SILVER (I) CATALYZED CYCLOISOMERIZATIONS OF ENESULFONAMIDES AND ENECARBAMATES

by

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B.Sc., University of British Columbia, 2005

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE STUDIES
(Chemistry)

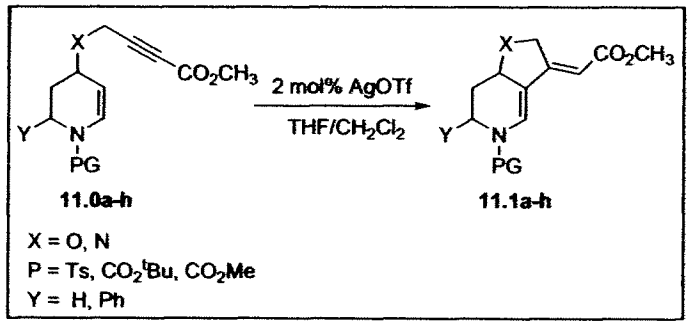
UNIVERSITY OF BRITISH COLUMBIA

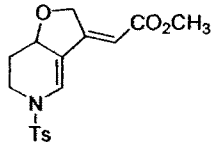
(Vancouver)

August 2008

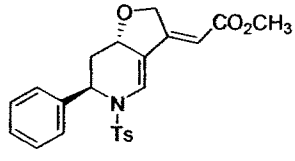
Abstract

Eight substrates with the general structure **11.0** were synthesized. The substrates differed with respect to the heteroatom tether (X = oxygen or nitrogen), nitrogen protecting group (PG = *p*-toluenesulfonamide, *tert*-butylcarbamate, methyl carbamate), and substitution on the ring (Y = H or Ph). Silver (I)-catalyzed cycloisomerizations of the enesulfonamide and enecarbamate substrates successfully gave eight diene products **11.1a-h** in poor to good yields (36-81%). Diene **11.1a** was also further subjected to the Diels Alder reaction, with acrolein and methacrolein to give tricyclic cycloadducts **11.21a** and **11.22a**.





11.1a



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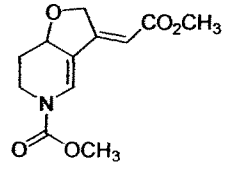

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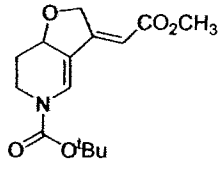

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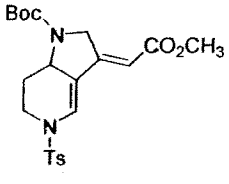

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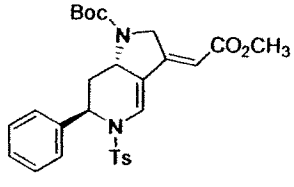

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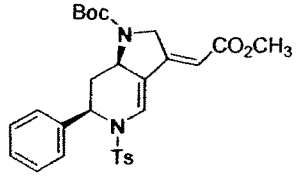
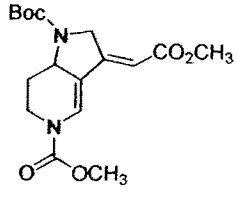


11.1g



11.1h

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δ	chemical shift
Å	Angstroms
$A^{1,3}$	allylic 1,3
Ac	acetyl
Anal.	analysis
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
brsm	based on recovered starting materials
^{t}Bu	*tert*-butyl
^{n}BuLi	*n*-butyllithium
^{o}C	degree Celcius
calcd	calculated
cm^{-1}	wavenumbers
COSY	correlational spectroscopy
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
ddd	doublet of doublet of doublets
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminum hydride
DMAP	*N,N*-(dimethylamino)pyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPPA	diphenylphosphorylazide
dt	doublet of triplets
EI	electron impact ionization

equiv	equivalent(s)
ESI	electrospray ionization
et. al	*et alii* (Latin)
g	gram(s)
h	hour(s)
HMQC	Heteronuclear Multiple-Quantum Correlation
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
J	coupling constant
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram(s)
MHz	MegaHertz
min	minute(s)
mL	milliliter(s)
μL	microliter(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonate
MS	mass spectroscopy, molecular sieves
N	Normal
NEt_3	triethylamine
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
OEt_2	diethyl ether
OMe	methoxy
OTf	trifluoromethanesulfonate
P	protecting group
PCy_3	tricyclohexylphosphine

Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
^{i}Pr	isopropyl
q	quartet
rt	room temperature
s	singlet
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
t	triplet
TBDPS	*tert*-butyldiphenylsilyl
td	triplet of doublets
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts, tosyl	*para*-toluenesulfonamide
UV	Ultraviolet
Z	zusammem (configuration)

Acknowledgements

First of all, I would like to thank my research supervisor, Gregory Dake, who led me through grad school with his guidance, patience, and continual encouragement through any difficulties and frustrations. I thank him for his dedication and the interest he takes in his students.

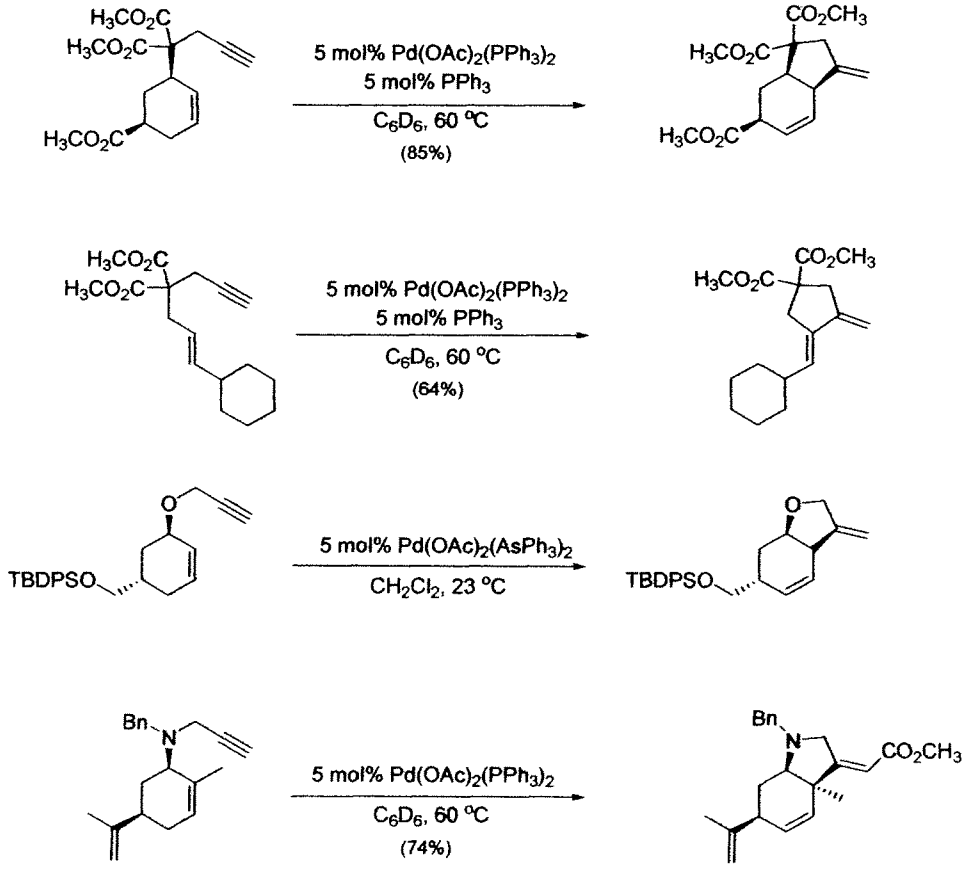
I would like to thank the past and present members of the Dake group: Paul Hurley, Tyler Harrison, Leah Easton, Jenn Kozak, Julien Dugal-Tessier, Jenny Dodd, and Emmanuel Castillo for their moral support and all the laughs we have shared together. I would especially like to thank Paul, Tyler, and Jenn for kindly helping me out when I first joined the group.

I would like to thank my parents, Benny and Fe Guieb, who have always been supportive in everything that I have done. I am where I am today because of what they have taught me and because of everything they have given me.

Last, but certainly not least, I would like to thank my boyfriend Justin Colobong who has been there for me through it all. I could not have accomplished this without his constant love and support, his understanding, and his undying faith in me.

I. Introduction

Transition metal catalyzed reactions allow the transformation of relatively simple starting materials into interesting and more complex structures, using relatively simple reaction conditions. Cycloisomerization reactions catalyzed by palladium, platinum, and gold have been widely studied and reviewed in the past 20 years.[1-6] Scheme 1 shows some cycloisomerizations of 1,6-enynes that can be achieved using transition metal catalysis. In each example, the reaction is typically initiated by coordination of the transition metal to a site of unsaturation (ie. alkenes or alkynes) in the substrate. Compared with platinum and palladium catalysis, silver catalysis has been studied to a lesser extent; however, more examples have been appearing in the literature.



Scheme 1: Palladium-Catalyzed Cycloisomerizations of 1,6-Enynes [4-6]

The ability of silver (I) to complex to alkenes was first demonstrated by Lucas *et al.* in 1937, through the formation of a water soluble isobutene-silver complex.[7] Winstein and Lucas expanded the scope of these studies in 1938, when they showed that silver (I) could rapidly and reversibly complex to a variety of alkenes, such as 1-hexene, cyclohexene, dimethylbutadiene, and allyl alcohol as shown in Figure 1.[8] Their research was based on a distribution method, which involved distributing the olefin between carbon tetrachloride and aqueous silver nitrate, then determining the quantity of alkene in the aqueous layer. When the olefin was distributed between carbon tetrachloride and various mixtures of aqueous silver nitrate/potassium nitrate, the quantity of olefin in the aqueous layer was again determined. The changes in the quantity of olefin in the aqueous layer could be compared to the changes in concentration of Ag^+ in the aqueous layer. Applying the same distribution method, Dorsey and Lucas found in 1956 that silver (I) also complexes with alkynes such as 3-hexyne.[9]

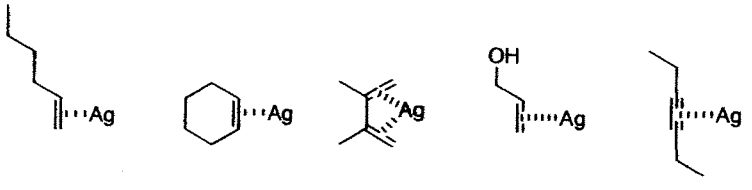
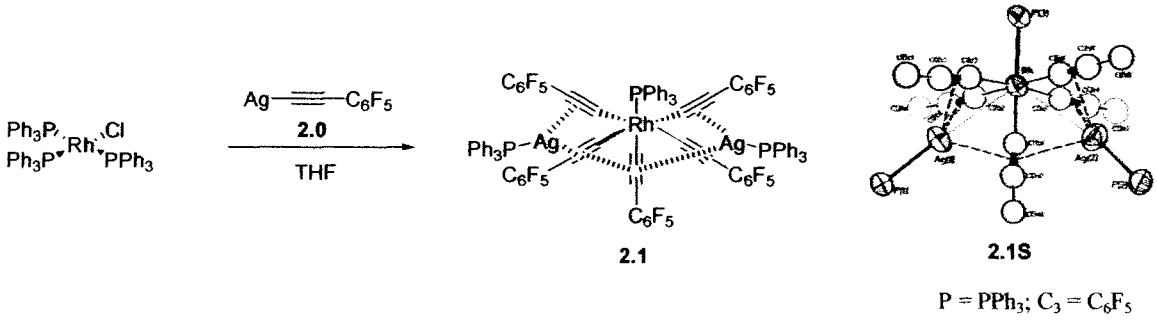


Figure 1: Silver (I) complexes with alkenes and 3-hexyne.[8,9]

In 1976, Lewandos *et al.* further studied silver (I) π-complexes with olefins and alkynes using NMR spectroscopy and IR spectroscopy.[10] In the ^1H NMR spectrum of cyclohexene the signals at 5.65 ppm and 1.97 ppm, due to the vinylic and allylic protons respectively, were shifted downfield to 5.87 ppm and 2.05 ppm respectively after 0.36 equiv of silver trifluoromethanesulfonate were added. The α and β protons in 3-hexyne were shifted downfield from 2.14 ppm to 2.23 ppm and from 1.04 ppm to 1.08 ppm, respectively, after the addition of 0.36 equiv of silver trifluoromethanesulfonate. The signals in the ^{13}C NMR spectra of various internal alkynes were all shifted downfield by 0.8 to 1.6 ppm, upon coordination to silver trifluoromethanesulfonate.[11] IR spectroscopy showed the stretching frequency of the carbon-carbon double bond in cyclohexene

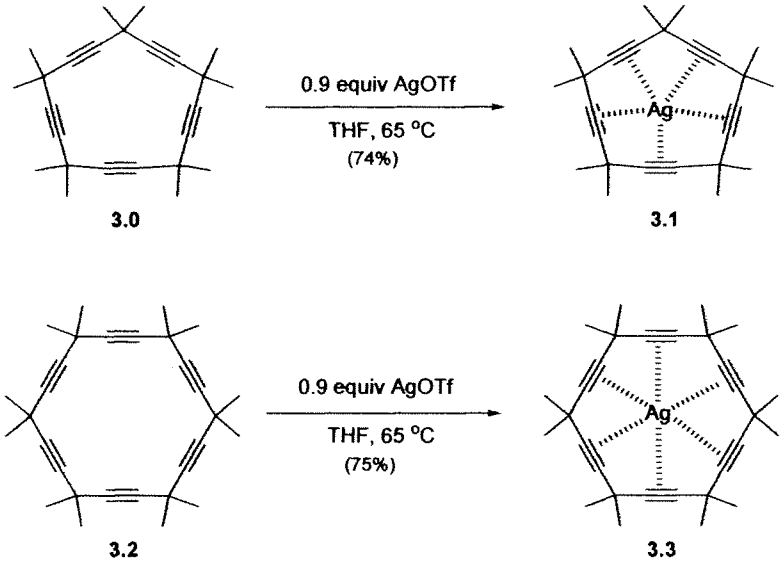
decrease from 1651 cm^{-1} to 1577 cm^{-1}.[10] The stretching frequency of the carbon-carbon triple bond in 2-hexyne decreased from 2210 cm^{-1} to 2181 cm^{-1} after the coordination of silver trifluoromethanesulfonate.[10] Finally, formation of the silver (I) π-complexes were also confirmed by elemental analysis.[10]

In 1974, Churchill and DeBoer reported solid state molecular structure **2.1S** in Scheme 2, that contained two silver atoms asymmetrically π-coordinated to three alkynes.[12] Complex **2.1** was synthesized from the reaction of Wilkinson's catalyst and



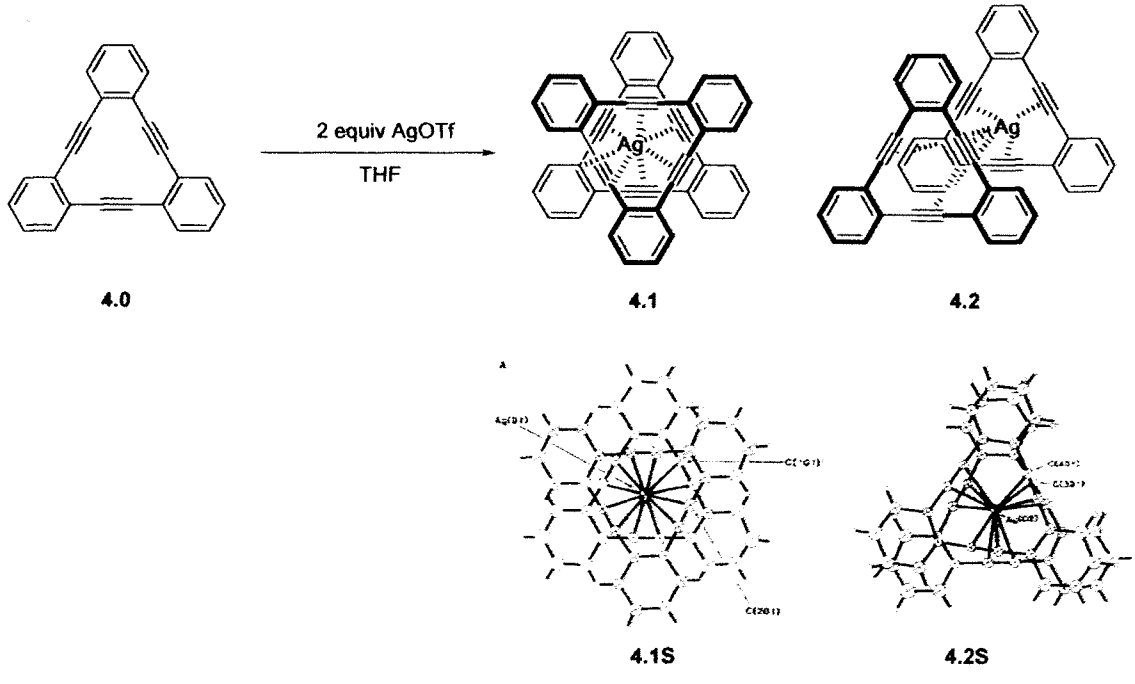
Scheme 2: Churchill's Molecular Structure and Solid State Molecular Structure of Tris(triphenylphosphine)pentakis(pentafluorophenylethynyl)rhodiumdisilver.[12]

silver acetylide **2.0**. The silver-carbon bond distances in the complex ranged from 2.33 – 3.12 Å. The acetylene bond lengths ranged from 1.20 – 1.23 Å, which is typical for a carbon-carbon triple bond.[13] In 1985, Scott *et al.* isolated two stable silver (I) complexes when polyacetylenes **3.0** and **3.2** in Scheme 3 were treated with silver trifluoromethanesulfonate and heated at 65 °C.[14] In 1988, Youngs *et al.* also isolated sandwich complexes of silver (I) with polyacetylene 1,2:5,6:9,10-tribenzocyclododec-1,5,9,-triene-3,7,11-triyne **4.0** (TBC).[15] In Scheme 4, both the staggered conformation (**4.1**) and the eclipsed conformation (**4.2**) of the complexes were isolated. The reported silver-carbon bond lengths ranged from 2.67 – 2.81 Å for **4.1S**, while the silver-carbon bond lengths for **5.2S** ranged from 2.47 – 2.94 Å. These are consistent with the silver-carbon bond lengths of 2.33 – 3.12 Å previously reported by Churchill.[16]

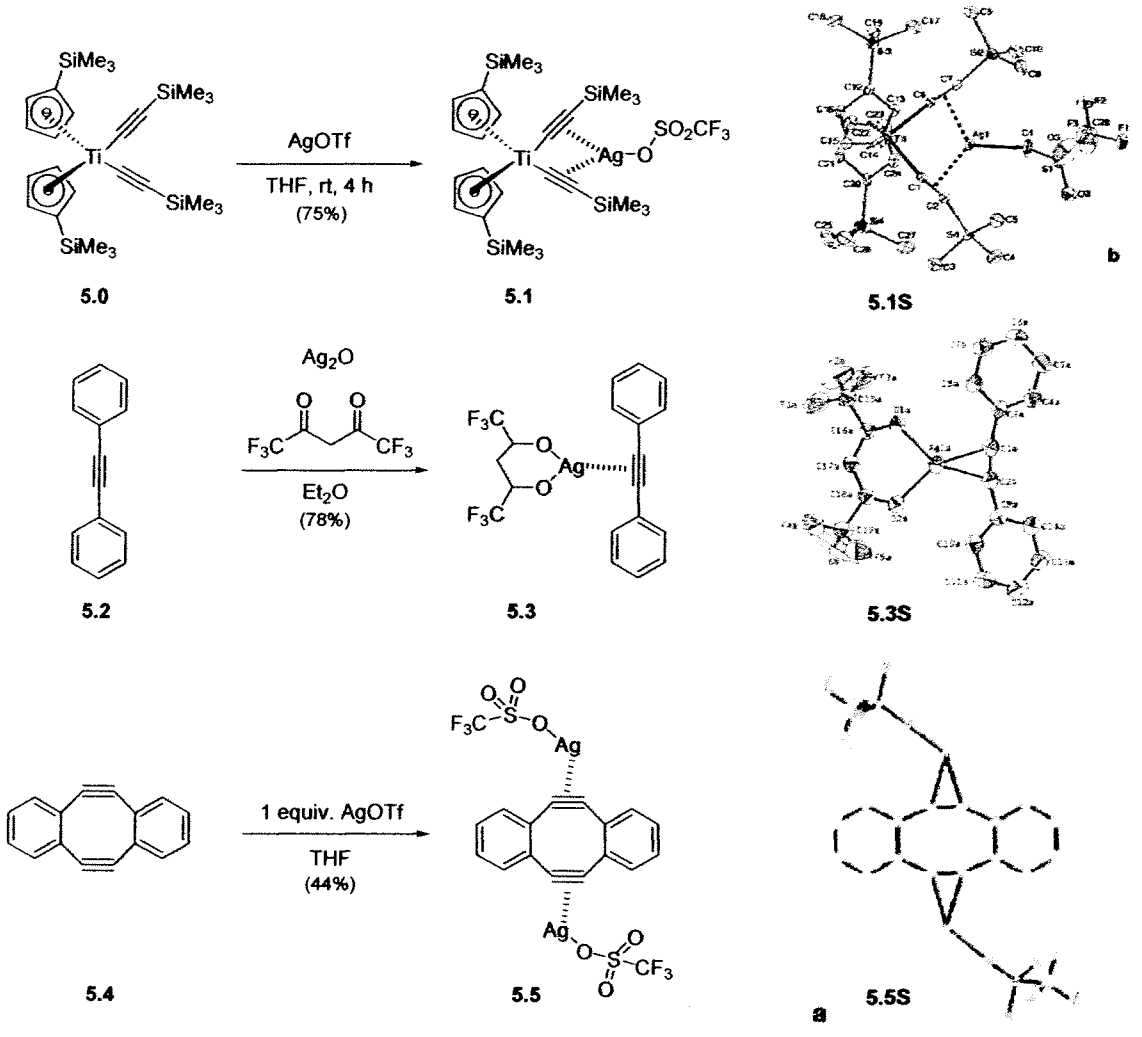


Scheme 3: Scott's Silver (I) complexes with Cyclic Polyacetylenes.[14]

Scheme 5 shows other examples of silver (I) alkyne complexes and their solid state molecular structures that have been reported in the literature.[17-19] Solid state molecular structures **5.1S**, **5.3S**, and **5.5S** show that the triflate anion remains coordinated



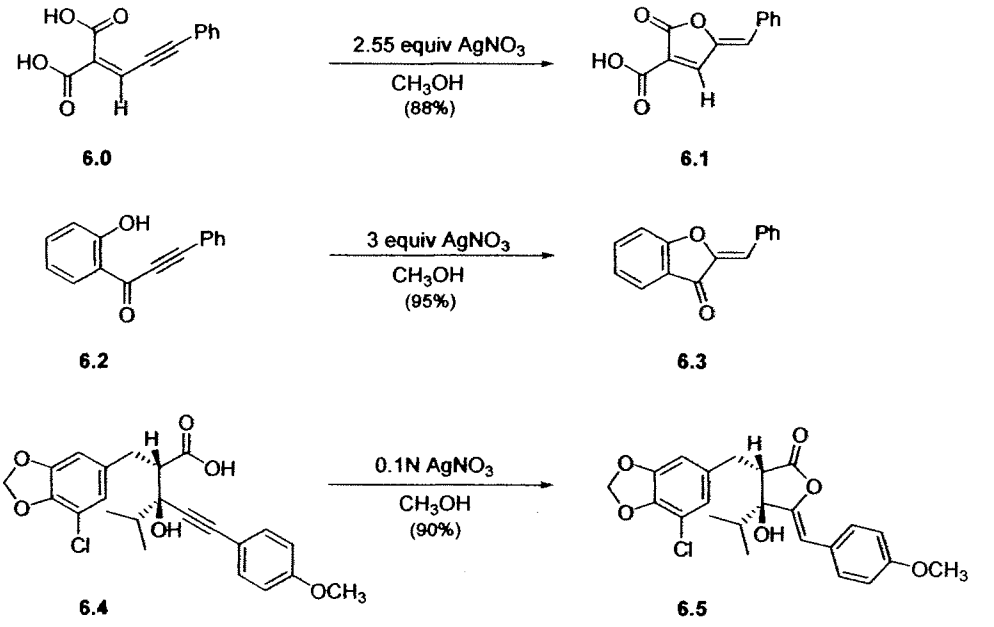
Scheme 4: 12-Membered Macrocycle Sandwich Complexes of Tribenzocyclododeca-1,5,9-triene-3,7,11-triyne (TCB) and the Solid State Molecular Structures.[15]



Scheme 5: Silver (I) Complexes and their Solid State Molecular Structures.[17-19]

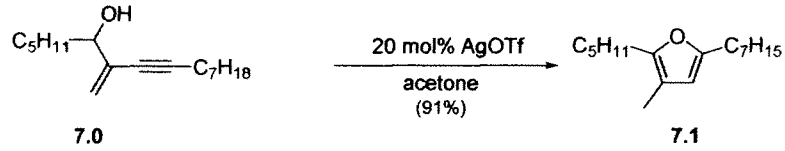
to silver while it coordinates to the alkyne. The silver-carbon bond lengths in all the complexes range from 2.26 - 2.48 Å and the acetylene bond lengths range from 1.20 Å to 1.24 Å. Gleiter *et. al* compared the acetylene bond lengths in biscyclooctyne derivative **5.4** before and after formation of the silver (I) complex. They found that the acetylene bond length increased from 1.202 Å to 1.224 Å after silver (I) was complexed to the alkyne. This lengthening of the acetylene bond, upon complexation of silver(I), suggests that complexation might weaken the carbon- carbon triple bond and perhaps make it reactive enough to act as an electrophile.

In 1958, Castaner and Pascual discovered that when an alkyne tethered to a weak nucleophile was treated with silver (I), the substrate isomerized to produce a ring and a newly formed carbon-oxygen bond.[20] Scheme 6 shows this cycloisomerization of phenylpropargylidenemalonic acid **6.0** into butenolide **6.1** after treatment with aqueous silver nitrate. Similar conditions were later used to synthesize aurone **6.3** from arylpropynone **6.2**.[21] In 1984, Willard *et al.* used a silver(I)-catalyzed cycloisomerization to form the butenolide in the last step of the total synthesis of cyanobacterin **6.5**.[22] In each of these examples, silver (I) presumably coordinates to the acetylene, activating it for intramolecular nucleophilic attack by adjacent alcohols and carboxylic acids. In



Scheme 6: Early silver(I)-catalyzed cycloisomerizations afforded butenolides.[20-22]

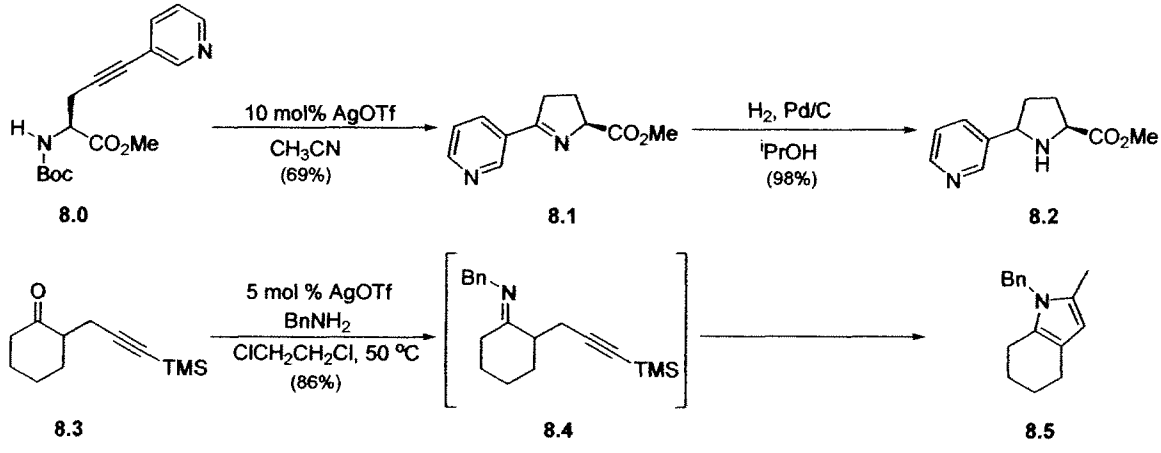
1995, Marshall and Sehon demonstrated that the treatment of β-alkynyl allylic alcohol **7.0** with catalytic silver trifluoromethanesulfonate would result in the formation of trisubstituted furan **7.1** (Scheme 7).[23]



7.0 7.1

Scheme 7: Marshall's synthesis of trisubstituted furans from alkynyl allylic alcohols.[23]

Several years later, Rutjes *et. al* showed that silver (I) salts could also catalyze the intramolecular addition of an amide to a carbon-carbon triple bond, to form a new carbon-nitrogen bond. In Scheme 8, propargyl glycine derivative **8.0** is treated with silver trifluoromethanesulfonate to afford pyrroline **8.1**, which can then be hydrogenated to give 2,5-disubstituted proline derivative **8.2**.[24] In 2006, Dake *et al.* found that β-alkynylimine **8.4**, formed *in situ* from β-alkynylketone **8.3**, would cyclize to produce trisubstituted benzyl-protected pyrrole **8.5** upon treatment with silver trifluoromethanesulfonate in 1,2-dichloroethane.[25]



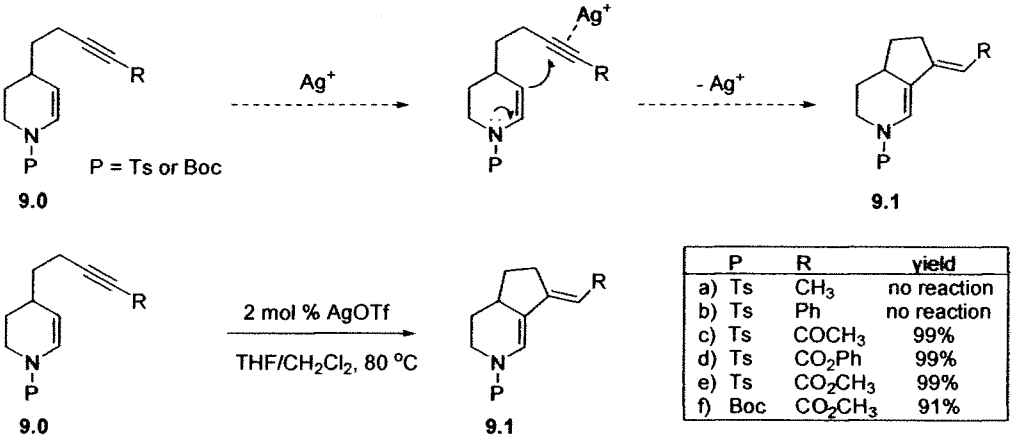
8.0 8.1 8.2

8.3 8.4 8.5

Scheme 8: Syntheses of prolines and pyrroles using Ag (I) Catalyzed Isomerizations.[24,25]

In 2004, Dake and Harrison presented examples of silver (I)-catalyzed cycloisomerization reactions in which intramolecular attack of enesulfonamide or enecarbamate onto an alkyne moiety resulted in a newly formed carbon-carbon bond, as

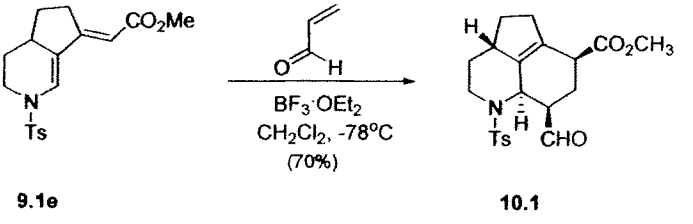
shown in Scheme 9.[26] Treatment of enesulfonamides **9.0** with 2 mol % silver trifluoromethanesulfonate in refluxing THF/CH_2Cl_2 afforded 1,3-dienes **9.1**. Several R groups attached to the alkyne in enesulfonamide **9.0** were tested. While alkyne substrates



P	R	yield
a) Ts	CH_3	no reaction
b) Ts	Ph	no reaction
c) Ts	$COCH_3$	99%
d) Ts	CO_2Ph	99%
e) Ts	CO_2CH_3	99%
f) Boc	CO_2CH_3	91%

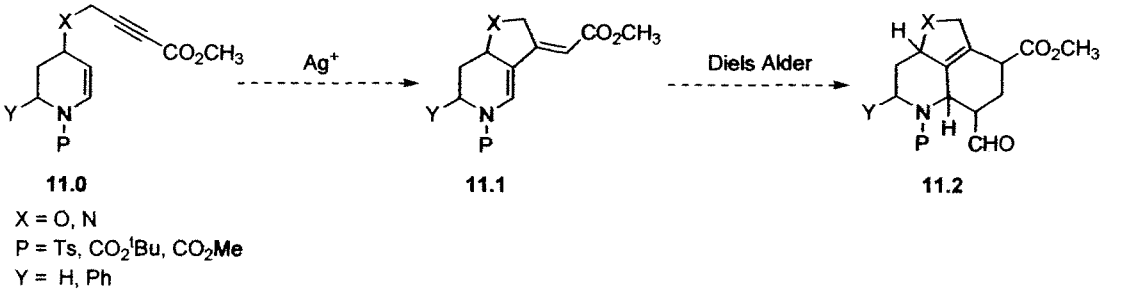
Scheme 9: Dake's Synthesis of 1,3-Dienes through Cycloisomerizations of Enesulfonamides and Enecarbamates.[26]

attached to alkyl groups (**9.0a-b**) showed no reaction, reactions using substrates containing conjugating electron-withdrawing groups such as ketones and esters **(9.0c-e)** were more successful. The electron-withdrawing groups served both to activate the alkyne and stabilize the reaction products. Enecarbamate **9.0f** also reacted under the same conditions to give diene **9.1f**. Diene **9.1e** was then used for a Diels Alder reaction with acrolein, in the presence of boron trifluoride diethyl etherate at -78 °C, to afford cycloadduct **10.1** in Scheme 10.



Scheme 10: Diels Alder Reactions on Diene **9.1e**[26]

The results from the silver (I) catalyzed cycloisomerizations of enesulfonamides and enecarbamate **9.0** were the inspiration of my research project. The reactions of these substrates resulted in the formation of a new carbon-carbon bond and a fused five-membered ring. If one carbon in substrate **9.0** could be substituted by a heteroatom (X = oxygen or nitrogen), as shown in Scheme 11, then perhaps the cycloisomerization of



Scheme 11: Proposed transformation for research project.

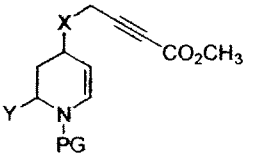
such a substrate **11.0** would result in the formation of a fused heterocycle **11.1**. Different protecting groups on nitrogen could also be varied and tested. Dienes such as **11.1** could then be subjected to further reactions such as the Diels Alder reaction, similar to reactions performed previously.

The next section will discuss the synthesis of the various substrates **11.0**, their reactions under silver (I) catalysis, and further reactivity that was studied.

II. Results and Discussion

A. Synthesis of Substrates

Eight cyclization substrates were synthesized in total; each substrate shares the same general structure shown in Figure 2. The substrates differ from one another by the heteroatom tethered to the ring (X = oxygen or nitrogen), the protecting group on nitrogen (P = Ts, $CO_2{}^tBu$, or CO_2Me), and the substitution pattern at position Y in the ring (Y = H or Ph). The synthesis of the oxygen-tethered substrates will first be discussed, followed by a discussion of the nitrogen-tethered substrates.



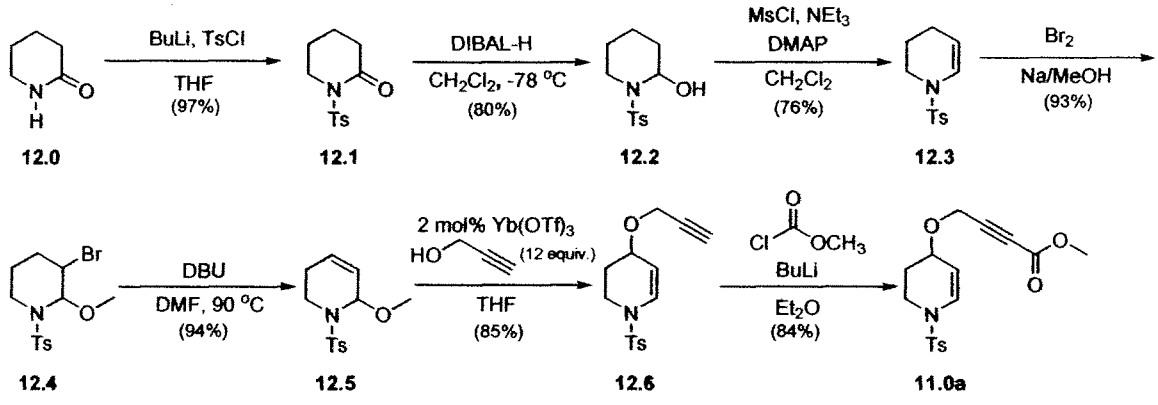
11.0

X = O, N
PG = Ts, $CO_2{}^tBu$, CO_2Me
Y= H, Ph

Figure 2: General structure of required substrates

1. Synthesis of Oxygen-Tethered Substrates 11.0a-d

The synthesis of enesulfonamide **11.0a** in Scheme 12 began with the tosylation of δ-valerolactam **12.0**.[27] Reduction of amide **12.1** to aminol **12.2** using diisobutylaluminum hydride, followed by elimination gave enesulfonamide **12.3**.[28] Methoxybromination, followed by elimination of the bromide ion using 1,8-diazabicyclo[5,4,0]undec-7-ene afforded allylic methyl ether **12.5**.[29] S_N1' reaction with propargyl alcohol in the presence of ytterbium (III) trifluoromethanesulfonate introduced the oxygen tether onto the ring of propargyl ether **12.6**.[30] Formation of **12.6** was confirmed by the disappearance of a 3-proton singlet in the ^1H NMR spectrum of

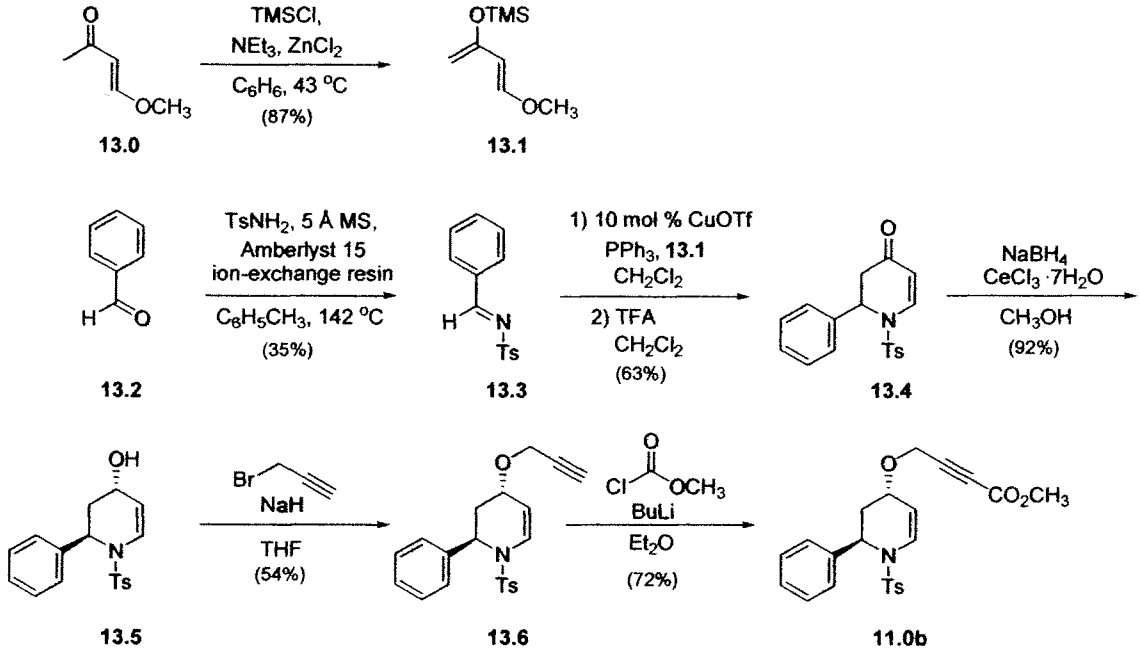


Scheme 12: Synthesis of Oxygen-Tethered Enesulfonamide **11.0a**

12.5 and the appearance of a 2-proton doublet in the ^{1}H NMR spectrum of **12.6**. The 4-proton multiplet at 2.37 – 2.41 ppm in the ^{1}H NMR spectrum of **12.6** is evidence of the presence of the terminal alkynyl proton, which overlaps with the 3-proton signal from the methyl group of the toluenesulfonamide functionality. Additionally, the 2-proton multiplet at 5.71 - 5.85 ppm, which corresponded to the alkene protons in the ^{1}H NMR spectrum of **12.5**, was replaced with two signals at 6.81 and 5.10 ppm that are characteristic of the newly formed double bond of the enesulfonamide moiety in **12.6**. The combination of these spectral data assists in differentiation between **12.5** and **12.6**. The presence of the enesulfonamide moiety in **12.6** means that the oxygen tether is no longer attached to the carbon adjacent to the nitrogen as in **12.5**, but rather is attached to the carbon allylic to the enesulfonamide, as in **12.6**. Functionalization of the terminal alkyne was accomplished by deprotonation of the alkyne with *n*-butyllithium at −78 °C, followed by quenching with methyl chloroformate to afford alkynyl ester **11.0a**.[33] The formation of **11.0a** was confirmed by the disappearance of the one proton singlet at 2.41 ppm, which corresponds to the terminal alkyne in the ^{1}H NMR spectrum **12.6**, and by the appearance of a 3-proton singlet at 3.75 ppm which corresponds to the methyl ester in **11.0a**.

The oxygen tether and enesulfonamide functionalities of alkynyl ester **11.0b** were constructed from an aza-Diels Alder reaction, as shown in Scheme 13. Danishefsky's

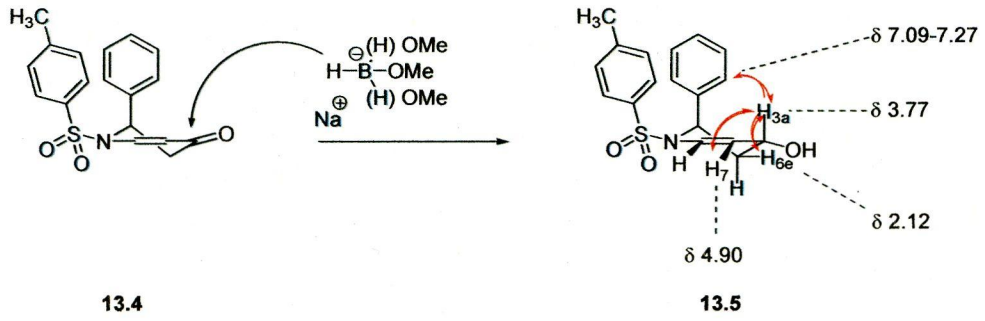
diene **13.1** was synthesized from the reaction of methoxybutenone **13.0** with triethylamine-zinc chloride, followed by subsequent trapping with trimethylchlorosilane.[31-32] Condensation of benzaldehyde **13.2** with *N*-toluenesulfonamide in the presence of an ion-exchange resin afforded *N*-tosylated aldimine **13.3**.[33] Copper (I)-catalyzed aza-Diels Alder reaction of diene **13.1** with aldimine **13.3**, followed by treatment with trifluoroacetic acid afforded enesulfonamide **13.4** as a racemic mixture.[34] Luche reduction of enesulfonamide **13.4** afforded alcohol



Scheme 13: Synthesis of Oxygen-Tethered, Phenyl-Substituted Enesulfonamide **11.0b**

13.5 with a relative trans stereochemistry.[35] The analysis for the assigned stereochemistry of **13.5** is shown in Figure 3. Due to $A^{1,3}$ strain, the phenyl ring is expected to adopt a pseudo-axial orientation. Luche reduction of dihydropyridones is known to preferentially occur through axial attack, to give equatorial alcohols.[36] Consequently, the hydride approaches enesulfonamide **13.4** from the pseudo-axial position, to give trans-alcohol **13.5**. ^{1}H selective NOE data in Figure 3 also support the

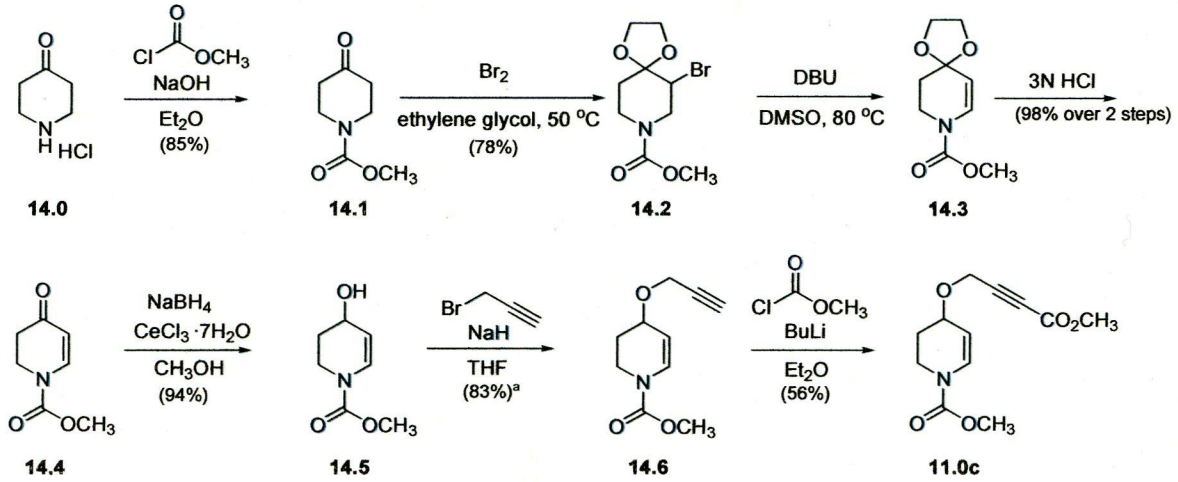
assigned trans stereochemistry. Selective irradiation of H-3a shows an NOE to the phenyl ring as well as to H-6a and H-7, supporting the assigned stereochemistry. Alkylation of alcohol **13.5** with propargyl bromide afforded propargyl ether **13.6**, which was finally functionalized with methyl chloroformate to give alkynyl ester **11.0b**.



13.4 **13.5**

Figure 3: Analysis of Stereochemistry and ^{1}H Selective NOE Data for Alcohol **13.5**

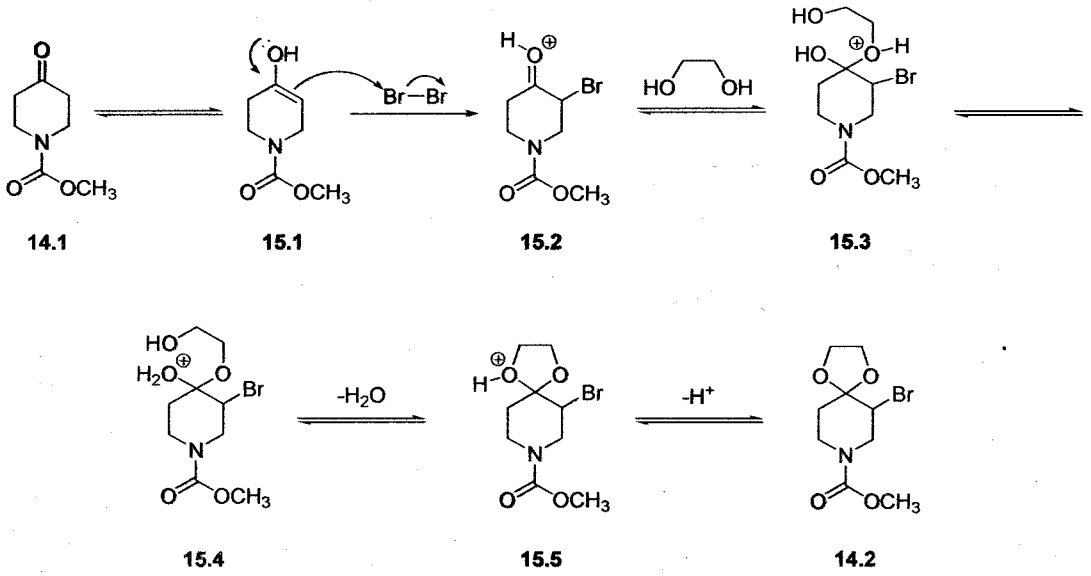
The synthesis of methyl carbamate **11.0c** in Scheme 14 was adapted from Kozikowski[37] and Schell,[38] with some modifications. Starting with piperidone hydrochloride **14.0**, the amine was protected using methyl chloroformate to afford methyl carbamate **14.1**. Using Garbisch's bromoketalization procedure, treatment of the



Scheme 14: Synthesis of Oxygen-Tethered Enecarbamate **11.0c**

[a] based on recovered starting material

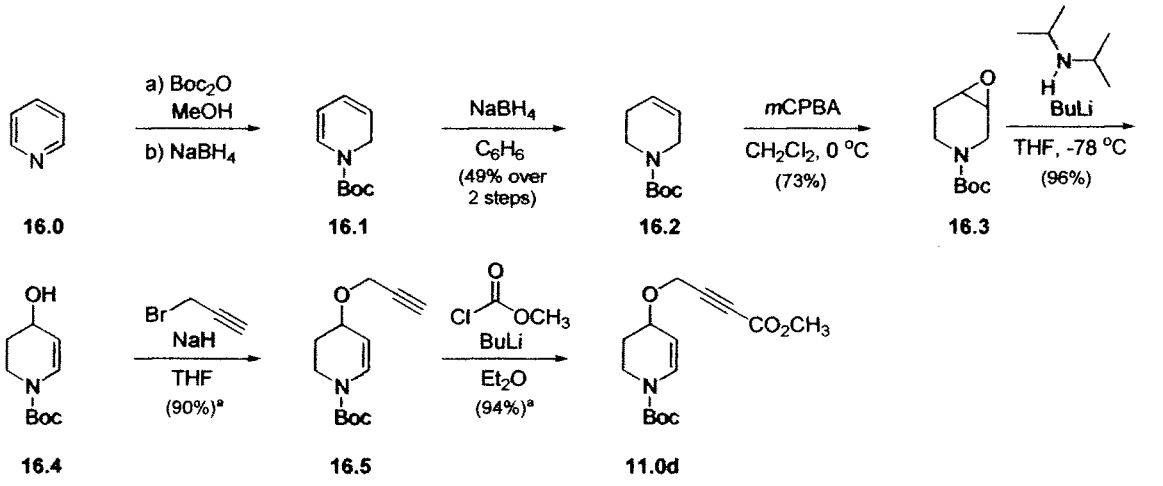
resulting carbamate with bromine and ethylene glycol served to α-brominate and protect the ketone in one step.[39] The mechanism of bromoketalization begins with the bromination of enol of **14.1**, as shown in Scheme 15. Protonated bromoketone **15.2** is activated for ketal formation with ethylene glycol. After proton transfer and production of water, bromoketal **14.2** is formed. With bromoketal **14.2** in hand, the synthesis of



Scheme 15: Mechanism of Bromoketalization.

enecarbamate **11.0c** continued with the elimination of the bromide ion of bromoketal **14.2** followed by ketal deprotection to afford enecarbamate **14.4**. Evidence for the formation of **14.4** is provided by the appearance of two doublets at 7.60 and 5.06 ppm in the ^{1}H NMR spectrum of **14.4**, which correspond to the double bond of the enecarbamate moiety. Luche reduction of enone **14.4** afforded alcohol **14.5** which was alkylated to give propargyl ether **14.6**.[40] Functionalization of **14.6** using methyl chloroformate afforded alkynyl ester **11.0c**.

Following a modified procedure of Oediger and Joop, the synthesis of *tert*-butyl carbamate **11.0d** began with the quaternization of pyridine **16.0** with di-*tert*-butyl-dicarbonate, followed by reduction with sodium borohydride to give *tert*-butyl carbamate **16.2**.[41,42] Treatment of *tert*-butyl carbamate **16.2** with *meta*-chloroperoxybenzoic acid



Scheme 16: Synthesis of Oxygen-Tethered *tert*-Butyl Carbamate **11.0d**.

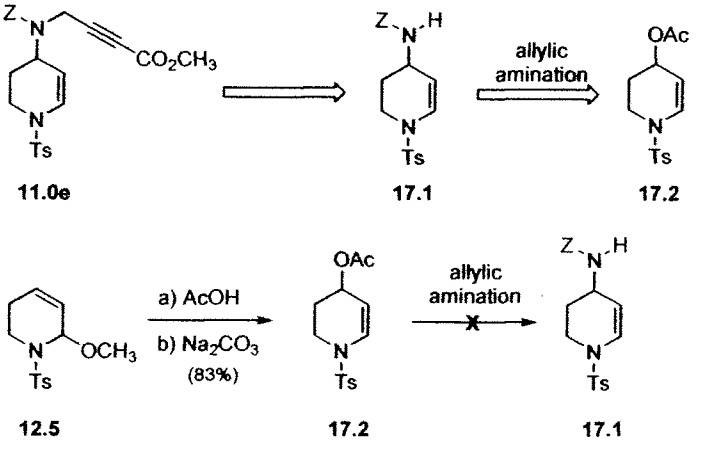
[a] based on recovered starting material

gave epoxide **16.3**. Lithium diisopropylamine, formed *in situ* from diisopropylamine and *n*-butyllithium at −78 °C, was used to open epoxide **16.3** and consequently introduce both the enecarbamate moiety and the alcohol at position 4 of enecarbamate **16.4**.[43] Again, the appearance of two multiplets 6.70 – 6.99 ppm and 4.79 – 5.08 ppm in the ^{1}H NMR spectrum of **16.4**, which correspond to the double bond of the enecarbamate moiety, confirm the formation of the enecarbamate. Finally, alkylation with propargyl bromide and functionalization with methyl chloroformate gave alkyl ester **11.0d**.

2. Synthesis of Nitrogen-Tethered Substrates 11.0e-h

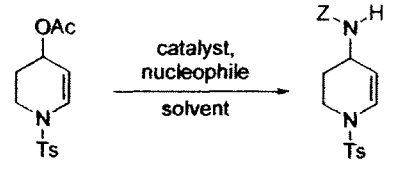
Substrates **11.0a-d** contain an oxygen-tether, with variations in the nitrogen protecting group and substitution pattern on the ring. The following substrates **11.0e-h** contain a nitrogen-tether, and also vary with respect to the nitrogen protecting group and the substitution pattern on the ring.

Retrosynthetically, the nitrogen tether of **11.0e** was envisioned to stem from amine **17.1**, which could be installed through an allylic amination of acetate **17.2** in Scheme 17. As a result, acetate **17.2** was synthesized from an S_N2' reaction of acetic acid and methyl ether **12.5**. Unfortunately, the proposed allylic amination was unsuccessful under the conditions that were tested. Allylic aminations of enesulfonamide acetates such as **17.2** have not been reported previously; however, they have been reported on cyclohexene rings.[44-48] In Table 1, reaction conditions using tetrakistriphenylphosphine palladium (0), triphenylphosphine, and sodium toluenesulfonamide, *p*-toluenesulfonamide gave no reaction (entry 1).[44] $[Pd(C_3H_5)Cl]_2$ and triphenylphosphine also gave no reaction (entry 2). Changing the nitrogen nucleophile to benzylamine (entries 3-6) or substituting triphenylphosphine for a bulkier ligand, such as



Scheme 17: Proposed Retrosynthesis of Nitrogen-Tethered Enesulfonamide **11.0e**, using an Allylic Amination

Table 1: Attempted Allylic Aminations to Introduce Nitrogen Tether [44-48]



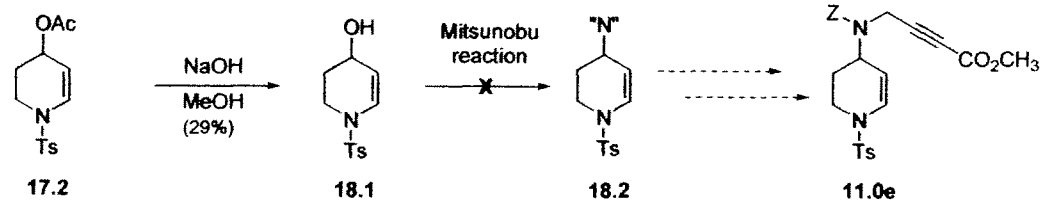
Z = Bn, Ts

Entry	Catalytic system	Nucleophile	Solvent	Temp (°C)	Result[a]
1	5 mol % $Pd(PPh_3)_4$, 5 mol % PPh_3	$TsNH_2$, NaNHTs	THF/DMSO (4:1)	50	NR
2	5 mol % $[Pd(C_3H_5)Cl]_2$, 5 mol % PPh_3	$TsNH_2$, NaNHTs	THF/DMSO (4:1)	50	NR
3	5 mol % $[Pd(C_3H_5)Cl]_2$, 5 mol % PPh_3	$BnNH_2$	CH_2Cl_2	45	NR
4	5 mol % $[Pd(C_3H_5)Cl]_2$, 5 mol % dppe	$BnNH_2$	CH_2Cl_2	45	NR
5	5 mol % $Pd_2(dba)_3$, 5 mol % PPh_3	$BnNH_2$	THF	80	NR
6	5 mol % $Pd_2(dba)_3$, 5 mol % PCy_3	$BnNH_2$	THF	80	NR

[a]NR = no reaction.

1,2- bis(diphenylphosphino)ethane (entry 4), did not give the desired product. Reactions using $Pd_2(dba)_3$ with triphenylphosphine (entry 5) or $Pd_2(dba)_3$ with electron-rich tricyclohexylphosphine (entry 6) were also unsuccessful.

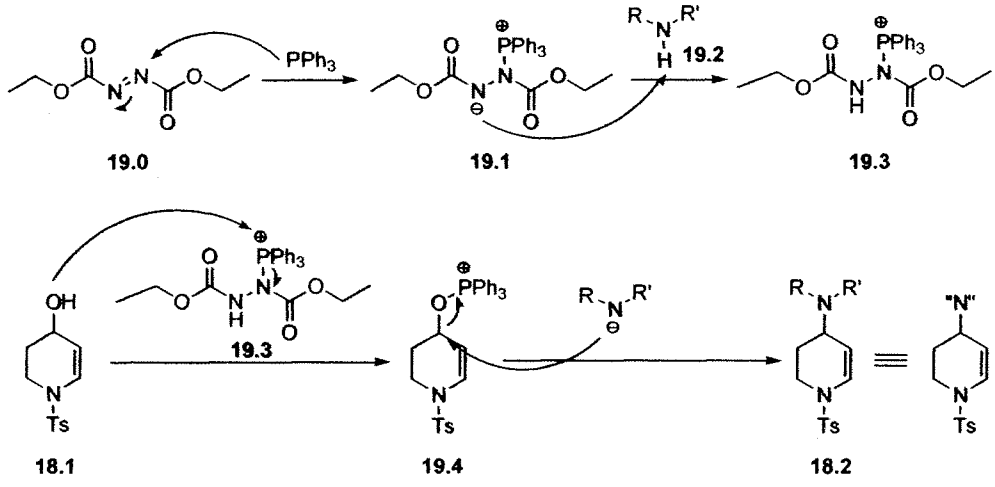
Another means of attaching the nitrogen tether could be through a Mitsunobu reaction from alcohol **18.1**, as shown in Scheme 18.[49] With this in mind, alcohol **18.1**



17.2 18.1 18.2 11.0e

Scheme 18: Proposed Synthesis for the Nitrogen Tether of Enesulfonamide **11.0e**, using a Mitsunobu reaction

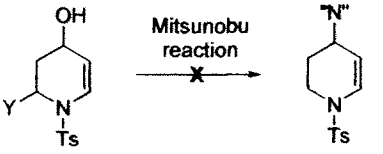
was synthesized from the saponification of acetate **17.2**. The mechanism of the ensuing Mitsunobu reaction is outlined in Scheme 19. The nitrogen-nitrogen double bond of

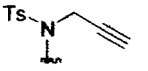
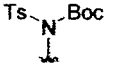
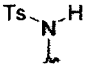
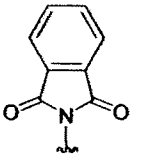


Scheme 19: Mechanism of the Mitsunobu Reaction

diethyl azodicarboxylate (DEAD) **19.0** is attacked by triphenylphosphine. Amine or amide **19.2** must be sufficiently acidic in order to protonate dicarboxylate **19.1**, to yield phosphonium cation **19.3**. Nucleophilic attack of alcohol **18.1** on phosphonium **19.3** forms phosphonium **19.4**, where alcohol **18.1** has been activated for nucleophilic attack by a nitrogen nucleophile. The result of the Mitsunobu reaction is the conversion of an alcohol to an amine or an amide in one step, with inversion of configuration. Unfortunately, the desired nitrogen-tethered products were not produced when alcohols **18.2** and **13.5** were treated under Mitsunobu conditions shown in Table 2. Reaction using 4-Methyl-*N*- prop-2-ynyl-benzenesulfonamide and DEAD (entry 1) gave no desired product.[50] Nitrogen nucleophiles such as *tert*-butyl-4-toluenesulfonyl carbamate (entry 2),[51,52] *p*-toluenesulfonamide (entry 3), and phthalimide (entry 4)[49,53,54] are more commonly used for Mitsunobu reactions because they are more acidic than 4- methyl-*N*-prop-2-ynyl-benzenesulfonamide (entry 1). Phthalimide and *p*-toluenesulfonamide were used in hopes that these nucleophiles were less sterically hindered and could more

Table 2: Attempted Mitsunobu Reaction Conditions to Introduce Nitrogen Tether [49-54]

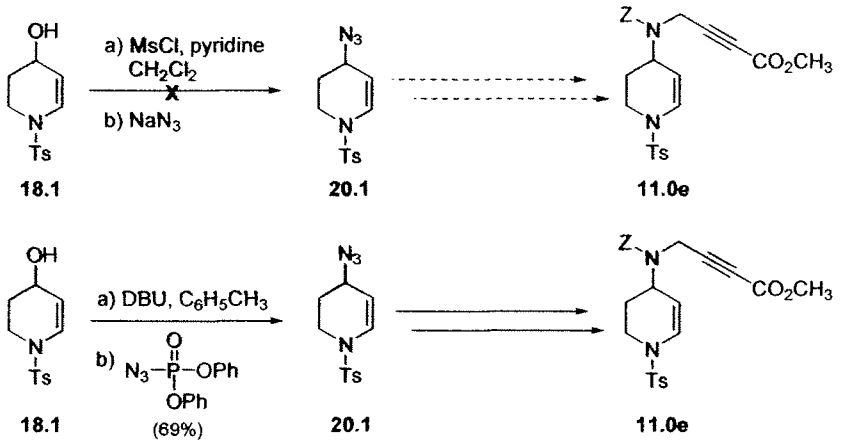


Entry	Y	Reaction Conditions	"N"	Result[a]
1	H	1.3 equiv. DEAD, 1.35 equiv. PPh_3		NR
2	H	1.0 equiv. DIAD, 1.0 equiv. PPh_3		NR
3	Ph	1.0 equiv. DIAD, 1.0 equiv. PPh_3		
4	Ph	1.3 equiv. DIAD, 1.35 equiv. PPh_3		NR
5	H	1.0 equiv. DIAD, 1.0 equiv. PPh_3		NR
6	Ph	3.0 equiv. DIAD, 3.0 equiv. PPh_3		

[a]NR = no reaction.

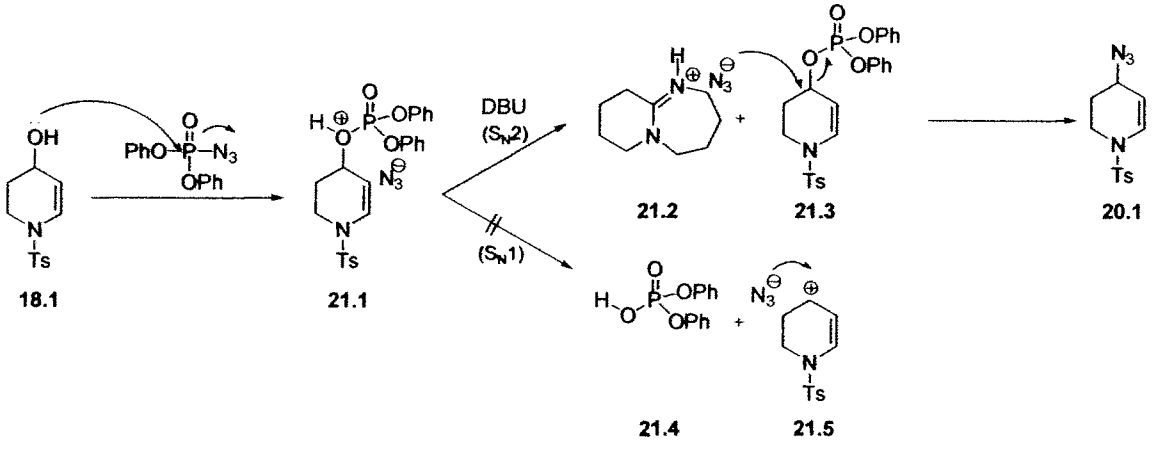
effectively attack the substrate. However, these reactions were also unsuccessful. Even the replacement of DEAD with the more reactive DIAD (diisopropyl azodicarboxylate), did not give the desired results.

With the failure of the Mitsunobu reaction, another approach was investigated. The nitrogen tether of enesulfonamide **11.0e** was envisioned to come from azide **20.1**, as shown in Scheme 20. Unfortunately, mesylation of alcohol **18.1** followed by treatment with sodium azide, did not give azide **20.1**. Gratifyingly, treatment of alcohol **18.1** with



Scheme 20: Proposed Synthesis for the Nitrogen Tether of Enesulfonamide **11.0e**, Through Conversion to an Azide.

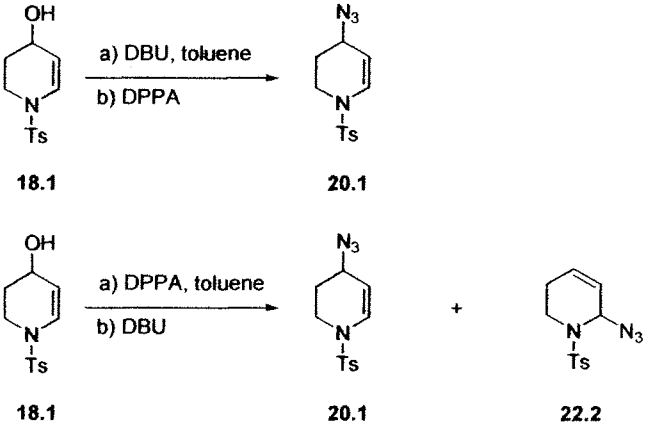
diphenylphosphorylazide (DPPA) and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in toluene afford the desired azide **20.1**.[55,56] In the mechanism of this reaction, shown in Scheme 21, the alcohol attacks diphenylphosphorylazide and generates an azide anion. Phosphate **21.1** is deprotonated by DBU to give salt **21.2** and phosphate **21.3**. The azide anion, produced *in situ*, attacks phosphate **21.3** in an S_N2 fashion to give azide **20.1**



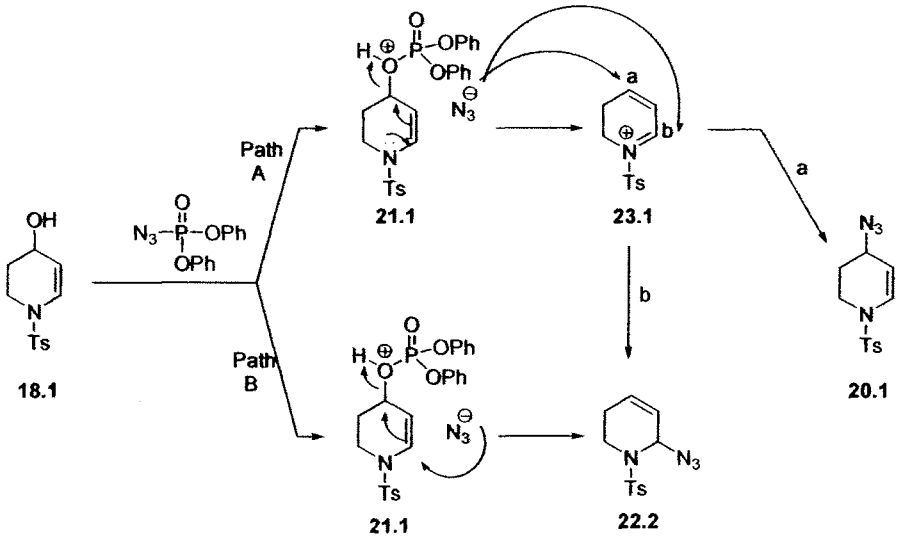
Scheme 21: Mechanism of Conversion from Alcohol to Azide using Diphenylphosphorylazide.

typically with inversion of configuration. Azidination using diphenylphosphorylazide can be considered an alternative to the Mitsunobu reaction.[55] Scheme 21 shows a competing S_N1 reaction pathway, in which phosphate **21.1** can dissociate into diphenylphosphate **21.4** and cation **21.5**. Addition of DBU to the reaction serves to deprotonate phosphate **21.1**, which prevents dissociation of phosphate **21.1** into diphenylphosphate **21.4** and cation **21.5**, and therefore suppresses the S_N1 reaction pathway.[55]

Consequently, the order in which the reagents were added to the reaction affected the experimentally observed products. When DPPA was added in the presence of DBU, as shown in Scheme 22, azide **20.1** was formed as the sole product. Presumably, the addition of DBU first allows phosphate **21.1** in Scheme 21 to be deprotonated as soon as it is formed, so that its reactivity towards other possible reaction pathways is inhibited. On the other hand, when DPPA is added before the addition of DBU, as shown in Scheme 22, azide **22.2** is observed alongside azide **20.1**. Scheme 23 shows two possible mechanistic pathways for the formation of azide **22.2**. Following Path A, the enesulfonamide moiety of phosphate **21.1** can displace the phosphate to give iminium ion **23.1**. Nucleophilic attack at position *a* would give the desired azide **20.1**, while



Scheme 22: Experimentally Observed Products,
based on the Order of Reagent Addition

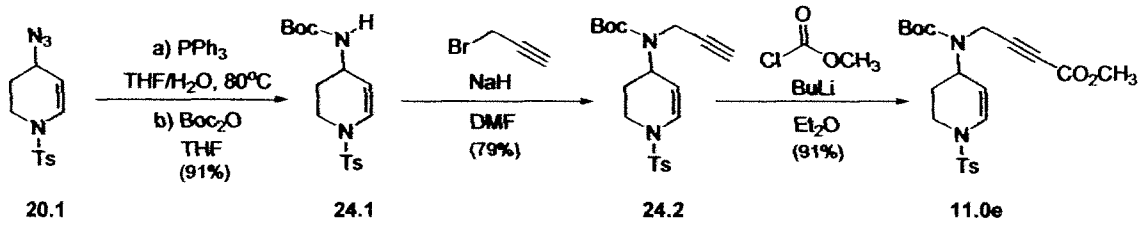


Scheme 23: Formation of unwanted side product, through two possible reaction pathways.

nucleophilic attack at position *b* would produce azide **22.2**. Alternatively, Path B shows formation of azide **22.2** through an S_N2' reaction mechanism. Since the addition of DPPA in the presence of DBU appeared to inhibit the formation of azide **22.2**, it is possible that Paths A and B are less likely to occur when phosphate **21.1** can be deprotonated as soon as it is formed.

The conversion to azide **20.1** from alcohol **18.1** is apparent from both the disappearance of the broad alcohol stretch at 3387 cm^{-1} in the IR spectrum of **18.1** and the appearance of an azide stretch at 2095 cm^{-1} in the IR spectrum of **20.1**. The formation of the desired azide **20.1** as opposed to azide **22.2** is confirmed by the signals at 6.93 and 5.02 ppm in the ^1H NMR spectrum of **20.1** which are characteristic of the polarized double bond of the enesulfonamide functionality.

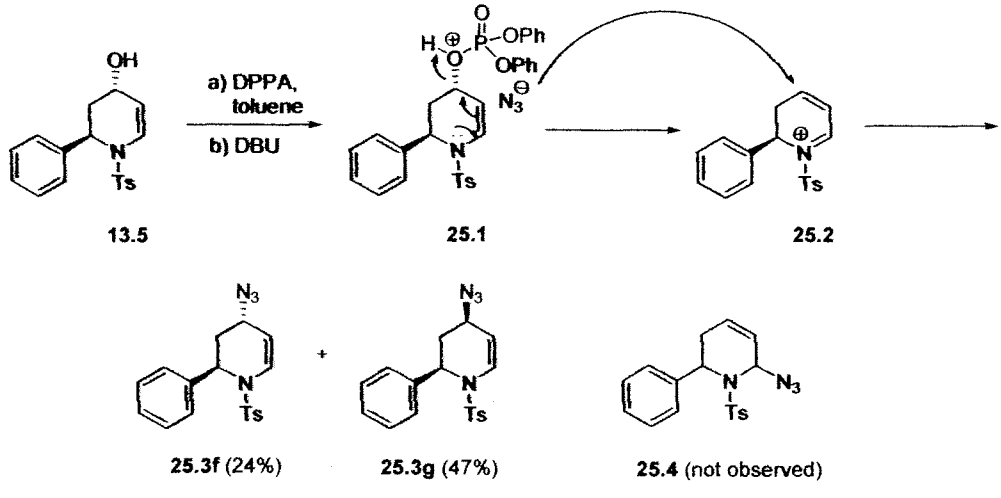
With azide **20.1** in hand, the synthesis of enesulfonamide **11.0e** in Scheme 24 continues with the reduction of azide **20.1** using the Staudinger reaction.[57] The resulting crude primary amine is immediately trapped with di-*tert*-butyl-dicarbonate to afford



Scheme 24: Synthesis of Nitrogen-Tethered Enesulfonamide **11.0e**

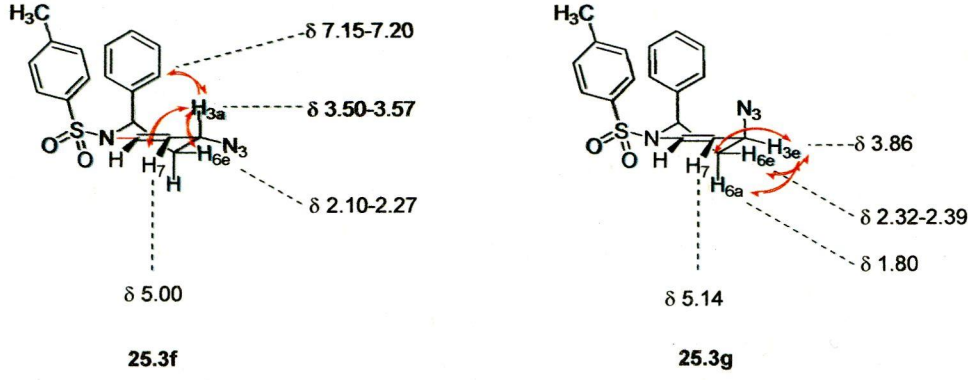
carbamate **24.1**.[58] Alkylation with propargyl bromide followed by functionalization with methyl chloroformate afforded alkyl ester **11.0e**.[59]

Alcohol **13.5** can also be converted into an azide, as shown in Scheme 25. As previously discussed, when DPPA is added before DBU, the enesulfonamide moiety of phosphate **25.1** can displace the phosphate to give iminium ion **25.2**. Nucleophilic attack of the azide anion on the nearly planar iminium ion generates two diastereomeric azides **25.3f** and **25.3g**. Azide **25.4** was not observed, perhaps due to steric bulk from the phenyl group and the tosyl group. The cis diastereomer **25.3g** is formed preferentially



Scheme 25: Mechanism for the Formation of diastereomers **25.3f** and **25.3g**

over the trans diastereomer **25.3f**. Since the phenyl ring prefers to be oriented in the axial orientation, the slight preference for the formation of the cis diastereomer can be rationalized by the stereoelectronic preference of axial attack of the azide anion.[36] The stereochemistries of the diastereomers were assigned using ^{1}H selective NOE data, as illustrated in Figure 4. Selective irradiation of H-3a in azide **25.3f** shows an NOE to H-6e, H-7, and the phenyl ring. Irradiation of H-3e in azide **25.3g** shows an NOE to H-6e, H-6a, and H-7, but does not show an NOE to the phenyl ring. This suggests that azide **25.3f** is the trans diastereomer and azide **25.3g** is the cis diastereomer. Furthermore, it is

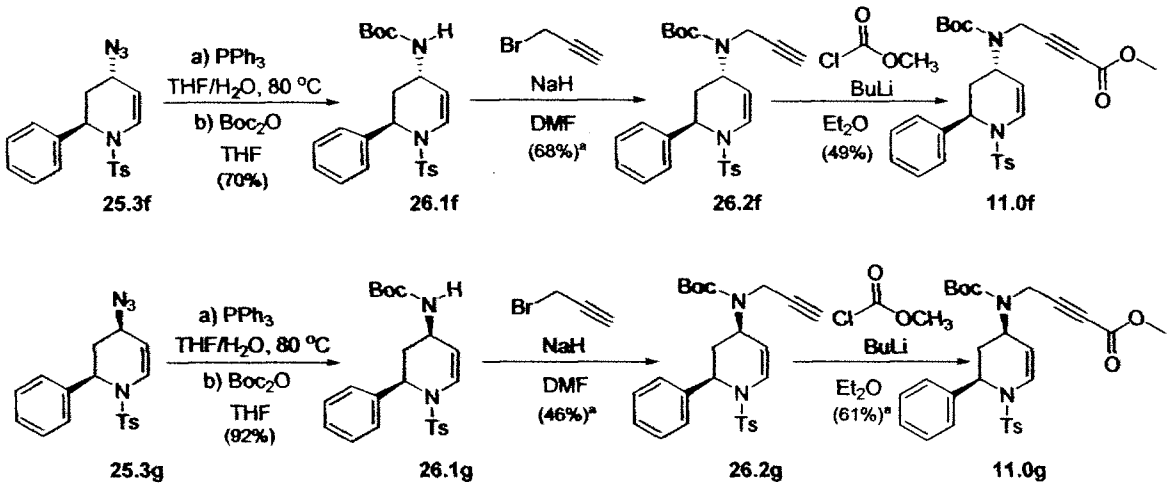


25.3f **25.3g**

Figure 4: ^{1}H Selective NOE Data for Azides **25.3f** and **25.3g**

known that axial protons typically resonate more upfield than equatorial protons, due to diamagnetic anisotropy.[60] The pseudo-axial proton H-3a in azide **25.3f** has a chemical shift of 3.50-3.57 ppm which is, as expected, more upfield than the pseudo-equatorial proton H-3e in azide **25.3g** whose chemical shift is 3.86 ppm.

The diastereomeric azides can then be separated and independently transformed into substrates **11.0f** and **11.0g** through the sequence of reactions previously discussed. In Scheme 26, azides **25.3f** and **25.3g** are subjected to the Staudinger reduction followed by trapping with di-*tert*-butyl-dicarbonate to give carbamates **26.1f** and **26.1g**.

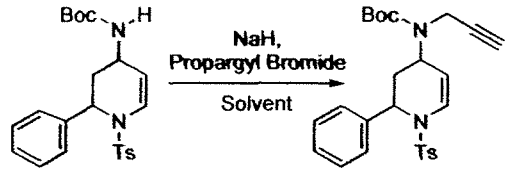


Scheme 26: Synthesis of Diastereomeric Enesulfonamides **11.0f** and **11.0g**.

[a] based on recovered starting material

The ensuing alkylation of *tert*-butyl carbamates **26.2f** and **26.2g** with propargyl bromide proved to be challenging, possibly due to the steric bulk of the phenyl ring, in addition to the steric bulk of the *tert*-butyl carbamate functionality. Table 3 outlines some conditions that were tested for the alkylation reaction for both carbamate **26.2f** and carbamate **26.2g**. Reactions performed in THF returned only starting material (entries 1-3). Reactions using 1.1 equiv NaH and 1.1 equiv propargyl bromide in DMF showed some product formation, from carbamate **26.1f** (entry 4). Increasing the equivalents of base and bromide used (2 equiv NaH and 6 equiv propargyl bromide) gave a slightly better yield (entry 5). This was also true for carbamate **26.2g** (entries 6 and 7). Further increasing the amount of base used or leaving the reaction longer did not improve reaction conditions (entry 8). Heating the reaction caused the formation of other products and therefore decreased product yield (entry 9). As expected, alkylation of **26.2g** (the cis diastereomer) gave lower yielding reactions compared with **26.2f** (the trans diastereomer). This difference in reactivity can be attributed to steric hinderance caused by the phenyl ring, in the cis diastereomer. Once terminal alkynes **26.2f** and **26.2g** were in hand, functionalization of with methyl chloroformate afforded enesulfonamides **11.0f** and **11.0g**.

Table 3: Reaction Conditions attempted for Alkylation of Carbamates **26.1f** and **26.2g**

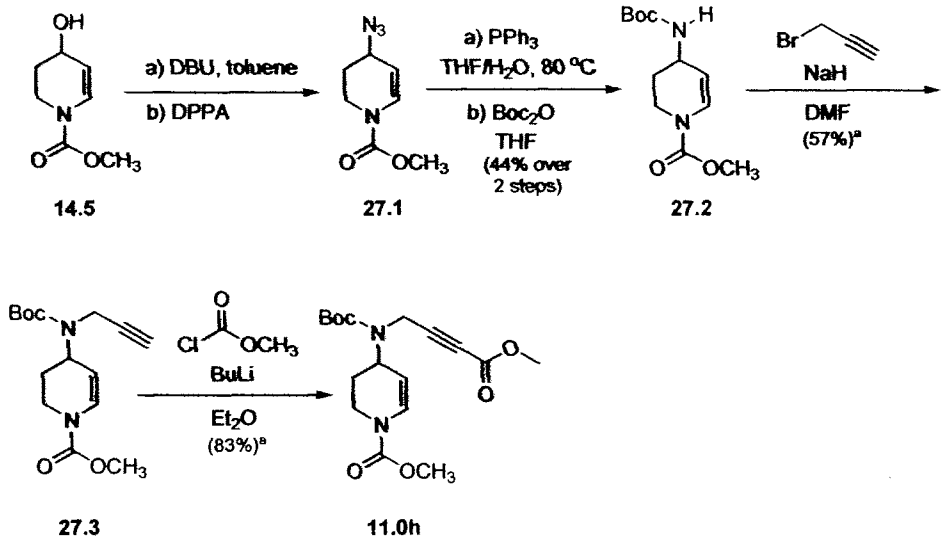


26.1 **26.2**

Entry	Diastereomer	Equiv NaH	Equiv Propargyl bromide	Solvent	Temp (°C), Reaction time[a]	Yield (%)[b,c]
1	**26.1f**	1.2	1.2	THF	rt, ON	NR
2	**26.1g**	1.2	1.2	THF	rt, ON	NR
3	**26.1g**	1.1	12	THF	rt, ON	NR
4	**26.1f**	1.1	1.1	DMF	rt, ON	31 (35 brsm)
5	**26.1f**	2.0	6	DMF	rt, ON	48 (68 brsm)
6	**26.1g**	1.6	7	DMF	rt, ON	17 (31 brsm)
7	**26.1g**	2	6	DMF	rt, ON	31 (46 brsm)
8	**26.1f**	5	5	DMF	rt, 2 days	25 (30 brsm)
9	**26.1g**	5	5	DMF	50°C, ON	7

[a]ON = overnight, [b]NR = no reaction, [c]brsm = based on recovered starting material

Enecarbamate **11.0h** was synthesized according to Scheme 27. Azidination of alcohol **14.5** using diphenylphosphorylazide, followed by Staudinger reduction and trapping with di-*tert*-butyl-dicarbonate gave carbamate **27.2**. Alkylation with propargyl bromide and functionalization of the terminal alkyne with methyl chloroformate gave enecarbamate **11.0h**.

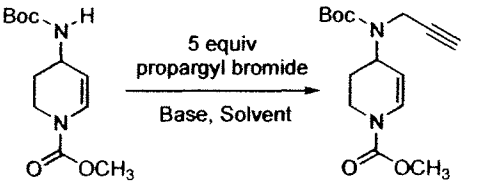


Scheme 27: Synthesis of Nitrogen-Tethered Enecarbamate **11.0h**.

[a] based on recovered starting material

The alkylation of **27.2** was again, more difficult than expected. This is most likely due to sterics from the *tert*-butyl carbamate. Table 4 shows some conditions that were tested. Reactions were unsuccessful when performed in THF, even when the base was changed to KH (entry 2) or when KI was used as an additive (entry 3). Reactions heated at 80 °C in DMSO or DMF showed decomposition (entries 4 and 5). Of the conditions that were tested, reaction at room temperature in DMF gave the best results, although the yield was still poor (entry 6). Heating the reaction at 50 °C in DMF did not produce more product (entry 7).

Table 4: Reaction Conditions attempted for Alkylation of Carbamates **26.2**

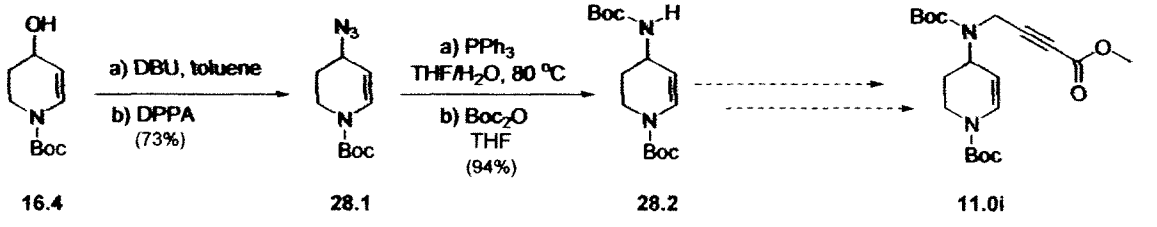


27.2 **27.3**

Entry	Base (equiv)	Additives (equiv)	Solvent	Temp (°C)	Yield (%)[a,b]
1	NaH (2)		THF	80	NR
2	NaH (2)	KI (0.5)	THF	80	NR
3	KH (1.5)		THF	80	NR
4	NaH (2)		DMSO	80	Decomposition
5	NaH (2)		DMF	80	Decomposition
6	NaH (2)		DMF	rt	39 (57 brsm)
7	NaH (2)		DMF	50	27

[a]NR = no reaction, [b]brsm = based on recovered starting material

The synthesis of nitrogen-tethered *tert*-butyl enecarbamate **11.0i** was attempted, as shown in Scheme 28, but was not completely successful. Azidination of alcohol **16.4** followed by Staudinger reduction and trapping with di-*tert*-butyl-dicarbonate successfully afforded carbamate **28.2**. However, further attempts to alkylate carbamate **28.2** were

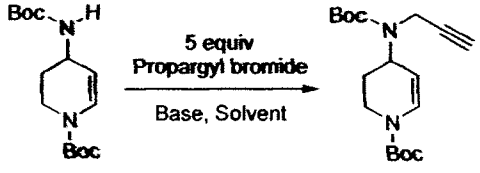


16.4 **28.1** **28.2** **11.0i**

Scheme 28: Attempted Synthesis of *tert*-Butyl carbamate Cyclization Precursor

problematic. Conditions for the alkylation reaction, shown in Table 5, that produced at least a little product for carbamates **26.1** and **27.2** gave no either no reaction or decomposition. Although this reaction was not further investigated, there are still a variety of other reactions conditions that can be attempted.

Table 5: Reaction Conditions attempted for Alkylation of Carbamate **28.2**



28.2

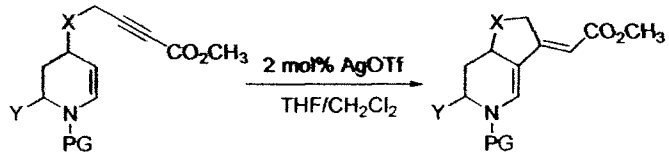
Entry	Equiv NaH	Solvent	Temp (°C)	Yield (%)[a]
1	2	DMF	rt	NR
2	3	DMF	50	Decomposition

[a]NR = no reaction.

B. Cycloisomerization Reactions

With substrates **11.0a-h** in hand, treatment with silver(I) trifluoromethanesulfonate gave cycloisomerization products **11.1a-h**, as anticipated (Table 6). While both enesulfonamides **11.0a** and **11.0b** showed fairly good reactivity, phenyl-substituted enesulfonamide **11.0b** reacted faster than its non-substituted counterpart **11.0a** (entries 1 and 2). It is possible that the bulky phenyl ring forces the alkyne tether away from one side of the 6-membered ring, and closer to the side where it can react with the enesulfonamide moiety. Oxygen-tethered enecarbamates **11.0c** and **11.0d** were more reactive than enesulfonamides **11.0a** and **11.0b**, and they did not require

Table 6: AgOTf-Catalyzed Cycloisomerizations of **11.0a-h**



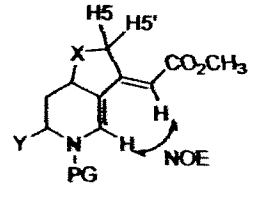
Entry	Substrate	X	Y	P	Temp (°C)	Time (h)	Product	Yield (%)
1	**11.0a**	O	H	Ts	80	16	**11.1a**	73
2	**trans-11.0b**	O	Ph	Ts	80	6	**trans-11.1b**	70
3	**11.0c**	O	H	CO_2Me	rt → 60	1.25	**11.1c**	36
4	**11.0d**	O	H	$CO_2{}^tBu$	rt	0.3	**11.1d**	75
5	**11.0e**	N-Boc	H	Ts	80	3	**11.1e**	81
6	**trans-11.0f**	N-Boc	Ph	Ts	80	3.5[a]	**trans-11.1f**	20
7	**cis-11.0g**	N-Boc	Ph	Ts	80	3.5	**cis-11.1g**	63
8	**11.0h**	N-Boc	H	CO_2Me	rt	24	**11.1h**	52

[a] 5 mol% AgOTf was used.

heating to promote product formation (entries 3 and 4). Nitrogen-tethered enesulfonamides **11.0e-g** were overall more reactive than the oxygen-tethered enesulfonamides, based on reaction time. Cycloisomerization of nitrogen-tethered **11.0e** was complete in 3 hours with good yield (entry 5). Diastereomer **11.0g** cyclized similarly, but with a poorer yield (entry 7). Diastereomer **11.0f** showed only 30% conversion after 23 h when 2 mol% AgOTf was used. Using 5 mol% AgOTf decreased reaction time, but the yield was poor. The cycloisomerization product was very difficult to separate from another byproduct formed. Surprisingly, the cis diastereomer **11.0g** cyclizes more readily than trans diastereomer **11.0f**. With the phenyl ring and the nitrogen tether on the same side of the ring in **11.0g**, perhaps the steric bulk of the phenyl ring is more pronounced and keeps the alkyne tether locked in the correct position to react with the enesulfonamide moiety. That is, steric bulk from the phenyl ring minimizes rotation

about the C-X bond, so that the alkyne is more likely to be in the correct position to cyclize with the enesulfonamide. Similar to the oxygen-tethered substrates, nitrogen-tethered enecarbamate **11.0h** cyclized successfully at room temperature, although the yield was poor (entry 8).

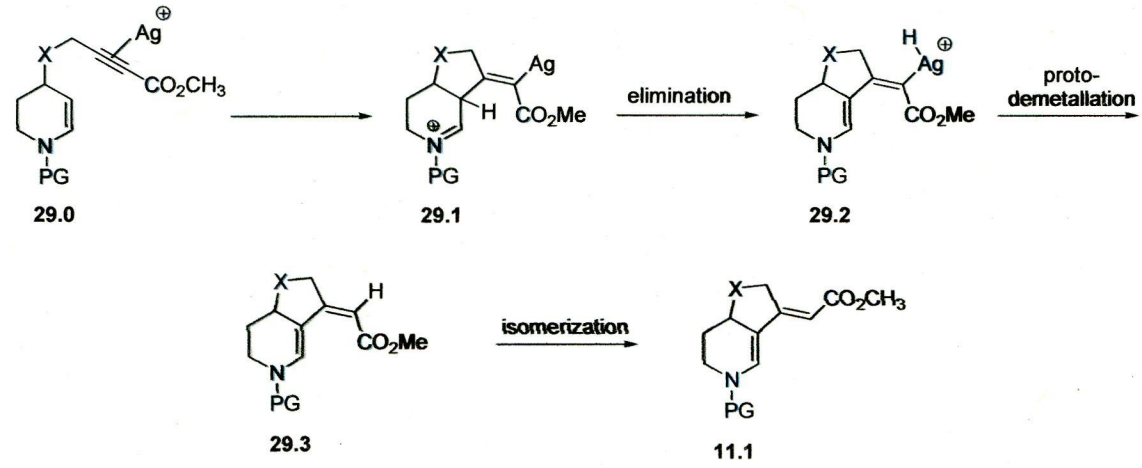
The NMR data for all cyclization products **11.11a-h** can be found in the Appendix. Formation of the diene products **11.1** can be confirmed by NMR spectroscopy. Structural assignments of substrates **11.1b, 11.1d,** and **11.1e** were established by ^{1}H-^{1}H COSY 2D NMR spectroscopy, as well as HMQC spectroscopy (see Appendix). In the ^{13}C NMR spectra, the two signals between 75-95 ppm due to the alkynyl carbons in the cyclization substrates **11.0** are replaced with two new signals between 100-130 ppm, due to the newly formed carbon-carbon double bond. In the ^{1}H NMR spectra of the oxygen-tethered substrates, the cyclization products can be recognized by the formation of two doublet of doublets between 4.5-5.1 ppm, that are characteristic of the two diastereotopic protons formed after cyclization (H-5 and H-5' in Figure 5). In the nitrogen-tethered substrate, the signals from the two diastereotopic protons overlap, to form a broad singlet. The cis configuration of the diene is confirmed by the NOE correlation between the alkenyl protons, as shown in Figure 5.



11.1

Figure 5: ^{1}H Selective NOE Correlation between alkenyl protons in **11.1**

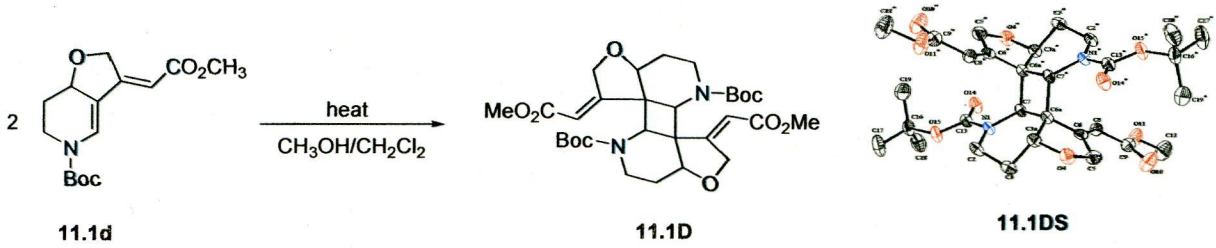
A mechanism for the cycloisomerization is proposed in Scheme 29, based on literature precedent of other metal-catalyzed cycloisomerizations.[30, 65] Silver (I) can coordinate to the alkyne of substrate **11.0** and activate it for nucleophilic attack from the enesulfonamide moiety, to give iminium ion **29.1**. Elimination would give



Scheme 29: Proposed Mechanism of Cycloisomerization Reaction.

enesulfonamide or enecarbamate **29.2**. Protodemetallation followed by isomerization would give the experimentally observed product **11.1**.

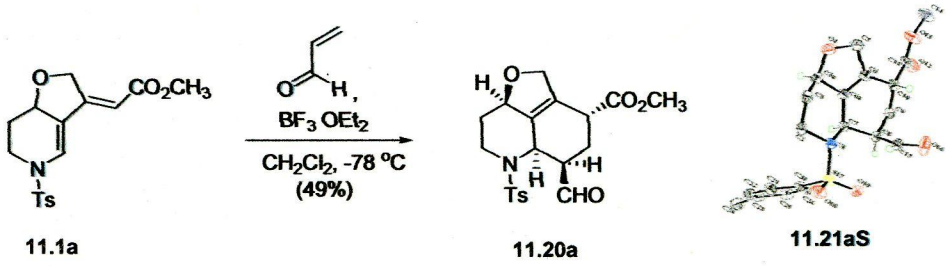
As previously mentioned, the enecarbamate substrates were more reactive than the enesulfonamide substrates, and they underwent cycloisomerization at room temperature. Enecarbamate **11.1d** was heated in a mixture of methanol/dichloromethane in a test tube about 5 cm above a hotplate. Upon heating, diene **11.1d** had formed dimer **11.1D** through a [2+2] cycloaddition of the enecarbamate moiety. Such [2+2] cycloadditions of enecarbamates have been previously reported in the literature.[61,62] Solid state molecular structure **11.1DS** in Scheme 30 confirms the formation of diene **11.1d** and also confirms the Z orientation of the ester on the alkene.



Scheme 30: Solid State Molecular Structure of Dimer **11.1D**

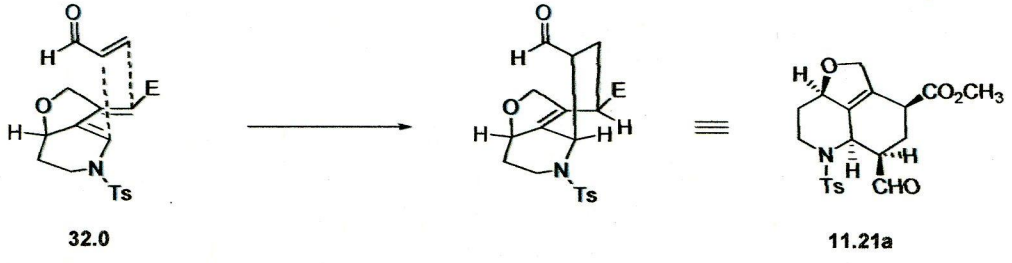
C. Further Results

Further reactivity of diene **11.1** to the Diels Alder reaction was tested. Scheme 31 shows that treatment of diene **11.1a** with acrolein and boron trifluoride diethyl etherate at −78 °C affords cycloadduct **11.21a.** Solid state molecular structure **11.21aS** verifies the stereochemistry of product **11.20a**. However, the transition state depiction of this

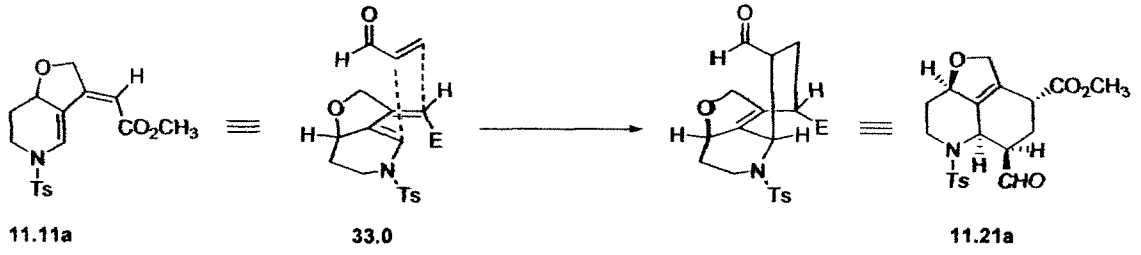


Scheme 31: Diels Alder Reaction of Diene **11.1a** with Acrolein

reaction, shown in **32.0** of Scheme 32, predicts formation of cycloadduct **11.21a**. However, the expected product **11.21a** is different than the obtained product **11.20a**, with respect to the stereochemistry at the center alpha to the ester group. There are three possible explanations for this discrepancy. One explanation is that the stereochemistry of



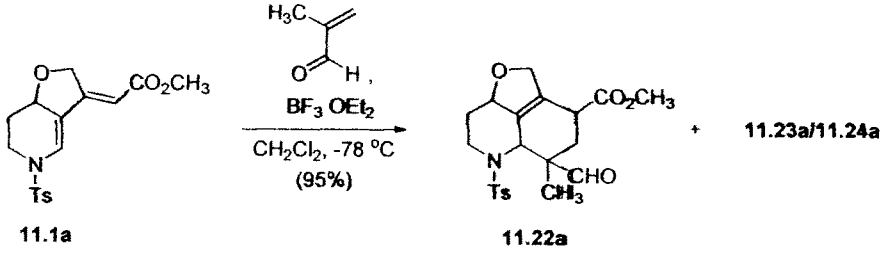
Scheme 32: Transition State Depiction for
Diels Alder Reaction of Diene **11.1a** with Acrolein



Scheme 33: Transition State Depiction for
Diels Alder Reaction of Diene **11.11a** with Acrolein

starting material is not that shown in **11.0a**, but is actually that shown in **11.11a** in Scheme 33. The transition state depiction of the Diels Alder reaction starting with **11.11a** predicts a product with the same stereochemistry as the obtained product. Another possible explanation is epimerization at the center alpha to the ester group, since that proton is slightly acidic. Finally, if the reaction proceeds through a stepwise mechanism, rather than a concerted mechanism, this can also explain the stereochemistry of the obtained product. In order to fully understand what occurring, it would be necessary to conduct further investigations.

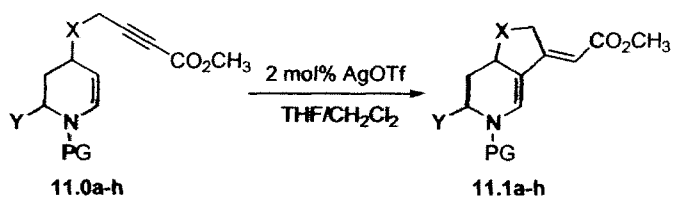
Diene **11.1a** also undergoes reaction with methacrolein in the presence of boron trifluoride diethyl etherate at −78 °C to afford cycloadduct **11.22a** and an inseparable mixture of diastereomers **11.23a** and **11.24a** (Scheme 34).



Scheme 34: Diels Alder Reaction of Diene **11.1a** with Methacrolein

III. Conclusion and Future Research

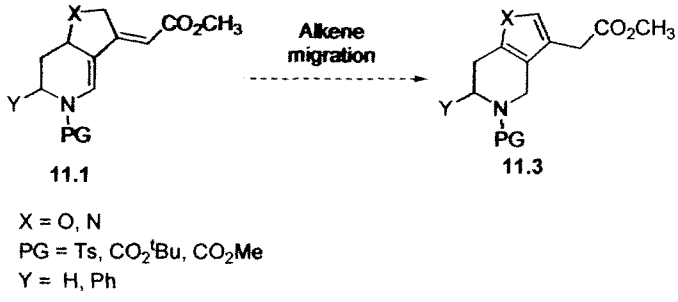
Eight substrates of the general structure **11.0** in Scheme 35 were synthesized. The substrates differed with respect to the heteroatom tether, nitrogen protecting group, and substitution on the ring. The key silver(I)-catalyzed cycloisomerizations of each substrate successfully gave products **11.1a-h**. The enecarbamate substrates were generally more reactive than the enesulfonamide substrates, and they underwent cycloisomerization at room temperature. The product yields were generally good (63-81%), except for the poor yields of the methyl carbamate products (36-52%). While these product yields are generally reasonable, they are not as good as the 99% yields obtained from the cycloisomerizations of the all-carbon substrates.[26] The routes to synthesize cyclization precursors **11.0a-h** could also be optimized either to minimize the number steps or to improve the yields of individual steps.



Scheme 35: Key silver (I)-catalyzed cycloisomerization

On the other hand, one advantage of the methodology is the success of the cycloisomerizations using different nitrogen protecting groups. The reaction times are also fairly reasonable (0.3 – 24 h). Furthermore, the cyclization products **11.1a-h** are useful for other reactions such as the Diels Alder reaction, where more complex carbon frameworks can be synthesized in one step. Further research can also be conducted using dienes **11.1a-h** as precursors to furans and pyrroles through migration of the two alkenes

into the five-membered ring, as shown in Scheme 36. This sort of alkene migration is precedented in the literature.[63,64]



Scheme 36: Alkene Migration for Formation of Furans and Pyrroles

Overall, the silver(I)-catalyzed cyclizations were successful in producing the desired diene products in fair yields, reasonable reaction times, and functional group variability.

IV. Experimental

A. General

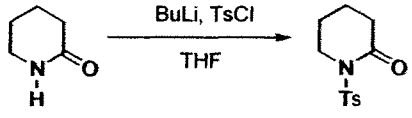
All reactions were performed under a nitrogen atmosphere in flame-dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl under an atmosphere of dry argon. Dichloromethane, triethylamine and toluene were distilled from calcium hydride under an atmosphere of dry argon. Reagents were purchased from Aldrich and purified by standard distillation. Solutions of *n*-BuLi were purchased from commercial sources and standardized by titration with a solution of *N*-benzylbenzamide in tetrahydrofuran. Methanesulfonyl chloride and methyl chloroformate were distilled from phosphorus pentoxide. Methanol, pentane, and pyridine were distilled from calcium hydride under an atmosphere of nitrogen. *N,N*-dimethylformamide was distilled from magnesium chloride under an atmosphere of nitrogen, then sequentially stored over flame dried 4 Å molecular sieves. Propargyl alcohol and benzaldehyde were vacuum distilled over potassium carbonate and anhydrous magnesium sulfate, respectively. Benzene and diisopropylamine were distilled over sodium under an atmosphere of nitrogen. Acrolein and methacrolein were distilled over quinoline under an atmosphere of nitrogen.

Thin layer chromatography (TLC) was performed on DC-Fertigplatten SIL G-25 UV_{254} pre-coated TLC plates. Column chromatography was performed on Silicycle ultrapure silica gel (40-63μm, 230-400 mesh). Triethylamine washed silica gel was stirred with triethylamine before packing, then sequentially flushed with polar solvent component and solvent system of choice.

Proton nuclear magnetic resonance spectra and carbon nuclear magnetic resonance spectra were both recorded in deuterochloroform using either a Bruker AV-300, a Bruker WH-400 or a Bruker AV-400 spectrometer. Chemical shifts are recorded in parts per million and are referenced to the centerline of deuterochloroform (7.24 ppm ^1H NMR; 77.0 ppm ^{13}C NMR). Coupling constants (J values) are given in Hertz (Hz).

Infrared (IR) spectra were obtained using a Perkin-Elmer 1710 FT-IR spectrometer. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Low resolution mass spectra were recorded by the Microanalytical Laboratory at the University of British Columbia on an Waters/Micromass LCT spectrometer for electrospray ionization (ESI) or on a Kratos MS-50 spectrometer for electron ionization (EI). Microanalyses were performed by the Microanalytical Laboratory at the University of British Columbia on a Carlo Erba Elemental Analyzer EA 1008.

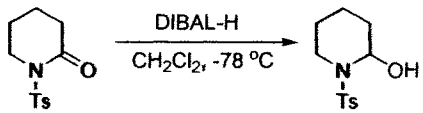
B. Synthesis of Substrates



1-(Toluene-4-sulfonyl)-piperidin-2-one (12.1)[27,30]

A solution of *n*-butyllithium (80.0 mL, 0.128 mol, 1.60 M in hexanes) was added dropwise to a solution of 12.1 g of δ-valerolactam (0.122 mol, 1.00 equiv) in 300 mL of THF at −78 °C. The reaction mixture was stirred for 3 h at −78 °C before a solution of 25.6 g of toluenesulfonyl chloride (0.134 mol, 1.10 equiv) in 100 mL THF was added dropwise. The reaction mixture was warmed to rt and stirred overnight. The white reaction mixture was diluted with dichloromethane and washed sequentially with water and a saturated aqueous brine solution. The combined aqueous washes were extracted with dichloromethane. The combined organic fractions were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a pale yellow powder. Trituration with diethyl ether afforded 29.9 g (97%) of a white powder (mp 139-141 °C).

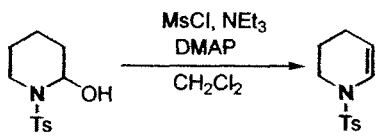
IR (film): 2954, 1687, 1349 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ ppm 7.87 (d, *J*=8.2 Hz, 2 H), 7.28 (d, *J*=8.2 Hz, 2 H), 3.87 (t, *J*=5.9 Hz, 2 H), 2.41 - 2.31 (m, 5 H), 1.93 - 1.80 (m, 2 H), 1.80 - 1.67 (m, 2 H).



1-(Toluene-4-sulfonyl)-piperidin-2-ol (12.2)[28,30]

A solution of diisobutylaluminum hydride (129 mL, 0.129 mol, 1.00 M in hexanes) was added dropwise to a solution of **12.1** in 350 mL dichloromethane at −78 °C. The reaction mixture was stirred for 1 h at −78 °C before it was quenched by slow addition of 40 mL of a solution of saturated aqueous ammonium chloride. The white reaction mixture was stirred and warmed to rt over 45 min. Anhydrous magnesium sulfate was added, and the reaction mixture was stirred for 30 min before it was filtered through a pad of Celite. Concentration by rotary evaporation *in vacuo* afforded 16.4 g (80%) of a white powder (mp 102-104 °C).

IR (film): 3487, 2957, 1327, 1158 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, *J*=8.7 Hz, 2 H), 7.27 (d, *J*=8.2 Hz, 2 H), 5.47 - 5.56 (m, 1 H), 3.57 - 3.46 (m, 1 H), 3.07 (td, *J*=12.2, 2.5 Hz, 1 H), 2.56 (d, *J*=3.2 Hz, 1 H), 2.38 (s, 3 H), 1.84 - 1.42 (m, 6 H).

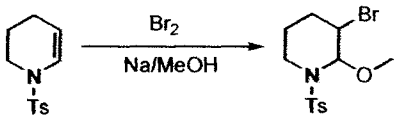


1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (12.3)[28,30]

To a solution of 16.4 g of alcohol **12.2** (64.3 mmol, 1.00 equiv) in 300 mL of dichloromethane was added 0.391 g of 4-(dimethyl)-aminopyridine (3.20 mmol, 0.05 equiv). The reaction was cooled to 0 °C before the dropwise addition of 10.0 mL of methanesulfonyl chloride (0.129 mol, 2.00 equiv) to give a pale yellow reaction mixture. After the reaction mixture was stirred at 0 °C for 15 min, it was allowed to warm to rt over 15 min. To the orange reaction mixture was added 300 mL of a saturated solution of aqueous ammonium chloride and allowed to stir for 20 minutes. The resulting reaction mixture was diluted with water and the separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed sequentially with a saturated solution of aqueous ammonium chloride and brine, dried over anhydrous

sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford bright orange solid. Purification by column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 11.6 g (76%) of a white solid (mp 48-50 °C).

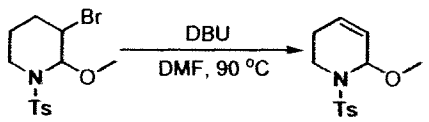
IR (film): 3060, 2936, 1650, 1340, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.2 Hz, 2 H), 7.28 (d, *J*=7.8 Hz, 2 H), 6.61 (ddd, *J*=8.3, 2.1, 1.9 Hz, 1 H), 4.98 - 4.91 (m, 1 H), 3.37 - 3.31 (m, 2 H), 2.41 (s, 3 H), 1.92 - 1.85 (m, 2 H), 1.68 - 1.59 (m, 1 H).



3-Bromo-2-methoxy-1-(toluene-4-sulfonyl)-piperidine (12.4)[29,30]

A solution of 11.6 g of **12.3** (48.9 mmol, 1.00 equiv) in 50 mL of methanol was transferred dropwise by cannula into a solution of 1.24 g of sodium (0.154 mol, 1.10 equiv) in 200 mL of methanol at 0 °C. To this reaction mixture was added dropwise 2.76 mL of bromine (53.8 mmol, 1.10 equiv). The resulting orange reaction mixture was warmed to rt and stirred for 3 h, before being concentrated to one half volume by rotary evaporation *in vacuo*. The reaction mixture was diluted with diethyl ether, then washed with water. The separated aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a white powder. Purification by column chromatography on triethylamine washed silica gel afforded (5:2 hexanes/ethyl acetate) afforded 38.1 g (93%) of a white solid, 102-104 °C.

IR (film): 2952, 1598, 1335, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J*=8.3 Hz, 2 H), 7.28 (d, *J*=7.9 Hz, 2 H), 5.28 (d, *J*=1.7 Hz, 1 H), 4.33 (q, *J*=2.8 Hz, 1 H), 3.40 (s, 3 H), 3.37 - 3.30 (m, 1 H), 3.12 - 3.02 (m, 1 H), 2.41 (s, 3 H), 2.28 - 2.18 (m, 1 H), 1.88 - 1.73 (m, 2 H), 1.44 - 1.35 (m, 1 H).

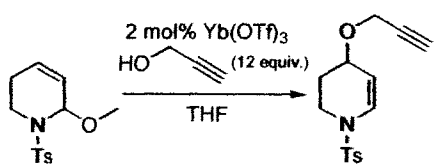


6-Methoxy-1-(toluene-4-sulfonyl)-1, 2, 3, 6-tetrahydro-pyridine (12.5)[29,30]

To a solution of 38.1 g of **12.4** (0.109 mol, 1.00 equiv) in 500 mL of *N,N*-dimethylformamide was added 19.6 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (0.131 mol, 1.20 equiv). The reaction mixture was stirred overnight at 90 °C. The yellow solution was diluted with diethyl ether then washed with water. The separated aqueous layer was washed with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 11.6 g (74% brsm) of a white powder and 17.5 g of starting material.

When the above procedure was performed using the following quantities of reagents and solvents: 1.97 g of **12.4** (5.66 mmol, 1.0 equiv) in 250 mL of *N,N*-dimethylformamide, 1.02 mL of 1,8-diazabicyclo[5,4,0]undec-7-ene (6.79 mmol, 1.20 equiv), workup and purification afforded 1.41 g (94%) of a white powder (mp 53-55 °C).

IR (film): 3042, 2933, 1656, 1598, 1338, 1162 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J*=8.2 Hz, 2 H), 7.24 (d, *J*=7.8 Hz, 2 H), 5.85 - 5.71 (m, 2 H), 5.29 - 5.24 (m, 1 H), 3.76 - 3.66 (m, 1 H), 3.39 (s, 3 H), 3.31 - 3.19 (m, 1 H), 2.39 (s, 3 H), 1.76 - 1.68 (m, 2 H).



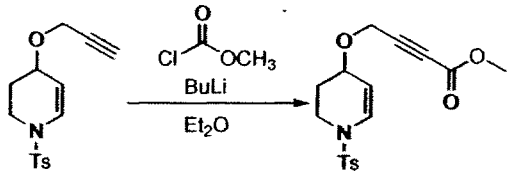
4-Prop-2-ynyloxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (12.6)[30]

To a solution of 41.1 mg of ytterbium (III) trifluoromethanesulfonate (0.0748 mmol, 0.0200 equiv) in 2.61 mL of propargyl alcohol (44.9 mmol, 12.0 equiv) was added a

solution of 1.00 g of **12.5** (3.74 mmol, 1.00 equiv) in 10 mL THF. The reaction mixture was stirred for 5 h before it was diluted with diethyl ether. The separated organic layer was washed sequentially with a solution of saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a colourless oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/ether) afforded 0.336 g (31% brsm) of a colourless oil.

Ytterbium (III) trifluoromethanesulfonate (5.0 mg, 0.0093 mmol) was dried under vacuum for 2 h before being dissolved in 0.26 mL of propargyl alcohol. To the resulting solution was added a solution of 0.10 g of **12.5** (0.37 mmol, 1.0 equiv) in 1 mL of THF. The reaction mixture was stirred for 22 h before the addition of 5.0 mg of ytterbium (III) trifluoromethanesulfonate. After 1 h, the reaction mixture was diluted with diethyl ether. The separated organic layer was washed sequentially with a solution of saturated sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a colourless oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/ether) afforded 0.093 g (85%) of a colourless oil.

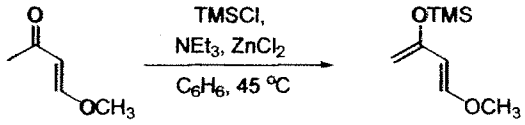
IR (film): 3284, 2932, 2116, 1641, 1354, 1169, 1067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.3 Hz, 2 H), 7.28 (d, *J*=8.3 Hz, 2 H), 6.81 (d, *J*=8.7 Hz, 1 H), 5.10 (ddd, *J*=8.3, 4.8, 1.3 Hz, 1 H), 4.08 (d, *J*=2.2 Hz, 2 H), 3.94 (q, *J*=4.2 Hz, 1 H), 3.64 (dt, *J*=11.8, 4.4 Hz, 1 H), 3.07 (td, *J*=12.2, 3.1 Hz, 1 H), 2.41 (s, 4 H), 1.95 - 1.87 (m, 1 H), 1.69 - 1.58 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 134.8, 129.7, 128.4, 126.8, 105.5, 79.8, 74.2, 65.7, 54.7, 39.4, 26.8, 21.4. HRMS (ESI): Calcd for $C_{15}H_{17}NO_3NaS$ ($M + Na^+$) 314.0827, found 314.0834.



4-[1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yloxy]-but-2-ynoic acid methyl ester (11.0a)[30]

A solution of *n*-butyllithium (0.732 mL, 1.17 mmol, 1.60 M in hexanes) was added dropwise to a solution of 0.310 g of **12.6** (1.06 mmol, 1.00 equiv) in 11 mL of diethyl ether at −78 °C. After the reaction mixture was stirred at −78 °C for 1 h, 0.428 mL of methyl chloroformate (5.53 mmol, 5.20 equiv) was added. The reaction mixture was stirred at −78 °C for 20 min, then warmed to rt over 45 min. After 4 mL of THF were added, the reaction mixture was stirred overnight. The reaction mixture was diluted with diethyl ether, then washed sequentially with water and brine. The aqueous washes were back-extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford an orange oil. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate to 4:1 hexanes ethyl acetate) afforded 0.310 g (84%) of a pale yellow oil.

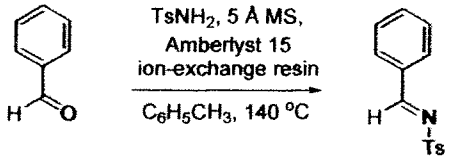
IR (film): 2954, 2238, 1718, 1641, 1354, 1262, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 - 7.60 (m, 2 H), 7.28 (d, *J*=7.0 Hz, 2 H), 6.83 (dd, *J*=8.3, 3.1 Hz, 1 H), 5.13 - 5.04 (m, 1 H), 4.20 (s, 2 H), 3.97 - 3.90 (m, 1 H), 3.75 (s, 3 H), 3.70 - 3.62 (m, 1 H), 3.10 - 2.99 (m, 1 H), 2.40 (s, 3 H), 1.90 (d, *J*=14.0 Hz, 1 H), 1.70 - 1.58 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 144.0, 134.9, 129.9, 129.0, 126.9, 104.8, 83.7, 77.5, 66.4, 54.5, 52.8, 39.3, 26.9, 21.5. HRMS (ESI): Calcd for $C_{17}H_{19}NO_5NaS$ ($M + Na^+$) 372.0882, found 372.0885.



(3-Methoxy-1-methylene-allyloxy)-trimethyl-silane (13.1)[31,32]

Zinc chloride was dried by being heated at 150 °C overnight under vacuum, then stored under a nitrogen atmosphere in a boxglove. A suspension of 81.8 mg of anhydrous zinc chloride (0.600 mmol, 0.0120 equiv) in 15.9 mL of triethylamine (0.114 mol, 2.28 equiv) was stirred for 1 h. A solution of 5.60 mL of 4-methoxy-3-buten-2-one (50.0 mmol, 1.00 equiv) in 15 mL of benzene was added to the reaction mixture in one portion. After the yellow reaction mixture was stirred for 5 min, it was cooled to 0 °C and 13.0 mL of trimethylchlorosilane (0.100 mol, 2.00 equiv) were added in one portion. The pinkish-orange reaction was stirred at 0 °C for 45 min before the resulting brown reaction mixture was warmed to rt and stirred overnight at 45 °C. The thick dark brown reaction mixture was poured into 50 mL of anhydrous diethyl ether and was stirred for 5 min, until white smoke no longer evolved from the reaction mixture. The reaction mixture was filtered over a pad of Celite, dissolved in 50 mL of anhydrous ether, and re-filtered over a pad of Celite. Concentration by rotary evaporation *in vacuo* afforded 7.51 g (87%) of a dark brown oil.

IR (film): 2960, 1654, 1322, 1023, 849 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.81 (d, *J*=12.3 Hz, 1 H), 5.33 (d, *J*=12.3 Hz, 1 H), 4.07 (d, *J*=12.3 Hz, 2 H), 3.56 (s, 3 H), 0.26 - 0.16 (s, 9 H).



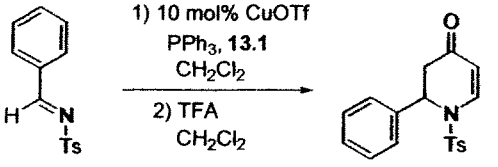
N-Benzylidene-4-methyl-benzenesulfonamide (13.3)[33]

To a solution of 55.1 g of *p*-toluenesulfonamide (0.316 mol, 1.00 equiv) in 500 mL of toluene was added 33.8 mL of benzaldehyde (0.316 mol, 1.00 equiv), 48.0 g of 5 Å molecular sieves, and 0.640 g of Amberlyst 15 ion-exchange resin. The reaction mixture was heated to reflux overnight with a Dean Starks apparatus before it was filtered through

a glass frit and washed with toluene. Concentration by rotary evaporation *in vacuo* afforded a yellow oil, which solidified after 3 h of storage in the refrigerator. The pale yellow solid was washed with pentane then recrystallized in ethyl acetate/pentane to afford 18.9 g (23%) of white crystals.

To a solution of 17.1 g of *p*-toluenesulfonamide (0.101 mol, 1.00 equiv) in 165 mL toluene was added 10.3 mL of benzaldehyde (0.101 mol, 1.00 equiv), 15.0 g of 5 Å molecular sieves, and 0.200 g of Amberlyst 15 ion-exchange resin. The reaction mixture was heated to reflux overnight with a Dean Starks apparatus before it was filtered through a glass frit and washed with toluene. Concentration by rotary evaporation *in vacuo* afforded a pale yellow solid, which was washed with pentane then recrystallized in ethyl acetate/pentane and filtered to afford 3.71 g of white crystals. The filtrate was concentrated again by rotary evaporation *in vacuo* and recrystallized to afford 4.72 g of white crystals. Recrystallization of the filtrate a third time afforded 0.552 g of white crystals, which gave a total of 8.98 g (35%) of white crystals (mp 89-92 °C).

IR (film): 3259, 1597, 1446, 1301, 1223, 1156 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 9.01 (s, 1 H), 8.02 - 7.79 (m, 4 H), 7.59 (t, *J*=7.3 Hz, 1 H), 7.46 (t, *J*=7.5 Hz, 2 H), 7.32 (d, *J*=8.2 Hz, 2 H), 2.41 (s, 3 H).

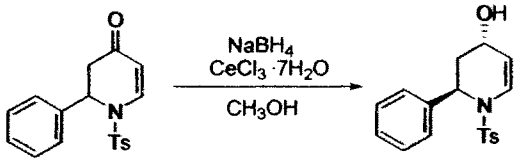


2-Phenyl-1-(toluene-4-sulfonyl)-2,3-dihydro-1H-pyridin-4-one (13.4)[34]

A solution of 2.59 g of copper (I) trifluoromethanesulfonate toluene complex (5.00 mmol, 0.100 equiv) and 2.62 g of triphenylphosphine (10.0 mmol, 0.200 equiv) in 280 mL of dichloromethane was stirred for 2 h. To the resulting olive green solution was cannulated a solution of 12.9 g of *N*-Benzylidene-4-methyl-benzenesulfonamide **13.3** (50.0 mmol, 1.00 equiv) in 350 mL of dichloromethane. After the reaction mixture was stirred for 10 min, to the reaction mixture was added 11.7 g of (3-methoxy-1-methylene-

allyloxy)-dimethyl-silane **13.1** (68.0 mmol, 1.36 equiv). The resulting brown solution was stirred for 4 h before 90 mL of trifluoroacetic acid were added. After the reaction mixture was stirred for 1 h, it was neutralized by the addition of a solution of saturated sodium bicarbonate. The reaction mixture was extracted with dichloromethane, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation *in vacuo* to afford a thick brown sludge. Purification by column chromatography on triethylamine washed silica gel (2:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) afforded 10.3 g (63%) of a bright orange solid (mp 102-104.5 °C).

IR (film): 3063, 1674, 1597, 1367, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=8.3 Hz, 2 H), 7.35 - 7.14 (m, 7 H), 5.53 (d, *J*=6.5 Hz, 1 H), 5.42 (d, *J*=8.3 Hz, 1 H), 2.85 (dd, *J*=16.6, 7.0 Hz, 1 H), 2.75 - 2.62 (m, 1 H), 2.41 (s, 3 H).

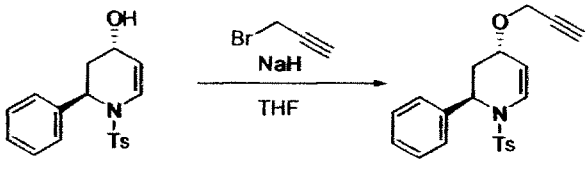


2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-ol (13.5)[35,37]

To a solution of 10.3 g of **13.4** (31.4 mmol, 1.00 equiv) in 80 mL of methanol and 6 mL of THF was added 11.7 g of cerium trichloride heptahydrate (31.4 mmol, 1.00 equiv). The reaction mixture was cooled to 0 °C and 1.19 g of sodium borohydride (31.4 mmol, 1.00 equiv) was added in portions, over 30 min. After the reaction mixture was stirred for 5 min, 30 mL of water was added and the reaction mixture was concentrated to one half volume by rotary evaporation *in vacuo*. The reaction mixture was extracted with diethyl ether, dried over potassium carbonate, and concentrated by rotary evaporation *in vacuo* to afford a thick yellow paste. Purification by column chromatography on triethylamine washed silica gel (2:1 hexanes/ethyl acetate) afforded 8.49 g (82%) of a white solid.

When the above procedure was performed using the following quantities of reagents and solvents: 3.0 g of **13.4** (9.16 mmol, 1.0 equiv) in 22 mL methanol and 6 mL THF; 3.41 g of cerium trichloride heptahydrate (9.16 mmol, 1.0 equiv); and 0.35 g of sodium borohydride (9.16 mmol, 1.0 equiv), purification by column chromatography on triethylamine washed silica gel (3:2 hexanes/ethyl acetate) afforded 2.77 g (92%) of a white solid (mp 80-82 °C).

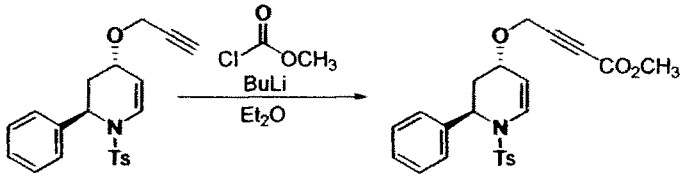
IR (film): 3529, 3031, 1646, 1342, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J*=7.9 Hz, 2 H), 7.27 - 7.09 (m, 8 H), 6.80 (d, *J*=8.3 Hz, 1 H), 5.06 (br. s., 1 H), 4.90 (d, *J*=8.3 Hz, 1 H), 3.77 (br. s., 1 H), 2.62 (br. s., 1 H), 2.35 (s, 3 H), 2.12 (d, *J*=10.0 Hz, 1 H), 1.50 - 1.36 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 139.3, 135.5, 129.5, 128.1, 127.0, 126.5, 125.2, 124.7, 111.8, 60.0, 55.8, 35.1, 21.2. MS (ESI): 352.2 ($M + Na^+$). Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.84; H, 5.80; N, 4.24.



2-Phenyl-4-prop-2-ynyloxy-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (13.6)[40]

A solution of 0.372 g of **13.5** (1.13 mmol, 1.00 equiv) and 0.0429 g of sodium hydride (1.70 mmol, 1.50 equiv) in 12.0 mL of THF was stirred for 1 h. To the pale yellow solution was added 0.630 mL of propargyl bromide (5.66 mmol, 5.00 equiv). The resulting light brown solution was stirred overnight. The reaction mixture was diluted with ethyl ether and washed with water. The combined aqueous phases were back-extracted with diethyl ether, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a light brown liquid. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.140 g (54%) of a pale yellow solid (mp 116.5 - 118 °C).

IR (film): 3283, 2929, 1649, 1347, 1169, 1086 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.3 Hz, 2 H), 7.33 - 7.20 (m, 8 H), 6.94 (d, *J*=8.3 Hz, 1 H), 5.17 - 5.08 (m, 2 H), 4.02 (d, *J*=2.2 Hz, 2 H), 3.80 - 3.73 (m, 1 H), 2.41 (s, 3 H), 2.37 - 2.30 (m, 2 H), 1.56 (ddd, *J*=12.6, 10.5, 4.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 139.3, 135.7, 130.0, 128.4, 127.2, 126.7, 126.0, 125.5, 108.7, 79.5, 74.3, 67.6, 55.8, 55.7, 32.3, 21.4. MS (ESI): 390.2 ($M + Na^+$). Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.83; H, 5.78; N, 3.82. Found: C, 68,41; H, 5.76; N, 3.84.

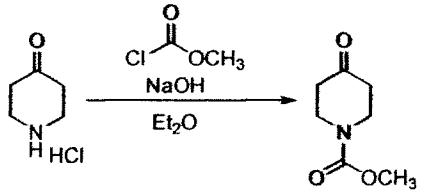


4-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yloxy]-but-2-ynoic acid methyl ester (11.0b)[30]

A solution of *n*-butyllithium (0.49 mL, 0.61 mmol, 1.2 M in hexanes) was added dropwise to a solution of 0.20 g of **13.6** in 5.5 mL of diethyl ether and 1 mL THF at −78 °C. After the reaction mixture was stirred at −78 °C for 1 h, 0.22 mL of methyl chloroformate (2.9 mmol, 5.2 equiv) were added. The reaction mixture was stirred at −78 °C for 20 min, then warmed to rt and stirred overnight. The reaction mixture was diluted with diethyl ether, then washed sequentially with water and brine. The aqueous washes were back-extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford an orange oil. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate to 4:1 hexanes ethyl acetate) afforded 0.17 g (72%) of a pale yellow oil.

IR (film): 2955, 2240, 1718, 1347, 1261, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.3 Hz, 2 H), 7.33 - 7.20 (m, 7 H), 6.95 (d, *J*=7.9 Hz, 1 H), 5.16 - 5.06 (m, 2 H), 4.14 (s, 2 H), 3.75 (s, 4 H), 2.42 (s, 3 H), 2.39 - 2.29 (m, 1 H), 1.64 - 1.53 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 143.9, 139.2, 135.8, 130.0, 128.5, 127.4, 126.8,

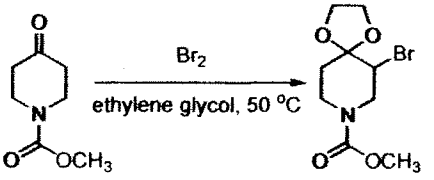
126.5, 125.6, 108.2, 83.5, 77.5, 68.6, 55.8, 55.7, 52.7, 32.4, 21.5. HRMS (ESI): Calcd for $C_{23}H_{23}NO_5NaS$ ($M + Na^+$) 448.1195, found 448.1192.



4-Oxo-piperidine-1-carboxylic acid methyl ester (14.1)[37]

A solution of 13.0 g of sodium hydroxide (0.326 mol, 1.00 equiv) in 75 mL of deionized water was added dropwise to a solution of 50.0 g of 4-piperidone monohydrate hydrochloride (0.326 mol) in 75 mL of deionized water at 0 °C. The reaction mixture was diluted with 250 mL of diethyl ether then 12.6 mL of methyl chloroformate (0.163 mol, 0.500 equiv) were added dropwise over 15 min at 0 °C. The reaction mixture was stirred for 5 min before 12.6 mL of methyl chloroformate (0.163 mol, 0.500 equiv) and a solution of 13.0 g of sodium hydroxide (0.326 mol, 1.00 equiv) in 75 mL of deionized water were added dropwise simultaneously over 15 min. After the reaction mixture was stirred for 1.5 h, the separated aqueous layer was extracted with diethyl ether. The combined organics were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford 43.3 g (85%) of a colourless viscous oil.

IR (film): 2959, 1702, 1451, 1236, 1125 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.68 - 3.46 (m, 7 H), 2.29 (t, *J*=6.2 Hz, 4 H).

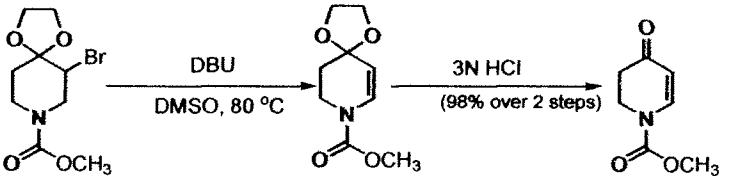


6-Bromo-1,4-dioxa-8-aza-spiro[4.5]decane-8-carboxylic acid methyl ester (14.2)[37]

To a solution of 53.3 g of **14.1** (0.341 mol, 1.00 equiv) in 450 mL of ethylene glycol at 50 °C was added 31.2 mL of bromine (0.606 mol, 1.78 equiv) in small portions over 3 h.

The orange-red reaction mixture was stirred for 3 h at 50 °C before 47.1 g of anhydrous potassium carbonate (0.341 mol, 1.00 equiv) were added in portions over 30 min. The reaction mixture was extracted with diethyl ether, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford an orange solid. Purification by column chromatography on silica gel (5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 74.1 g (78%) of a pale orange solid (mp 61-63 °C).

IR (film): 2958, 1718, 1447, 1239, 1136 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.98 - 3.75 (m, 6 H), 3.59 - 3.51 (m, 1 H), 3.49 (s, 3 H), 3.35 (br. s., 1 H), 3.23 - 3.11 (m, 1 H), 1.82 (d, *J*=13.1 Hz, 1 H), 1.46 (ddd, *J*=13.6, 9.5, 4.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 105.7, 65.3, 52.3, 51.6, 48.5, 41.2, 33.6. MS (ESI): 302.1 ($M + Na^+$). Anal. Calcd for $C_9O_4H_{14}BrN$: C, 38.59; H, 5.04; N 5.00. Found: C, 38.64; H, 5.00; N, 4.97.



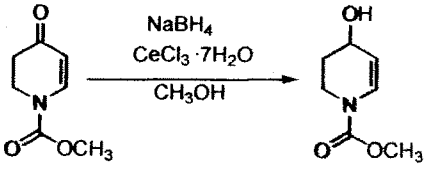
4-Oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (14.4)[37]

To a solution of 68.4 g of **14.2** (0.244 mol, 1.00 equiv) in 500 mL of dimethyl sulfoxide was added 43.8 mL of 1,8-diazobicyclo[5,4,0]undec-7-ene (0.293 mol, 1.20 equiv). The reaction mixture was stirred overnight at 80 °C before it was diluted with water and extracted with diethyl ether. The combined organic phases were washed with water, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation *in vacuo* to afford 35.0 g of a crude brown oil. The crude product was dissolved in 430 mL of methanol and 28.5 mL of a 3 N aqueous solution of hydrochloric acid were added. After the reaction mixture was stirred for 30 min, the reaction mixture was concentrated to one half volume by rotary evaporation *in vacuo*. The reaction mixture was diluted with water and extracted with diethyl ether. The combined organic phases were dried over anhydrous potassium carbonate and concentrated by rotary evaporation *in vacuo* to afford an orange oil. Purification by column chromatography on triethylamine washed

silica gel (3:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) afforded 7.87 g (21% over two steps) of a white solid.

To a solution of 2.13 g of **14.3** (10.7 mmol, 1.00 equiv.) in 43 mL of dimethyl sulfoxide was added 3.11 mL of 1,8-diazobicyclo[5,4,0]undec-7-ene (20.4 mmol, 2.00 equiv.). The reaction mixture was stirred overnight at 80 °C before it was diluted with water and extracted with diethyl ether. The combined organic phases were washed with water, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation *in vacuo* to afford 2.13 g of a crude brown oil. The crude product was dissolved in 20 mL of methanol and 1.3 mL of a 3 N aqueous solution of hydrochloric acid were added. After the reaction mixture was stirred for 15 min, the reaction mixture was concentrated to by rotary evaporation *in vacuo* to afford a biphasic oil. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate) afforded 1.55 g (98% over two steps) of a white solid (mp 50-58 °C).

IR (film): 3086, 2956, 1738, 1663, 1600, 1450, 1223, 1185, 765 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J*=7.0 Hz, 1 H), 5.06 (d, *J*=8.3 Hz, 1 H), 3.79 (t, *J*=7.2 Hz, 2 H), 3.62 (s, 3 H), 2.30 (t, *J*=7.4 Hz, 2 H).

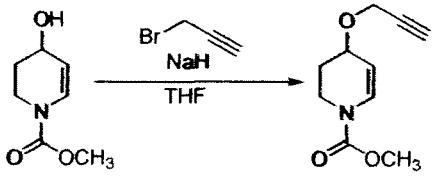


4-Hydroxy-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (14.5)[35,37]

To a solution of 3.95 g of **14.4** (25.5 mmol, 1.00 equiv) in 65 mL of methanol was added 9.49 g of cerium trichloride heptahydrate (25.5 mmol, 1.00 equiv). The reaction mixture was cooled to 0 °C and 0.965 g of sodium borohydride (25.5 mmol, 1.00 equiv) were added in portions, over 1 h. After the reaction mixture was stirred for 5 min, 30 mL of water were added and the reaction mixture was concentrated to one half volume by rotary evaporation *in vacuo*. The reaction mixture was extracted with diethyl ether, dried over

potassium carbonate, and concentrated by rotary evaporation *in vacuo* to afford a thick yellow paste. Purification by column chromatography on silica gel (1:2 hexanes/ethyl acetate) afforded 3.76 g (94%) of a white solid (mp 29-31 °C).

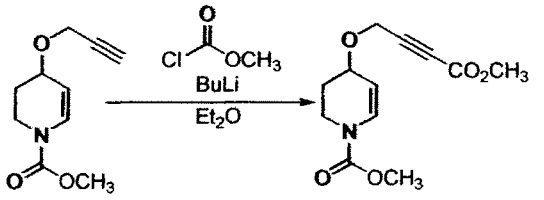
IR (film): 3411, 2957, 1718, 1651, 1449, 1364, 1236, 1121, 1061, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 - 6.29 (m, 1 H), 4.71 - 4.52 (m, 1 H), 3.93 (br. s., 1 H), 3.74 (br. s., 1 H), 3.44 - 3.25 (m, 4 H), 3.01 (br. s., 1 H,), 1.40 (br. s., 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 125.5, 107.5, 59.2, 52.0, 37.1, 29.4. MS (ESI): 180.2 ($M + Na^+$). Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.43; H 7.13; N, 8.76.



4-Prop-2-ynyloxy-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (14.6)[40]
A solution of 0.51 g of **14.5** (3.3 mmol, 1.0 equiv) and 0.12 g of sodium hydride (4.9 mmol, 1.5 equiv) in 50 mL of THF was stirred for 15 min. To the pale yellow solution was added 1.8 mL of propargyl bromide (16 mmol, 5.0 equiv) in one portion. The resulting light brown solution was stirred overnight. The reaction mixture was diluted with ethyl ether and washed with water. The combined aqueous phases were back-extracted with diethyl ether, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a light brown liquid. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.36 g (83% brsm) of a yellow oil.

IR (film): 3279, 2957, 2238, 1718, 1646, 1446, 1361, 1256, 1059 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.99 - 6.68 (m, 1 H), 5.01 - 4.80 (m, 1 H), 4.01 (s, 2 H), 3.91 (q, J=3.9 Hz, 1 H), 3.79 - 3.62 (m, 1 H), 3.58 (s, 3 H), 3.19 (t, J=12.2 Hz, 1 H), 2.33 (t, J=2.4 Hz, 1 H), 1.81 (br. s., 1 H), 1.69 - 1.54 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 128.0,

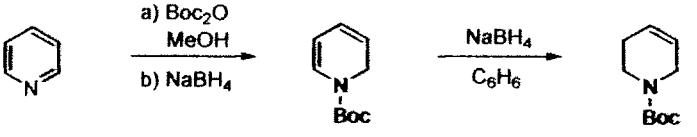
103.8, 79.7, 74.0, 66.1, 54.3, 52.7, 37.6, 26.8. HRMS (ESI): Calcd for $C_{10}H_{13}NO_3Na$ (M + Na^+) 218.0793, found 218.0788.



4-(3-Methoxycarbonyl-prop-2-ynyloxy)-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (11.0c)[30]

Following the procedure for the synthesis of methyl ester **11.0a**, methyl ester **11.0c** was synthesized using the following quantities of reagents and solvents: 1.5 mL of *n*-butyllithium (1.9 mmol, 1.2 M in hexanes); 0.33 g of **14.6** (1.7 mmol, 1.0 equiv) in 17 mL of diethyl ether; 0.68 mL of methyl chloroformate (8.8 mmol, 5.2 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.21 g (56%) of a pale yellow oil.

IR (film): 2957, 2238, 1718, 1445, 1361, 1255, 1058 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 - 6.86 (m, 1 H), 5.19 - 4.93 (m, 1 H), 4.29 (s, 2 H), 4.12 - 4.01 (m, 1 H), 3.88 - 3.72 (m, 7 H), 3.33 (t, *J*=12.2 Hz, 1 H), 1.97 (d, *J*=12.2 Hz, 1 H), 1.88 - 1.70 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 153.5, 129.0, 104.1, 84.1, 77.2, 67.2, 54.5, 53.2, 52.8, 37.8, 27.2. HRMS (ESI): Calcd for $C_{12}H_{15}NO_5Na$ (M + Na^+) 276.0848, found 276.0844.



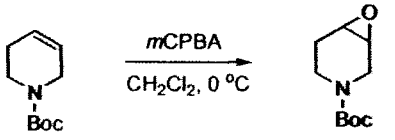
3,6-Dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (16.2)[42]

To a solution of 30.2 g of di-*tert*-butyl-dicarbonate (13.8 mmol, 1.20 equiv) in 230 mL of methanol at 0 °C was added 9.29 mL of pyridine (11.5 mmol, 1.00 equiv). The reaction mixture was stirred for 30 min before 13.1 g of sodium borohydride (34.6 mmol, 3.00

equiv) were added over 40 min. After the reaction mixture was stirred at 0 °C for 9 h, it was poured into 200 mL of crushed ice. The separated aqueous layer was extracted with diethyl ether and the combined organic phases were concentrated by rotary evaporation *in vacuo*. The resulting biphasic oil was diluted with diethyl ether and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford 10.5 g of a crude yellow oil **16.1**, which was used without further purification.

To a solution of 13.1 g of **16.1** (0.0724 mol, 1.00 equiv) in 330 mL of benzene at 0 °C was sequentially added 5.48 g of sodium borohydride (0.145 mol, 2.00 equiv) and 18.6 g of 10-camphorsulfonic acid (0.0797 mol, 1.10 equiv). The reaction mixture was stirred at 0 °C for 4 h before it was poured into a saturated aqueous solution of sodium bicarbonate in crushed ice. The separated aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (15:1 hexanes/ethyl acetate) afforded 6.56 g (49% over two steps) of a colourless oil.

IR (film): 2976, 1698, 1655, 1366, 1248, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 - 5.48 (m, 2 H), 3.85 - 3.73 (m, 2 H), 3.42 (t, *J*=5.7 Hz, 2 H), 2.06 (br. s., 2 H), 1.40 (s, 9 H).

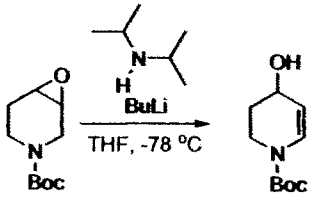


7-Oxa-3-aza-bicyclo[4.1.0]heptane-3-carboxylic acid *tert*-butyl ester (16.3)[30]

To a solution of 6.35 g of **16.2** (34.7 mmol, 1.00 equiv) in 130 mL of dichloromethane at 0 °C was added 11.7 g (52.0 mmol, 1.50 equiv) of *m*-chloroperbenzoic acid. The reaction mixture was stirred at 0 °C for 15 min before it was warmed to rt and stirred for 11 h. The white mixture was diluted with dichloromethane and washed with water. The

separated aqueous layer was extracted with dichloromethane washed with a 1N aqueous solution of sodium hydroxide. The combined organic phases were dried over sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a colourless oil. Purification by column chromatography on triethylamine washed silica gel (hexanes to 3:1 hexanes/ethyl acetate to 2:1 hexanes/ethyl acetate) afforded 5.02 g (73%) of a pale yellow oil.

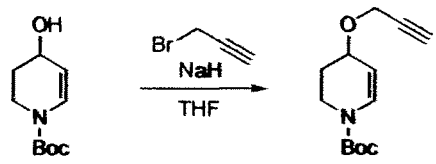
IR (film): 2976, 1693, 1249, 1174 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.98 - 3.73 (m, 1 H), 3.73 - 3.56 (m, 1 H), 3.48 - 3.34 (m, 1 H), 3.23 (br. s., 1 H), 3.16 (br. s., 1 H), 3.07 (ddd, *J*=13.3, 9.1, 4.1 Hz, 1 H), 2.07 - 1.93 (m, 1 H), 1.93 - 1.79 (m, 1 H), 1.41 (s, 9 H).



4-Hydroxy-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (16.4)[43]

To a solution of 7.08 mL of diisopropylamine (50.6 mmol, 2.00 equiv) in 110 mL of THF at −78 °C was added 36.0 mL of a solution of *n*-butyllithium (46.8 mmol, 1.85 equiv). The reaction mixture was stirred at −78 °C for 30 min before a solution of 5.04 g of **16.3** (25.3 mmol, 1.0 equiv) in 150 mL of THF was added. The reaction mixture was stirred for 2.5 h at −78 °C before 100 mL of a 1:1 solution of water-saturated aqueous solution of sodium bicarbonate was added. The reaction mixture was warmed to rt and the separated aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation to afford a light brown oil. Purification by column chromatography on triethylamine washed silica gel afforded 4.81 g (96%) of a yellow oil.

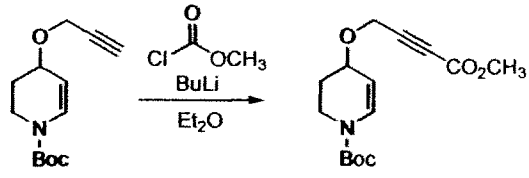
IR (film): 3423, 2977, 1708, 1646, 1370, 1169, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.99 - 6.70 (m, 1 H), 5.08 - 4.79 (m, 1 H), 4.19 – 4.06 (m, 1 H), 3.75 (br. s., 1 H), 3.41 – 3.17 (m, 1 H), 2.48 (br. s., 1 H), 1.87 - 1.66 (m, 2 H), 1.40 (s, 9 H).



4-Prop-2-ynyloxy-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (16.5)[40]

Following the procedure for the synthesis of ether **13.6**, ether **16.5** was synthesized using the following quantities of reagents and solvents: 1.27 g of **16.4** (6.39 mmol, 1.00 equiv); 0.242 g of sodium hydride (9.58 mmol, 1.50 equiv) in 100 mL of THF; 3.56 mL of propargyl bromide (31.9 mmol, 5.00 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (hexanes to 5:1 hexanes/ethyl acetate to ethyl acetate) afforded 0.518 g of starting material and 0.649 g (90% brsm) of a yellow oil.

IR (film): 3294, 2976, 1708, 1642, 1367, 1241, 1169, 1072 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.98 - 6.64 (m, 1 H), 4.96 - 4.73 (m, 1 H), 4.02 (s, 2 H), 3.91 (q, *J*=3.9 Hz, 1 H), 3.80 - 3.57 (m, 1 H), 3.14 (d, *J*=10.0 Hz, 1 H), 2.31 (t, *J*=2.4 Hz, 1 H), 1.82 (d, *J*=13.5 Hz, 1 H), 1.59 (dddd, *J*=14.0, 12.3, 4.1, 4.0 Hz, 1 H), 1.32 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 128.5, 102.8, 80.6, 79.8, 73.9, 66.3, 54.3, 37.4, 27.8, 26.9. HRMS (ESI): Calcd for $C_{13}H_{19}NO_3Na$ ($M + Na^+$) 260.1263, found 260.1259.

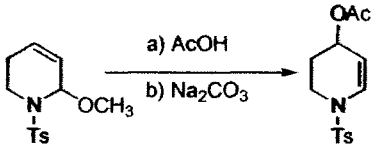


4-(3-Methoxycarbonyl-prop-2-ynyloxy)-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (11.0d)[30]

Following the procedure for the synthesis of methyl ester **11.0a**, methyl ester **11.0d** was synthesized using the following quantities of reagents and solvents: 3.08 mL of *n*-butyllithium (3.97 mmol, 1.29 M in hexanes); 0.857 g of **16.5** (3.61 mmol, 1.00 equiv) in 36 mL of diethyl ether; 1.54 mL of methyl chloroformate (19.9 mmol, 5.50 equiv). Workup and purification by column chromatography on triethylamine washed silica gel

(hexanes to 9:1 hexanes/ethyl acetate) afforded 0.347 g of starting material and 0.598 g (94% brsm) of a yellow oil.

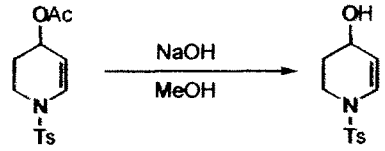
IR (film): 2979, 2241, 1718, 1641, 1368, 1256, 1168, 1057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 - 6.74 (m, 1 H), 4.99 - 4.75 (m, 1 H), 4.19 (s, 2 H), 3.93 (q, *J*=3.9 Hz, 1 H), 3.76 (br. s., 1 H), 3.64 (s, 3 H), 3.16 (d, *J*=10.0 Hz, 1 H), 1.85 (d, *J*=11.3 Hz, 1 H), 1.68 - 1.57 (m, 1 H), 1.35 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 151.8, 129.0, 102.0, 83.9, 80.8, 77.1, 67.1, 54.1, 52.4, 37.3, 27.9, 26.9. MS (ESI): 318.3 ($M + Na^+$).



Acetic acid 1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl ester (17.2)[30]

6-Methoxy-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydro-pyridine **12.5** (8.19 g, 30.6 mmol) was dissolved in a 5 mL of glacial acetic acid. After the solution was stirred for 5 min, it was neutralized by the slow addition of a saturated solution of sodium bicarbonate. The separated aqueous layer was then extracted with diethyl ether. The combined organic phases were dried anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. Purification by triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 3.28 g (83%) of a yellow oil.

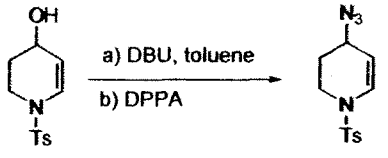
IR (film): 3095, 2936, 1734, 1645, 1358 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.3 Hz, 2 H), 7.29 (d, *J*=7.9 Hz, 2 H), 6.84 (d, *J*=7.9 Hz, 1 H), 5.12 - 5.01 (m, 2 H), 3.67 (dt, *J*=12.2, 4.4 Hz, 1 H), 3.09 (td, *J*=12.0, 3.1 Hz, 1 H), 2.40 (s, 3 H), 1.93 (s, 3 H), 1.90 - 1.81 (m, 1 H), 1.77 - 1.67 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 144.1, 134.9, 129.9, 129.2, 126.9, 104.7, 62.8, 39.5, 27.1, 21.5, 21.1. MS (ESI): 318.3



1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-ol (18.1)

To a solution of 6.4 g of **16.2** (22 mmol, 2.0 equiv) in 150 mL of methanol was added 0.43 g of sodium hydroxide (11 mmol, 1.0 equiv). The reaction mixture was stirred for 5 h before it was neutralized by a 1 M solution of hydrochloric acid. A saturated solution of sodium bicarbonate was added, and the separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to afford a yellow oil. Purification by column chromatography on triethylamine washed silica gel (5:1 ethyl/acetate to 3:1 hexanes/ethyl acetate to 1:1 hexanes/ethyl acetate to ethyl acetate) afforded 1.6 g (29%) of a white solid (mp 59-61 °C).

IR (film): 3387, 3066, 2927, 1645, 1353, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J*=8.3 Hz, 2 H), 7.20 (d, *J*=8.3 Hz, 2 H), 6.59 (d, *J*=8.3 Hz, 1 H), 4.93 (dd, *J*=7.9, 4.4 Hz, 1 H), 3.87 (br. s., 1 H), 3.51 - 3.40 (m, 1 H), 3.11 - 2.96 (m, 2 H), 2.28 (s, 3 H), 1.67 - 1.55 (m, 1 H), 1.55 - 1.43 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 134.5, 129.7, 126.8, 126.7, 129.3, 59.3, 39.3, 29.8, 21.3. MS (ESI): 276.2 ($M + Na^+$). Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.9; H, 5.97; N 5.53. Found: C, 57.19; H, 5.89, N, 5.49.

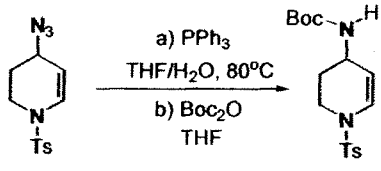


4-Azido-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (20.1)[56]

To a solution of 1.0 g of **17.1** (4.1 mmol, 1.0 equiv) in 16 mL of toluene was added 0.63 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (4.1 mmol, 1.0 equiv). The reaction mixture was cooled to 0 °C, and 0.92 mL of diphenylphosphoryl azide (4.1 mmol, 1.0 equiv) were added. The reaction mixture was warmed to rt and stirred overnight. After the reaction mixture was diluted with water, the separated aqueous layer was extracted with

dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a light brown oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate to ethyl acetate) afforded 0.30 g of starting material and 0.79 g (69%) of a light brown oil.

IR (film): 2929, 2095, 1640, 1358, 1169 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.2 Hz, 2 H), 7.30 (d, *J*=7.8 Hz, 2 H), 6.93 (d, *J*=8.2 Hz, 1 H), 5.07 – 4.95 (m, 1 H), 3.83 (q, *J*=4.4 Hz, 1 H), 3.62 - 3.71 (m, 1 H), 3.04 (ddd, *J*=12.3, 10.3, 4.3 Hz, 1 H), 2.41 (s, 3 H), 1.89 - 1.71 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 134.4, 129.9, 129.4, 127.0, 102.9, 51.02, 39.6, 27.5, 21.5. HRMS (EI): Calcd for $C_{17}H_{19}NO_5NaS$ (M^+) 278.0838, found 278.0839.

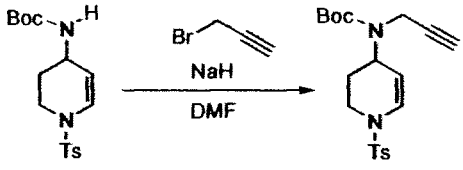


[1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid *tert*-butyl ester (24.1)[58]

A solution 0.51 g of **23.0** (1.8 mmol, 1.0 equiv) and 0.96 g of triphenylphosphine (3.7 mmol, 2.0 equiv) in 18 mL of THF and 0.7 mL of water was heated to reflux for 2 h. The reaction mixture was concentrated by rotary evaporation *in vacuo*. To the pale yellow solid was added 0.80 g of di-*tert*-butyl-dicarbonate (3.7 mmol, 2.0 equiv) and 18 mL of THF. The reaction mixture was heated to reflux for 1.5 h. Concentration by rotary evaporation *in vacuo* afforded a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (10:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 0.59 g (91%) of a white solid (mp 133-135 °C).

IR (film): 3377, 2977, 1702, 1646, 1510, 1366, 1169 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.2 Hz, 2 H), 7.30 (d, *J*=7.9 Hz, 2 H), 6.74 (d, *J*=8.7 Hz, 1 H), 4.89 (dd, *J*=8.3, 4.4 Hz, 1 H), 4.35 (br. s., 1 H), 4.04 (br. s., 1 H), 3.57 - 3.44 (m, 1 H), 3.24 - 3.08

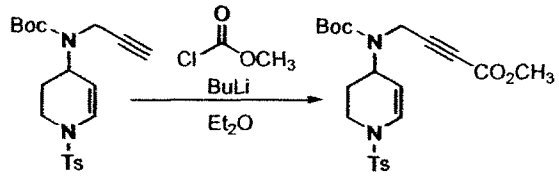
(m, 1 H), 2.42 (s, 3 H), 1.82 - 1.68 (m, 2 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.6, 144.0, 134.8, 129.9, 127.8, 127.0, 107.1, 79.7, 41.7, 40.4, 30.3, 28.3, 21.6. HRMS (ESI): Calcd for $C_{17}H_{24}N_2O_4NaS$ ($M + Na^+$) 375.1354, found 375.1355.



Prop-2-ynyl-[1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid *tert*-butyl ester (24.2)[59]

A suspension of 0.67 g of **23.1** (1.91 mmol, 1.00 equiv) and 0.097 g of sodium hydride (3.8 mmol, 2.0 equiv) in 20 mL of *N,N*-dimethyl formamide was stirred for 1 h. The reaction mixture was stirred at 0 °C before 1.0 mL of propargyl bromide (12 mmol, 6.0 equiv) were added dropwise. The reaction mixture was warmed to rt and stirred overnight. After the reaction mixture was diluted with water, it was extracted with dichloromethane. The separated organic layer was washed sequentially with water and brine. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford a yellow oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.59 g (79%) of a colourless oil.

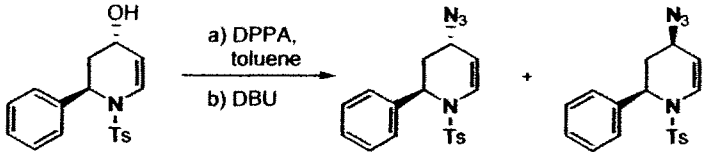
IR (film): 3288, 2976, 1696, 1365, 1267, 1167 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J*=8.3 Hz, 2 H), 7.28 (d, *J*=8.3 Hz, 2 H), 6.78 (dd, *J*=8.5, 2.0 Hz, 1 H), 4.80 (d, *J*=6.5 Hz, 1 H), 3.78 - 3.66 (m, 1 H), 3.65 – 3.51 (m, 2 H), 3.26 - 3.07 (m, 1 H), 2.38 (s, 3 H), 2.03 (t, *J*=2.4 Hz, 1 H), 1.87 - 1.74 (m, 2 H), 1.40 (s, 9 H), 1.36 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 143.9, 134.4, 129.7, 128.8, 126.8, 107.6, 81.1, 80.4, 70.0, 47.7, 42.1, 32.4, 28.1, 25.9, 21.4. HRMS (ESI): Calcd for $C_{20}H_{26}N_2O_4NaS$ ($M + Na^+$) 413.1511, found 413.1513.



4-{tert-Butoxycarbonyl-[1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-amino}-but-2-ynoic acid methyl ester (11.0e)[30]

Following the synthesis of methyl ester **11.0a**, methyl **11.0e** was synthesized using the following quantities of reagents and solvents: 0.96 mL of *n*-butyllithium (1.2 mmol, 1.2 M in hexanes); 0.39 g of **23.2** (0.99 mmol, 1.0 equiv) in 10 mL of diethyl ether; 0.40 mL of methyl chloroformate (5.1 mmol, 5.2 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.40 g (91%) of a yellow oil.

IR (film): 2978, 2241, 1698, 1366, 1256, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J*=8.3 Hz, 2 H), 7.28 (d, *J*=8.3 Hz, 2 H), 6.80 (dd, *J*=8.3, 1.7 Hz, 1 H), 4.76 (d, *J*=6.5 Hz, 1 H), 4.62 (br. s., 1 H), 3.86 - 3.67 (m, 2 H), 3.72 (s, 3 H), 3.60 - 3.51 (m, 1 H), 3.20 (t, *J*=10.0 Hz, 1 H), 2.38 (s, 3 H), 1.91 - 1.79 (m, 1 H), 1.71 (br. s., 1 H), 1.40 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 153.5, 144.2, 134.4, 129.8, 129.5, 126.9, 107.1, 85.2, 81.1, 71.8, 52.6, 47.8, 42.1, 32.6, 28.2, 26.1, 21.4. HRMS (ESI): Calcd for $C_{22}H_{28}N_2O_6NaS$ ($M + Na^+$) 471.1566, found 471.1575.



Trans-4-Azido-2-phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (24.3f) and Cis-4-Azido-2-phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine (25.3g)[56]

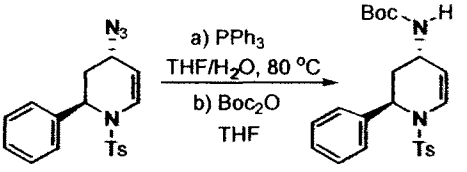
To a solution of 1.2 g of **13.5** (3.6 mmol, 1.0 equiv) in 15 mL of toluene was added 2.4 mL of diphenylphosphoryl azide (11 mmol, 3.0 equiv). The yellow reaction mixture was cooled to 0 °C and 1.6 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (11 mmol, 3.0 equiv) were added. The light brown reaction mixture was stirred at 0 °C for 1 h and the

resulting dark brown reaction mixture was warmed to rt and stirred overnight. The reaction mixture was diluted with water and filtered through a pad of Celite. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a thick dark brown oil. The above procedure was performed using the following quantities of reagents and solvents: 0.57 g of **13.5** (1.7 mmol, 1.0 equiv) in 7 mL of toluene, 1.2 mL of diphenylphosphoryl azide (5.2 mmol, 3.0 equiv) and 11 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (5.2 mL, 3.0 equiv). The combined crude materials from both experiments were purified by column chromatography on triethylamine washed silica gel (12:1 hexanes/ethyl acetate, 5% benzene) to afford 0.67 g (35%) of a yellow oil **25.3f** and 0.43 g (23%) of a yellow solid **25.3g**.

To a solution of 0.72 g of **13.5** (2.2 mmol, 1.0 equiv) in 8.8 mL of toluene was added 1.4 mL of diphenylphosphoryl azide (6.6 mmol, 3.0 equiv). The yellow reaction mixture was cooled to 0 °C and 0.99 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (6.6 mmol, 3.00 equiv) were added. The light brown reaction mixture was warmed to rt and stirred for 2 days. The reaction mixture was diluted with water and filtered over a pad of Celite. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation *in vacuo* to afford a thick dark brown oil. Purification by column chromatography on triethylamine washed silica gel (10:1 hexanes/ethyl acetate) afforded 0.19 g (24%) of a yellow oil **25.3f** and 0.36 (47%) of a yellow solid **25.3g** (mp 36-38 °C).

25.3f - IR (film): 2928, 2101, 1646, 1364, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J*=8.3 Hz, 2 H), 7.31 - 7.24 (m, 5 H), 7.20 - 7.15 (m, 2 H), 7.08 - 7.03 (m, 1 H), 5.16 (t, *J*=3.7 Hz, 1 H), 5.03 - 4.98 (m, 1 H), 3.57 - 3.50 (m, 1 H), 2.42 (s, 3 H), 2.27 - 2.20 (m, 1 H), 1.59 - 1.49 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 138.7, 135.6, 130.0, 128.7, 127.6, 127.5, 126.9, 125.5, 106.4, 55.6, 50.6, 32.2, 21.6. HRMS (EI): Calcd for $C_{18}H_{18}N_4O_2S$ (M^+) 354.1151, found 354.1153.

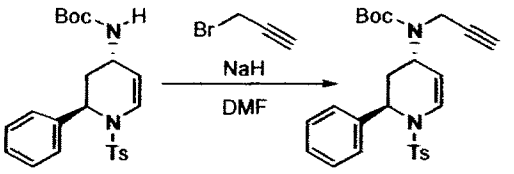
25.3g - IR (film): 3063, 2101, 1646, 1364, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.3 Hz, 2 H), 7.39 - 7.32 (m, 2 H), 7.29 - 7.17 (m, 6 H), 5.29 (dd, *J*=4.8, 2.6 Hz, 1 H), 5.17- 5.11 (m, 1 H), 3.86 (t, *J*=5.0 Hz, 1 H), 2.40 (s, 3 H), 2.39 - 2.32 (m, 1 H), 1.80 (dt, *J*=14.4, 5.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.1, 138.1, 136.0, 129.8, 128.8, 128.3, 127.0, 125.8, 120.2, 103.6, 53.9, 49.6, 33.6, 21.6. HRMS (EI): Calcd for $C_{18}H_{18}N_4O_2S$ (M^+) 354.1151, found 354.1151.



Trans-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid *tert*-butyl ester (26.1f)[58]

Following the procedure for the synthesis of carbamate **24.1**, carbamate **26.1f** was synthesized using the following quantities of reagents and solvents: 0.84 g of **25.3f** (2.4 mmol, 1.0 equiv); 1.2 g of triphenylphosphine (4.7 mmol, 2.0 equiv) in 24 mL of THF and 1 mL of water; 1.0 g of di-*tert*-butyl-dicarbonate (4.7 mmol, 2.0 equiv) in 24 mL of THF. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate to 3:1 hexanes/ethyl acetate) afforded 0.72 g (70%) of a white solid (mp 118-120 °C).

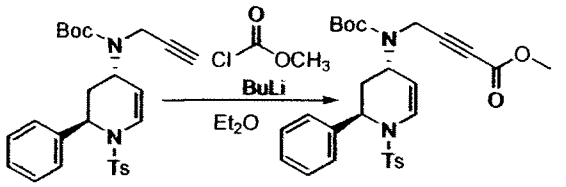
IR (film): 3392, 2976, 1703, 1651, 1496, 1365, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.59 (d, *J*=7.0 Hz, 2 H), 7.33 - 7.12 (m, 7 H), 6.93 (d, *J*=8.3 Hz, 1 H), 5.16 (br. s., 1 H), 4.89 (d, *J*=7.9 Hz, 1 H), 4.40 - 4.25 (m, 1 H), 3.89 (br. s., 1 H), 2.41 (s, 3 H), 2.33 (d, *J*=10.5 Hz, 1 H), 1.37 (br. s., 10 H). δ ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 143.7, 138.9, 136.0, 129.7, 128.5, 127.4, 126.9, 126.1, 125.7, 109.7, 79.6, 56.1, 40.8, 33.4, 28.3, 21.5. HRMS (ESI): Calcd for $C_{23}H_{28}N_2O_4NaS$ ($M + Na^+$) 451.1667, found 451.1653.



Trans-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid *tert*-butyl ester (26.2f)[59]

A suspension of 0.19 g of **26.1f** (0.43 mmol, 1.0 equiv) and 0.016 g of sodium hydride (0.65 mmol, 1.5 equiv) in 1.5 mL of *N*, *N*-dimethyl formamide was stirred for 1.5 h. The reaction mixture was cooled to 0 °C before 0.14 mL of propargyl bromide (1.3 mmol, 3.0 equiv) were added dropwise. The reaction mixture was warmed to rt and stirred for 6 h before 0.013 g of sodium hydride (0.32 mmol, 0.75 equiv) and 0.14 mL of propargyl bromide (1.3 mmol, 3.0 equiv) were added. The reaction mixture was stirred overnight. After the reaction mixture was diluted with water, it was extracted with dichloromethane. The separated organic layer was washed sequentially with water and brine. The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford a brown oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.097 g (68% brsm) of a colourless oil.

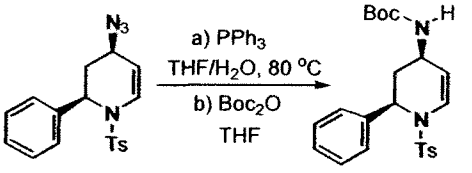
IR (film): 3305, 2975, 1696, 1393, 1365, 1167 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.67 (br. s., 2 H), 7.34 - 7.20 (m, 7 H), 7.02 (d, *J*=8.3 Hz, 1 H), 5.23 (br. s., 1 H), 4.99 (br. s., 1 H), 4.65 - 4.11 (m, 1 H), 3.86 - 3.44 (m, 2 H), 2.43 (s, 3 H), 2.12 (br. s., 1 H), 2.06 (s, 1 H), 1.68 (td, *J*=12.2, 4.8 Hz, 2 H), 1.52 - 1.20 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 143.9, 138.7, 135.8, 129.7, 128.5, 128.0, 127.3, 126.9, 125.6, 109.5, 81.4, 80.5, 70.1, 56.2, 46.4, 32.4, 29.7, 28.2, 21.5. HRMS (ESI): Calcd for $C_{28}H_{32}N_2O_6NaS$ ($M + Na^+$) 547.1879, found 547.1870.



Trans-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid *tert*-butyl ester (11.0f)[30]

Following the procedure for the synthesis of methyl ester **11.0a**, methyl ester **11.0f** was synthesized using the following quantities of reagents and solvents: 0.33 mL of *n*-butyllithium (0.41 mmol, 1.2 M in hexanes); 0.12 g of **26.2f** in 2.6 mL of diethyl ether; 0.11 mL of methyl chloroformate (1.4 mmol, 5.5 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether to 3:2 petroleum ether/diethyl ether) afforded 0.066 g (49%) of a yellow oil.

IR (film): 2976, 2240, 1714, 1366, 1256, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (br. s., 2 H), 7.33 - 7.08 (m, 7 H), 6.99 (d, *J*=7.4 Hz, 1 H), 5.20 (br. s., 1 H), 4.97 - 4.75 (m, 1 H), 4.54 – 4.07 (m, 1 H), 3.88 - 3.70 (m, 1 H), 3.75 (s, 3 H), 3.70 - 3.51 (m, 1 H), 2.38 (s, 3 H), 2.19 - 1.99 (m, 1 H), 1.54 (td, *J*=12.2, 4.8 Hz, 1 H), 1.45 - 1.18 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 153.6, 144.1, 138.5, 135.7, 129.7, 128.5, 127.4, 126.9, 125.6, 125.5, 109.1, 85.3, 81.1, 73.9, 56.2, 52.6, 46.4, 32.4, 30.3, 28.1, 21.5. MS (ESI): 547.1 ($M + Na^+$).

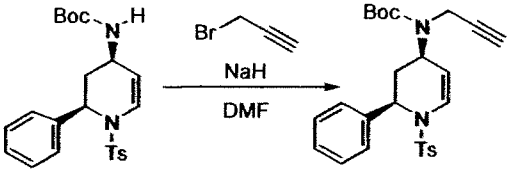


Cis-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-carbamic acid *tert*-butyl ester (26.1g)[58]

Following the experimental procedure for the preparation of carbamate **24.1**, carbamate **26.1g** was prepared using the following quantities of reagents and solvents: 0.92 g of **25.3g** (2.6 mmol, 1.0 equiv), 1.4 g of triphenylphosphine (5.2 mmol, 2.0 equiv) in 26 mL of THF and 1 mL of water, 1.1 g of di-*tert*-butyl-dicarbonate (5.2 mmol, 2.0 equiv) and

26 mL of THF. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.91 g (92%) of a white solid (mp 159-160 °C).

IR (film): 3437, 2977, 1708, 1649, 1494, 1366, 1168 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J*=8.3 Hz, 2 H), 7.30 - 7.18 (m, 7 H), 7.03 (d, *J*=8.3 Hz, 1 H), 5.25 (br. s., 1 H), 5.10 - 5.02 (m, 1 H), 3.95 - 3.87 (m, 1 H), 3.41 (d, *J*=9.2 Hz, 1 H), 2.45 - 2.35 (m, 1 H), 2.40 (s, 3 H), 1.61 (ddd, *J*=14.2, 5.0, 4.8 Hz, 1 H), 1.22 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.4, 144.0, 139.0, 136.0, 129.8, 128.7, 127.0, 126.8, 126.7, 125.5, 108.2, 78.9, 54.1, 40.3, 34.0, 28.1, 21.5. MS (ESI): 451.3 ($M + Na^+$). Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.58; N, 6.54. Found: C, 64.28; H 6.57; N, 6.38.

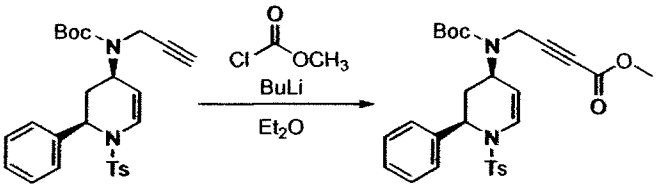


Cis-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid *tert*-butyl ester (26.2g)[59]

A suspension of 0.19 g of **26.1g** (0.45 mmol, 1.0 equiv) and 0.017 g of sodium hydride (0.68 mmol, 1.5 equiv) in 1.5 mL of *N*, *N*-dimethyl formamide was stirred for 1 h before 0.15 mL of propargyl bromide (1.4 mmol, 3.0 equiv) were added dropwise. The reaction mixture was stirred for 5 h before the addition of 0.014 g of sodium hydride (0.34 mmol, 1.3 equiv) and 0.15 mL of propargyl bromide (1.4 mmol, 3.0 equiv). The reaction mixture was stirred overnight before it was diluted with water and extracted with dichloromethane. The combined organic phases were washed sequentially with water and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford a brown oil. Purification by column chromatography on triethylamine washed silica gel (2:1 petroleum ether/diethyl ether) afforded 66.4 mg of starting material and 0.060 g (46% brsm) of a white solid (50-52 °C).

IR (film): 3307, 2977, 1690, 1366, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J*=8.7 Hz, 2 H), 7.33 - 7.19 (m, 7 H), 7.10 (dd, *J*=8.3, 1.7 Hz, 1 H), 5.20 (br. s., 1 H), 4.95

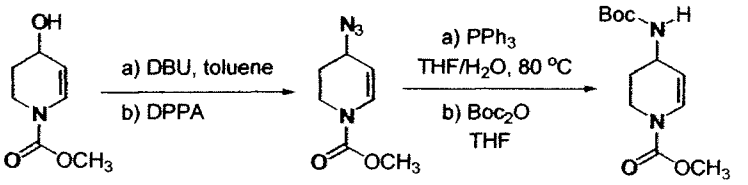
(br. s., 1 H), 4.32 (br. s., 1 H), 2.92 (br. s., 2 H), 2.69 – 2.57 (m, 1 H), 2.44 (s, 3 H), 2.02 (s, 1 H), 1.65 (br. s., 1 H), 1.51 - 1.37 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 144.1, 139.6, 135.4, 129.8, 128.9, 128.3, 127.1, 127.0, 126.1, 107.6, 81.6, 80.2, 69.7, 55.2, 46.8, 34.3, 32.7, 28.3, 21.5. HRMS (ESI): Calcd for $C_{26}H_{30}N_2O_4NaS$ ($M + Na^+$) 489.1824, found 489.1815.



Cis-[2-Phenyl-1-(toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridin-4-yl]-prop-2-ynyl-carbamic acid *tert*-butyl ester (11.0g)[30]

Following the procedure for the synthesis of methyl ester **11.0a**, methyl ester **11.0g** was synthesized using the following quantities of reagents and solvents: 0.53 mL of *n*-butyllithium (0.65 mmol, 1.2 M in hexanes); 0.20 g of **26.2g** in 4.3 mL of diethyl ether; 0.18 mL of methyl chloroformate (2.4 mmol, 5.5 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate) afforded 0.047 g of starting material and 0.11 g (61% brsm) of a yellow oil.

IR (film): 2975, 2239, 1718, 1367, 1251, 1170 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J*=8.3 Hz, 2 H), 7.33 - 7.18 (m, 7 H), 7.13 (d, *J*=8.7 Hz, 1 H), 5.18- 5.03 (m, 2 H), 4.28 (br. s., 1 H), 3.71 (s, 3 H), 3.03 - 2.77 (m, 2 H), 2.71 – 2.61 (m, 1 H), 2.43 (s, 3 H), 1.64 - 1.53 (m, 1 H), 1.39 (br. s., 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 153.7, 144.1, 139.1, 135.5, 129.9, 129.3, 128.4, 127.2, 126.9, 126.0, 106.6, 85.8, 80.7, 73.5, 54.5, 52.5, 46.4, 33.7, 32.8, 28.2, 21.5. HRMS (ESI): Calcd for $C_{28}H_{32}N_2O_6NaS$ ($M + Na^+$) 547.1879, found 547.1880.



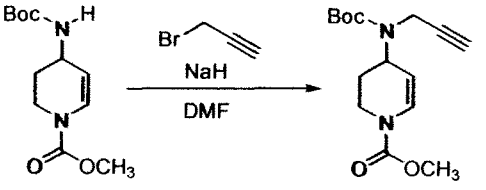
4-tert-Butoxycarbonylamino-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (27.2)[56,58]

To a solution of 2.11 g of **14.5** (13.4 mmol, 1.00 equiv) in 38 mL of toluene was added 1.02 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (26.9 mmol, 2.00 equiv). The reaction mixture was cooled to 0 °C, and 6.00 mL of diphenylphosphoryl azide (26.9 mmol, 2.00 equiv) were added. The reaction mixture was warmed to rt and stirred for 1 h before it was diluted with water. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a light brown oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate) afforded 2.45 g of a mixture of **27.1** and diphenylphosphoryl azide.

A solution 2.45 g of **27.1** (13.4 mmol, 1.00 equiv) and 7.00 g of triphenylphosphine (26.8 mmol, 2.00 equiv) in 13 mL of THF and 4.8 mL of water was heated at 50 °C for 40 min. The reaction mixture was concentrated by rotary evaporation *in vacuo*. To the pale yellow solid was added 5.83 g of di-*tert*-butyl-dicarbonate (26.8 mmol, 2.00 equiv) and 13 mL of THF. The reaction mixture was heated at 50 °C for 2 h then at 60 °C for 1 h. Concentration by rotary evaporation *in vacuo* to afforded a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 1.51 g (44% over two steps) of a white solid (mp 133-135 °C).

27.1 - IR (film): 2957, 2095, 1718, 1647, 1445, 1358, 1235, 1191, 768 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 - 6.96 (m, 1 H), 5.10 - 4.86 (m, 1 H), 3.94 (q, *J*=4.4 Hz, 1 H), 3.91 - 3.79 (m, 1 H), 3.75 (s, 3 H), 3.43 - 3.32 (m, 1 H), 1.97 - 1.82 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.3, 120.2, 101.6, 53.2, 51.9, 38.2, 27.8. HRMS (EI): Calcd for $C_7H_{10}N_4O_2$ (M^+) 182.0804, found 182.0803.

27.2 - IR (film): 3344, 2977, 1712, 1652, 1447, 1366, 1238, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 - 6.76 (m, 1 H), 4.93 - 4.74 (m, 1 H), 4.55 (d, *J*=4.8 Hz, 1 H), 4.15 (br. s., 1 H), 3.82 - 3.66 (m, 4 H), 3.38 (ddd, *J*=13.1, 9.6, 3.5 Hz, 1 H), 1.97 - 1.74 (m, 2 H), 1.40 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.1, 153.9, 127.5, 106.1, 79.7, 53.3, 42.5, 39.2, 28.8, 28.6. HRMS (ESI): Calcd for $C_{12}H_{20}N_2O_4Na$ ($M + Na^+$) 279.1321, found 279.1316.

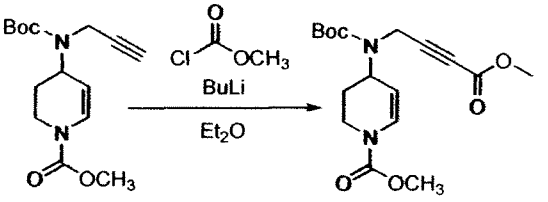


4-(tert-Butoxycarbonyl-prop-2-ynyl-amino)-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (27.3)[59]

A suspension of 1.1 g of **26.2** (4.1 mmol, 1.0 equiv) and 0.052 g of sodium hydride (21 mmol, 5.0 equiv) in 25 mL of *N*, *N*-dimethyl formamide and 1 mL of THF was stirred for 15 min before 2.3 mL of propargyl bromide (21 mmol, 5.0 equiv) were added dropwise. The reaction mixture was stirred overnight before it was diluted with water and extracted with dichloromethane. The combined organic phases were washed sequentially with water and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford a brown oil. Purification by column chromatography on triethylamine washed silica gel (13:1 hexanes/ethyl acetate) afforded 0.32 g of starting material and 0.48 g (57% brsm) of a white solid (mp 97-99.5 °C).

IR (film): 3307, 2977, 2252, 1695, 1652, 1446, 1397, 1167, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 - 6.77 (m, 1 H), 4.71 (br. s., 1 H), 4.65 (br. s., 1 H), 4.03 - 3.77 (m, 2 H), 3.73 (br. s., 1 H), 3.67 (s, 3 H), 3.47 - 3.33 (m, 1 H), 2.07 (t, *J*=2.4 Hz, 1 H), 1.89 (br. s., 2 H), 1.39 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 153.0, 128.9, 105.9,

81.6, 80.6,70.2, 53.2, 48.6, 40.8, 32.9, 28.4, 26.9. HRMS (ESI): Calcd for $C_{15}H_{22}N_2O_4Na$ ($M + Na^+$) 317.1477, found 317.1473.

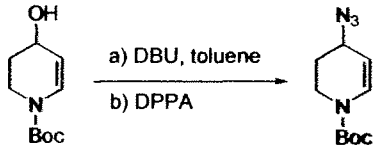


4-[tert-Butoxycarbonyl-(3-methoxycarbonyl-prop-2-ynyl)-amino]-3,4-dihydro-2H-pyridine-1-carboxylic acid methyl ester (11.0h)[30]

A solution of *n*-butyllithium (1.9 mL, 2.5 mmol, 1.4 M in hexanes) was added dropwise to a solution of 0.46 g of **27.3** in 16 mL of diethyl ether at − 78 °C. After the reaction mixture was stirred at − 78 °C for 1 h, 0.66 mL of methyl chloroformate (8.6 mmol, 5.5 equiv) were added. The reaction mixture was stirred at − 78 °C for 30 min, then warmed to rt and stirred for 1 h. After 1.7 mL of THF were added, the reaction mixture was stirred overnight. The above procedure was repeated using the following quantities of reagents and solvents: 0.21 mL of *n*-butyllithium (0.29 mmol, 1.4 M in hexanes); 0.053 g of **27.3** in 16 mL of diethyl ether; and 7.7 μL of methyl chloroformate (0.99 mmol, 5.5 equiv). After both of the above reaction mixtures were diluted with diethyl ether, they were combined and washed sequentially with water and brine. The aqueous washes were back-extracted with diethyl ether. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a yellow oil. Purification by column chromatography on triethylamine washed silica gel (9:1 hexanes/ethyl acetate to 7:1 hexanes/ethyl acetate 3:1 hexanes/ethyl acetate) afforded 0.080 g of starting material and 0.430 g (83% brsm) of a yellow oil.

IR (film): 2956, 2239, 1718, 1652, 1445, 1255, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.14- 6.84 (m, 1 H), 5.03 - 4.58 (m, 2 H), 3.98 (br. s., 2 H), 3.95 - 3.76 (m, 1 H), 3.73 (d, *J*=3.1 Hz, 6 H), 3.53 - 3.41 (m, 1 H), 2.09 - 1.78 (m, 2 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 154.0, 153.7, 129.7, 105.0, 85.6, 81.1, 73.9, 53.1, 52.6,

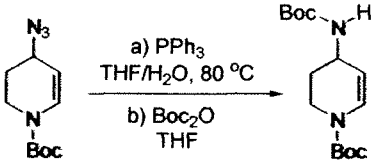
48.5, 40.6, 32.8, 28.3, 26.8. HRMS (ESI): Calcd for $C_{17}H_{24}N_2O_6Na$ $(M + Na^+)$ 375.1532, found 375.1539.



4-Azido-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (28.1)[56]

Following the procedure for the synthesis of azide **27.1**, azide **28.1** was synthesized using the following quantities of reagents and solvents: 2.1 g of alcohol **16.4** (11 mmol, 1.0 equiv) in 30 mL of toluene; 3.2 mL of 1,8-diazabicyclo[5, 4, 0]undec-7-ene (21 mmol, 2.0 equiv); 4.7 mL of diphenylphosphoryl azide (21 mmol, 2.0 equiv). Workup and purification by column chromatography on triethylamine washed silica gel (hexanes to 15:1 hexanes/ethyl acetate) afforded 1.7 g (73%) of a colourless oil.

IR (film): 2978,2093, 1713, 1645, 1359,1237, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 - 6.85 (m, 1 H), 5.00 - 4.72 (m, 1 H), 3.96 - 3.68 (m, 2 H), 3.33 - 3.17 (m, 1 H), 1.91 - 1.75 (m, 2 H), 1.41 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 129.6, 100.4, 81.3, 51.8, 37.8, 28.0, 27.7. MS (ESI): 228 (M). Anal. Calcd for $C_{10}H_{16}N_4O_2$: C, 52.61; H, 7.06; N, 24.54. Found: C, 56.24; H, 7.48; N, 23.12.



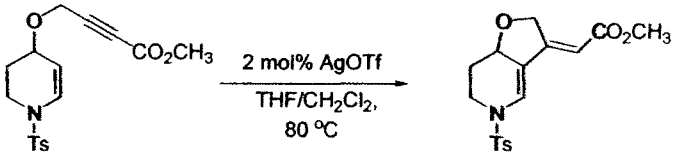
4-tert-Butoxycarbonylamino-3,4-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (28.2)[58]

A solution 0.76 g of **28.1** (3.34 mmol, 1.00 equiv) and 1.8 g of triphenylphosphine (6.7 mmol, 2.0 equiv) in 33 mL of THF and 1.2 mL of water was heated to reflux for 1 h. The reaction mixture was concentrated by rotary evaporation *in vacuo*. To the pale yellow solid was added 1.5 g of di-*tert*-butyl-dicarbonate (6.7 mmol, 2.0 equiv) and 33 mL of

THF. The reaction mixture was heated to reflux for 4 h. Concentration by rotary evaporation *in vacuo* to afforded a pale yellow oil. Purification by column chromatography on triethylamine washed silica gel (hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 0.94 g (94%) of a white solid (mp 112-114 °C).

IR (film): 3341, 2979, 1696, 1651, 1515, 1367, 1239, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.92 - 6.58 (m, 1 H), 4.77 (d, *J*=6.1 Hz, 1 H), 4.72 - 4.55 (m, 1 H), 4.02 (br. s., 1 H), 3.58 (br. s., 1 H), 3.29 – 3.16 (m, 1 H), 1.75 (br. s., 1 H), 1.68 (br. s., 1 H), 1.24 - 1.40 (m, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 151.8, 127.6, 104.7, 99.8, 80.7, 78.9, 42.1, 38.4, 28.4, 28.1, 27.9. MS (ESI): 321.3 ($M + Na^+$). Anal. Calcd for $C_{15}H_{26}N_2O_4$: C, 60.38; H, 8.78; N, 9.39. Found: C, 60.12; H, 8.53; N, 9.28.

C. Cycloisomerization reactions

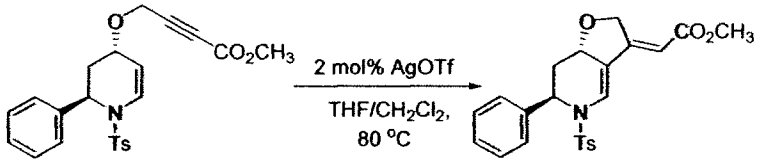


[5-(Toluene-4-sulfonyl)-5,6,7,7a-tetrahydro-furo[3,2-c]pyridin-3-ylidene]-acetic acid methyl ester (11.1a)

A solution of 0.22 g of **11.0** (0.63 mmol, 1.0 equiv) and 3.2 mg of silver trifluoromethanesulfonate (0.013 mmol, 0.02 equiv) in 10 mL of THF and 40 μL of dichloromethane was heated to reflux for 16 h. Concentration of the reaction mixture by rotary evaporation *in vacuo* afforded a yellow oil. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate) afforded 0.16 g (73%) of a pale yellow oil.

IR (film): 2950, 1703, 1621, 1354, 1280, 1163 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J*=8.3 Hz, 2 H), 7.37 - 7.28 (m, 3 H), 5.93 (t, *J*=2.4 Hz, 1 H), 5.09 (dd, *J*=16.1, 2.2 Hz,

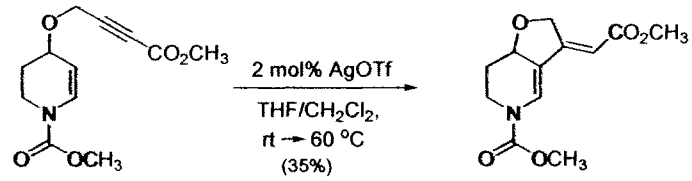
1 H), 4.63 (dd, *J*=16.6, 2.6 Hz, 1 H), 4.22 (ddd, *J*=10.4, 5.6, 1.5 Hz, 1 H), 3.90 (dt, *J*=13.1, 3.5 Hz, 1 H), 3.69 (s, 3 H), 3.03 (td, *J*=13.4, 2.8 Hz, 1 H), 2.41 (s, 3 H), 2.29 - 2.21 (m, 1 H), 1.42 - 1.38 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 155.4, 144.6, 134.4, 130.1, 127.0, 122.3, 120.0, 103.7, 74.0, 73.3., 51.3, 41.4, 26.2, 21.6. HRMS (ESI): Calcd for $C_{17}H_{19}NO_5NaS$ ($M + Na^+$) 372.0882, found 372.0875.



[6-Phenyl-5-(toluene-4-sulfonyl)-5,6,7,7a-tetrahydro-furo[3,2-c]pyridin-3-ylidene]-acetic acid methyl ester (11.1b)

A solution of 0.057 g of **11.0b** (0.13 mmol, 1.0 equiv) and 0.7 mg of silver trifluoromethanesulfonate (0.0027 mmol, 0.02 equiv) in 2.2 mL of THF and 10 μL of dichloromethane was heated to reflux for 6 h. Concentration of the reaction mixture by rotary evaporation *in vacuo* afforded an off white solid. Purification by column chromatography on triethylamine washed silica gel (6:1 hexanes/ethyl acetate) afforded 0.040 g (70%) of a white solid.

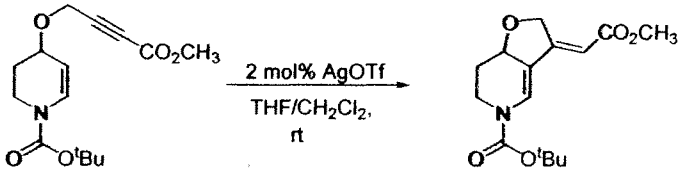
IR (film): 2918, 1704, 1622, 1357, 1164 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 - 7.54 (m, 3 H), 7.29 - 7.17 (m, 5 H), 7.09 - 7.01 (m, 2 H), 6.00 (t, *J*=2.5 Hz, 1 H), 5.24 (dd, *J*=4.6, 2.3 Hz, 1 H), 5.07 (dd, *J*=16.7, 2.1 Hz, 1 H), 4.55 (dd, *J*=16.5, 2.7 Hz, 1 H), 3.90 (ddd, *J*=10.5, 5.5, 1.4 Hz, 1 H), 3.70 (s, 3 H), 2.48 - 2.35 (m, 4 H), 1.37 (ddd, *J*=12.1, 10.7, 4.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 155.6, 144.6, 139.0, 135.3, 130.0, 128.6, 127.6, 127.0, 125.4, 122.7, 119.6, 103.6, 73.2, 71.4, 56.3, 51.3, 32.1, 21.6. HRMS (ESI): Calcd for $C_{23}H_{23}NO_5NaS$ ($M + Na^+$) 448.1195, found 448.1195.



3-Methoxycarbonylmethylene-2,3,7,7a-tetrahydro-6H-furo[3,2-c]pyridine-5-carboxylic acid methyl ester (11.1c)

A solution of 0.078 g of **11.0c** (0.31 mmol, 1.0 equiv) and 1.6 mg of silver trifluoromethanesulfonate (0.0062 mmol, 0.02 equiv) in 5.0 mL of THF and 20 μL of dichloromethane was stirred at rt for 1h 15min. The reaction mixture was then heated to 60 °C and stirred for 35 min. Concentration of the reaction mixture by rotary evaporation *in vacuo* afforded a brown residue. Purification by column chromatography on triethylamine washed silica gel (5:1 hexanes/ethyl acetate) afforded 0.028 g (36%) of a white solid.

IR (film): 2955, 1712, 1617, 1441, 1197 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 - 7.36 (m, 1 H), 5.92 (br. s., 1 H), 5.14 (dd, *J*=16.6, 2.2 Hz, 1 H), 4.70 (dd, *J*=16.6, 2.6 Hz, 1 H), 4.44 - 4.35 (m, 1 H), 4.12 (br. s., 1 H), 3.82 (s, 3 H), 3.72 (s, 3 H), 3.20 (br. s., 1 H), 2.38 (br. s., 1 H), 1.31 - 1.21 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 156.0, 153.7, 122.5, 119.1, 103.1, 74.7, 73.4, 53.7, 51.2, 40.4, 22.4. MS (ESI): 254.2 ($M + Na^+$).

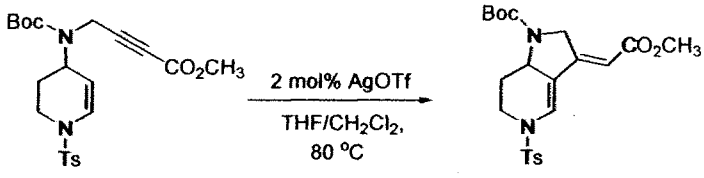


3-Methoxycarbonylmethylene-2,3,7,7a-tetrahydro-6H-furo[3,2-c]pyridine-5-carboxylic acid *tert*-butyl ester (11.1d)

A solution of 0.054 g of **11.0d** (0.18 mmol, 1.0 equiv) and 0.9 mg of silver trifluoromethanesulfonate (0.0036 mmol, 0.02 equiv) in 1.8 mL of THF and 0.50 mL of dichloromethane was stirred at rt for 20 min. The reaction mixture was cooled to −78 °C and concentrated by rotary evaporation *in vacuo* afforded a brown solid. Purification by

column chromatography on triethylamine washed silica gel (7:1 hexanes/ethyl acetate) afforded 0.041 g (75%) of a white solid.

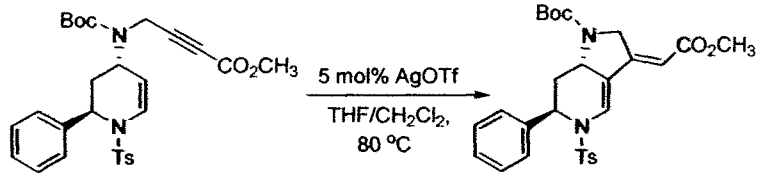
IR (film): 2976, 1705, 1620, 1367, 1152 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 - 7.29 (m, 1 H), 5.88 (s, 1 H), 5.14 (dd, *J*=16.1, 2.2 Hz, 1 H), 4.70 (dd, *J*=16.4, 2.4 Hz, 1 H), 4.38 (ddd, *J*=10.3, 5.5, 1.3 Hz, 1 H), 4.27 - 3.99 (m, 1 H), 3.70 (s, 3 H), 3.17 (br. s., 1 H), 2.35 (br. s., 1 H), 1.55 - 1.48 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 156.3, 152.9, 123.1, 113.6, 103.2, 82.5, 74.8, 73.5, 51.2, 40.2, 28.3, 28.2. HRMS (ESI): Calcd for $C_{15}H_{21}NO_5Na$ ($M + Na^+$) 318.1317, found 318.1316.



3-Methoxycarbonylmethylene-5-(toluene-4-sulfonyl)-2,3,5,6,7,7a-hexahydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (11.1e)

A solution of 0.074 g of **11.0e** (0.16 mmol, 1.0 equiv) and 0.8 mg of silver trifluoromethanesulfonate (0.0033 mmol, 0.02 equiv) in 2.7 mL of THF and 10 μL of dichloromethane was heated to reflux for 3 h. Concentration by rotary evaporation *in vacuo* afforded a golden-brown oil. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.060 g (81%) of a colourless oil.

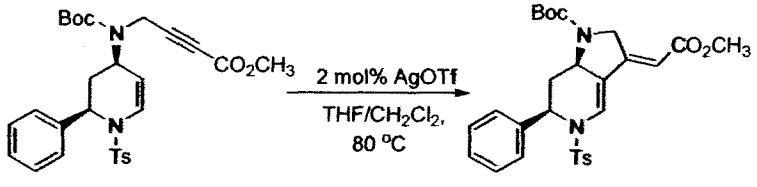
IR (film): 2932, 1702, 1616, 1358, 1164 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J*=8.3 Hz, 2 H), 7.35 - 7.29 (m, 3 H), 5.94 (t, *J*=2.4 Hz, 1 H), 4.50 (br. s., 2 H), 4.00 - 3.91 (m, 1 H), 3.86 (dt, *J*=13.1, 3.3 Hz, 1 H), 3.69 (s, 3 H), 3.06 (td, *J*=13.1, 3.1 Hz, 1 H), 2.41 (s, 3 H), 1.48 - 1.35 (m, 10 H), 1.27 - 1.13 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 155.1, 152.5, 144.6, 134.3, 130.1, 127.0, 123.3, 118.2, 104.1, 80.3, 54.7, 53.4, 51.2, 42.2, 28.4, 27.8, 21.6. MS (ESI): 471.1 ($M + Na^+$).



Trans-3-Methoxycarbonylmethylene-6-phenyl-5-(toluene-4-sulfonyl)-2,3,5,6,7,7a-hexahydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (11.1f)

A solution of 0.025 g of **11.0f** (0.048 mmol, 1.0 equiv) and 0.6 mg of silver trifluoromethanesulfonate (0.0024 mmol, 0.05 equiv) in 0.80 mL of THF and 10 μL of dichloromethane was heated to reflux for 3.5 h. Concentration by rotary evaporation *in vacuo* afforded a golden-brown oil. Purification by column chromatography on triethylamine washed silica gel (5:1 petroleum ether/diethyl ether) afforded 0.0052 g (20%) of a colourless oil.

IR (film): 2027, 1702, 1617, 1358, 1193 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 - 7.54 (m, 4 H), 7.23 - 7.15 (m, 4 H), 7.09 - 7.03 (m, 2 H), 6.00 (t, *J*=2.6 Hz, 1 H), 5.23 - 5.19 (m, 1 H), 4.57- 4.43 (m, 2 H), 3.71 (s, 3 H), 3.09 (br. s., 1 H), 2.40 (s, 3 H), 1.41 (s, 3 H), 1.36 (br. s., 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 154.6, 144.2, 135.9, 135.2, 132.4, 130.0, 129.7, 128.6, 128.4, 127.5, 127.3, 125.8, 106.7, 80.2, 56.3, 55.0, 53.0, 51.3, 51.2, 28.3, 21.5. HRMS (ESI): Calcd for $C_{28}H_{32}N_2O_6NaS$ ($M + Na^+$) 547.1879, found 547.1874.

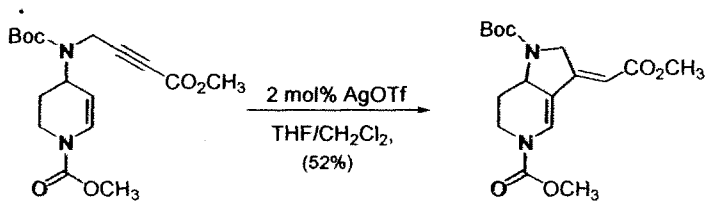


Cis-3-Methoxycarbonylmethylene-6-phenyl-5-(toluene-4-sulfonyl)-2,3,5,6,7,7a-hexahydro-pyrrolo[3,2-c]pyridine-1-carboxylic acid *tert*-butyl ester (11.1g)

A solution of 0.051 g of **11.0g** (0.098 mmol, 1.0 equiv) and 0.5 mg of silver trifluoromethanesulfonate (0.0020 mmol, 0.02 equiv) in 0.80 mL of THF and 10 μL of dichloromethane was heated to reflux for 3.5 h. Concentration by rotary evaporation *in vacuo* afforded a golden-brown oil. Purification by column chromatography on

triethylamine washed silica gel (7:1 hexanes/ethyl acetate to 5:1 hexanes/ethyl acetate) afforded 0.032 g (63%) of a yellow solid.

IR (film): 2976, 1701, 1616, 1358, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.47- 7.32 (m, 3 H), 7.20 - 7.09 (m, 8 H), 6.09 (t, *J*=2.5 Hz, 1 H), 4.54 (br. s., 3 H), 3.97 (ddd, *J*=10.7, 3.2, 3.0 Hz, 1 H), 3.73 (s, 3 H), 3.07 (br. s., 1 H), 2.38 (s, 3 H), 1.76 - 1.56 (m, 1 H), 1.43 - 1.32 (m, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 154.8, 151.6, 144.1, 140.0, 134.9, 129.6, 128.3, 127.6, 127.0, 126.8, 124.8, 123.1, 105.6, 80.4, 59.5, 54.6, 53.2, 51.4, 29.4, 28.3, 21.5. HRMS (ESI): Calcd for $C_{28}H_{32}N_2O_6NaS$ ($M + Na^+$) 547.1879, found 547.1866.

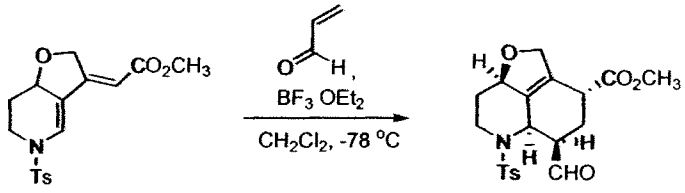


3-Methoxycarbonylmethylene-2,3,7,7a-tetrahydro-6H-pyrrolo[3,2-c]pyridine-1,5-dicarboxylic acid 1-*tert*-butyl ester 5-methyl ester (11.1h)

A solution of 0.044 g of **11.0h** (0.12 mmol, 1.0 equiv) and 0.6 mg of silver trifluoromethanesulfonate (0.0025 mmol, 0.02 equiv) in 1.3 mL of THF and 30 μL of dichloromethane was stirred at room temperature for 24 h. Concentration by rotary evaporation *in vacuo* afforded a yellow solid. Purification by column chromatography on triethylamine washed silica gel (3:1 petroleum ether/diethyl ether) afforded 0.023 g (52%) of a yellow solid.

IR (film): 2954, 1708, 1614, 1365, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 - 7.34 (m, 1 H), 5.94 (br. s., 1 H), 4.56 (br. s., 2 H), 4.12 (br. s., 2 H), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.25 (br. s., 1 H), 2.93 (br. s., 1 H), 1.64 - 1.39 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 155.3, 154.0, 153.2, 123.6, 117.9, 103.7, 80.2, 55.2, 53.7, 51.2, 41.4, 30.0, 28.5, 27.3. HRMS (ESI): Calcd for $C_{17}H_{24}N_2O_6Na$ ($M + Na^+$) 375.1532, found 375.1521.

D. Diels Alder reactions



8-Hydroxymethyl-1-(toluene-4-sulfonyl)-2,3,3a,5,6,7,8,8a-octahydro-1H-furo[2,3,4-de]quinoline-6-carboxylic acid methyl ester (11.20a)

To a solution of 0.062 g of diene **11.1a** (0.18 mmol, 1.0 equiv.) in 2.5 mL of dichloromethane was added 94 μL of acrolein (1.4 mmol, 7.8 equiv.). The reaction mixture was cooled to −78 °C and 4.0 μL of boron trifluoride diethyl etherate (0.029 mmol, 0.16 equiv.) were added. The reaction mixture was stirred at −78 °C for 1 h before 4.0 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) were added. The reaction mixture was stirred at −78 °C for another hour before it was warmed to rt. After the reaction was stirred at rt for another hour, 2.0 μL of boron trifluoride diethyl etherate (0.0054 mmol, 0.080 equiv.) were added. A 1:1 mixture of methanol/water was added to the reaction mixture, and the reaction mixture was then diluted with dichloromethane. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by rotary evaporation *in vacuo* to afford a yellow solid. Purification by column chromatography on silica gel (3:1 hexanes/ethyl acetate) afforded 0.035 g of **11.20a** (49%).

11.21a: IR (film): 2956, 1738, 1347, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 10.03 (s, 1 H), 7.68 (d, *J*=8.3 Hz, 1 H), 7.35 (d, *J*=7.9 Hz, 1 H), 4.62 - 4.55 (m, 1 H), 4.49 - 4.36 (m, 1 H), 4.16 - 4.11 (m, 1 H), 3.76 - 3.68 (m, 1 H), 3.66 (s, 2 H), 3.42 - 3.34 (m, 1 H), 2.80 (ddd, *J*=12.75, 9.92, 3.05 Hz, 1 H), 2.58 (ddd, *J*=14.06, 5.78, 3.71 Hz, 1 H), 2.44 (s, 3 H), 2.07 (dddd, *J*=12.92, 6.38, 6.21, 2.83 Hz, 1 H), 1.87 (dddd, *J*=14.28, 10.79, 3.49, 1.53 Hz, 1 H), 1.63 - 1.53 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.2, 172.1, 144.6, 133.7, 132.8, 132.1, 130.0, 127.8, 80.8, 75.8, 54.0, 52.2, 48.0, 44.4, 37.0, 31.7, 25.7, 21.6. HRMS (ESI): Calcd for $C_{20}H_{23}NO_6NaS$ ($M + Na^+$) 428.1144, found 428.1138.

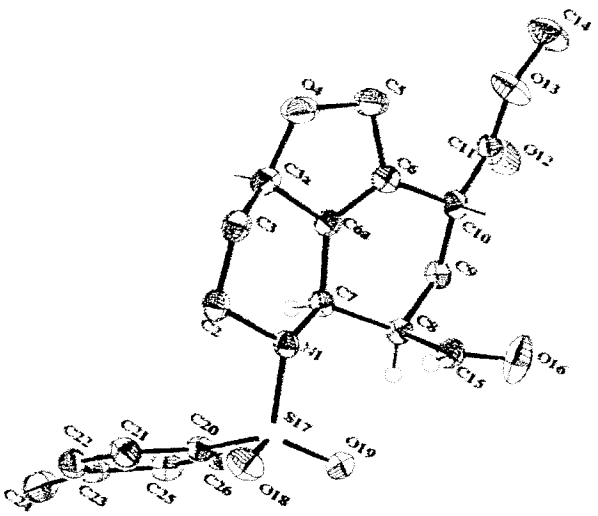
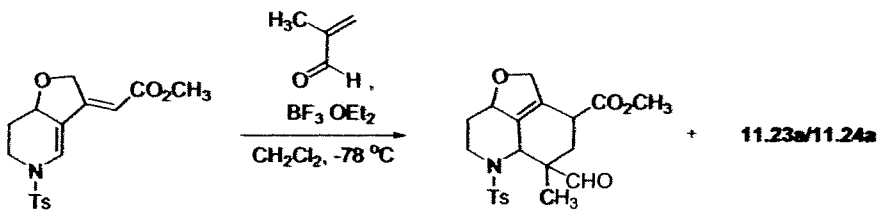


Figure 6: Solid State Molecular Structure of **11.20a**



11.1a 11.22a

8-Formyl-8-methyl-1-(toluene-4-sulfonyl)-2,3,3a,5,6,7,8,8a-octahydro-1H-furo[2,3,4-de]quinoline-6-carboxylic acid methyl ester (11.22a)

To a solution of 0.023 g of diene **11.1a** (0.067 mmol, 1.0 equiv.) in 1 mL of dichloromethane was added 43 μL of methacrolein (0.52 mmol, 7.8 equiv.). The reaction mixture was cooled to −78 °C and 1.0 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) was added. The reaction mixture was stirred at −78 °C for 1 h before 1 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) was added. Over a period of 3h, 1 μL of boron trifluoride diethyl etherate (0.011 mmol, 0.16 equiv.) was added every hour. The reaction mixture was then warmed to rt over 2 h and a 1:1 mixture of methanol/water was added. The reaction mixture was diluted with dichloromethane. The separated aqueous layer was extracted with dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and concentrated by

rotary evaporation *in vacuo* to afford a cloudy oil. Purification by column chromatography on silica gel (3:1 hexanes/ethyl acetate) afforded 0.015 g of **11.22a** (53%) and 0.012 g of a mixture of **11.23a** and **11.24a** (42%).

11.22a: IR (film): 2954, 1734, 1348, 1162 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.65 (d, *J*=1.74 Hz, 1 H), 7.73 (d, *J*=8.28 Hz, 2 H), 7.32 (d, *J*=7.85 Hz, 2 H), 4.70 (br. s., 1 H), 4.61 - 4.52 (m, 1 H), 4.48 - 4.40 (m, 1 H), 4.19 - 4.10 (m, 1 H), 3.76 - 3.64 (m, 5 H), 2.87 (ddd, *J*=15.48, 12.42, 5.67 Hz, 1 H), 2.43 (s, 3 H), 2.29 (dd, *J*=14.17, 5.89 Hz, 1 H), 1.94 - 1.78 (m, 2 H), 1.43 (s, 3 H), 1.34 (dddd, *J*=14.55, 5.94, 3.27, 1.09 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 171.6, 144.0, 137.3, 133.4, 132.1, 130.1, 127.5, 78.4, 75.4, 59.1, 52.2, 50.7, 42.4, 38.2, 33.6, 30.7, 21.6, 21.5. HRMS (ESI): Calcd for $C_{21}H_{25}NO_6NaS$ ($M + Na^+$) 442.1300, found 442.1292.

11.23a and 11.24a : IR (film): 2926, 1724, 1698, 1325, 1161 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 9.70 – 9.67 (m, 1 H), 7.75 – 7.66 (m, 2 H), 7.30 (d, *J*=7.8 Hz, 2 H), 4.86 – 4.80 (m, 1 H), 4.61 (br. s., 1 H), 4.54 – 4.45 (m, 1 H), 4.34 – 4.25 (m, 1 H), 3.72 (s, 3 H), 3.54 (dd, *J*=15.3, 7.0 Hz, 1 H), 3.18 – 3.12 (m, 1 H), 3.09 – 2.98 (m, 1 H), 2.49 (dd, *J*=14.6, 3.3 Hz, 1 H), 2.42 (s, 3 H), 2.05 – 1.97 (m, 1 H), 1.92 (dd, *J*=14.4, 7.4 Hz, 1 H), 1.58 (br. s., 1 H), 1.39 – 1.34 (m, 3H).

Signals attributable to **11.23a**:

^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 171.9, 144.3, 136.9, 132.7, 132.3, 130.0, 127.6, 79.0, 75.8, 58.2, 52.4, 49.5, 42.6, 37.2, 33.3, 31.6, 21.6, 21.6.

Signals attributable to **11.24a**:

^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 171.9, 144.3, 136.9, 132.3, 132.3, 130.0, 127.6, 78.7, 75.0, 53.9, 52.4, 51.3, 42.0, 37.2, 31.9, 31.3, 29.4, 12.4.

V. References

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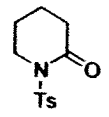
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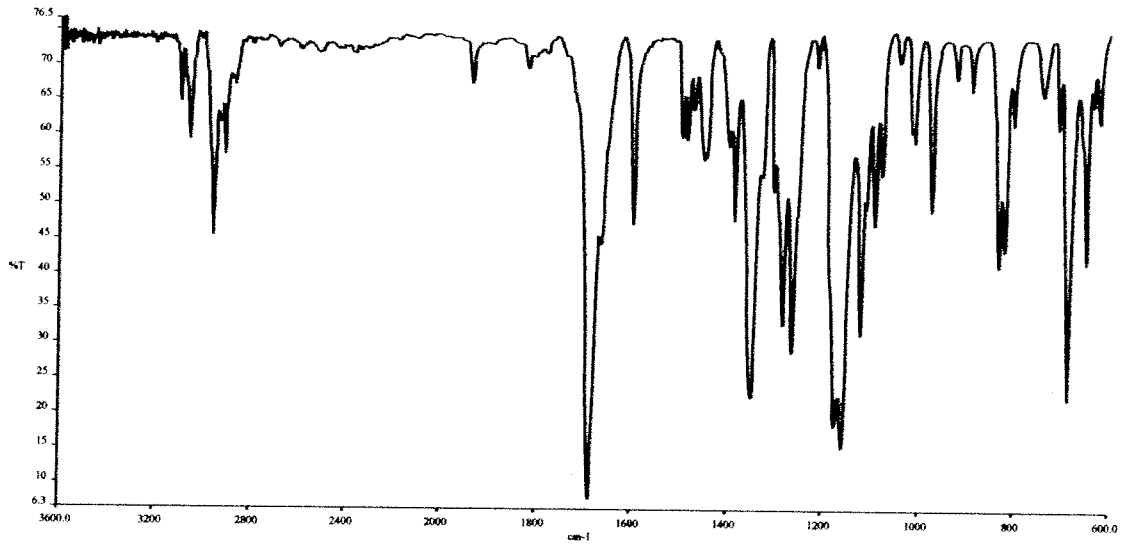
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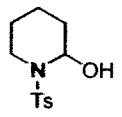
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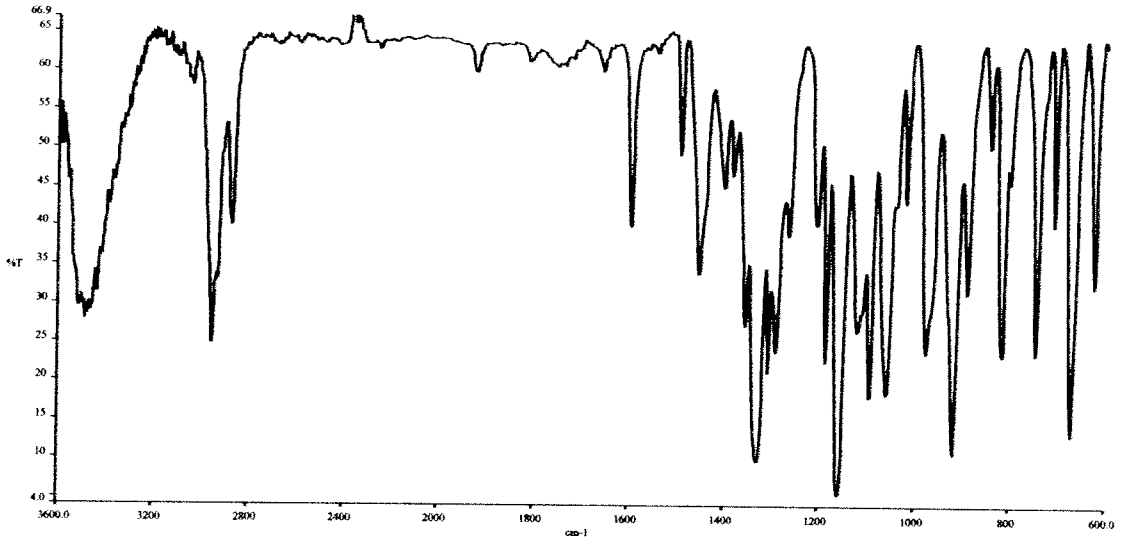
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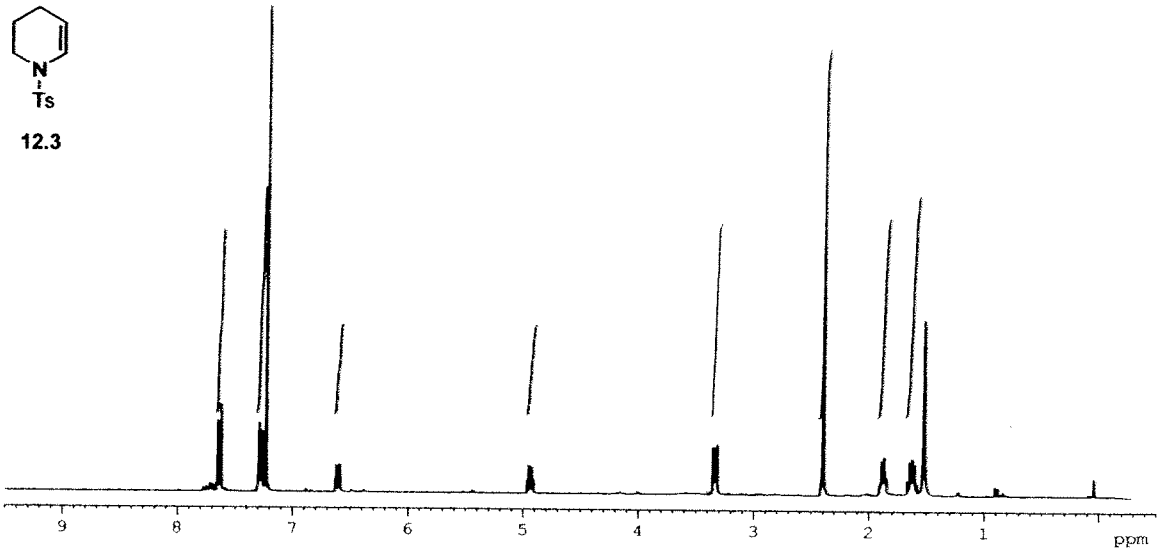
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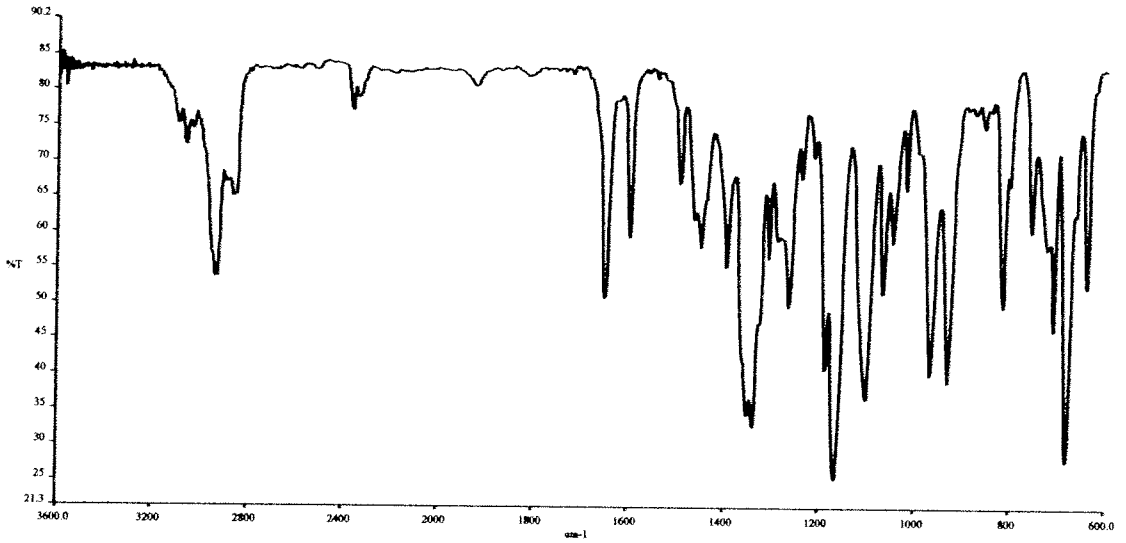
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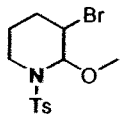
Br
N
O
Ts

12.4

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3
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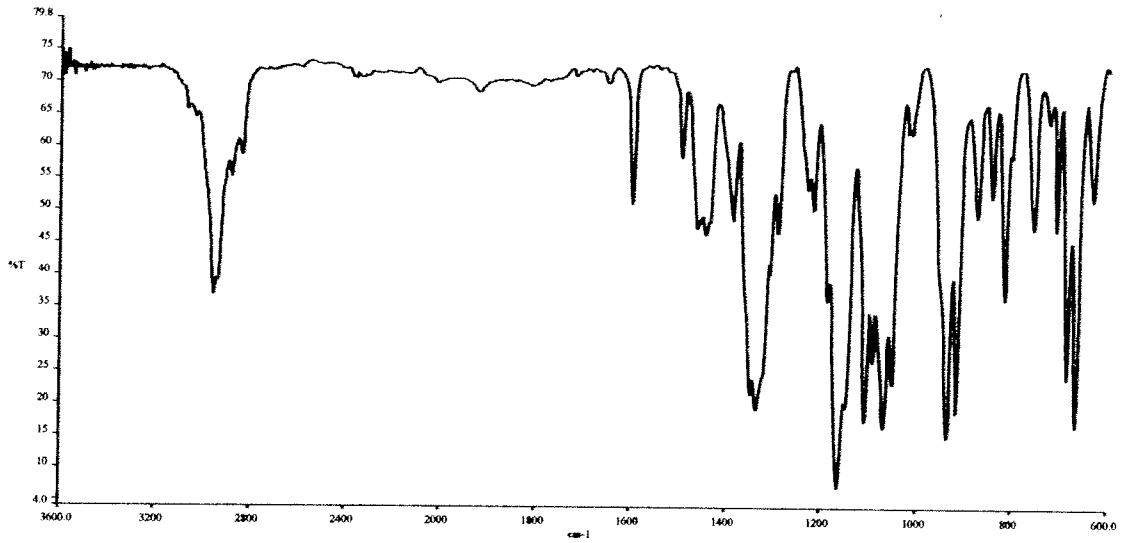
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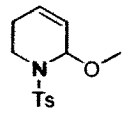
N
O
Ts

12.5

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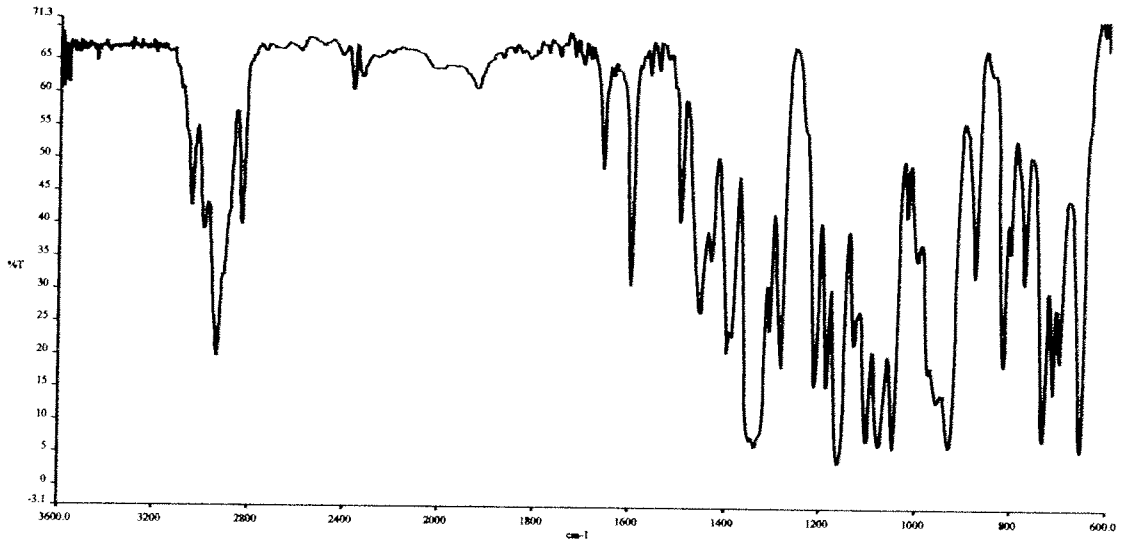
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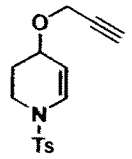
cm-1


O
N
Ts

12.6

9
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4
3
2
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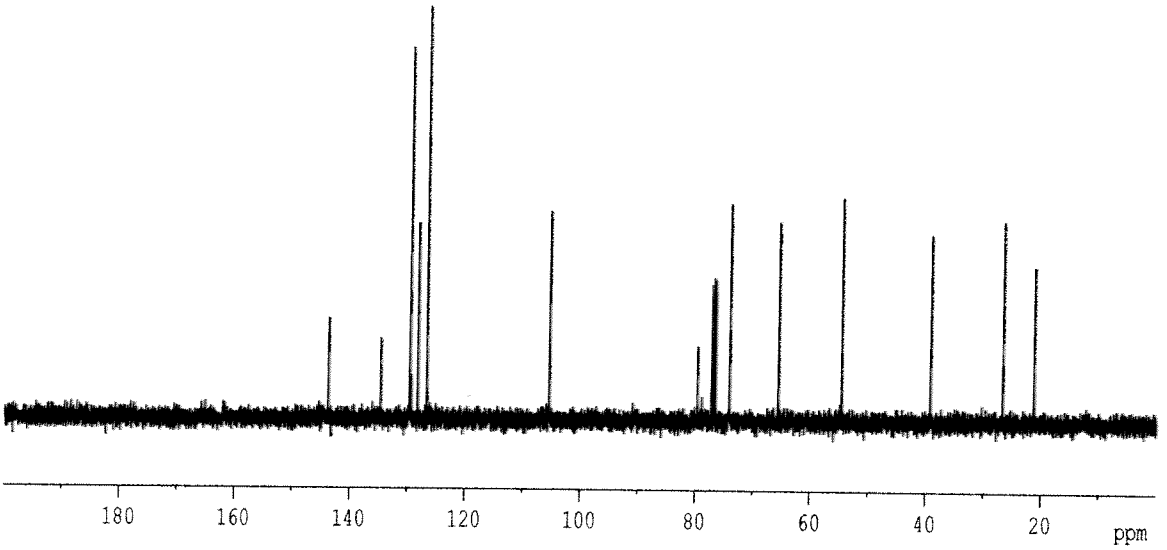
ppm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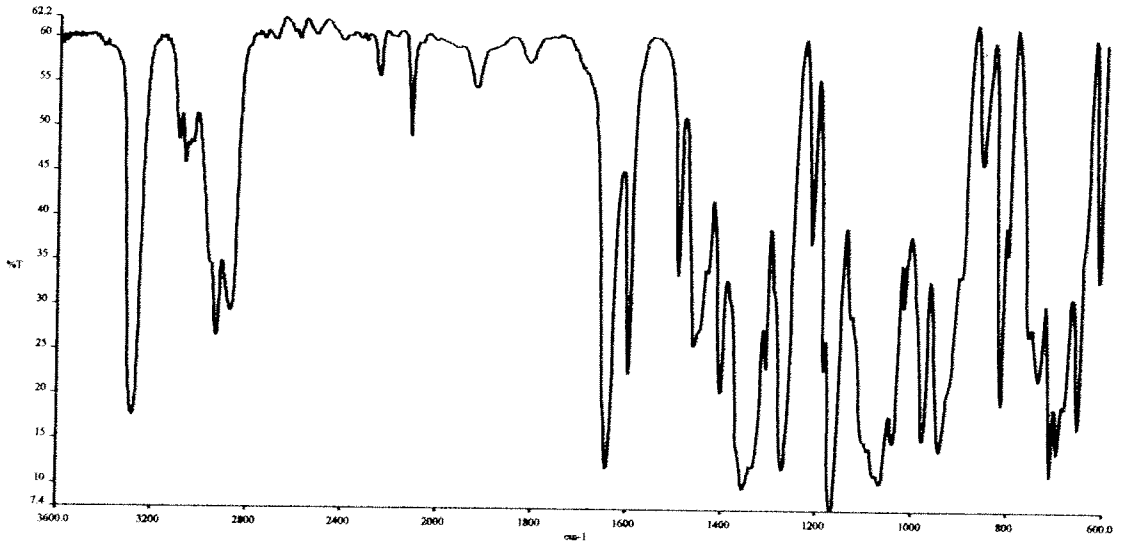
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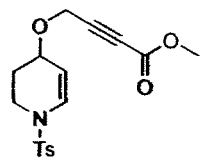
cm-1


O
O
O
N
Ts

11.0a

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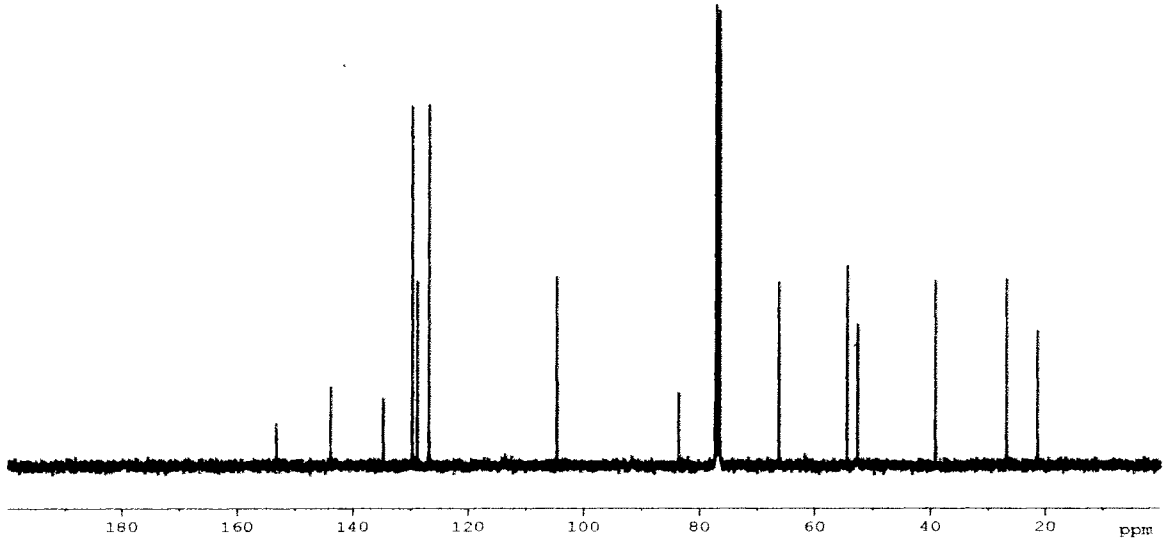
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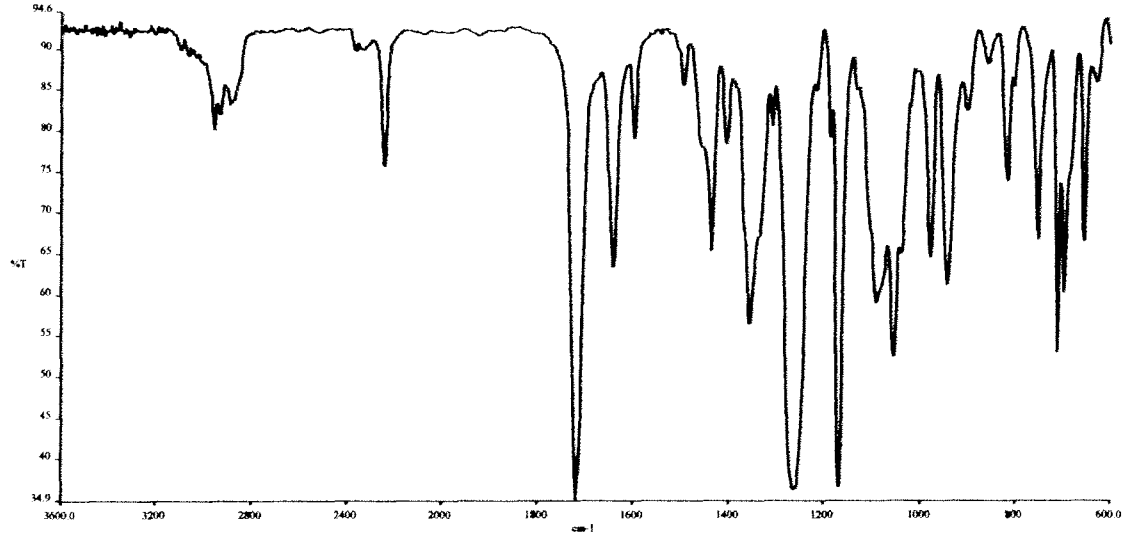
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1600
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1000
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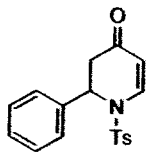
cm-1


O
N
Ts

2.3

9
8
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6
5
4
3
2
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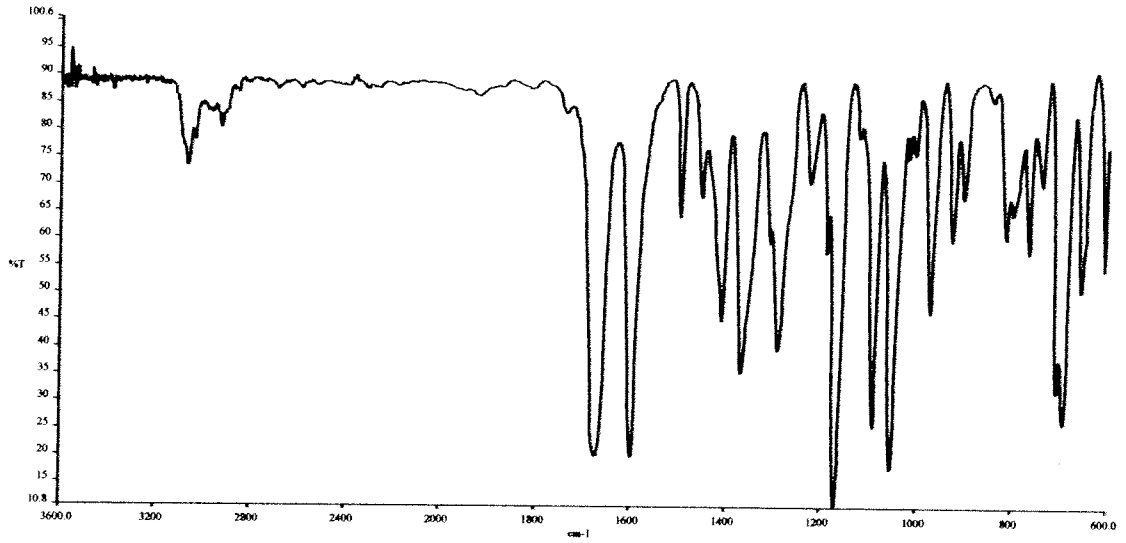
ppm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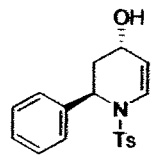
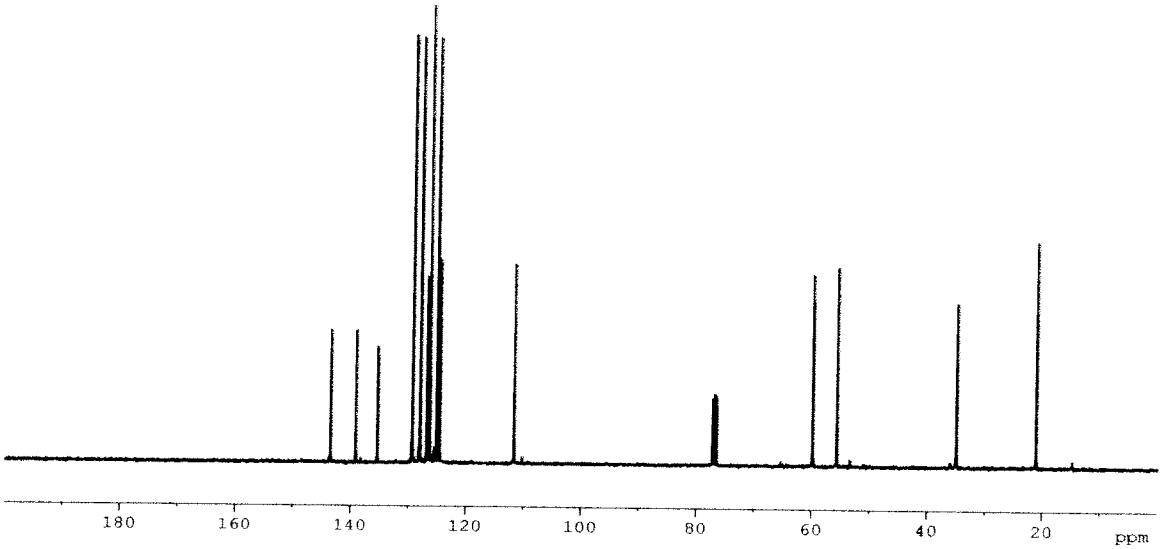
cm-1


OH
N
Ts

13.5

9
8
7
6
5
4
3
2
1
ppm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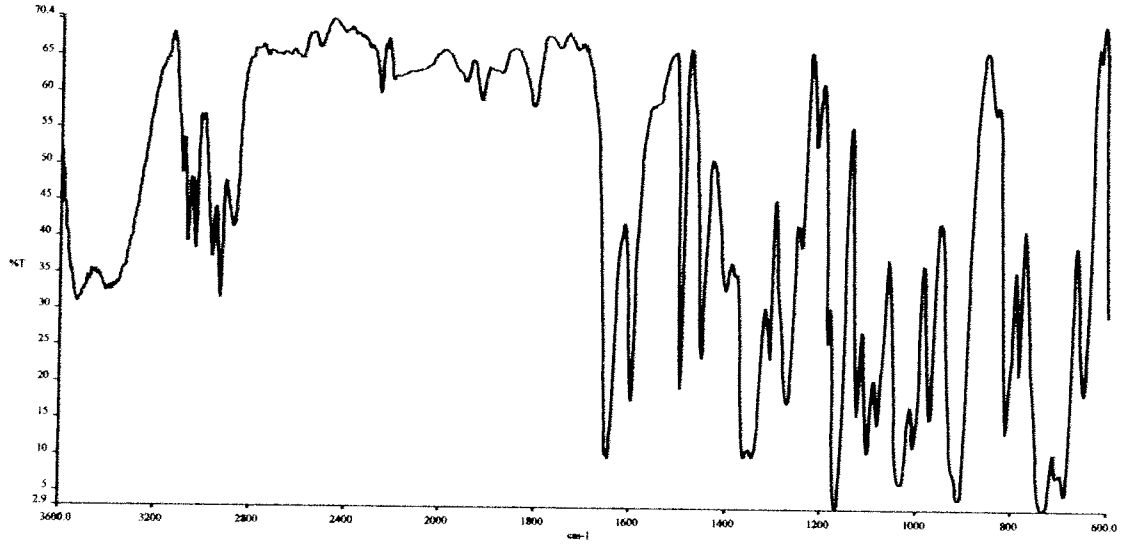
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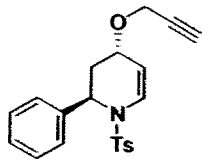
cm-1


O
N
Ts

13.6

9
8
7
6
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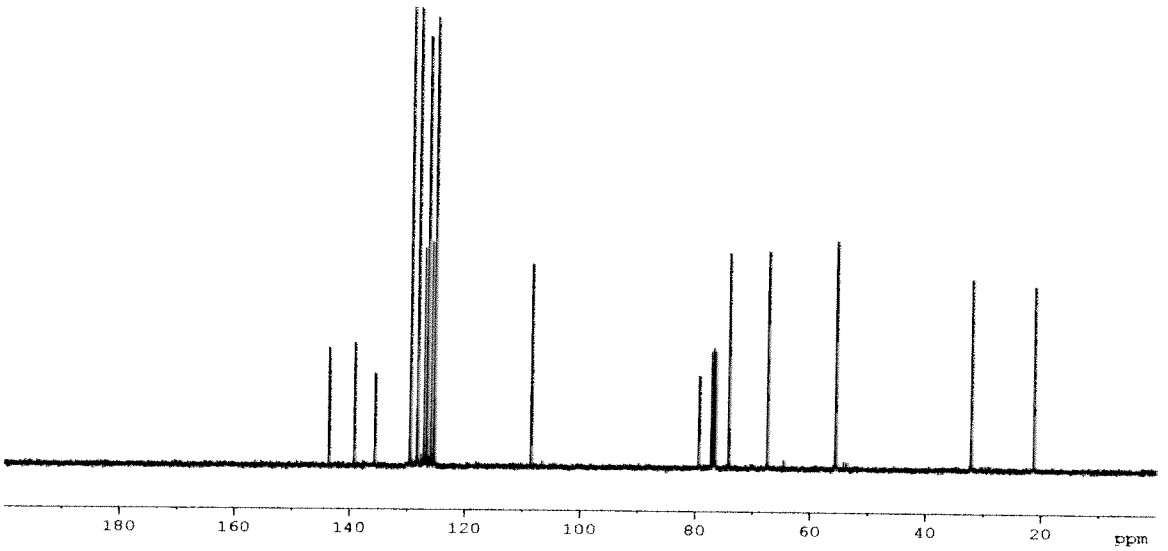
4
3
2
1
ppm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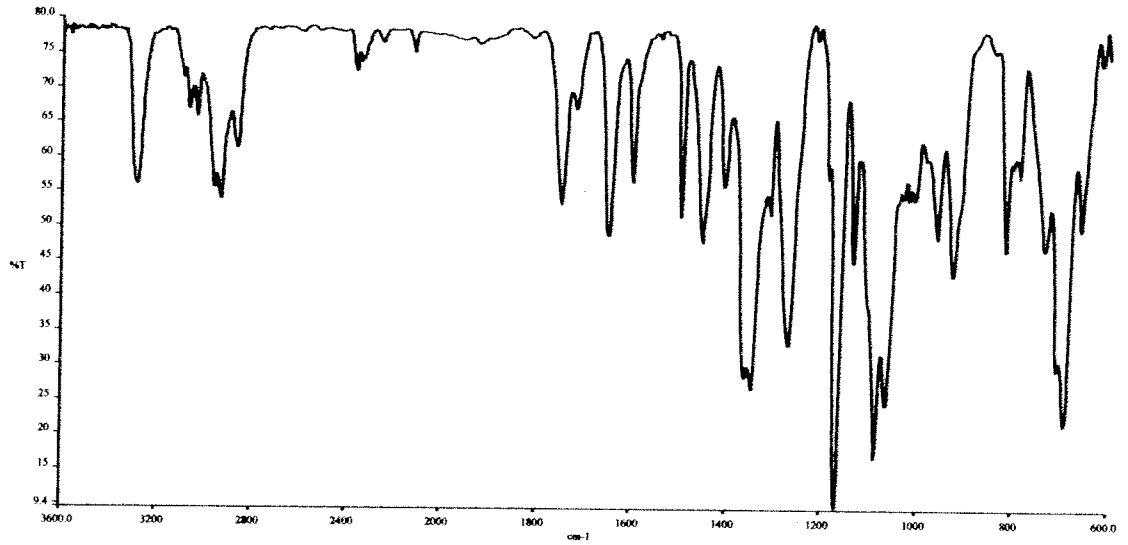
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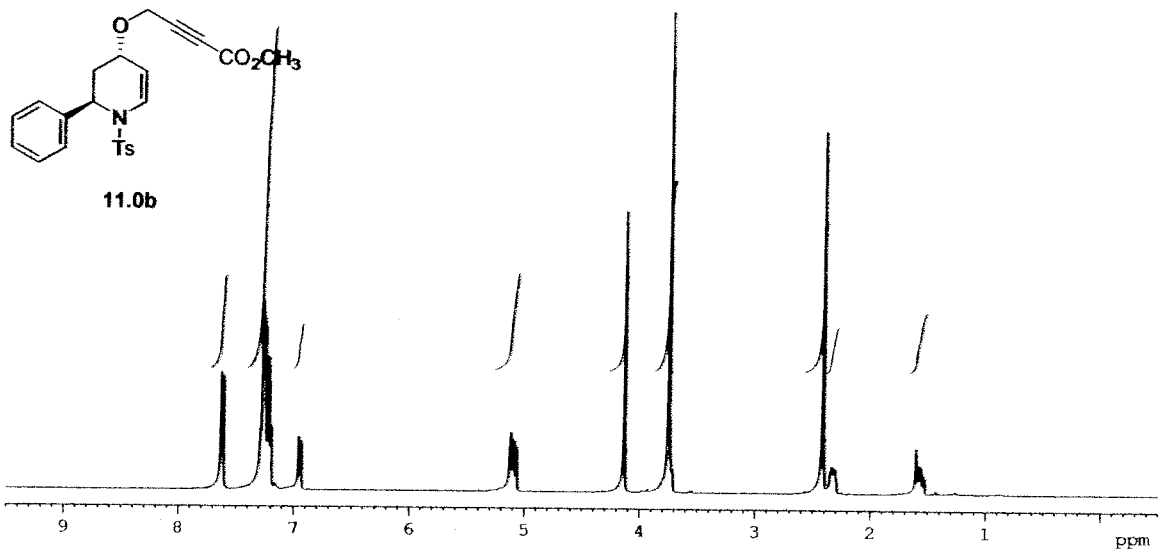
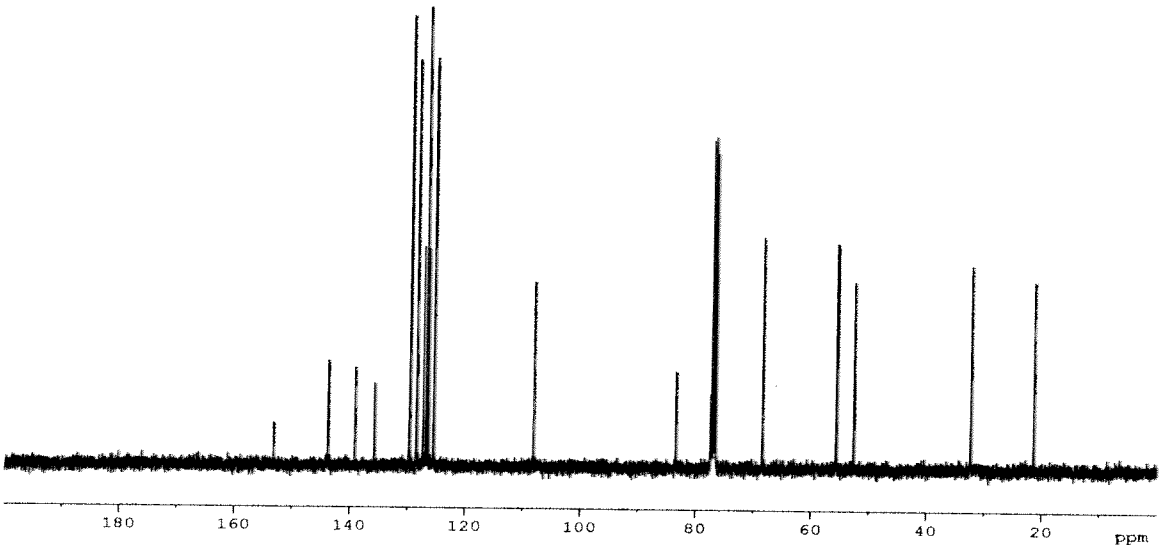
cm-1


O
CO2CH3
N
Ts
11.0b
9
8
7
6
5
4
3
2
1
ppm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20
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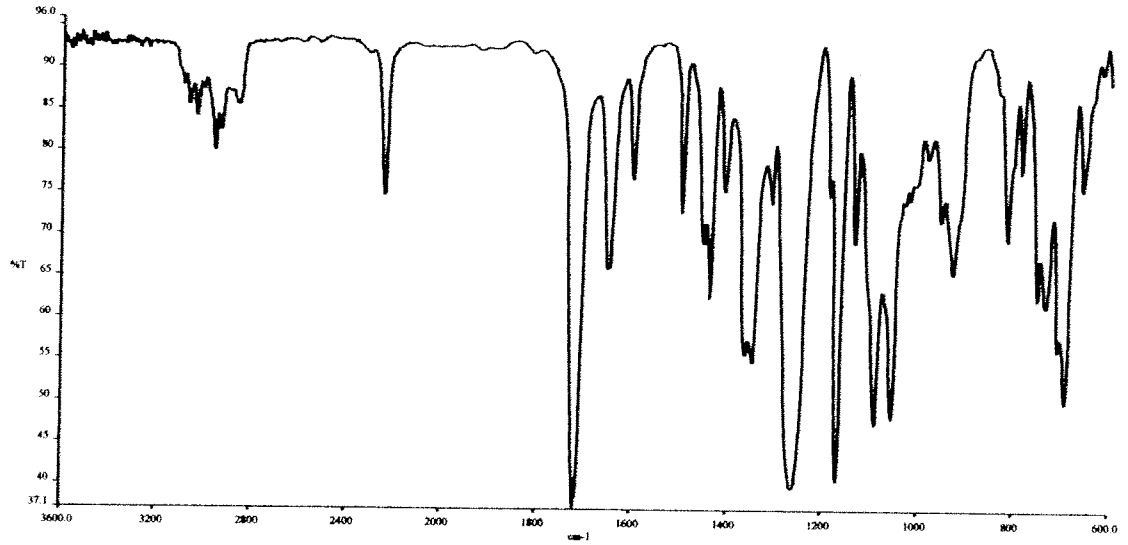
%T
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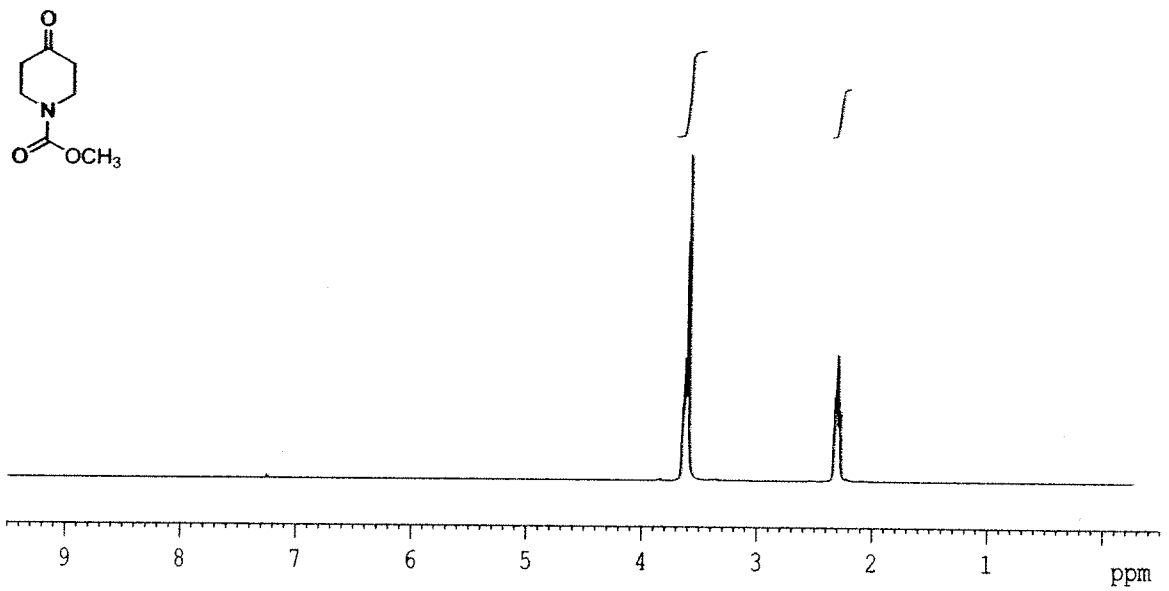
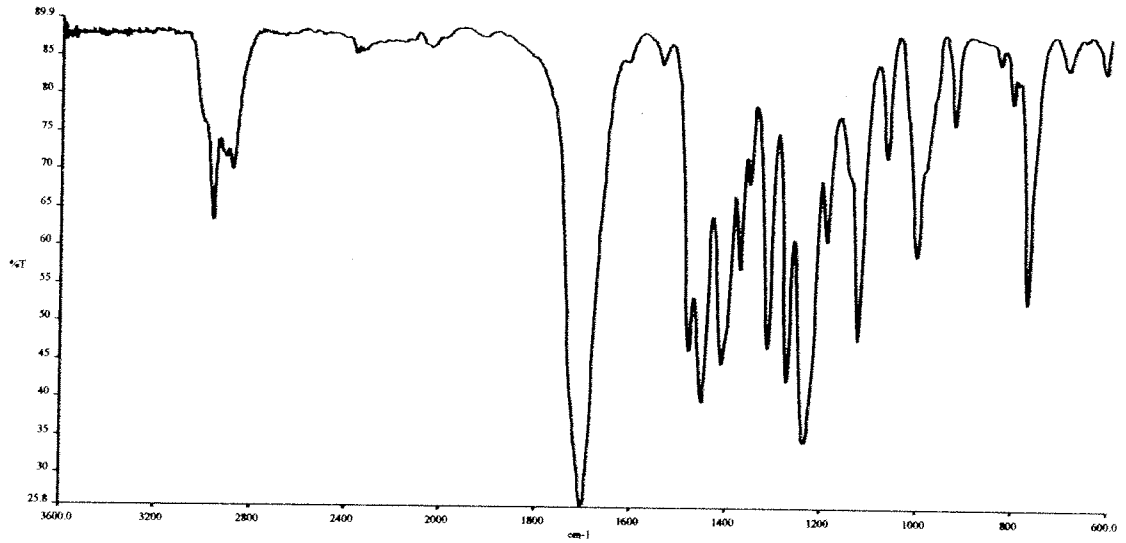
cm-1


O
N
O
OCH3
9
8
7
6
5
4
3
2
1
ppm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80
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70
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50
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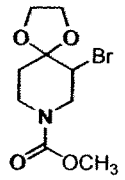
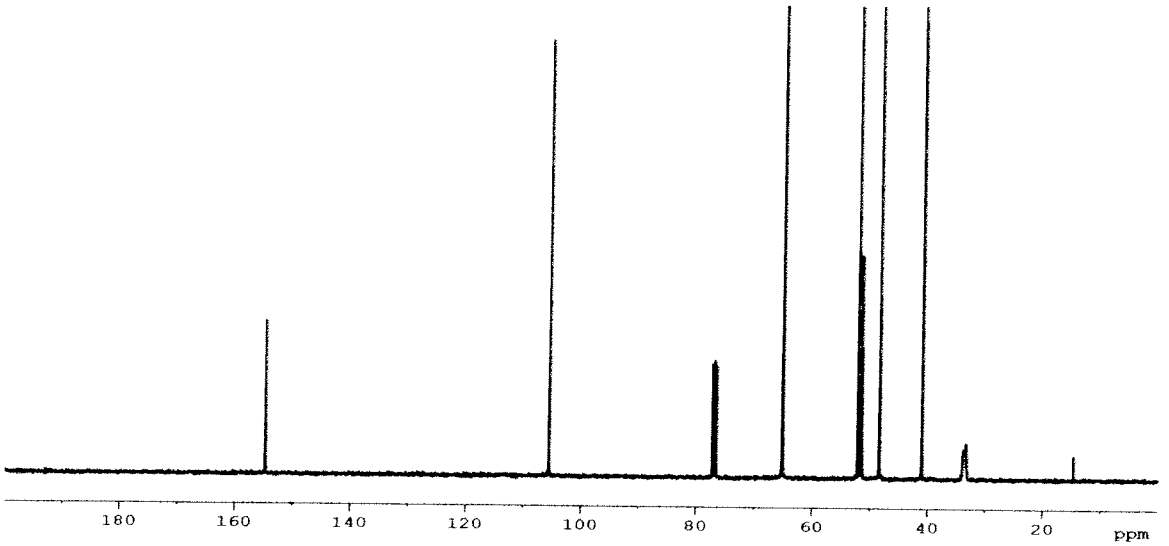
800
600.0
cm-1


O
O
Br
N
O
OCH3

14.2

9
8
7
6
5
4
3
2
1
ppm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60
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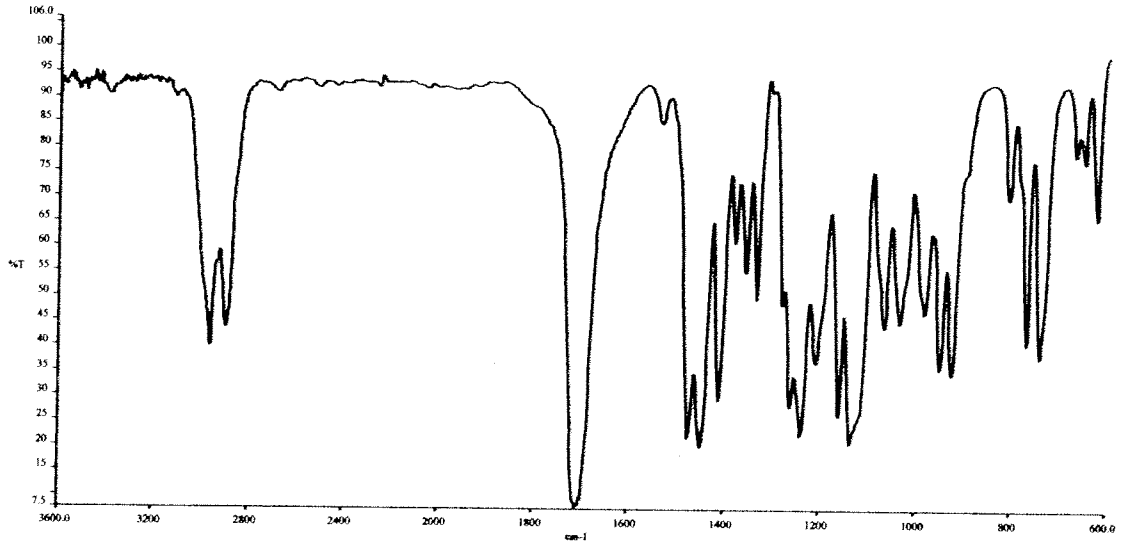
ppm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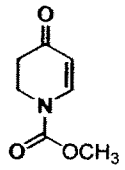
O
N
O
OCH3

14.4

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7
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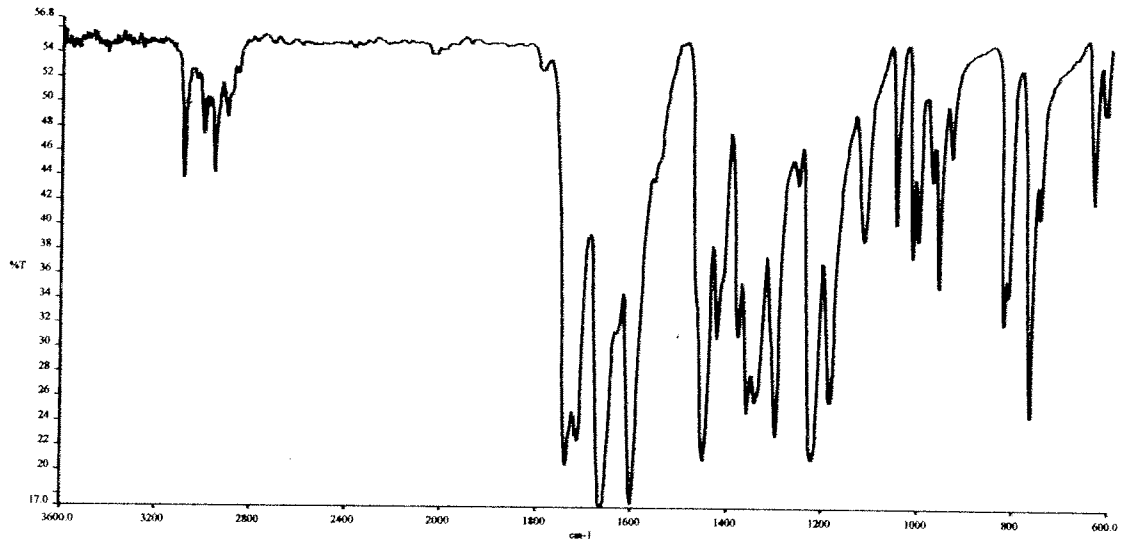
4
3
2
1
ppm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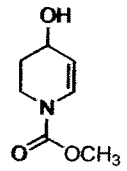
cm-1


OH
N
O
OCH3

14.5

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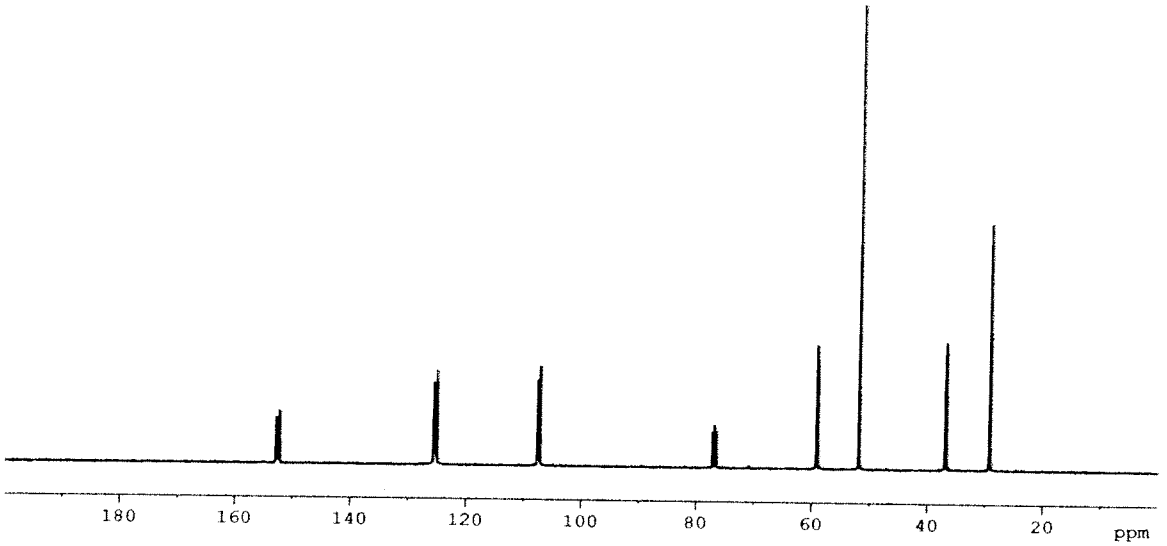
7
6
5
4
3
2
1
ppm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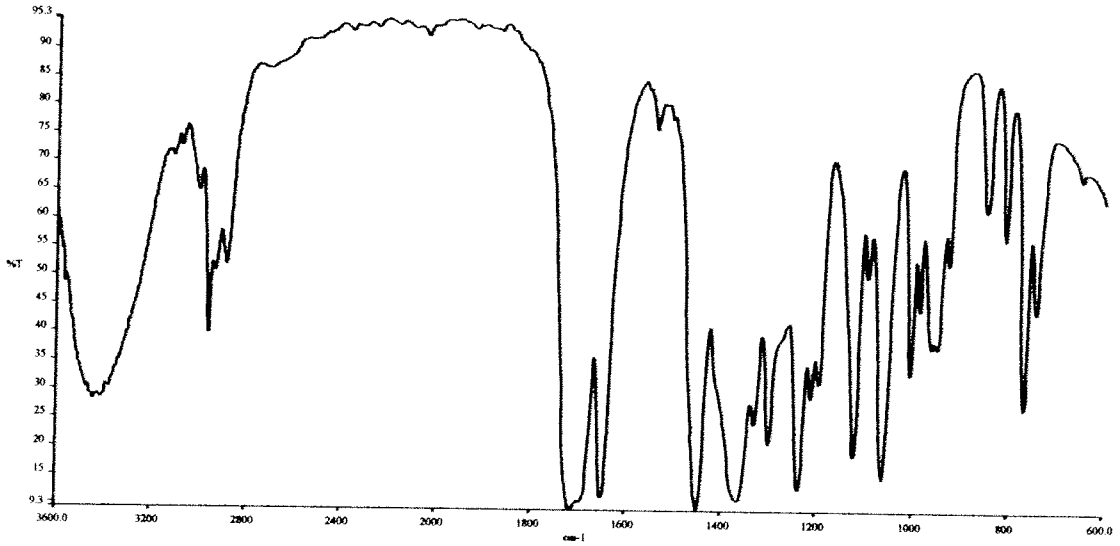
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45
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35
30
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3600.0
3200
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2400
2000
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1600
1400
1200
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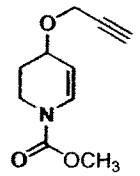
800
600.0
cm-1


O
N
O
OCH3

14.6

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3
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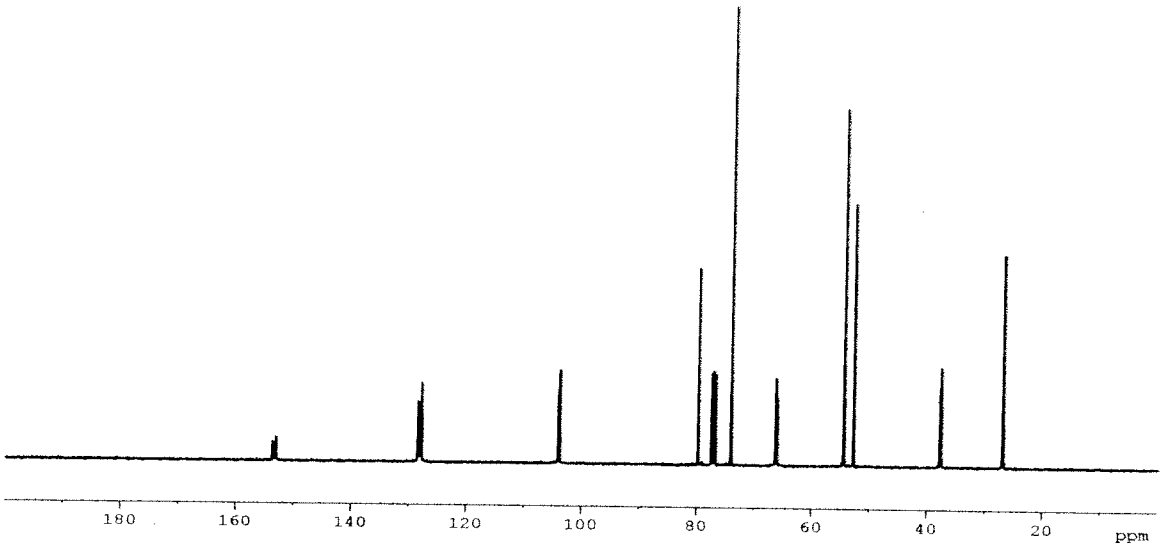
1
ppm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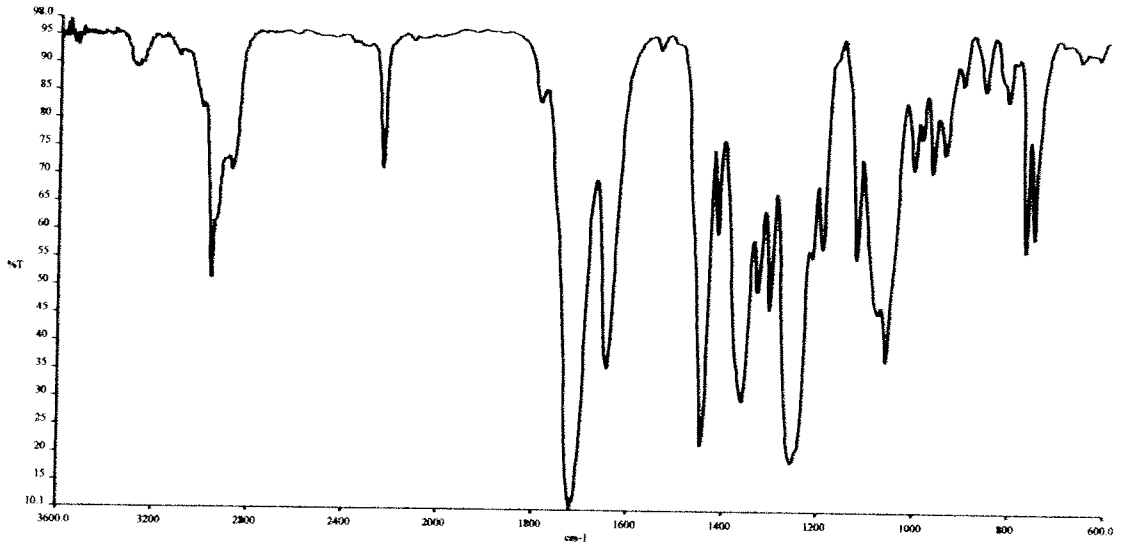
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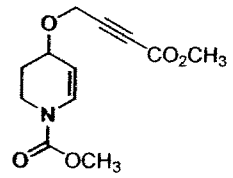
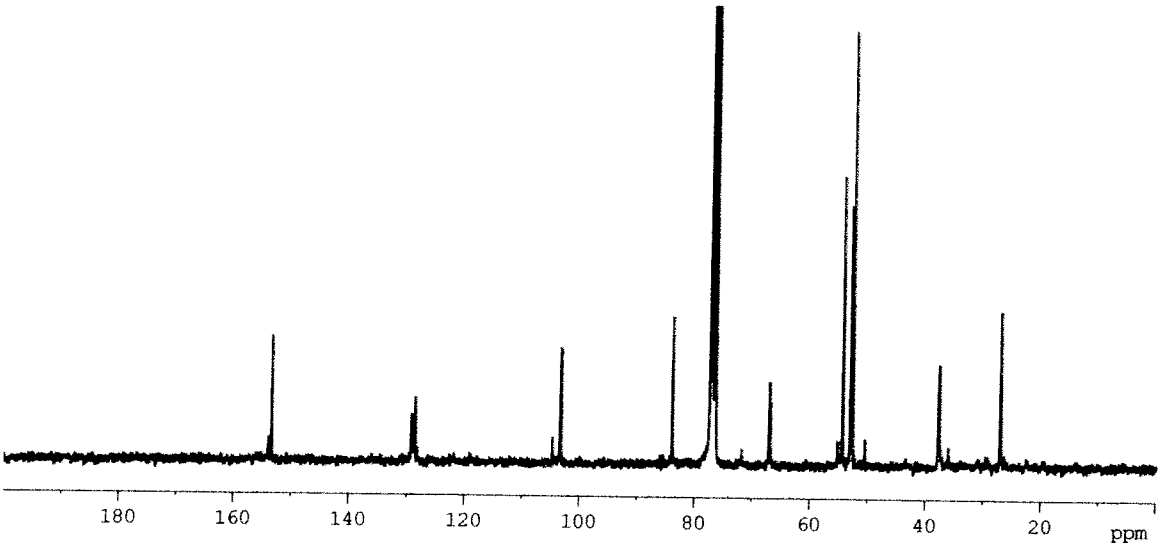
cm-1


O
CO2CH3
N
O
OCH3

11.0c

9
8
7
6
5
4
3
2
1
ppm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100
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60
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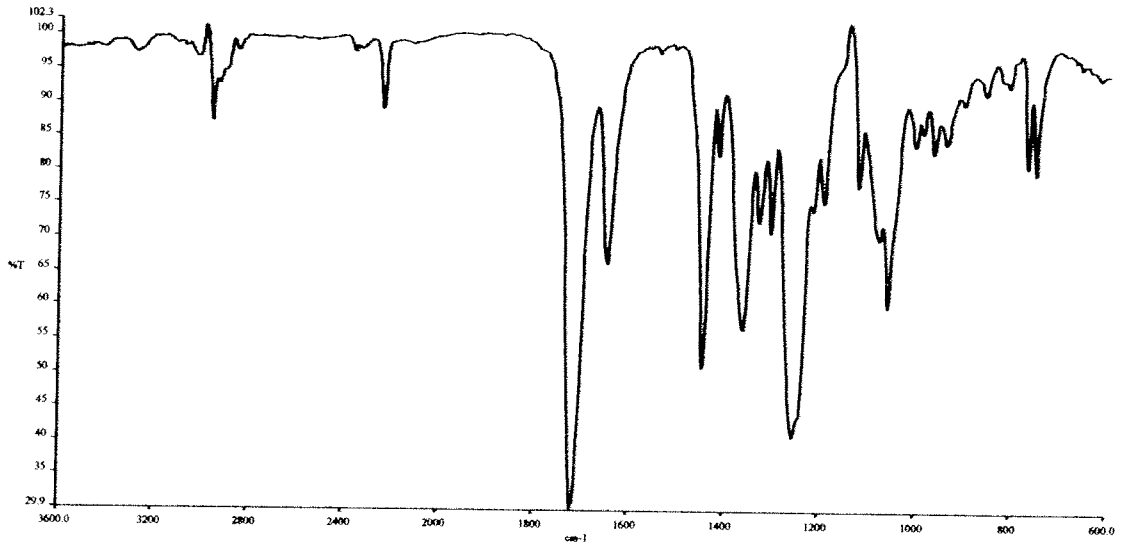
20
ppm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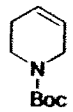
N
Boc

16.2

9
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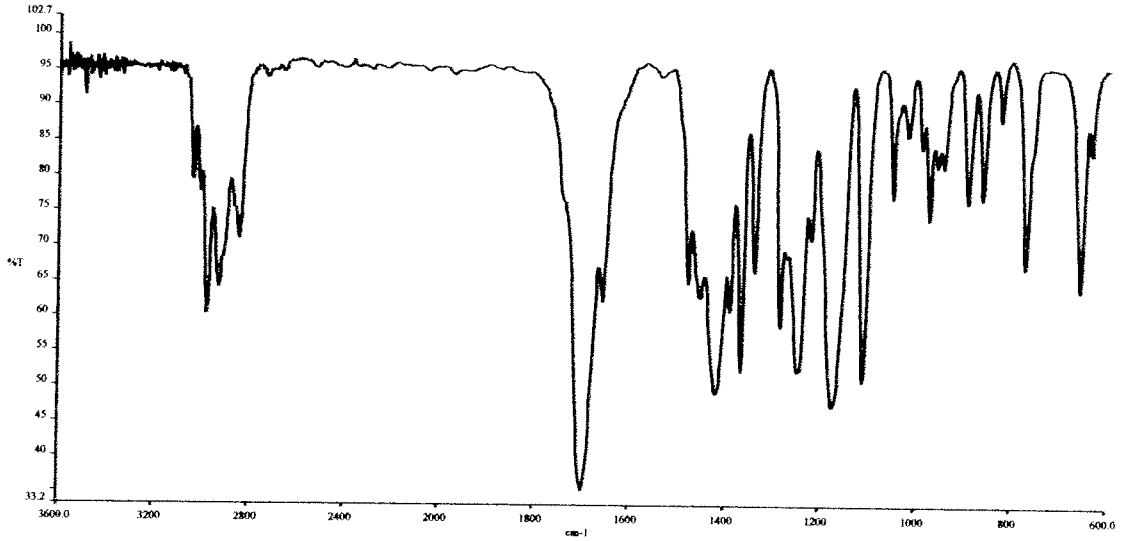
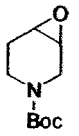
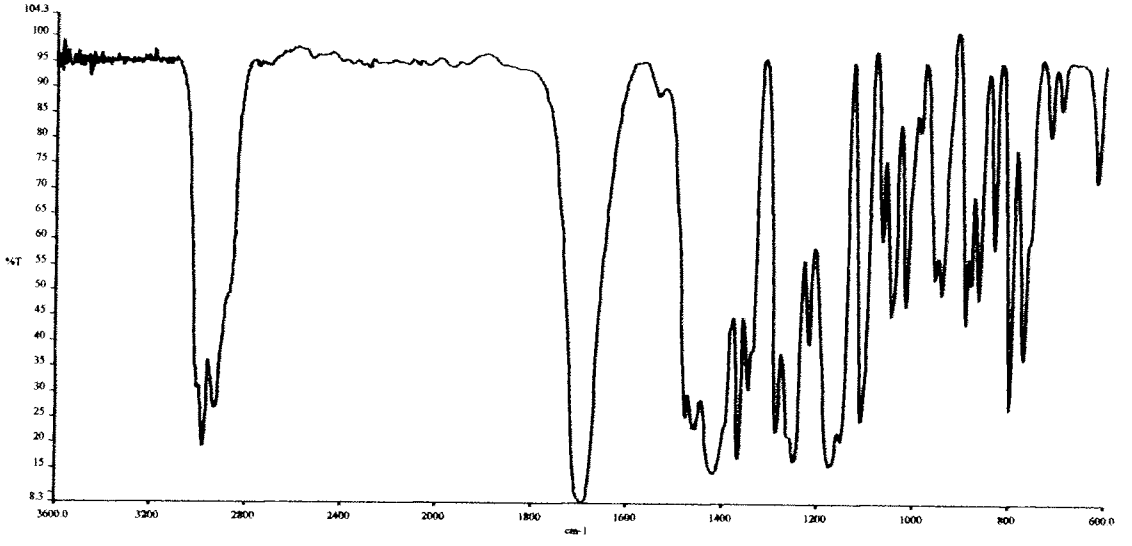
7
6
5
4
3
2
1
ppm


102.7
100
95
90
85
80
75
70
65
60
55
50
45
40
33.2
%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1


O
N
Boc

16.3

9
8
7
6
5
4
3
2
1
ppm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2400
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1600
1400
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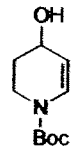
cm-1


OH
N
Boc

16.4

9
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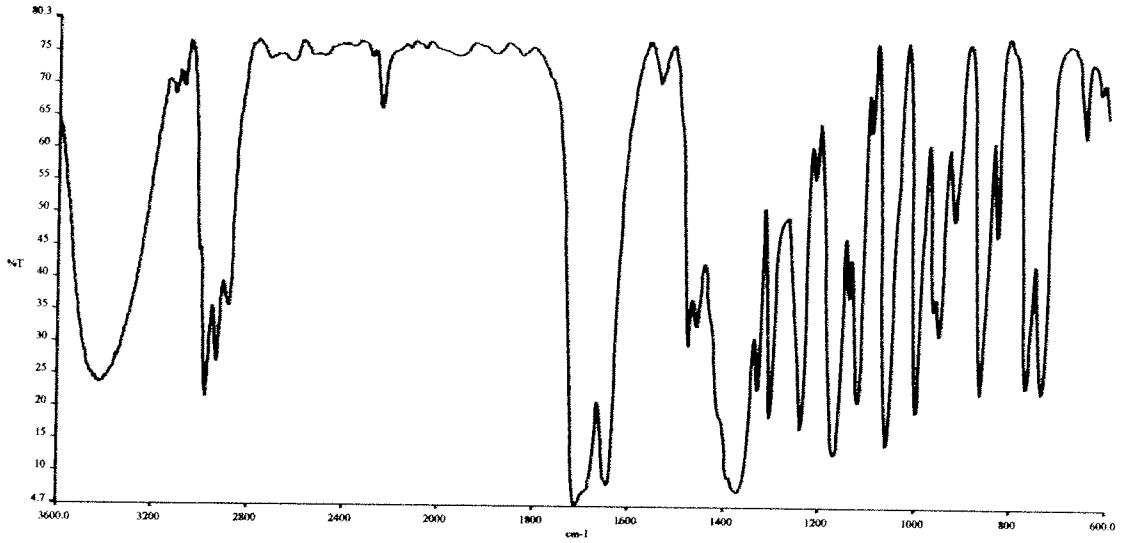
6
5
4
3
2
1
ppm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2400
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1600
1400
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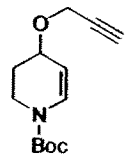
800
600.0
cm-1


O
N
Boc

16.5

9
8
7
6
5
4
3
2
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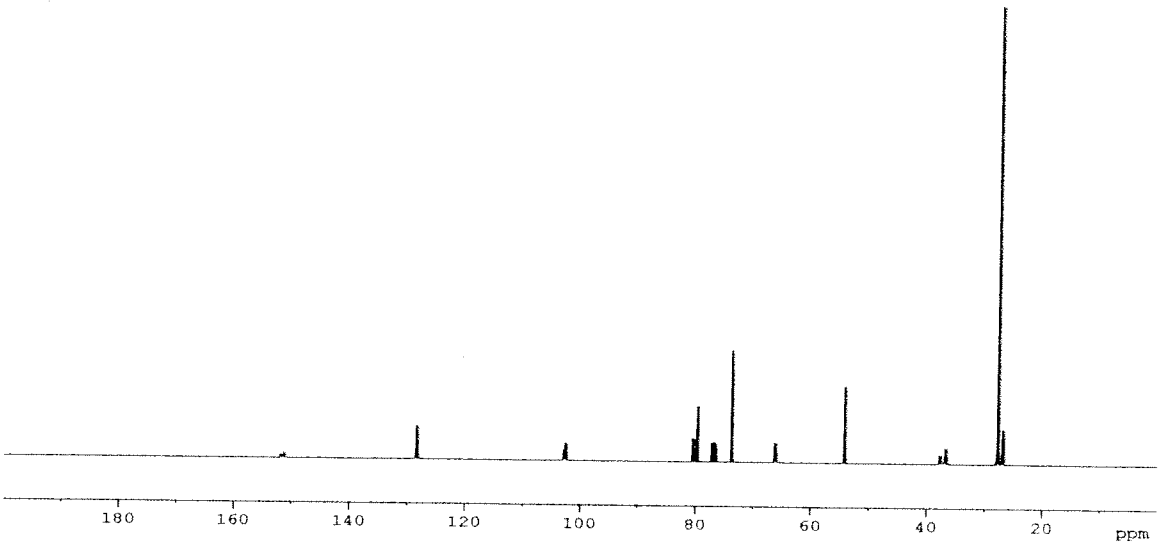
ppm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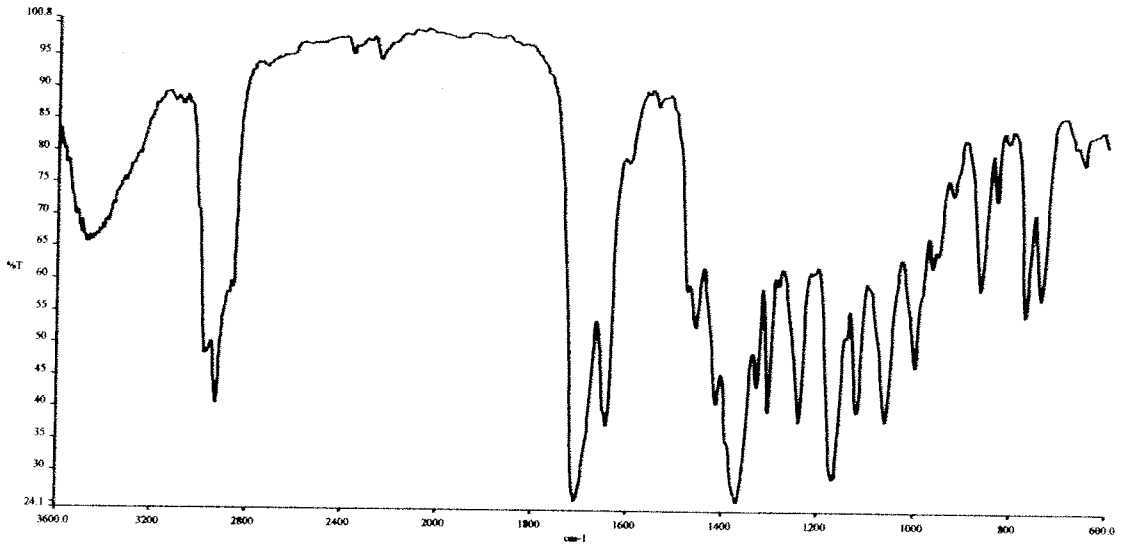
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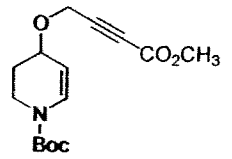
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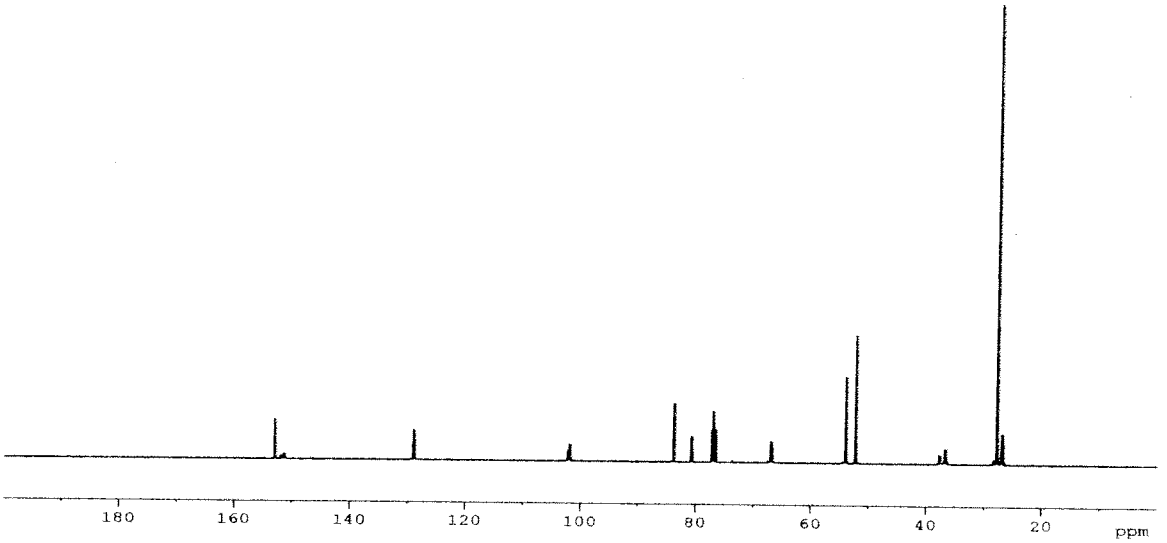
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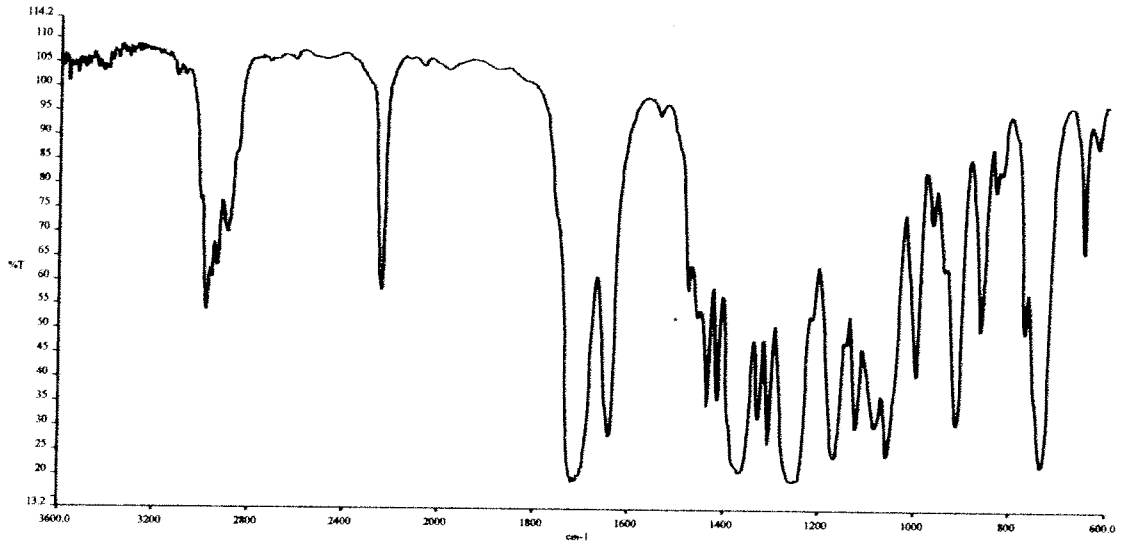
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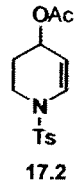
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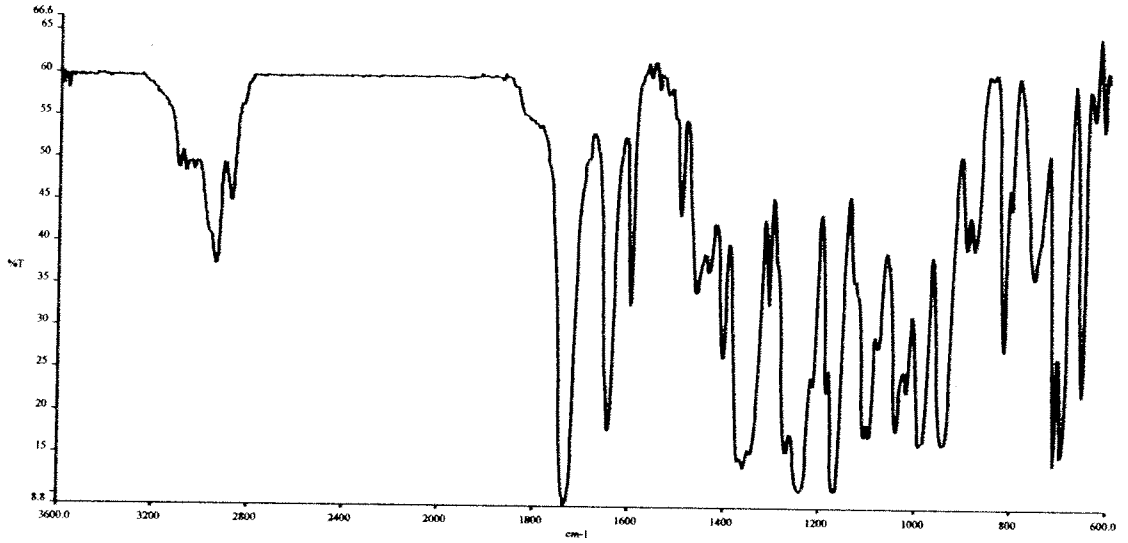
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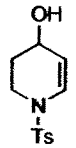
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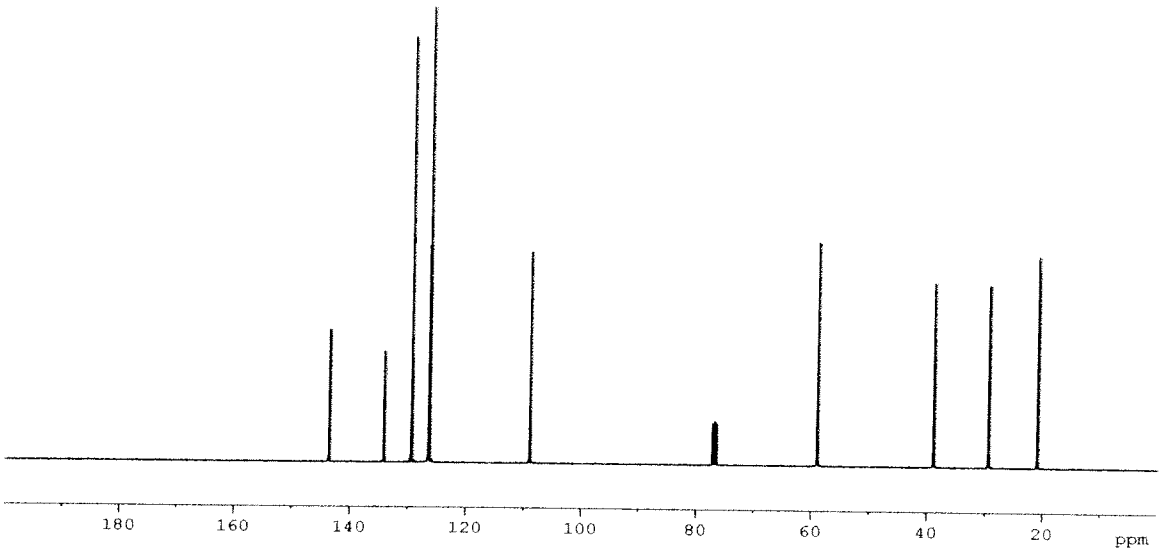
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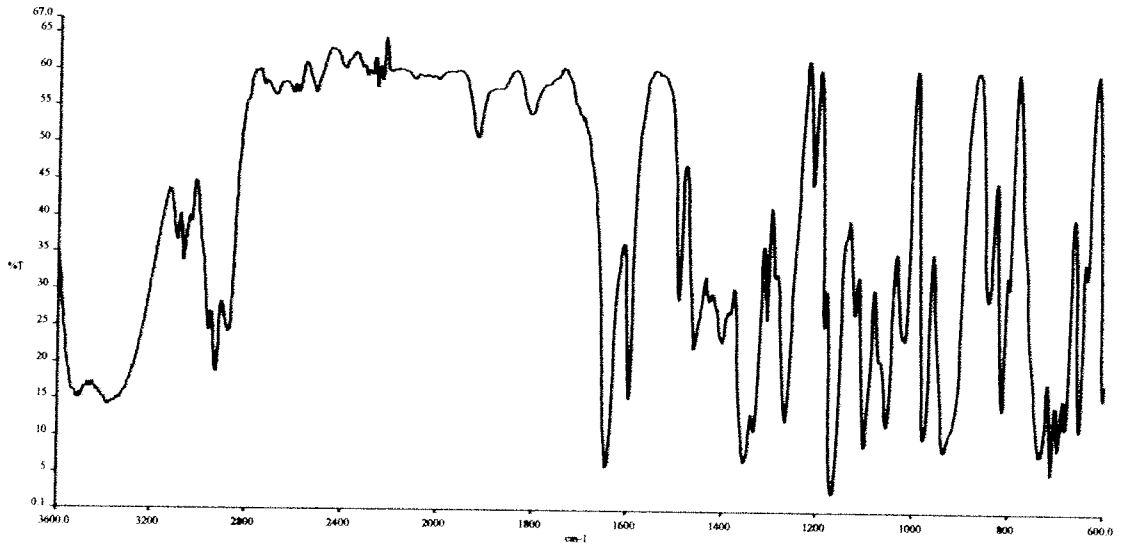
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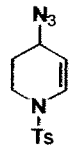
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Ts

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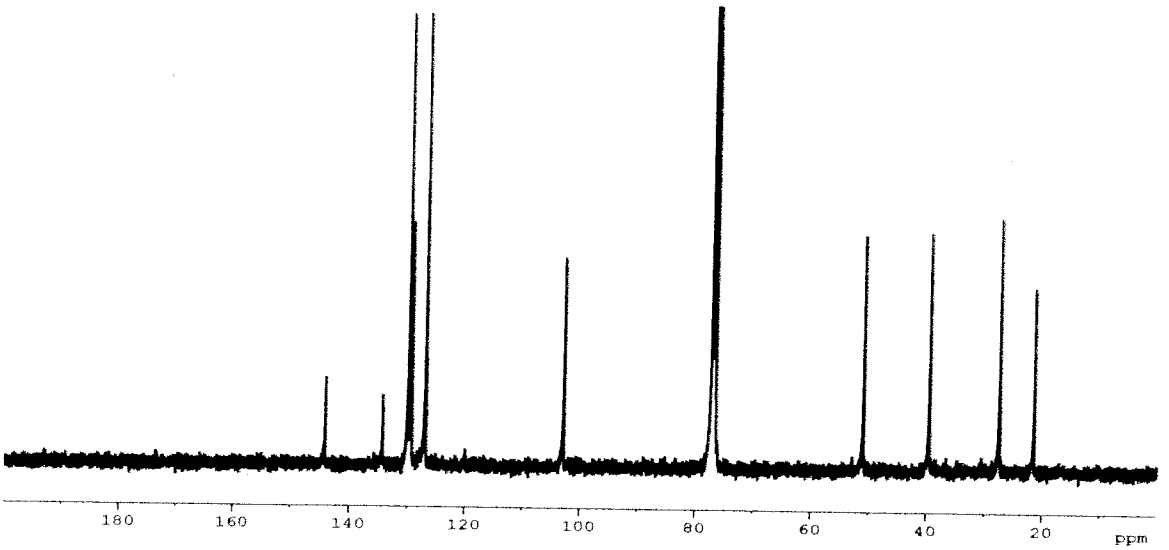
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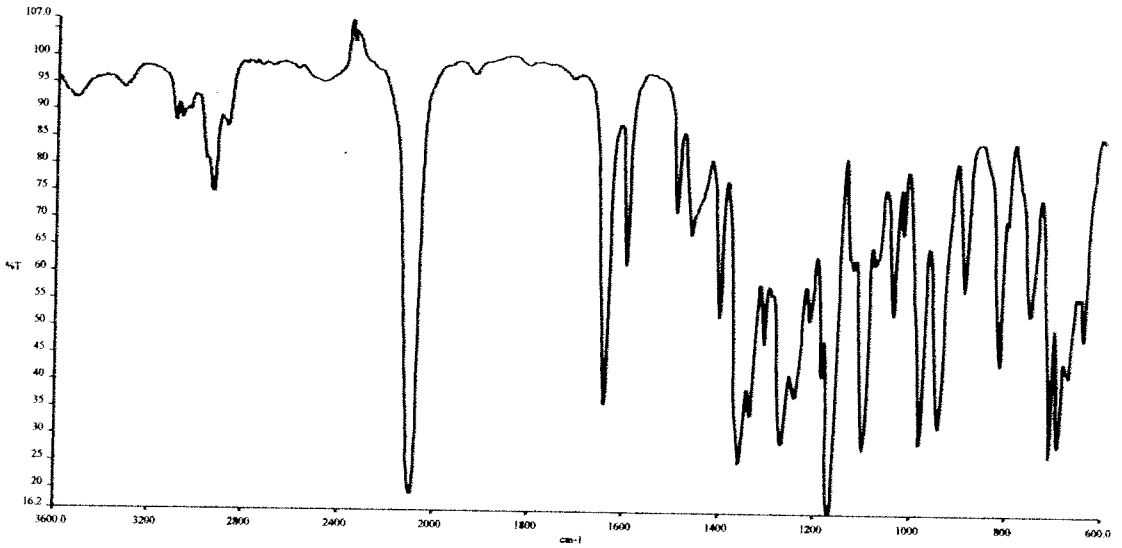
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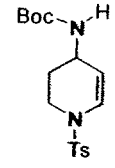
Boc
N
H
N
Ts

24.1

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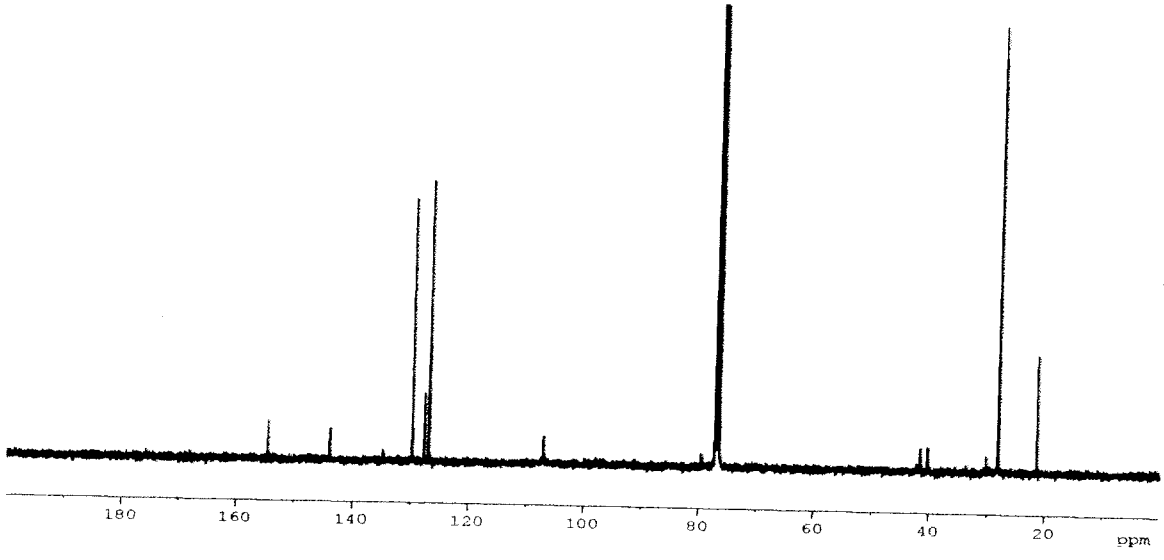
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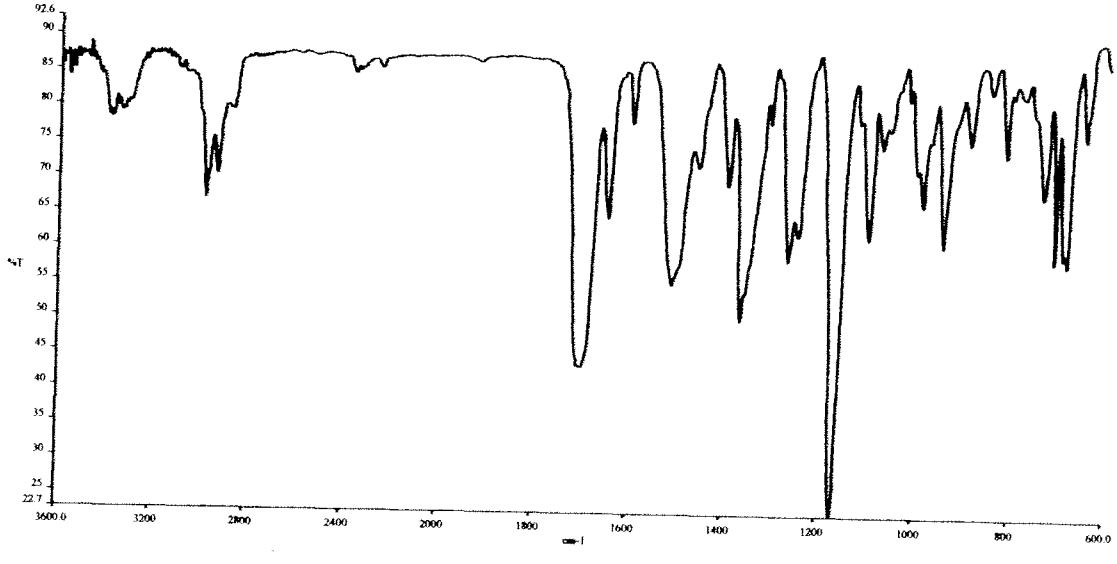
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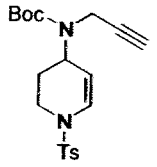
Boc
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N
Ts

24.2

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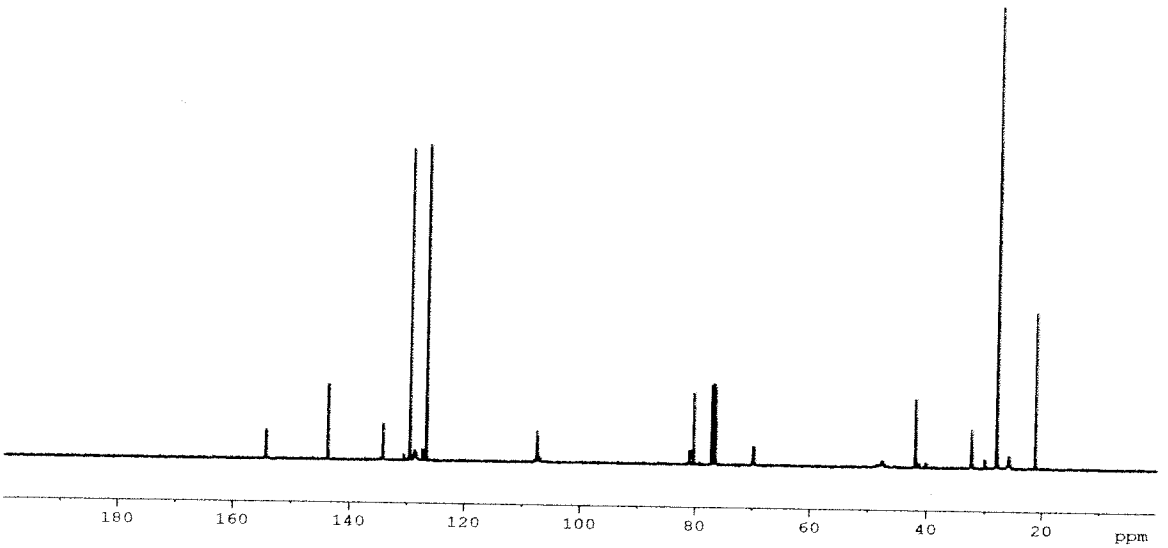
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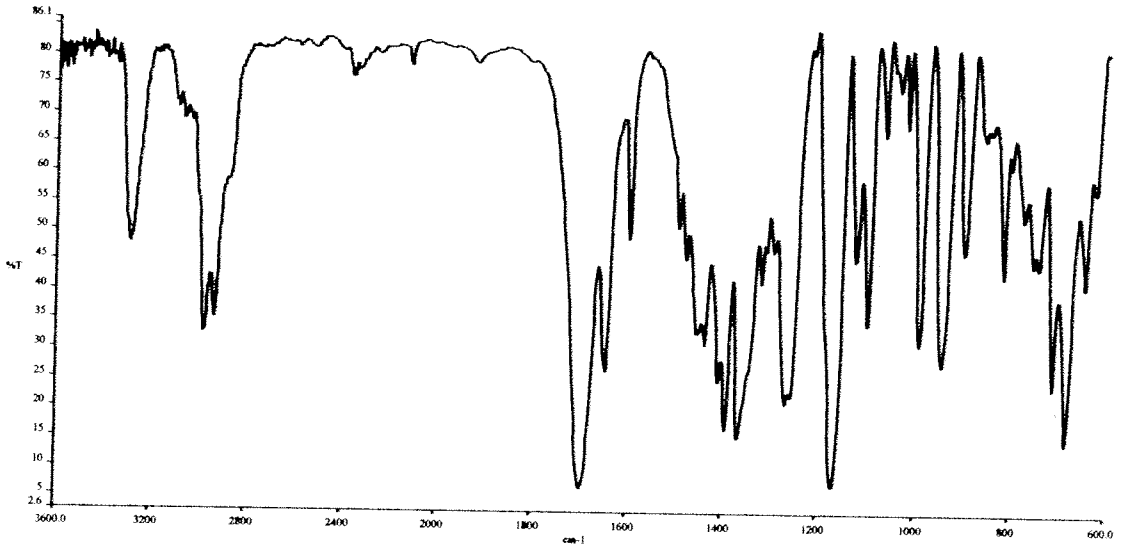
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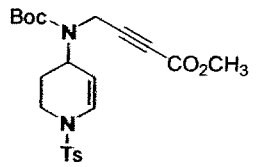
Boc
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Ts

11.0e

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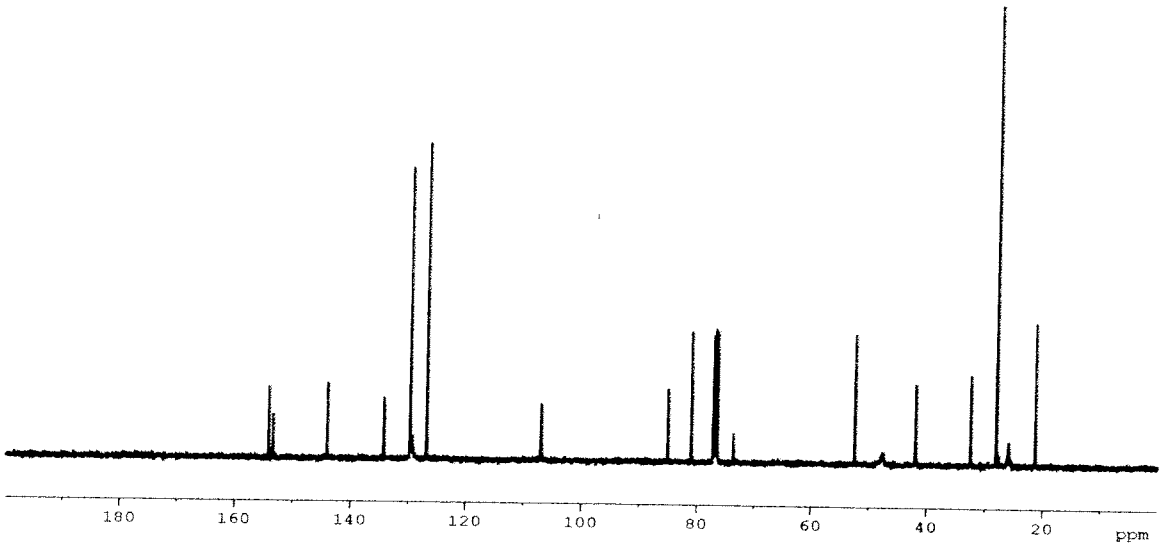
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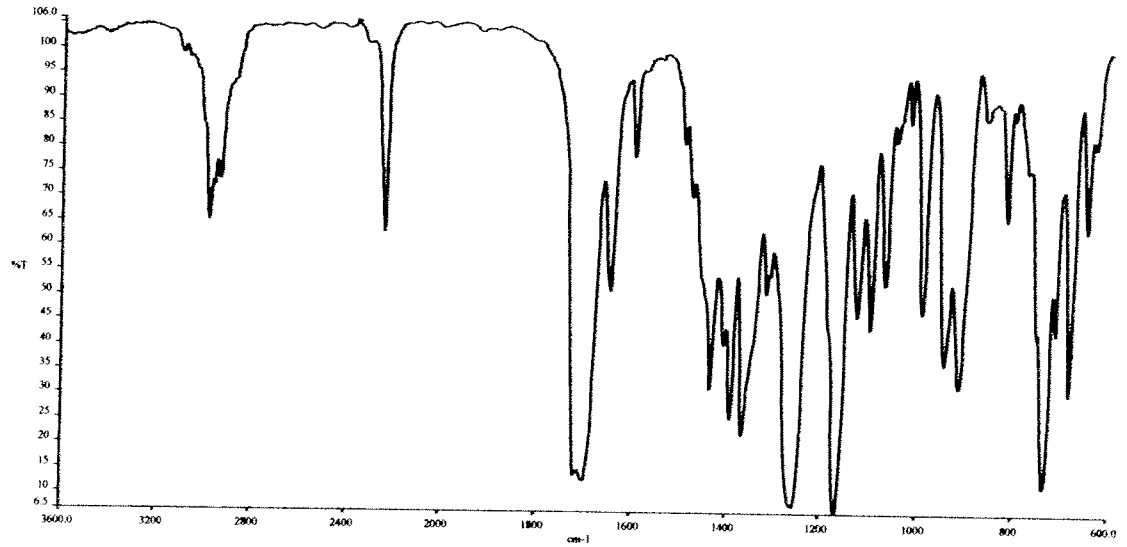
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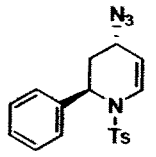
N3
N
Ts

25.3f

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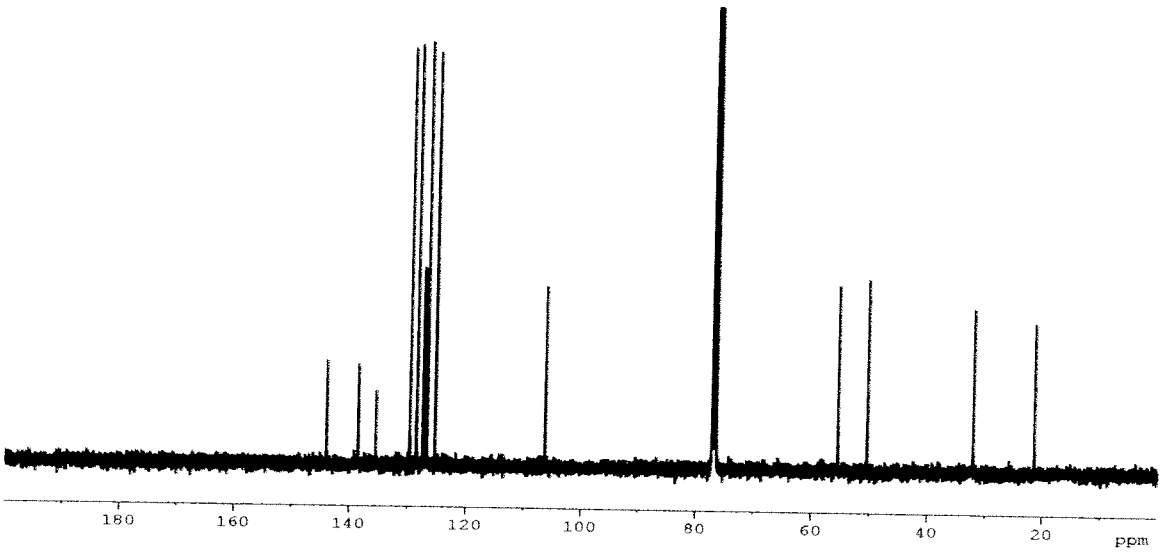
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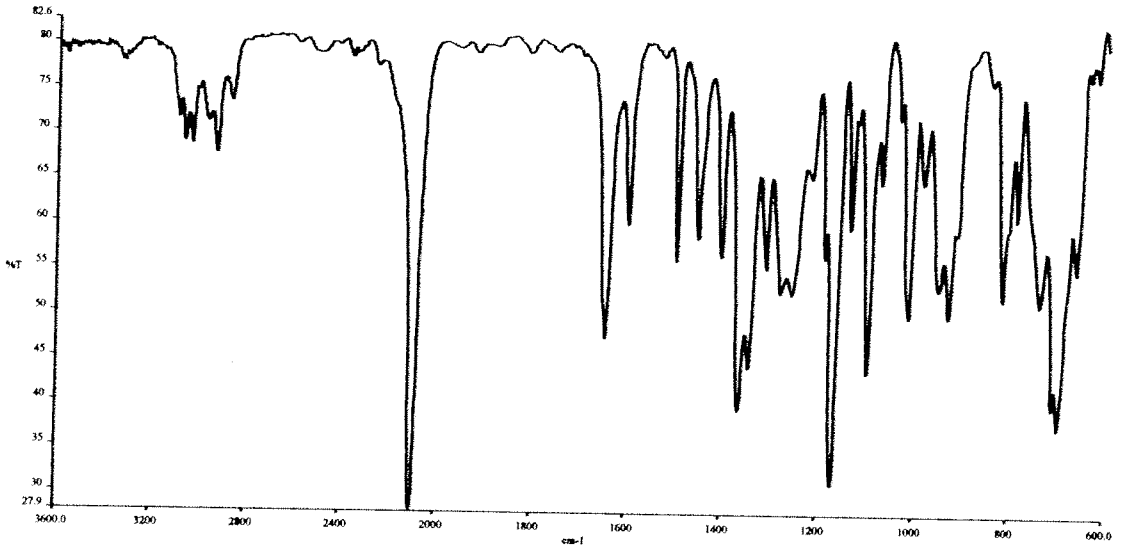
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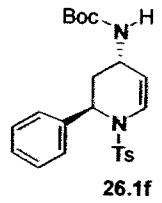
Boc
N
H
N
Ts

26.1f

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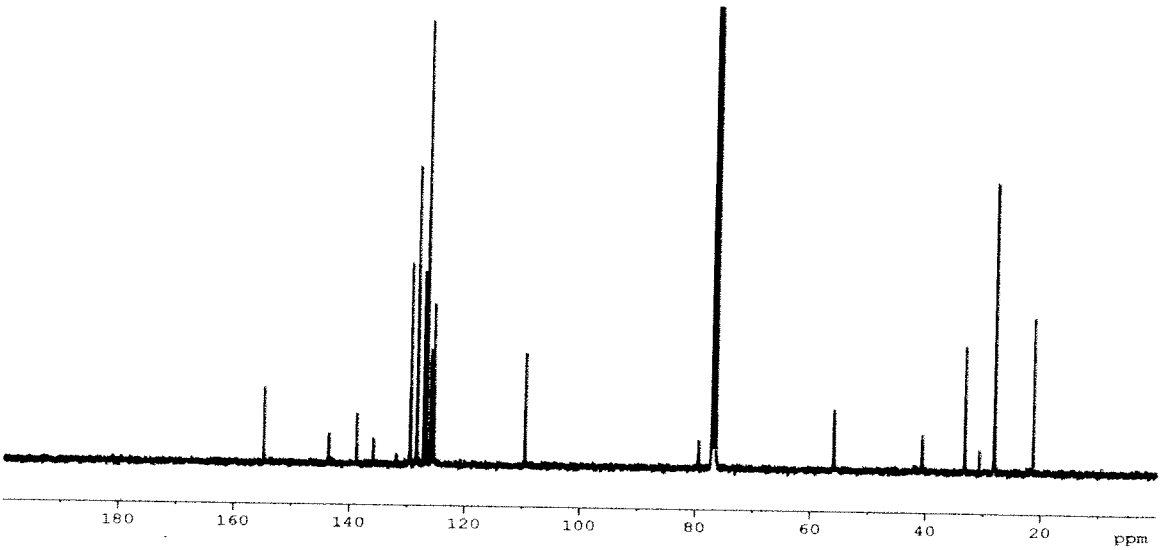
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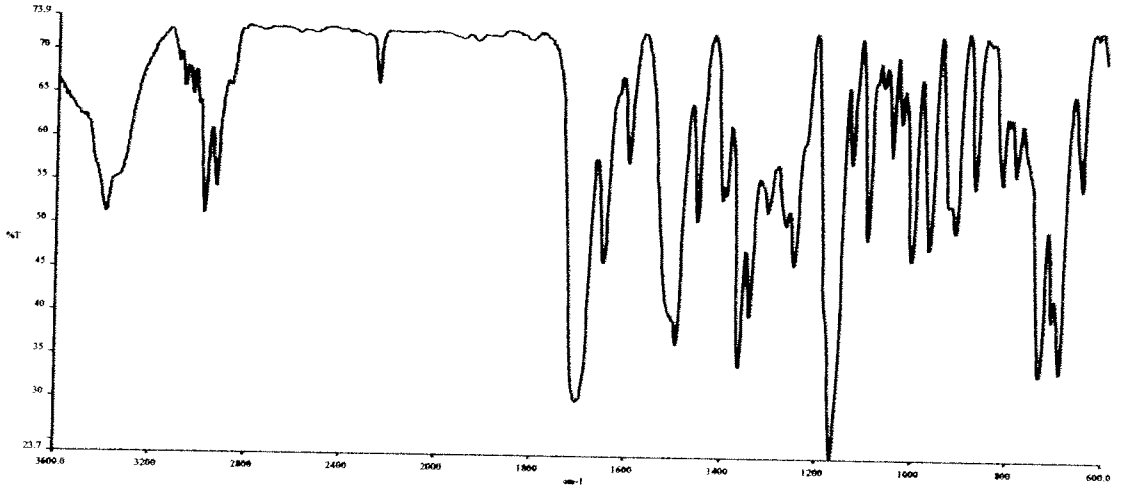
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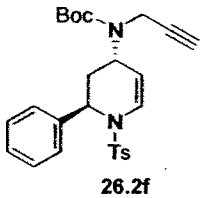
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Ts

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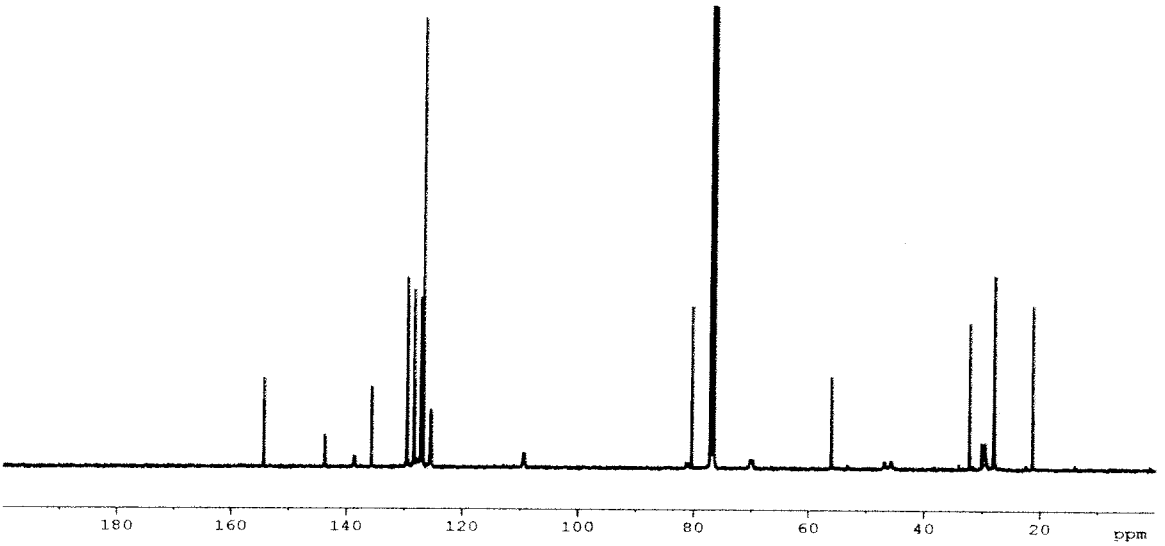
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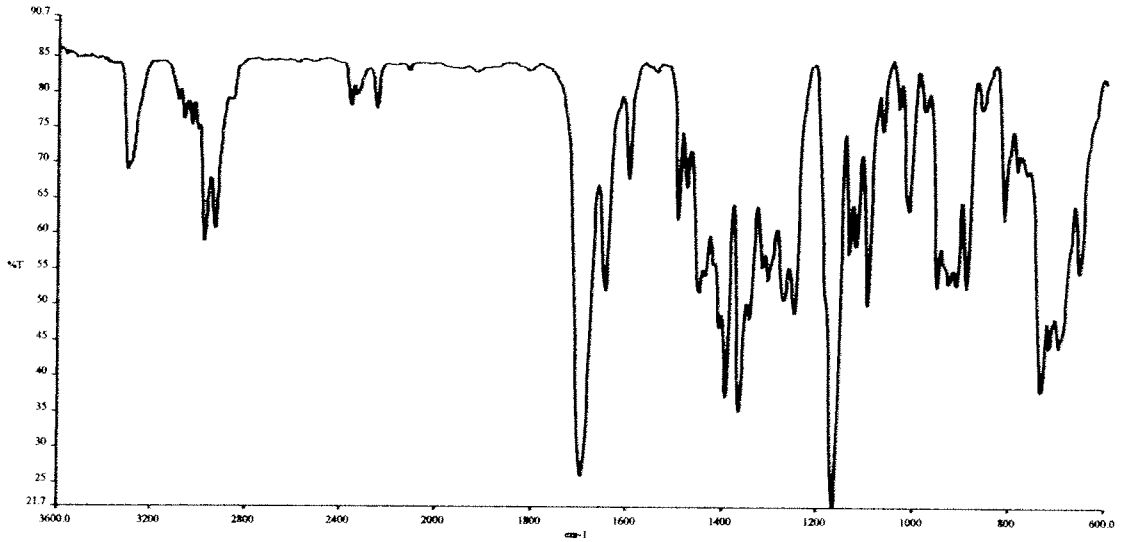
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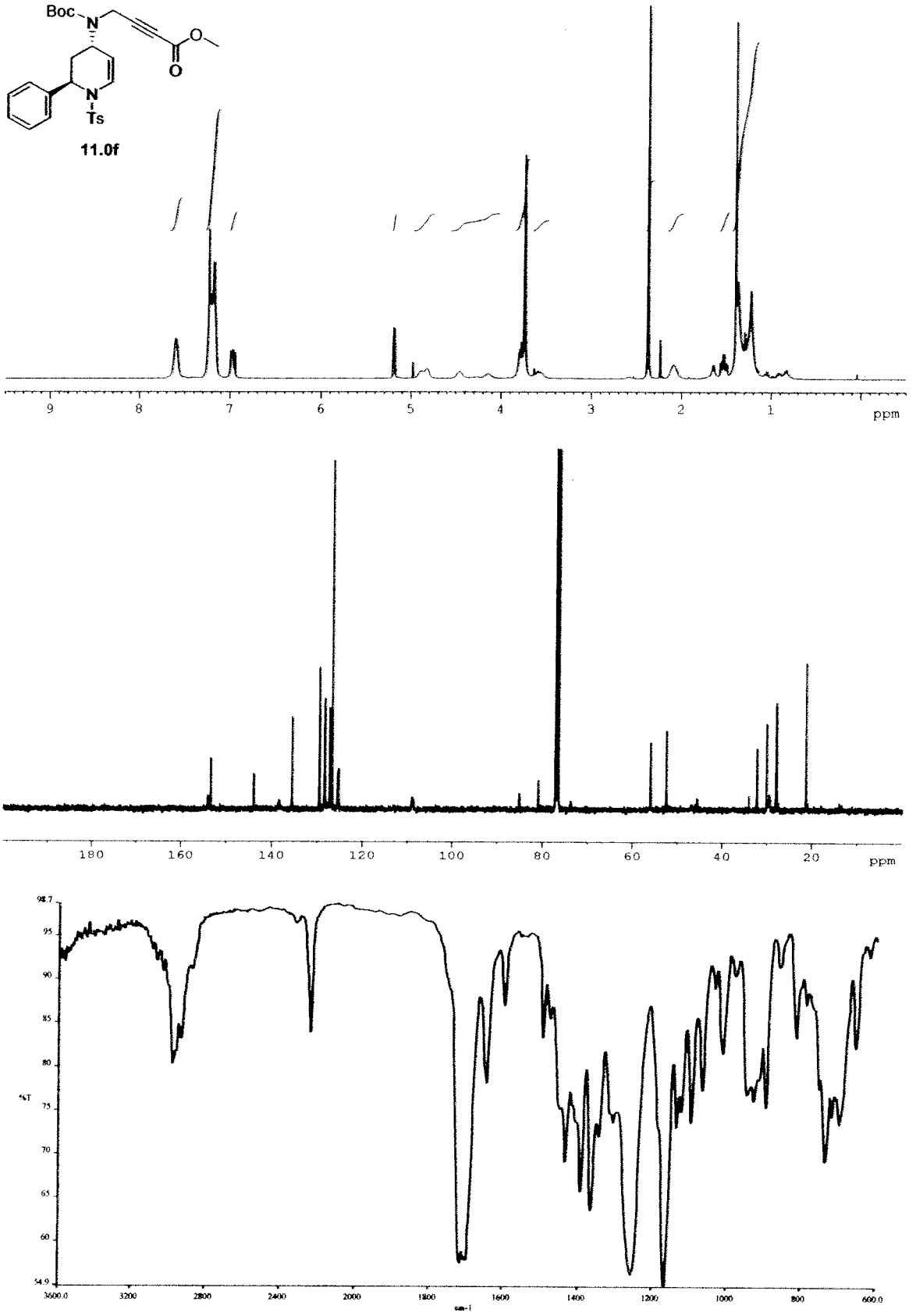
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O
N
Ts
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20
ppm
%T
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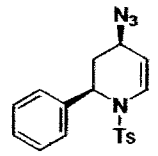
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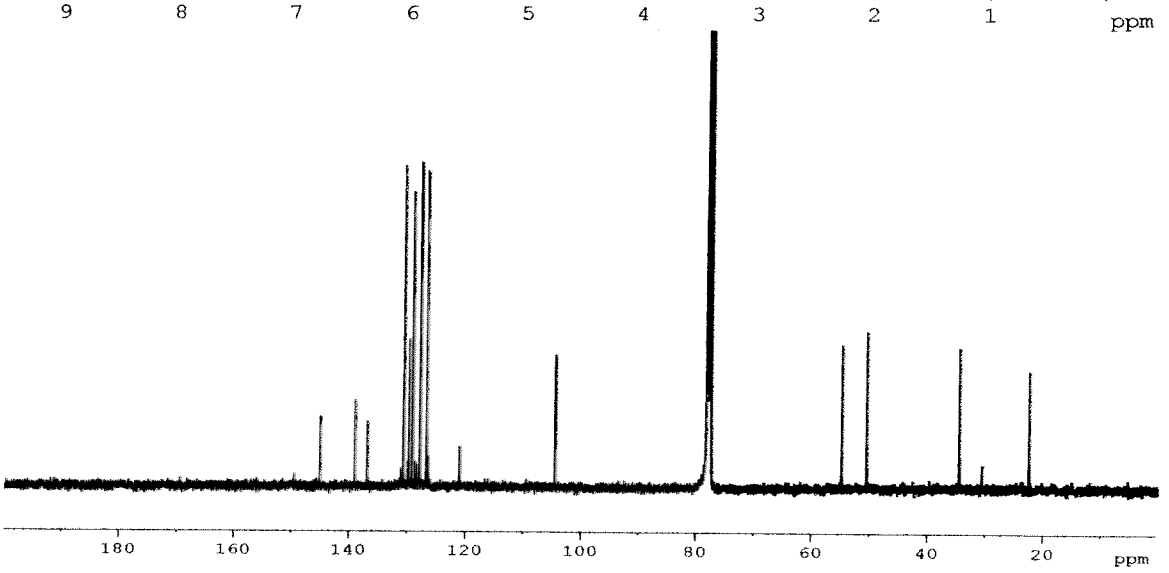
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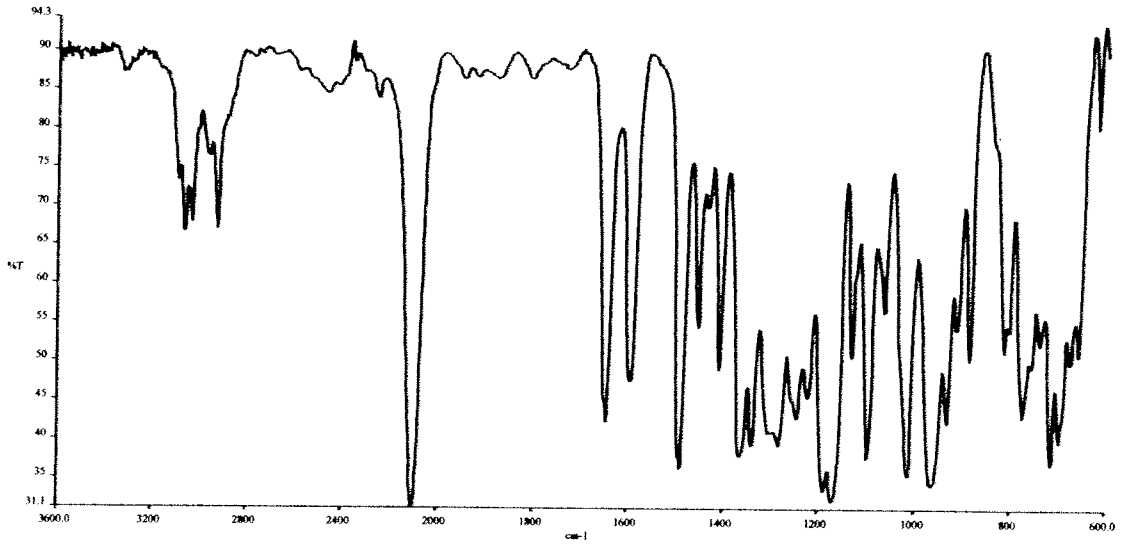
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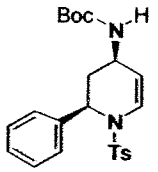
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Ts

26.1g

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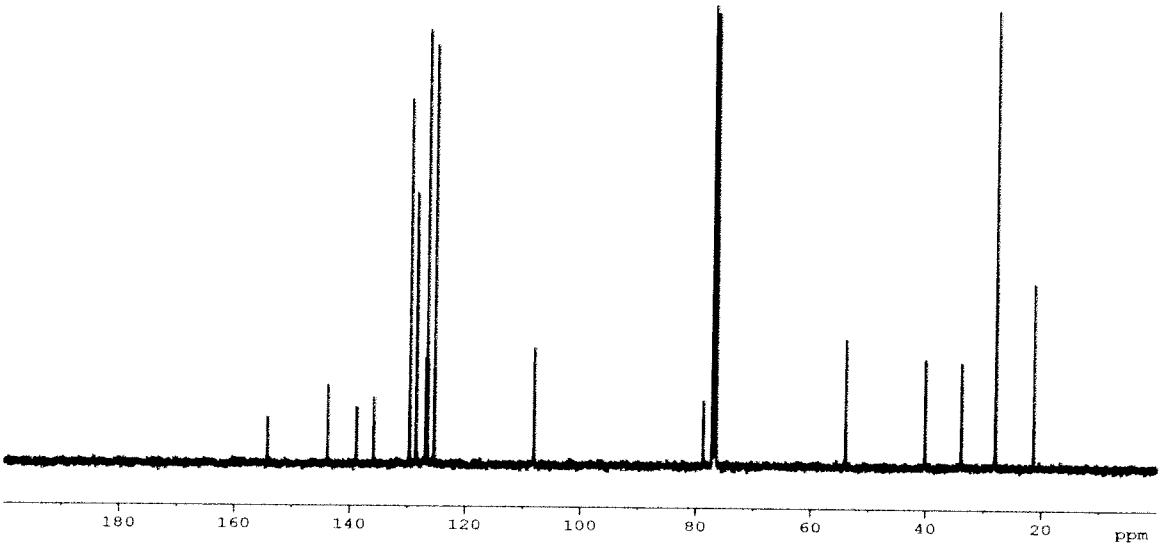
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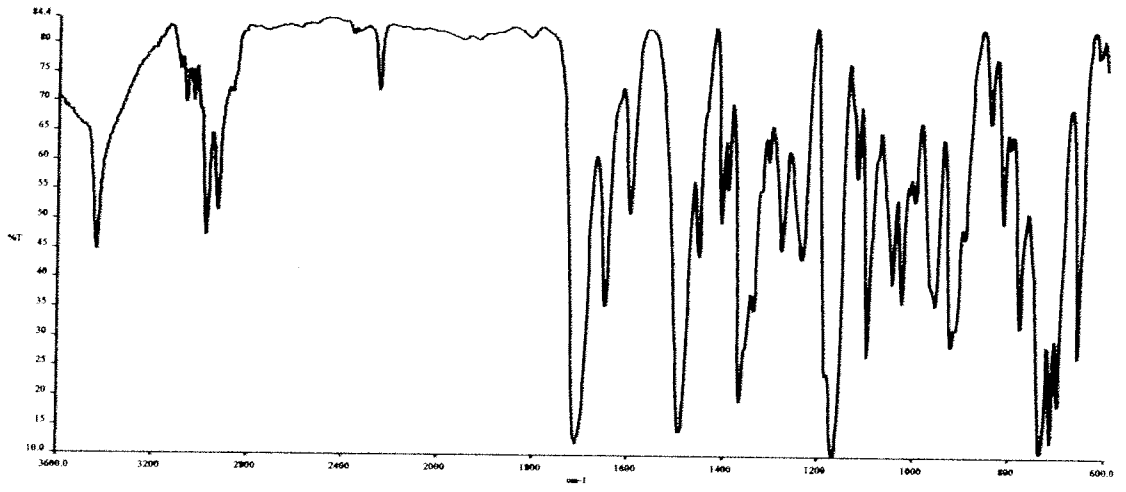
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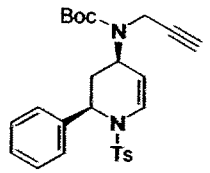
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Ts

26.2g

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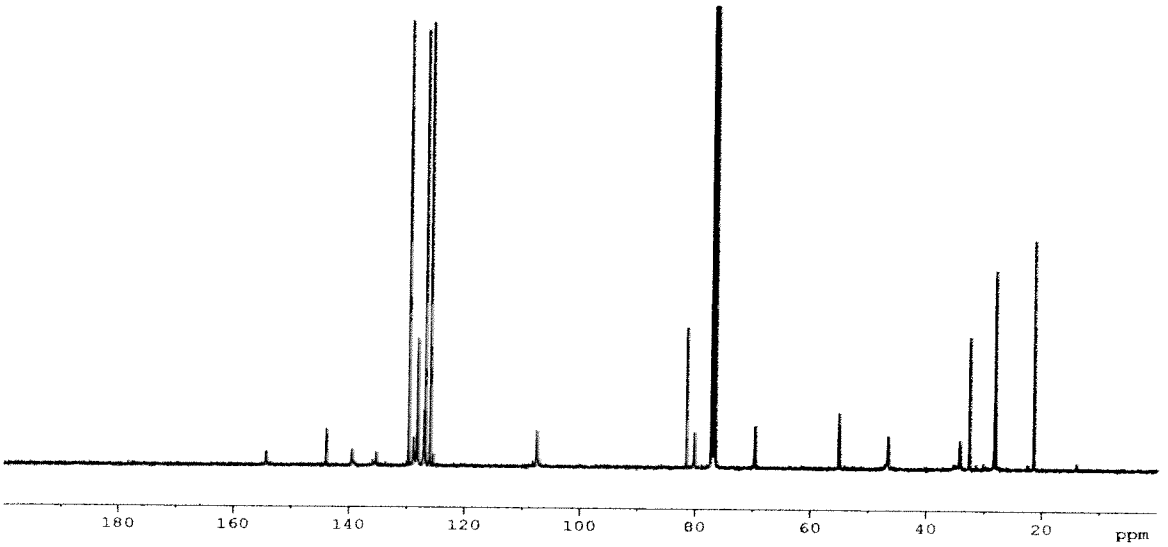
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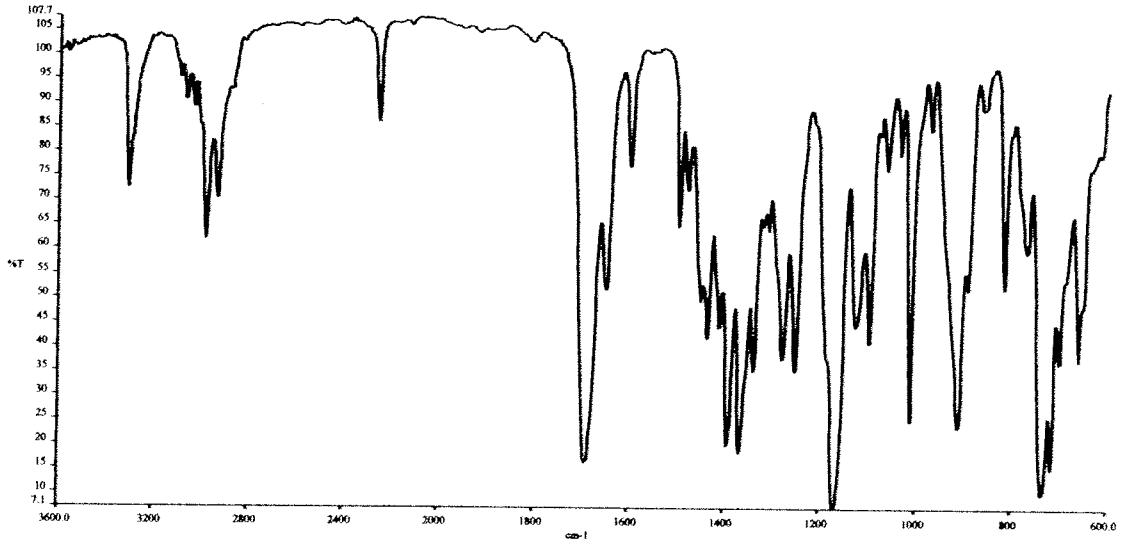
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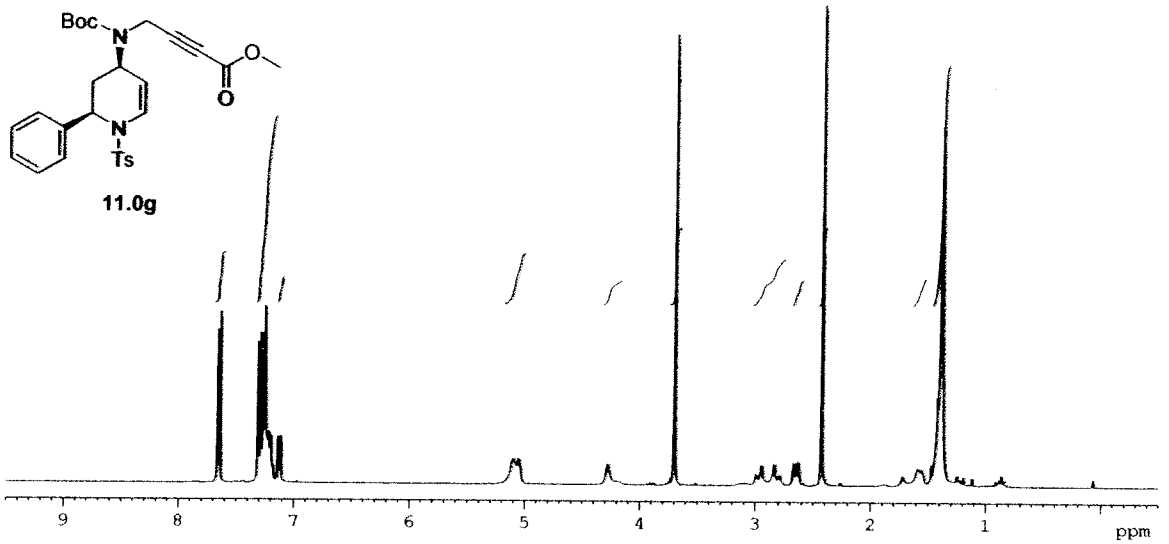
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Ts
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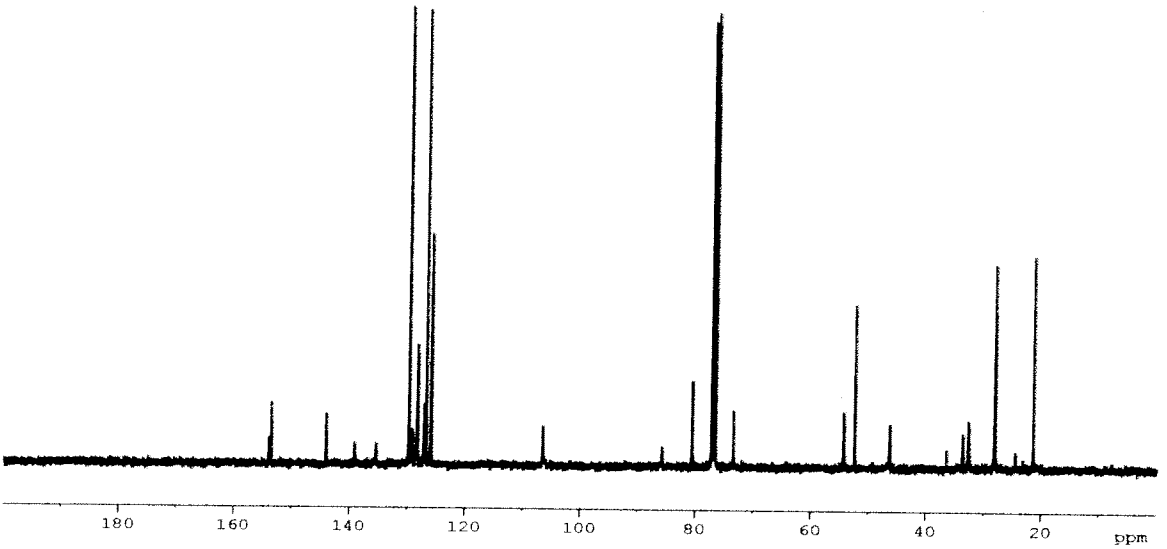
ppm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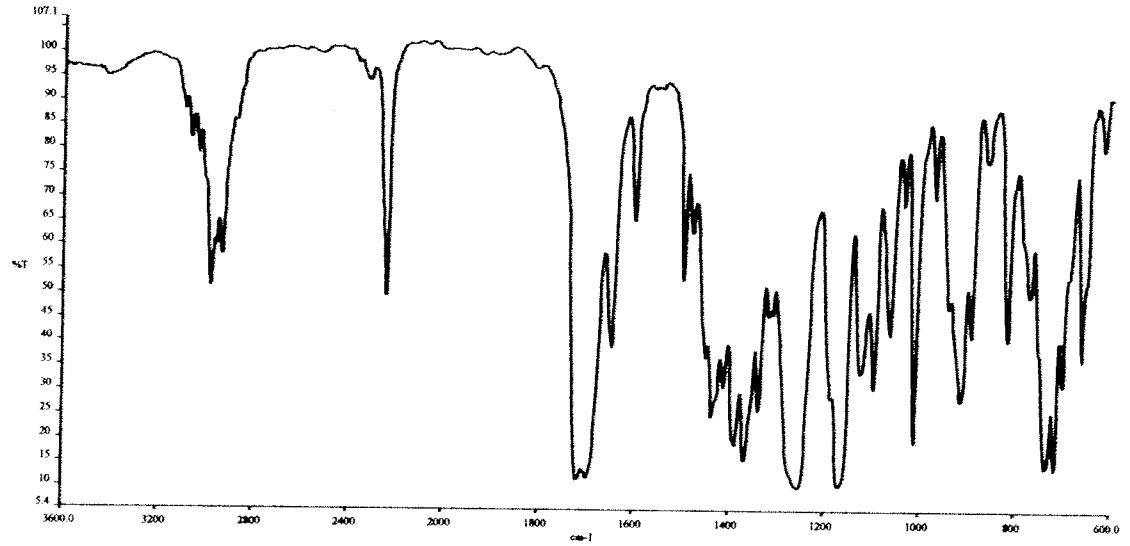
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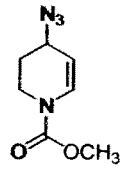
N3
N
O
OCH3

27.1

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8
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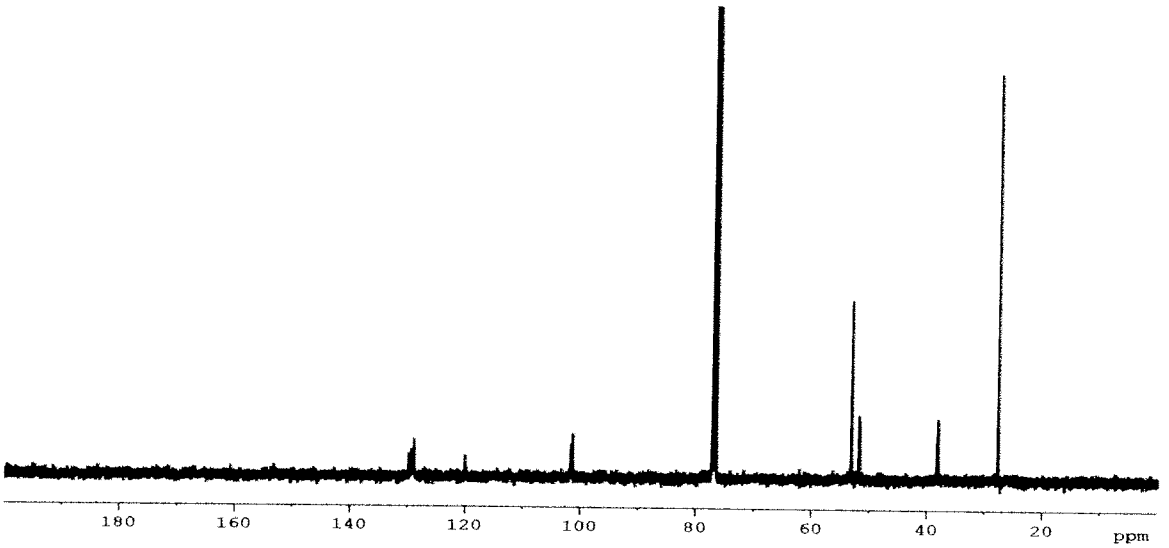
6
5
4
3
2
1
ppm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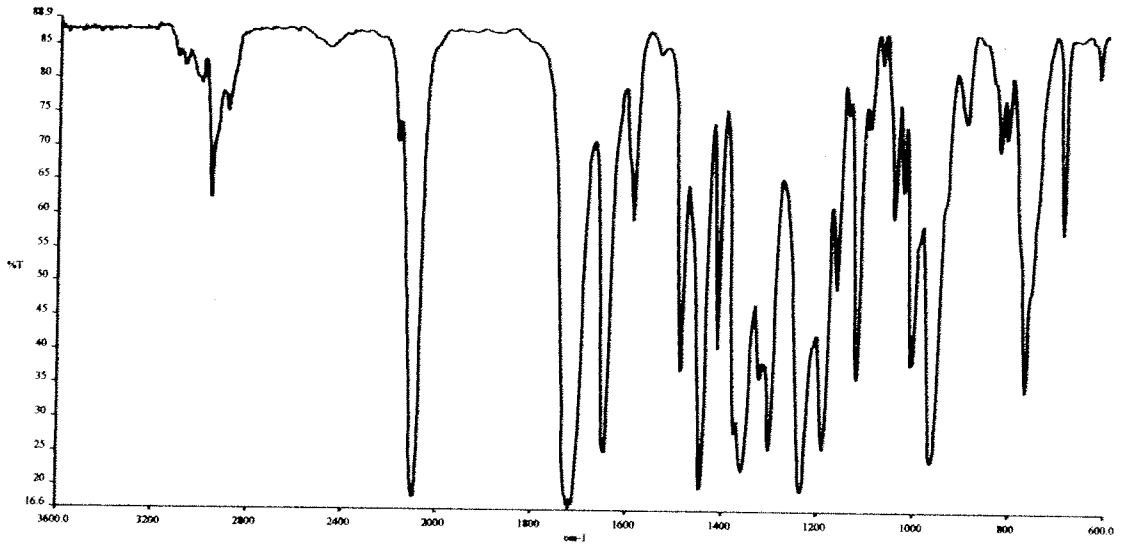
160
140
120
100
80
60
40
20
ppm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1800
1600
1400
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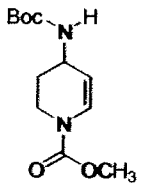
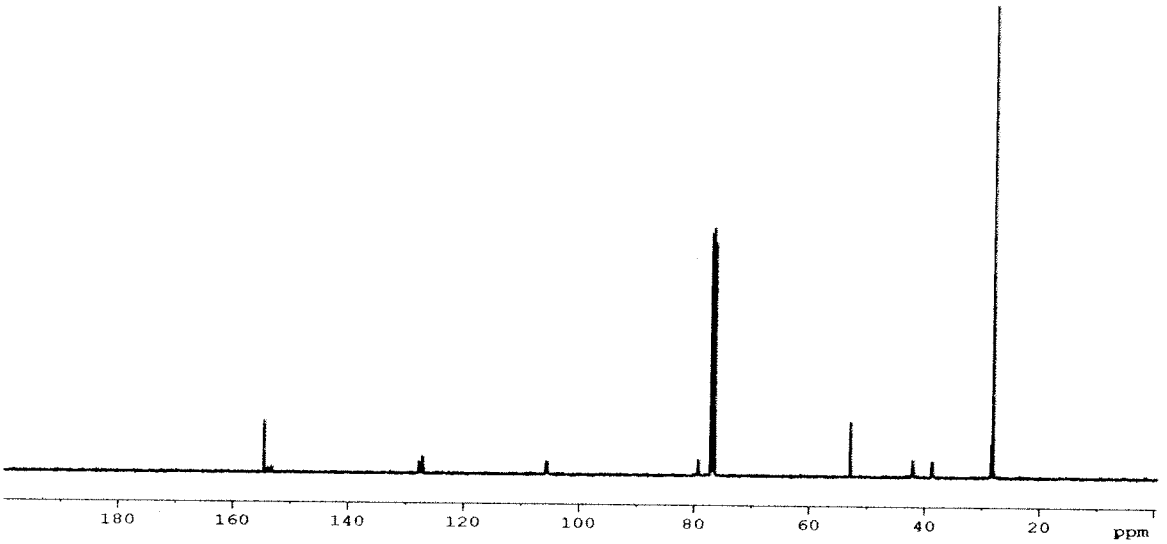
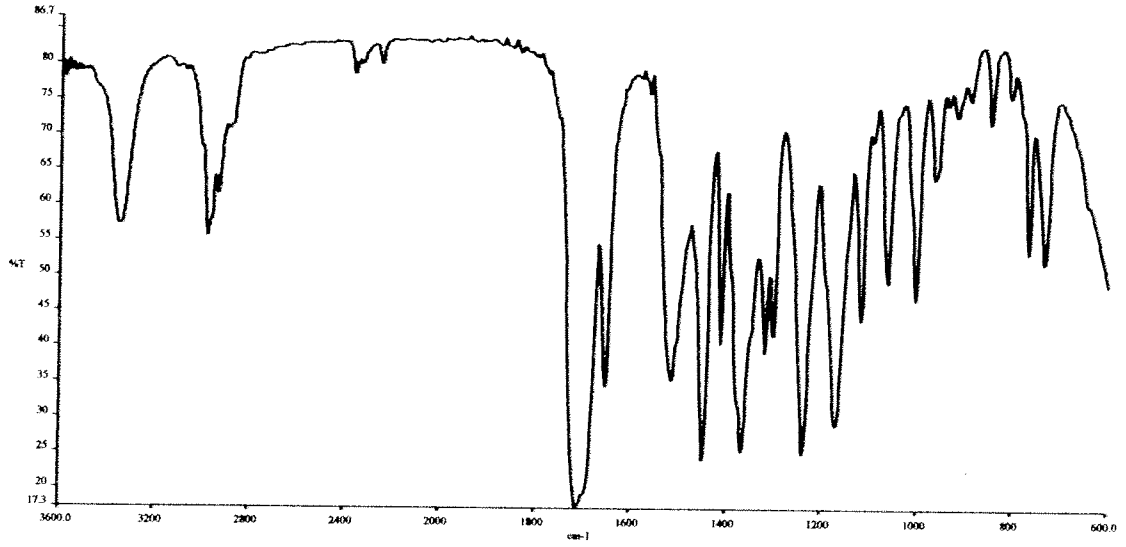
1000
800
600.0


Boc
N
H
N
O
OCH3

27.2

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm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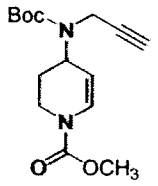
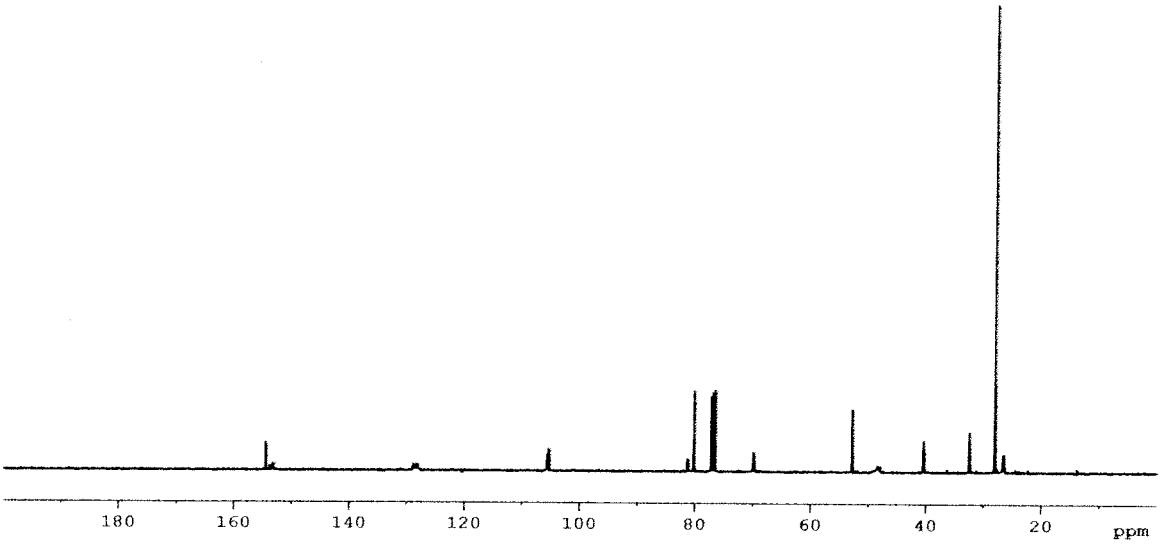
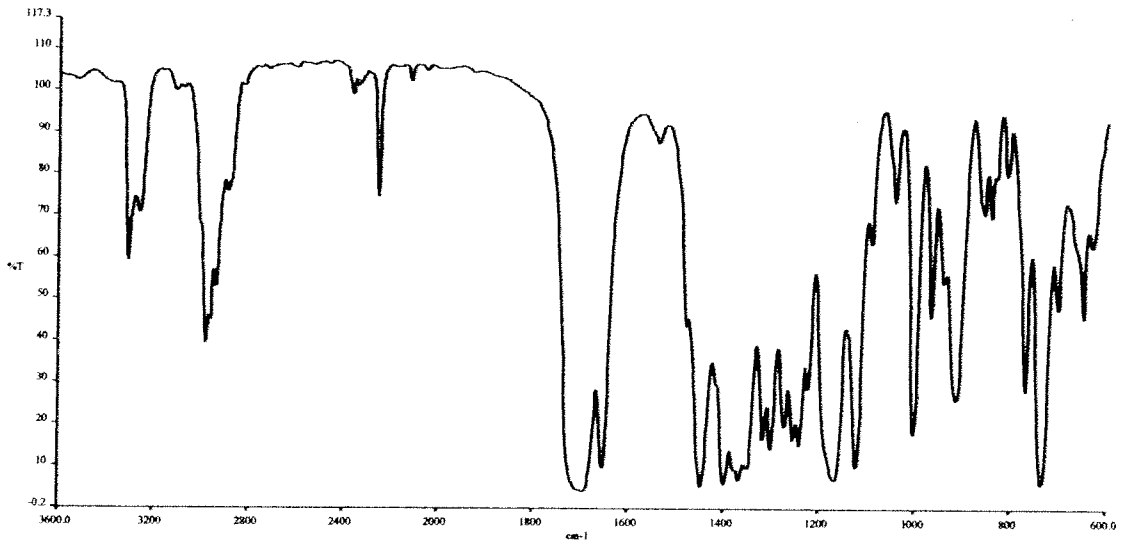
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

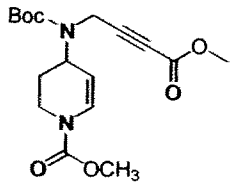

Boc
N
N
O
OCH3

27.3

9
8
7
6
5
4
3
2
1
ppm

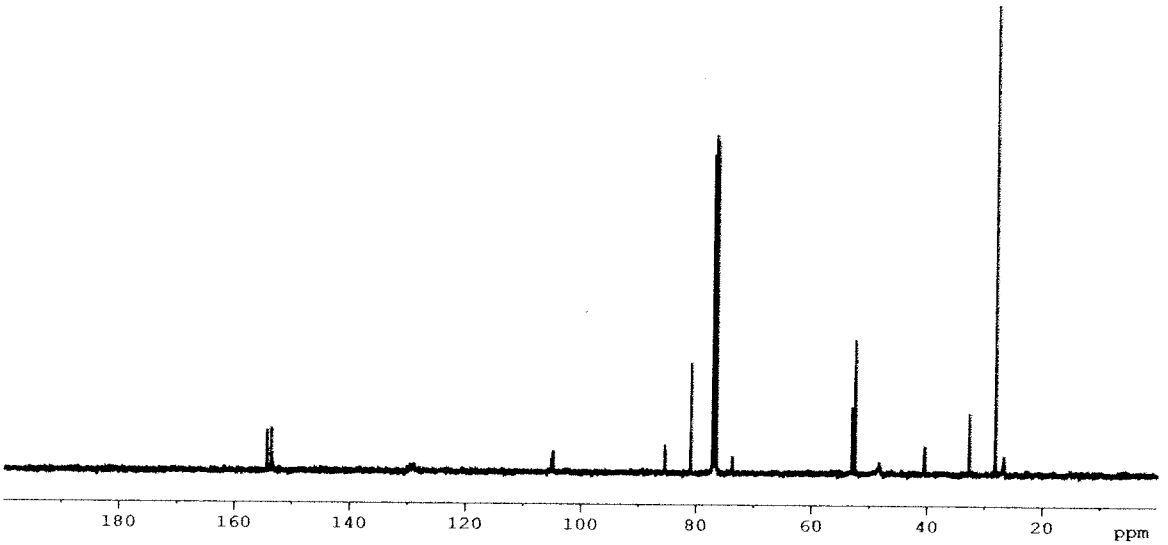

180
160
140
120
100
80
60
40
20
ppm

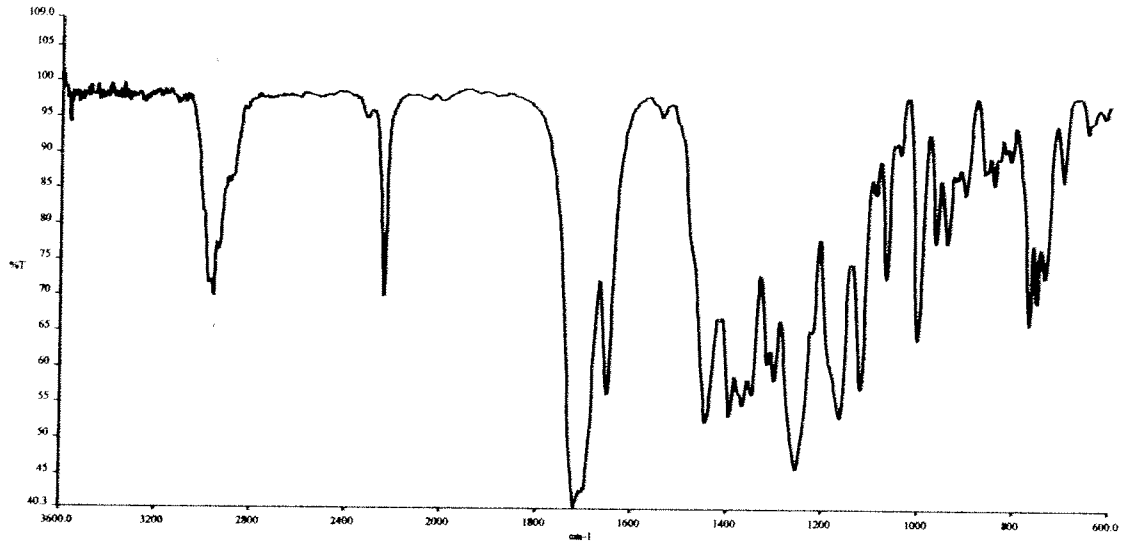

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

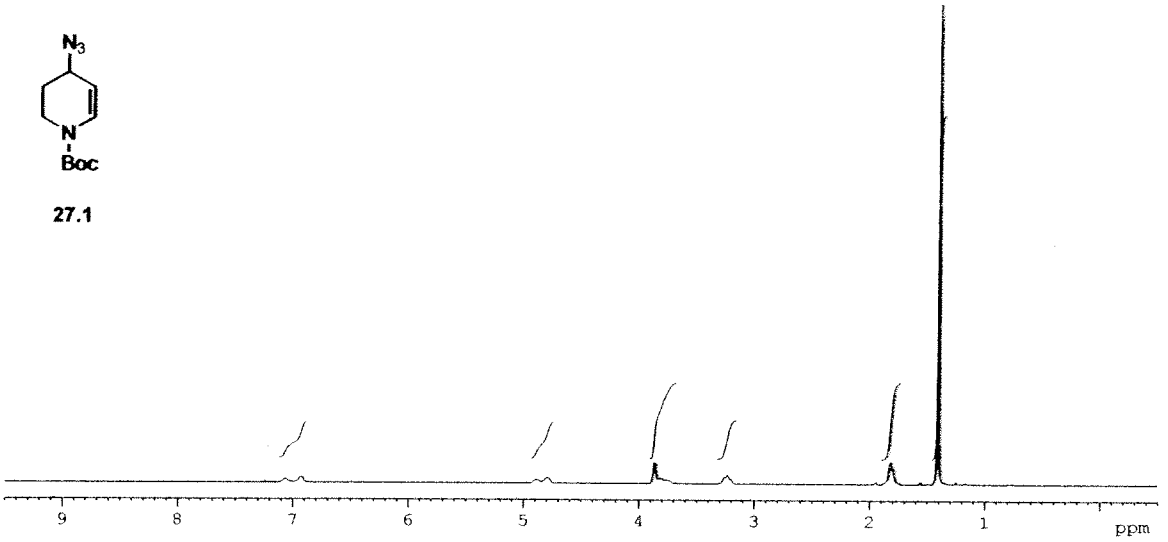

Boc
N
O
O
N
O
OCH3

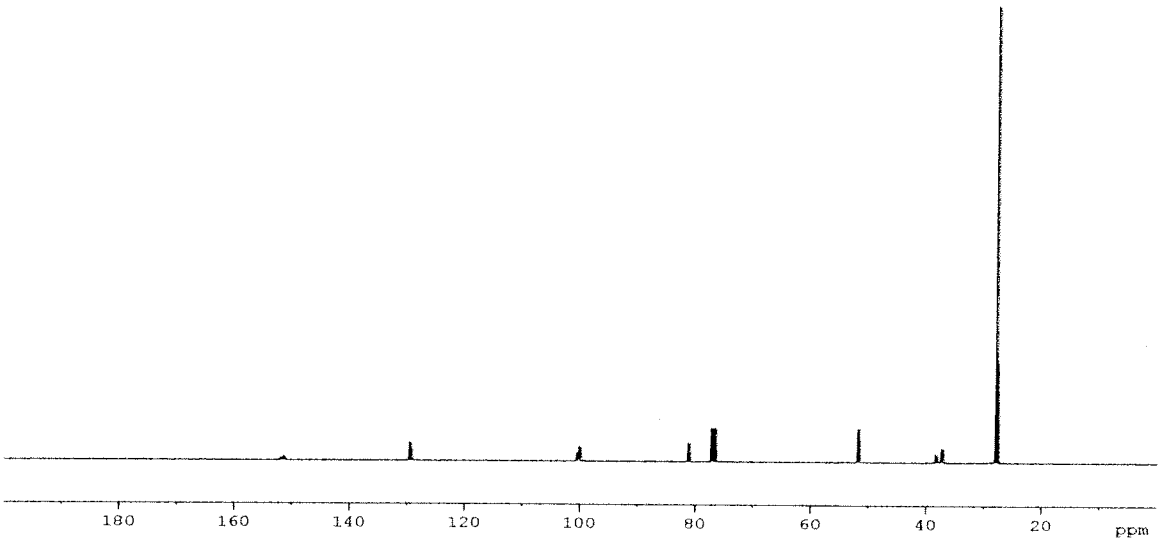
11.0h

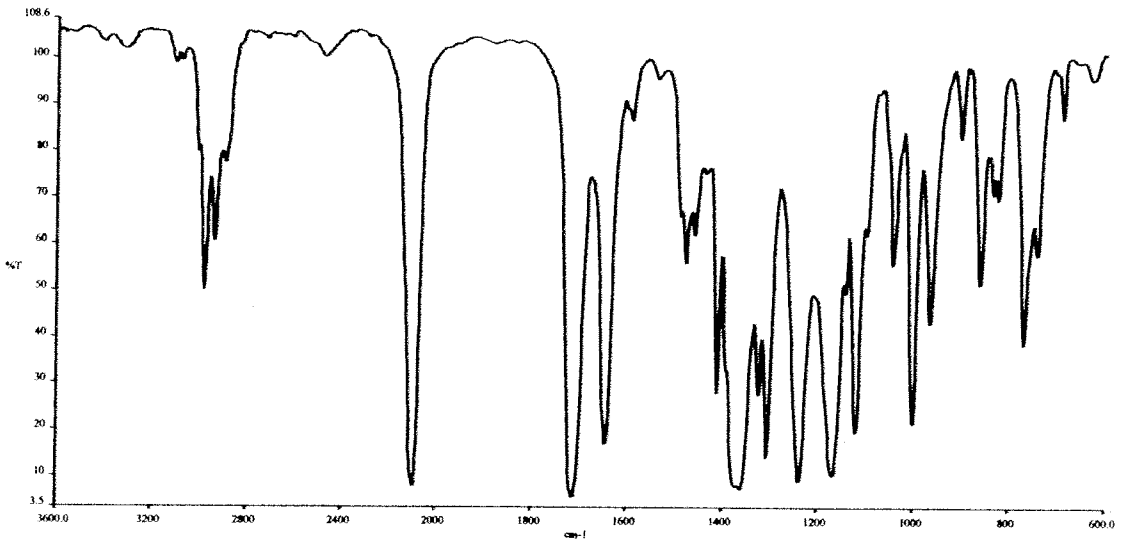
9
8
7
6
5
4
3
2
1
ppm

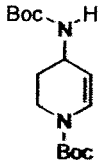

180
160
140
120
100
80
60
40
20
ppm


%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0


N3
N
Boc
27.1
9
8
7
6
5
4
3
2
1
ppm

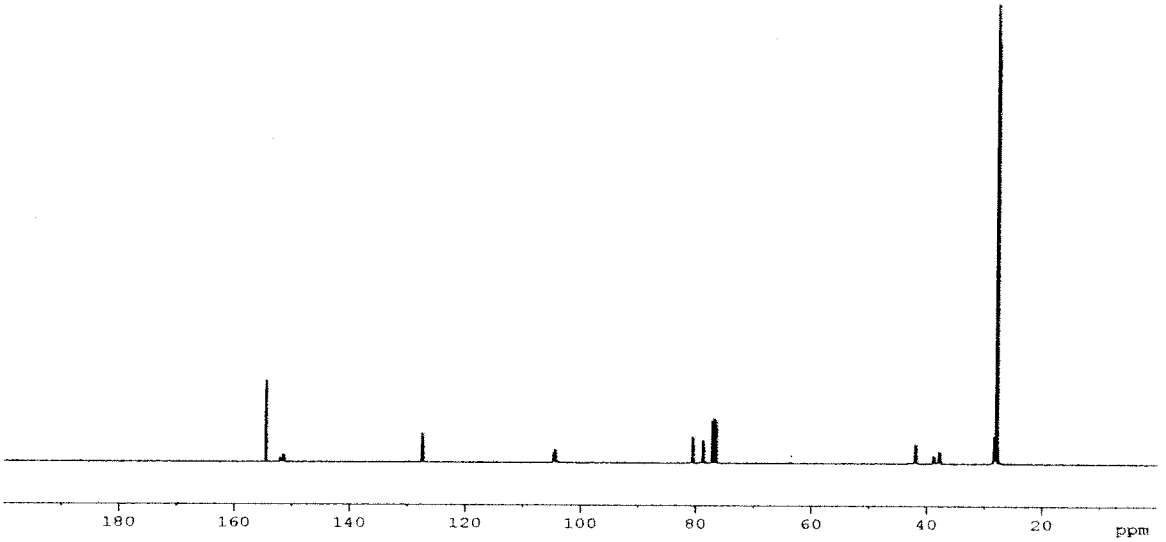

180
160
140
120
100
80
60
40
20
ppm

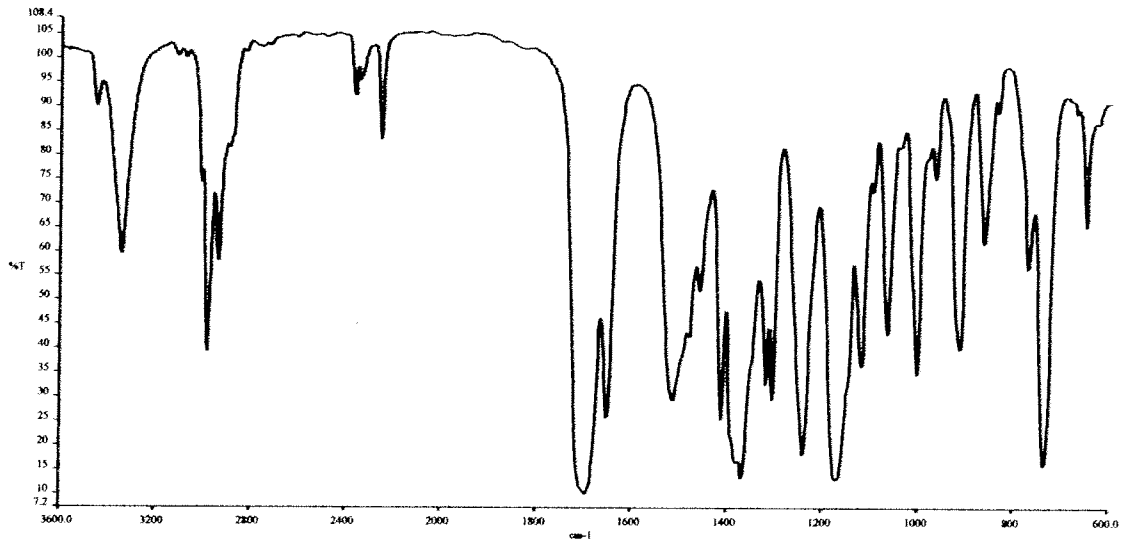

108.6
100
90
80
70
60
%T
50
40
30
20
10
3.5
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

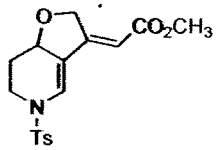

Boc
N
H
N
Boc

27.2

9
8
7
6
5
4
3
2
1
ppm

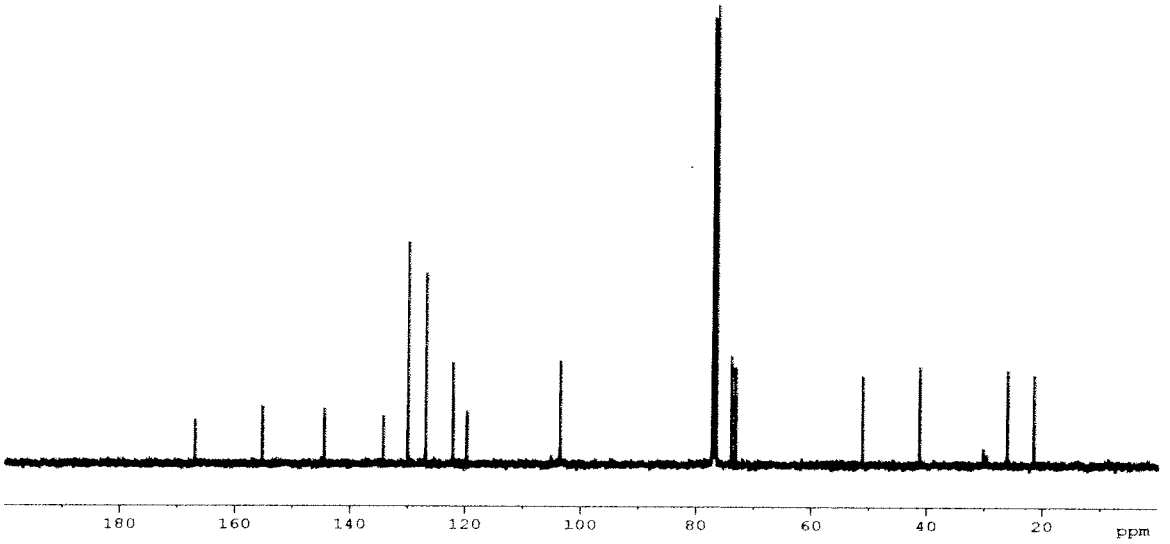

180
160
140
120
100
80
60
40
20
ppm


%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1


O
CO2CH3
N
Ts

11.1a

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

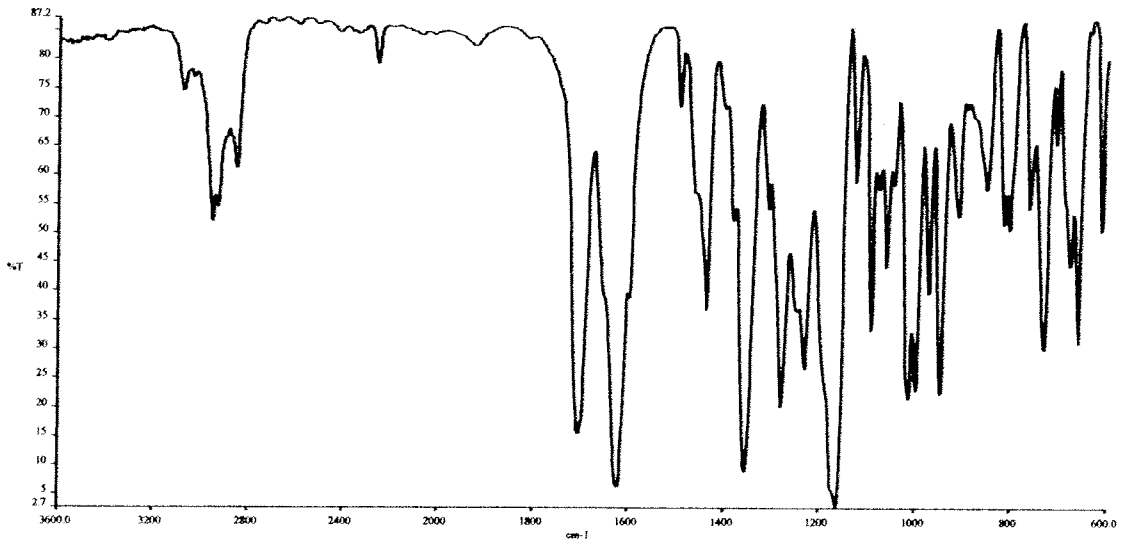
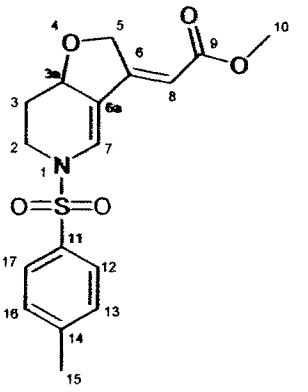
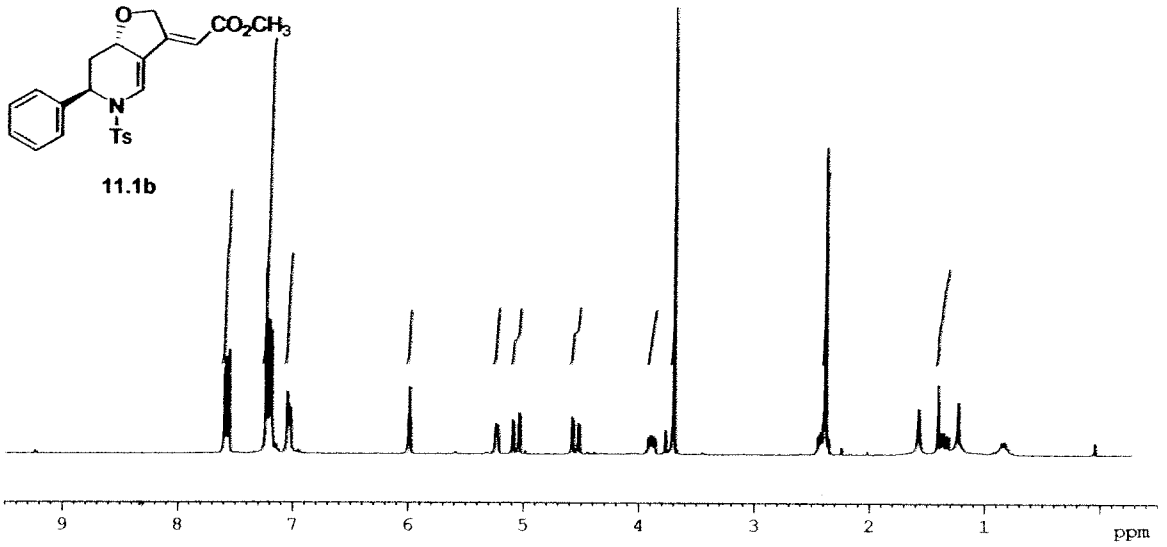

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

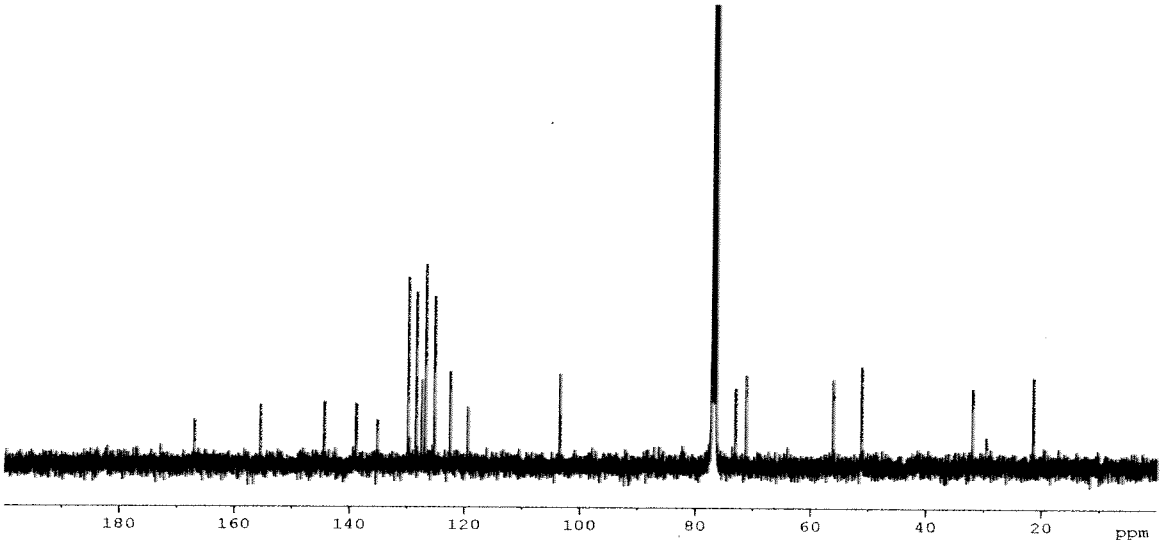
Table 7: NMR data for **11.0a**



Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]
2	41.4	CH_2	H-2: 3.90 (dt, 13.1, 3.5) H-2': 3.03 (td, 13.4, 2.8)
3	26.2	CH_2	H-3: 2.25 (dddd, 9.1,6.1, 2.9, 2.8) H-3': 1.42-1.38 (m)
3a	74.0	CH	H-3a: 4.22 (ddd, 10.4, 5.6, 1.5)
5	73.3	CH_2	H-5: 5.09 (dd, 16.1, 2.2) H-5': 4.63 (dd, 16.6, 2.6)
6, 6a	155.4, 120.0	Q	
7	122.3	CH	H-7: 7.37-7.28 (m)
8	103.7	CH	H-8: 5.93 (t, 2.4)
9	167.1	Q	
10	51.3	CH_3	H-10: 3.69 (s)
11, 14	134.4, 144.6	Q	
12, 17	127.0	CH	H-12, H-17: 7.65 (d, 8.3)
13,16	130.1	CH	H-13, H-16: 7.37-7.28 (m)
15	21.6	CH_3	H-15: 2.41 (s)

[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-7 and H-13/H-16 overlap.


O
CO2CH3
N
Ts
11.1b
9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

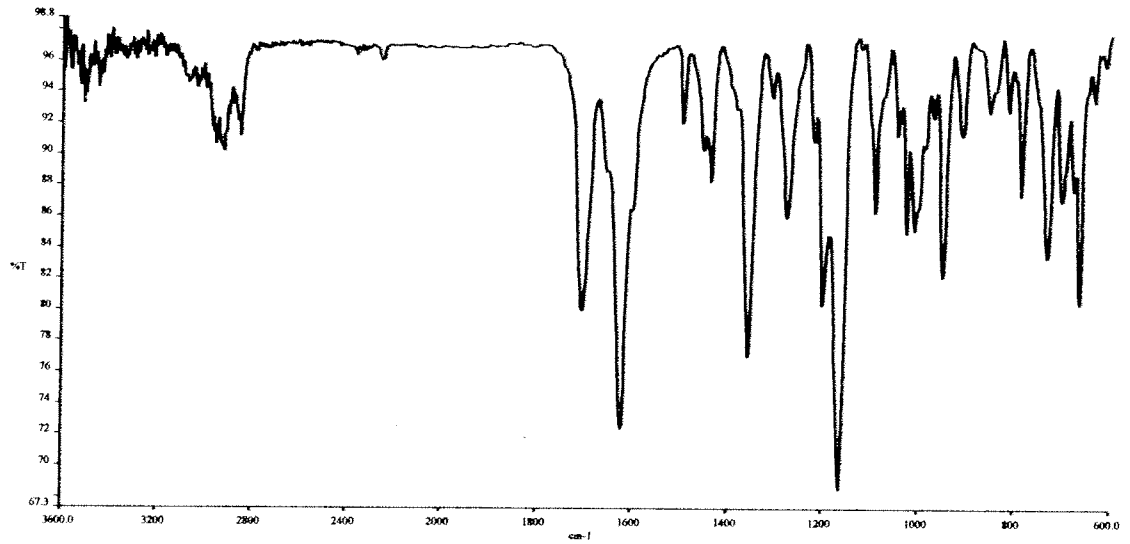
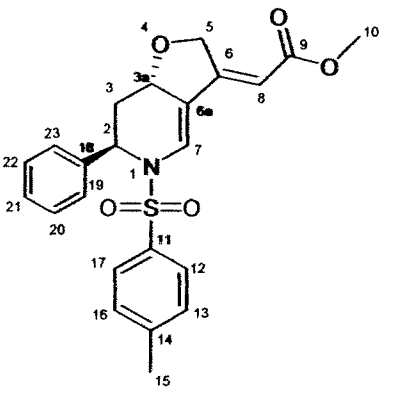

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

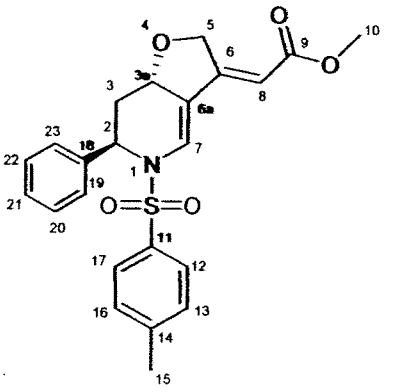
Table 8: NMR data for **11.0b**



Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]	COSY Correlations[e]
2	56.3	CH_2	H-2: 5.24 (dd, 4.6, 2.3)	H-3, H-3'
3	32.1	CH_2	H-3: 2.48-2.35 (m) H-3': 1.35 (dd, 11.0, 4.0, 4.1)	H-2, H-3', H-3a H-2, H-3, H-3a
3a	71.4	CH	H-3a: 3.90 (ddd, 10.5, 5.5, 1.4)	H-3, H-3'
5	73.2	CH_2	H-5: 4.55 (dd, 16.5, 2.7) H-5': 5.07 (dd, 16.7, 2.1)	H-5', H-8 H-5, H-8
6, 6a	155.6, 119.6	Q		
7	103.6	CH	H-7: 7.65-7.54 (m)	
8	122.7	CH	H-8: 6.00 (t, 2.5)	H-5, H-5'
9	167.1	Q		
10	51.3	CH_3	H-10: 3.70 (s)	
11, 14	134.4, 144.6	Q		
12, 17	127.0	CH	H-12, H-17: 7.65-7.54 (m)	
13,16	130.0	CH	H-13, H-16: 7.29-7.17 (m)	
15	21.6	CH_3	H-15: 2.41 (s)	
18	129.0	Q		
21	125.4	CH	H-21: 7.29-7.17 (m)	
19, 23	127.6	CH	H-19, H-23: 7.09-7.01 (m)	
20, 22	128.6	CH	H-20, H-22: 7.29-7.17 (m)	

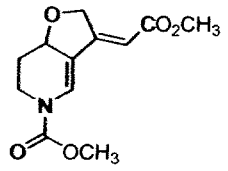
[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-3 and H-15 overlap. The signals for H-7 and H-12, H-17 overlap. [e]Only those correlations which could be unambiguously assigned are recorded.

Table 9: ^{1}H Selective NOE Data for **11.0b**



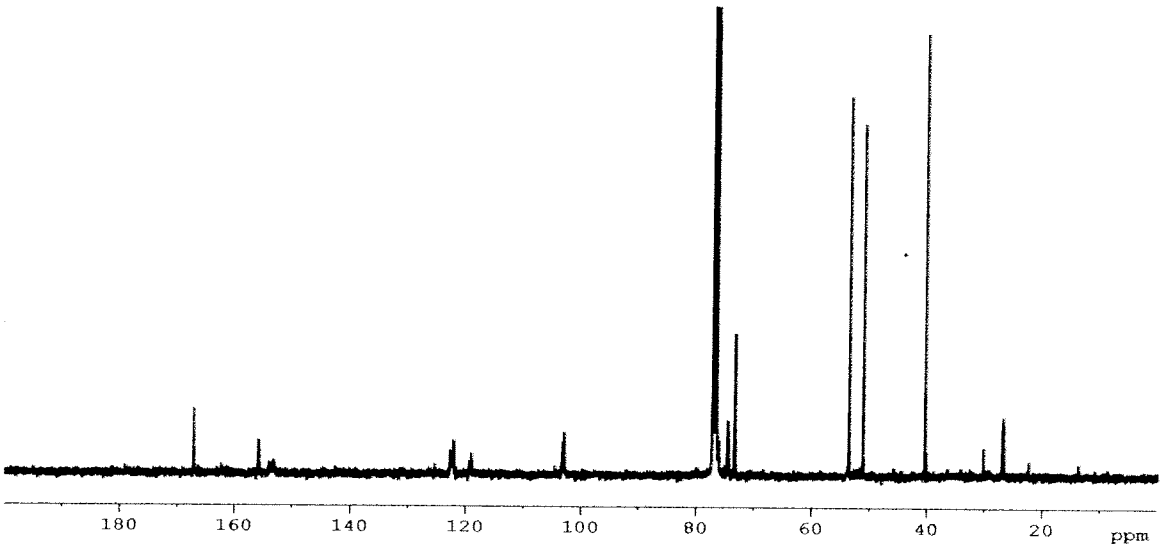
Proton No. Irradiated	^{1}H δ (ppm) (mult., J (Hz))[a]	^{1}H Selective NOE Correlation[b]
H-8	6.00 (t, 2.5)	H-7
H-2	5.24 (dd, 4.6, 2.3)	H-3, H-3', H-19, H-23

[a]Recorded at 400 MHz. [b]Only those correlations which could be unambiguously assigned are recorded.


O
CO2CH3
N
O
OCH3

11.1c

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

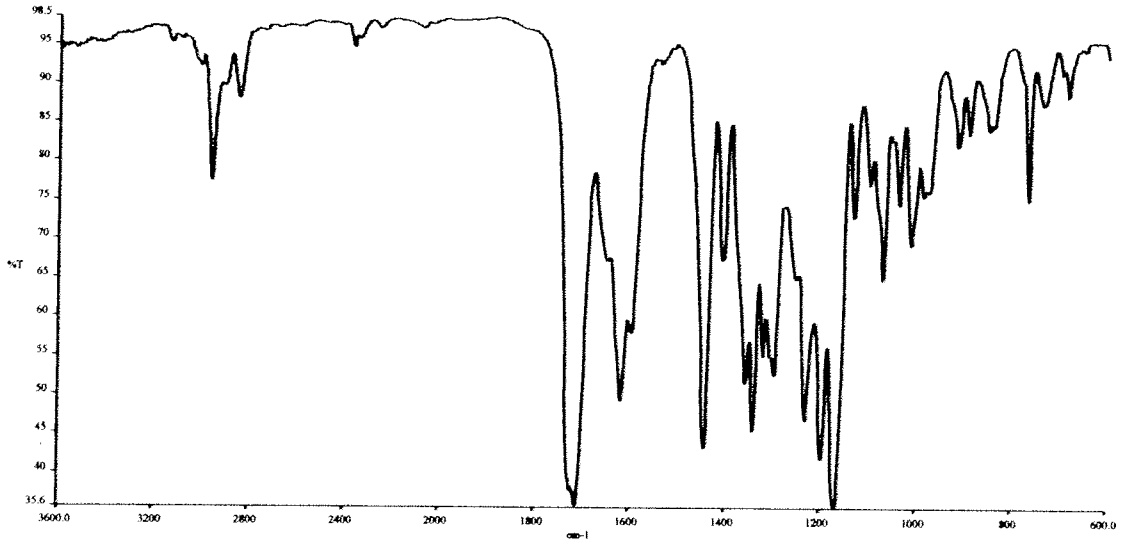
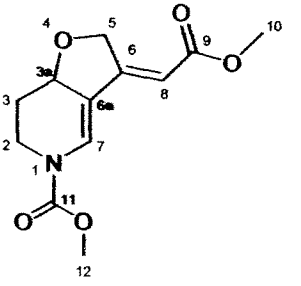
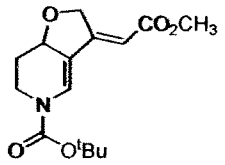

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

Table 10: NMR data for **11.0c**



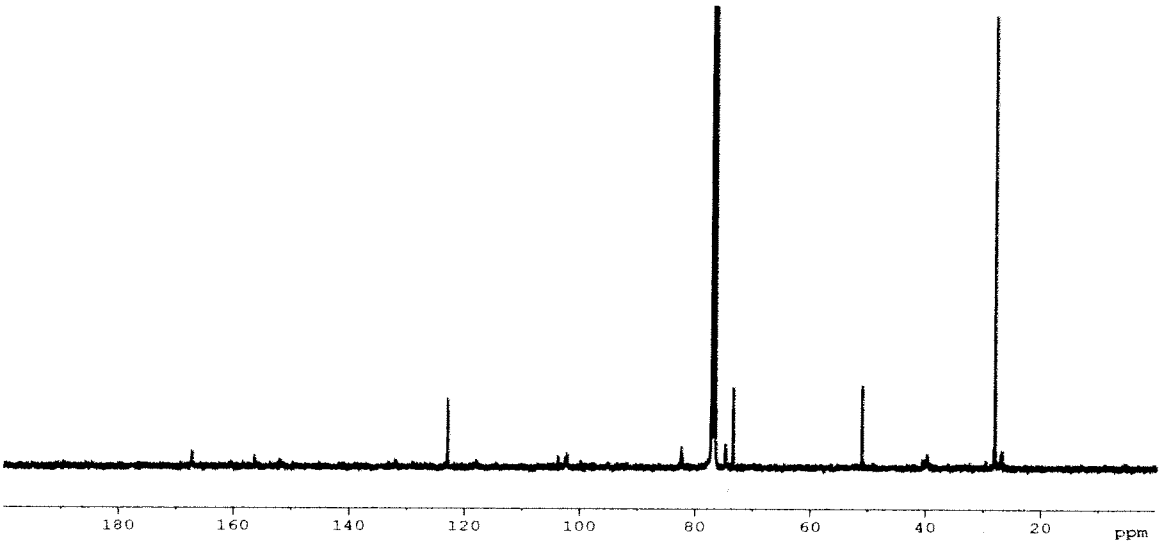
Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c]
2	40.4	CH_2	H-2: 3.20 (br. s.) H-2': 4.12 (br. s.)
3	22.4	CH_2	H-3: 2.38 (br. s.) H-3': 1.31-1.21 (m)
3a	74.7	CH	H-3a: 4.44-4.35 (m)
5	73.4	CH_2	H-5: 5.14 (dd, 16.6, 2.2) H-5': 4.70 (dd, 16.6, 2.6)
6, 6a	153.7, 119.1	Q	
7	122.5	CH	H-7: 5.92 (br. s.)
8	103.1	CH	H-8: 7.60-7.36 (m)
9	167.3	Q	
10	53.7	CH_3	H-10: 3.82 (s)
11	156.0	Q	
12	51.2	CH_3	H-12: 3.72 (s)

[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. .


O
CO2CH3
N
O
OtBu

11.1d

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

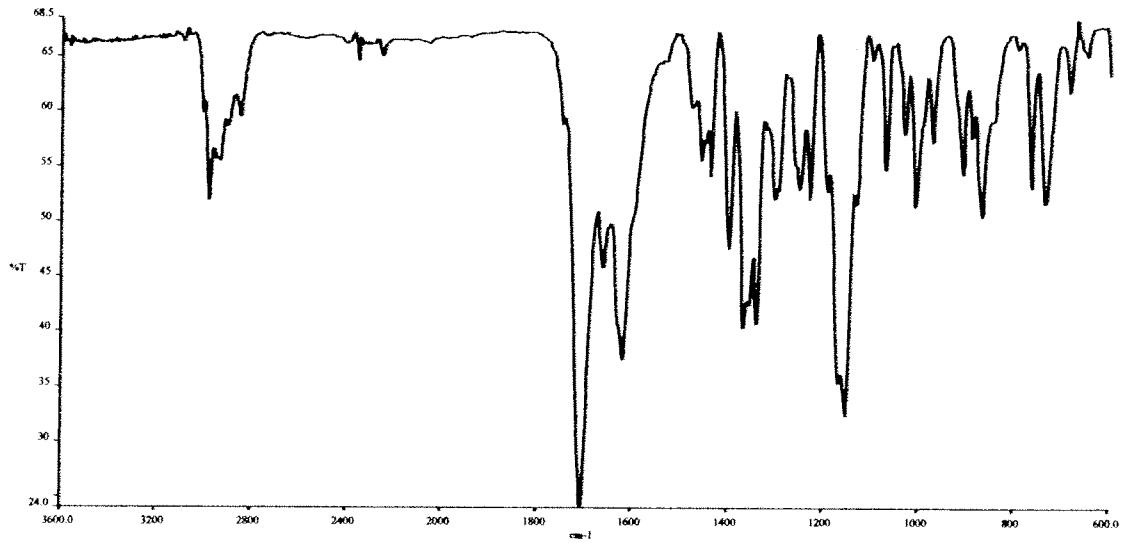
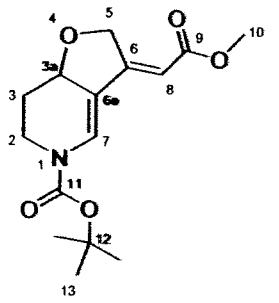

%T
68.5
65
60
55
50
45
40
35
30
24.0
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

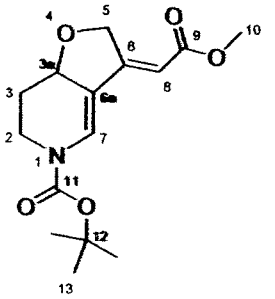
Table 11: NMR data for **11.0d**



Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]	COSY Correlation
2	40.2	CH_2	H-2: 4,24-3.99 (m) H-2': 3.17 (br. s.)	H-2' H-2
3	28.2	CH_2	H-3: 2.35 (br. s.) H-3': 1.55-1.48 (m)	H-3', H-3a H-3, H-3a
3a	74.8	CH	H-3a: 4.38 (ddd, 10.3, 5.5, 1.3)	H-3, H-3'
5	73.5	CH_2	H-5: 5.14 (dd, 16.1, 2.2) H-5': 4.70 (dd, 16.4, 2.4)	H-5', H-8 H-5, H-8
6, 6a	152.9, 113.6	Q		
7	123.1	CH	H-7: 7.67-7.29 (m)	
8	102.3	CH	H-8: 5.88 (t, 2.4)	H-5, H-5'
9	167.3	Q		
10	51.2	CH_3	H-10: 3.70 (s)	
11	156.3	Q		
12	82.5	Q		
13	28.3	CH_3	H-13: 1.55-1.48 (m)	

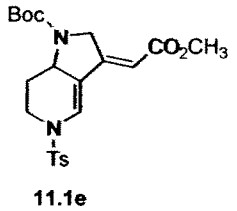
[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-3' and H-13 overlap.

Table 12: ^{1}H Selective NOE Data for **11.0d**



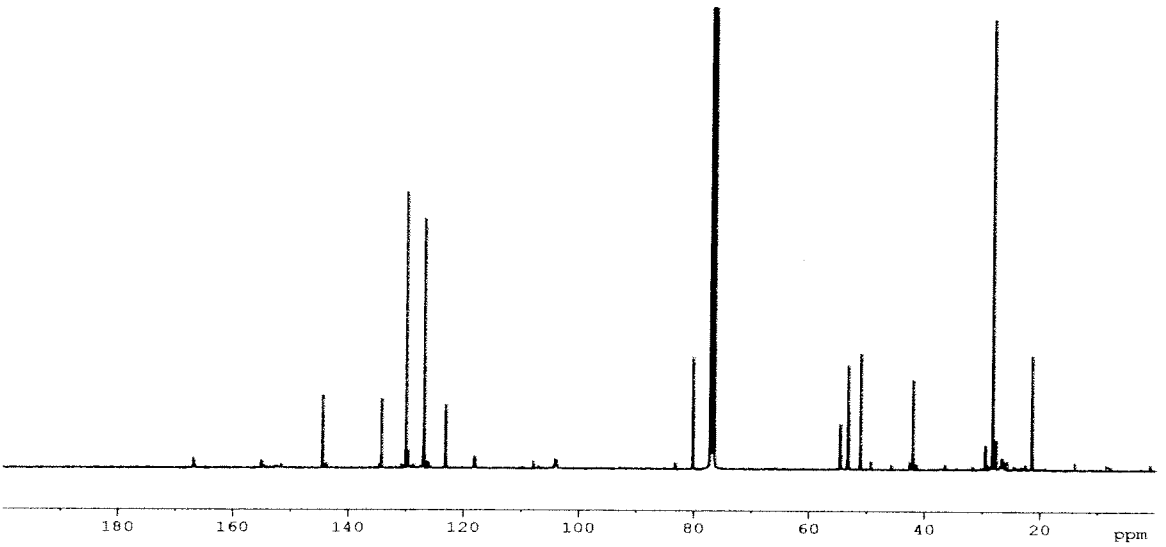
Proton No. Irradiated	^{1}H δ (ppm) (mult., J (Hz))[a]	^{1}H Selective NOE Correlation[b]
H-8	5.88 (s)	H-7

[a]Recorded at 400 MHz. [b]Only those correlations which could be unambiguously assigned are recorded.


Boc
N
CO2CH3
N
Ts

11.1e

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

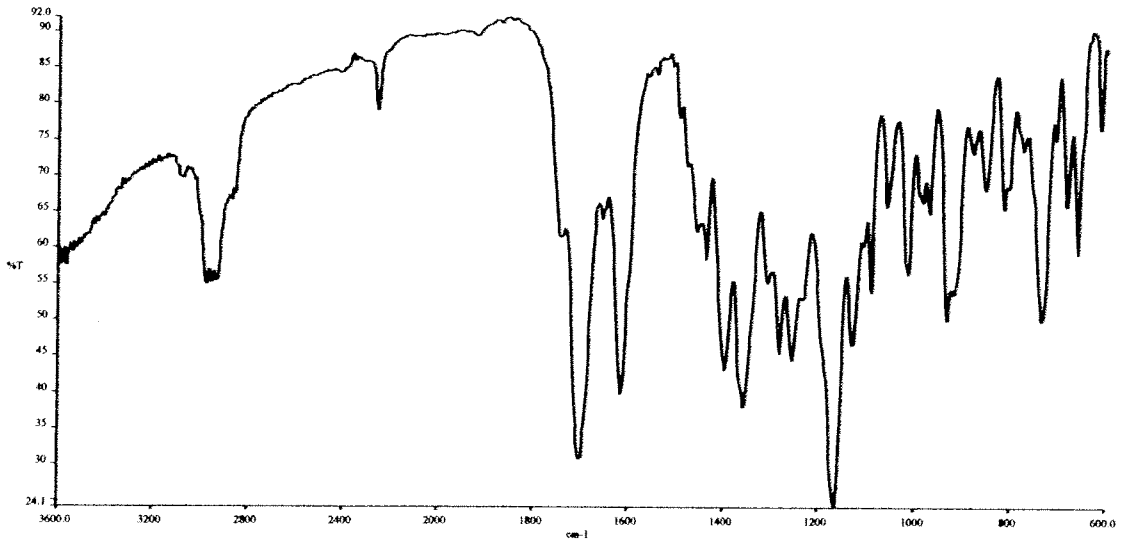
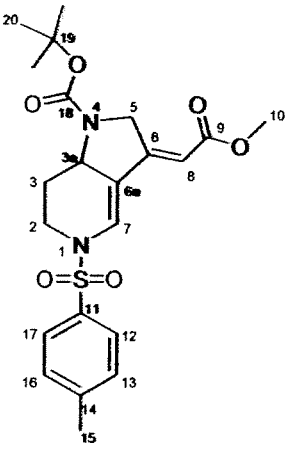

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

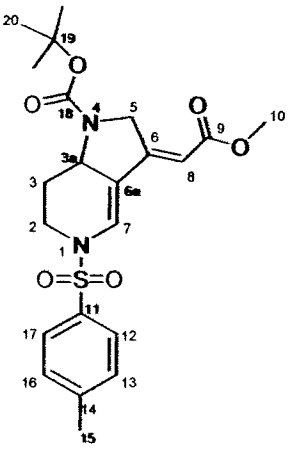
Table 13: NMR data for **11.0e**



Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]	COSY Correlations[e]
2	42.2	CH_2	H-2: 3.86 (dt, 13.1, 3.3) H-2': 3.06 (td, 13.1, 3.1)	H-2', H-3', H-3a H-2, H-3, H-3a
3	27.8	CH_2	H-3: 1.48-1.35 (m) H-3': 1.27-1.13 (m)	 H-2, H-3a
3a	54.7	CH	H-3a: 4.00-3.90 (m)	H-3, H-7, H-8
5	53.4	CH_2	H-5: 4.50 (br. s.)	H-8
6, 6a	152.5 118.2	Q		
7	123.3	CH	H-7: 7.35-7.29 (m)	H-3a, H-8
8	104.1	CH	H-8: 5.94 (t, 2.4)	H-3a, H-5', H-7
9	166.9	Q		
10	51.2	CH_3	H-10: 3.69 (s)	
11, 14	134.3, 144.6	Q		
12, 17	127.0	CH	H-12, H-17: 7.35-7.29 (m)	
13,16	130.1	CH	H-13, H-16: 7.65 (d,8.3)	
15	21.6	CH_3	H-15: 2.41 (s)	
18	155.1	Q		
19	80.3	Q		
20	28.4	CH_3	H-20: 1.48-1.35 (m)	

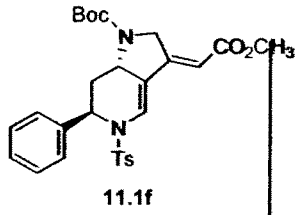
[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-3 and H-20 overlap. The signals for H-7 and H-12/H-17 overlap. [e]Only those correlations which could be unambiguously assigned are recorded.

Table 14: ^{1}H Selective NOE Data for **11.0e**



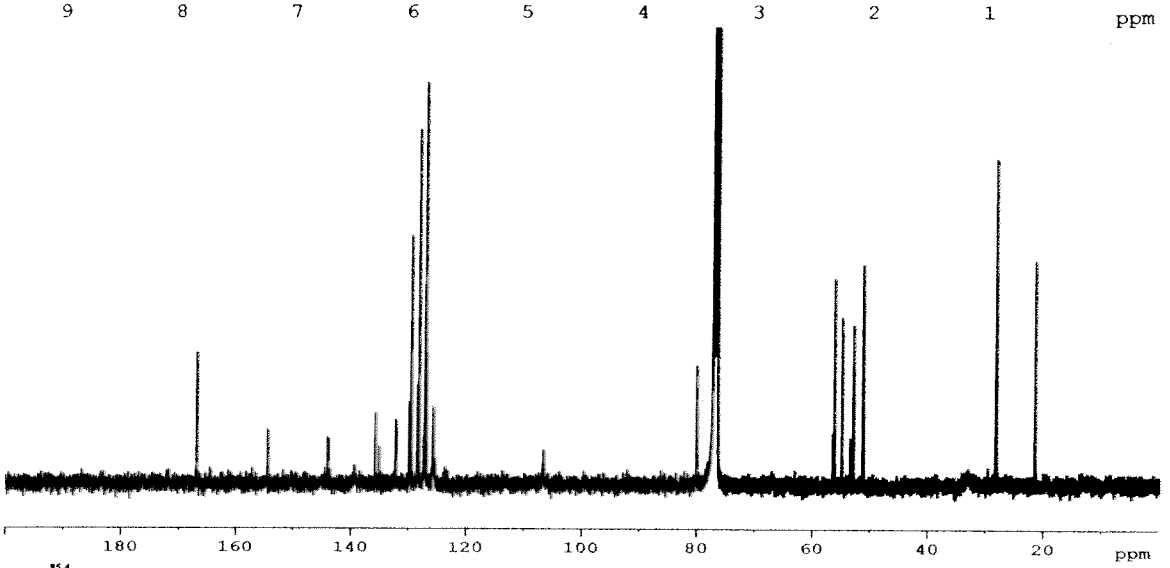
Proton No. Irradiated	^{1}H δ (ppm) (mult., J (Hz))[a]	^{1}H Selective NOE Correlation[b]
H-8	5.94 (s)	H-7

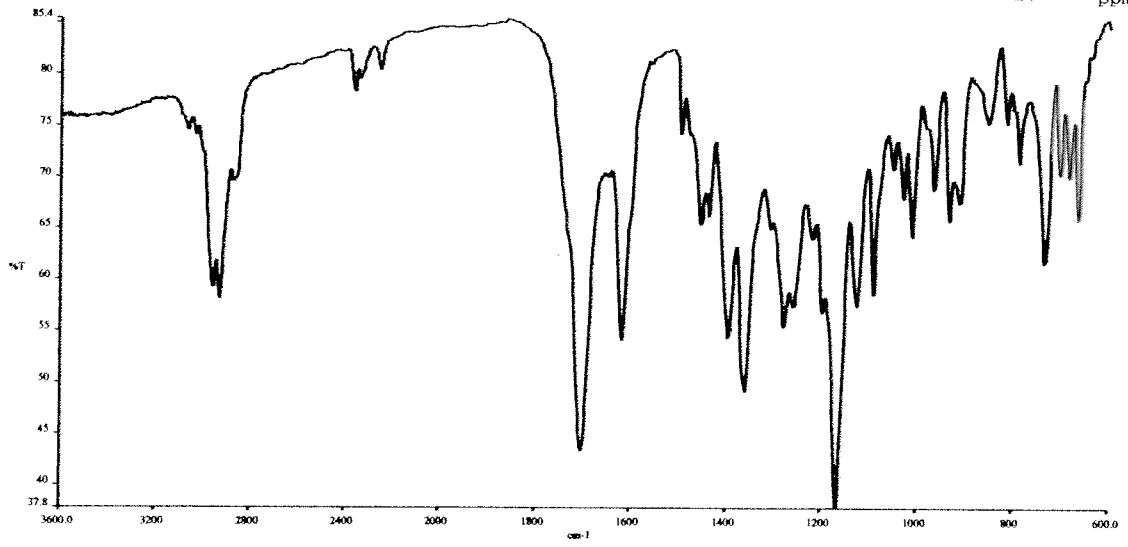
[a]Recorded at 400 MHz. [b]Only those correlations which could be unambiguously assigned are recorded.

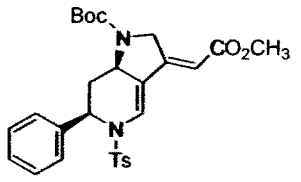

Boc
N
CO2CH3
N
Ts

11.1f

9
8
7
6
5
4
3
2
1
ppm

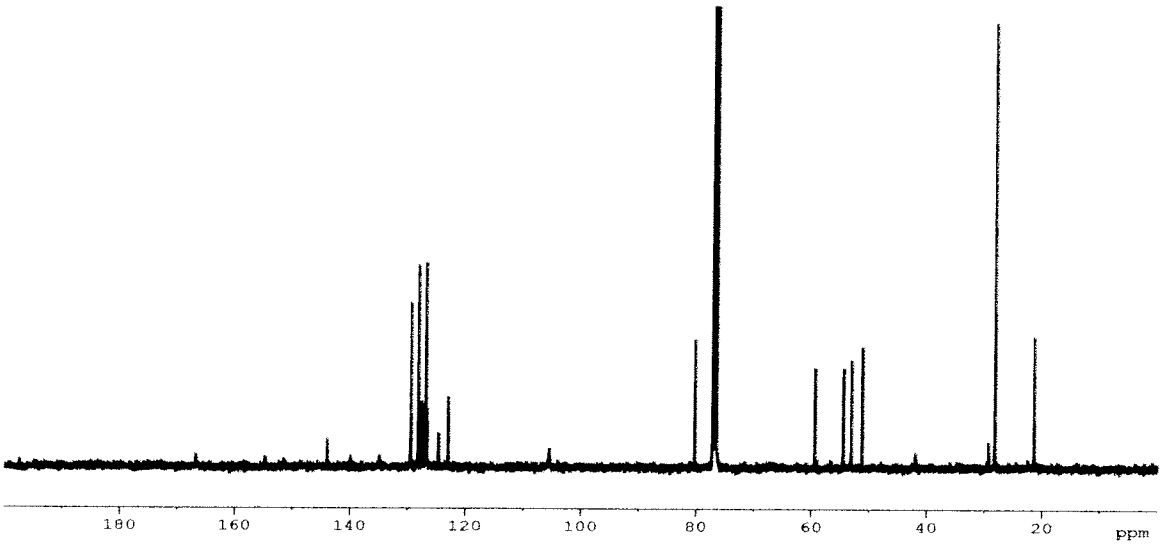

180
160
140
120
100
80
60
40
20
ppm


%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1


Boc
N
CO_2CH_3
N
Ts

11.1g

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

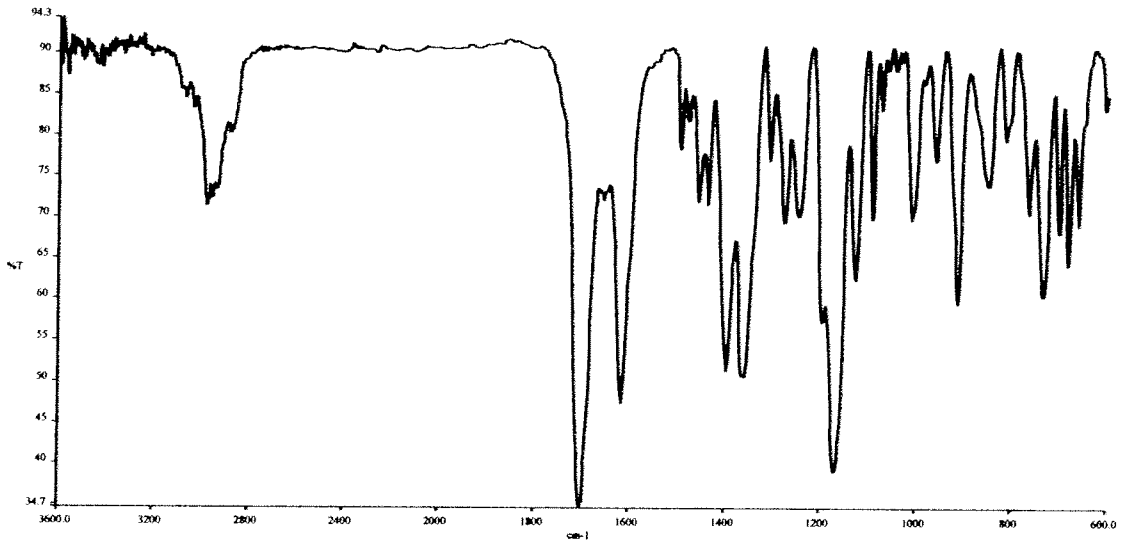
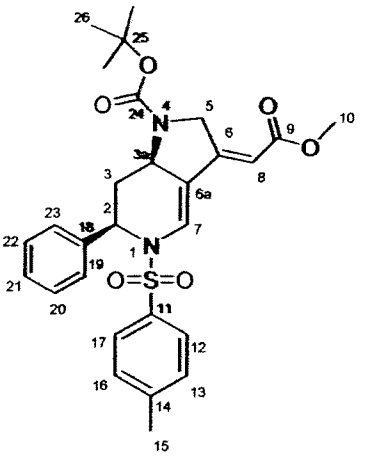

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
660.0
cm-1

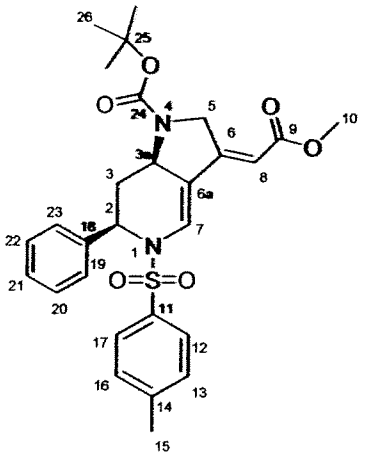
Table 15: NMR data for **11.0g**



Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]
2	54.6	CH_2	H-2: 4.54 (br. s.)
3	28.3	CH_2	H-3: 3.07 (br. s.) H-3': 1.76-1.56 (m)
3a	59.5	CH	H-3a: 3.97 (dd, 10.5)
5	53.2	CH_2	H-5: 4.54 (br. s.)
6, 6a	151.6, 123.1	Q	
7	124.8	CH	H-7: 7.20-7.09 (m)
8	105.6	CH	H-8: 6.09 (t, 2.5)
9	166.9	Q	
10	51.4	CH_3	H-10: 3.73 (s)
11, 14	134.9, 144.1	Q	
12, 17	126.8	CH	H-12, H-17: 7.47-7.32 (m)
13,16	129.6	CH	H-13, H-16: 7.20-7.09 (m)
15	21.5	CH_3	H-15: 2.38 (s)

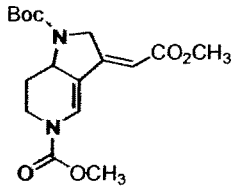
[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-3 and H-15 overlap. [e]Only those correlations which could be unambiguously assigned are recorded.

Table 15: NMR data for **11.0g** (cont.)



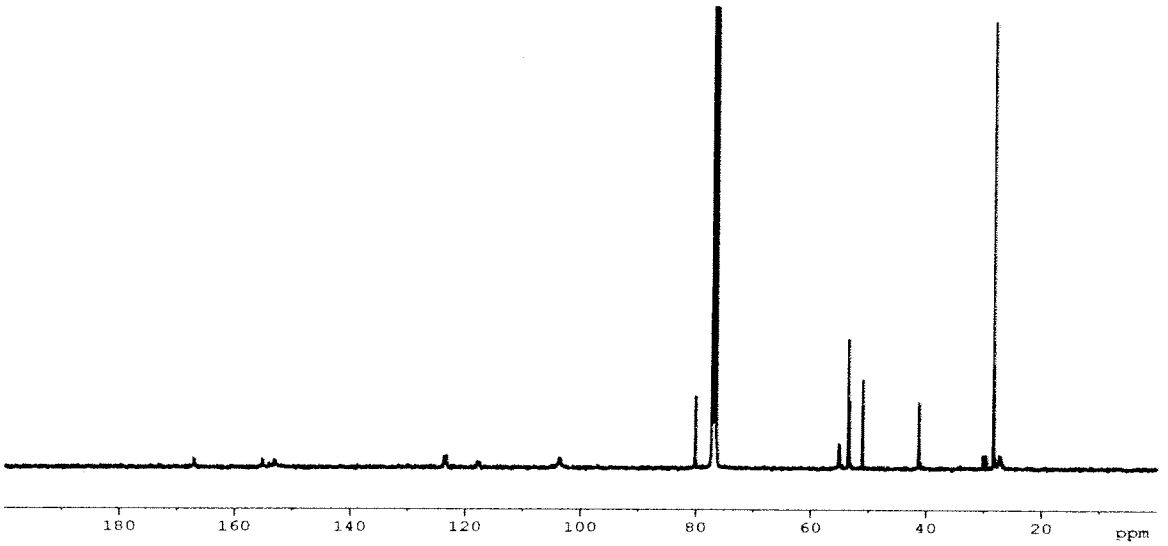
Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]
18	140.0	Q	
19, 23	127.6	CH	H-19, H-23: 7.20-7.09 (m)
20, 22	128.3	CH	H-20, H-22: 7.20-7.09 (m)
21	125.4	CH	H-21: 7.47-7.32 (m)
24, 25	154.8, 80.4	Q	
26	29.4	CH_3	H-26: 1.43-1.32 (m)

[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-3 and H-15 overlap. [e]Only those correlations which could be unambiguously assigned are recorded.


Boc
N
CO_2CH_3
N
O
OCH_3

11.1h

9
8
7
6
5
4
3
2
1
ppm


180
160
140
120
100
80
60
40
20
ppm

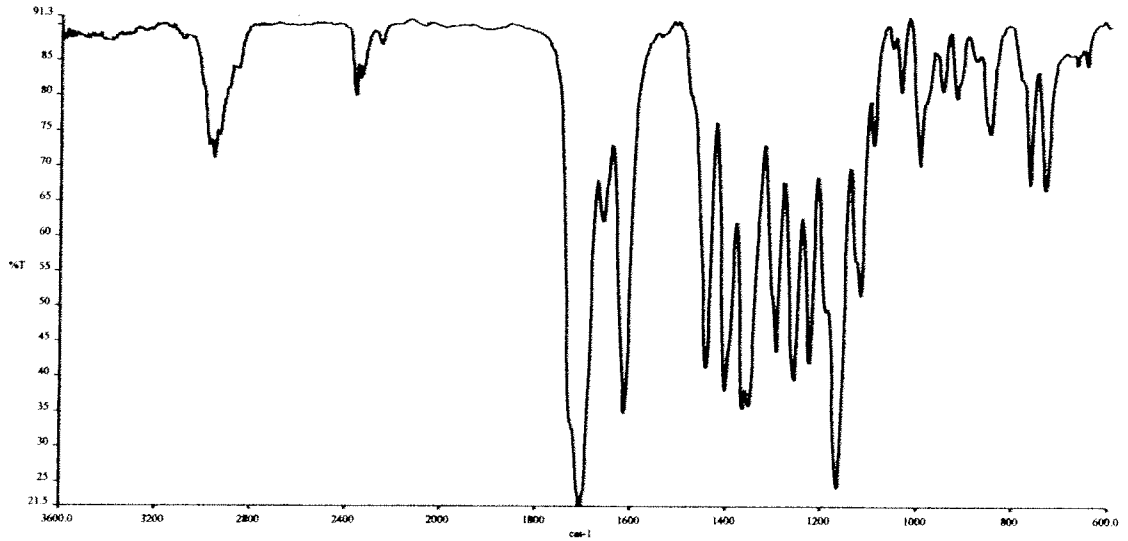
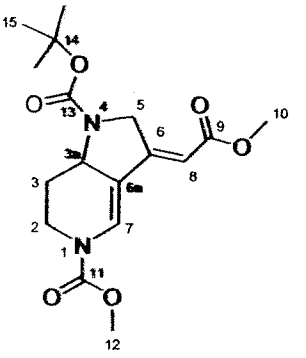
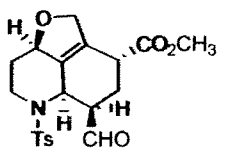

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

Table 16: NMR data for **11.0h**



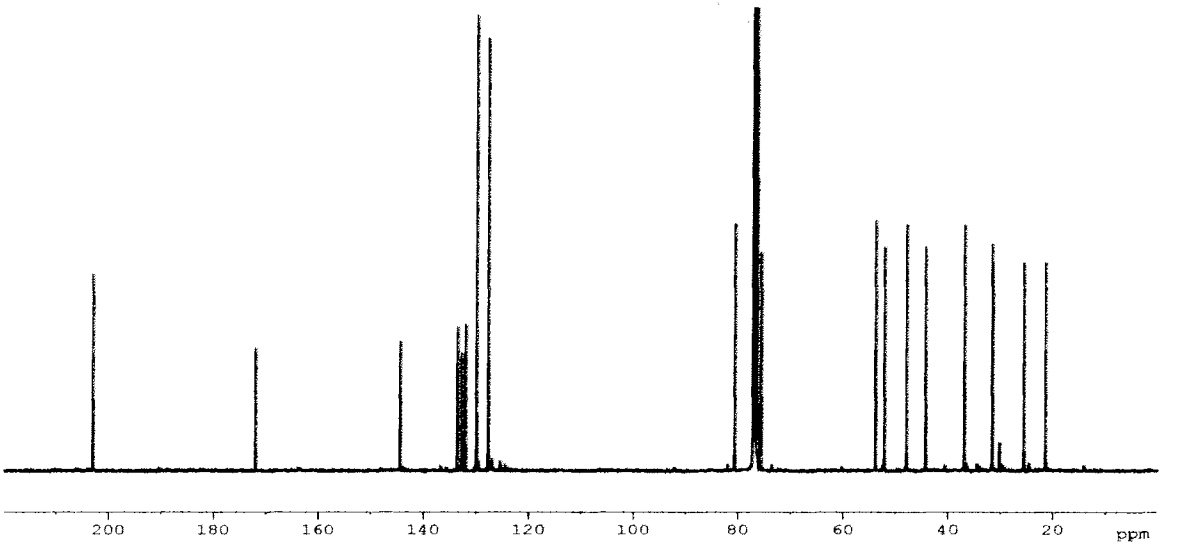
Carbon No.	^{13}C (ppm)[a]	Mult.	^{1}H (ppm) (mult., J (Hz))[b,c,d]
2	30.0	CH_2	H-2: 4.12 (br. s.) H-2': 3.25 (br. s.)
3	27.3	CH_2	H-3: 2.93 (br. s.) H-3': 1.64-1.39 (m)
3a	51.2	CH	H-3a: 4.12 (br. s.)
5	41.4	CH_2	H-5: 4.56 (br. s.)
6, 6a	153.2, 117.9	Q	
7	123.6	CH	H-7: 7.65-7.34 (m)
8	103.7	CH	H-8: 5.94 (br. s.)
9	167.1	Q	
10	55.2	CH_3	H-10: 3.81 (s)
11	154.0	Q	
12	53.7	CH_3	H-12: 3.69 (s)
13	155.3	Q	
14	80.2	Q	
15	28.5	CH_3	

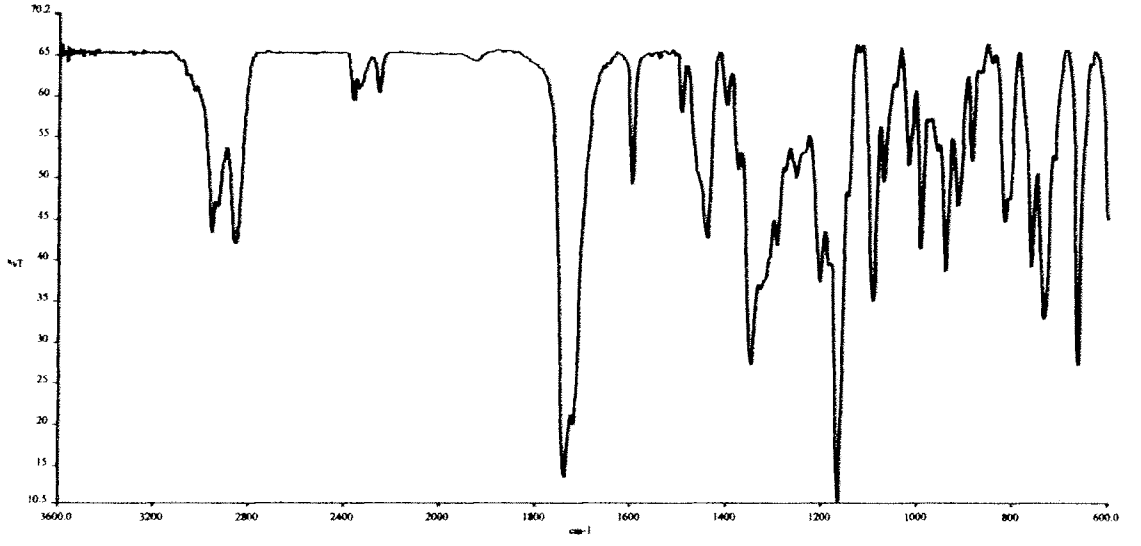
[a]Recorded at 100 MHz. [b]Recorded at 400 MHz. [c]Methylene protons are arbitrarily designated H-X and H-X'. [d]The signals for H-7 and H-13/H-16 overlap.

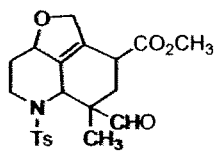

O
CO_2CH_3
N
H
H
Ts
CHO

11.20a

10
9
8
7
6
5
4
3
2
1
ppm

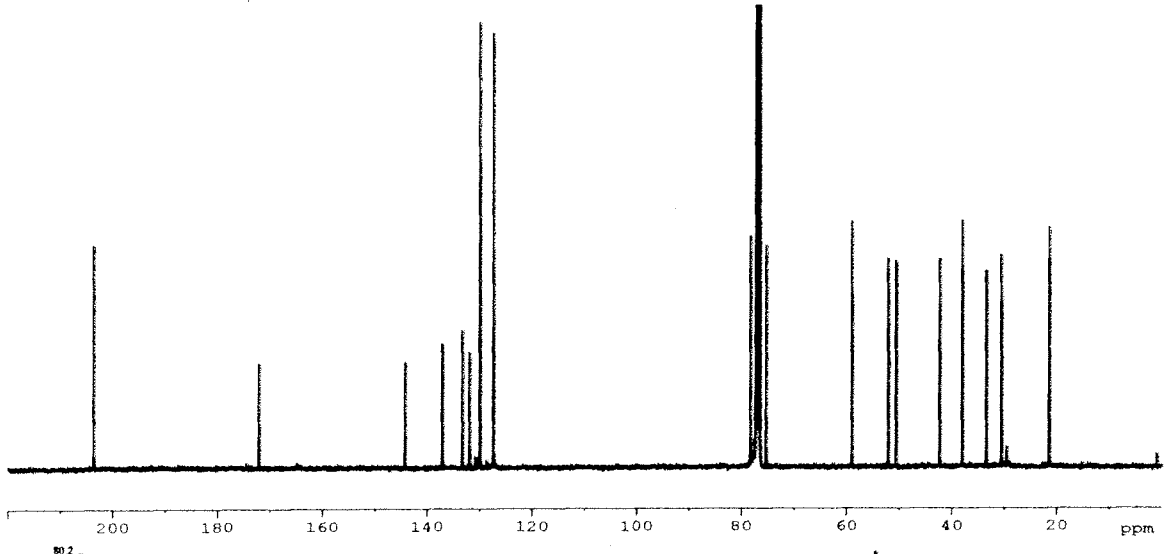

200
180
160
140
120
100
80
60
40
20
ppm

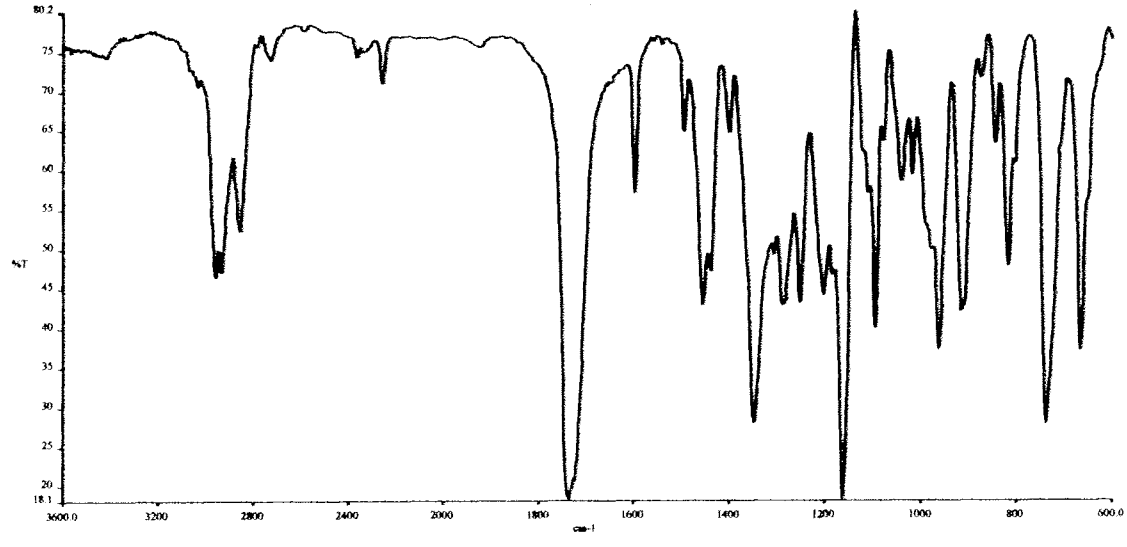

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0

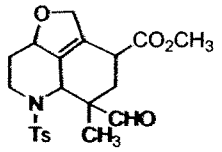

O
CO2CH3
N
Ts
CHO
CH3

11.22a

10
9
8
7
6
5
4
3
2
1
ppm

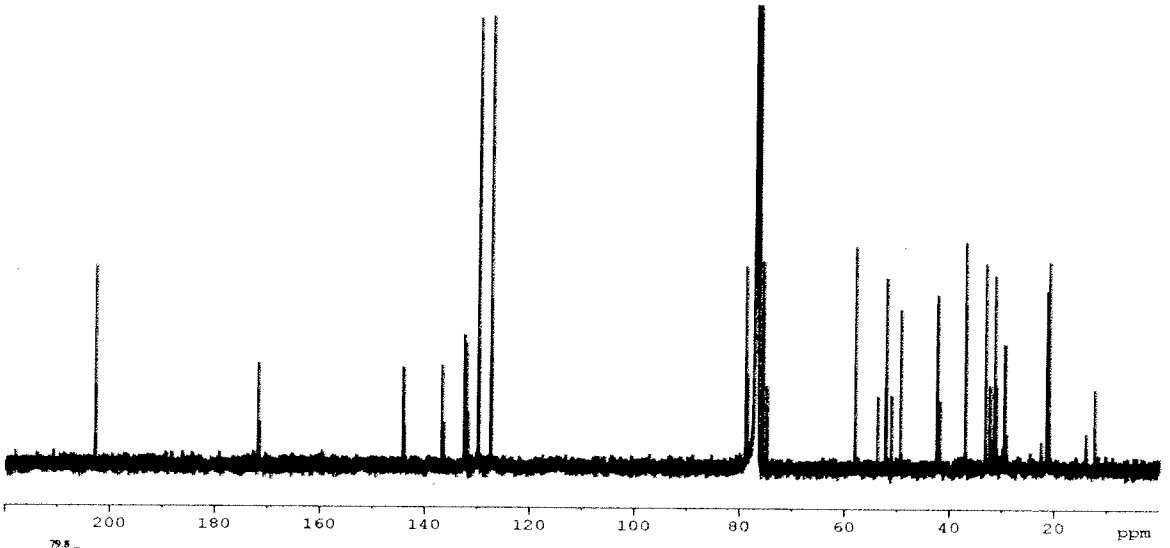

200
180
160
140
120
100
80
60
40
20
ppm


%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1


O
CO2CH3
N
Ts
CHO
CH3

11.23a/11.24a

10
9
8
7
6
5
4
3
2
1
ppm


200
180
160
140
120
100
80
60
40
20
ppm

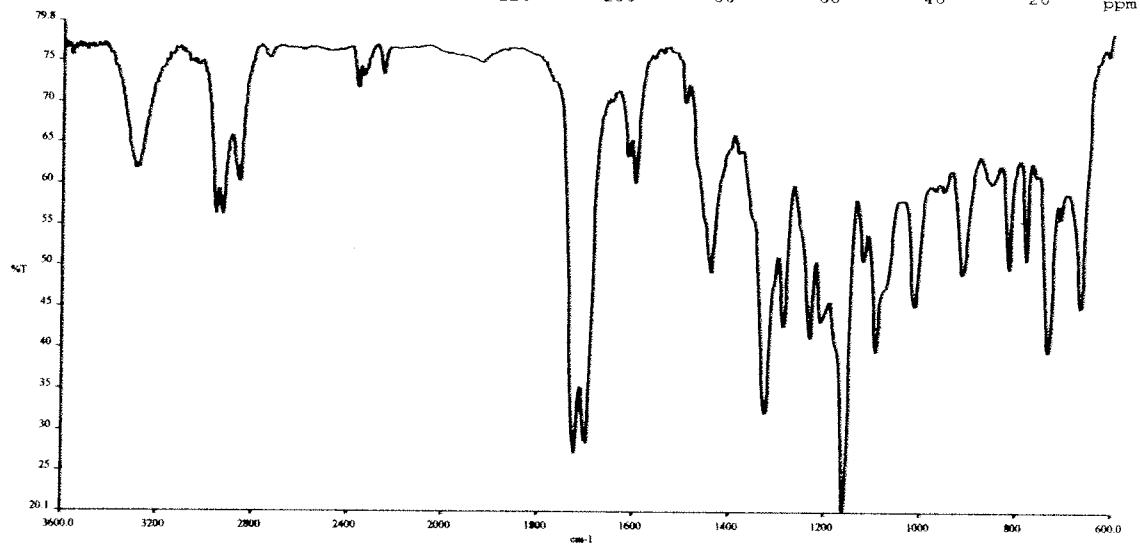

%T
3600.0
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600.0
cm-1

Table 17: X-Ray Crystallographic Experimental Data

Compound	**11.1DS**	**11.21aS**
Empirical Formula	$C_{30}H_{42}N_2O_{10}$	$C_{20}H_{23}NO_6S$
Formula Weight	590.66	405.45
Crystal Color, Habit	colourless, tablet	colourless, plate
Crystal Dimensions	**0.05 X 0.15 X 0.25 mm**	**0.05 X 0.30 X 0.35 mm**
Crystal System	triclinic	monoclinic
Lattice Type	primitive	primitive
Lattice Parameters		
a	6.6103(5) Å	21.244(2) Å
b	9.5311(8) Å	6.1472(5) Å
c	12.8219(11) Å	14.4329(13) Å
α	99.752(4) ^{o}	90.0 ^{o}
β	97.082(4) ^{o}	95.699(5) ^{o}
γ	107.239(4) ^{o}	90.0 ^{o}
V	747.36(11) $Å^3$	6848.2(2) $Å^3$
Space Group	*P* -1 (#2)	*P* $2_1/c$ (#14)
Z value	1	4
D_{calc}	1.312 g/cm^3	1.436 g/cm^3
F_{000}	316.00	856.00
μ(MoKα)	0.98 cm^{-1}	2.11 cm^{-1}