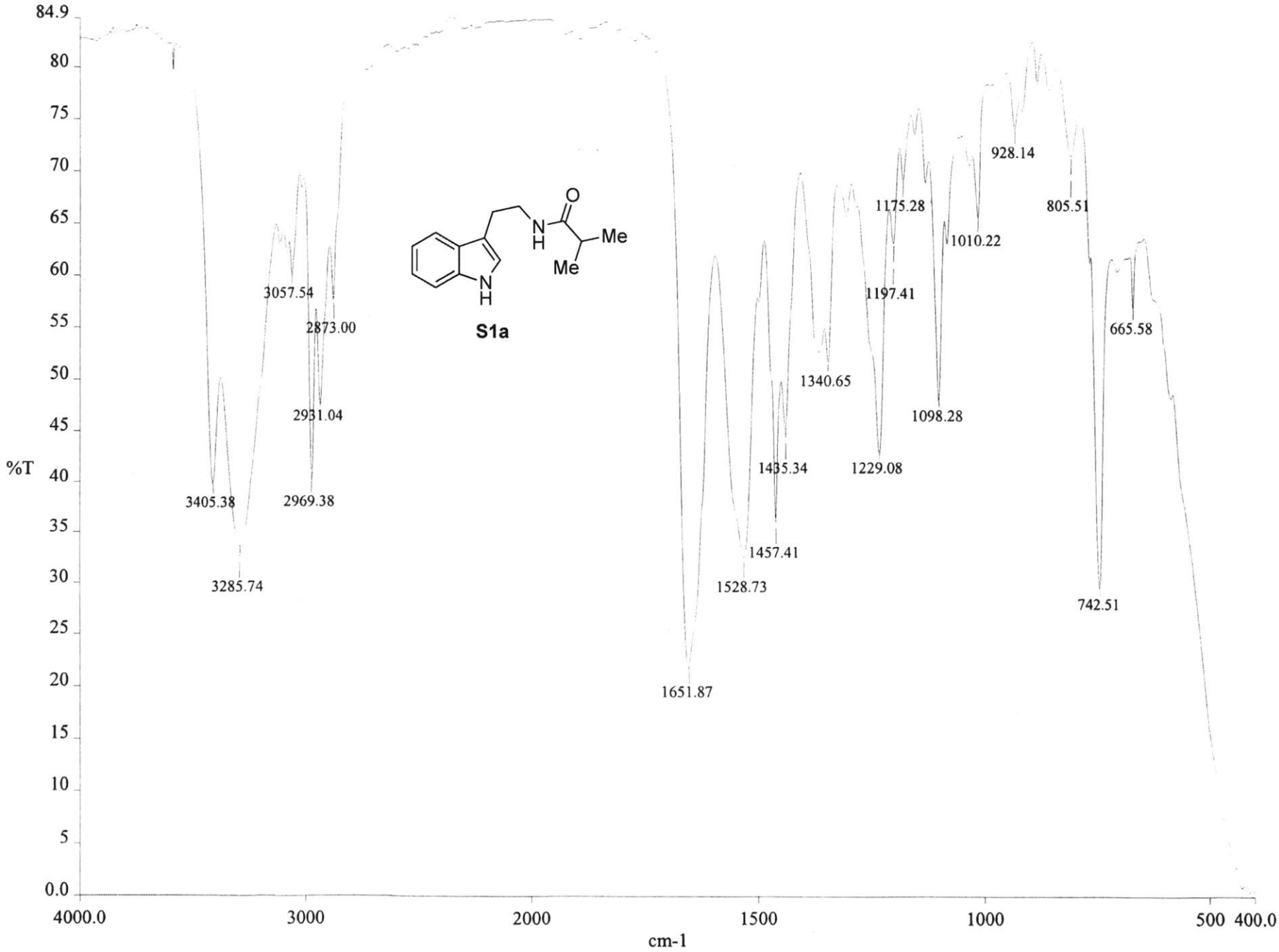
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
65536 repetitions
OBSERVE C13, 125.7822245 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



S1a

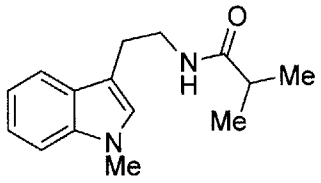

84.9
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3405.38
3285.74
3057.54
2969.38
2931.04
2873.00
1651.87
1528.73
1457.41
1435.34
1340.65
1229.08
1197.41
1175.28
1098.28
1010.22
928.14
805.51
742.51
665.58
S1a

250

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 72.4 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252862 MHz
DATA PROCESSING
FT size 262144



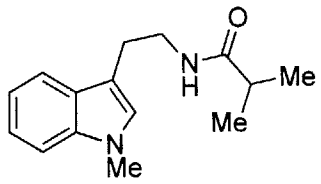
1a

STANDARD CARBON PARAMETERS

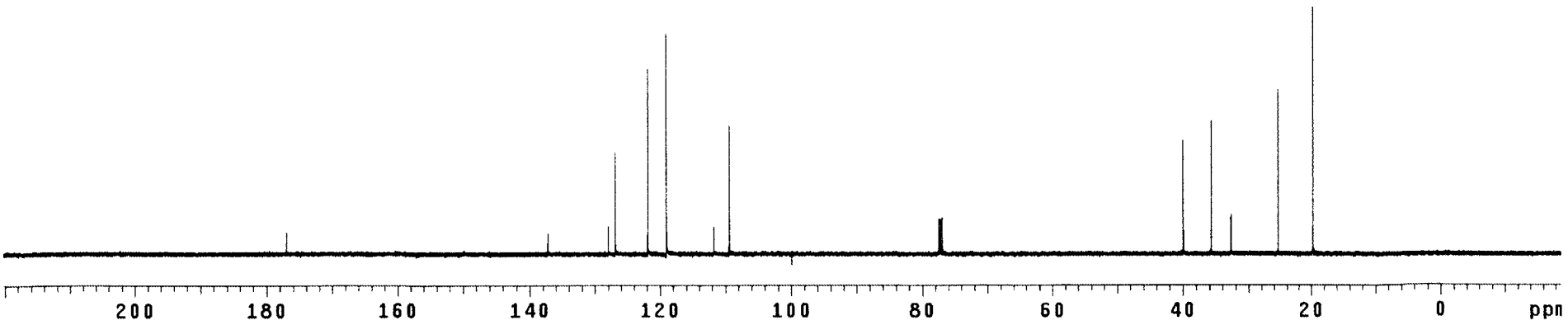
Pulse Sequence: s2pul

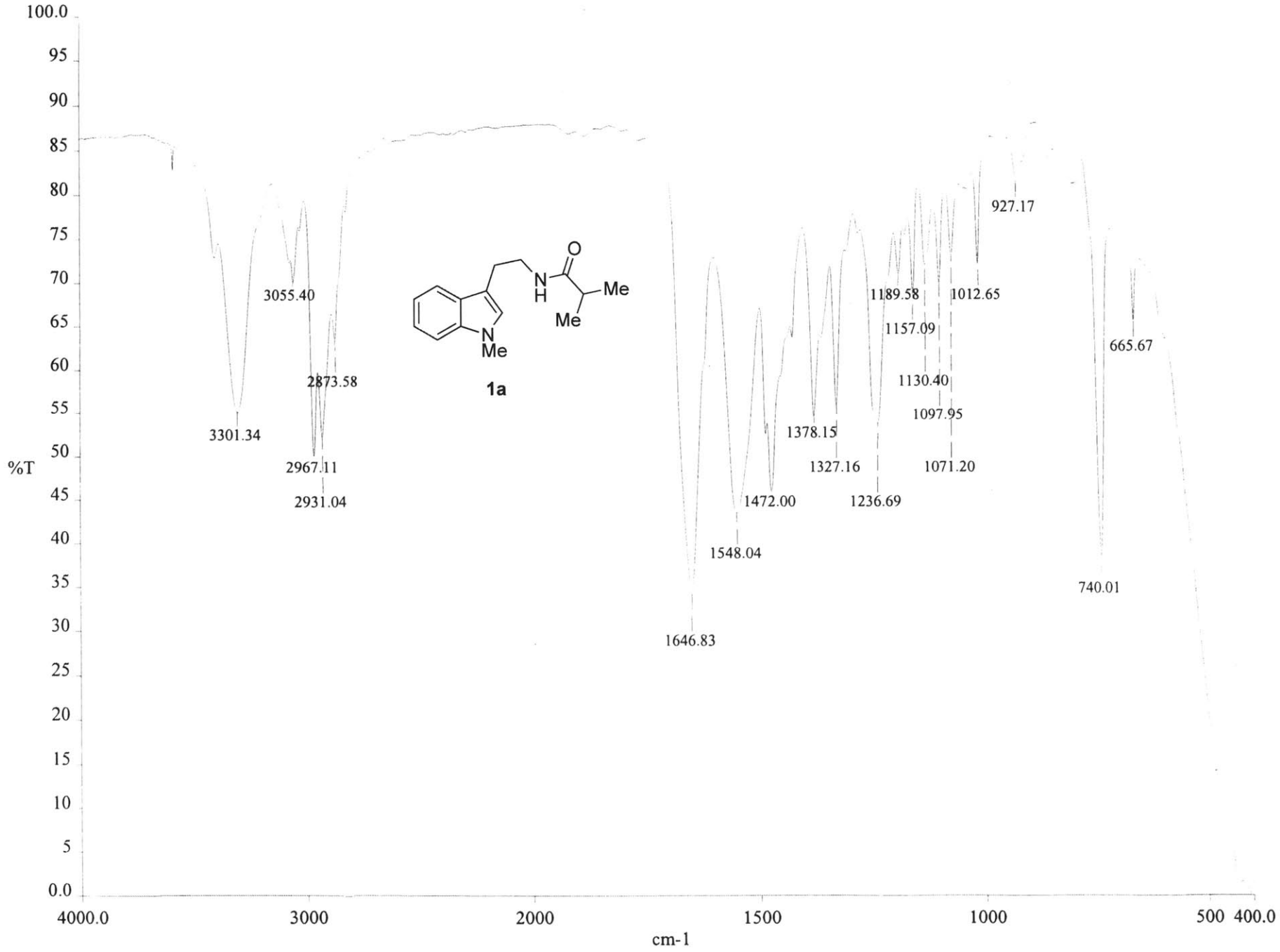
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
65536 repetitions
OBSERVE C13, 125.7822245 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



1a

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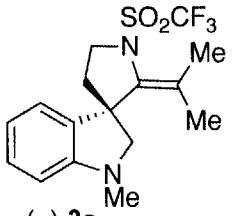
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3301.34
3055.40
2967.11
2931.04
2873.58
1646.83
1548.04
1472.00
1378.15
1327.16
1236.69
1189.58
1157.09
1130.40
1097.95
1071.20
1012.65
927.17
740.01
665.67
N
H
O
Me
Me
N
Me
1a

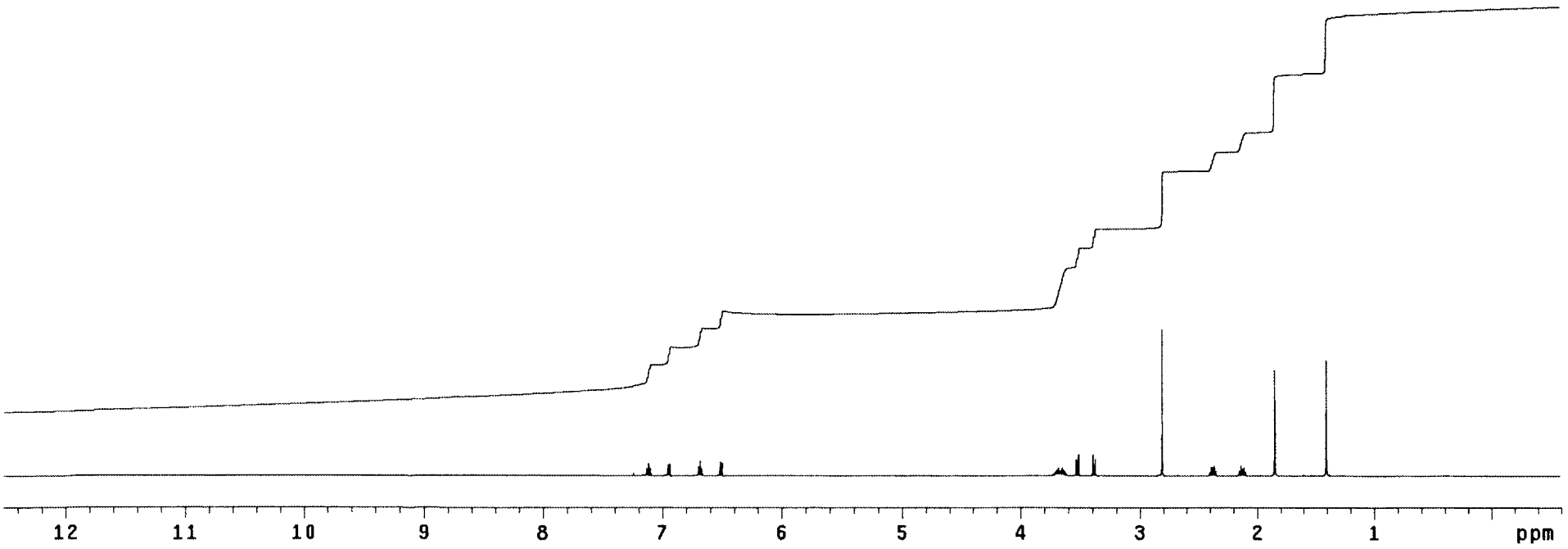
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417347 MHz
DATA PROCESSING
FT size 262144



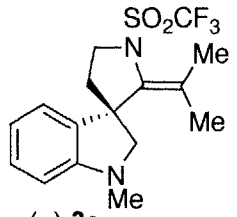
(±)-**3a**



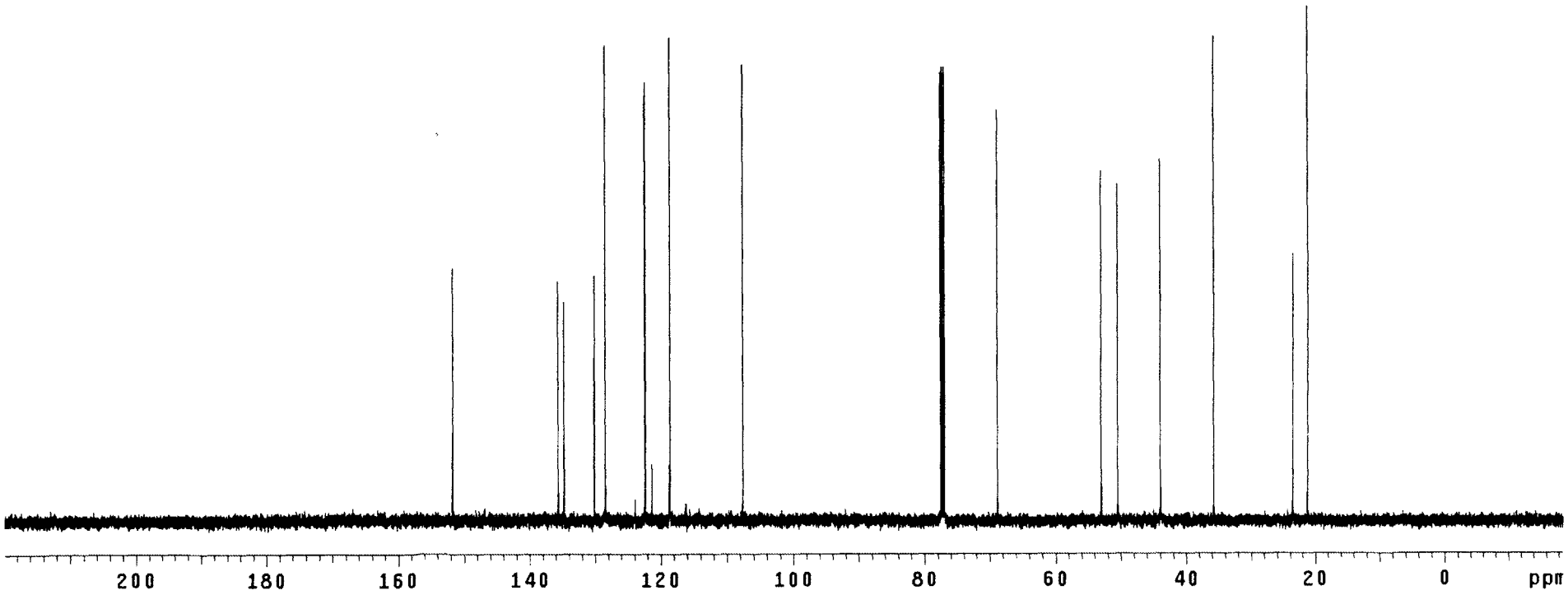
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
302 repetitions
OBSERVE C13, 125.6601362 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



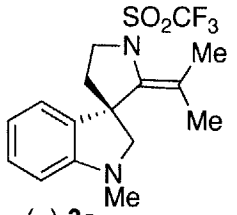
(±)-3a



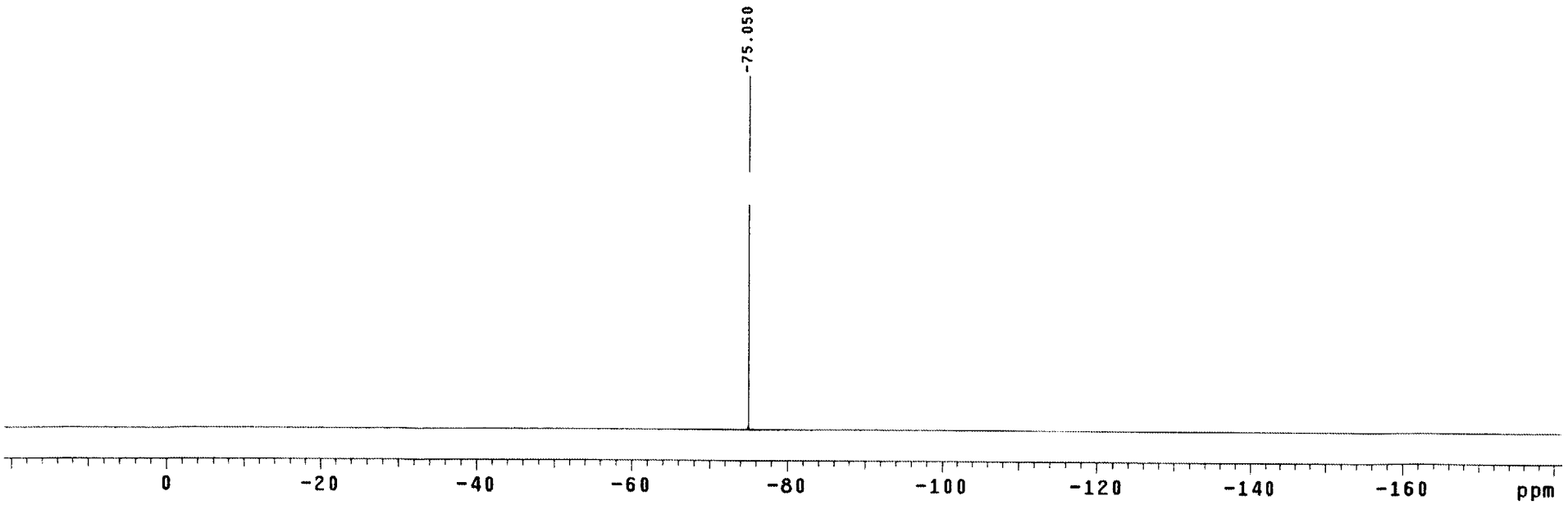
19F SENSITIVITY
0.05% TRIFLUOROTOLUENE

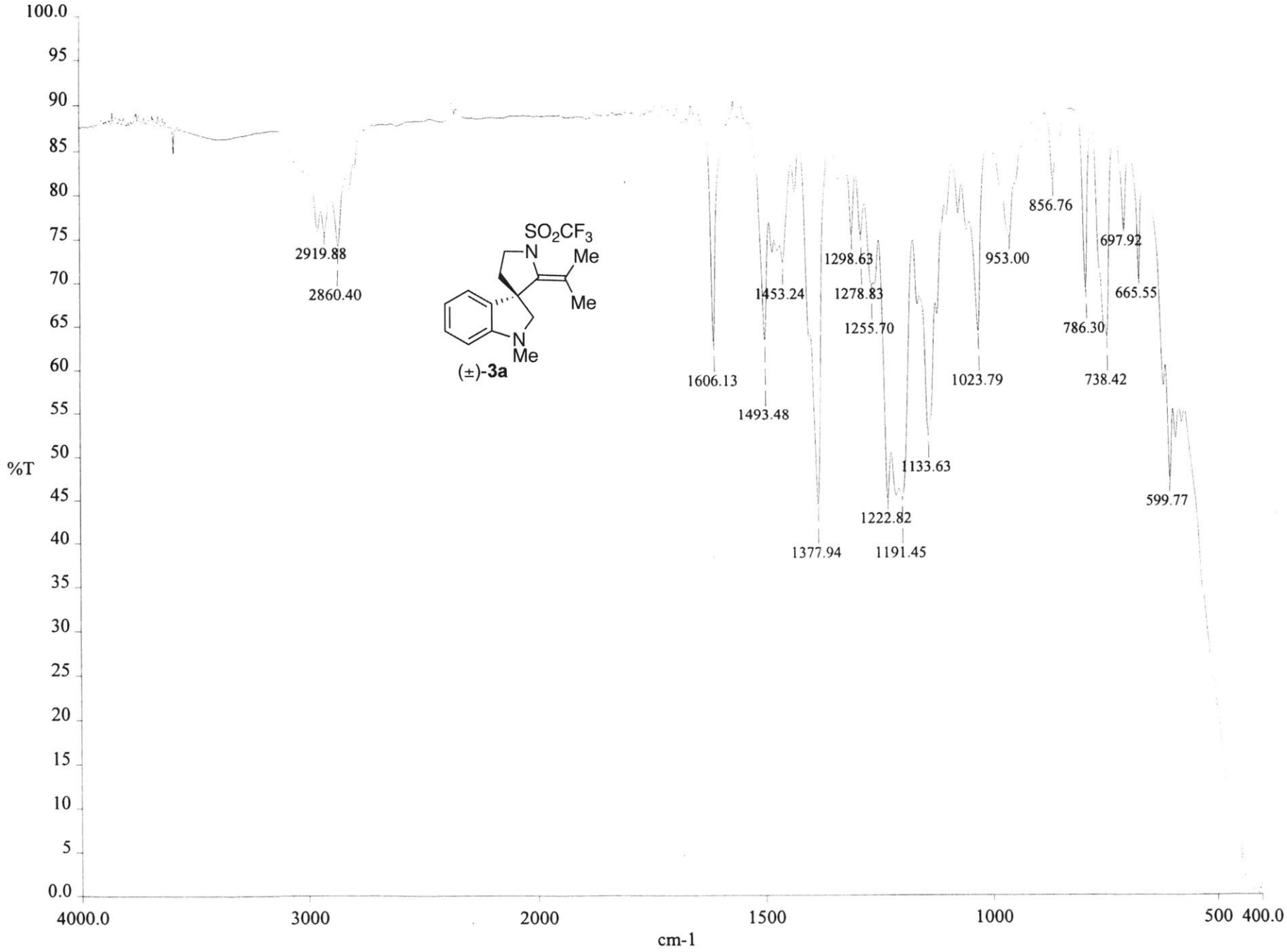
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 0.232 sec
Width 140.8 kHz
12 repetitions
OBSERVE F19, 470.2272133 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(±)-**3a**

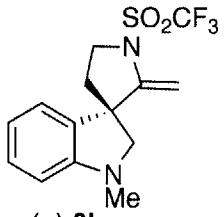



100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2919.88
2860.40
1606.13
1493.48
1453.24
1377.94
1298.63
1278.83
1255.70
1222.82
1191.45
1133.63
1023.79
953.00
856.76
786.30
738.42
697.92
665.55
599.77
SO2CF3
N
Me
Me
N
Me
(±)-3a

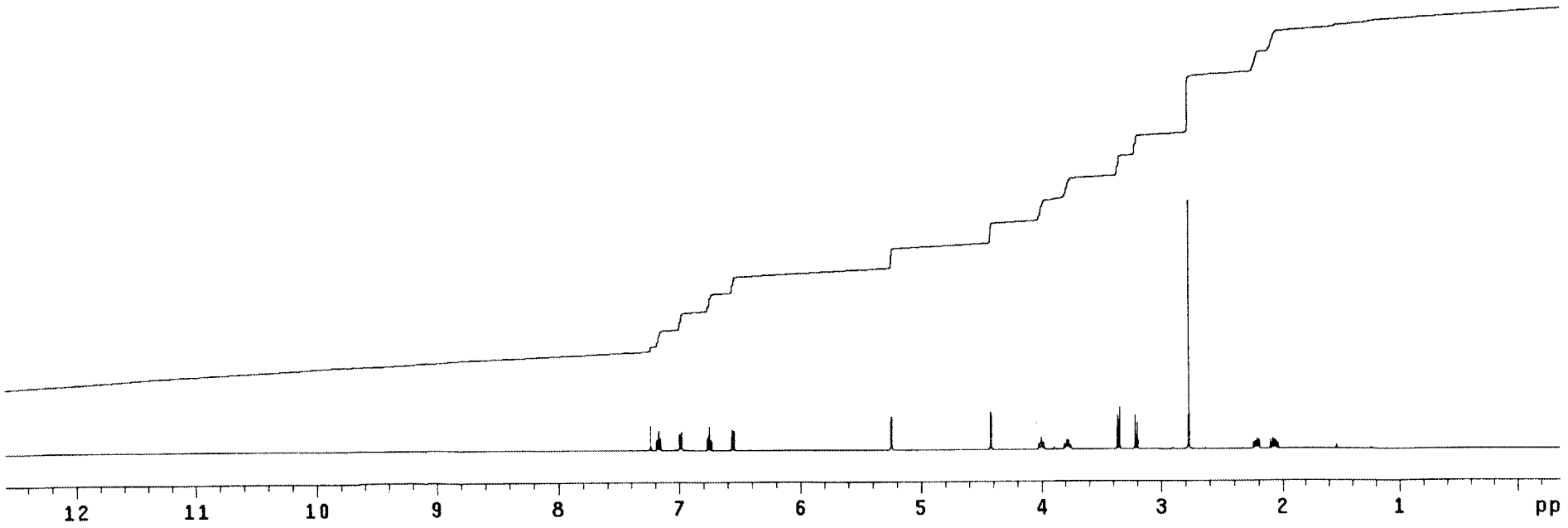
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417336 MHz
DATA PROCESSING
FT size 262144



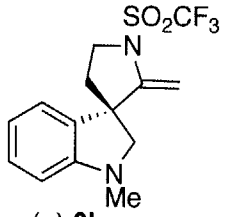
(±)-**3b**



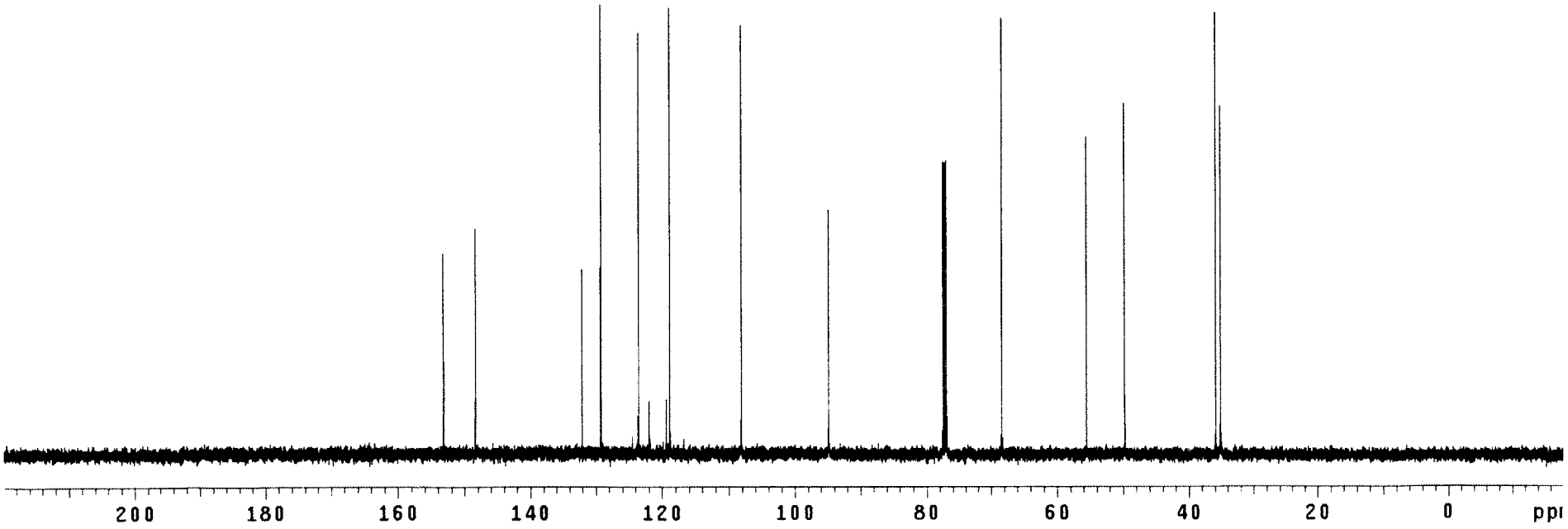
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
142 repetitions
OBSERVE C13, 125.6601405 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



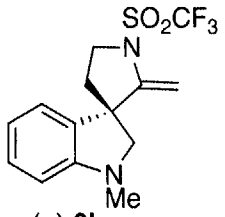
(±)-**3b**



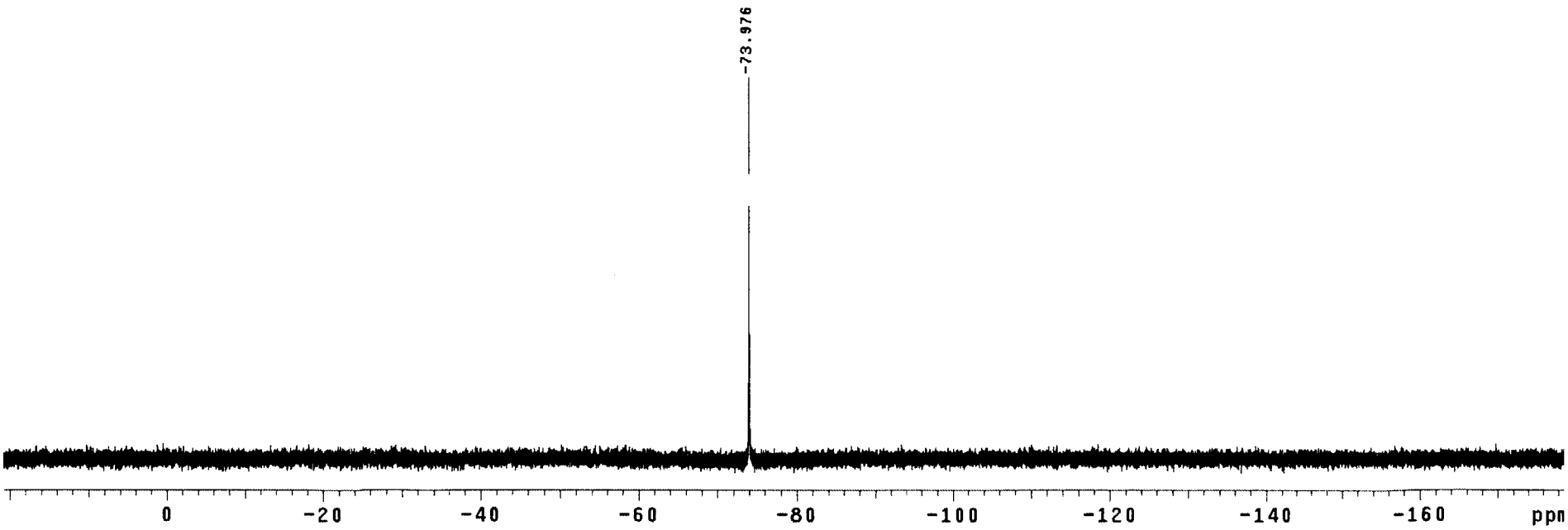
19F SENSITIVITY
0.05% TRIFLUOROTOLUENE

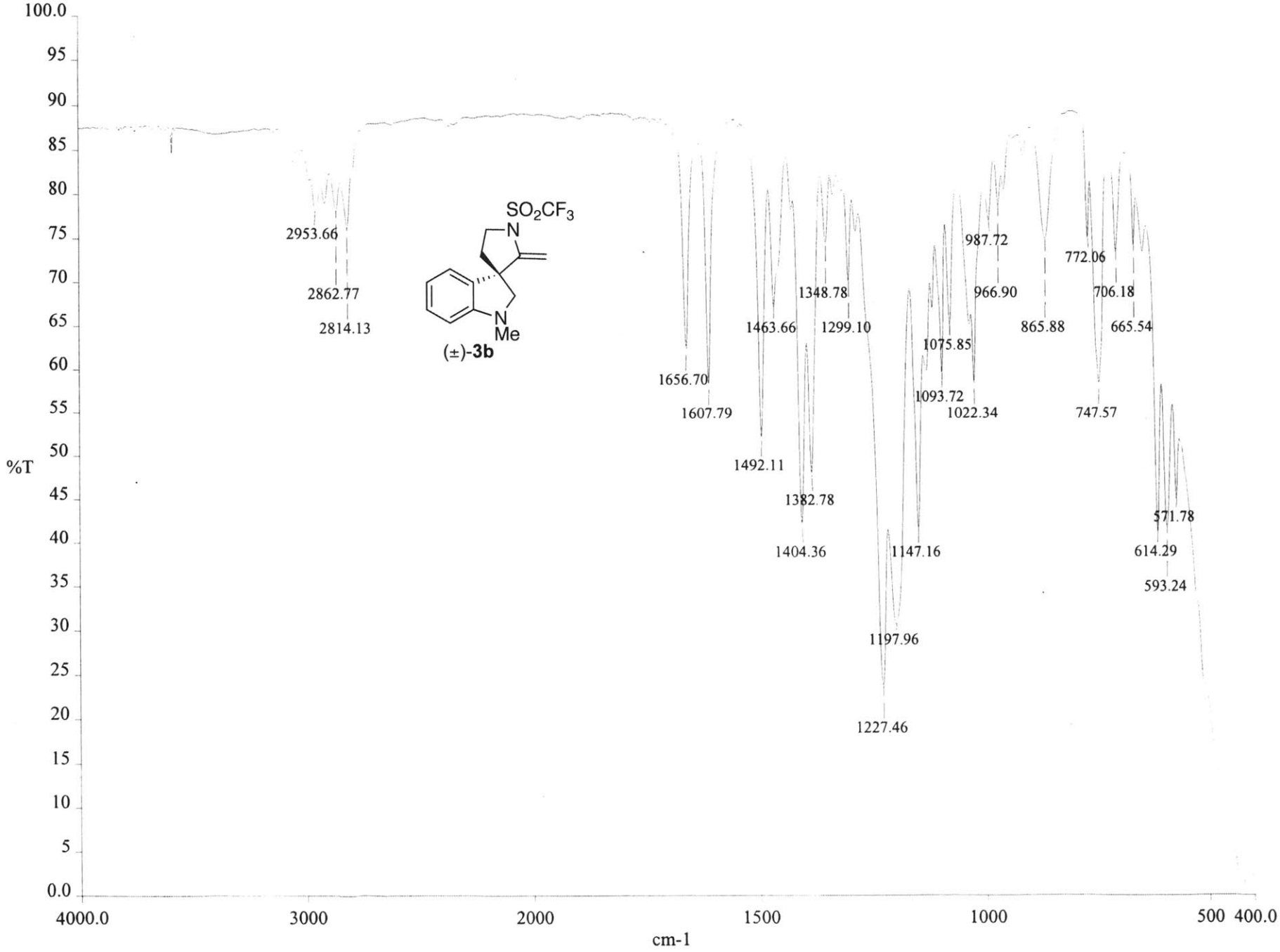
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 0.232 sec
Width 140.8 kHz
16 repetitions
OBSERVE F19, 470.2272133 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(±)-**3b**

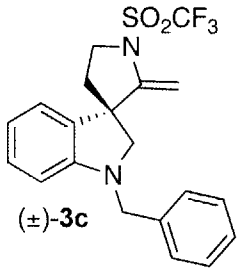



100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
2953.66
2862.77
2814.13
1656.70
1607.79
1492.11
1463.66
1404.36
1382.78
1348.78
1299.10
1227.46
1197.96
1147.16
1093.72
1075.85
1022.34
987.72
966.90
865.88
772.06
747.57
706.18
665.54
614.29
593.24
571.78
SO2CF3
N
N
Me
(±)-3b

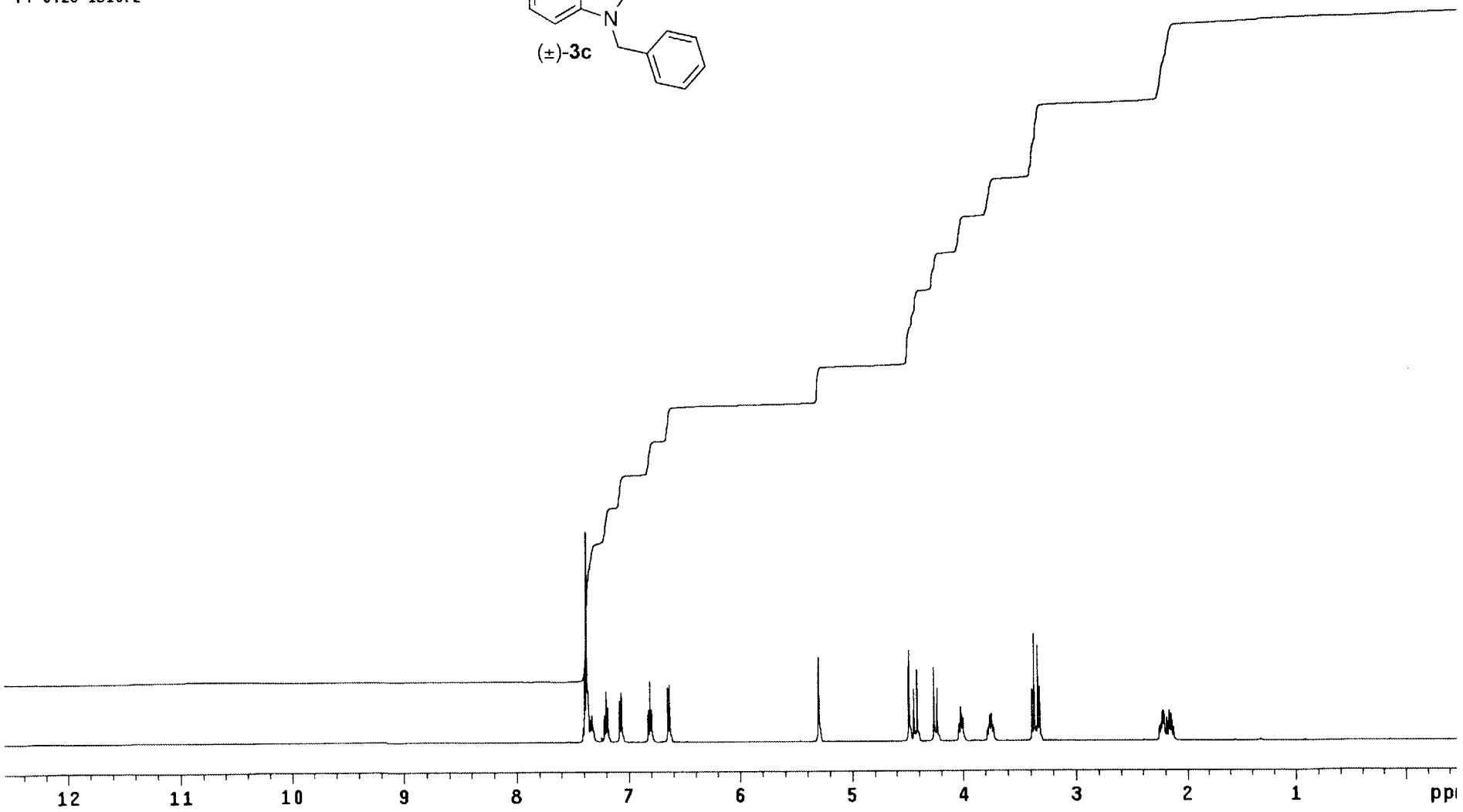
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
5 repetitions
OBSERVE H1, 500.2272318 MHz
DATA PROCESSING
FT size 131072



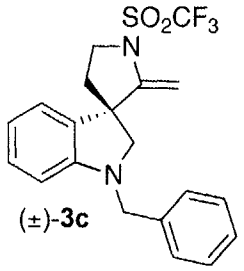
(±)-**3c**



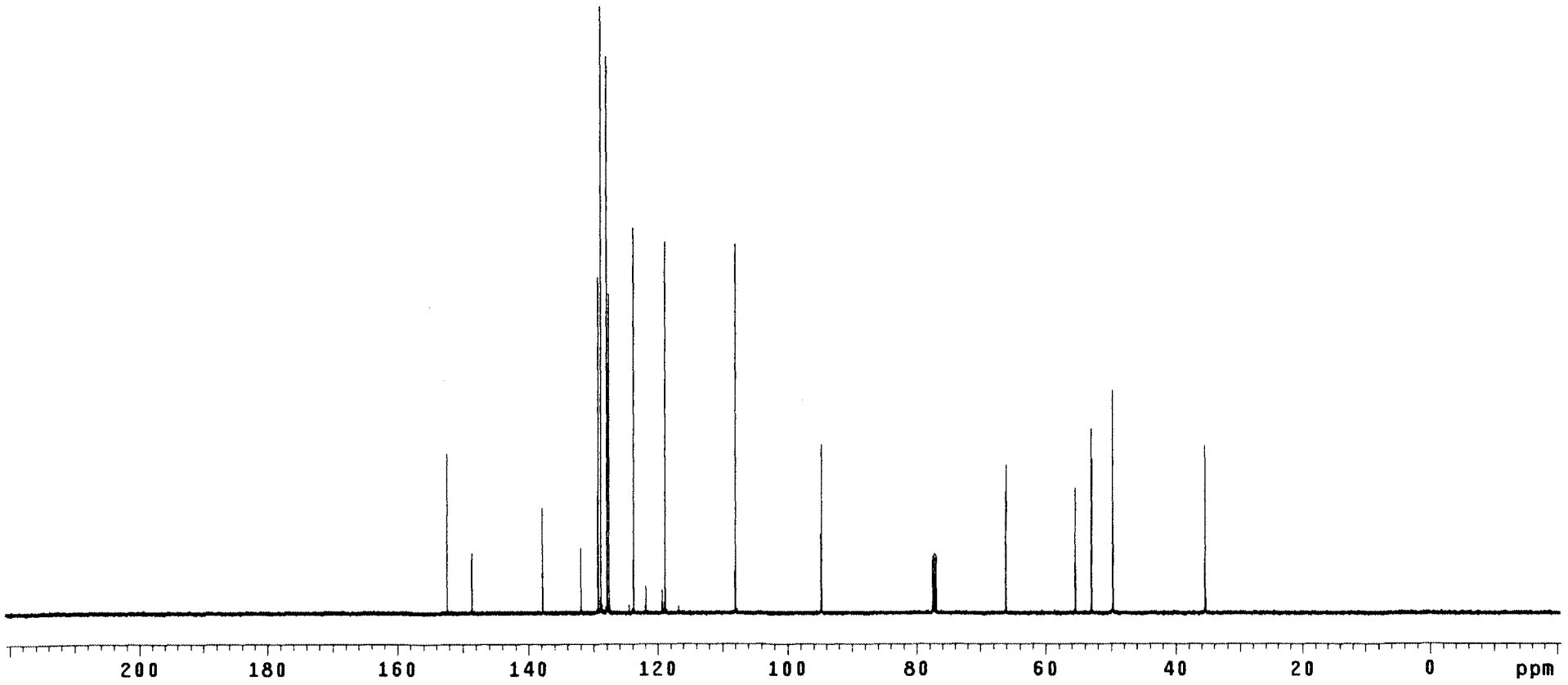
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
397 repetitions
OBSERVE C13, 125.7822193 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



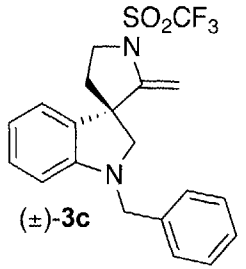
(±)-3c



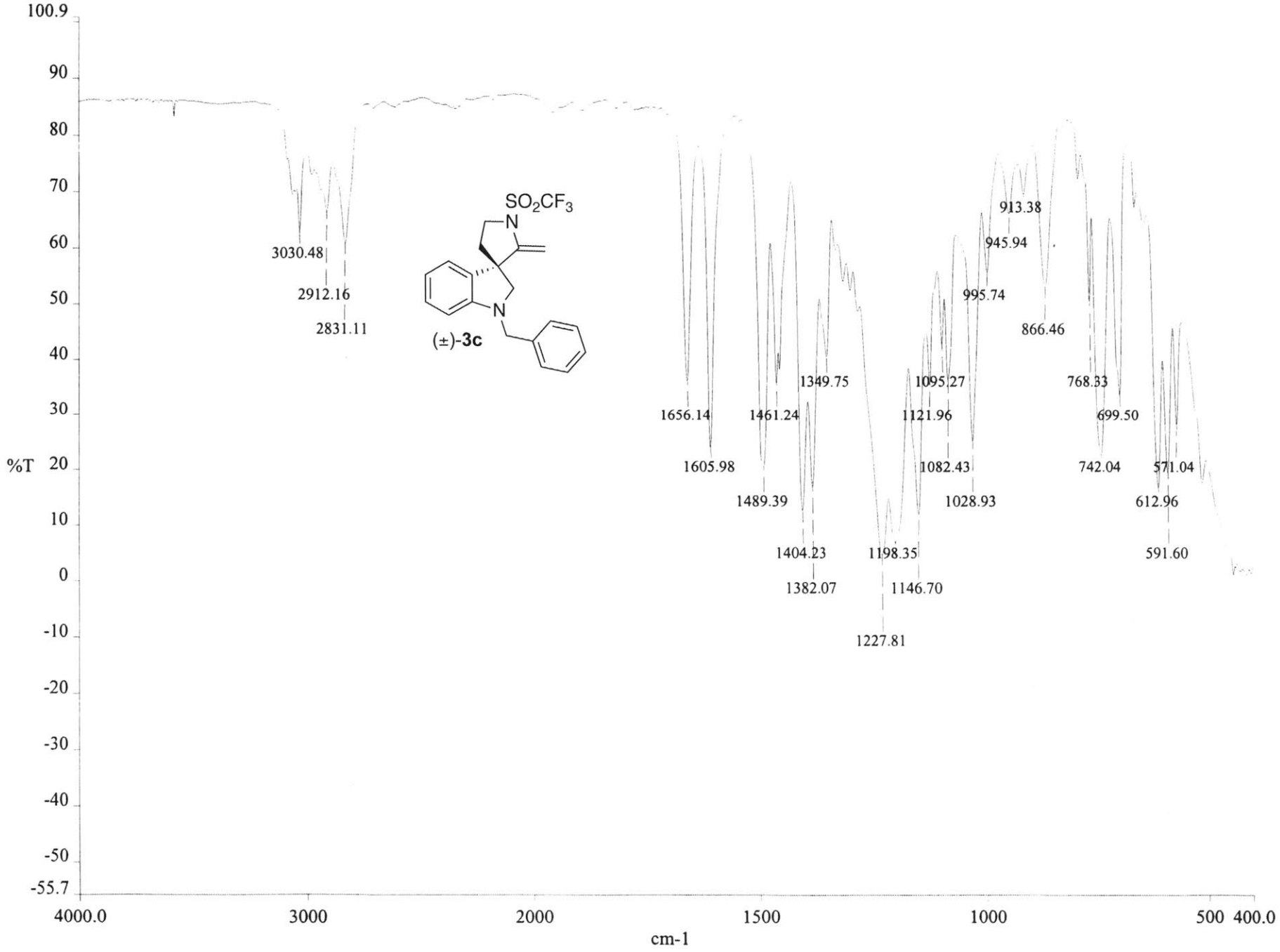
19F OBSERVE
STANDARD PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 0.300 sec
Width 100.0 kHz
6 repetitions
OBSERVE F19, 282.3814158 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144



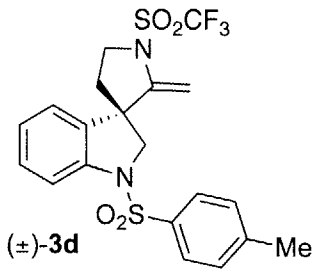
(±)-**3c**


100.9
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40
-50
-55.7
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3030.48
2912.16
2831.11
1656.14
1605.98
1489.39
1461.24
1404.23
1382.07
1349.75
1227.81
1198.35
1146.70
1121.96
1095.27
1082.43
1028.93
995.74
945.94
913.38
866.46
768.33
742.04
699.50
612.96
591.60
571.04
SO2CF3
N
N
(±)-3c

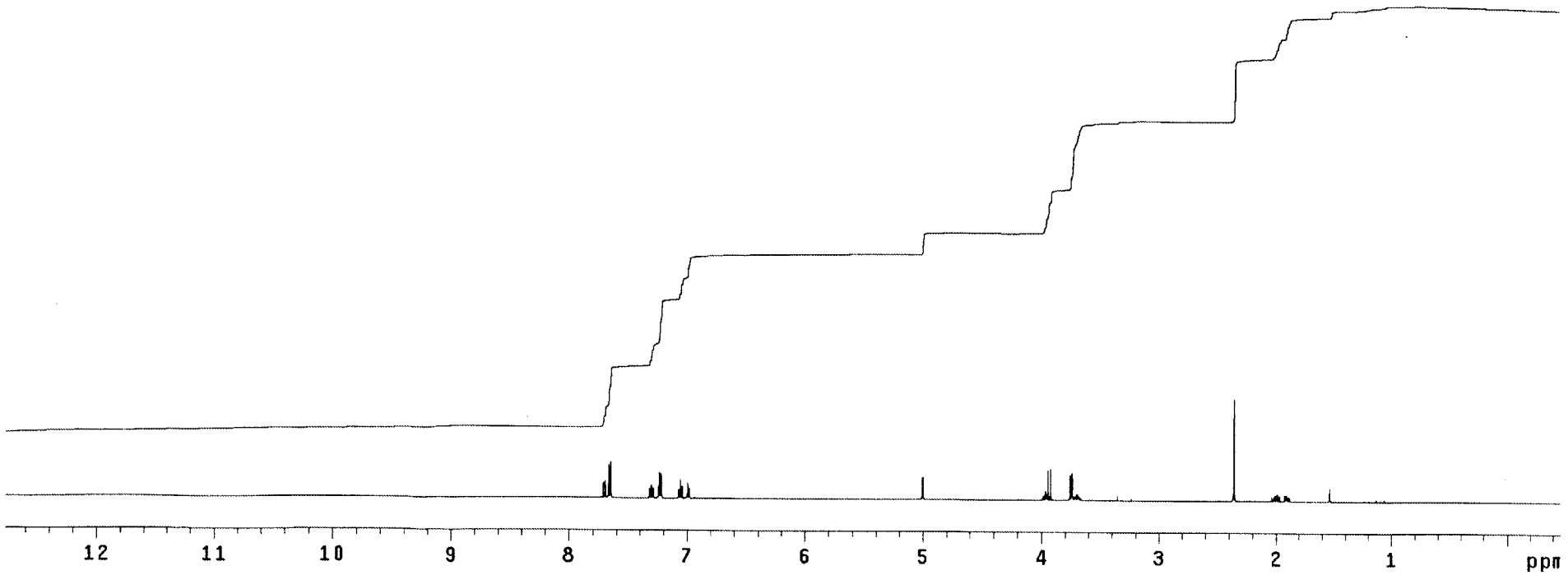
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 72.4 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252873 MHz
DATA PROCESSING
FT size 262144



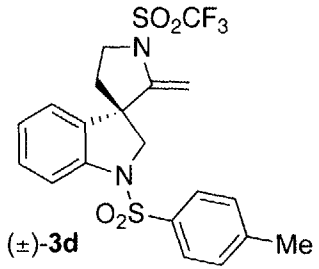
(±)-**3d**



STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
534 repetitions
OBSERVE C13, 125.7822118 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072

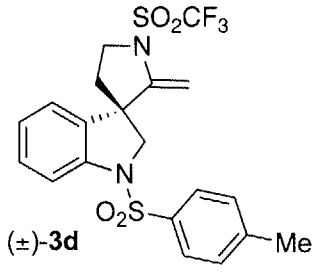


(±)-**3d**

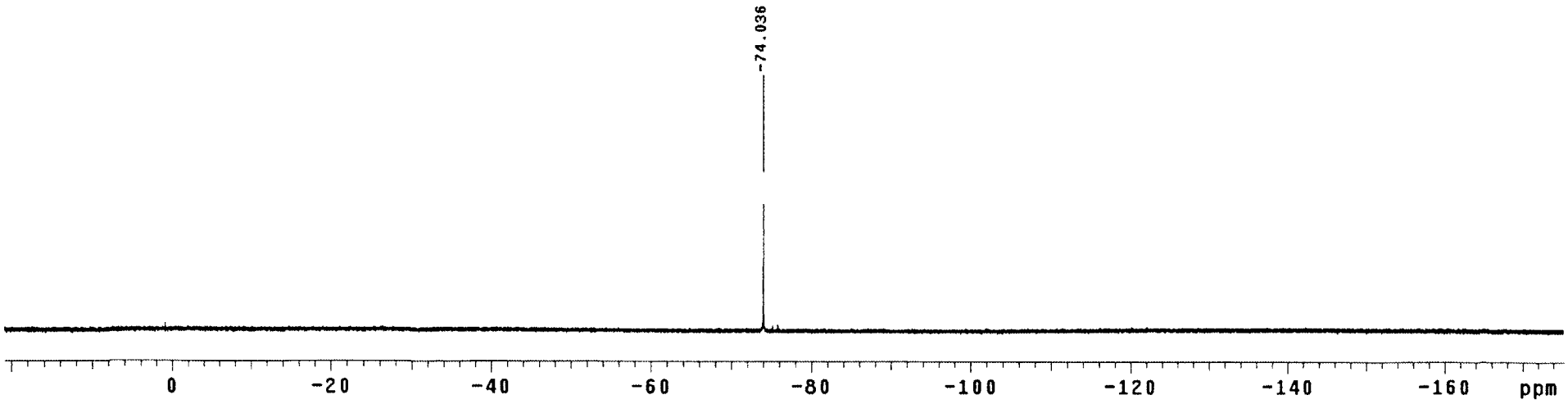
19F OBSERVE
STANDARD PARAMETERS

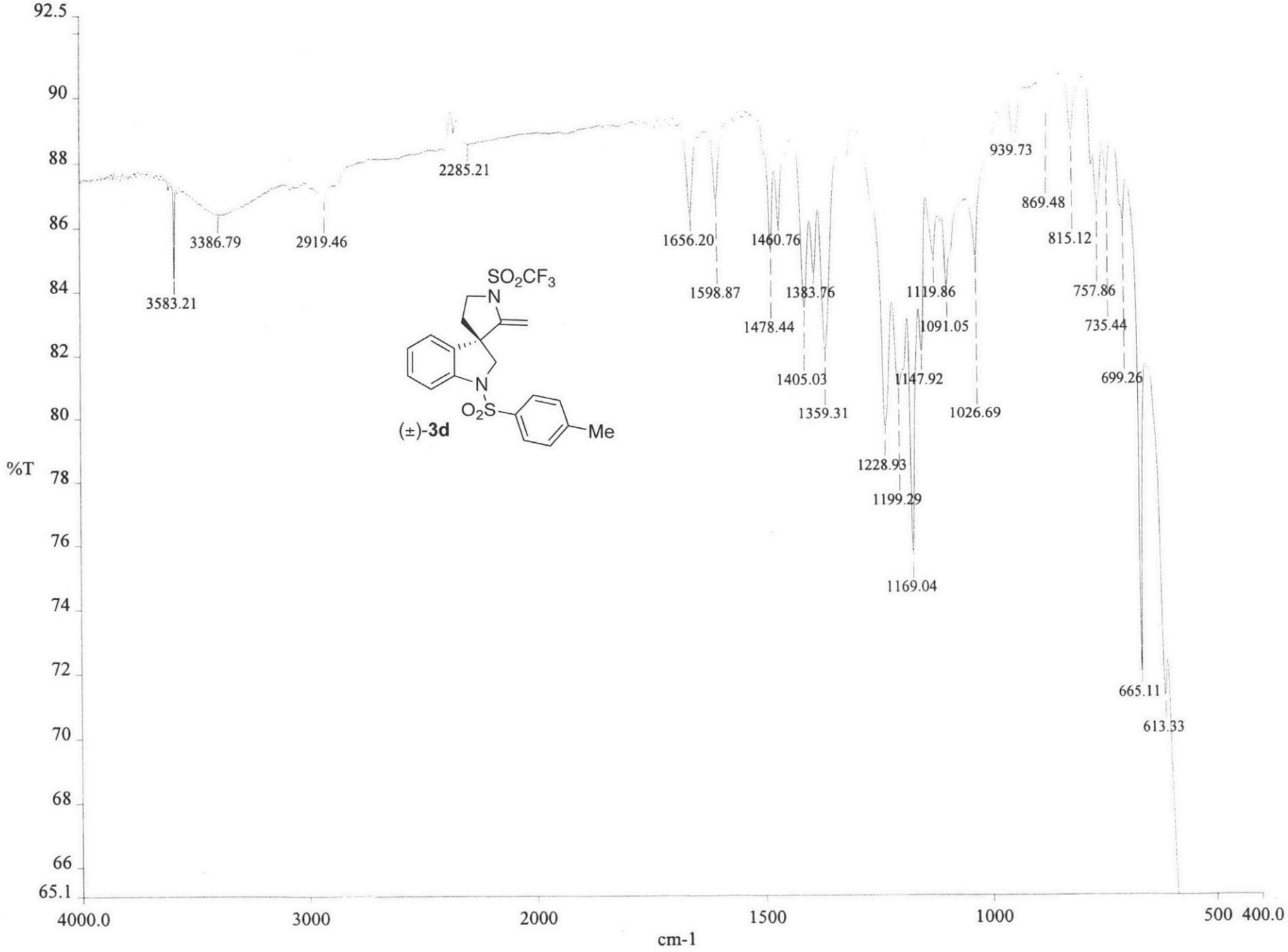
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 0.300 sec
Width 100.0 kHz
27 repetitions
OBSERVE F19, 282.3814158 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144



(±)-**3d**



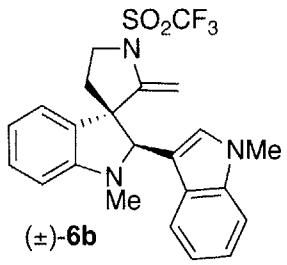

92.5
90
88
86
84
82
80
78
76
74
72
70
68
66
65.1
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.21
3386.79
2919.46
2285.21
1656.20
1598.87
1478.44
1460.76
1405.03
1383.76
1359.31
1228.93
1199.29
1169.04
1147.92
1119.86
1091.05
1026.69
939.73
869.48
815.12
757.86
735.44
699.26
665.11
613.33
SO2CF3
N
N
O2S
Me
(±)-3d

STANDARD PROTON PARAMETERS

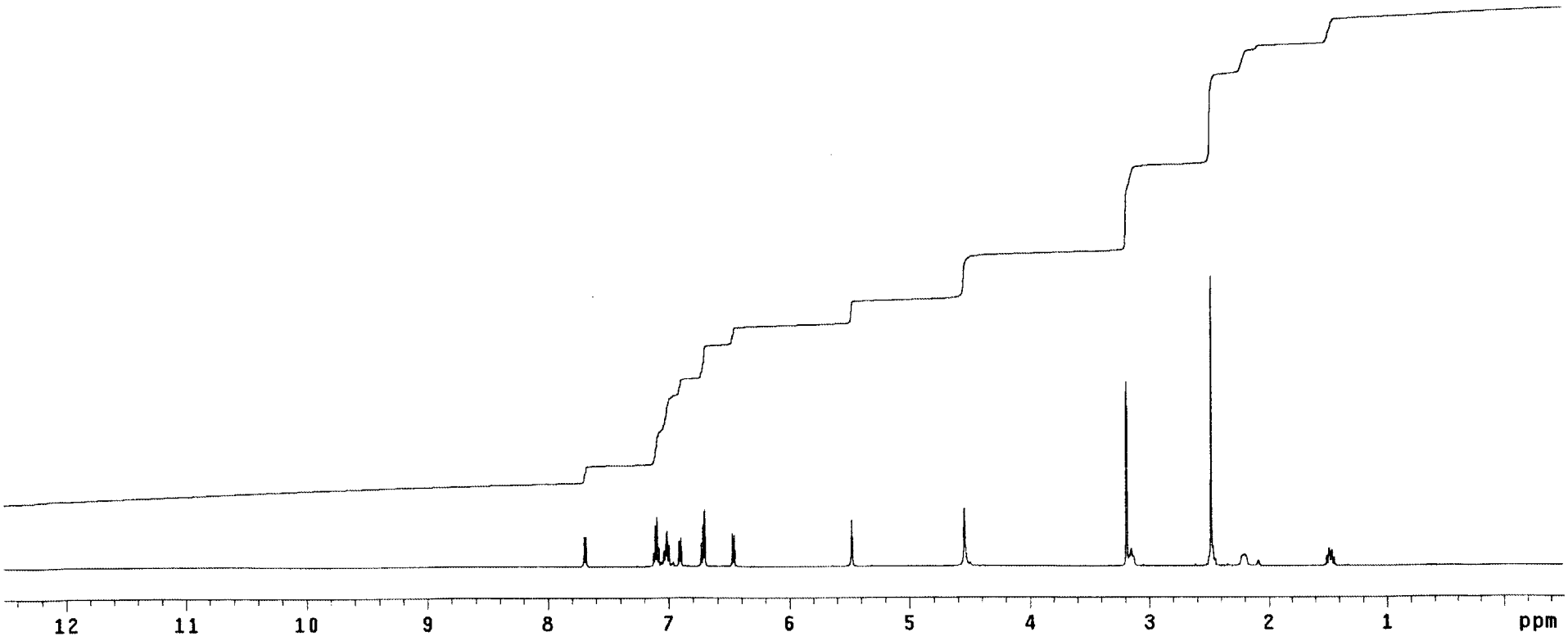
Pulse Sequence: s2pul

Solvent: toluene
Temp. 100.0 C / 373.1 K

Relax. delay 2.000 sec
Pulse 84.1 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
12 repetitions
OBSERVE H1, 499.7418474 MHz
DATA PROCESSING
FT size 262144



(±)-**6b**

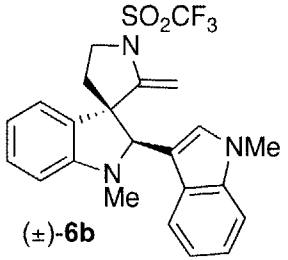


STANDARD CARBON PARAMETERS

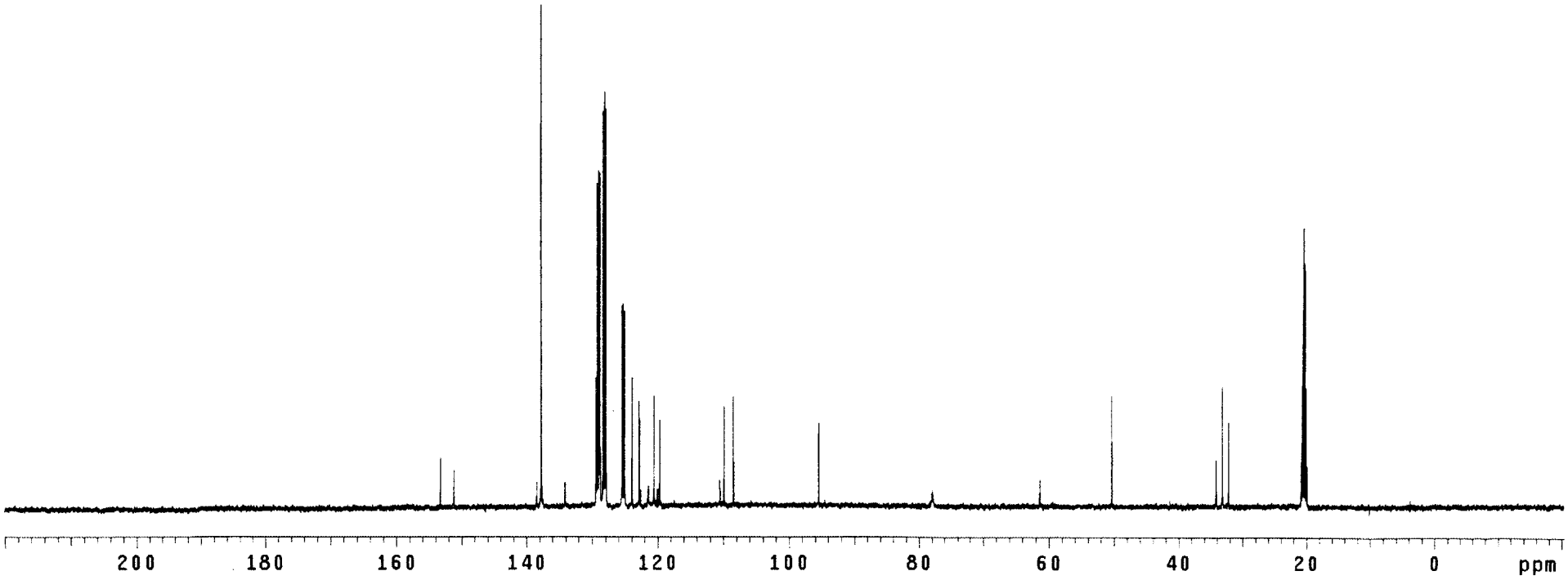
Pulse Sequence: s2pul

Solvent: toluene
Temp. 100.0 C / 373.1 K

Relax. delay 3.000 sec
Pulse 37.8 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
1581 repetitions
OBSERVE C13, 125.6600986 MHz
DECOUPLE H1, 499.7442944 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072



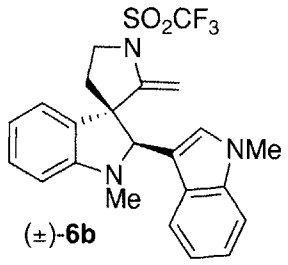
(±)-**6b**



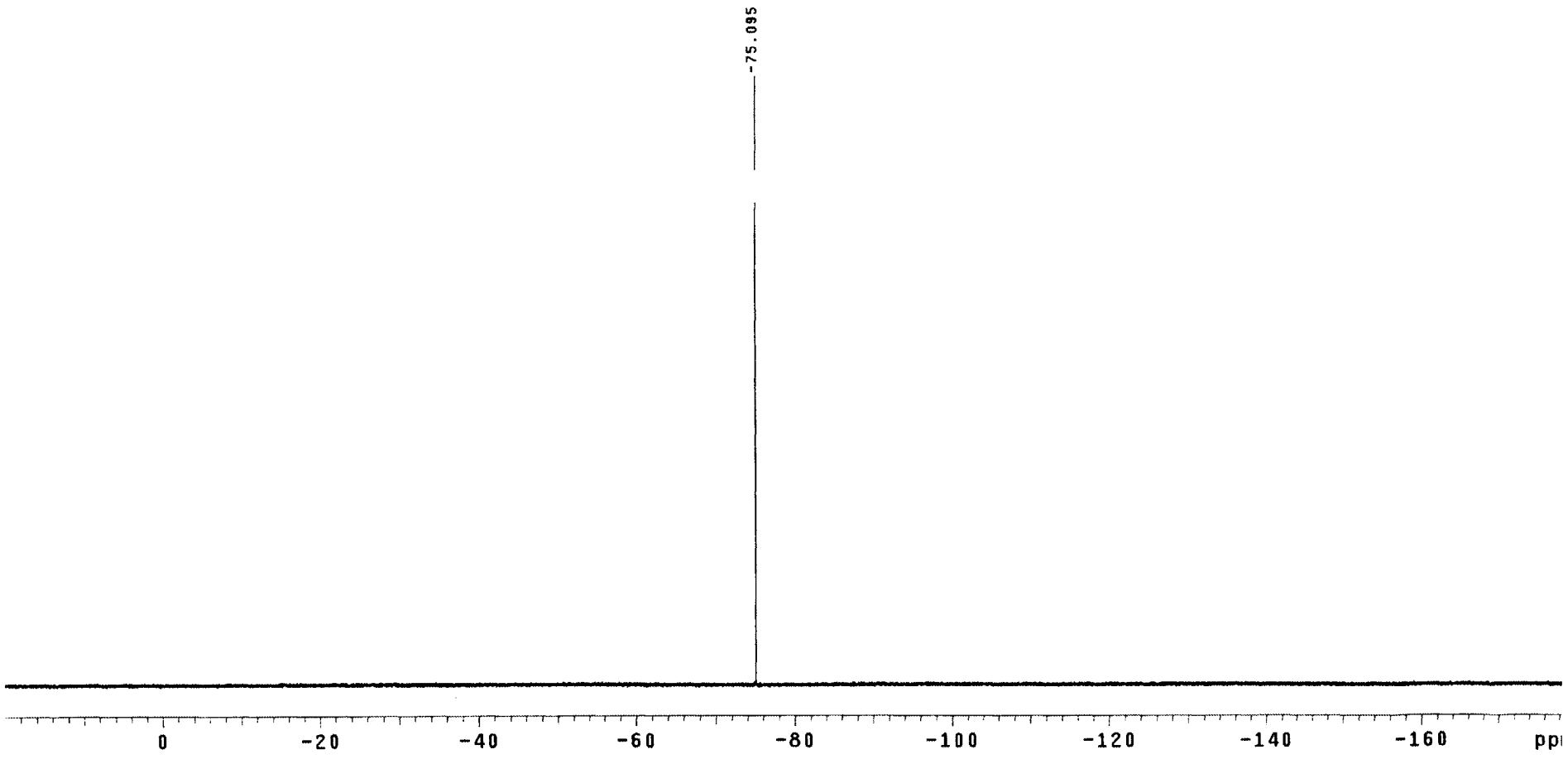
19F SENSITIVITY
0.05% TRIFLUOROTOLUENE

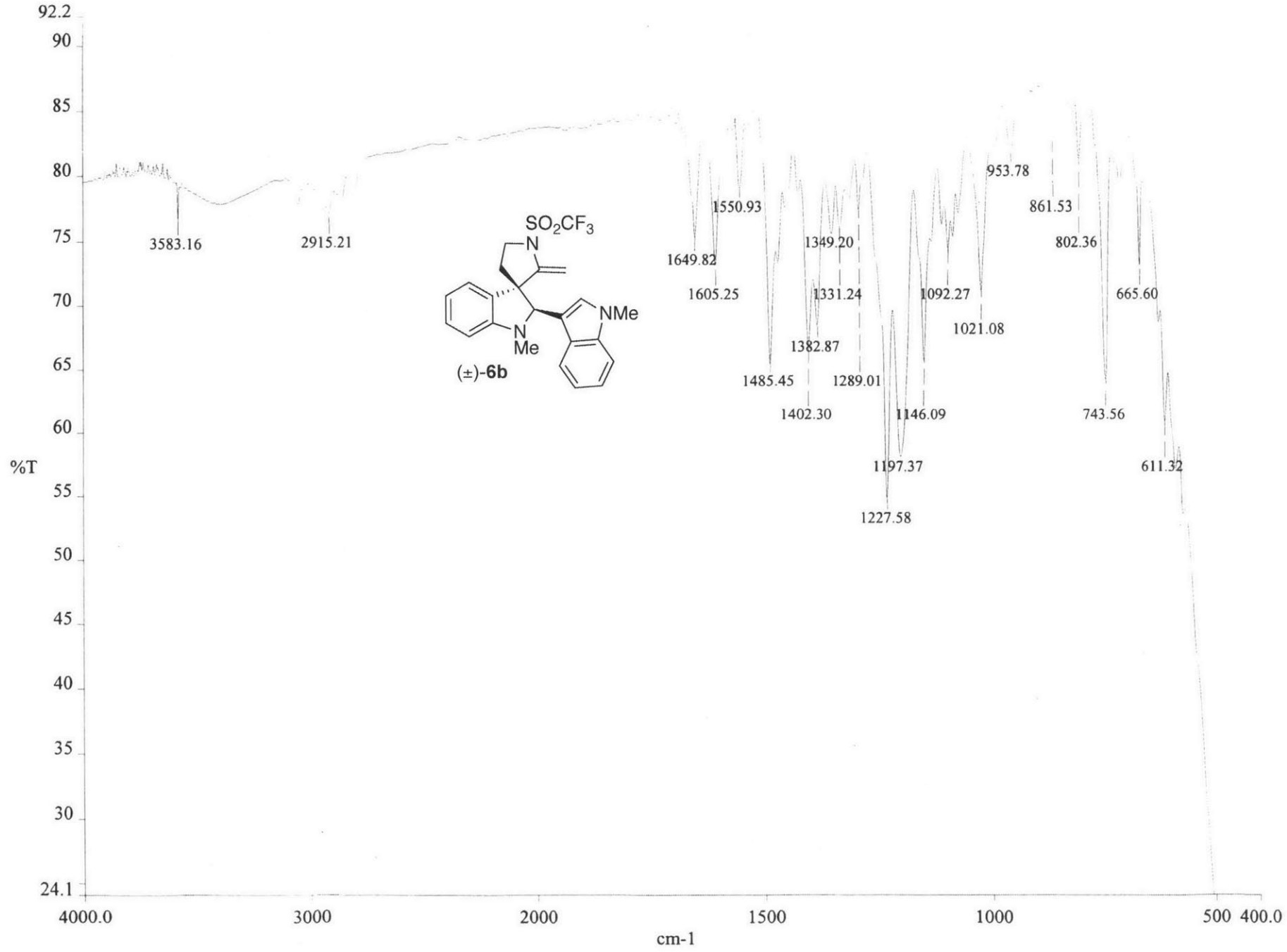
Pulse Sequence: s2pul
Solvent: toluene
Temp. 100.0 C / 373.1 K

Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 0.232 sec
Width 140.8 kHz
17 repetitions
OBSERVE F19, 470.2272838 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(±)-**6b**

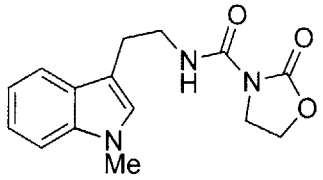



92.2
90
85
80
75
70
65
60
%T
55
50
45
40
35
30
24.1
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.16
2915.21
1649.82
1605.25
1550.93
1485.45
1402.30
1382.87
1349.20
1331.24
1289.01
1227.58
1197.37
1146.09
1092.27
1021.08
953.78
861.53
802.36
743.56
665.60
611.32
SO2CF3
N
N
Me
NMe
(±)-6b

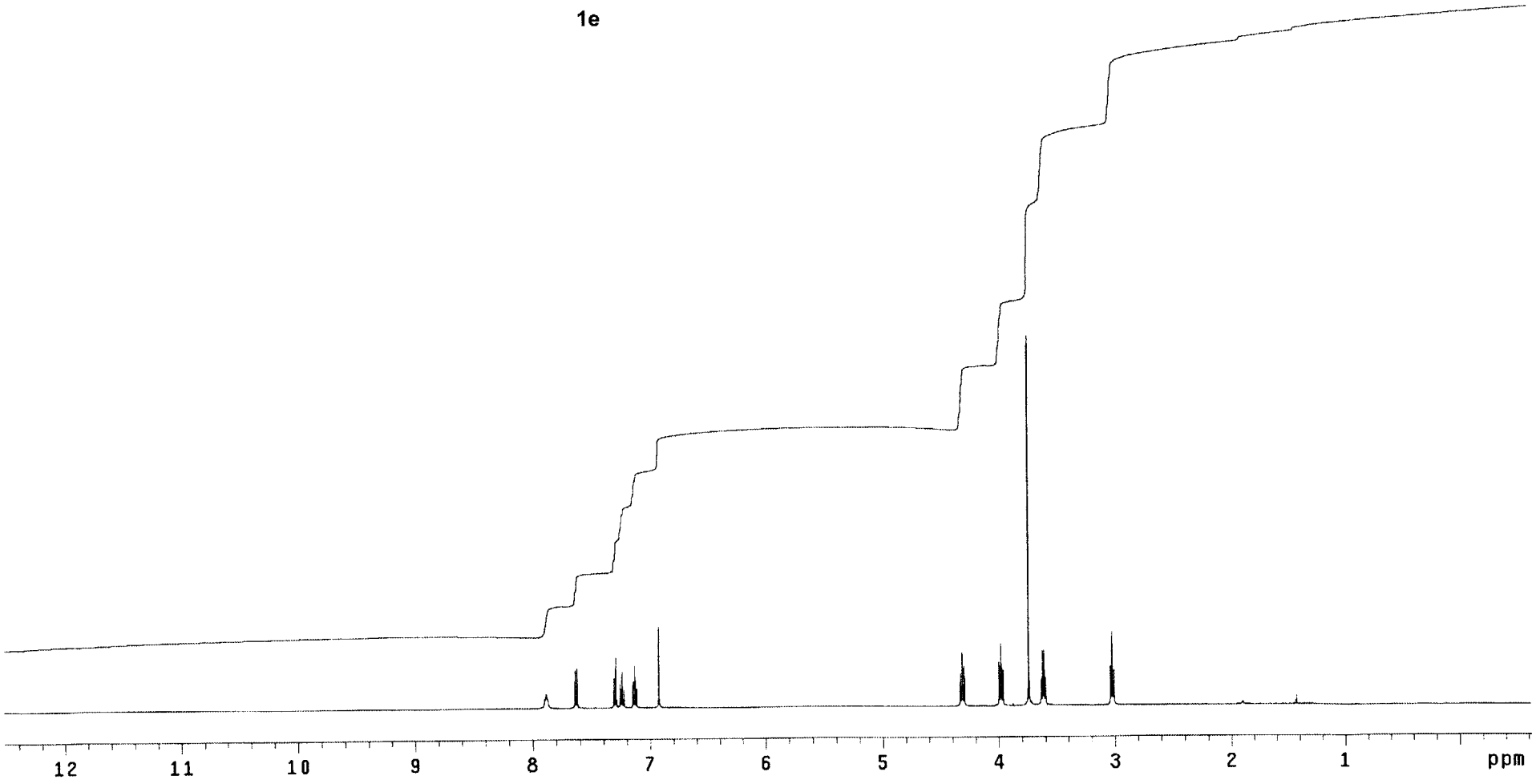
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
32 repetitions
OBSERVE H1, 500.2272234 MHz
DATA PROCESSING
FT size 131072



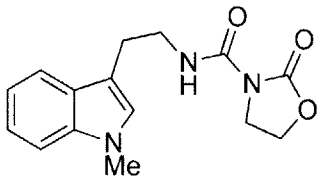
1e



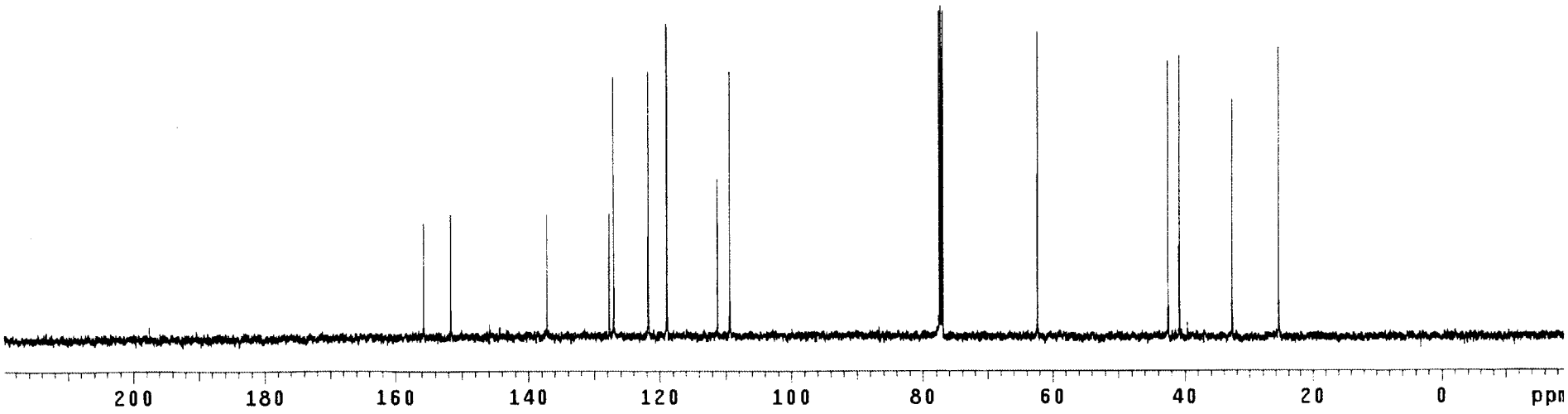
STANDARD CARBON PARAMETERS

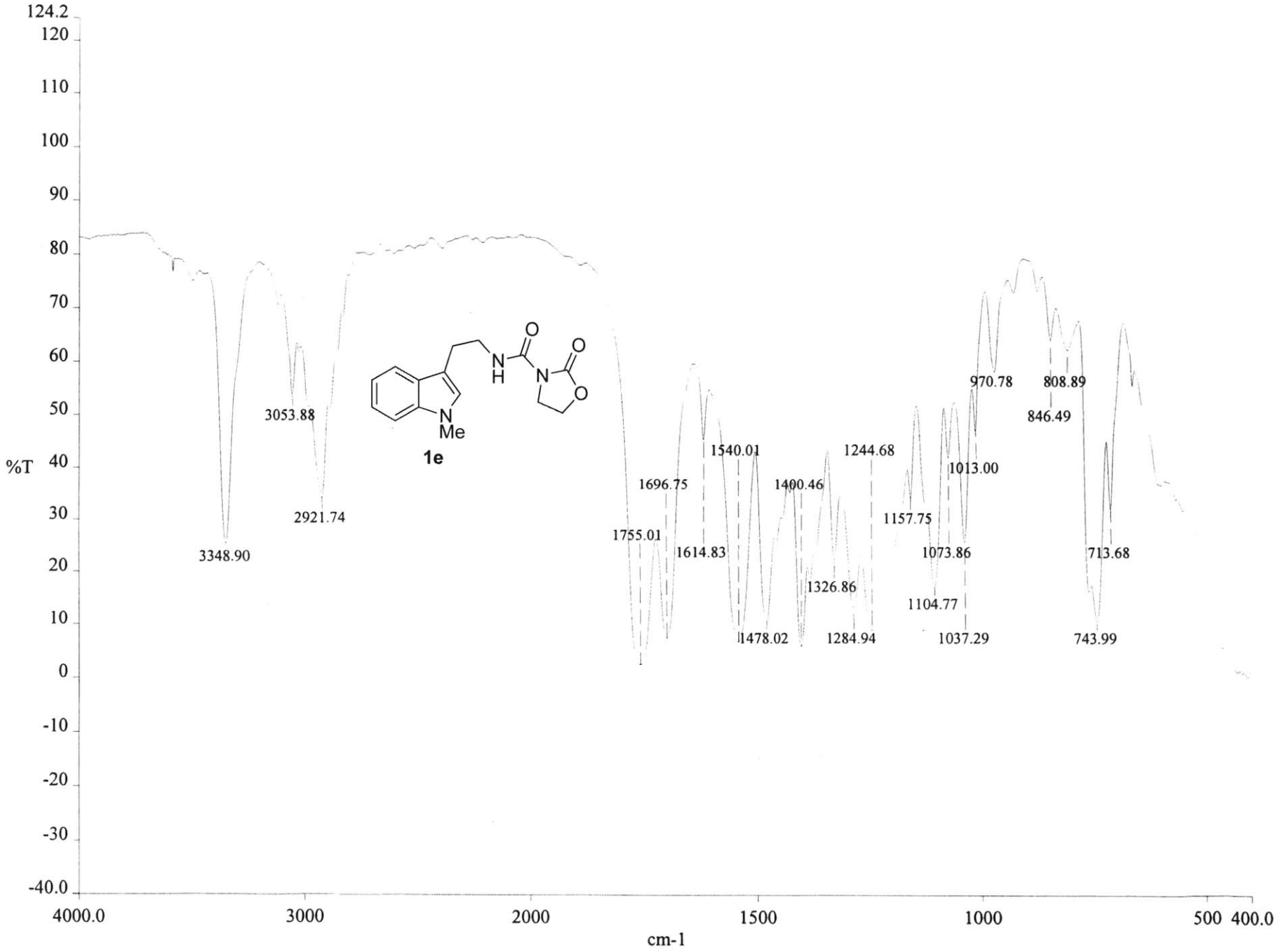
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 37.8 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
320 repetitions
OBSERVE C13, 125.6601534 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072



1e



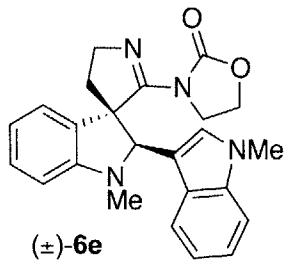

124.2
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-40.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3348.90
3053.88
2921.74
1755.01
1696.75
1614.83
1540.01
1478.02
1400.46
1326.86
1284.94
1244.68
1157.75
1104.77
1073.86
1037.29
1013.00
970.78
846.49
808.89
743.99
713.68
N
H
O
O
N
O
N
Me
1e

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: toluene
Temp. 100.0 C / 373.1 K

Relax. delay 2.000 sec
Pulse 84.1 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417947 MHz
DATA PROCESSING
FT size 262144

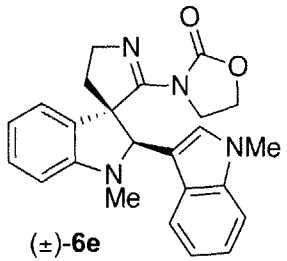


(±)-**6e**

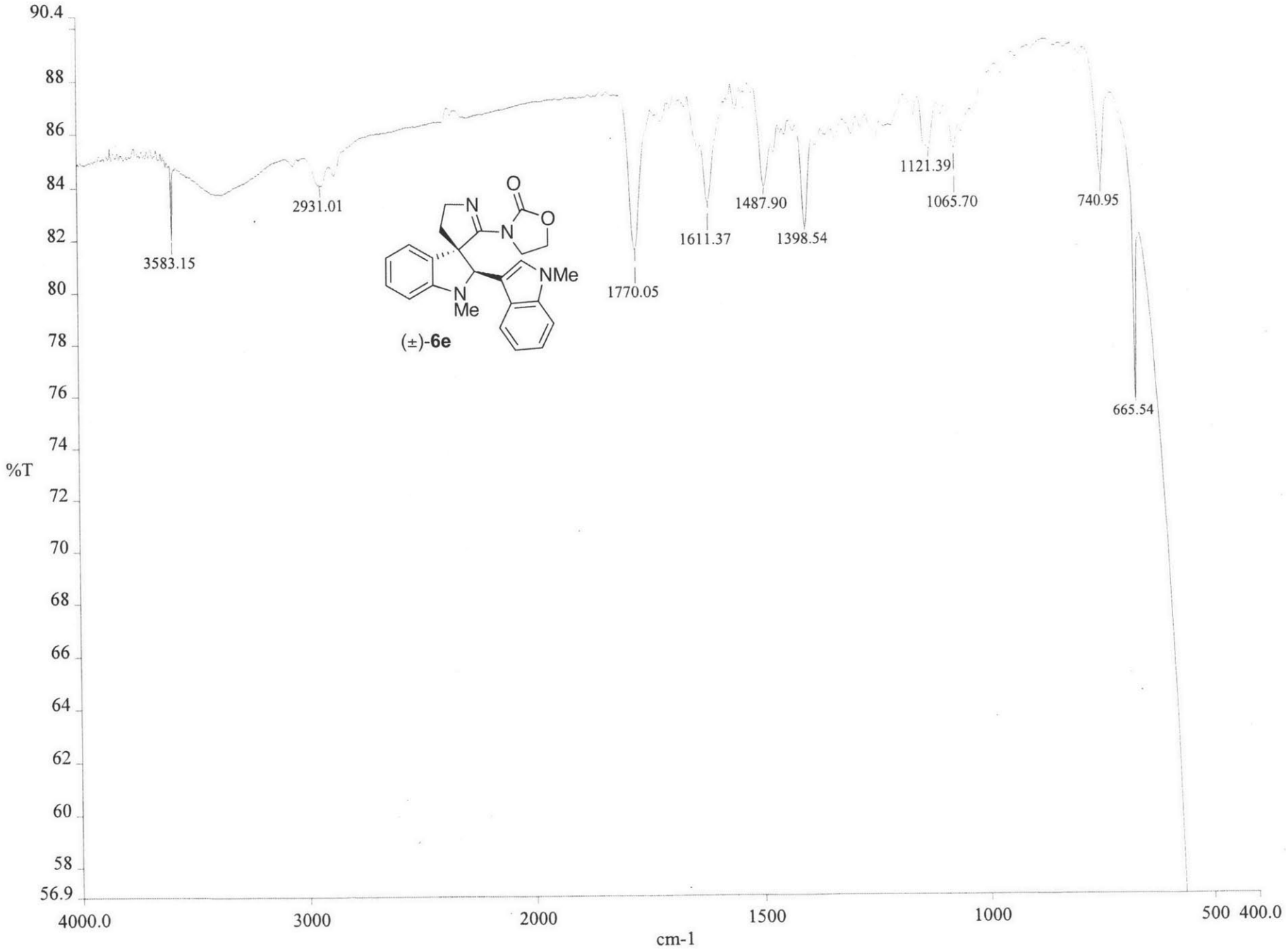
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: toluene
Temp. 80.0 C / 353.1 K

Relax. delay 3.000 sec
Pulse 37.8 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
10368 repetitions
OBSERVE C13, 125.6600952 MHz
DECOUPLE H1, 499.7442944 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072



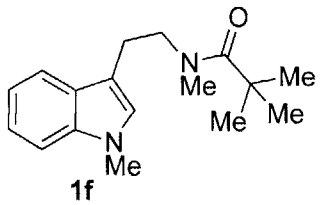
(±)-**6e**


90.4
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56.9
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.15
2931.01
1770.05
1611.37
1487.90
1398.54
1121.39
1065.70
740.95
665.54
O
N
N
O
NMe
N
Me
(±)-6e

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272299 MHz
DATA PROCESSING
FT size 131072

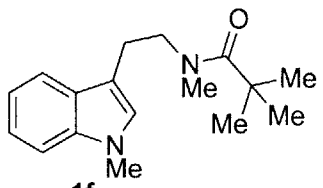


1f

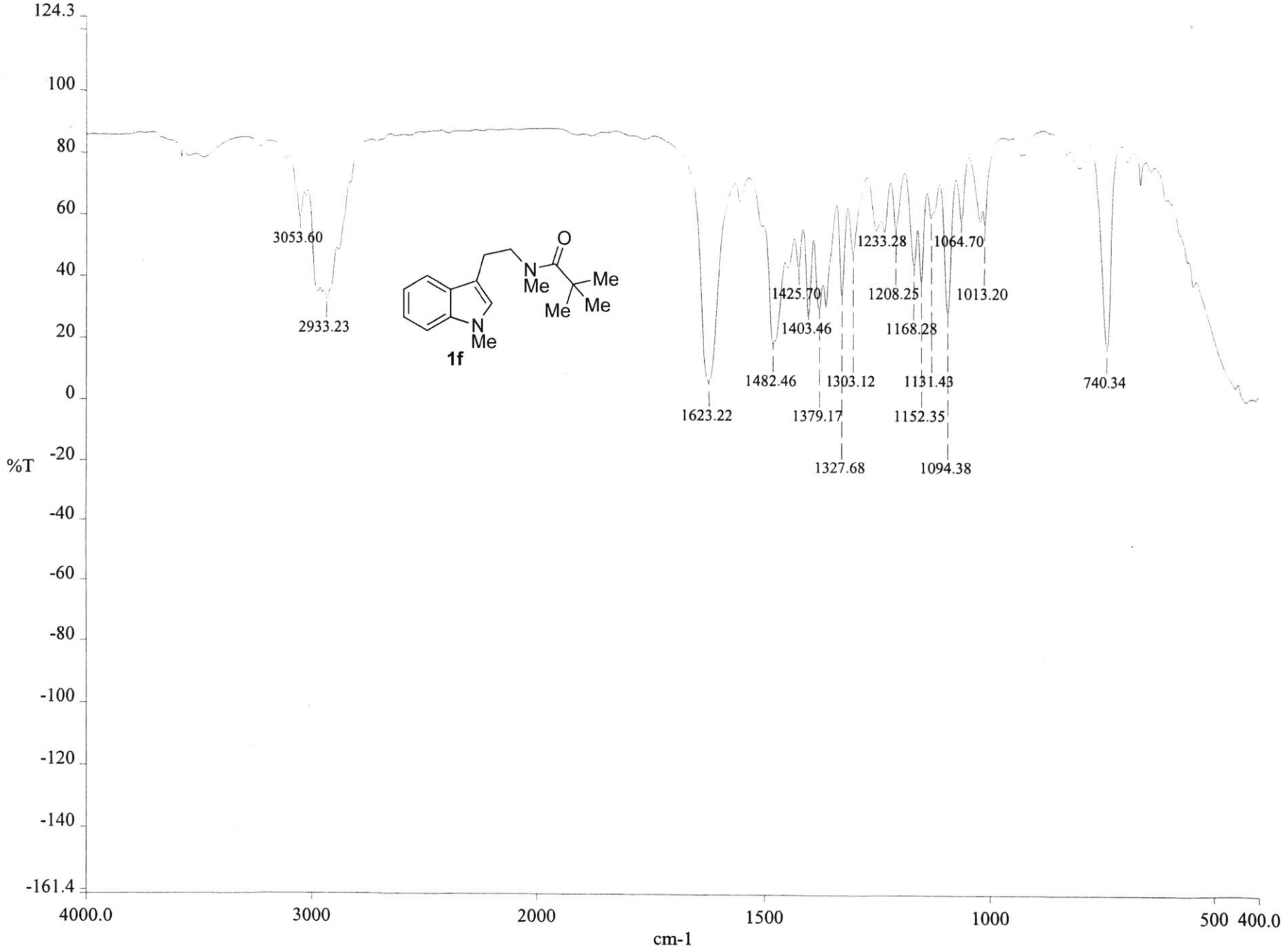
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
464 repetitions
OBSERVE C13, 125.7822280 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



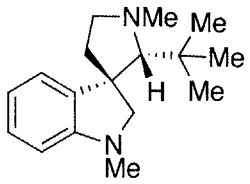
1f


124.3
100
80
60
40
20
0
-20
-40
-60
-80
-100
-120
-140
-161.4
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3053.60
2933.23
1623.22
1482.46
1425.70
1403.46
1379.17
1327.68
1303.12
1233.28
1208.25
1168.28
1152.35
1131.43
1094.38
1064.70
1013.20
740.34
N
Me
O
Me
Me
Me
N
Me
1f

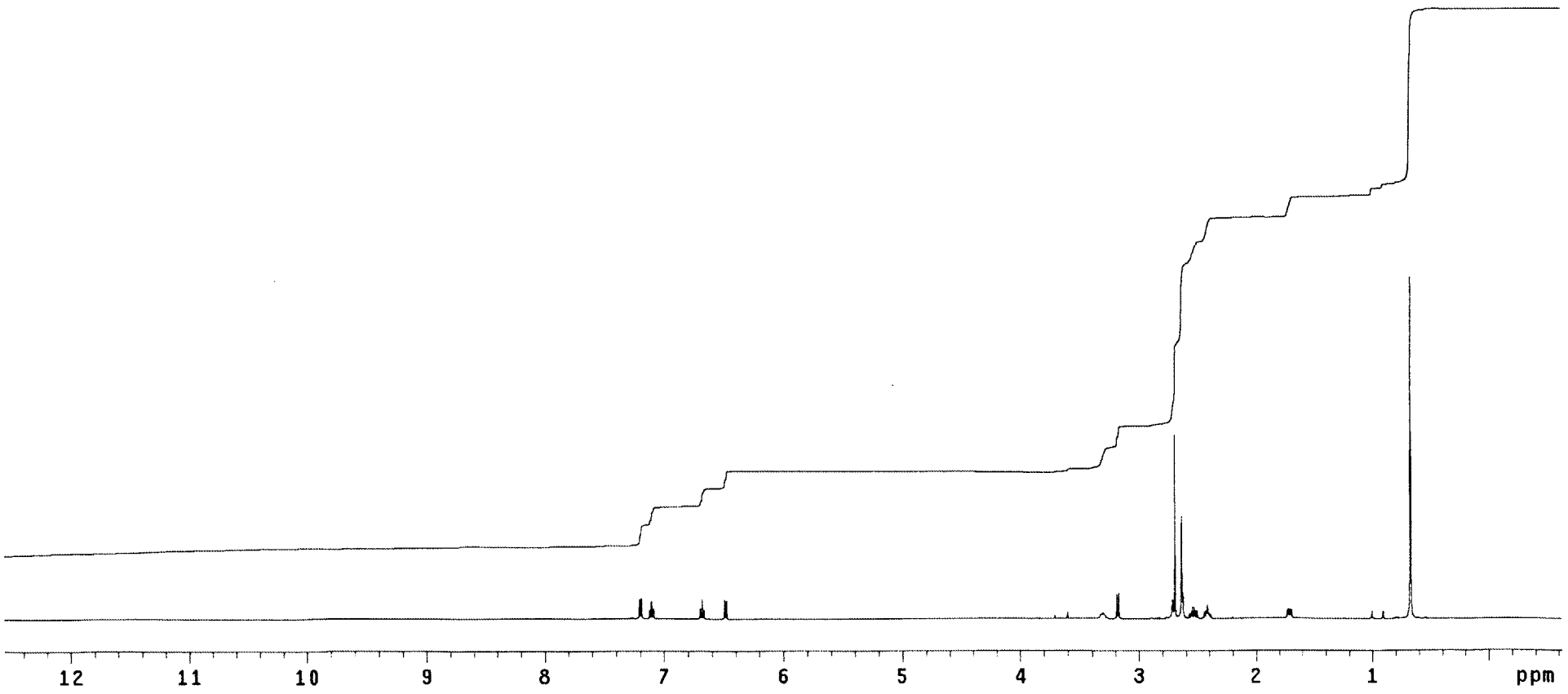
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 84.1 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417505 MHz
DATA PROCESSING
FT size 262144



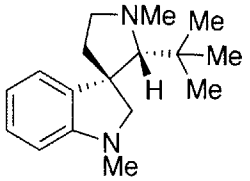
(±)-**7f**



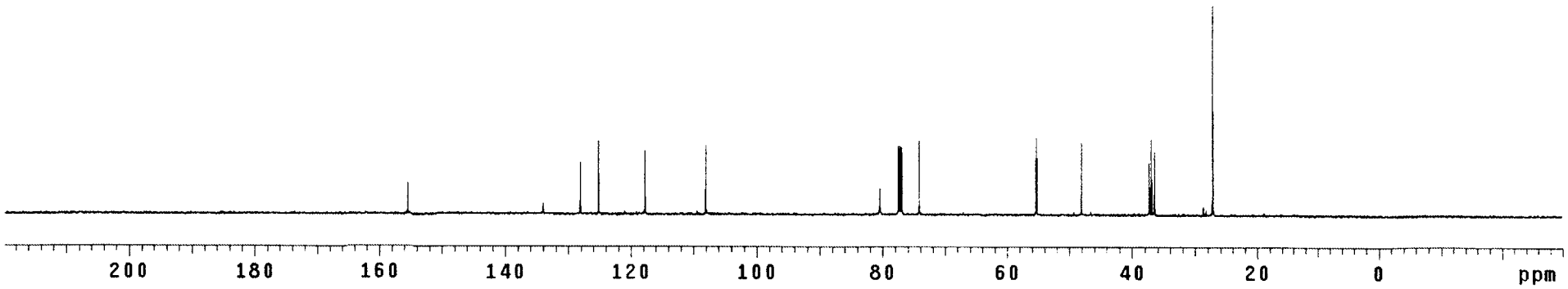
STANDARD CARBON PARAMETERS

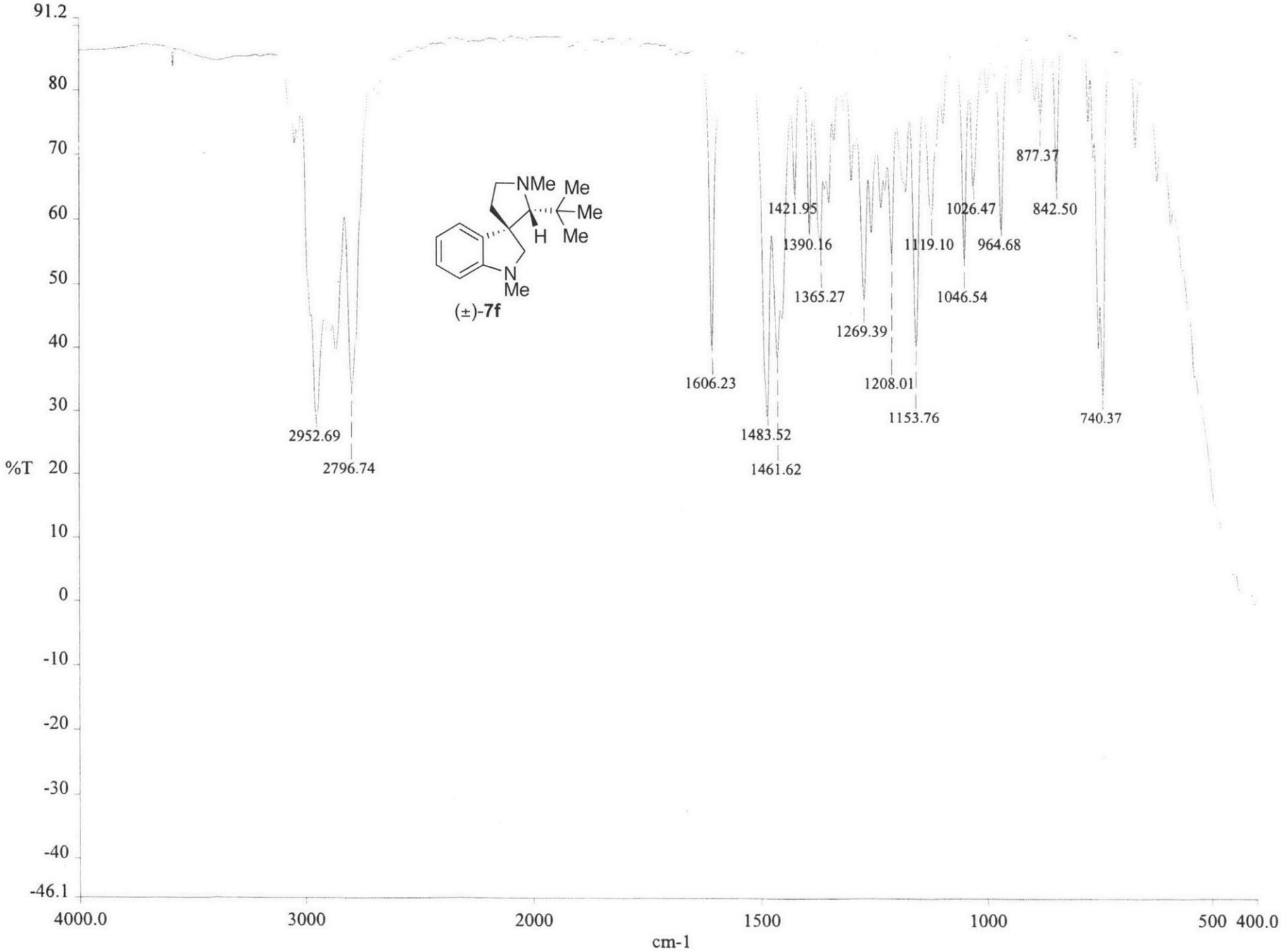
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 37.8 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
358 repetitions
OBSERVE C13, 125.6601405 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072



(±)-**7f**




91.2
80
70
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50
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10
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-10
-20
-30
-40
-46.1
4000.0
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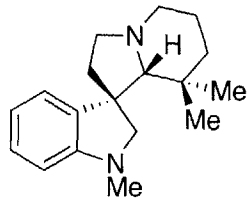
2000
1500
1000
500 400.0
cm-1
NMe Me
Me
H Me
N
Me
(±)-7f
2952.69
2796.74
1606.23
1483.52
1461.62
1421.95
1390.16
1365.27
1269.39
1208.01
1153.76
1119.10
1046.54
1026.47
964.68
877.37
842.50
740.37

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 84.1 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
17 repetitions
OBSERVE H1, 499.7417322 MHz
DATA PROCESSING
FT size 262144

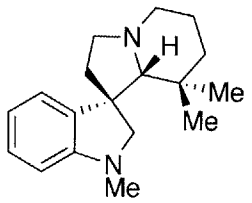


(±)-**7g**

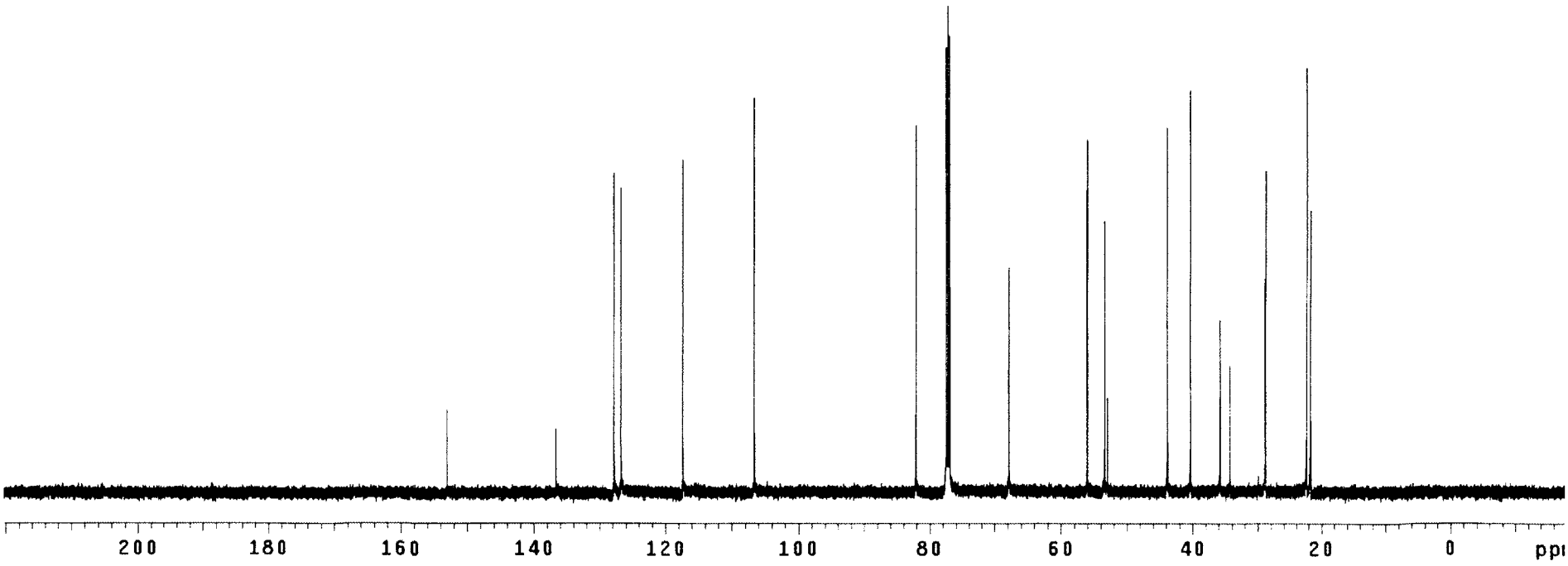
STANDARD CARBON PARAMETERS

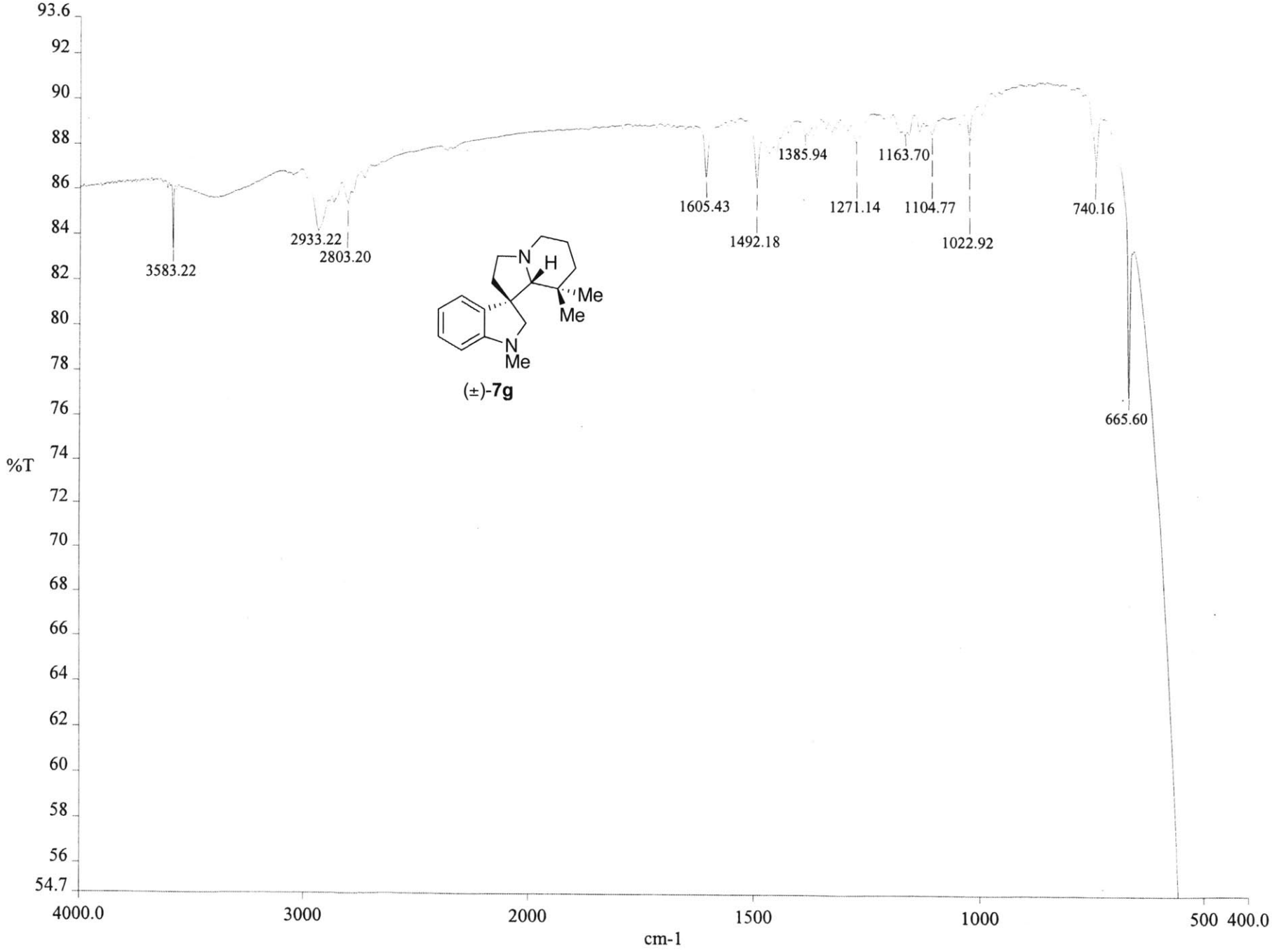
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
2165 repetitions
OBSERVE C13, 125.7822072 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



(±)-**7g**



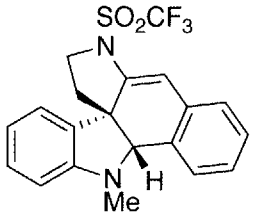

93.6
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54.7
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.22
2933.22
2803.20
1605.43
1492.18
1385.94
1271.14
1163.70
1104.77
1022.92
740.16
665.60
N
H
Me
Me
N
Me

(±)-**7g**

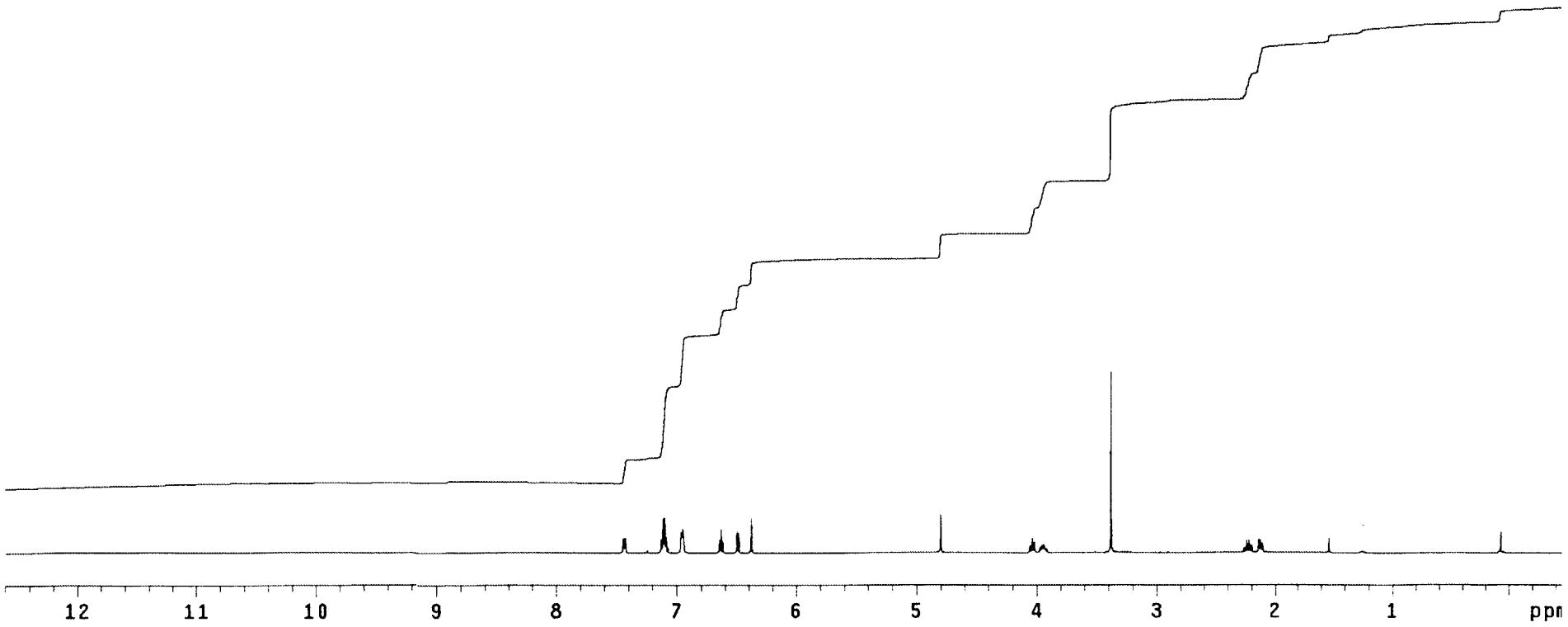
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
4 repetitions
OBSERVE H1, 499.7417343 MHz
DATA PROCESSING
FT size 262144



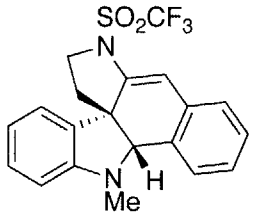
(±)-**8h**



STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
1995 repetitions
OBSERVE C13, 125.6601328 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072

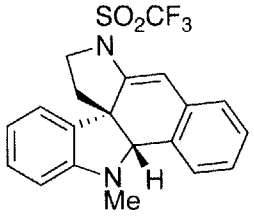


(±)-**8h**

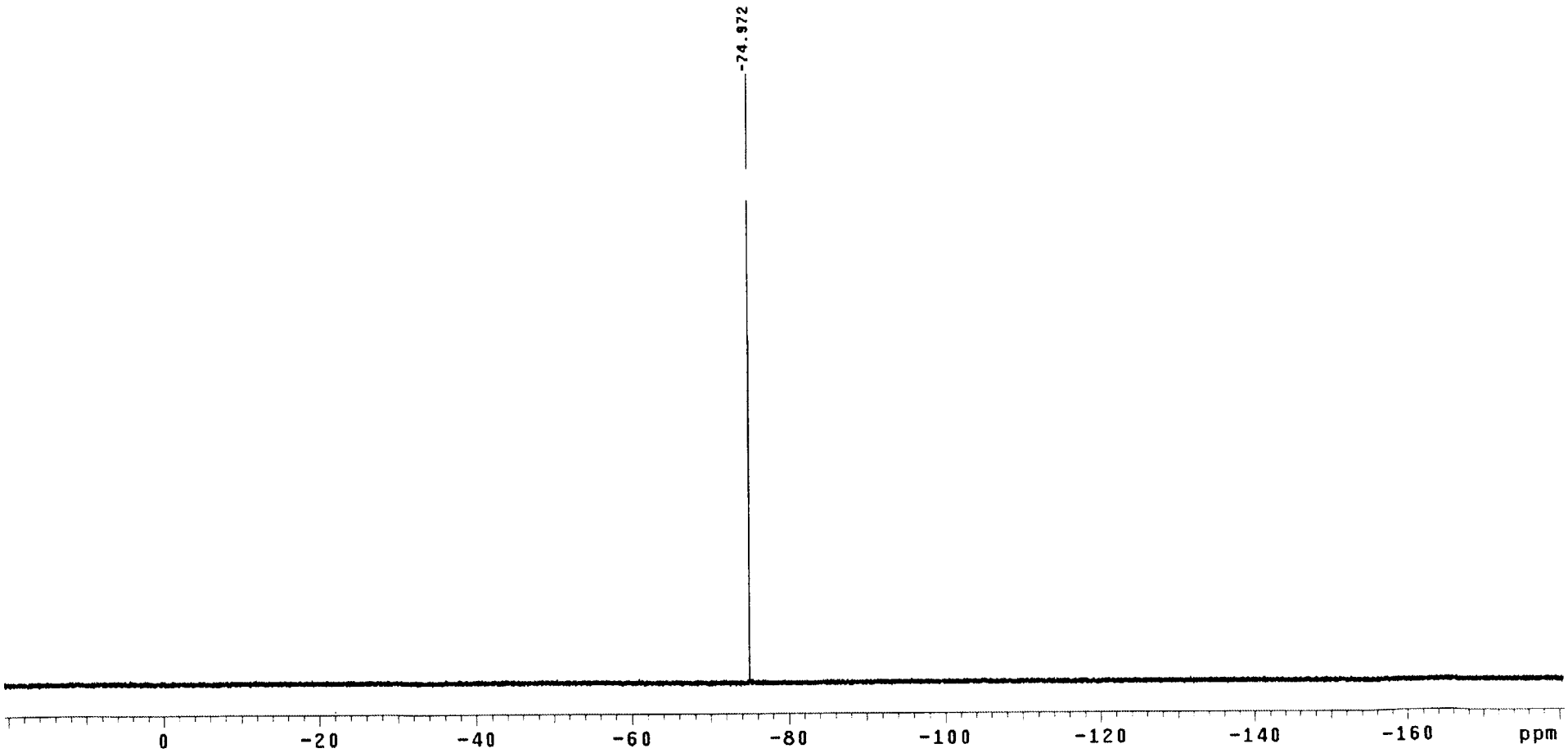
19F SENSITIVITY
0.05% TRIFLUOROTOLUENE

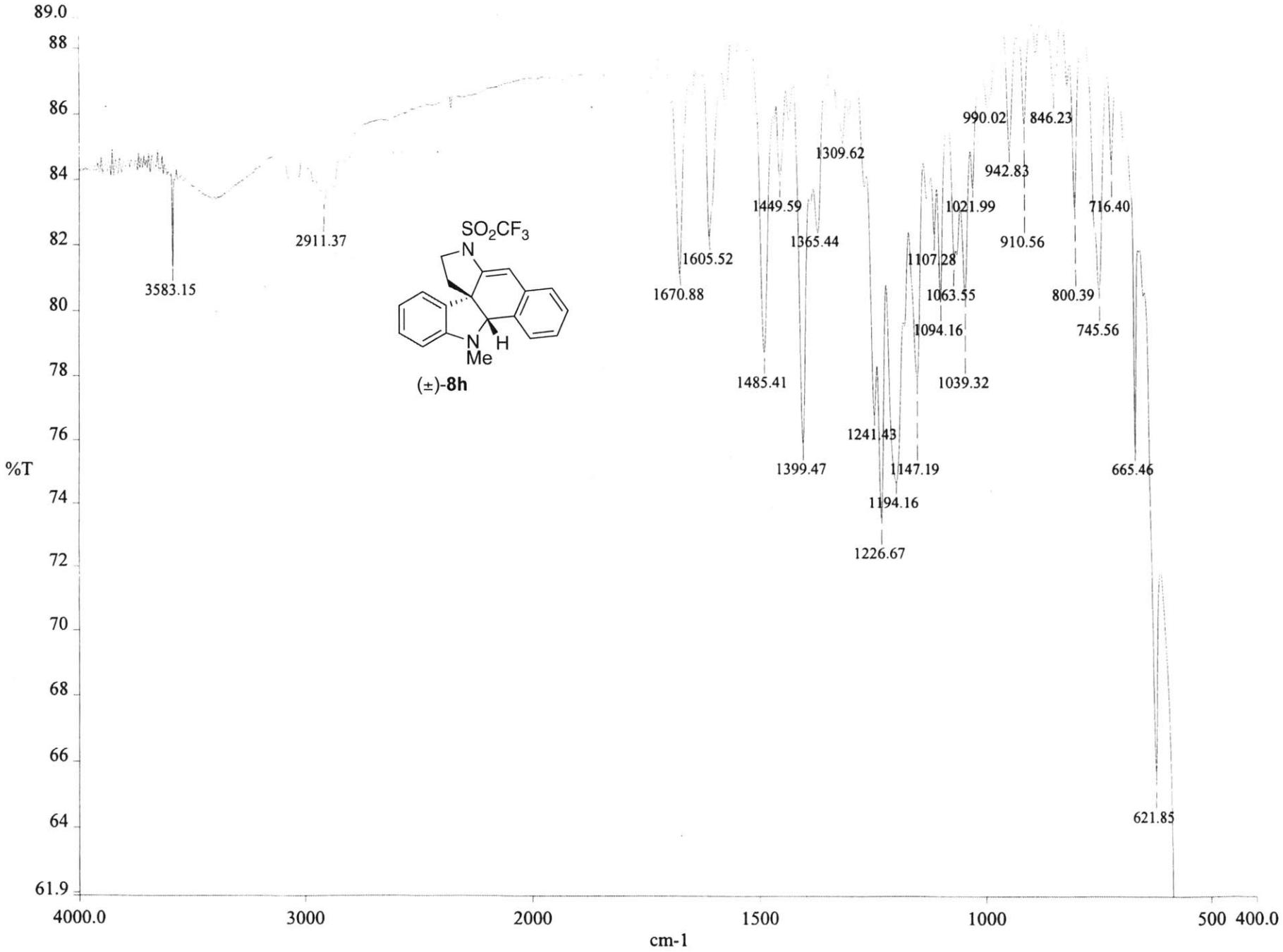
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 0.232 sec
Width 140.8 kHz
11 repetitions
OBSERVE F19, 470.2272133 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(±)-**8h**

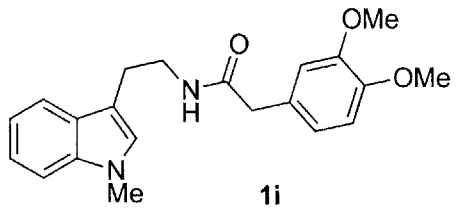



89.0
88
86
84
82
80
78
76
74
72
70
68
66
64
61.9
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.15
2911.37
1670.88
1605.52
1485.41
1449.59
1399.47
1365.44
1309.62
1241.43
1226.67
1194.16
1147.19
1107.28
1094.16
1063.55
1039.32
1021.99
990.02
942.83
910.56
846.23
800.39
745.56
716.40
665.46
621.85
SO2CF3
N
N
H
Me
(±)-8h

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
3 repetitions
OBSERVE H1, 500.2272281 MHz
DATA PROCESSING
FT size 131072

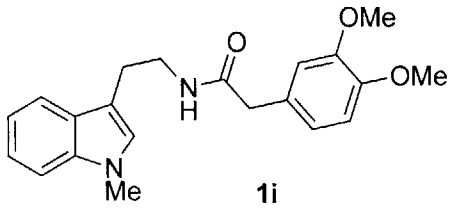


1i

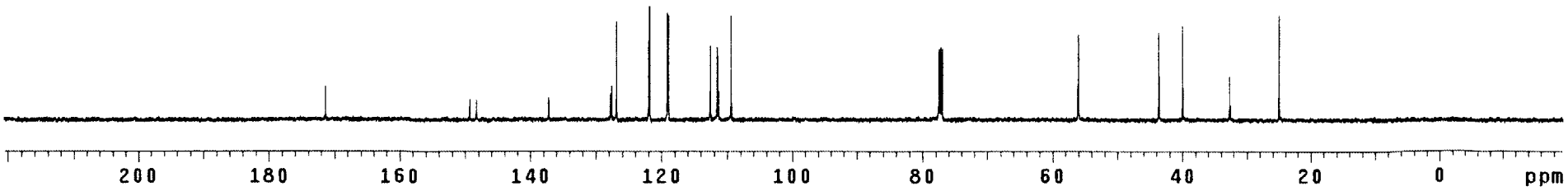
STANDARD CARBON PARAMETERS

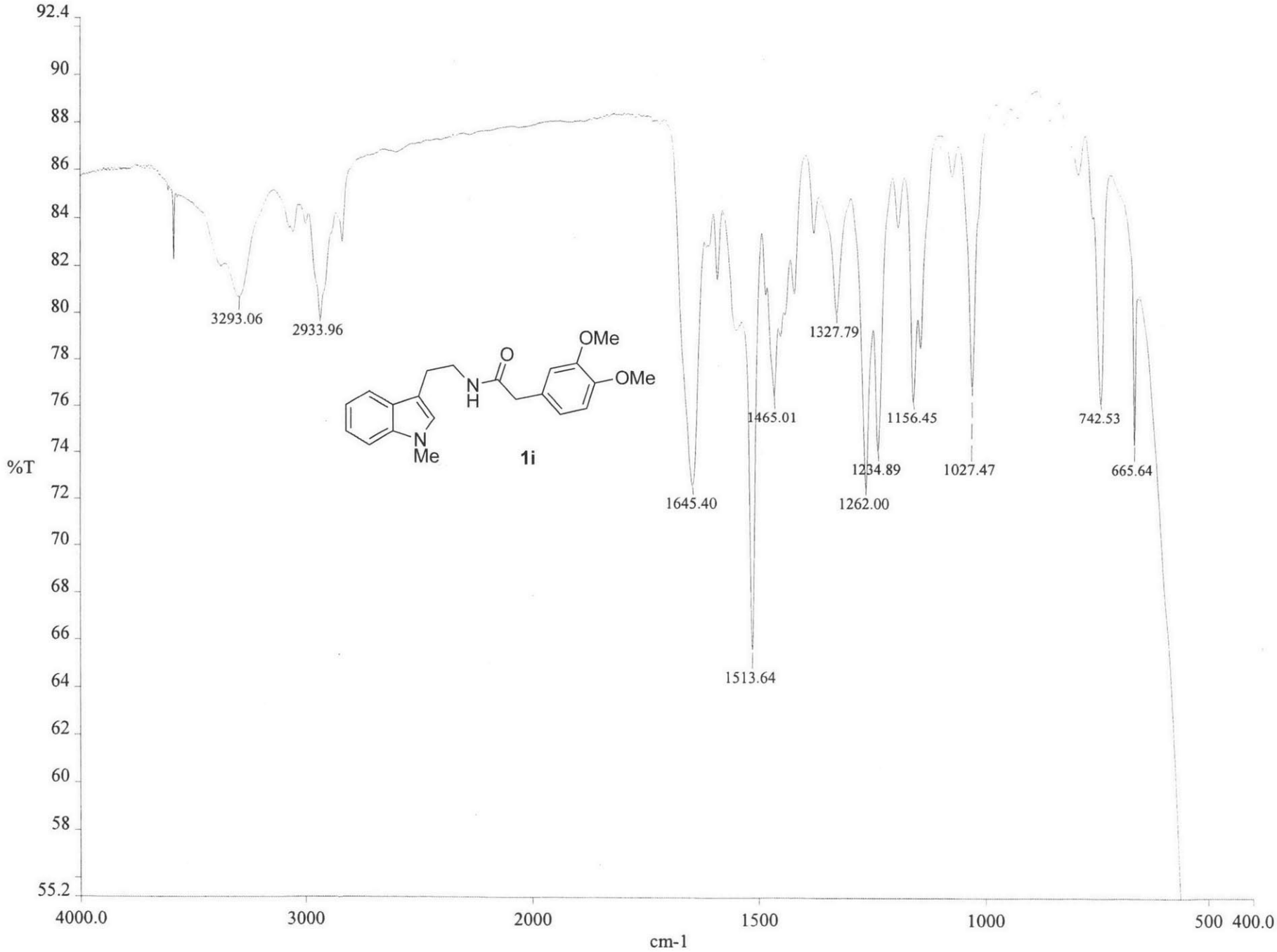
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
108 repetitions
OBSERVE C13, 125.7822170 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072



1i




92.4
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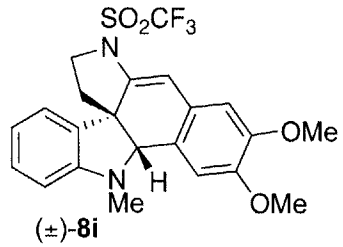
55.2
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3293.06
2933.96
1645.40
1513.64
1465.01
1327.79
1262.00
1234.89
1156.45
1027.47
742.53
665.64
OMe
OMe
O
N
H
N
Me
1i

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 73.1 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4295125 MHz
DATA PROCESSING
FT size 262144



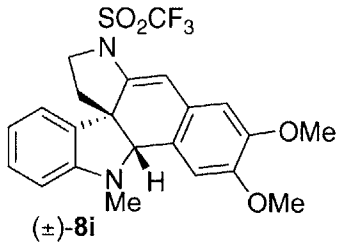
(±)-**8i**

STANDARD CARBON PARAMETERS

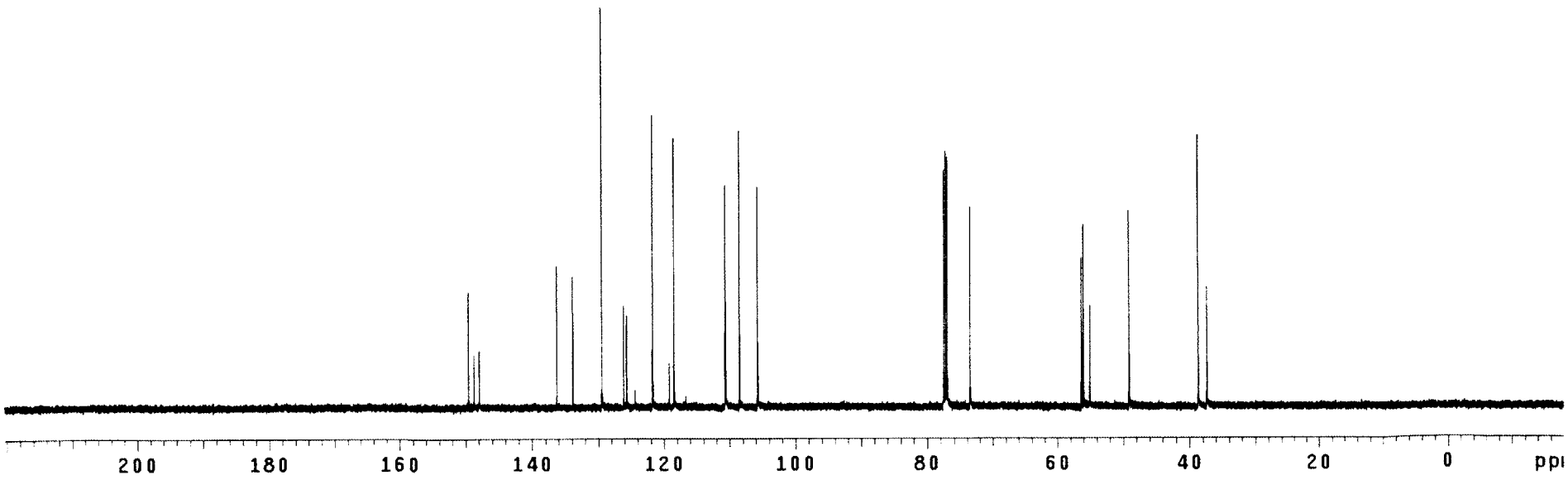
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
1272 repetitions
OBSERVE C13, 125.7822107 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



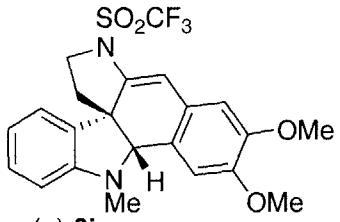
(±)-**8i**



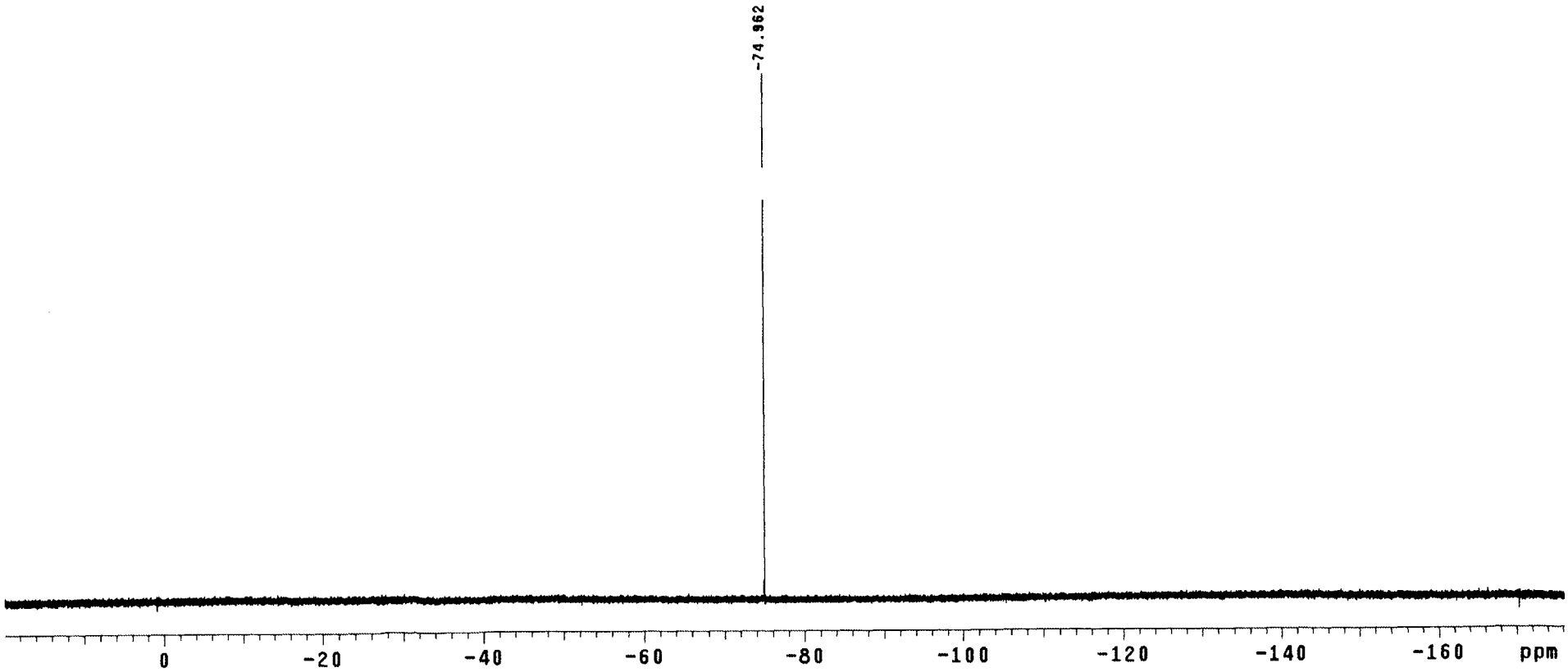
19F OBSERVE
STANDARD PARAMETERS

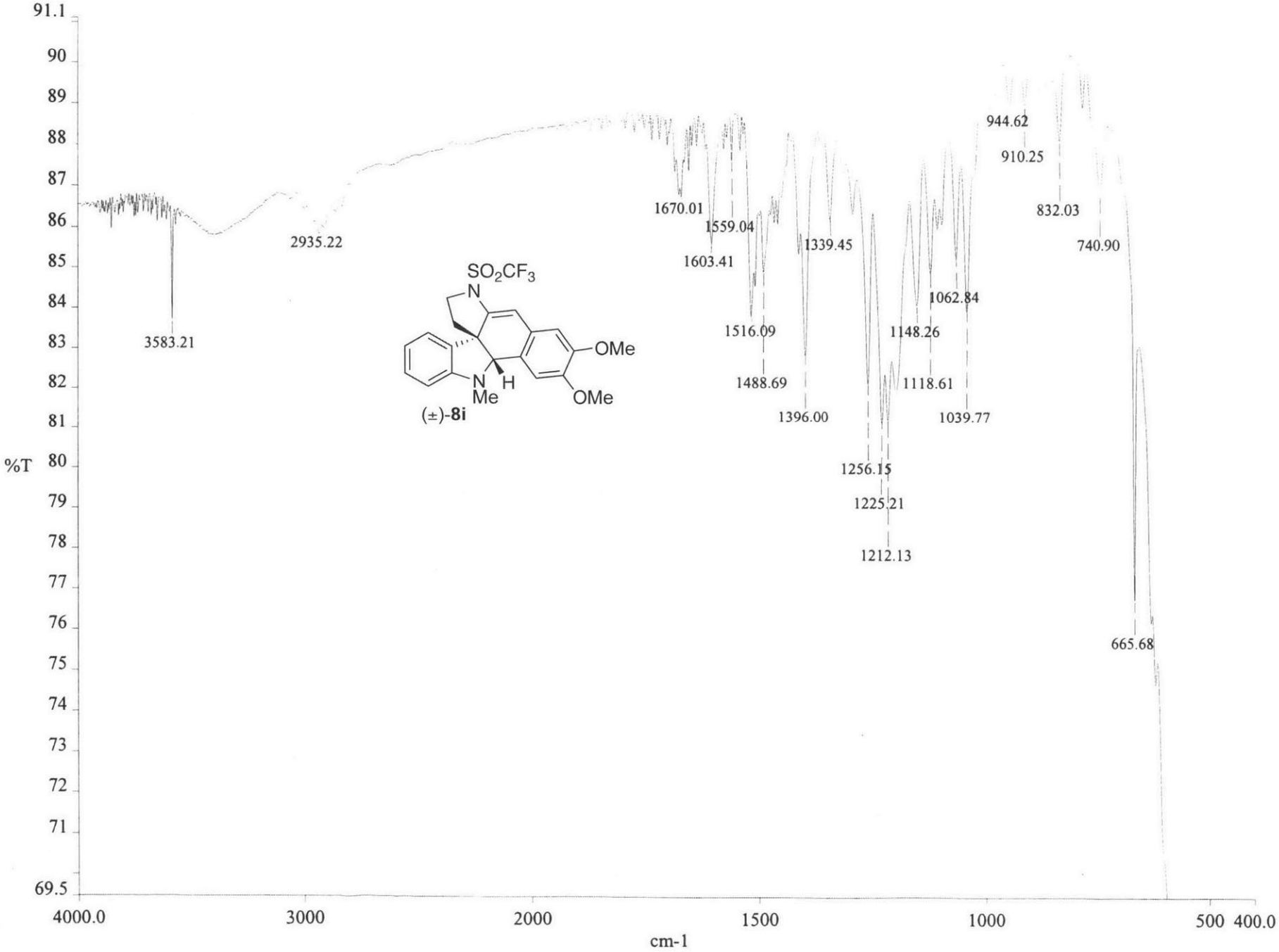
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 0.300 sec
Width 100.0 kHz
11 repetitions
OBSERVE F19, 282.3814158 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144



(±)-**8i**




91.1
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69.5
%T
4000.0
3000
2000
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1000
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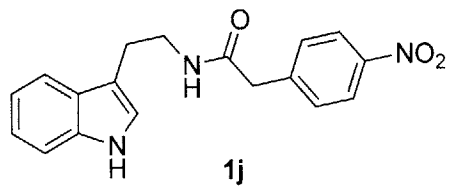
400.0
cm-1
3583.21
2935.22
1670.01
1603.41
1559.04
1516.09
1488.69
1396.00
1339.45
1256.15
1225.21
1212.13
1148.26
1118.61
1062.84
1039.77
944.62
910.25
832.03
740.90
665.68
SO2CF3
N
N
H
Me
OMe
OMe
(±)-8i

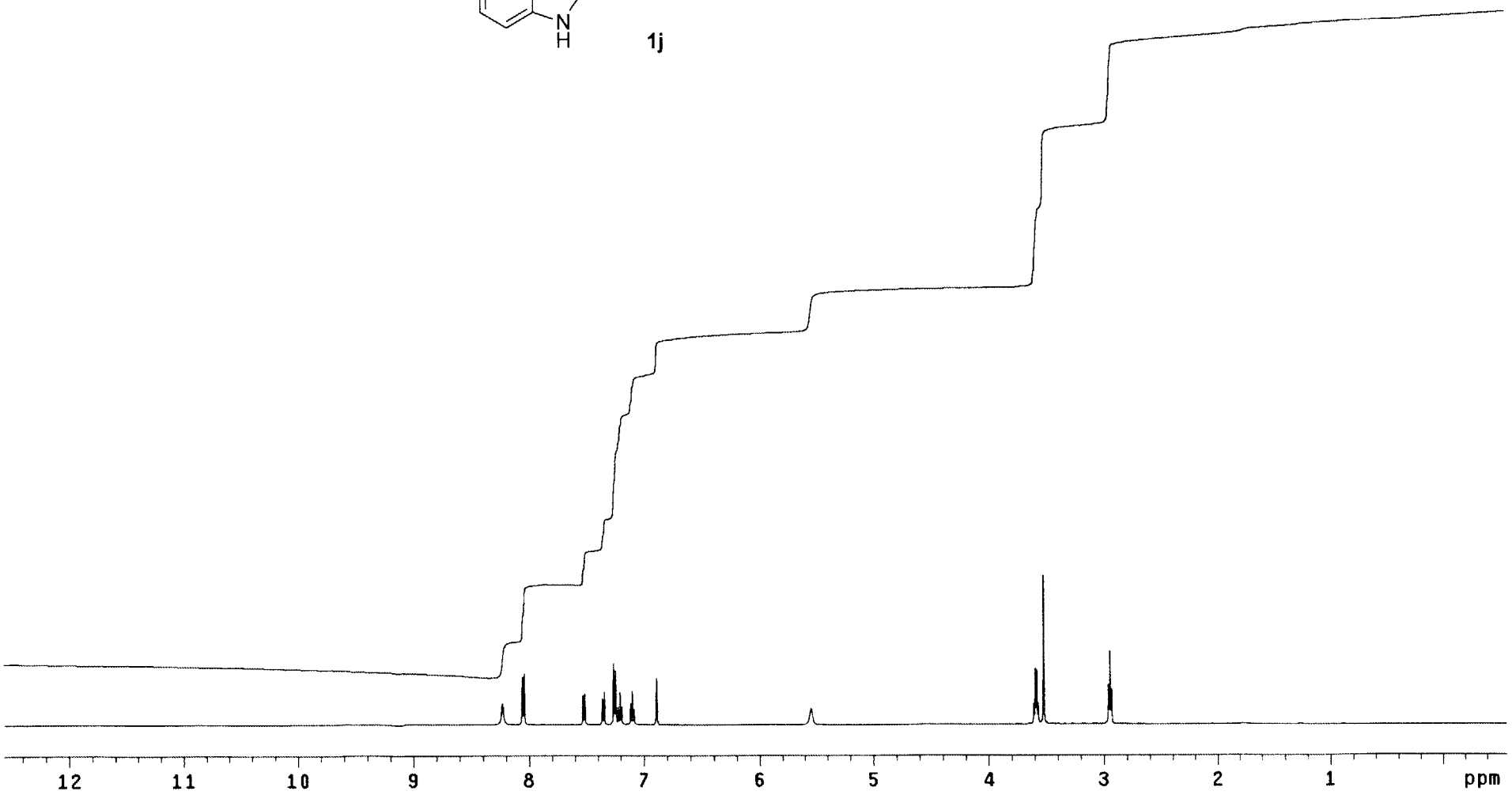
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
4 repetitions
OBSERVE H1, 500.2272224 MHz
DATA PROCESSING
FT size 131072



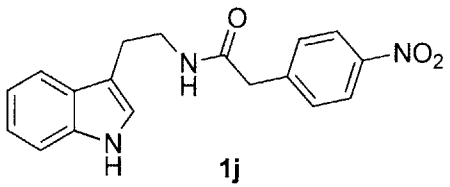
1j



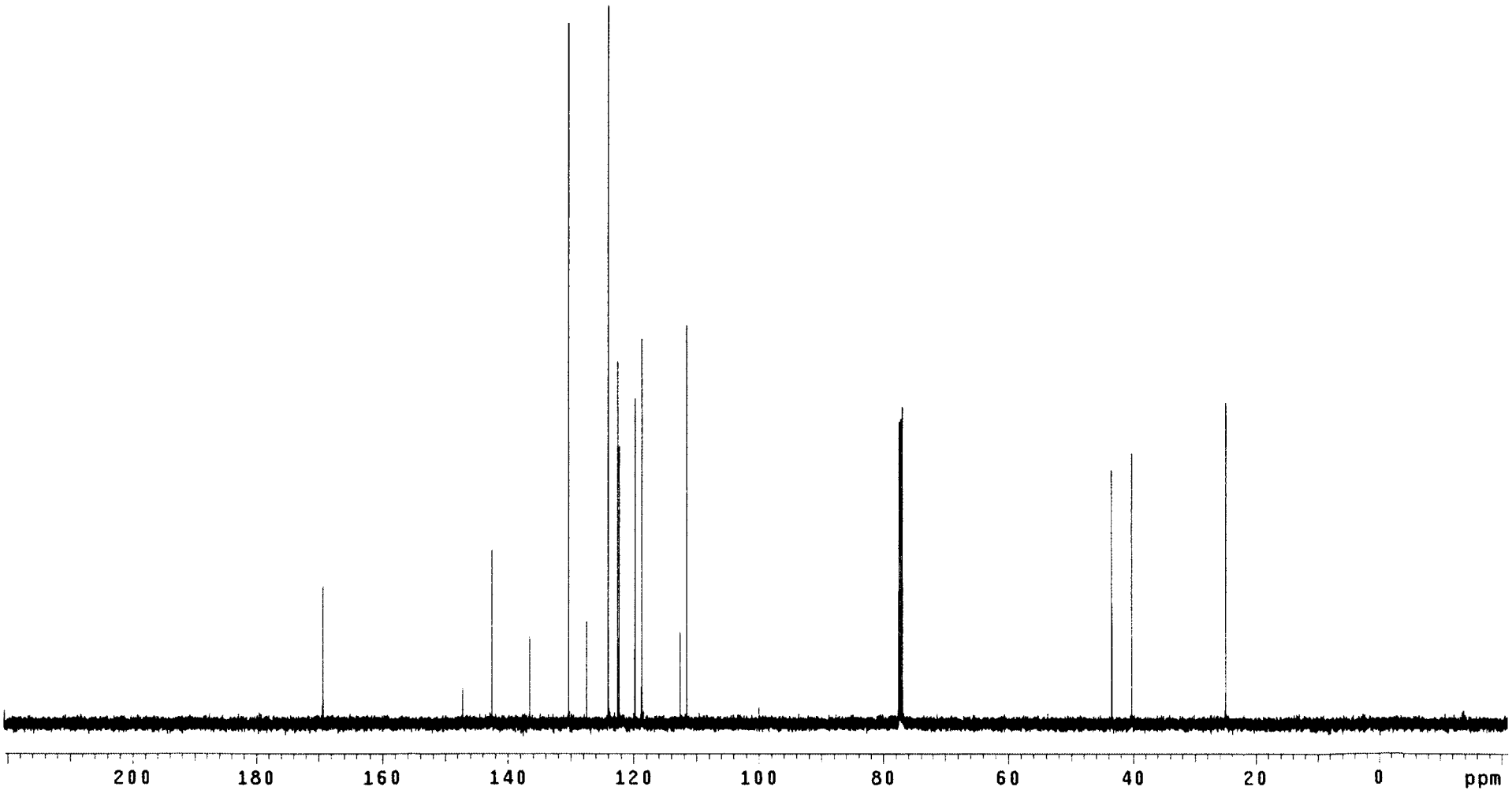
STANDARD CARBON PARAMETERS

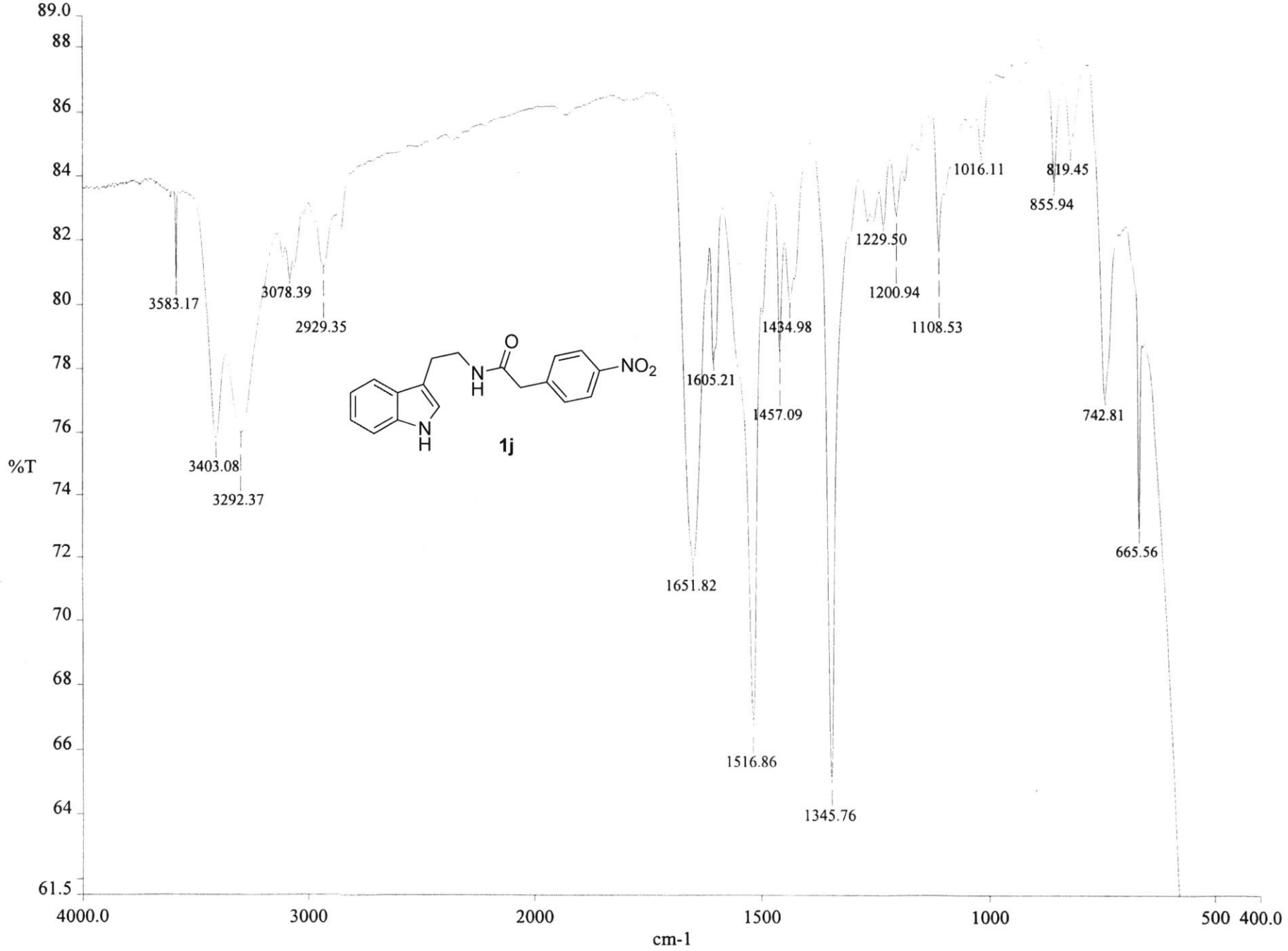
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
65536 repetitions
OBSERVE C13, 125.7822130 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



1j

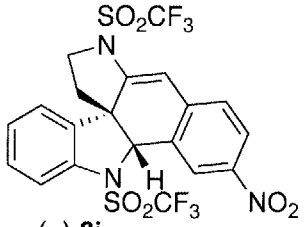



89.0
88
86
84
82
80
78
76
74
72
70
68
66
64
61.5
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.17
3403.08
3292.37
3078.39
2929.35
1651.82
1605.21
1516.86
1457.09
1434.98
1345.76
1229.50
1200.94
1108.53
1016.11
855.94
819.45
742.81
665.56
O
N
H
NO2
N
H
1j

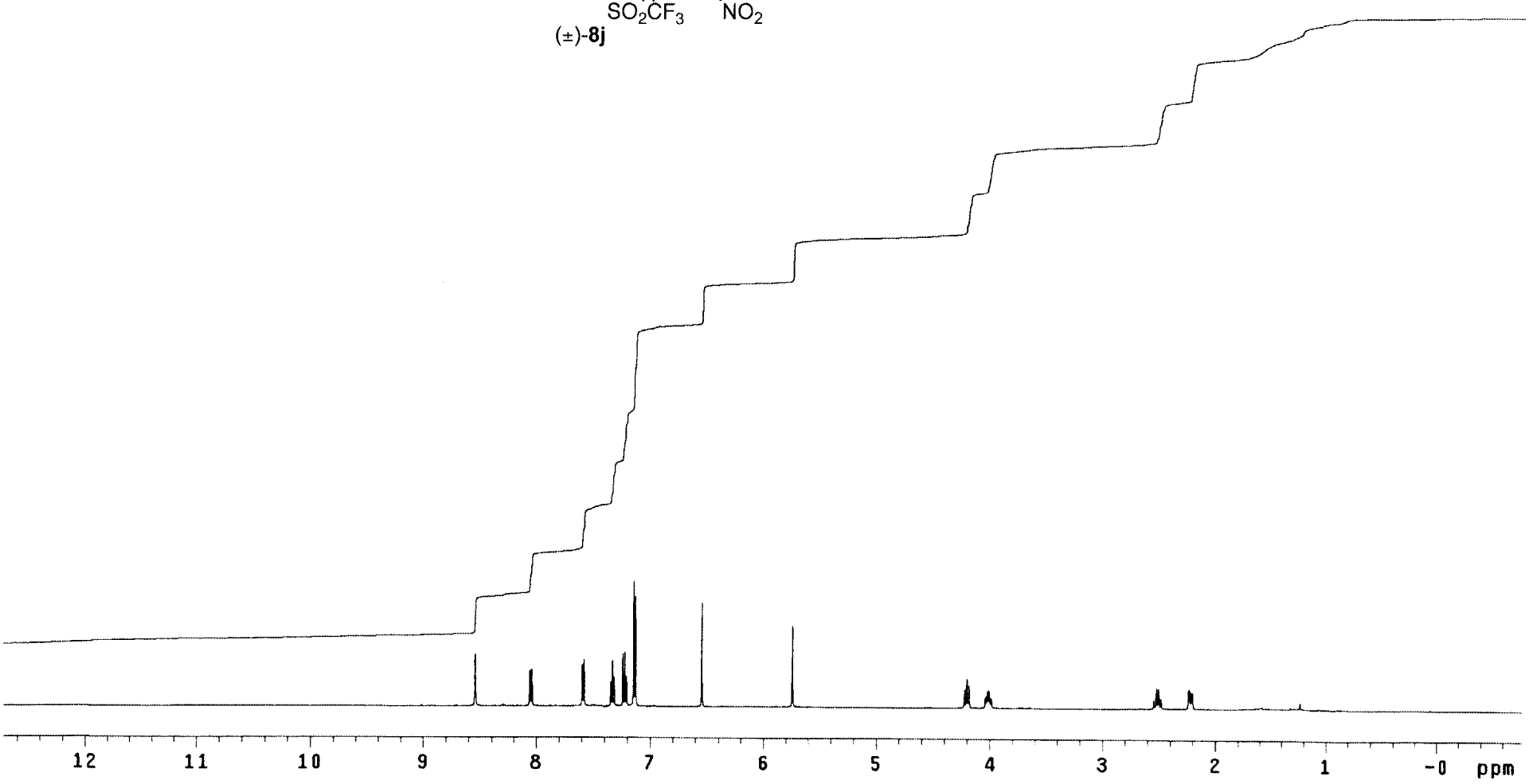
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 72.4 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
20 repetitions
OBSERVE H1, 500.4252876 MHz
DATA PROCESSING
FT size 262144



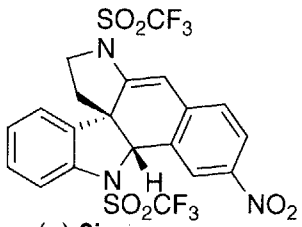
(±)-**8j**



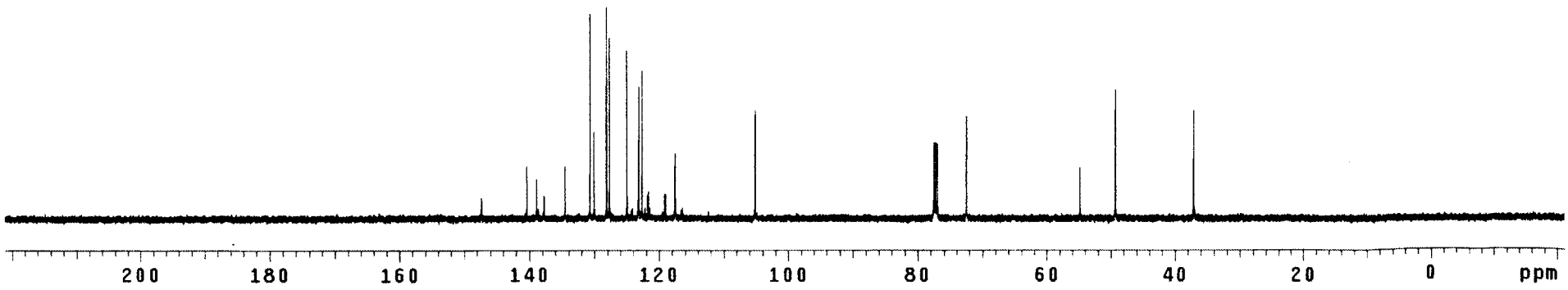
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
448 repetitions
OBSERVE C13, 125.7822049 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



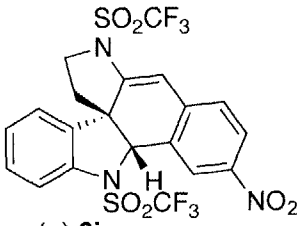
(±)-**8j**



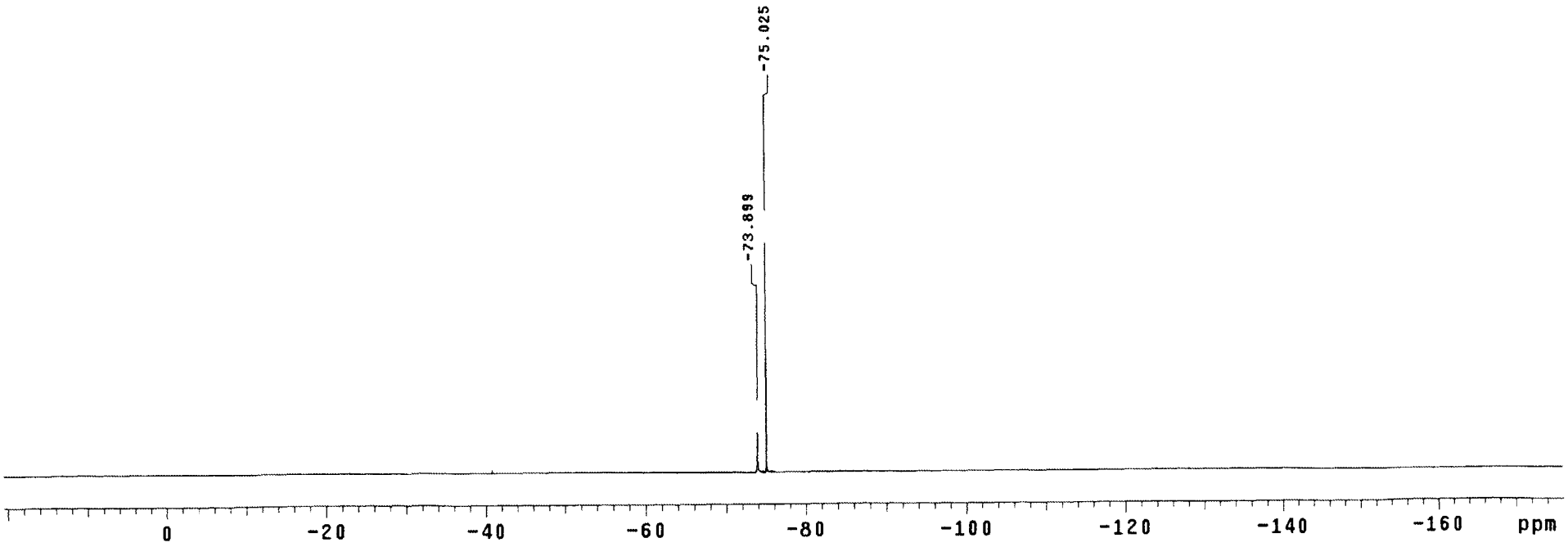
19F OBSERVE
STANDARD PARAMETERS

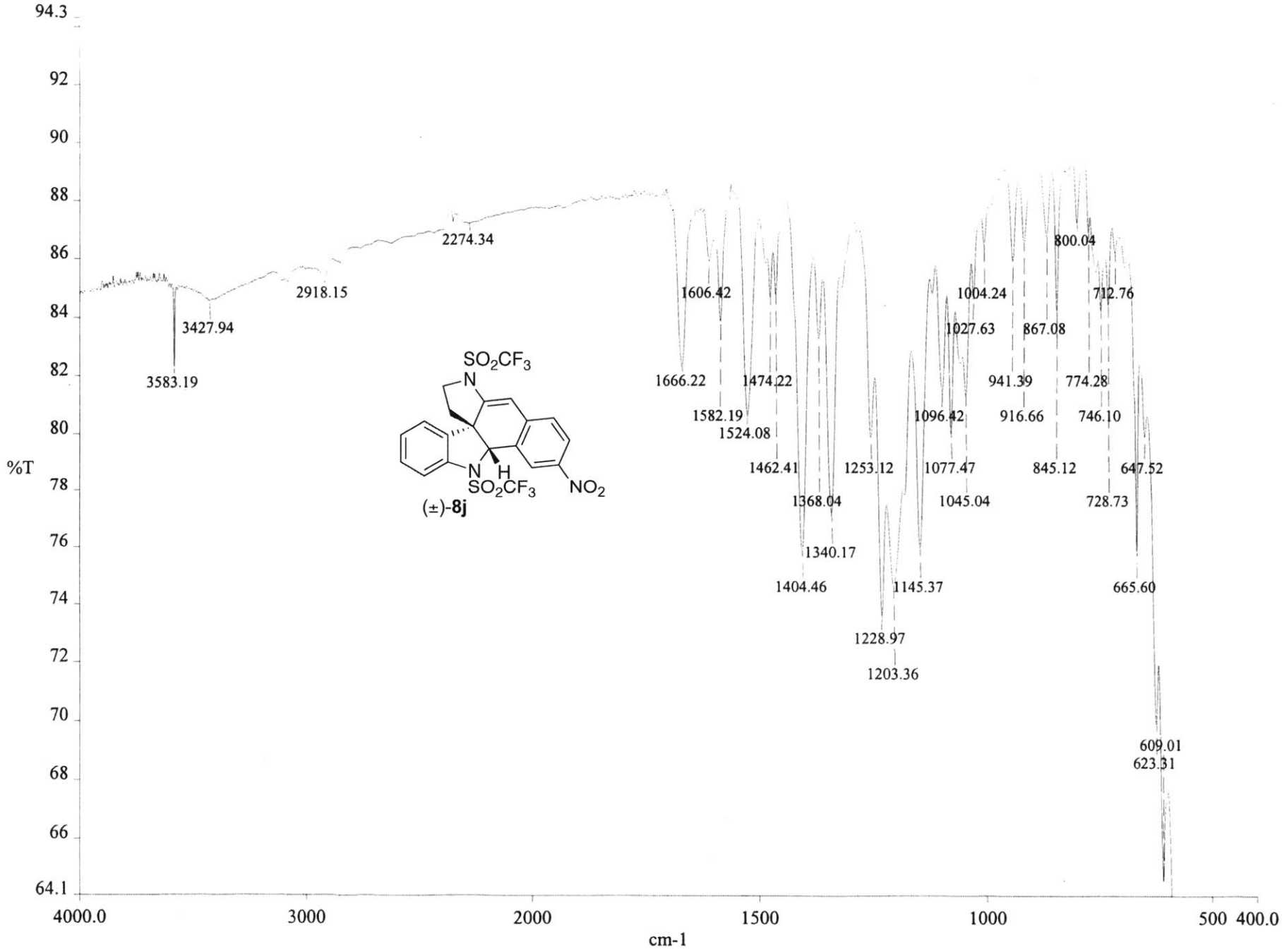
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 0.300 sec
Width 100.0 kHz
16 repetitions
OBSERVE F19, 282.3812074 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144



(±)-**8j**

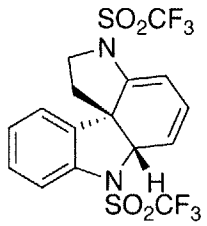



94.3
92
90
88
86
84
82
80
78
76
74
72
70
68
66
64.1
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.19
3427.94
2918.15
2274.34
1666.22
1606.42
1582.19
1524.08
1474.22
1462.41
1404.46
1368.04
1340.17
1253.12
1228.97
1203.36
1145.37
1096.42
1077.47
1045.04
1027.63
1004.24
941.39
916.66
867.08
845.12
800.04
774.28
746.10
728.73
712.76
665.60
647.52
623.31
609.01
SO2CF3
N
N H
SO2CF3
NO2
(±)-8j

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 53.0 C / 326.1 K

Relax. delay 2.000 sec
Pulse 84.1 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417326 MHz
DATA PROCESSING
FT size 262144



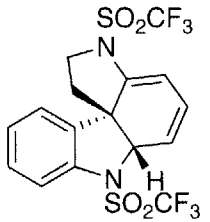
(±)-**8k**

STANDARD CARBON PARAMETERS

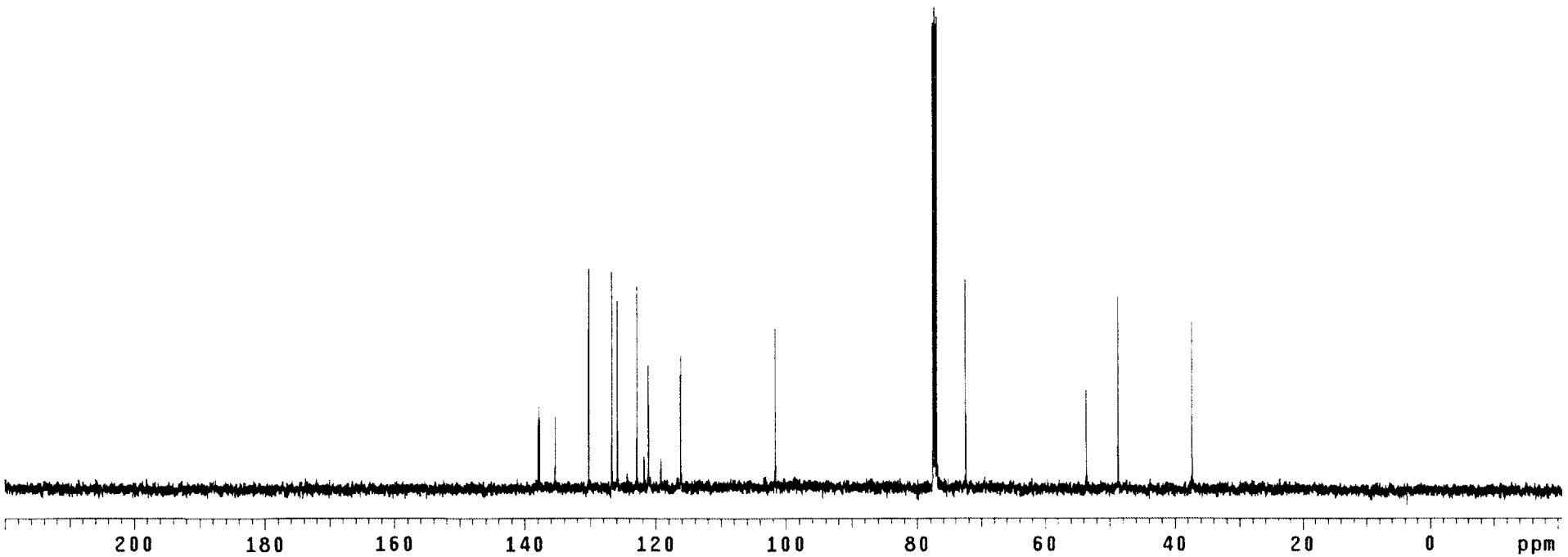
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 53.0 C / 326.1 K

Relax. delay 3.000 sec
Pulse 37.8 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
1331 repetitions
OBSERVE C13, 125.6601151 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072



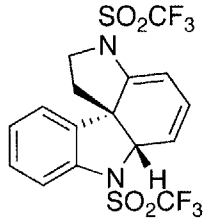
(±)-**8k**



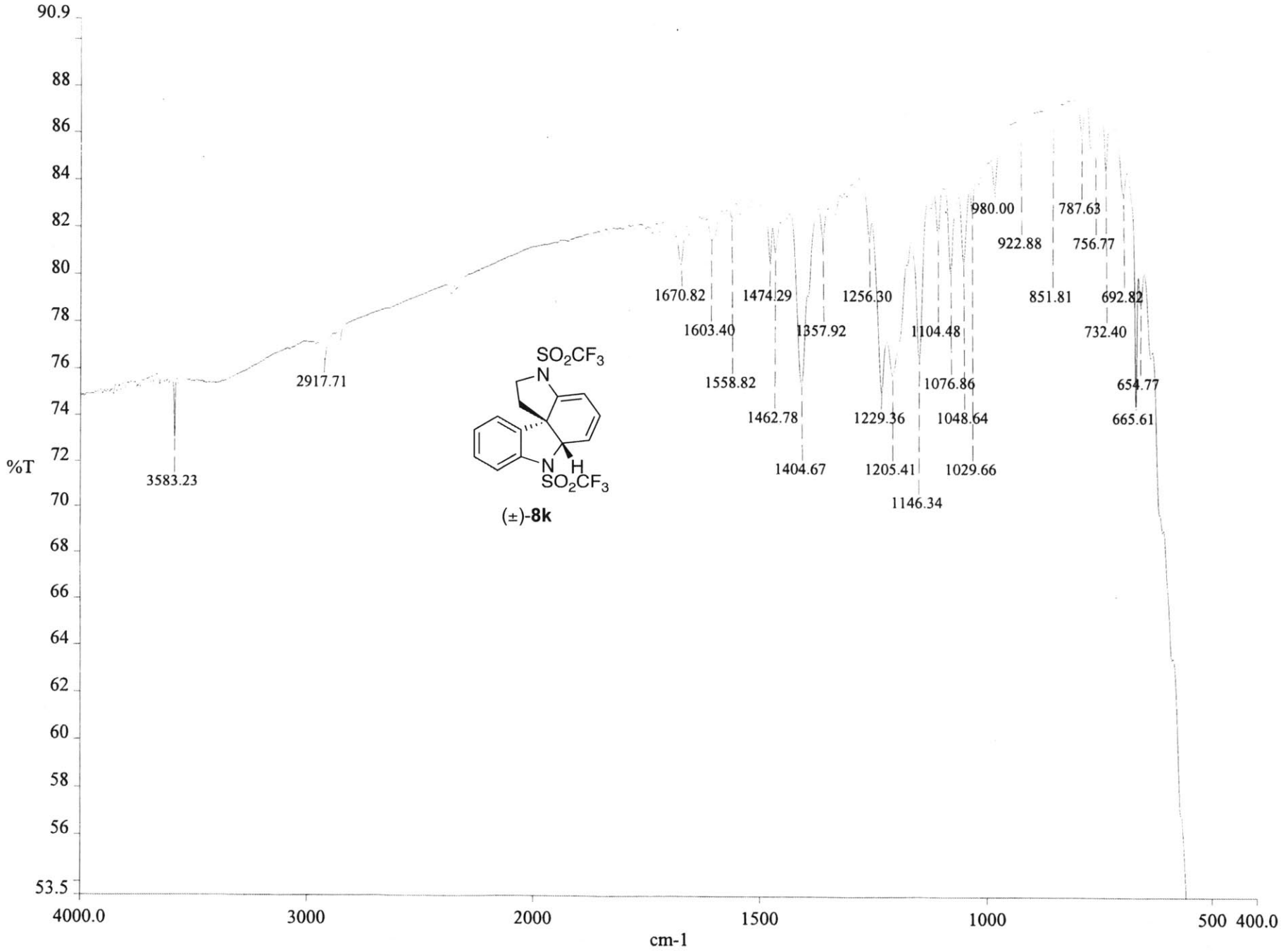
19F SENSITIVITY
0.05% TRIFLUOROTOLUENE

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 53.0 C / 326.1 K

Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 0.232 sec
Width 140.8 kHz
23 repetitions
OBSERVE F19, 470.2272133 MHz
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(±)-**8k**

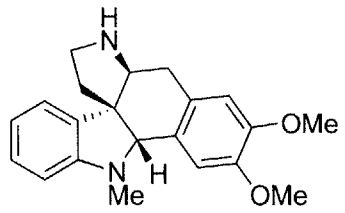

90.9
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
53.5
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.23
2917.71
1670.82
1603.40
1558.82
1474.29
1462.78
1404.67
1357.92
1256.30
1229.36
1205.41
1146.34
1104.48
1076.86
1048.64
1029.66
980.00
922.88
851.81
787.63
756.77
732.40
692.82
665.61
654.77
SO2CF3
N
N H
SO2CF3

(±)-**8k**

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 1.800 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272302 MHz
DATA PROCESSING
FT size 131072



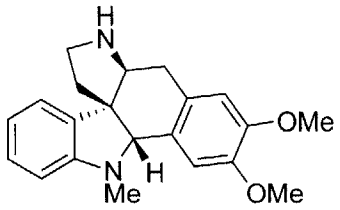
(±)-**9i**

STANDARD CARBON PARAMETERS

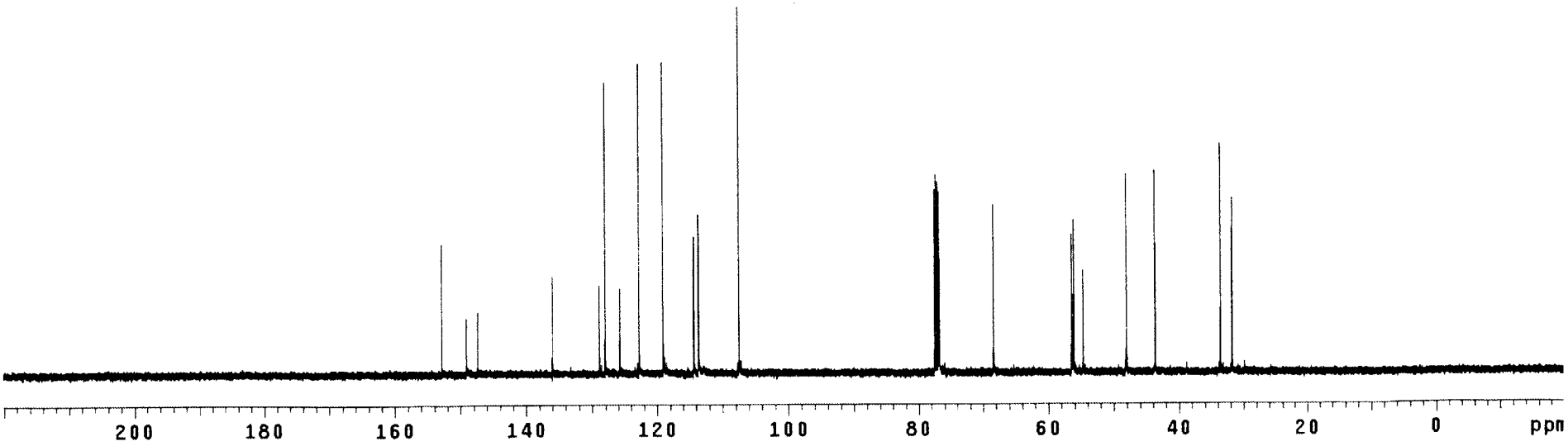
Pulse Sequence: s2pul

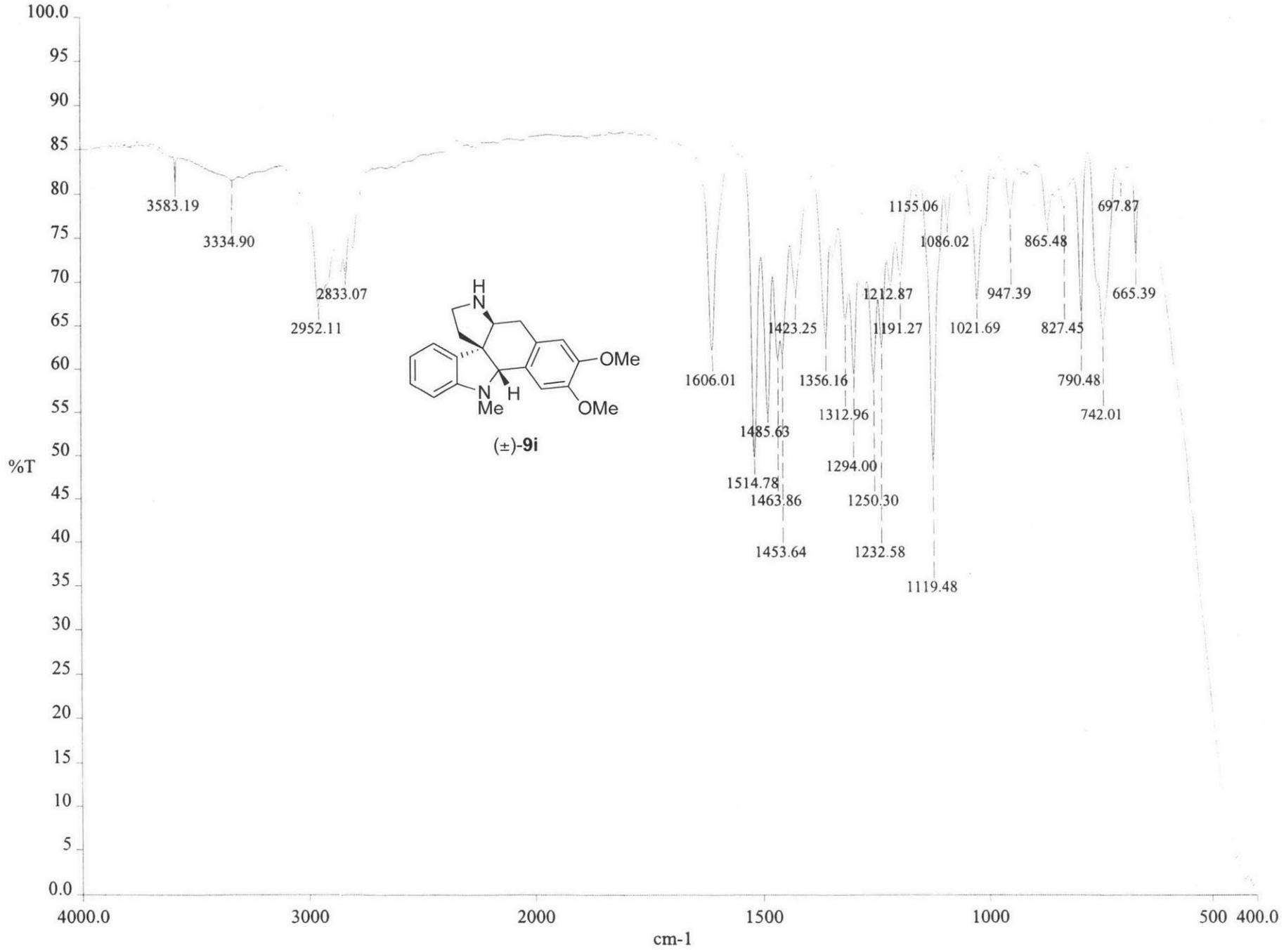
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
516 repetitions
OBSERVE C13, 125.7822176 MHz
DECOUPLE H1, 500.2292208 MHz
Power 46 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



(±)-**9i**

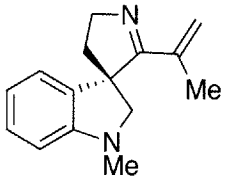



100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.19
3334.90
2952.11
2833.07
1606.01
1514.78
1485.63
1463.86
1453.64
1423.25
1356.16
1312.96
1294.00
1250.30
1232.58
1212.87
1191.27
1155.06
1119.48
1086.02
1021.69
947.39
865.48
827.45
790.48
742.01
697.87
665.39
OMe
OMe
N
H
Me
N
H
(±)-9i

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 72.4 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
17 repetitions
OBSERVE H1, 500.4252875 MHz
DATA PROCESSING
FT size 262144

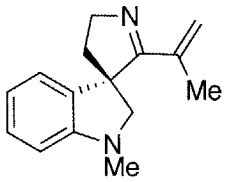


(±)-**10a**

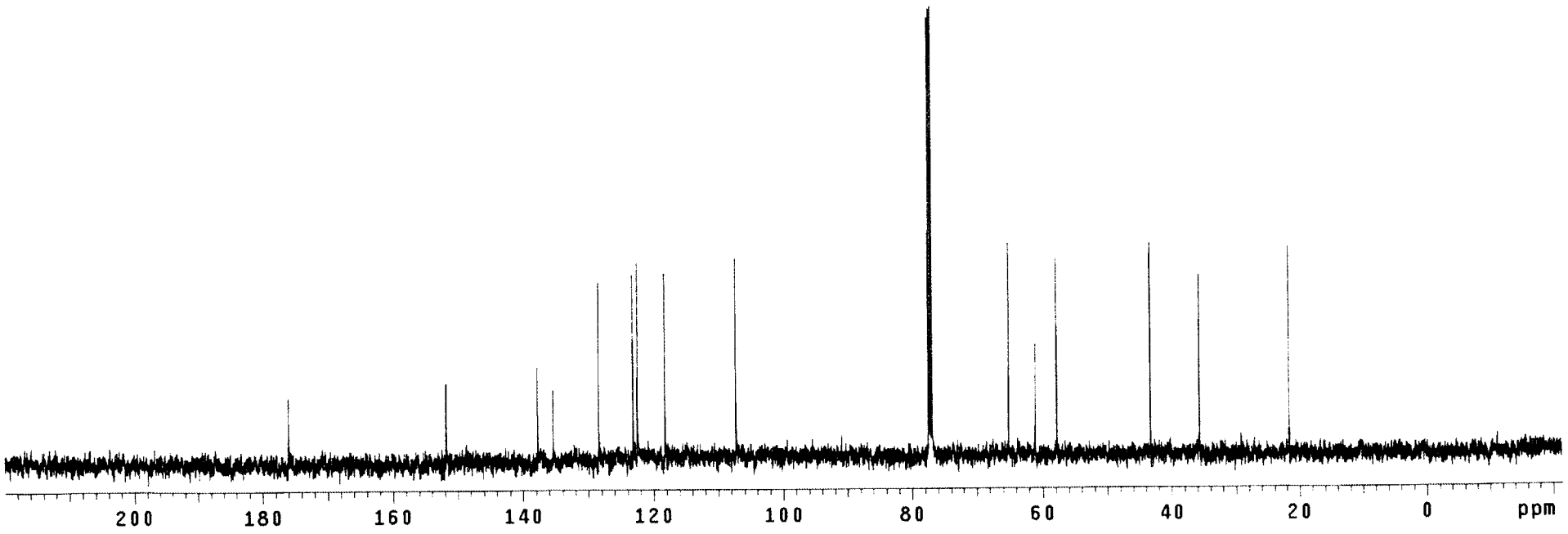
STANDARD CARBON PARAMETERS

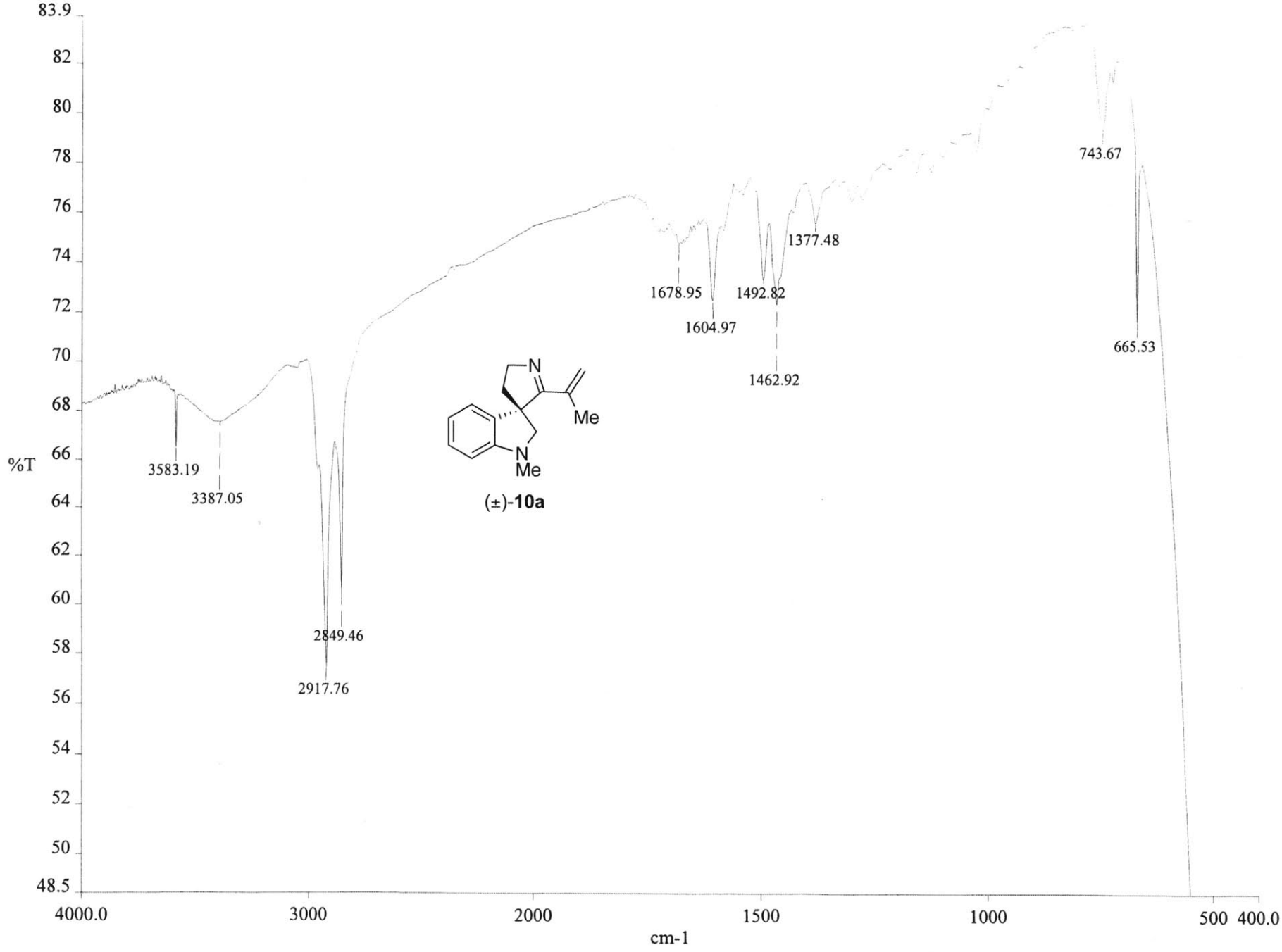
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 37.8 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
226 repetitions
OBSERVE C13, 125.6601333 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072



(±)-**10a**




83.9
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
52
50
48.5
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.19
3387.05
2917.76
2849.46
1678.95
1604.97
1492.82
1462.92
1377.48
743.67
665.53
N
Me
N
Me

(±)-**10a**

Appendix C

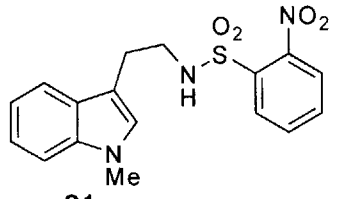
Spectra for Chapter III

STANDARD PROTON PARAMETERS

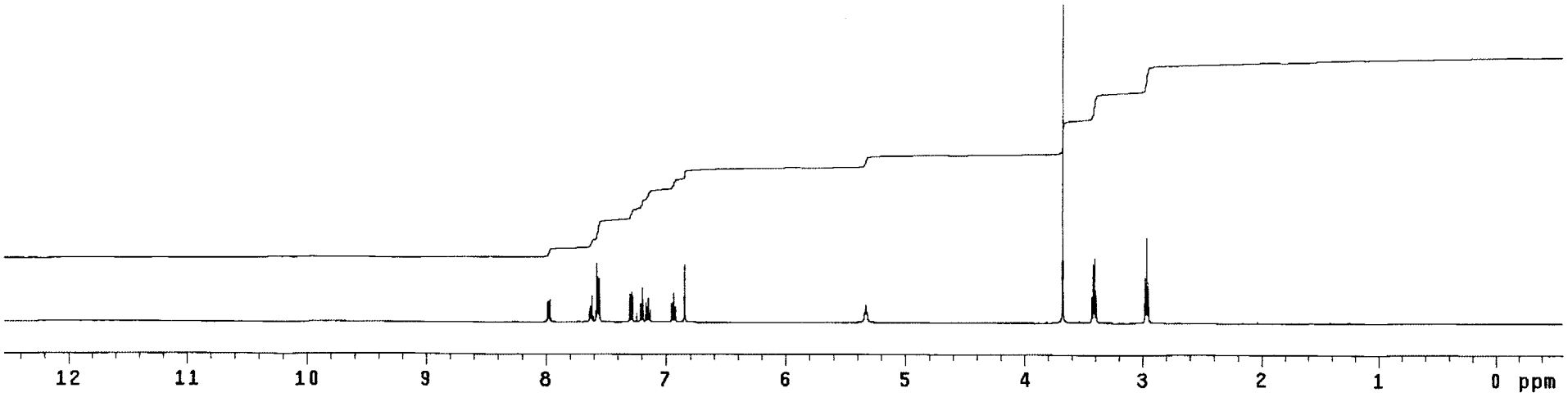
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Pulse 76.1 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272311 MHz
DATA PROCESSING
FT size 131072



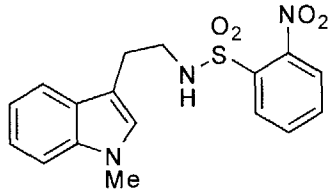
S1



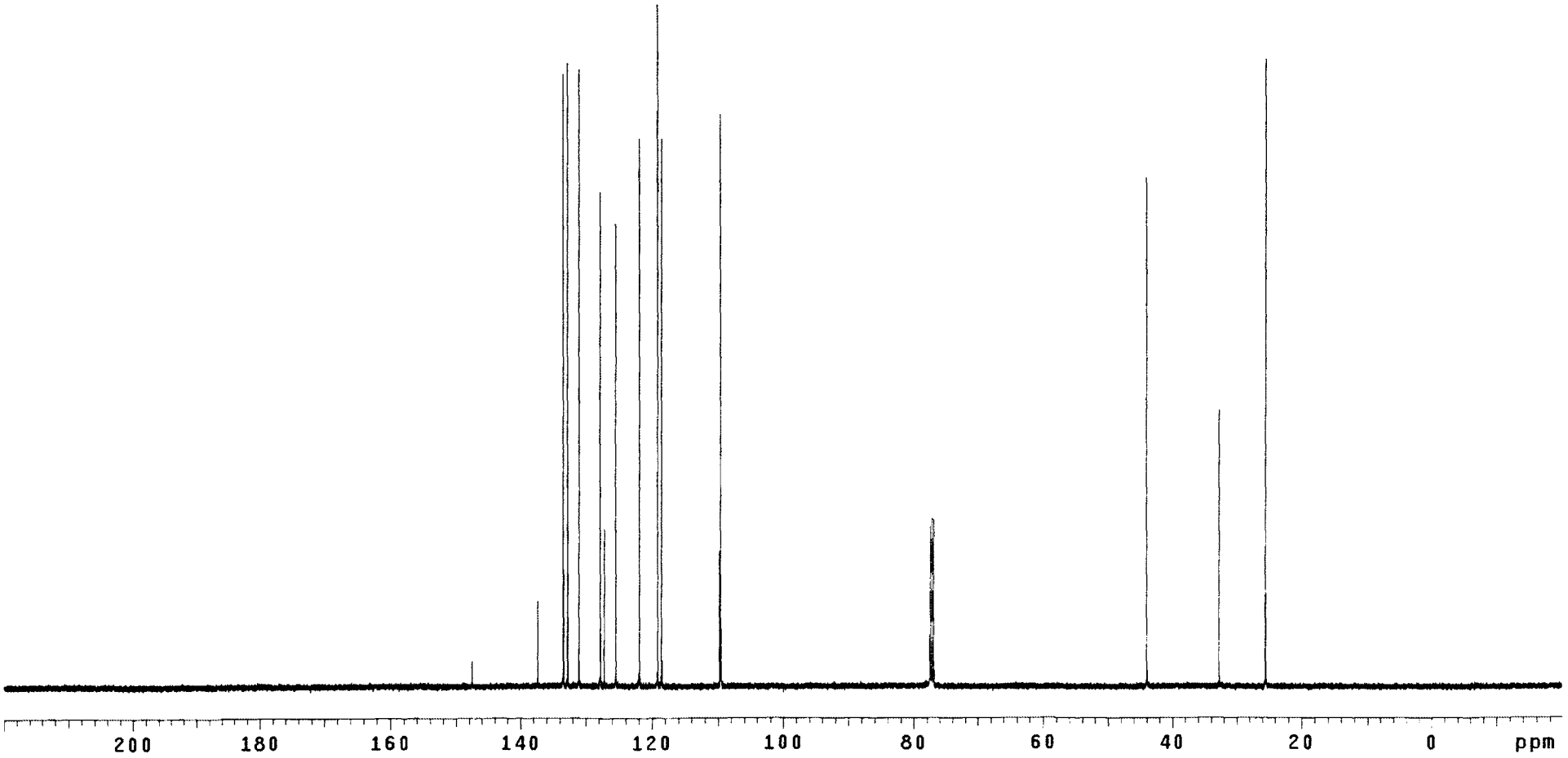
STANDARD CARBON PARAMETERS

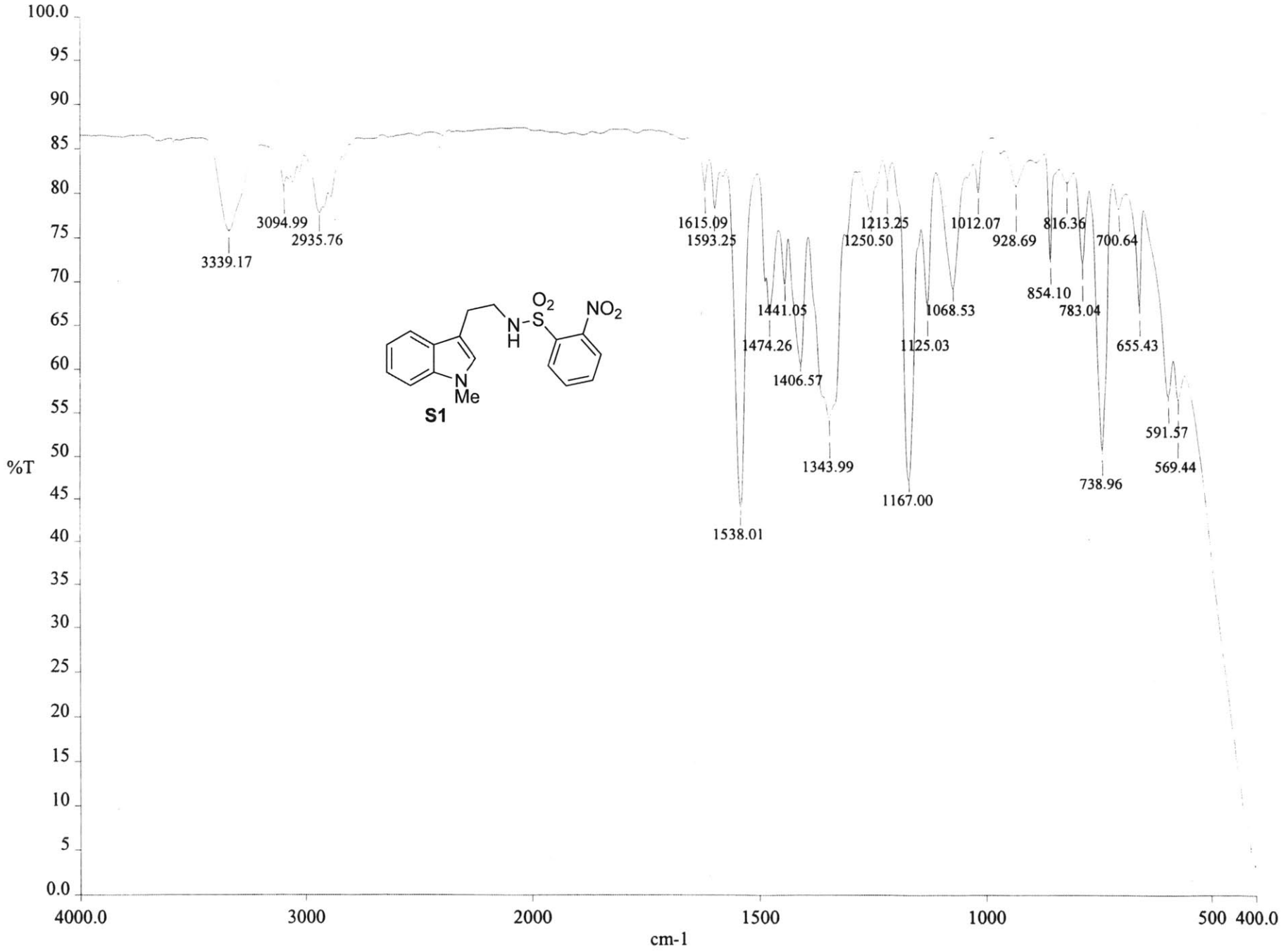
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
65536 repetitions
OBSERVE C13, 125.7822130 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



S1

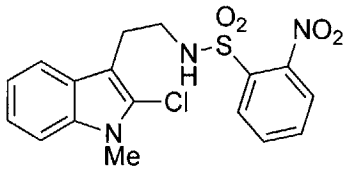



100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3339.17
3094.99
2935.76
1615.09
1593.25
1538.01
1474.26
1441.05
1406.57
1343.99
1250.50
1213.25
1167.00
1125.03
1068.53
1012.07
928.69
854.10
816.36
783.04
738.96
700.64
655.43
591.57
569.44
O2
NO2
N
S
H
N
Me
S1

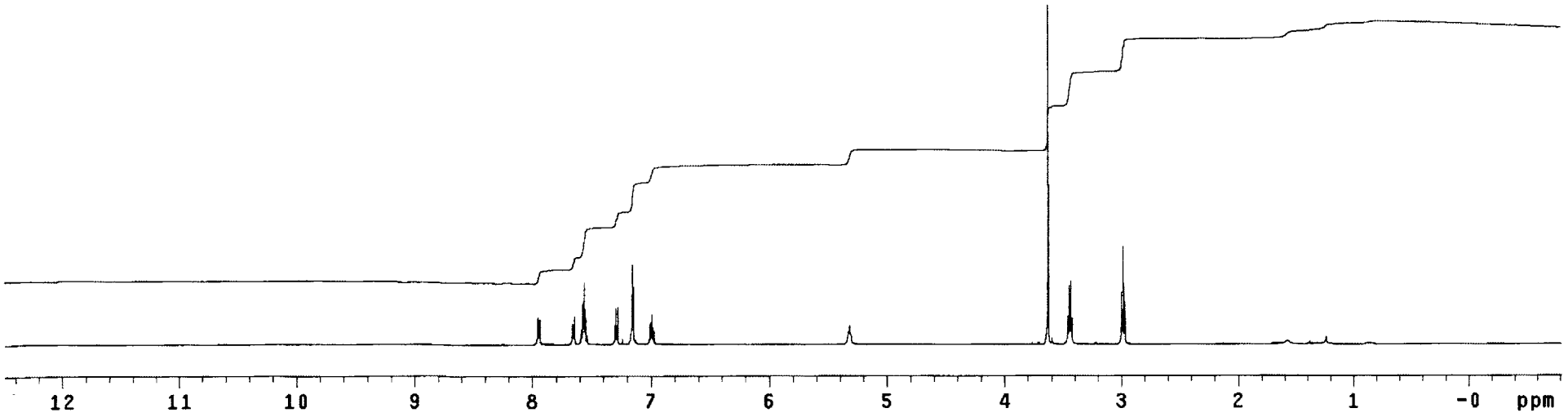
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 78.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
32 repetitions
OBSERVE H1, 500.4252887 MHz
DATA PROCESSING
FT size 262144



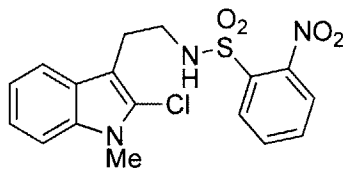
54



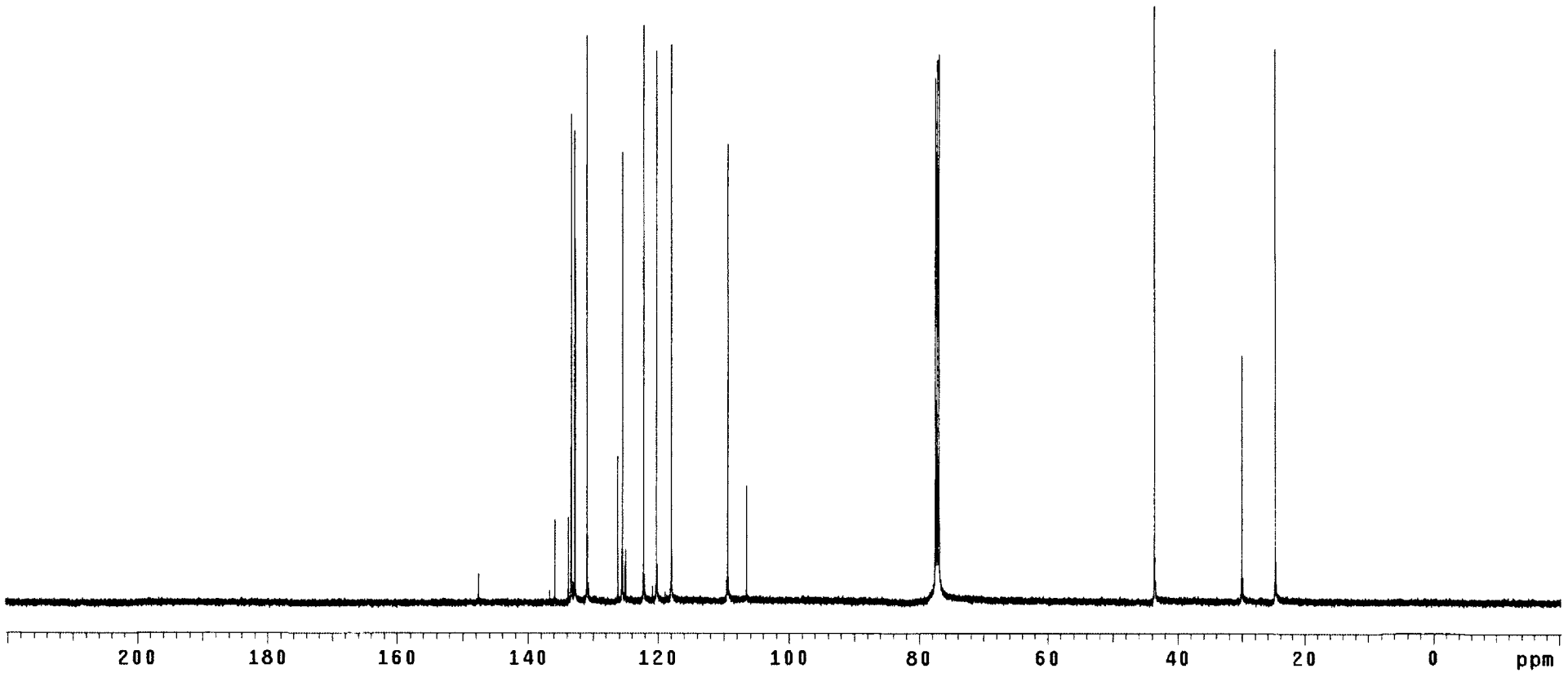
STANDARD CARBON PARAMETERS

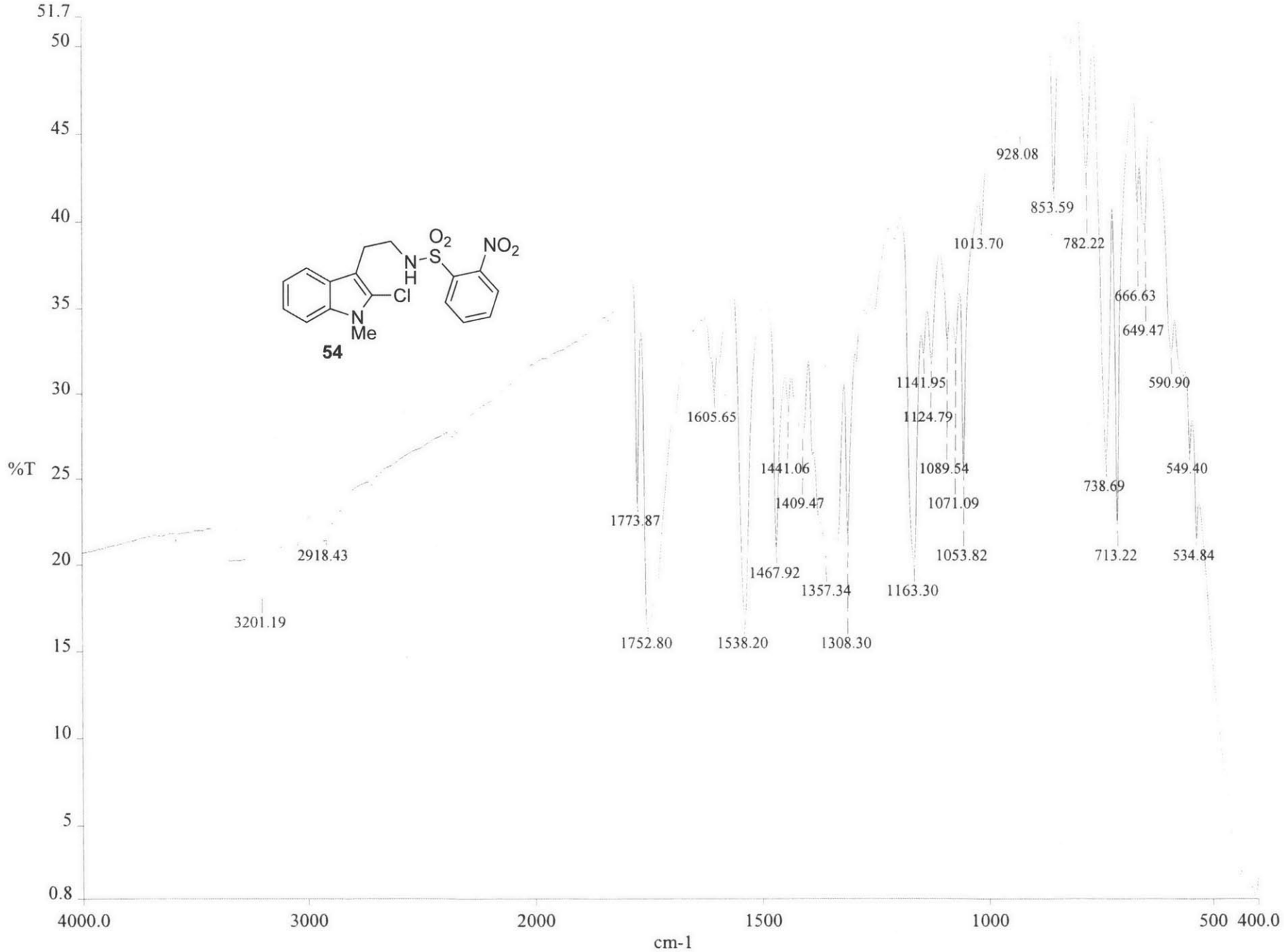
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
20631 repetitions
OBSERVE C13, 125.7822090 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



54

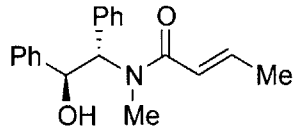



51.7
50
45
40
35
30
25
20
15
10
5
0.8
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
O2
NO2
N
S
H
Cl
N
Me
54
928.08
853.59
1013.70
782.22
666.63
649.47
590.90
1141.95
1605.65
1124.79
1441.06
1089.54
549.40
738.69
1409.47
1071.09
1773.87
2918.43
1053.82
713.22
534.84
1467.92
1357.34
1163.30
3201.19
1752.80
1538.20
1308.30

STANDARD PROTON PARAMETERS

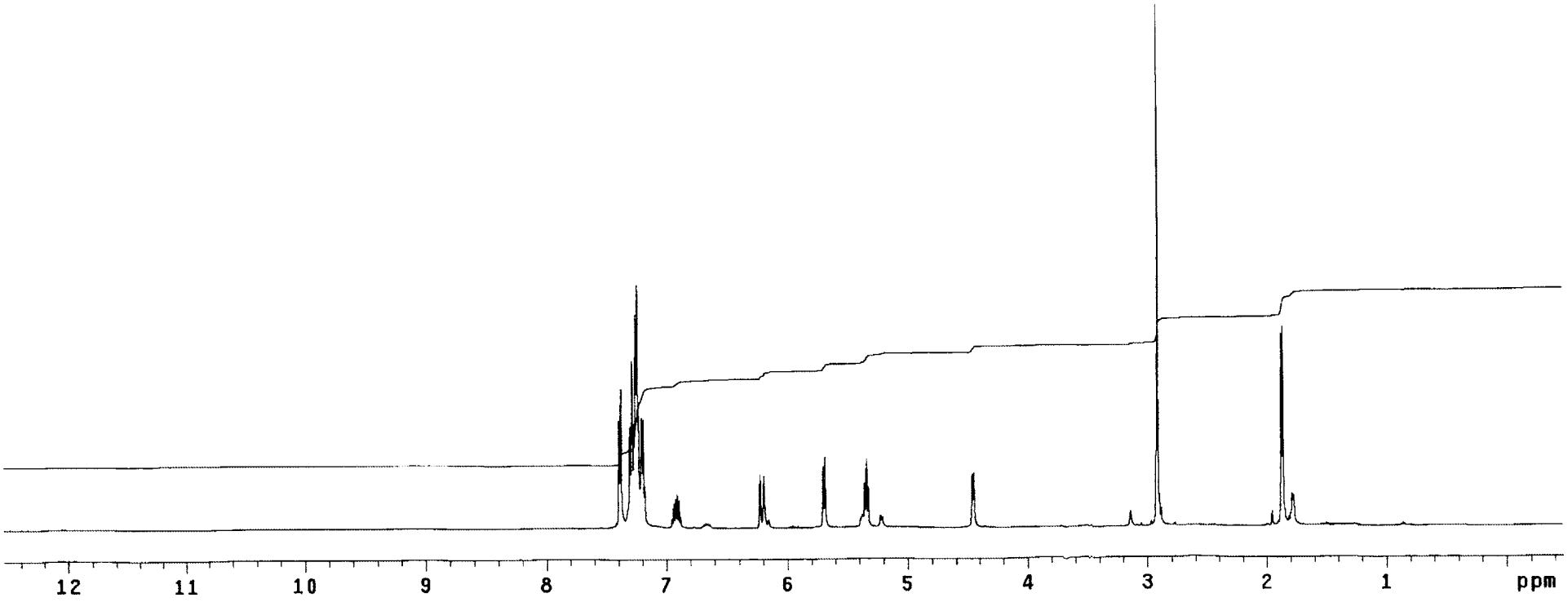
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Pulse 76.1 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272196 MHz
DATA PROCESSING
FT size 131072



(+)-**58**

6.0:1.0 mixture of atropisomers

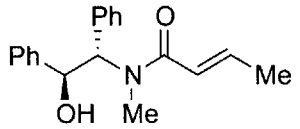


STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

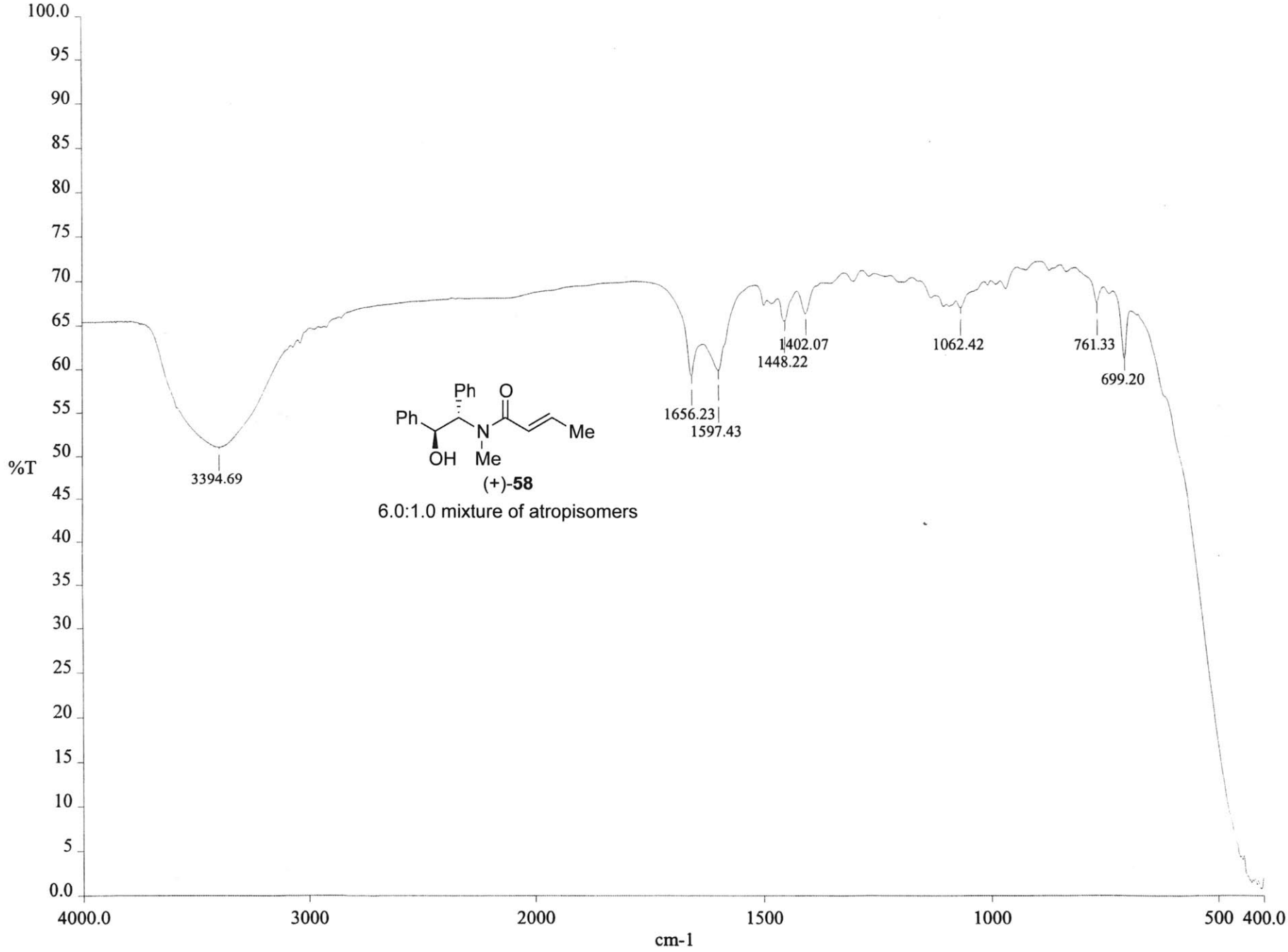
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
5151 repetitions
OBSERVE C13, 125.7822147 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



(+)-**58**

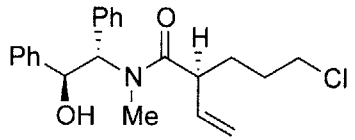
6.0:1.0 mixture of atropisomers


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3394.69
1656.23
1597.43
1448.22
1402.07
1062.42
761.33
699.20
Ph
O
Ph
N
Me
OH
Me
(+)-58
6.0:1.0 mixture of atropisomers

STANDARD PROTON PARAMETERS

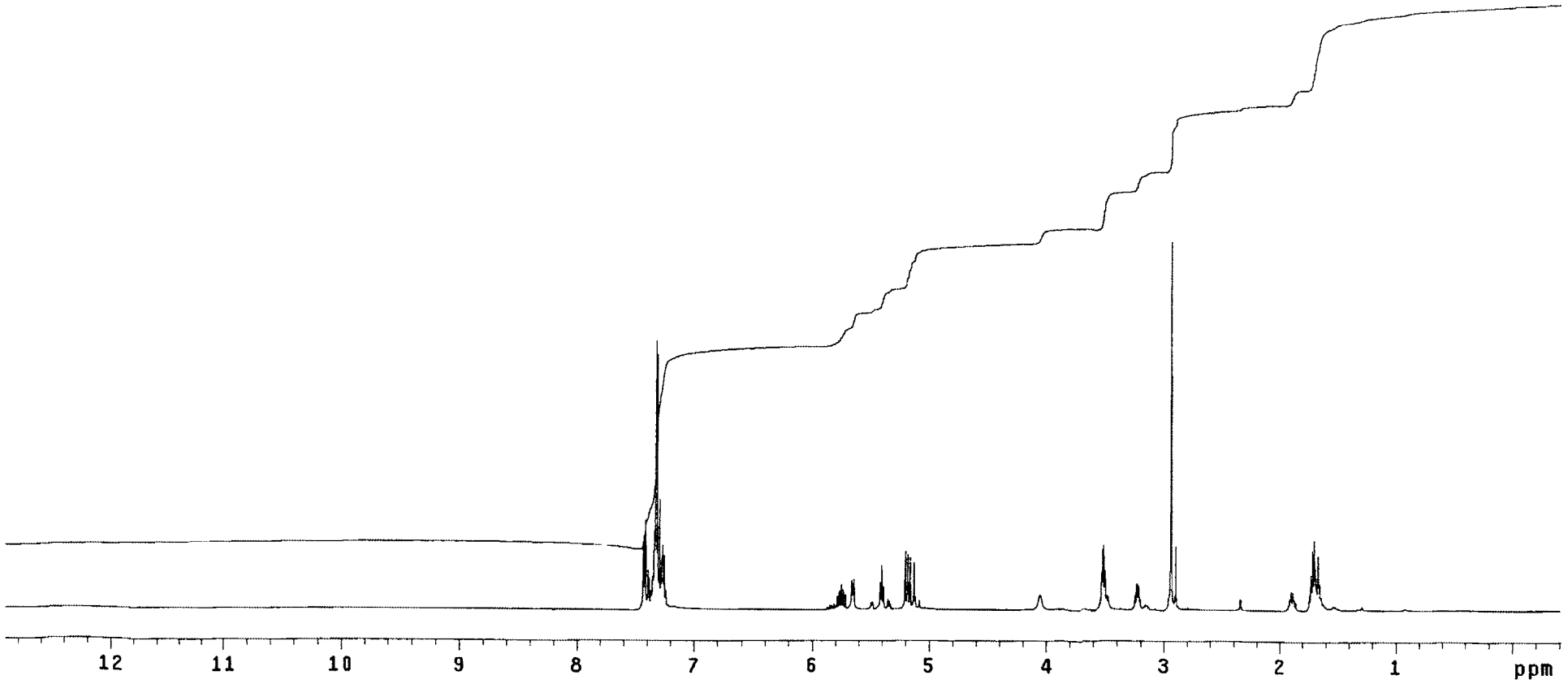
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 78.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252632 MHz
DATA PROCESSING
FT size 262144



(+)-**59**

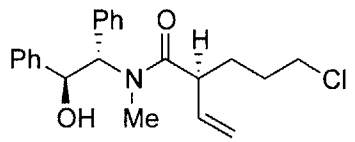
4.6:1.0 mixture of atropisomers



STANDARD CARBON PARAMETERS

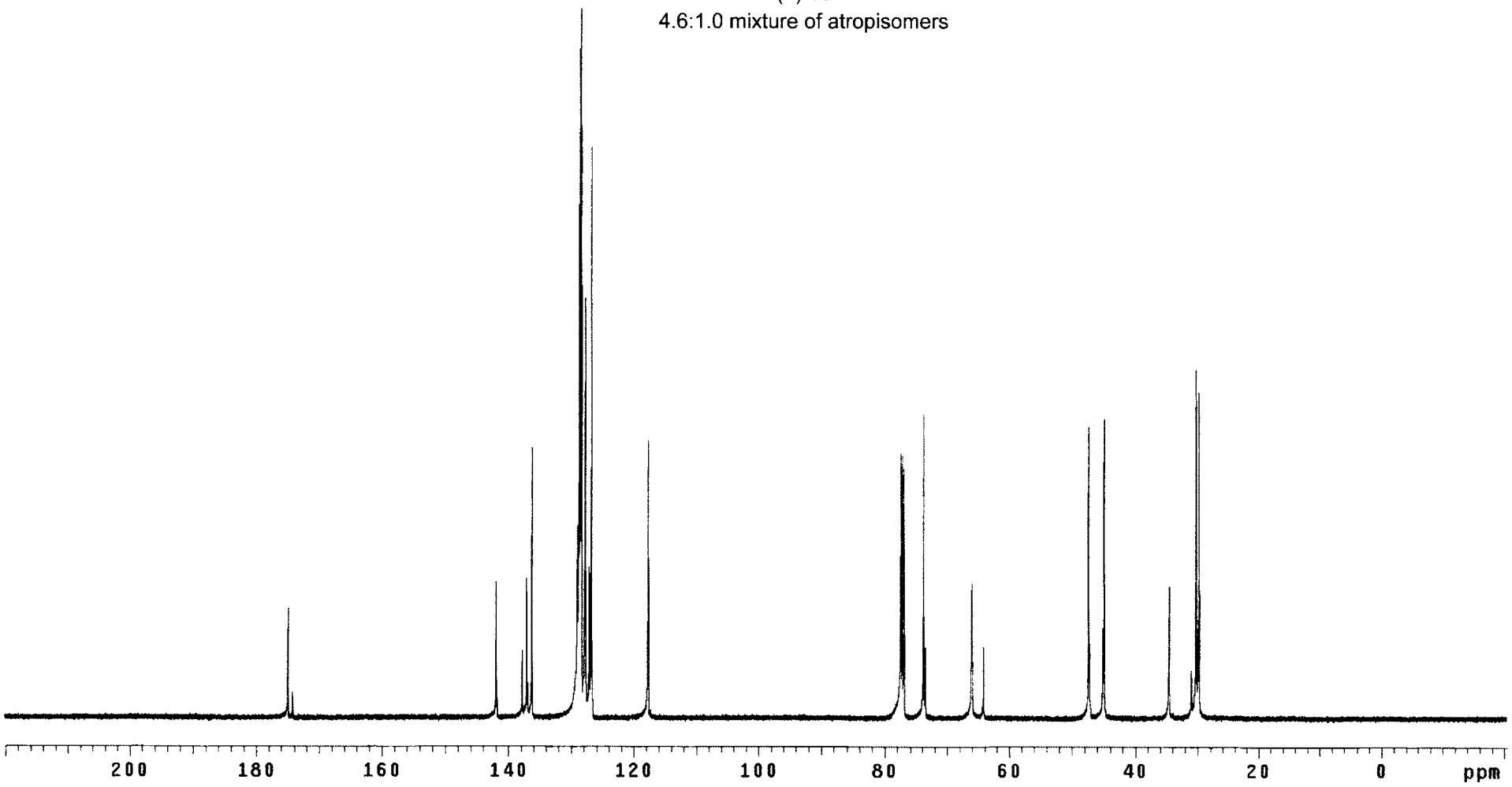
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

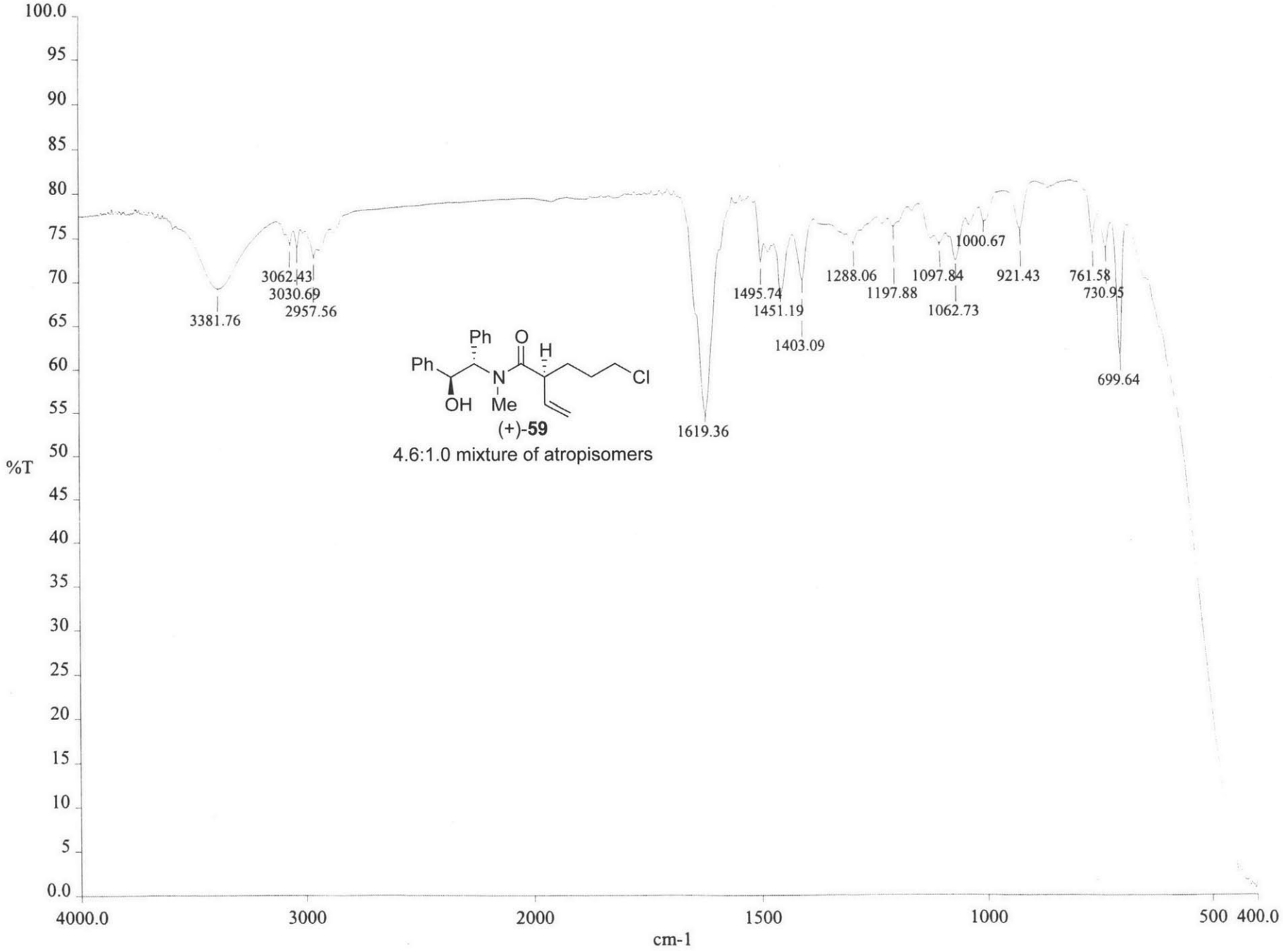
Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
23066 repetitions
OBSERVE C13, 125.7822009 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



(+)-**59**

4.6:1.0 mixture of atropisomers



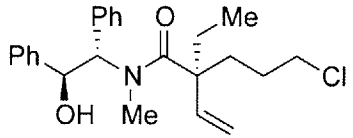

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3381.76
3062.43
3030.69
2957.56
1619.36
1495.74
1451.19
1403.09
1288.06
1197.88
1097.84
1062.73
1000.67
921.43
761.58
730.95
699.64
Ph
O
H
Ph
N
Cl
OH
Me
(+)-59
4.6:1.0 mixture of atropisomers

STANDARD PROTON PARAMETERS

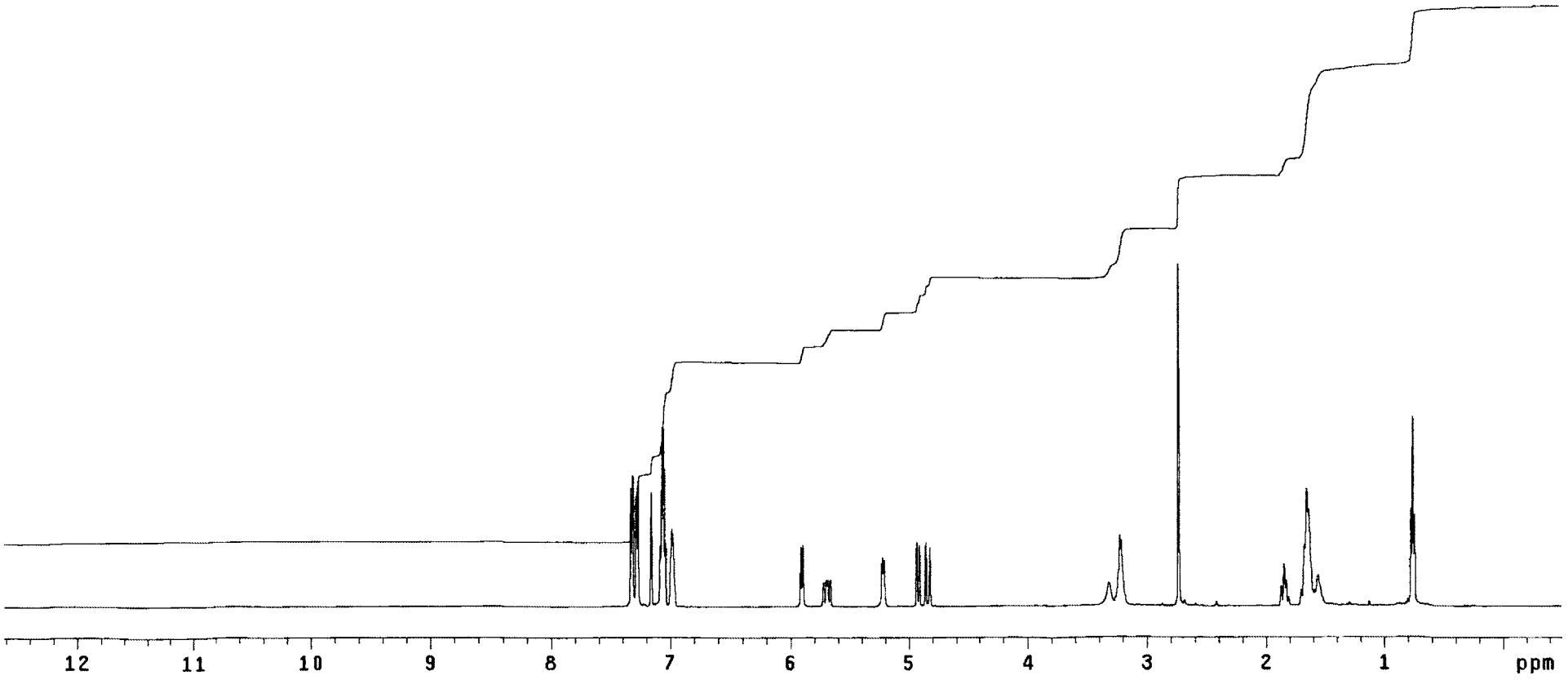
Pulse Sequence: s2pul

Solvent: Benzene
Temp. 73.0 C / 346.1 K

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417485 MHz
DATA PROCESSING
FT size 262144



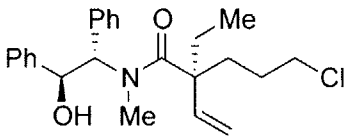
(+)-**55**



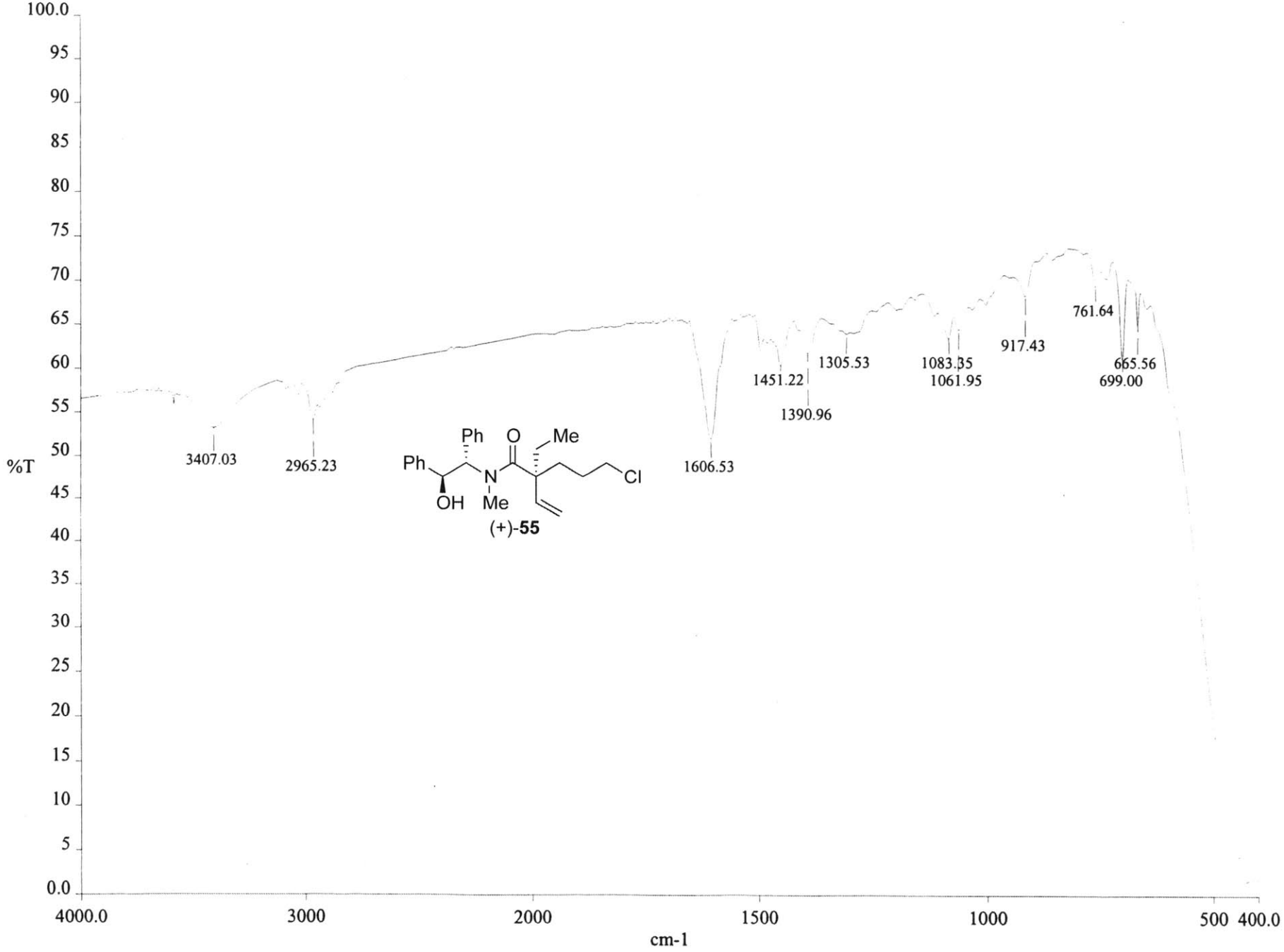
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: Benzene
Temp. 73.0 C / 346.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
341 repetitions
OBSERVE C13, 125.6600618 MHz
DECOUPLE H1, 499.7442644 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



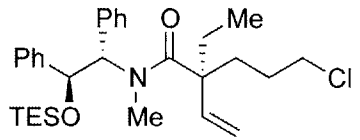
(+)-**55**


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
3407.03
2965.23
1606.53
1451.22
1390.96
1305.53
1083.35
1061.95
917.43
761.64
699.00
665.56
Ph
O
Me
Ph
N
Cl
OH
Me
(+)-55
4000.0
3000
2000
1500
1000
500
400.0
cm-1

STANDARD PROTON PARAMETERS

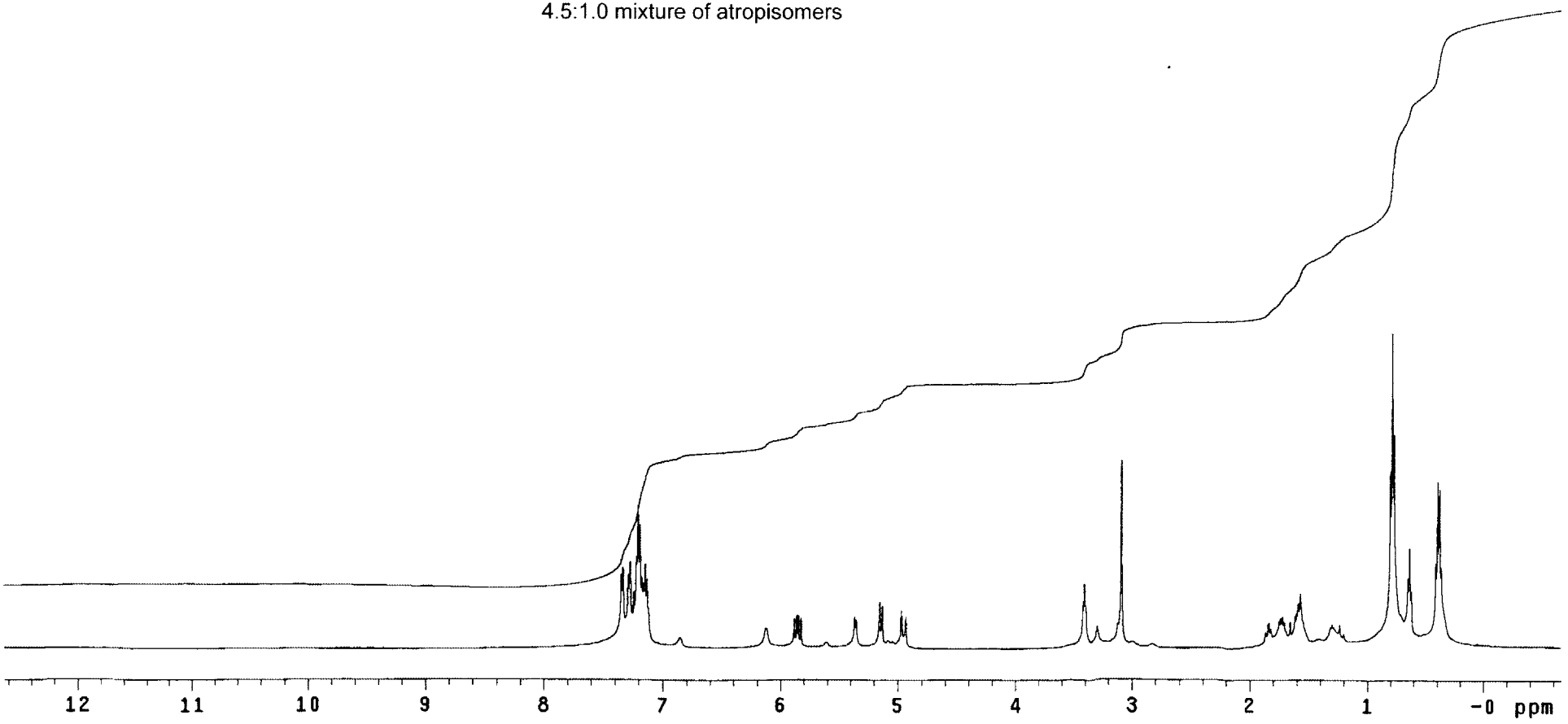
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

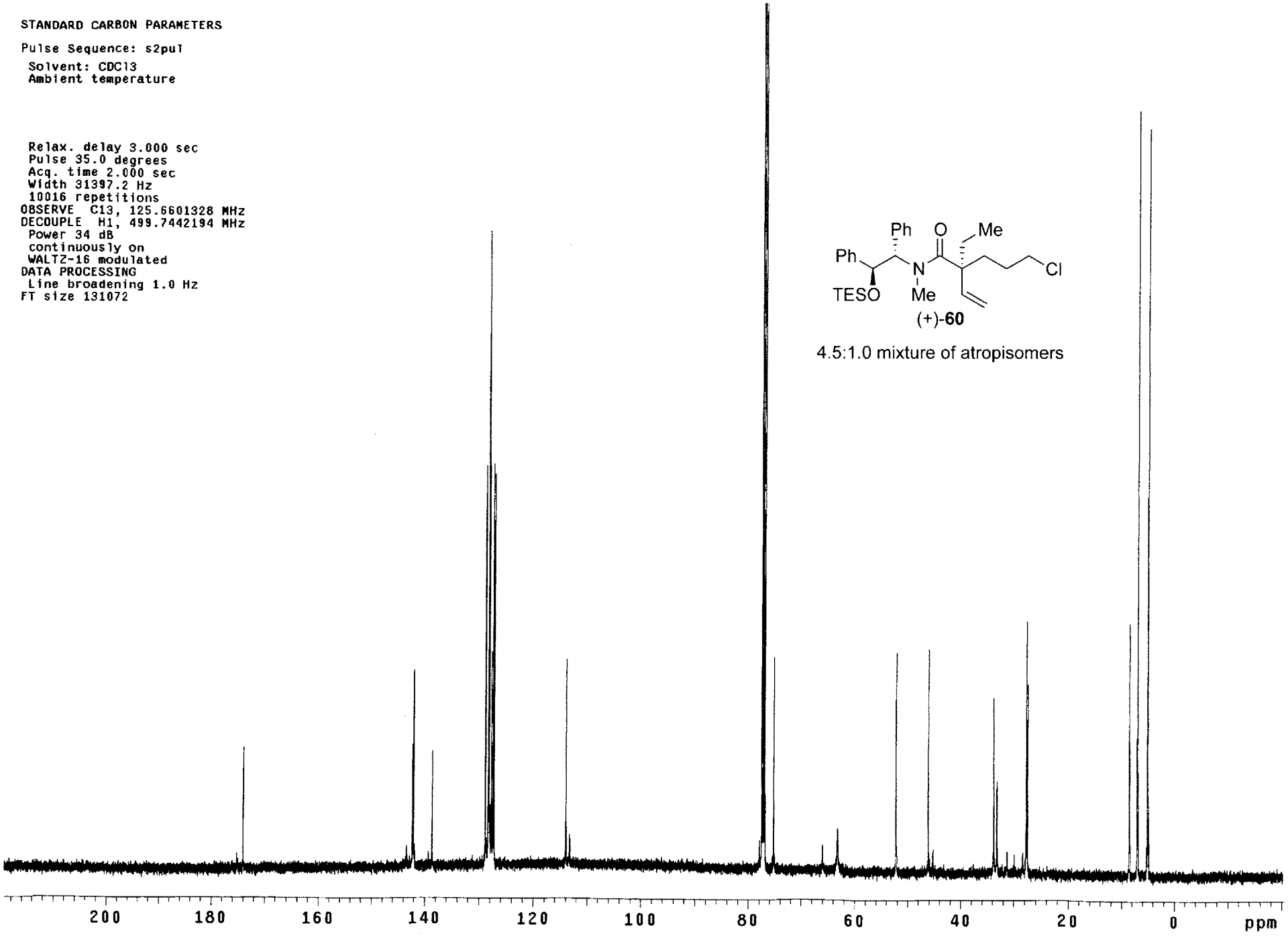
Relax. delay 0.100 sec
Pulse 78.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252874 MHz
DATA PROCESSING
FT size 262144

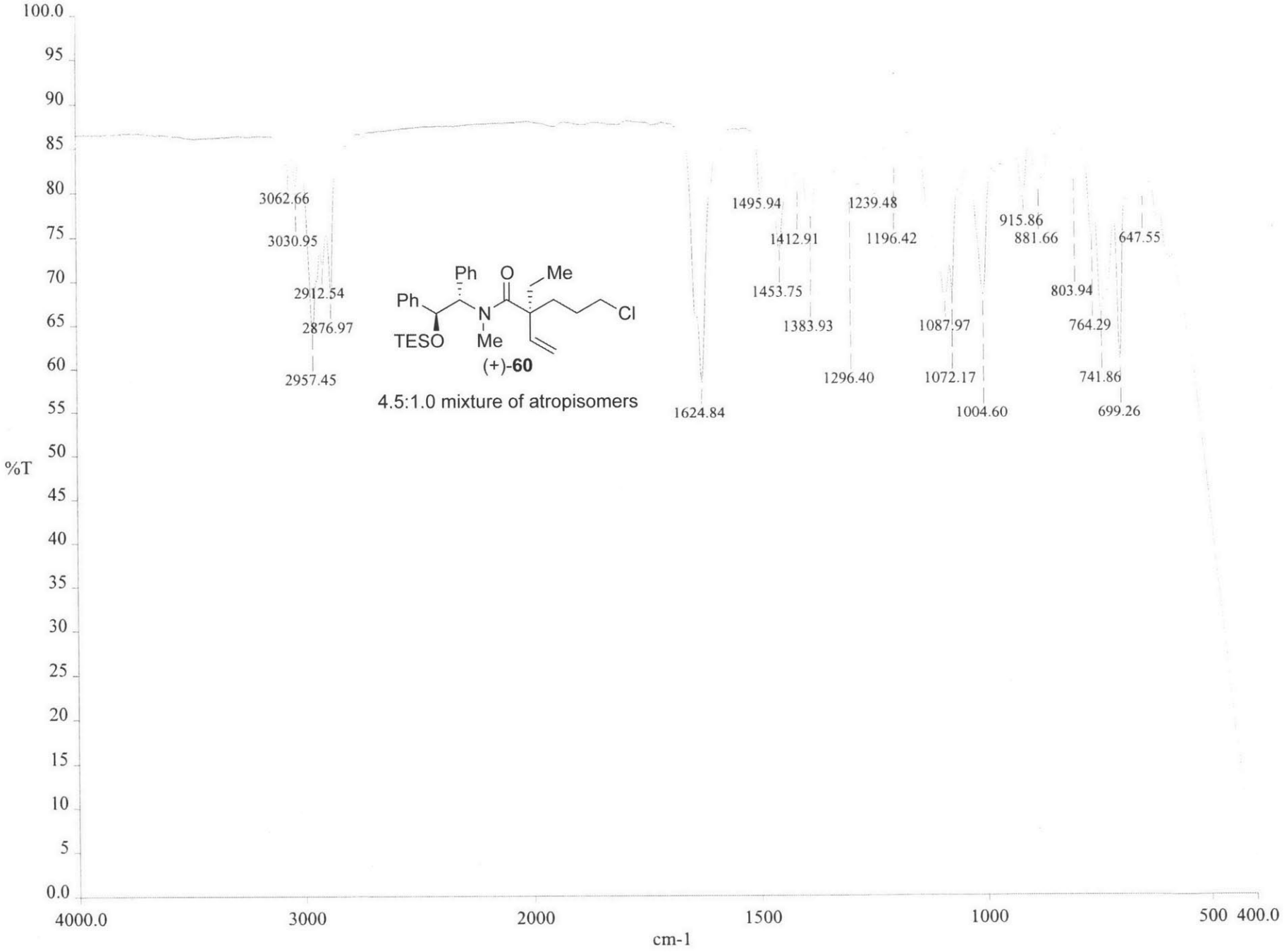


(+)-**60**

4.5:1.0 mixture of atropisomers



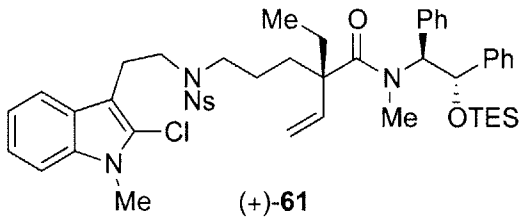

STANDARD CARBON PARAMETERS
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
10016 repetitions
OBSERVE C13, 125.6601328 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Ph
O
Me
Ph
N
Cl
TESO
Me
(+)-60
4.5:1.0 mixture of atropisomers
200
180
160
140
120
100
80
60
40
20
0
ppm


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3062.66
3030.95
2912.54
2876.97
2957.45
1624.84
1495.94
1412.91
1453.75
1383.93
1239.48
1196.42
1296.40
1087.97
1072.17
1004.60
915.86
881.66
803.94
764.29
741.86
699.26
647.55
Ph
O
Me
Ph
N
Cl
TESO
Me
(+)-60
4.5:1.0 mixture of atropisomers

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 78.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252879 MHz
DATA PROCESSING
FT size 262144



(+)-**61**

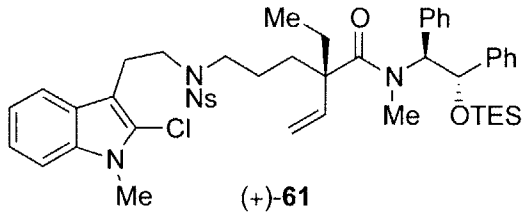
4.4:1.0 mixture of atropisomers

STANDARD CARBON PARAMETERS

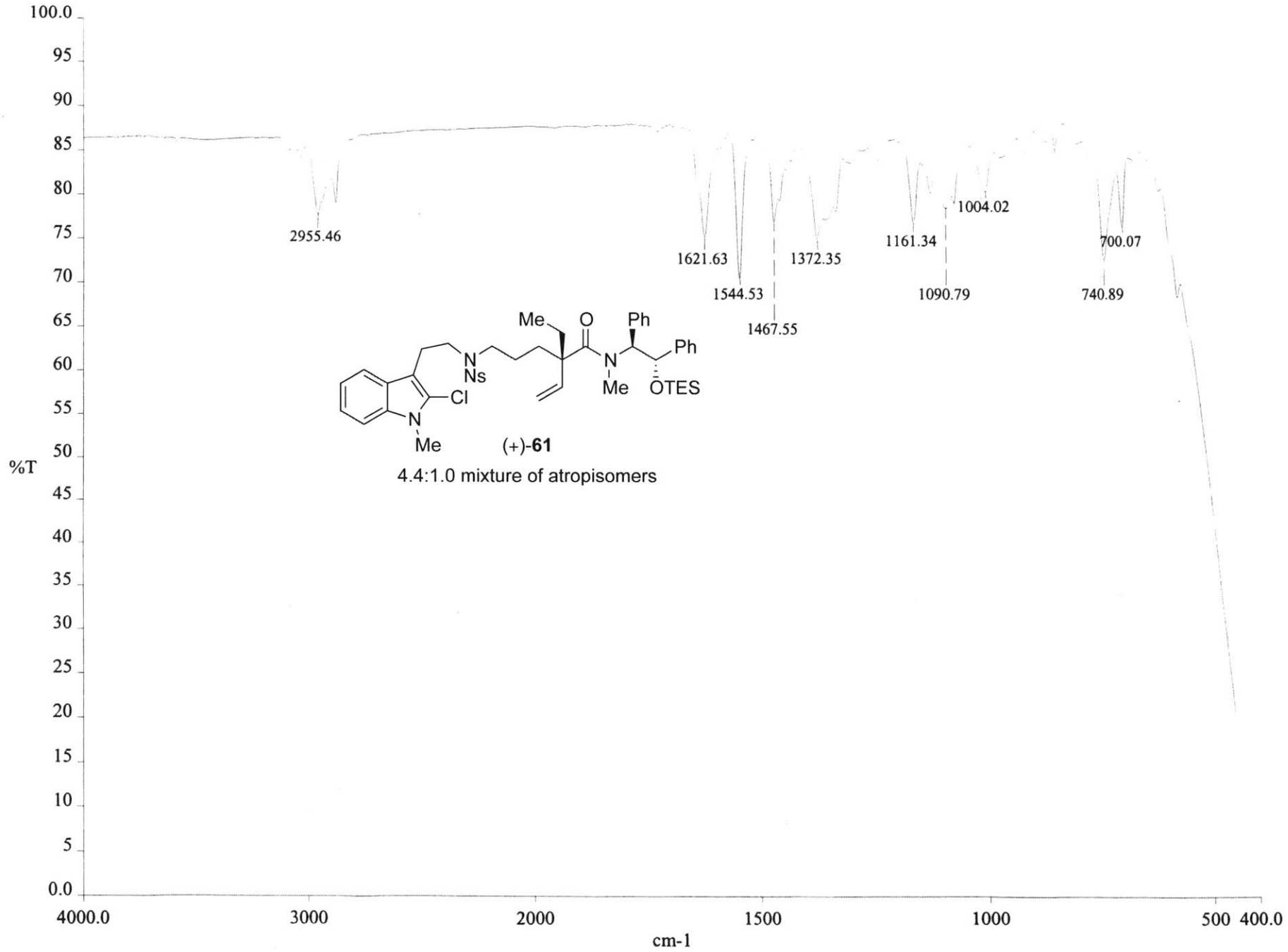
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
5312 repetitions
OBSERVE C13, 125.6601362 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(+)-**61**



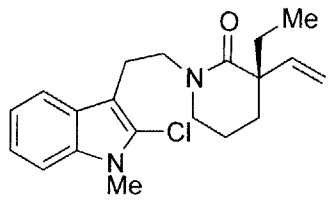
(+)-**61**

4.4:1.0 mixture of atropisomers

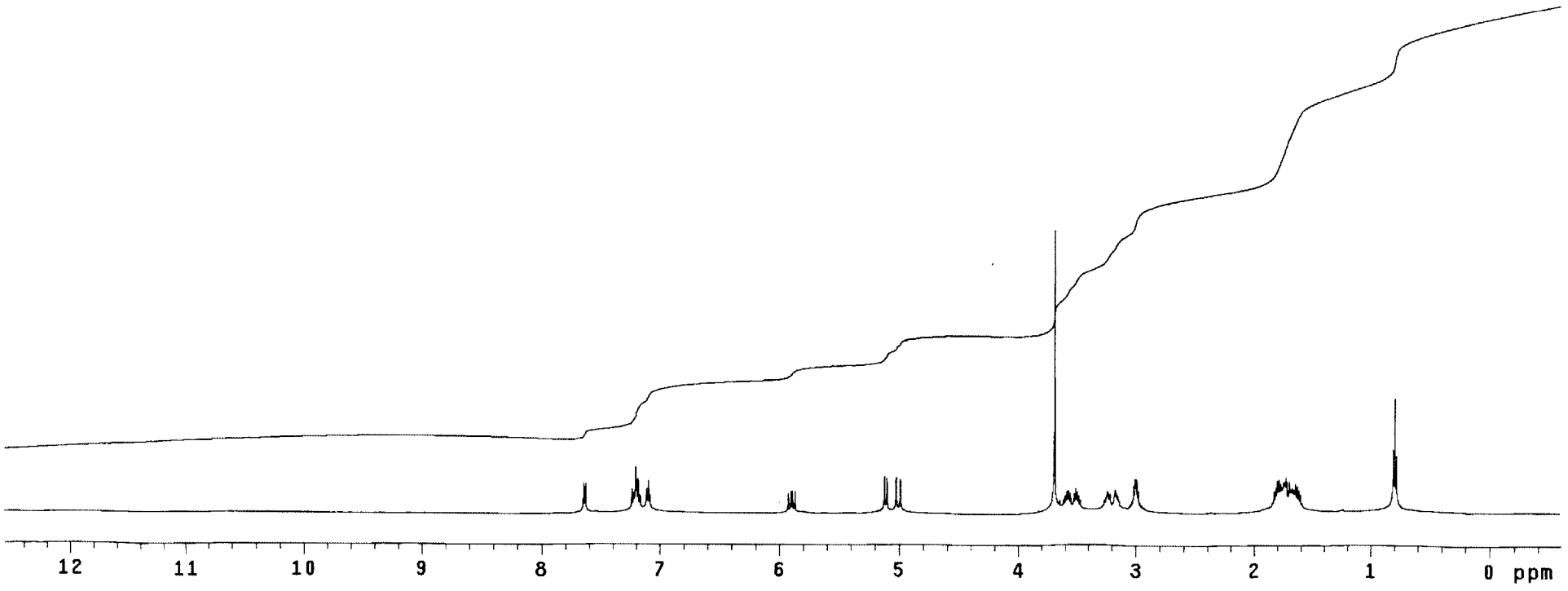
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 75.4 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4295113 MHz
DATA PROCESSING
FT size 262144



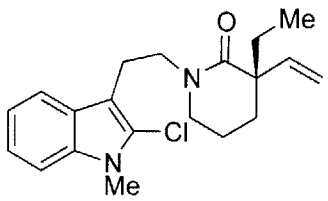
(–)-**53**



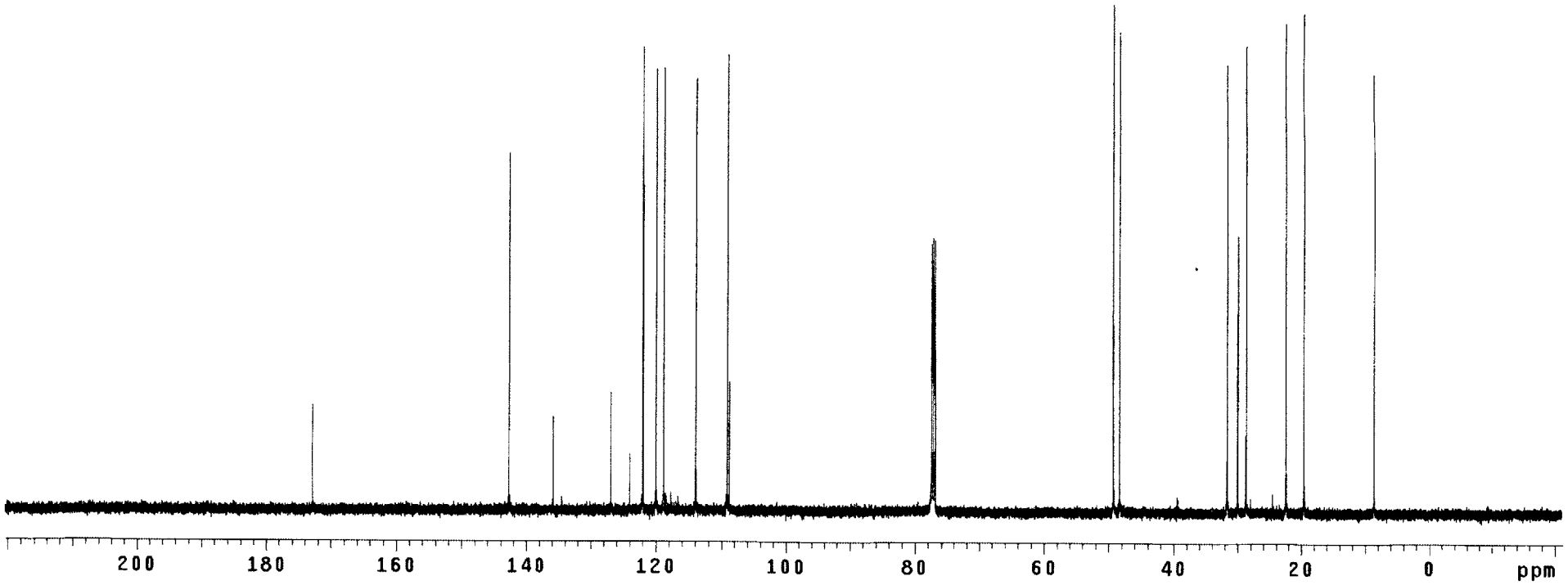
STANDARD CARBON PARAMETERS

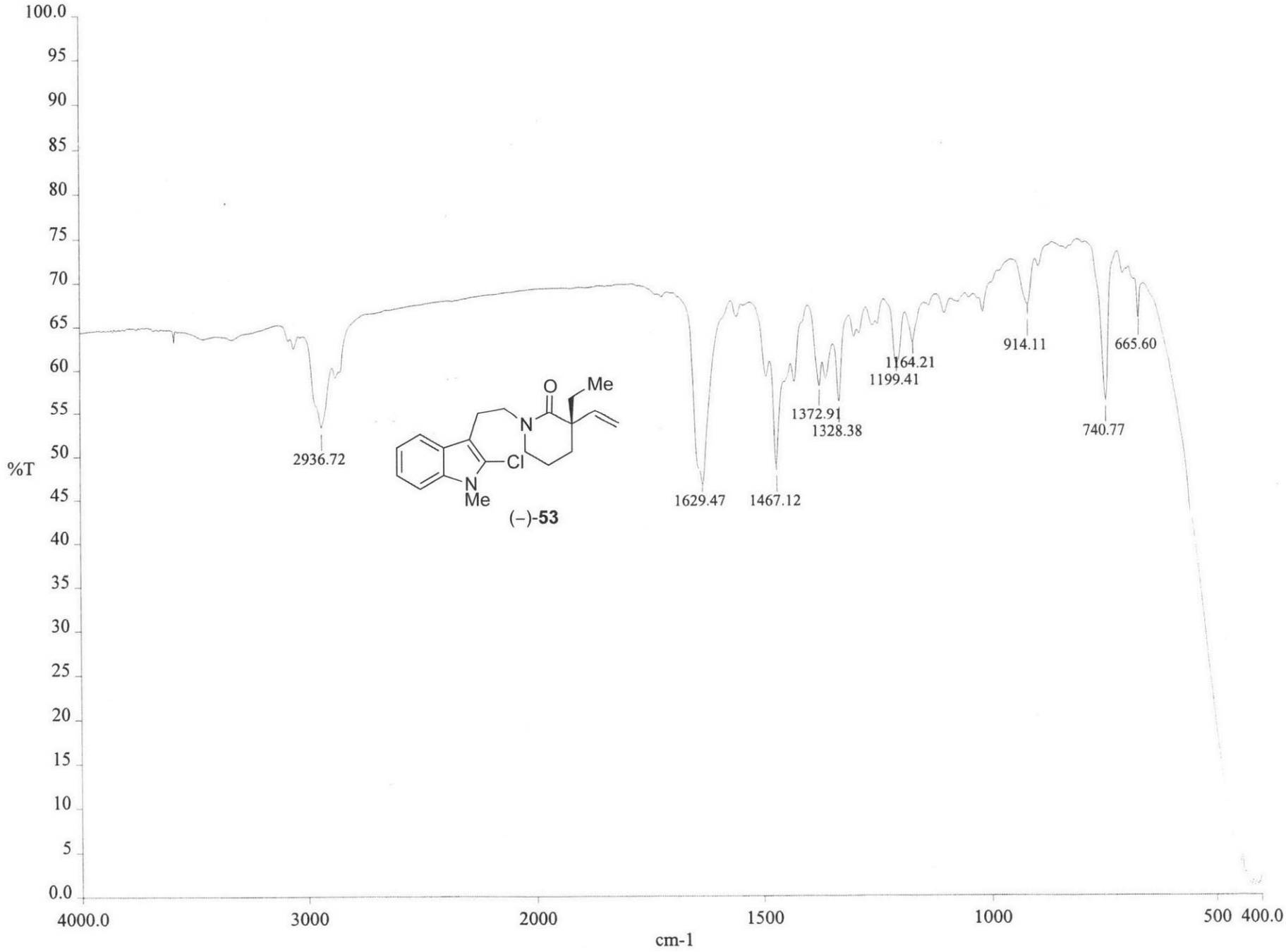
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
1095 repetitions
OBSERVE C13, 125.7822101 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



(–)-**53**




100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2936.72
1629.47
1467.12
1372.91
1328.38
1199.41
1164.21
914.11
740.77
665.60
O
Me
N
Cl
N
Me

(–)-**53**

75%hex
Chiralpak IC
.5 mL/min

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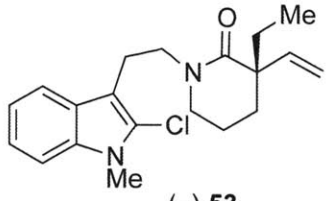

(–)-**53**

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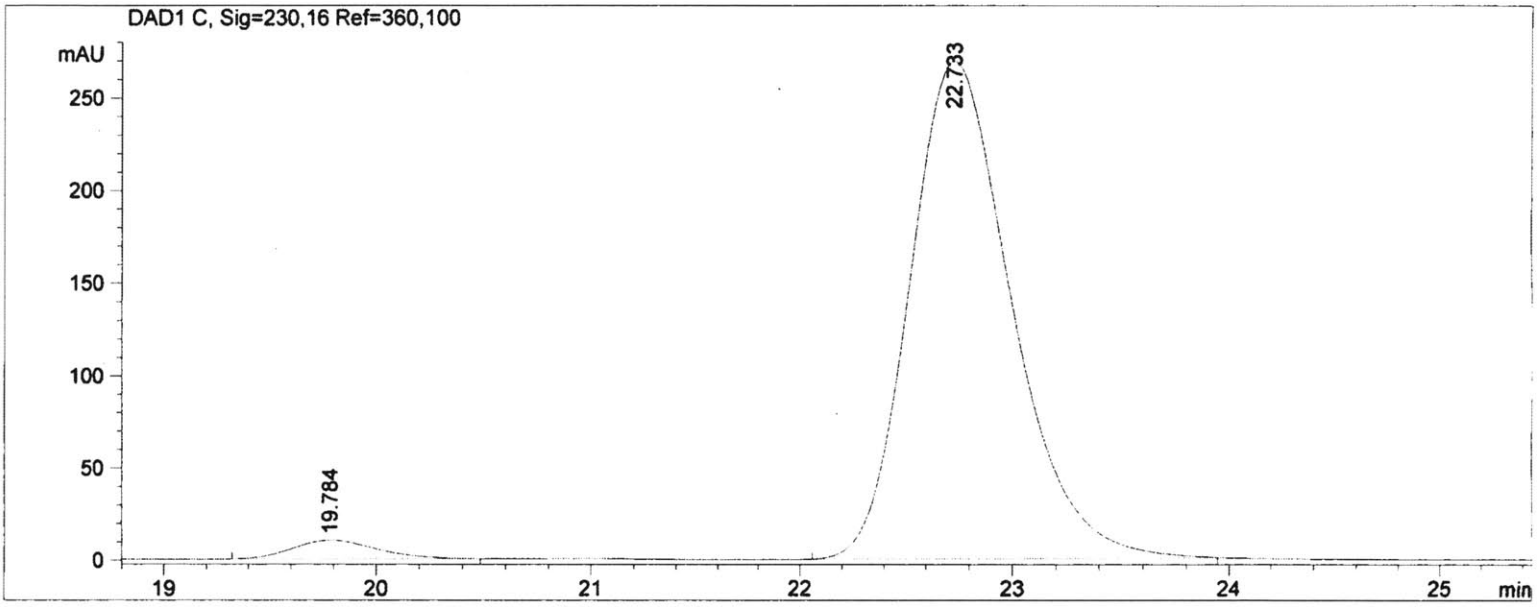

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Area Percent Report

==========

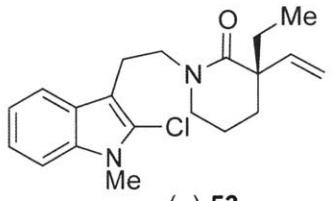
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 C, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.784	BB	0.3298	280.11615	10.21808	3.0750
2	22.733	BB	0.5051	8829.24609	268.90414	96.9250
Totals :				9109.36224	279.12222	

75%hex
Chiralpak IC
.5 mL/min

==========



(–)-**53**

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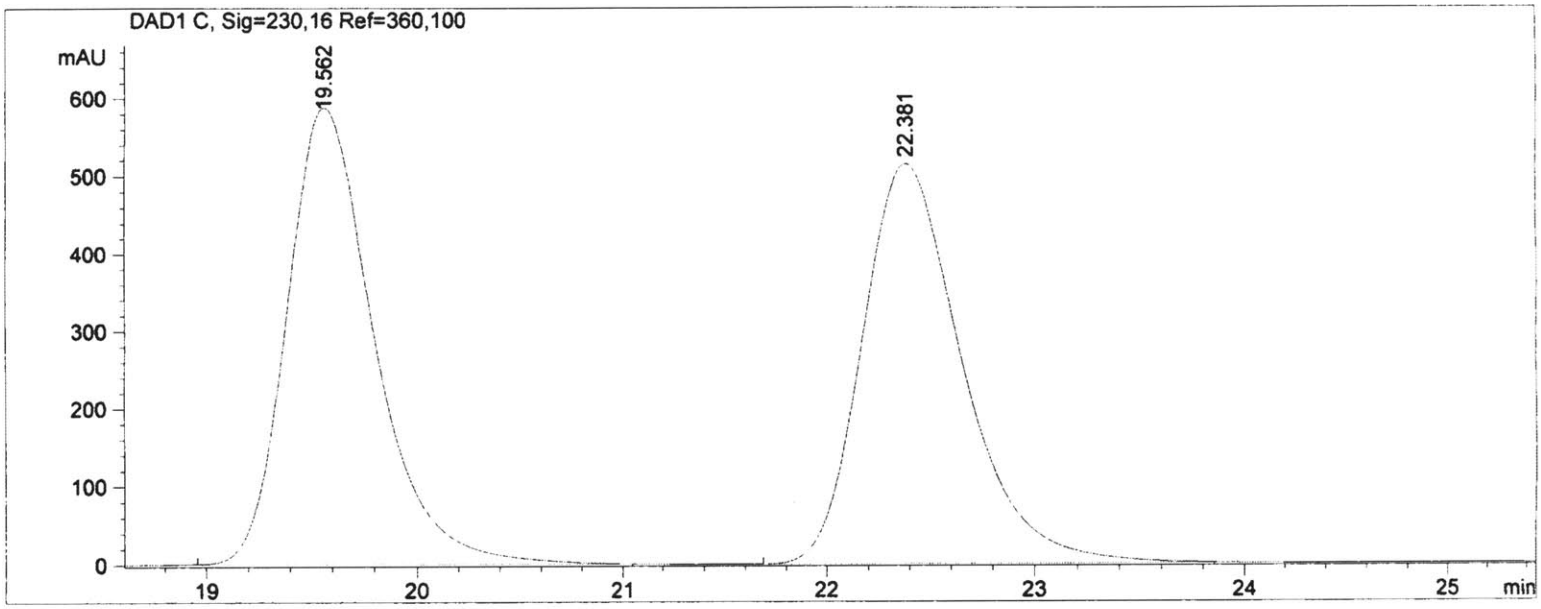

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Area Percent Report

==========

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

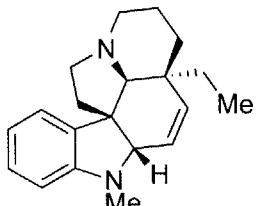
Signal 1: DAD1 C, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.562	BB	0.4421	1.69635e4	587.10394	49.7855
2	22.381	BB	0.5081	1.71097e4	514.37726	50.2145
Totals :				3.40731e4	1101.48120	

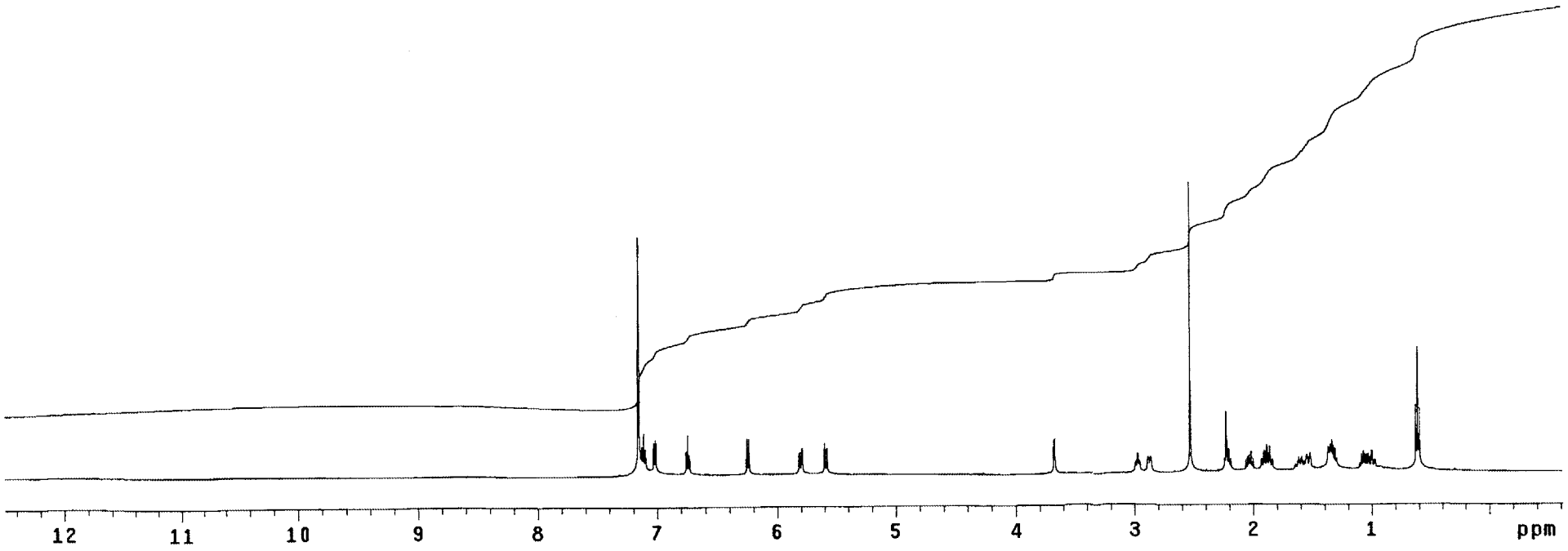
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature

Relax. delay 0.100 sec
Pulse 78.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4295272 MHz
DATA PROCESSING
FT size 262144



(–)-**62**

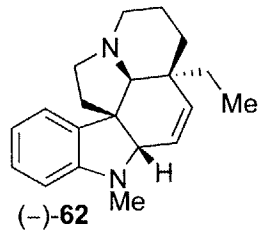


STANDARD CARBON PARAMETERS

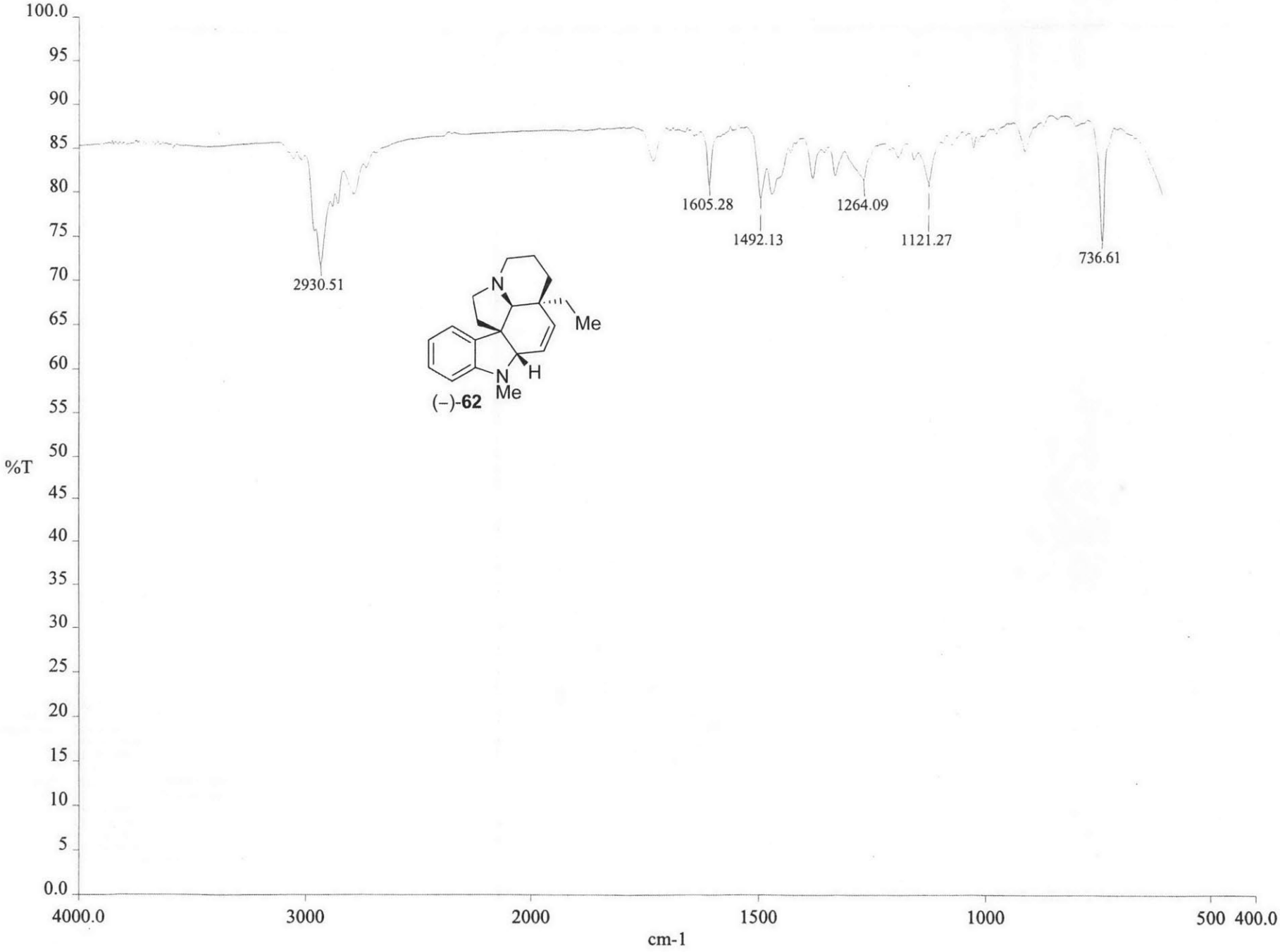
Pulse Sequence: s2pul

Solvent: Benzene
Ambient temperature

Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
18234 repetitions
OBSERVE C13, 125.7821556 MHz
DECOUPLE H1, 500.2292658 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



(–)-**62**

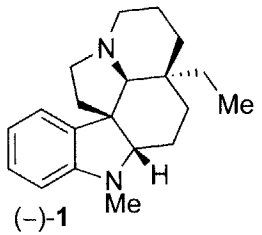

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
2930.51
1605.28
1492.13
1264.09
1121.27
736.61
N
Me
N
H
Me
(–)-62
4000.0
3000
2000
1500
1000
500 400.0
cm-1

STANDARD PROTON PARAMETERS

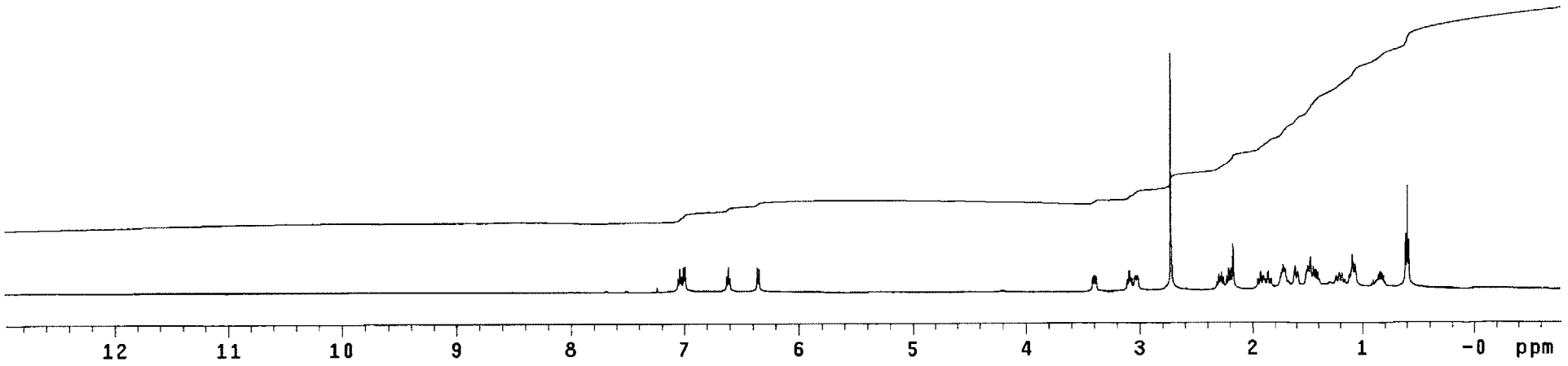
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Pulse 76.1 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2272319 MHz
DATA PROCESSING
FT size 131072



(–)-**1**

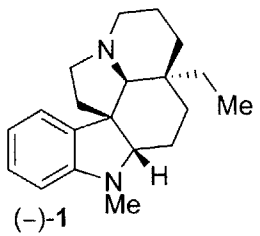


STANDARD CARBON PARAMETERS

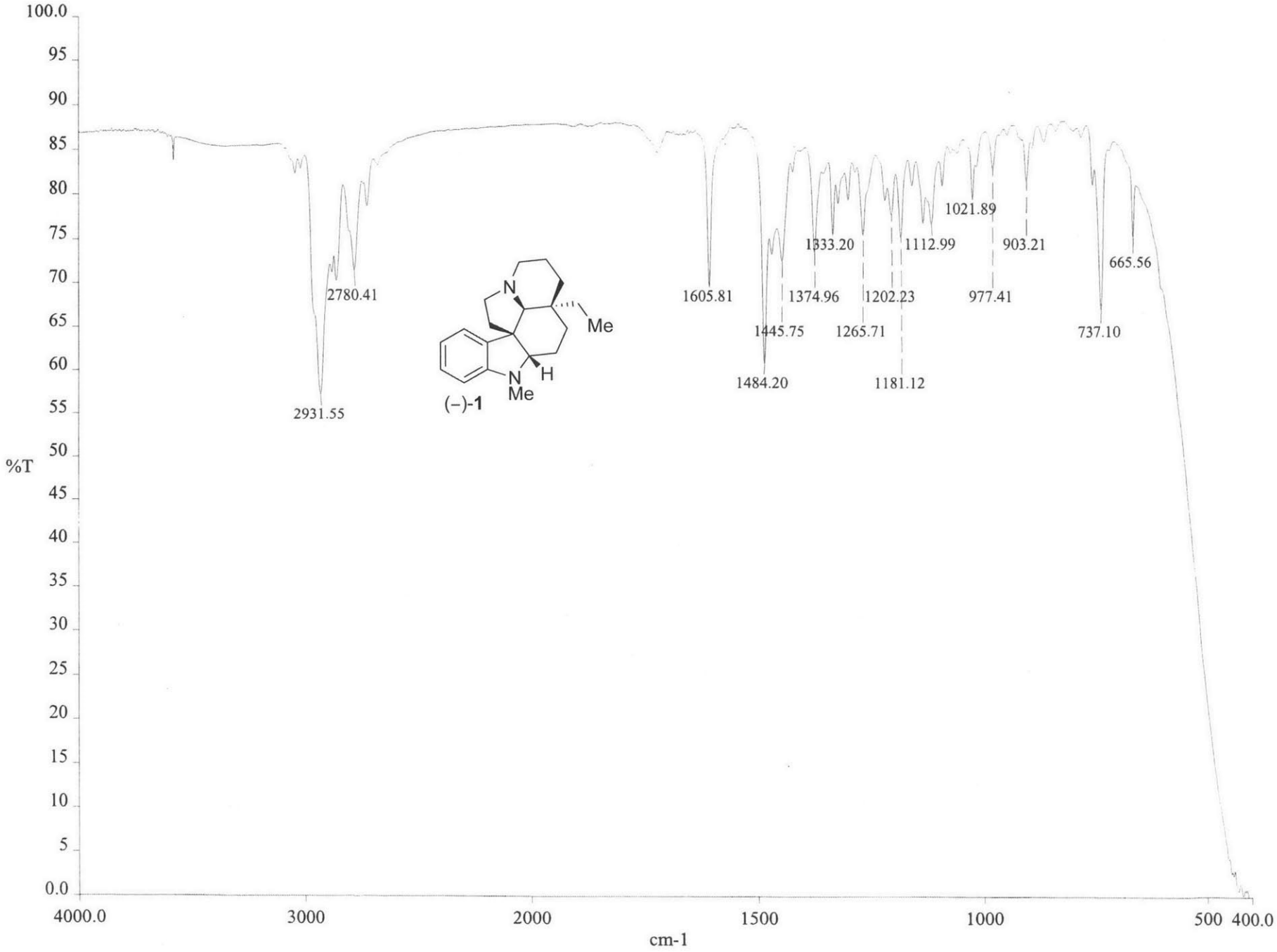
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 69.8 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
16226 repetitions
OBSERVE C13, 125.7822078 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.3 Hz
FT size 131072



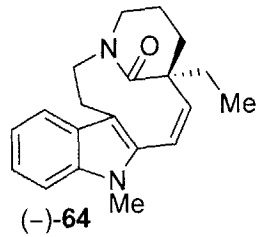
(−)-1


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2931.55
2780.41
1605.81
1484.20
1445.75
1374.96
1333.20
1265.71
1202.23
1181.12
1112.99
1021.89
977.41
903.21
737.10
665.56
N
Me
N
H
Me
(–)-1

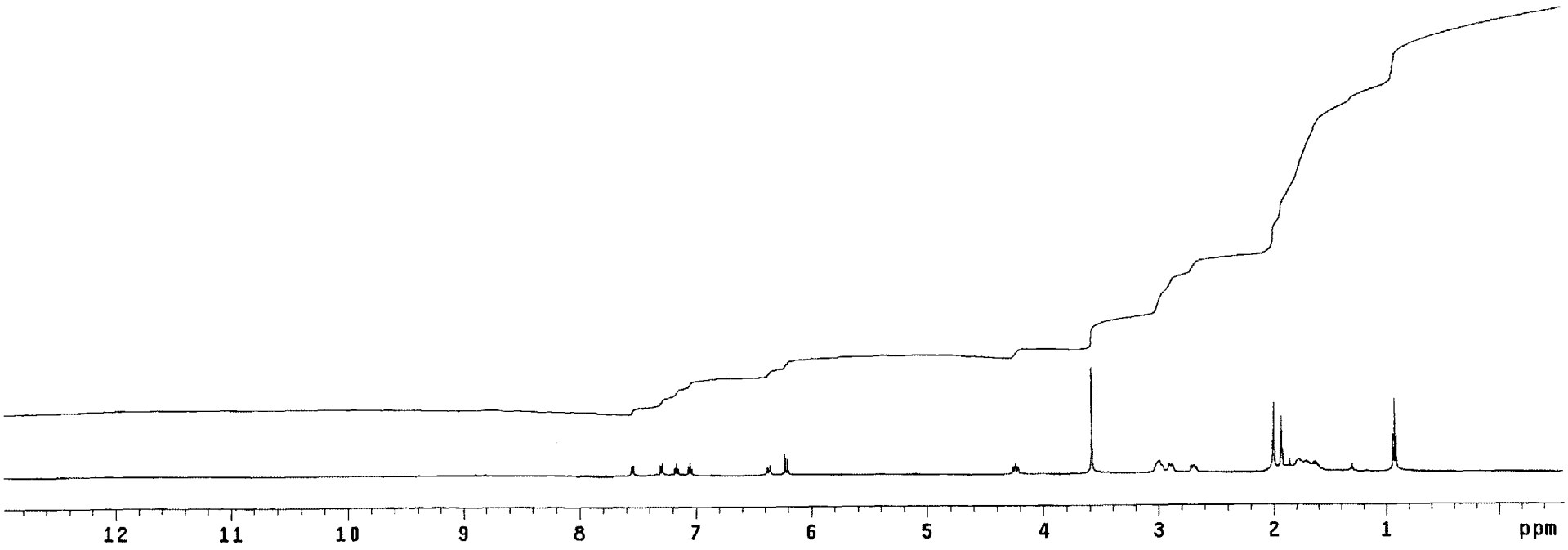
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CD3CN
Temp. 72.0 C / 345.1 K

Pulse 76.1 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
42 repetitions
OBSERVE H1, 500.2298782 MHz
DATA PROCESSING
FT size 131072



(–)-**64**

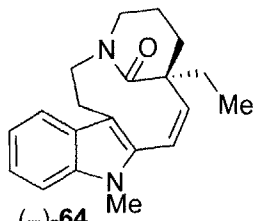


STANDARD CARBON PARAMETERS

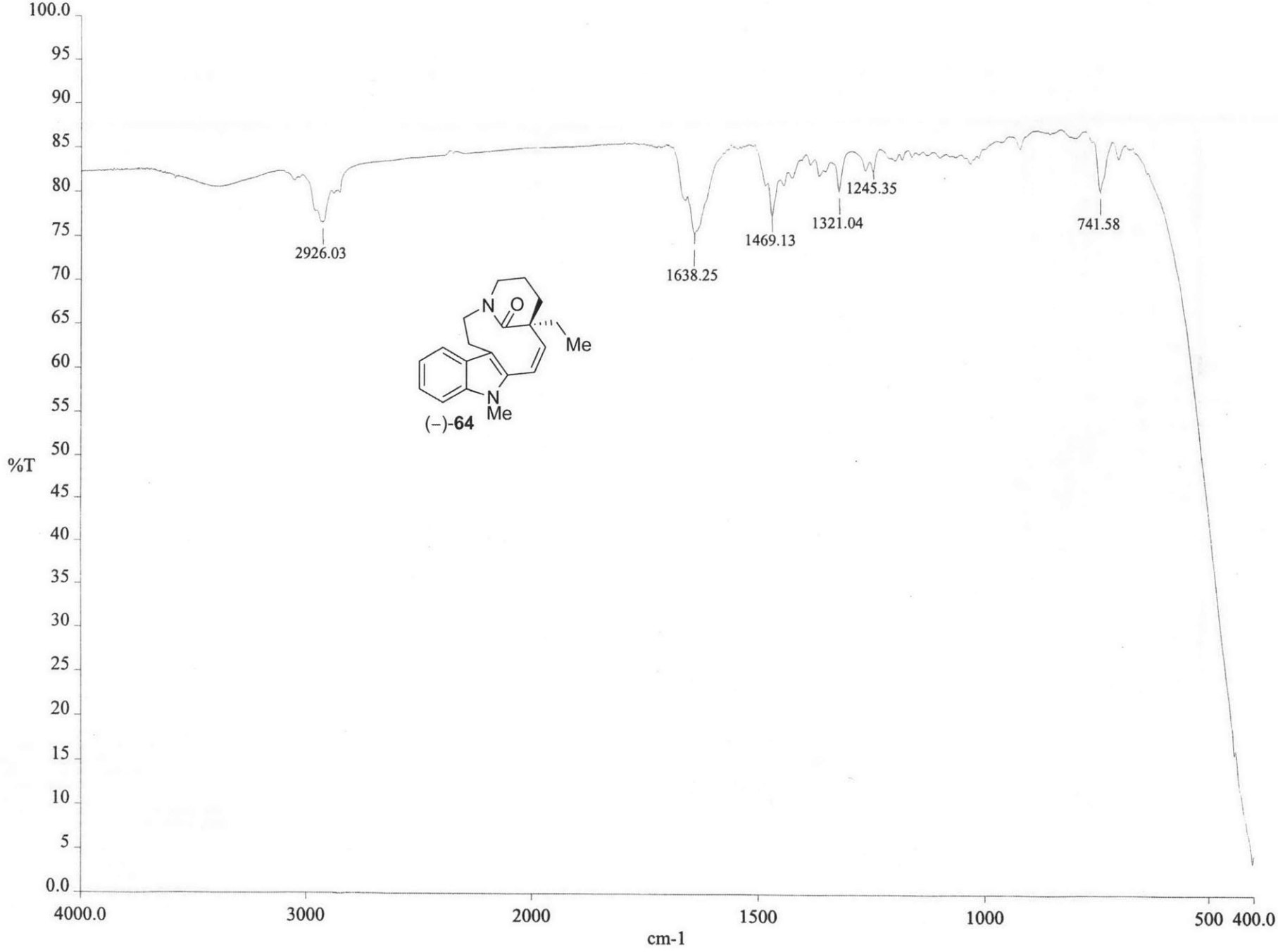
Pulse Sequence: s2pul

Solvent: CD3CN
Temp. 73.0 C / 346.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
3711 repetitions
OBSERVE C13, 125.6606536 MHz
DECOUPLE H1, 499.7468631 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



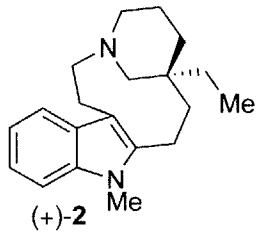
(–)-**64**


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
2926.03
1638.25
1469.13
1321.04
1245.35
741.58
N
O
Me
N
Me
(−)-64
4000.0
3000
2000
1500
1000
500
400.0
cm-1

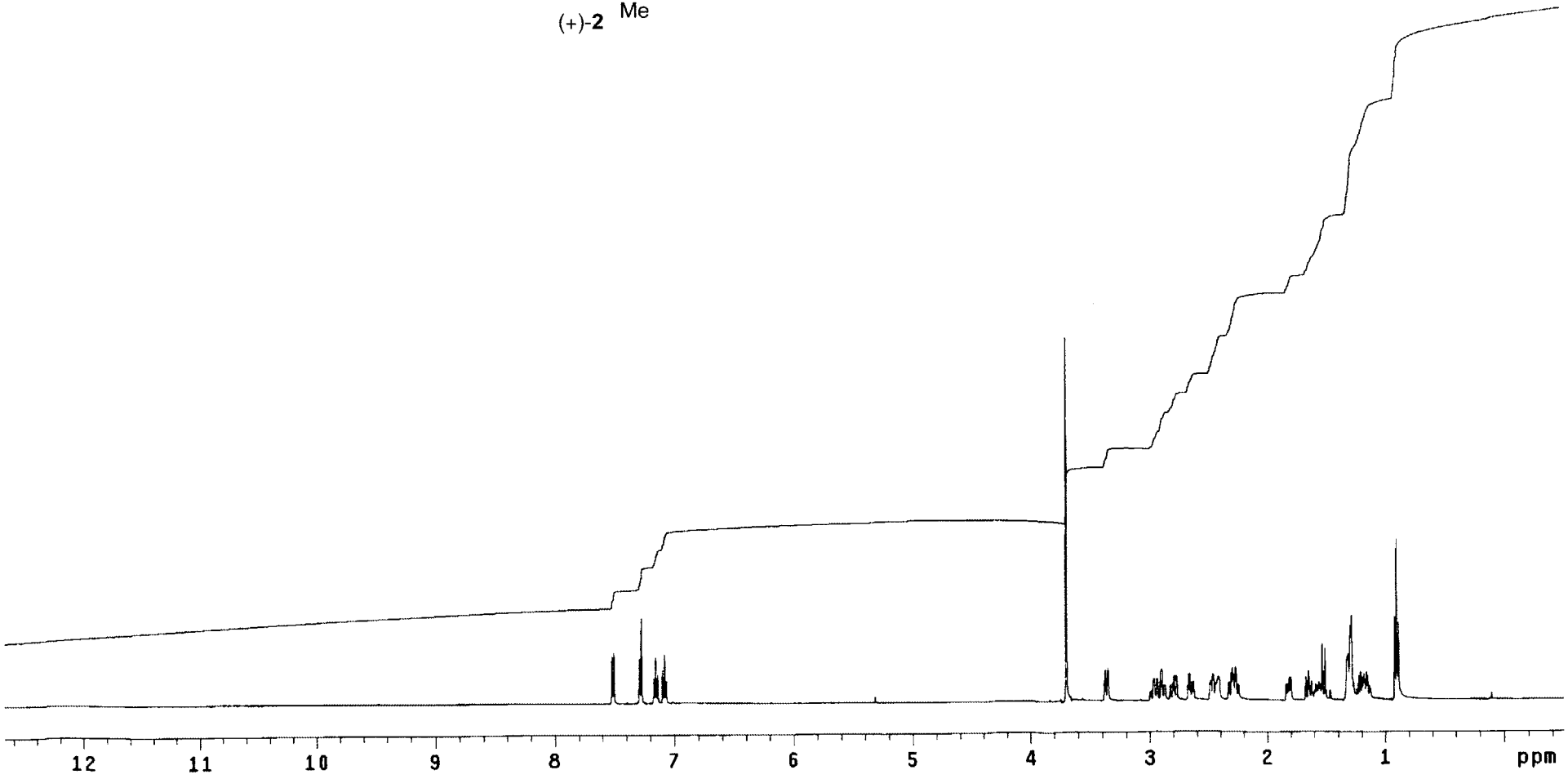
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 60.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
32 repetitions
OBSERVE H1, 500.4252688 MHz
DATA PROCESSING
FT size 262144



(+)-**2**

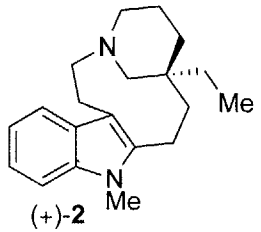


STANDARD CARBON PARAMETERS

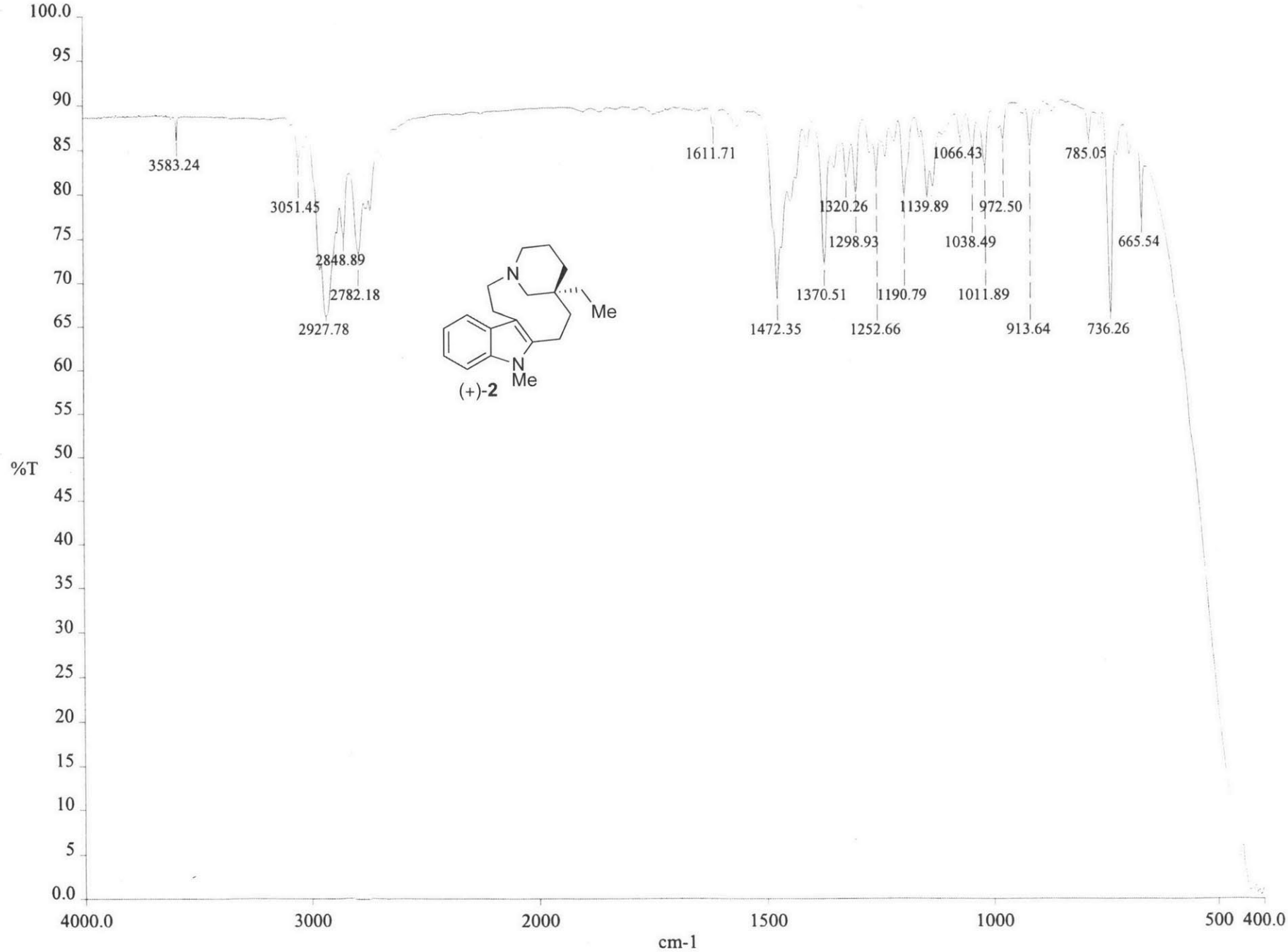
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
1332 repetitions
OBSERVE C13, 125.6601314 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(+)-**2**

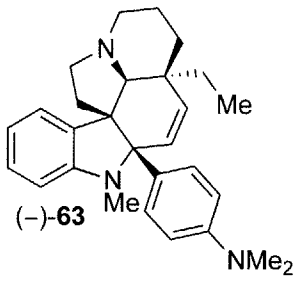

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.24
3051.45
2848.89
2782.18
2927.78
1611.71
1066.43
785.05
1320.26
1139.89
972.50
1298.93
1038.49
665.54
1370.51
1190.79
1011.89
1472.35
1252.66
913.64
736.26
N
Me
N
Me
(+)-2

STANDARD PROTON PARAMETERS

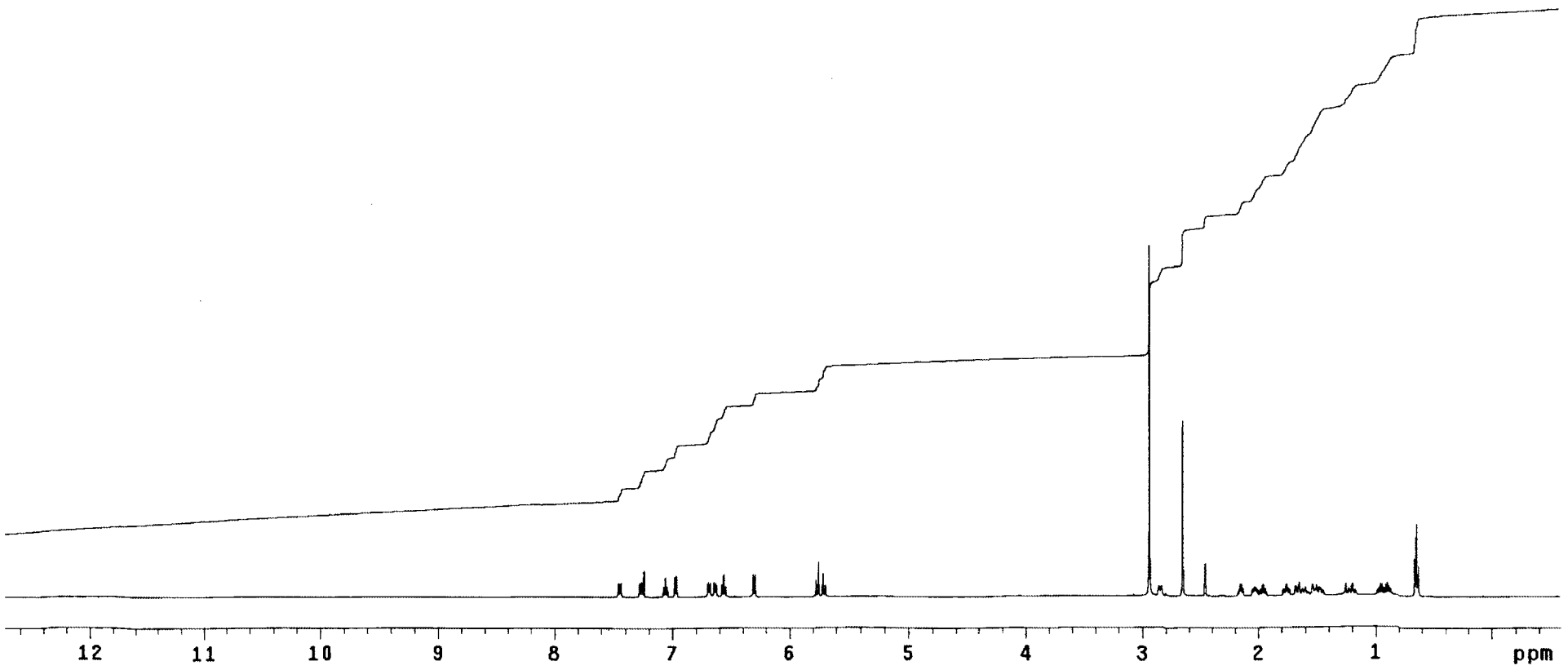
Pulse Sequence: s2pul

Solvent: CDCl3
Ambient temperature

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
32 repetitions
OBSERVE H1, 499.7417341 MHz
DATA PROCESSING
FT size 262144



(−)-**63**

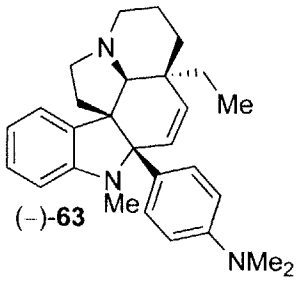


STANDARD CARBON PARAMETERS

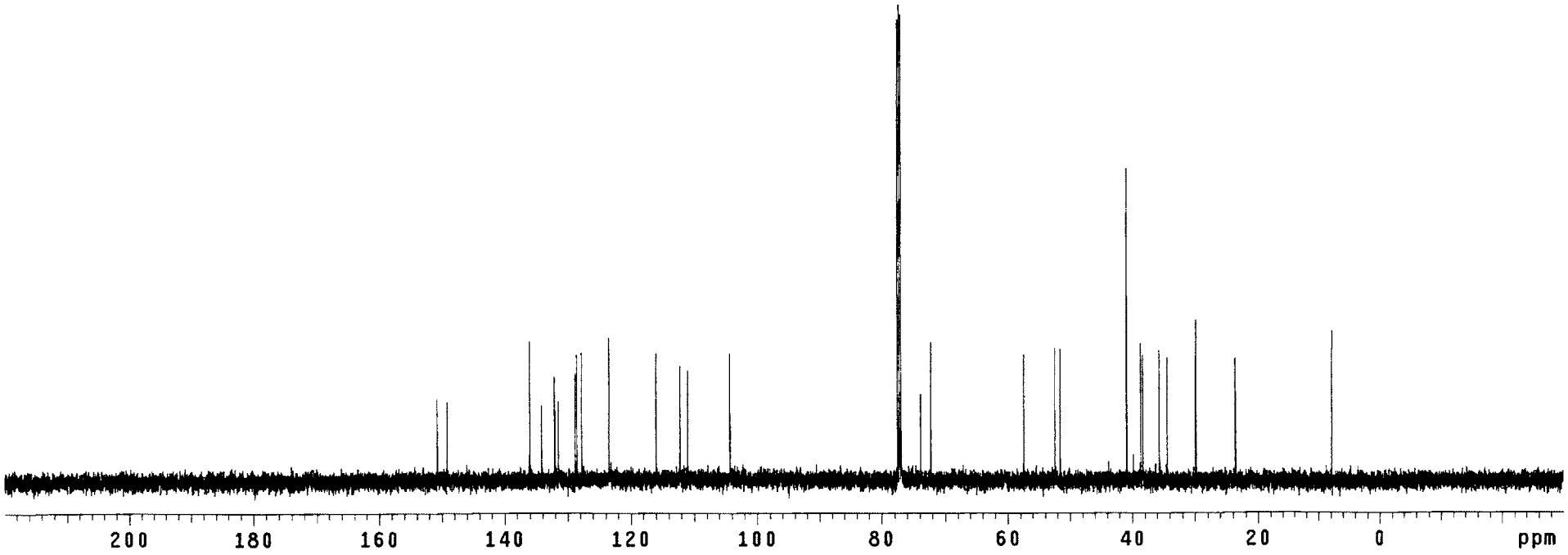
Pulse Sequence: s2pul

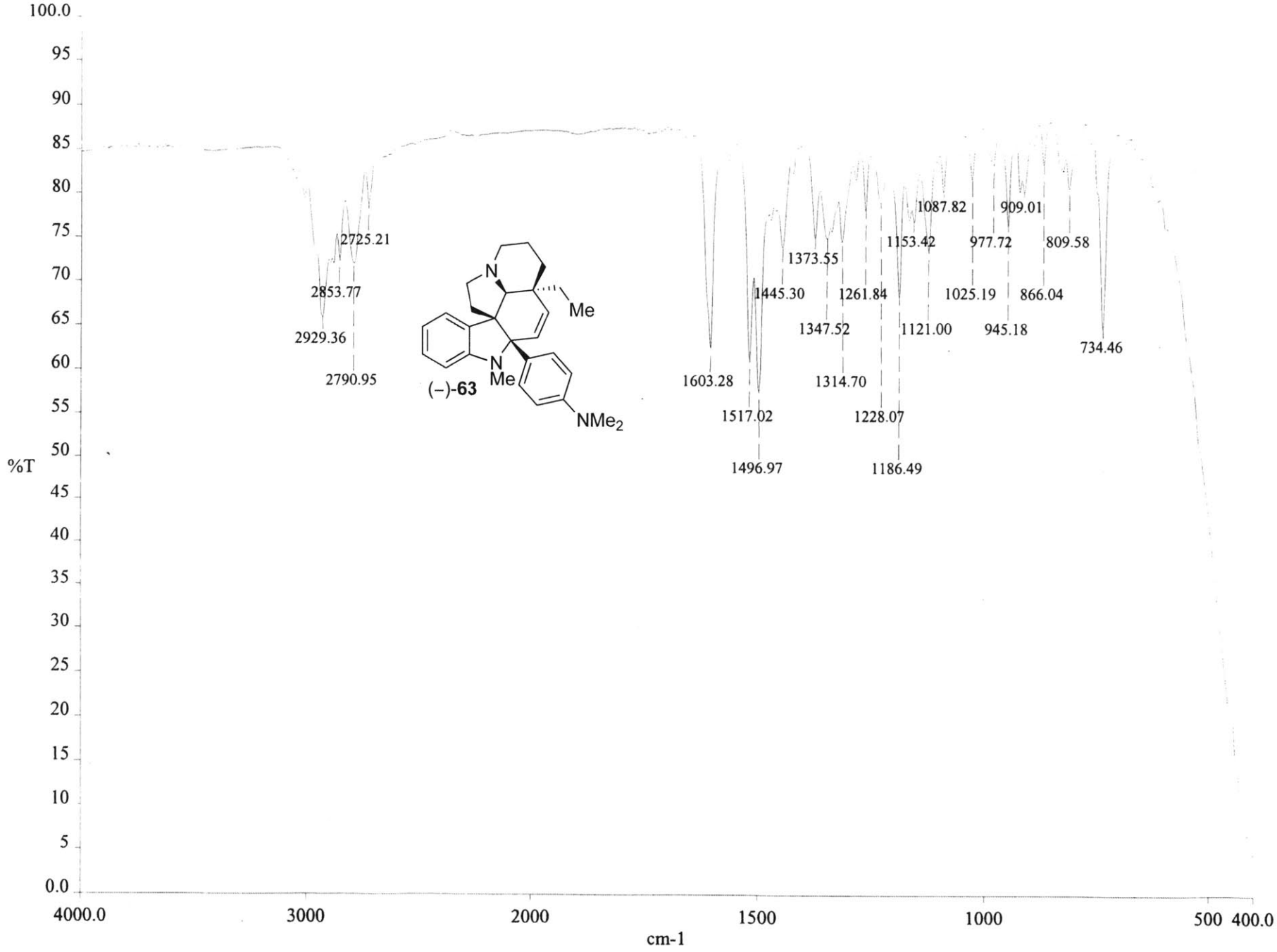
Solvent: CDCl3
Ambient temperature

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
264 repetitions
OBSERVE C13, 125.6601333 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(−)-63



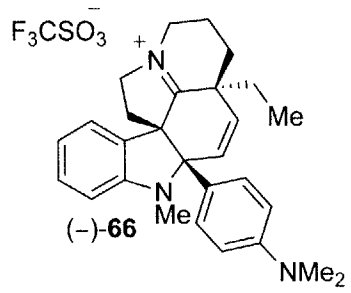

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
2725.21
2853.77
2929.36
2790.95
1603.28
1517.02
1496.97
1445.30
1373.55
1347.52
1314.70
1261.84
1228.07
1186.49
1153.42
1121.00
1087.82
1025.19
977.72
945.18
909.01
866.04
809.58
734.46
N
Me
N
Me
NMe2
(–)-63

STANDARD PROTON PARAMETERS

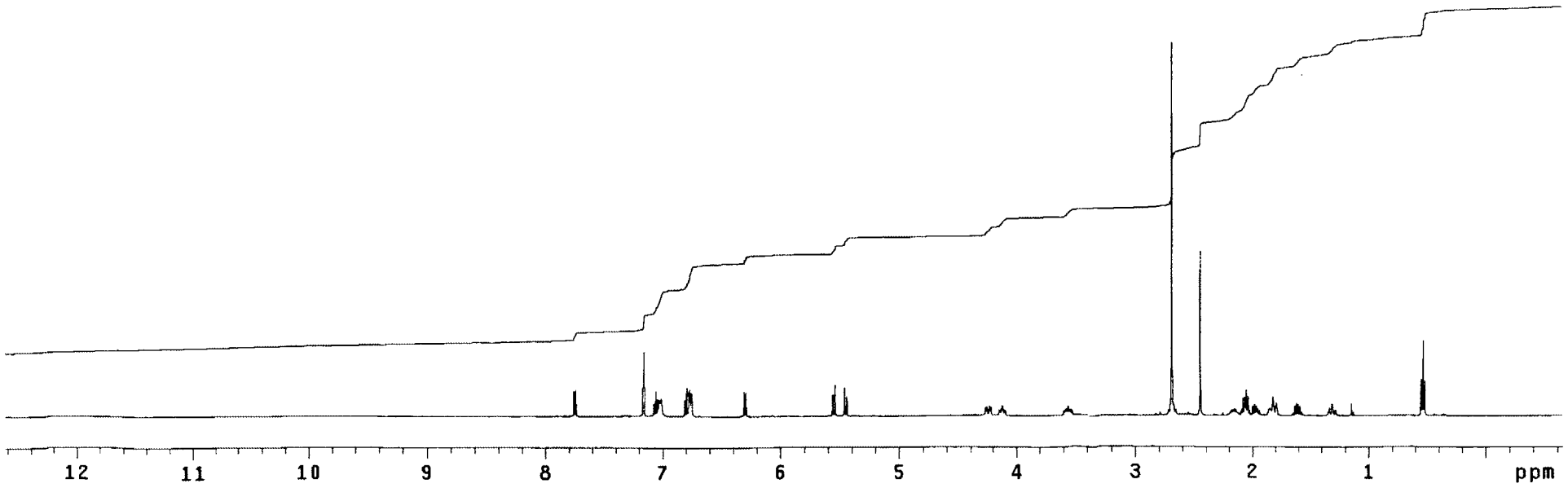
Pulse Sequence: s2pul

Solvent: Benzene
Temp. 72.0 C / 345.1 K

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417469 MHz
DATA PROCESSING
FT size 262144



(–)-**66**

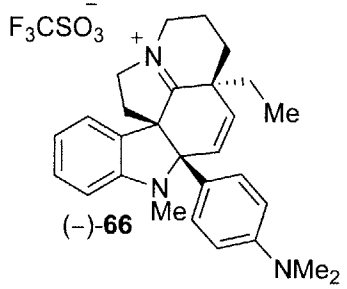


STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

Solvent: Benzene
Temp. 72.0 C / 345.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
13063 repetitions
OBSERVE C13, 125.6600613 MHz
DECOUPLE H1, 499.7442644 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072

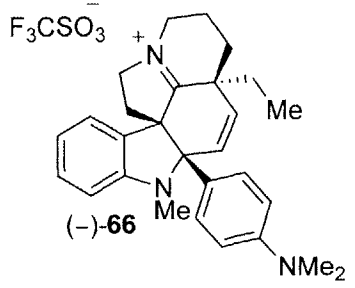


(–)-**66**

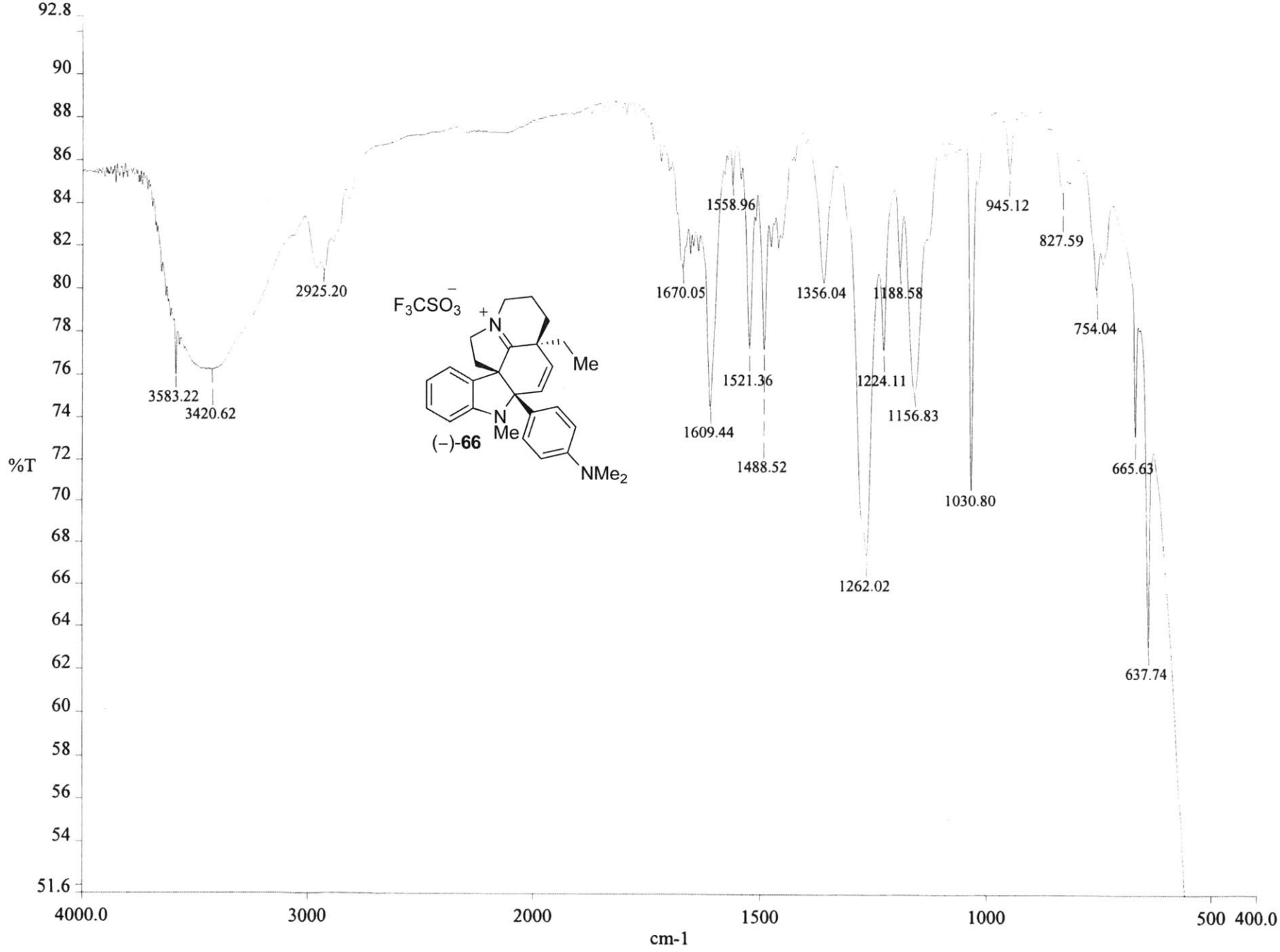
19F OBSERVE
STANDARD PARAMETERS

Pulse Sequence: s2pul
Solvent: Benzene
Ambient temperature

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 0.300 sec
Width 100.0 kHz
4 repetitions
OBSERVE F19, 282.3816196 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144



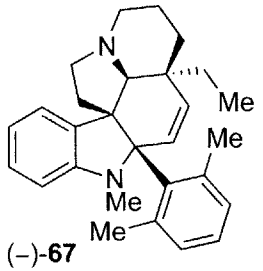
(–)-**66**


92.8
90
88
86
84
82
80
78
76
74
72
70
68
66
64
62
60
58
56
54
51.6
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3583.22
3420.62
2925.20
1670.05
1609.44
1558.96
1521.36
1488.52
1356.04
1262.02
1224.11
1188.58
1156.83
1030.80
945.12
827.59
754.04
665.63
637.74
F3CSO3
Me
N
Me
NMe2
(–)-66

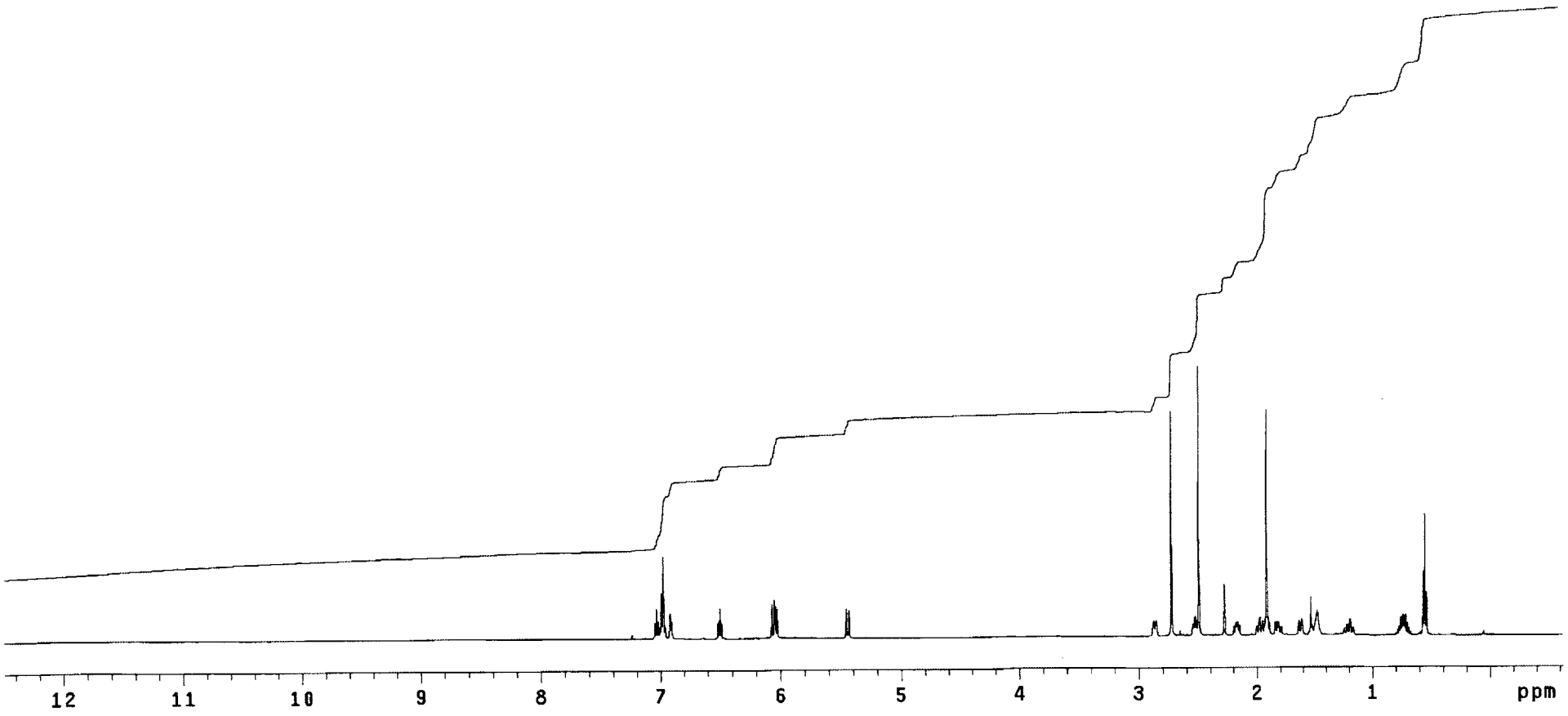
STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 22.0 C / 295.1 K

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417327 MHz
DATA PROCESSING
FT size 262144



(–)-**67**

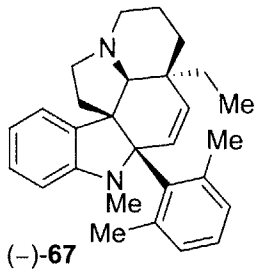


STANDARD CARBON PARAMETERS

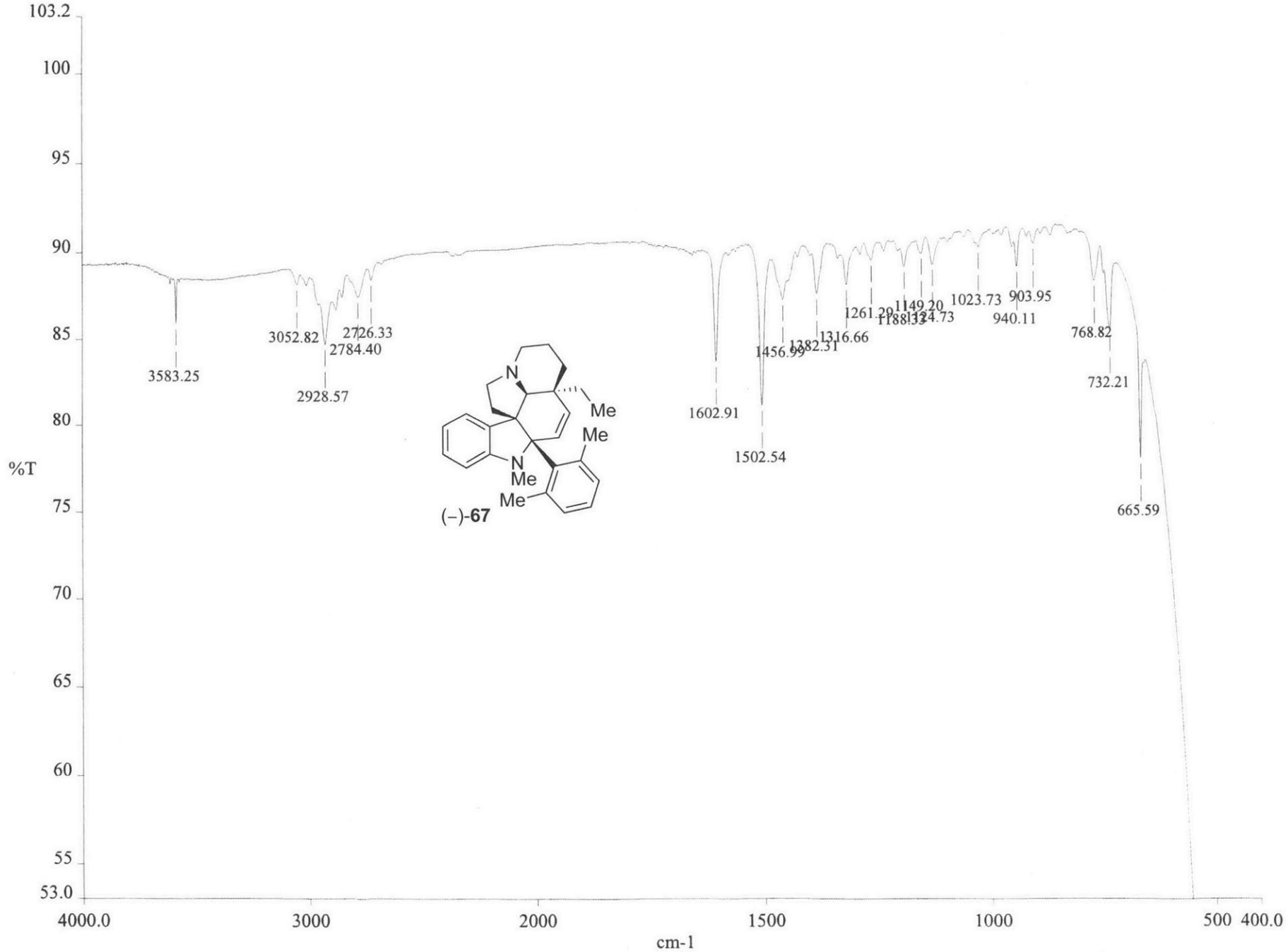
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 22.0 C / 295.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
709 repetitions
OBSERVE C13, 125.6601290 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(–)-**67**

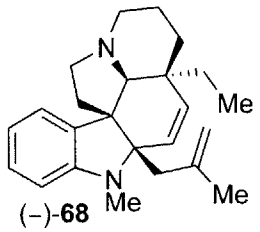

103.2
100
95
90
85
80
75
70
65
60
55
53.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.25
3052.82
2928.57
2784.40
2726.33
1602.91
1502.54
1456.99
1382.31
1316.66
1261.29
1188.33
1149.20
1124.73
1023.73
940.11
903.95
768.82
732.21
665.59
N
Me
Me
N
Me
Me
(–)-67

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 22.0 C / 295.1 K

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7417347 MHz
DATA PROCESSING
FT size 262144



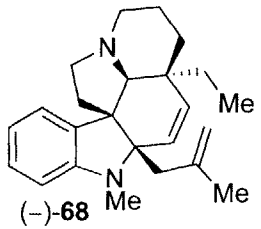
(−)-**68**

STANDARD CARBON PARAMETERS

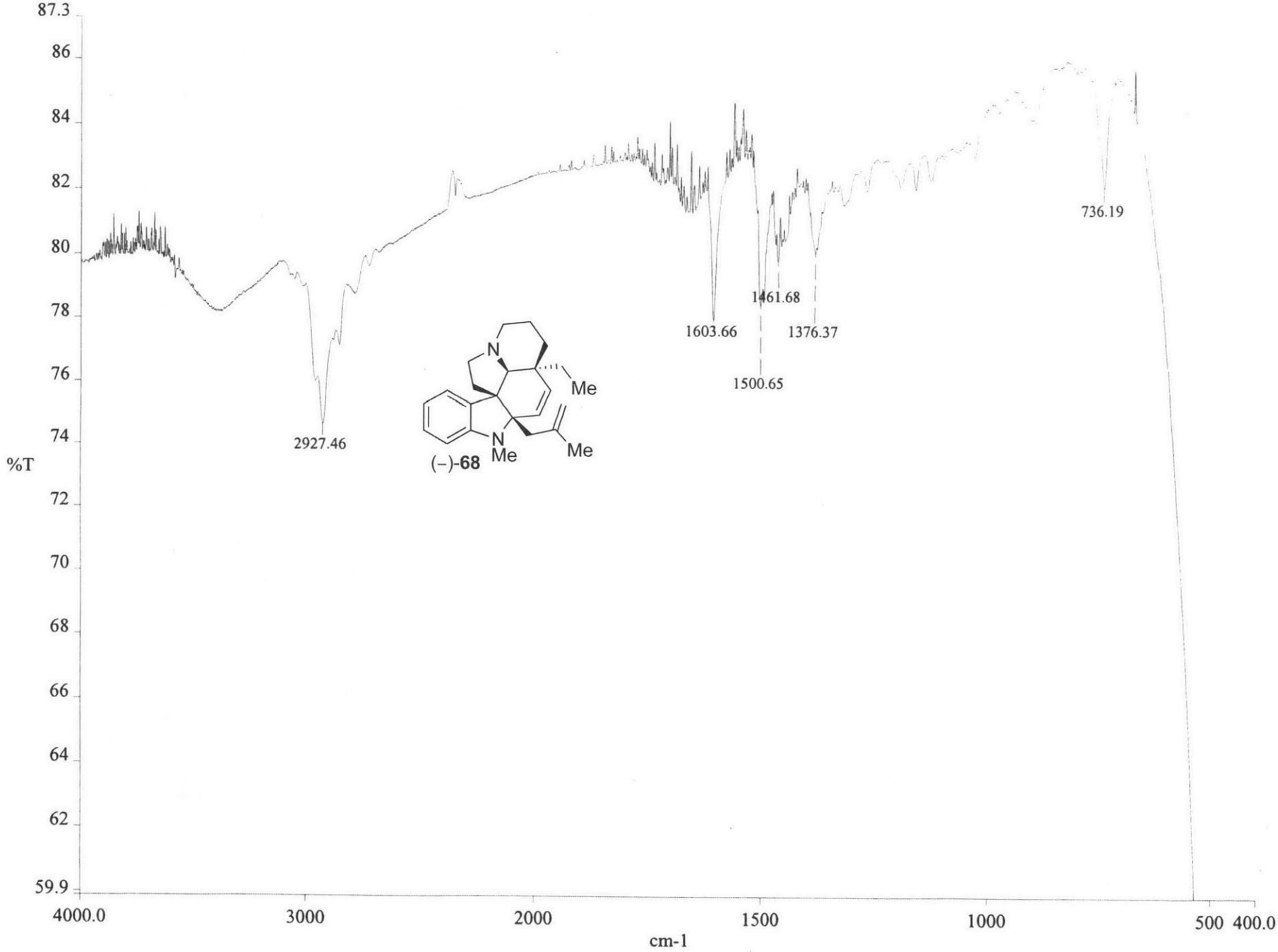
Pulse Sequence: s2pul

Solvent: CDCl3
Temp. 22.0 C / 295.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
11977 repetitions
OBSERVE C13, 125.6601290 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



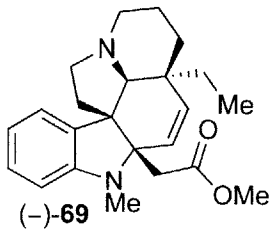
(–)-**68**


87.3
86
84
82
80
78
76
74
72
70
68
66
64
62
59.9
%T
2927.46
1603.66
1500.65
1461.68
1376.37
736.19
N
Me
N
Me
Me
(–)-68
4000.0
3000
2000
1500
1000
500
400.0
cm-1

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 60.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
16 repetitions
OBSERVE H1, 500.4252861 MHz
DATA PROCESSING
FT size 262144

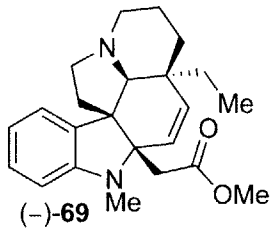


(–)-**69**

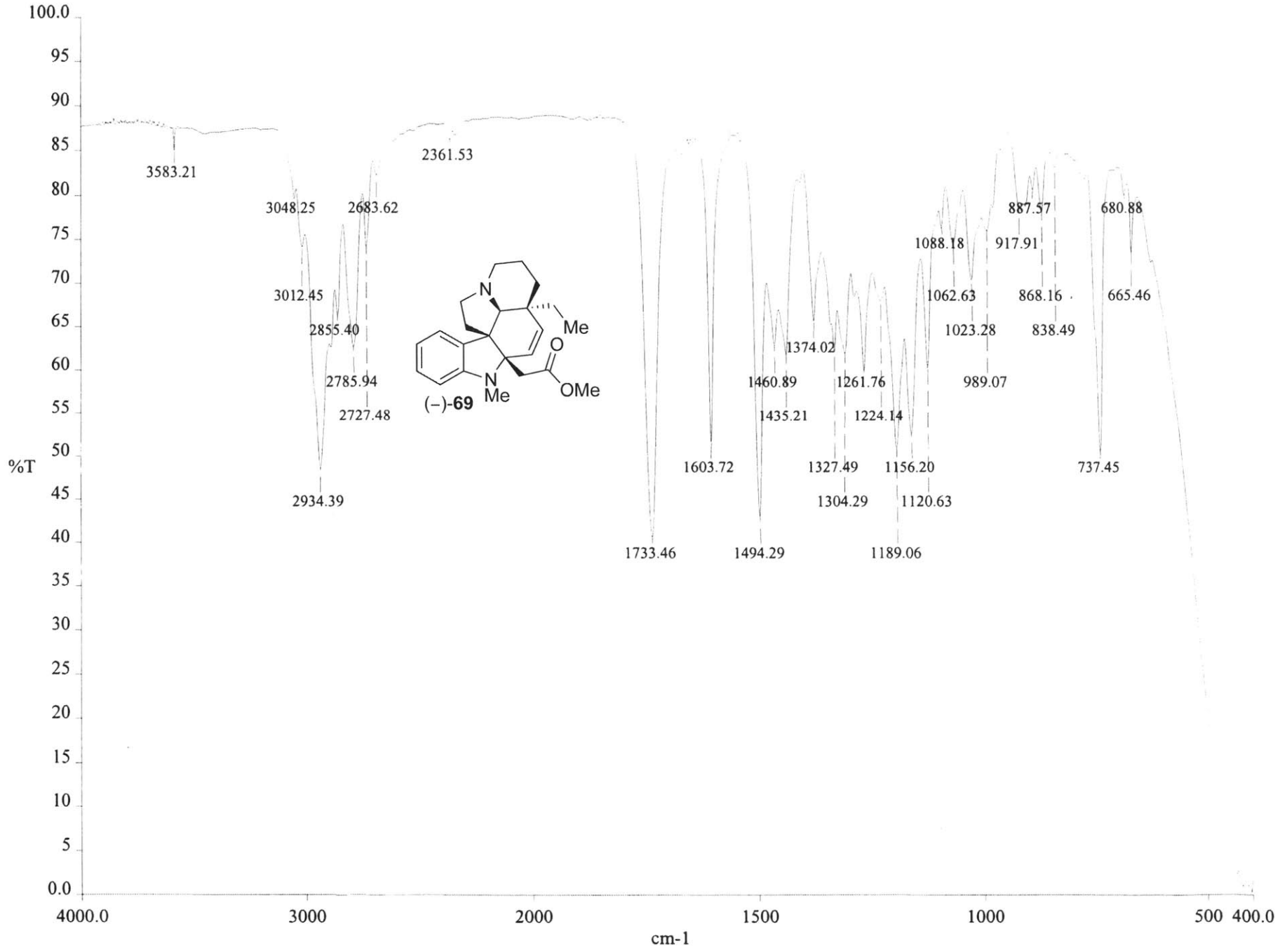
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 65.4 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
3524 repetitions
OBSERVE C13, 125.7822101 MHz
DECOUPLE H1, 500.2292208 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 131072



(–)-**69**

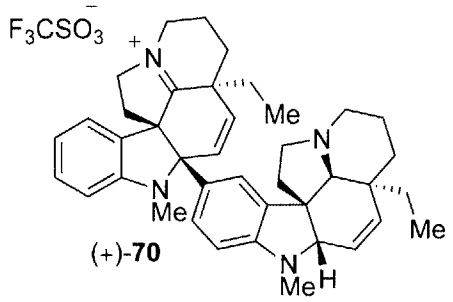

100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3583.21
3048.25
2683.62
2361.53
3012.45
2855.40
2785.94
2727.48
2934.39
1733.46
1603.72
1494.29
1460.89
1435.21
1374.02
1327.49
1304.29
1261.76
1224.14
1189.06
1156.20
1120.63
1088.18
1062.63
1023.28
989.07
917.91
887.57
868.16
838.49
737.45
680.88
665.46
N
Me
O
OMe
N
Me
(–)-69

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: toluene
Temp. 80.0 C / 353.1 K

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
16 repetitions
OBSERVE H1, 499.7418438 MHz
DATA PROCESSING
FT size 262144

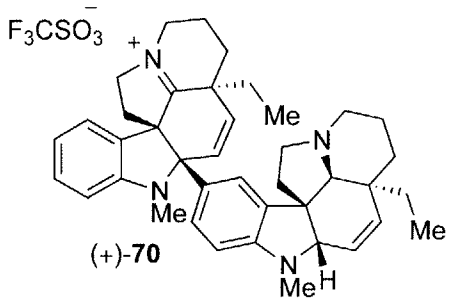


(+)-**70**

STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: toluene
Temp. 80.0 C / 353.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
10625 repetitions
OBSERVE C13, 125.6601082 MHz
DECOUPLE H1, 499.7442944 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072

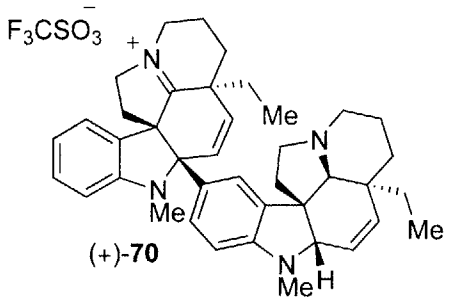


(+)-**70**

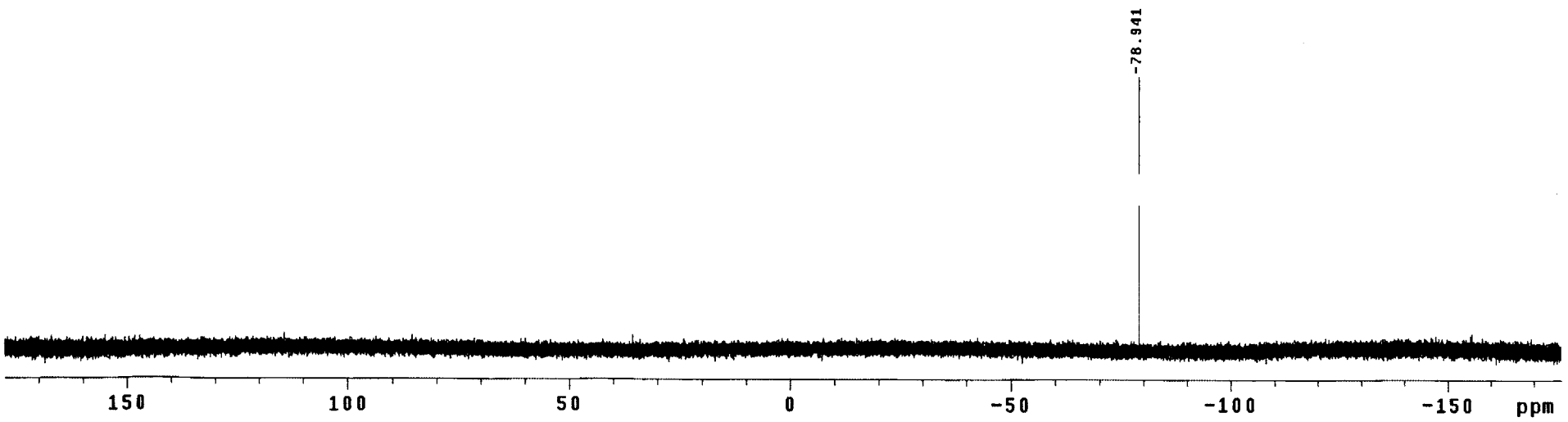
19F OBSERVE
STANDARD PARAMETERS

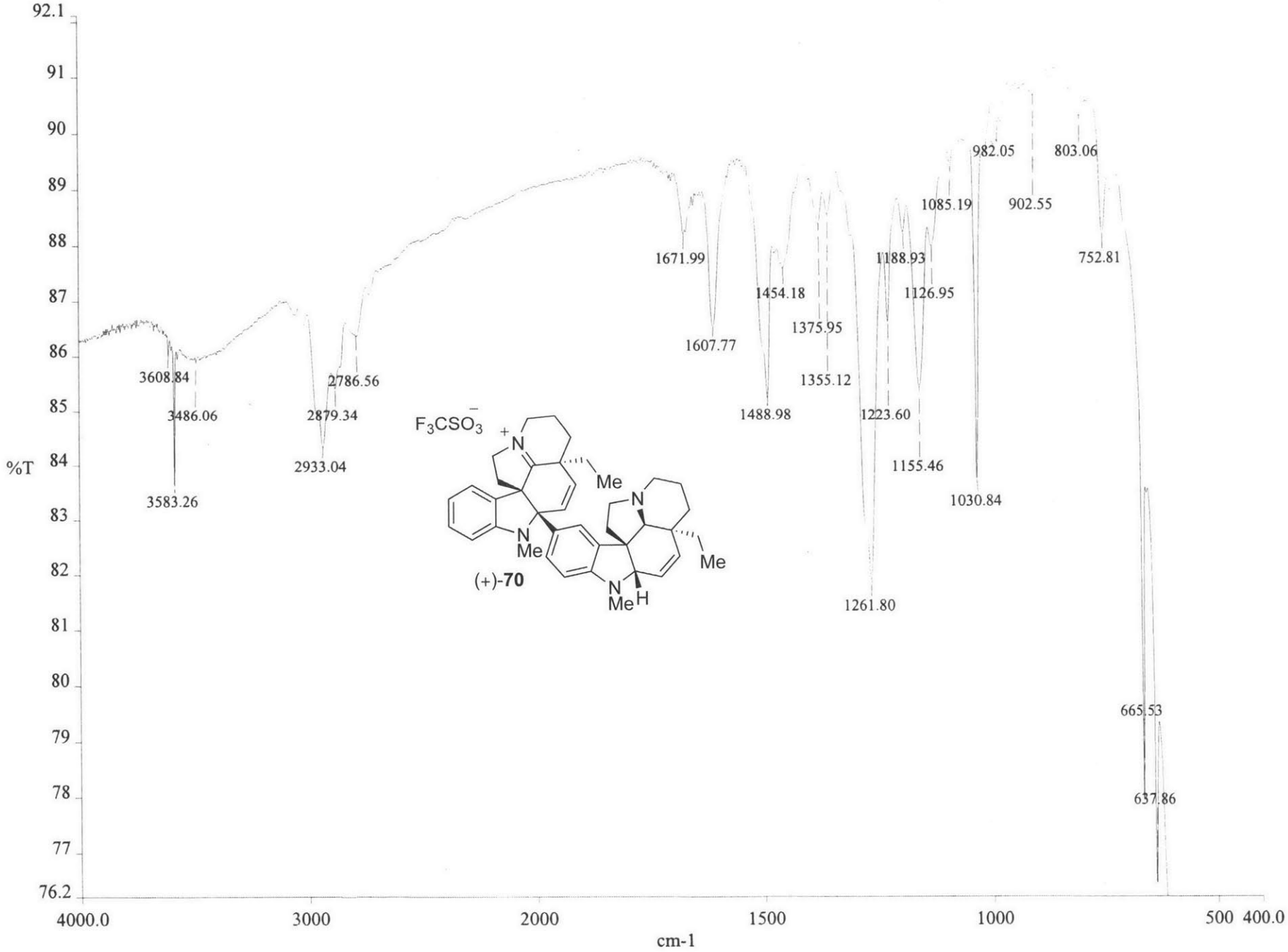
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 4.000 sec
Pulse 45.0 degrees
Acq. time 0.300 sec
Width 100.0 kHz
8 repetitions
OBSERVE F19, 282.3815086 MHz
DATA PROCESSING
Line broadening 0.3 Hz
FT size 262144



(+)-**70**

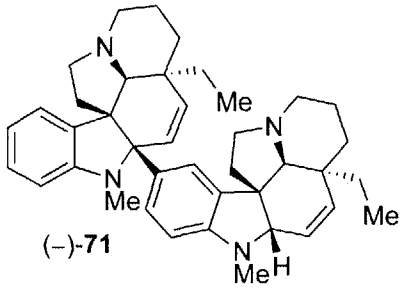



92.1
91
90
89
88
87
86
85
84
83
82
81
80
79
78
77
76.2
%T
4000.0
3000
2000
1500
1000
500
400.0
cm-1
3608.84
3486.06
3583.26
2933.04
2879.34
2786.56
1671.99
1607.77
1488.98
1454.18
1375.95
1355.12
1261.80
1223.60
1188.93
1155.46
1126.95
1085.19
1030.84
982.05
902.55
803.06
752.81
665.53
637.86
F3CSO3
(+)-70

STANDARD PROTON PARAMETERS

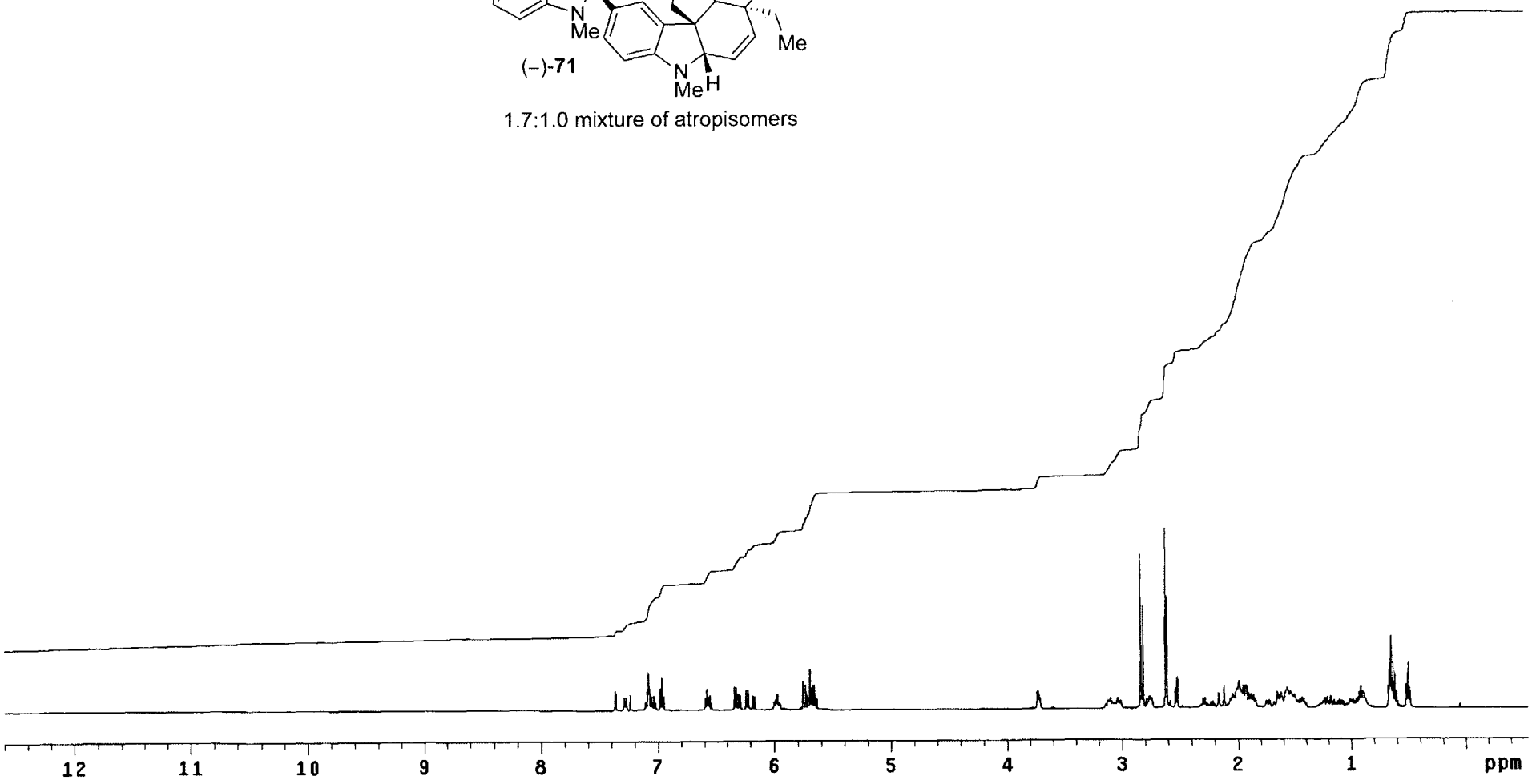
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.100 sec
Pulse 60.3 degrees
Acq. time 4.999 sec
Width 12012.0 Hz
32 repetitions
OBSERVE H1, 500.4252873 MHz
DATA PROCESSING
FT size 262144



(–)-**71**

1.7:1.0 mixture of atropisomers

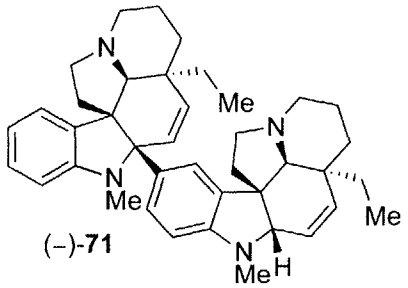


STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul

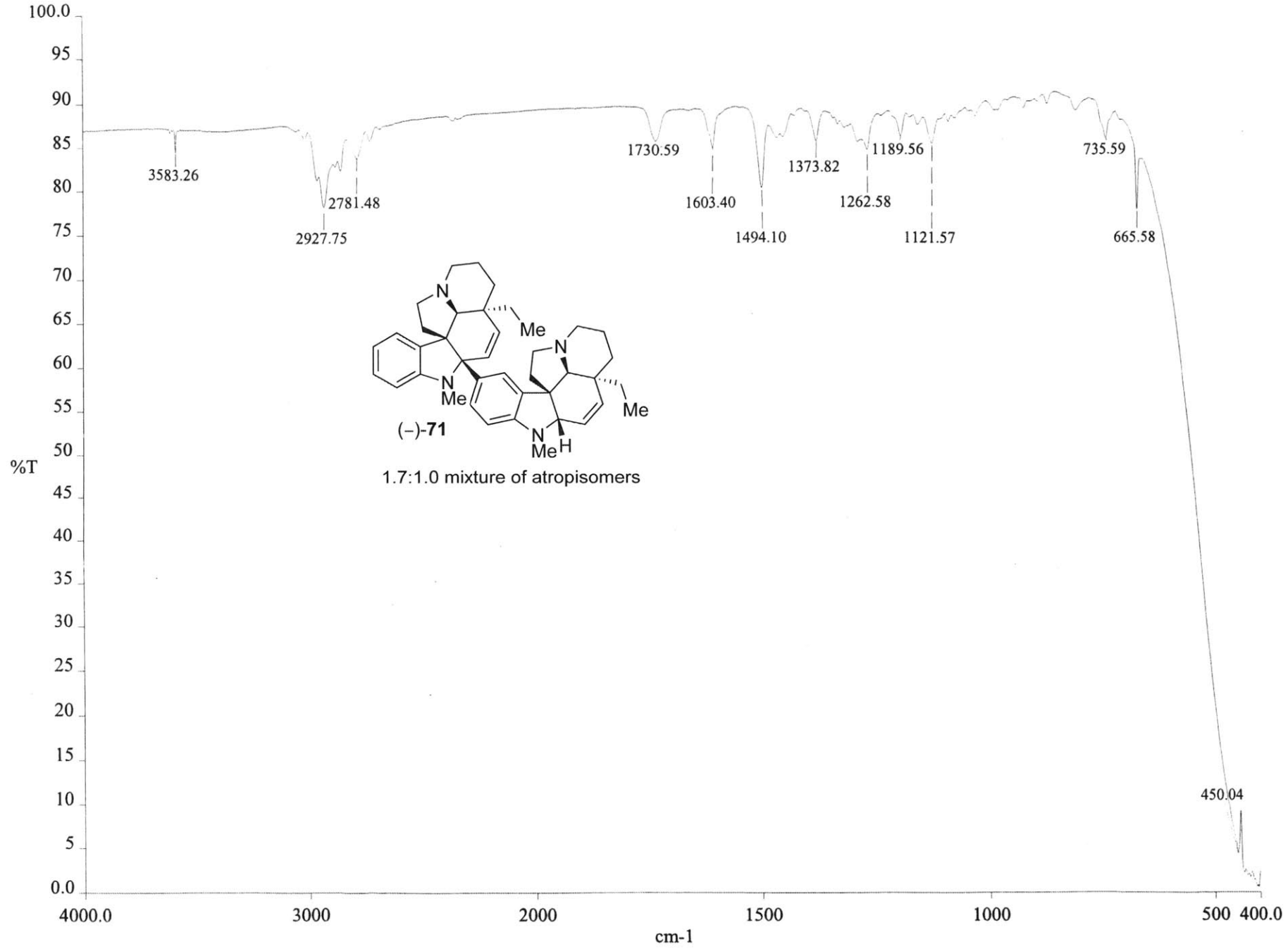
Solvent: CDCl3
Temp. 21.0 C / 294.1 K

Relax. delay 3.000 sec
Pulse 35.0 degrees
Acq. time 2.000 sec
Width 31397.2 Hz
9729 repetitions
OBSERVE C13, 125.6601314 MHz
DECOUPLE H1, 499.7442194 MHz
Power 34 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072



(–)-**71**

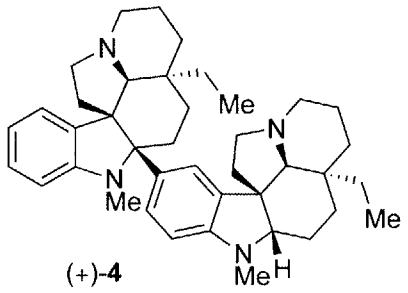
1.7:1.0 mixture of atropisomers


100.0
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0.0
%T
3583.26
2927.75
2781.48
1730.59
1603.40
1494.10
1373.82
1262.58
1189.56
1121.57
735.59
665.58
450.04
4000.0
3000
2000
1500
1000
500
400.0
cm-1
Me
N
N
Me
N
Me
Me
H
(–)-71
1.7:1.0 mixture of atropisomers

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 54.0 C / 327.1 K

Relax. delay 2.000 sec
Pulse 81.5 degrees
Acq. time 3.001 sec
Width 10504.2 Hz
354 repetitions
OBSERVE H1, 499.7417334 MHz
DATA PROCESSING
FT size 262144

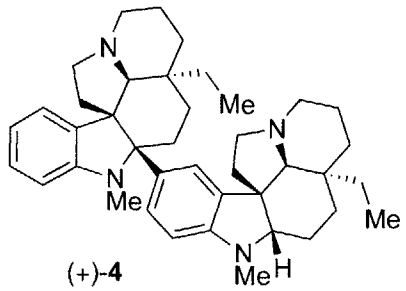


(+)-**4**

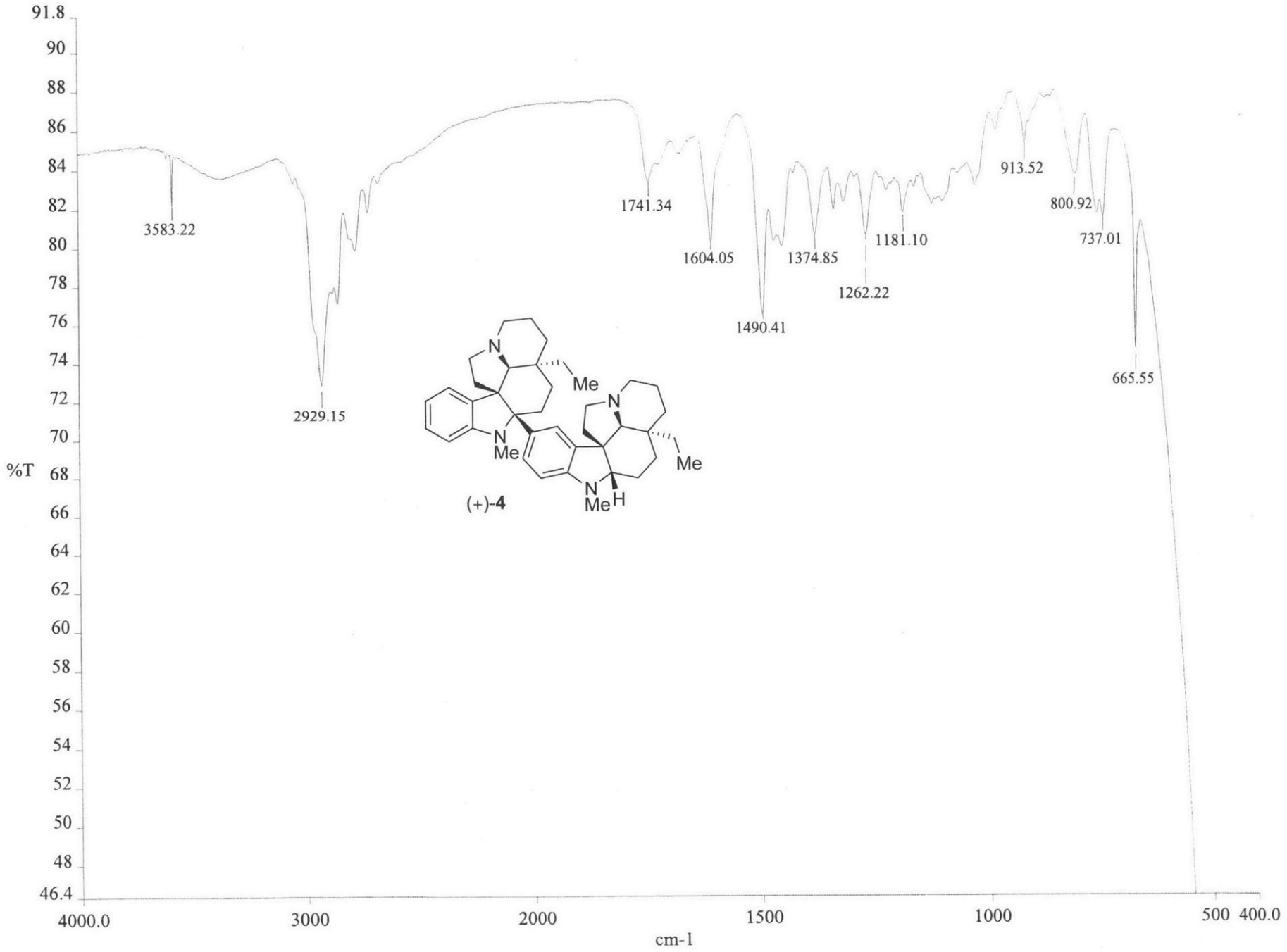
STANDARD CARBON PARAMETERS

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature

Relax. delay 0.763 sec
Pulse 60.9 degrees
Acq. time 1.736 sec
Width 37735.8 Hz
31639 repetitions
OBSERVE C13, 125.7822055 MHz
DECOUPLE H1, 500.2292208 MHz
Power 45 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 3.0 Hz
FT size 131072



(+)-**4**


91.8
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72
70
68
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64
62
60
58
56
54
52
50
48
46.4
%T
3583.22
2929.15
1741.34
1604.05
1490.41
1374.85
1262.22
1181.10
913.52
800.92
737.01
665.55
Me
N
N
Me
N
Me
Me
H
(+)-4
4000.0
3000
2000
1500
1000
500
400.0
cm-1

Jonathan William Medley

Curriculum Vitae

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EDUCATION

Massachusetts Institute of Technology, Cambridge, MA.
Ph.D. Organic Chemistry (expected 2013)
Thesis Title: "Direct Dehydrative *N*-Pyridinylation of Amides, the Interrupted Bischler–Napieralski Reaction, and the Enantioselective Total Synthesis and Arylative Dimerization of *Aspidosperma* Alkaloids."
GPA = 4.80/5.00

Harvard University, Cambridge, MA.
A.B. *Summa cum Laude* in Chemistry and Physics, minor in Mathematical Sciences (2007)
GPA = 3.91/4.00

RESEARCH EXPERIENCE

Graduate Research Associate, Massachusetts Institute of Technology (2007–present)
Professor Mohammad Movassaghi, Advisor.
- Development of a method for the direct dehydrative *N*-pyridinylation of amides.
- Spectroscopic and mechanistic studies of the structure and reactivity of electrophilically activated amides.
- Development of a method for the synthesis of spiroindolines.
- Enantioselective total syntheses and novel arylative dimerization of *aspidosperma* alkaloids.

Undergraduate Researcher, Harvard University (2005–2007)
Professor David A. Evans, Advisor.
- Development of a method for β-alkylation of 2-acyl imidazole homoenolates.
- Development of catalytic asymmetric pyrrole cyclizations.
- Studies toward the enantioselective total synthesis of aflastatin A.

Medicinal Chemistry Research Intern, Amgen, Thousand Oaks, CA (2006)
Dr. Holger Monenschein, Advisor.
- Development of a methodology for synthesis of enantioenriched aminotetralins.

Research Intern, Seattle VA Hospital (2004)
Dr. Michael Orendurff, Advisor.
- Studies on foot pressure during gait of diabetic patients.
- Studies on foot pressure during full gait of athletes.

ACADEMIC HONORS, DISTINCTIONS, AND FELLOWSHIPS

Morse Travel Grant (2012)
NDSEG Fellow (2008–2011)
Hertz Fellowship Finalist (2008)

NSF Graduate Fellowship Honorable Mention (2008)
SYNStar Award (2007)
Harvard College Scholar-Athlete of the Year Award (2007)
Phi Beta Kappa (2006)
Wayland Nolan Summer Fellowship for Chemistry Research (2005)
Detur Prize for Academic Excellence in the Freshman Year (2004)
John Harvard Scholarship (2004–2007)
Harvard College Dean's List (2004–2007)
National Merit Scholarship (2003–2007)
Rensselaer Medal Winner (2002)

PUBLICATIONS

• Ahmad, O. K.; Medley, J. W.; Coste, A.; Movassaghi, M. "Direct Synthesis of Azaheterocycles from *N*-Aryl/Vinyl Amides. Synthesis of 4-(Methylthio)-2-phenylquinazoline and 4-(4-Methoxyphenyl)-2-phenylquinoline." *Org. Synth.* **2012**, *89*, 549–561.

• Medley, J. W.; Movassaghi, M. "A Concise and Versatile Double-Cyclization Strategy for Highly Stereoselective Synthesis and Novel Arylative Dimerization of Aspidosperma Alkaloids." *Angew. Chem., Int. Ed.* **2012**, *51*, 4572–4576 (VIP).

• Medley, J. W.; Movassaghi, M. "Direct Dehydrative *N*-Pyridinylation of Amides." *J. Org. Chem.* **2009**, *74*, 1341–1344.

• Orendurff, M. S.; Rohr, E. S.; Segal, A. D.; Medley, J. W.; Green, J. R. III; Kadel, N. J. "Biomechanical Analysis of Stresses to the Fifth Metatarsal Bone during Sports Maneuvers: Implications for Fifth Metatarsal Fractures." *Phys. Sports Med.* **2009**, *37*, 87–92.

• Orendurff, M. S.; Rohr, E. S.; Segal, A. D.; Medley, J. W.; Green, J. R. III; Kadel, N. J. "Regional Foot Pressure During Running, Cutting, Jumping, and Landing." *Am. J. Sports Med.* **2008**, *36*, 566–71.

• Staples, R. J.; Medley, J. W. "(*S*)-(+)-1-(2-Bromophenyl)ethanol. *Acta Cryst.* **2008**, *E64*, o301.

PRESENTATIONS

• Medley, J. W. "Electrophilic Amide Activation: Mechanistic Insight and Synthetic Applications." MIT Graduate Research Symposium Oral Presentation (Cambridge, MA, May 2010).

• Orendurff, M. S.; Rohr, E. S.; Segal, A. D.; Medley, J. W.; Green, J. R. III; Kadel, N. J. "Metatarsal Fracture Mechanism: Acceleration Loads the Fifth Metatarsal More than Cutting." International Foot and Ankle Biomechanics Conference (Bologna, Italy, September 2008).

• Orendurff, M. S.; Rohr, E. S.; Segal, A. D.; Medley, J. W.; Green, J. R. III; Kadel, N. J. "Metatarsal Fracture Prevention: Can a More Flexible and Cushioned Boot Reduce 5th Metatarsal Pressures During Sporting Maneuvers?" Emed Scientific Meeting (Dundee, Scotland, July 2008).

• Medley, J. W. "Optically Active Amino Tetralins and Chromans: A Novel Highly Diastereoselective Lewis Acid Induced Intramolecular Cyclization Reaction." Amgen Department of Medicinal Chemistry (Thousand Oaks, CA, August 2006).

• Orendurff, M. S.; Rohr, E. S.; Segal, A. D.; Kweon, C.; Medley, J. W.; Green, J. R. III; Kadel, N. J. "Regional Foot Pressure During Running, Cutting, Jumping and Landing." International Society of Biomechanics 20th Conference (Cleveland, OH, August 2005).

TEACHING EXPERIENCE

- Head teaching assistant for undergraduate level second semester organic chemistry (MIT, 5.13, Professor Stephen Buchwald and Professor Timothy Jamison, Fall 2012).
- Head teaching assistant for undergraduate level first semester organic chemistry (MIT, 5.12, Professor Rick Danheiser and Professor Timothy Jamison, Spring 2008).
- Teaching assistant for undergraduate level first semester laboratory general chemistry (MIT, 5.310, Professor Jonas Peters, Fall 2007).

REFERENCES

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evans@chemistry.harvard.edu