PART I: INTERRUPTED NAZAROV CYCLIZATION ON SILICA GEL

PART II: TANDEM ALKYLATION-CYCLIZATION PROCESS VIA AN O,C DIANION

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We certify that we have read this thesis and that, in our opinion, it is satisfactory in scope and quality as a thesis for a degree of Master of Science in Chemistry.

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ABSTRACT

Part I: Exposure of a mixture of propargyl vinyl ketone and a nucleophilic primary or secondary amine to activated dry silica gel in the absence of solvent leads to a cascade of reactions that results in the formation of an aminocyclopentenone. The reaction with triethylamine leads to a cross-conjugated cyclopentadienone.

Part II: A general protocol for preparing densely functionalized cyclopentenones through a tandem alkylation-cyclization process is described. Addition of lithioallene **1.11** to enamide **1.5** generates tetrahedral intermediate **1.12**. Deprotonation of the γ-carbon atom of the allene function in situ, followed by trapping by a suitable electrophile and cyclization during workup leads to C6 substituted cyclopentenone **1.14**.

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LIST OF ABBREVIATIONS

Å	angstrom
Bn	benzyl
CON	conrotation
°C	degree Celsius
calcd	calculated
cm^{-1}	reciprocal centimeter
COSY	correlation spectroscopy
δ	chemical shift
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
ddt	doublet of doublets of doublets
dt	doublet of triplets
DMF	dimethylformamide
E	entgegen
EIMS	electron impact mass spectrometry
EtOAc	ethyl acetate
EtOH	ethanol
equiv	equivalent
g	gram
h	hour
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethyl phosphoric triamide

HREIMS	high resolution electron impact mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
m	multiplet
M	moles per liter
M^+	molecular ion
Me	methyl
mg	milligram
MHz	megahertz
ml	milliliter
mmol	millimole
MOM	methoxymethyl
mp	melting point
MS	mass spectrum
m/z	mass/charge
n	normal
n-BuLi	n-butyllithium
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
OMe	methoxide
Ph	phenyl
q	quartet
qd	quartet of doublets

quint	quintet
s	singlet
sec	secondary
t	triplet
TEA	triethylamine
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethysilyl chloride
TIPSCl	triisopropylsilyl chloride
v/v	volume/volume
Z	zusammen

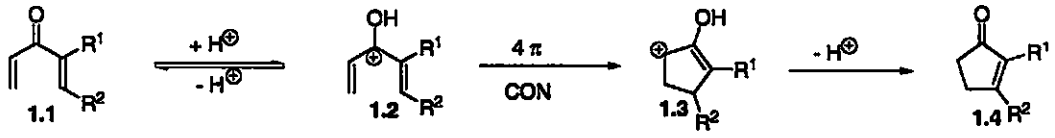
PART I:

INTERRUPTED NAZAROV CYCLIZATION ON SILICA GEL

1. Introduction

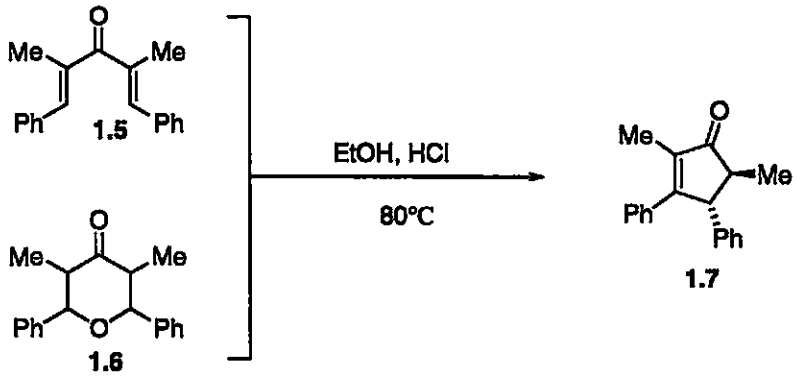
1.1. The Nazarov Reaction

The Nazarov cyclization is a pericyclic reaction belonging to the class of electrocyclizations, specifically it is a 4π conrotatory electrocyclic closure of a 3-hydroxypentadienylic cation such as **1.2** (scheme 1).[1] Cations such as **1.2** are obtained reversibly by treatment of divinyl ketones **1.1** with strong protic acids. The reaction is



Scheme 1

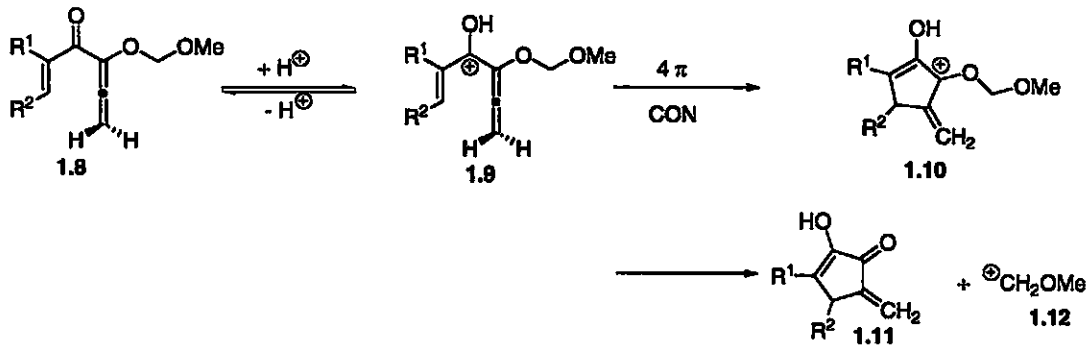
terminated by proton loss from the intermediate **1.3** resulting in cyclopentenone **1.4**. The more highly substituted enone is the reaction product, corresponding to a Saytzeff elimination process. A broader definition of the Nazarov cyclization includes a wide variety of precursors that under specific reaction conditions also produce 2-cyclopentenones via divinyl ketones or their functional equivalents. A case in point is the formation of cyclopentenone **1.7** by treatment of either divinyl ketone **1.5** or tetrahydropyrone **1.6** with ethanolic hydrochloric acid (scheme 2).[2] It is the structural



Scheme 2

variety of potential precursors that lends the versatility to the Nazarov cyclization. Several variants of this reaction have been reported in the literature[3] and have found applications in synthesis endeavors. For example synthesis of simple cyclopentanoids such as cis-jasmone,[4] prostaglandin analogs[5, 6, 7] and (±)- valleranal[8] feature different versions of the Nazarov cyclization as key steps. The reaction was also used in the synthesis of polyquinane natural products such as (±)-hirsutine,[9] (±)-modhephene,[10, 11] (±)-silphinene,[12, 13] (±)-pentalenene,[14] (±)$\Delta^{9(12)}$-capnellene,[15] and (±)-cedrene.[16]

The Nazarov cyclization which utilizes allenyl ketones (scheme **3**) has been an area of research interest in our group. In this reaction, allenyl ketone **1.8** is the precursor of the pentadienyl cation **1.9** which undergoes the thermally allowed 4π conrotation to **1.10**.



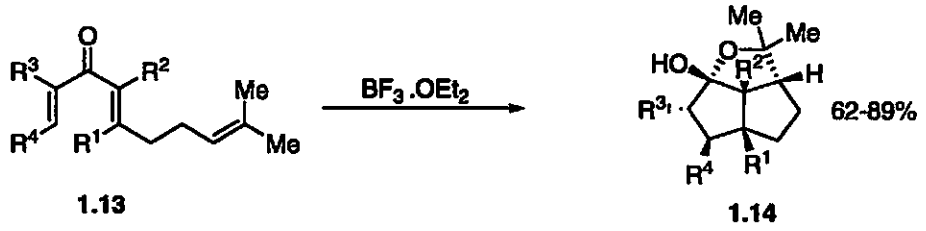
Scheme 3

Termination of the reaction is by loss of the methoxymethyl cation **1.12** from **1.10** to give a cross conjugated cyclopentenone **1.11**. Allenyl ketones **1.8** have never been isolated as intermediates but have in all cases undergone cyclization to **1.11** upon acidic workup.The beauty of the process is the mildness of the reaction conditions for cyclization.[17] Several variants of the reaction have been described[18a] and the methodology has since been applied in a number of syntheses of simple naturally

occurring cyclopentanoids.[19] The asymmetric version of this reaction employs sugar and camphor chiral auxiliaries also developed in our group.[20] This enantioselective version of the cyclopentannelation reaction was used in the first total synthesis of natural (22R,23R)-roseophilin.[21]

1.2. Interrupted Nazarov Reactions

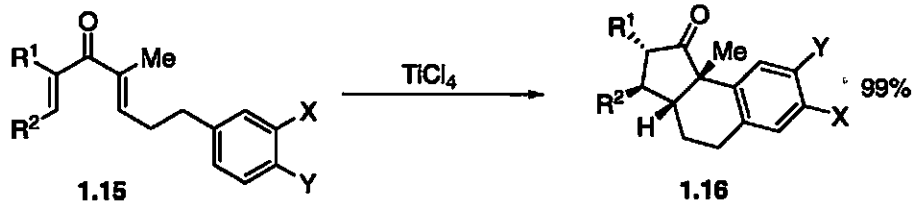
West and co-workers have reported many examples of the interrupted Nazarov reaction. They demonstrated that the oxyallyl cation formed during the Nazarov cyclization of cross conjugated dienones can be intercepted intramolecularly with olefins, dienes or arenes.[22] One example involved trapping the oxyallyl intermediate via cationic cyclization onto pendant olefins.[23] This process (scheme 4), promoted by $BF_3.OEt_2$,



1.13 1.14

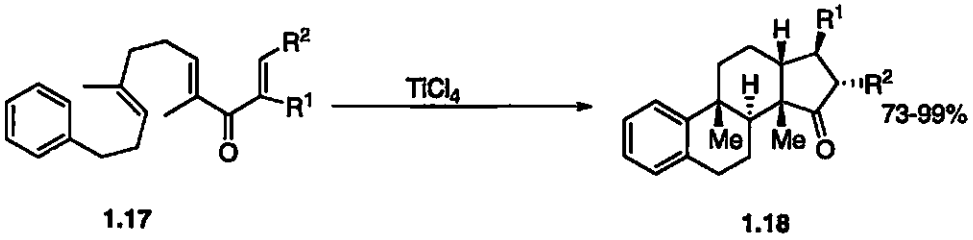
Scheme 4

efficiently converted acyclic, achiral dienones into polycyclic hemiketal products with complete diastereoselectivity when the dienone and the alkene trap were linked by a two carbon tether, and the dienone was substituted at both α-positions. The same methodology was applied to the formation of hydrindans and tricyclo[4.3.0.0 [24]] nonanes via trapping of the Nazarov oxyallyl intermediate. Another example of the intramolecular interrupted Nazarov reaction involved the trapping of the oxyallyl intermediate with pendant aryl groups. West showed that divinyl ketones bearing arylethyl side chains



Scheme 5

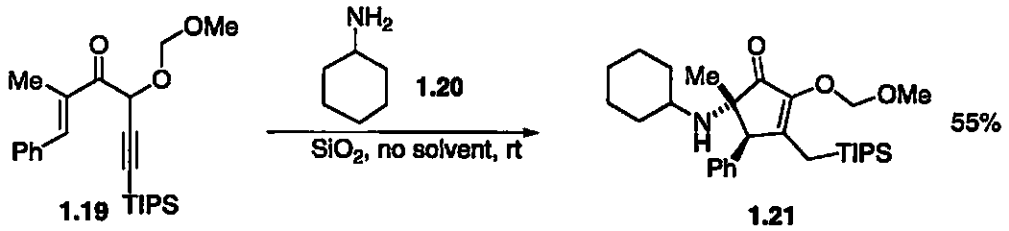
(scheme 5) underwent domino cyclization to give the benzohydrindenones in near quantitave yields and with complete diastereoselectivity when they were treated with $TiCl_4$.[25] This methodology was then used in a Nazarov- initiated diastereoselective



Scheme 6

cascade polycyclization of aryltrienones providing tetra- or pentacyclic skeletons (scheme 6).[26] West and co-workers further revealed that the oxyallyl cation can also participate in intramolecular cycloaddition reactions with pendant dienes on the side chain[27] and intermolecularly with simple dienes.[28] Other examples of the interrupted Nazarov reaction were reported by Langer[29] and Nair.[30]

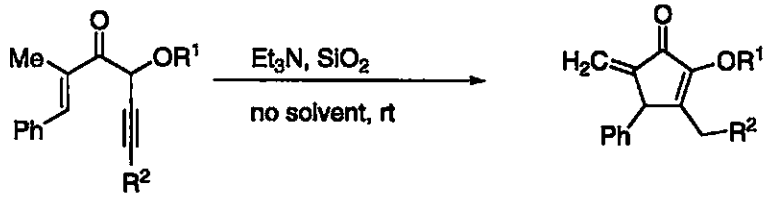
West's impressive *domino* Nazarov cyclization represents the first Nazarov reaction that is terminated by C-C bond formation.[23] My work, as presented in this thesis, describes the first example of a solid phase Nazarov cyclization reaction that is terminated by C-N bond formation (scheme 7). Exposure of enone **1.19** to activated dry silica gel that had been thoroughly mixed with 1.2 equiv cyclohexylamine gave an aminocyclopentenone **1.21**. The reaction of **1.22** and **1.23** with triethylamine under



1.19 1.21

Scheme 7

the same conditions led to cross-conjugated cyclopentenones **1.24** and **1.25** (scheme **8**).



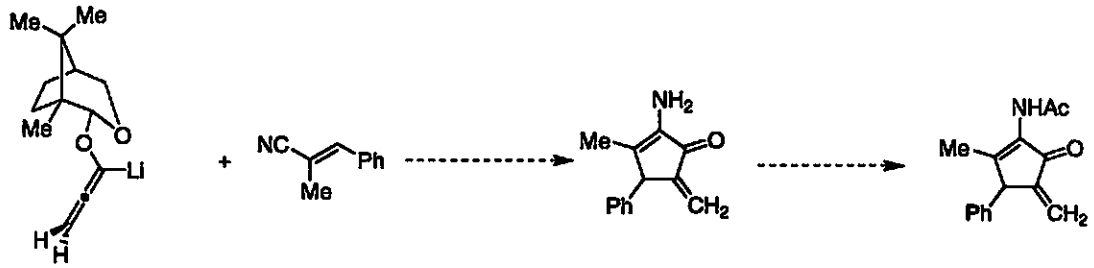
1.22 R^1 = Me, R^2 = TIPS
1.23 R^1 = MOM, R^2 = TMS

1.24 R^1 = Me, R^2 = TIPS 63 %
1.25 R^1 = MOM, R^2 = H 68%

Scheme 8

1.3. Discovery

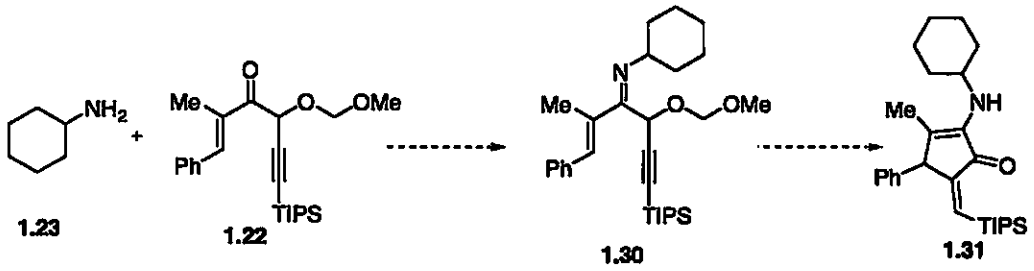
Our earlier attempts to carry out the asymmetric version of the imino Nazarov reaction[18b] proved unsuccessful when addition of lithio-anion **1.26** to



1.26 **1.27** **1.28** **1.29**

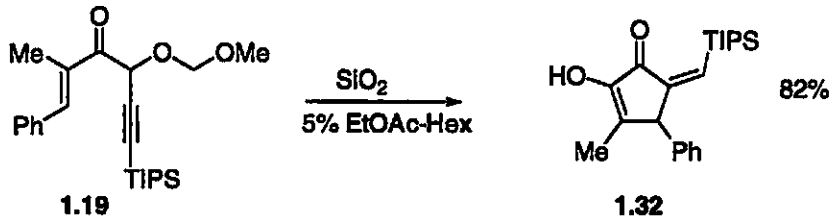
Scheme 9

α-methylcinnamonitrile **1.27** (scheme **9**) failed. This result prompted us to try an alternative route shown in scheme **10**. This choice was made on the basis of earlier work that had been done in our group.[18c] Propargyl ketone **1.19** had been introduced



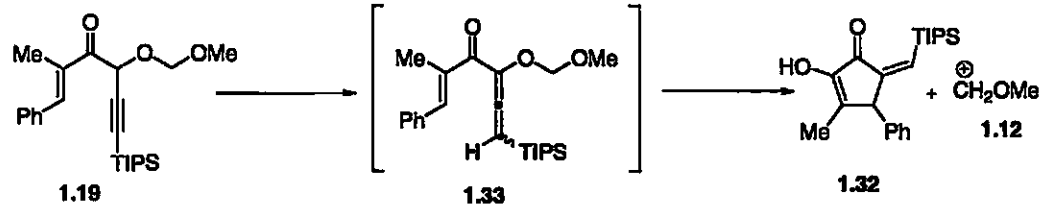
Scheme 10

to a chromatography column packed with 200-400 mesh silica gel in 5% ethyl acetate and hexanes and allowed to stand for 12 hours (scheme **11**). Elution of the column



Scheme 11

had providedcyclopentenone **1.32** in 82% yield. Apparently isomerization of **1.19** to allenyl ketone **1.33** had taken place on the column. Cyclization then followed to give **1.32**. The reaction is terminated by loss of the methoxymethyl cation **1.12** (scheme **12**). We hoped that aminocyclopentenone **1.31** could be obtained from imine **1.30**



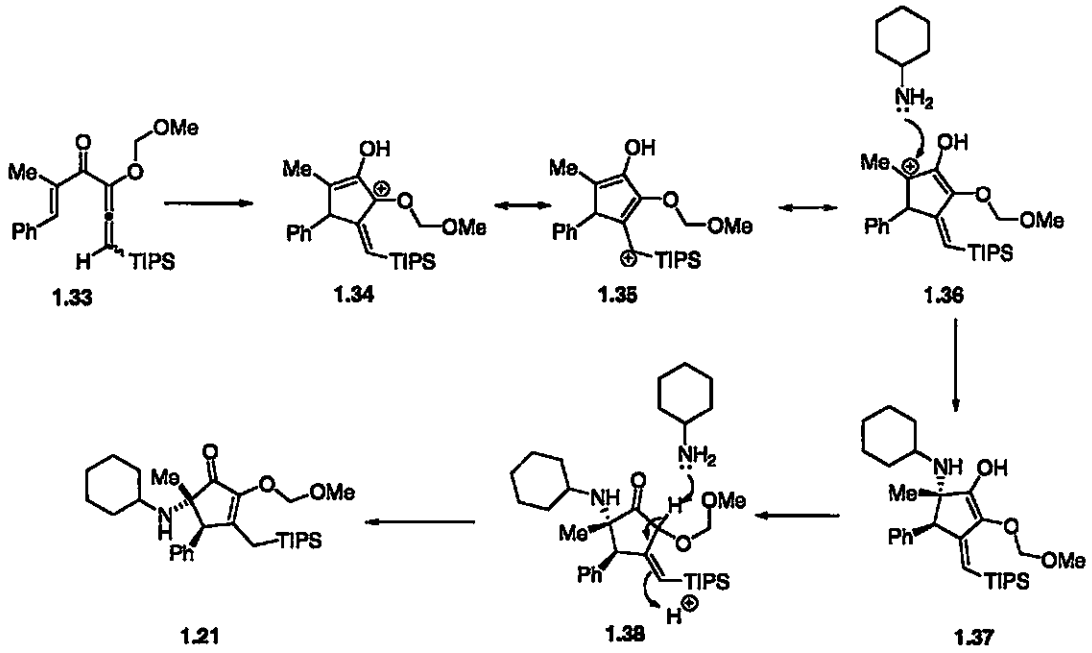
Scheme 12

in the same way.

Several solution phase reactions for obtaining imines are described in literature,[31] but the solid phase imine synthesis on dry activated silica gel described by Ranu and co-workers[32] became an attractive route for us because it offered the possibility of accomplishing our goal in one pot. We envisaged that the end product would be an aminocyclopentenone **1.31** (scheme **10**) when cyclohexylamine was used as the nucleophile. Exposure of enone **1.19** to activated dry silica gel that had been thoroughly mixed with cyclohexylamine did not lead to aminocyclopentenone **1.31** as expected. Instead **1.21** (scheme **7**) was determined to be the observed product after characterization using NMR methods (COSY, HMBC, HSQC, ^{1}H NMR and ^{13}C NMR).

1.4. Mechanism

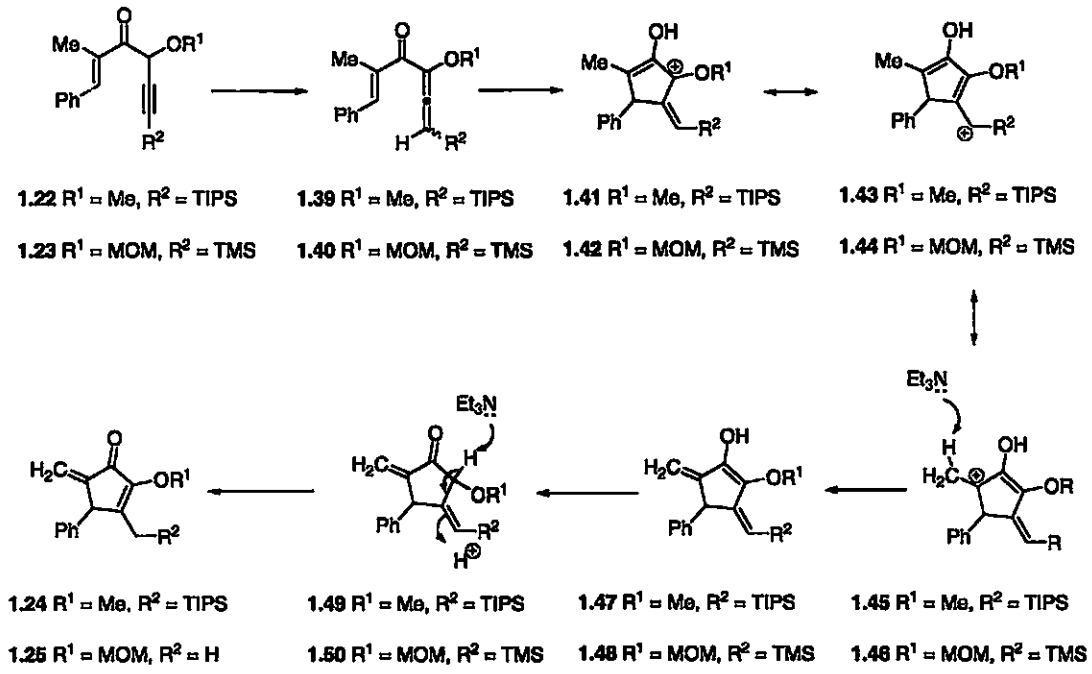
To understand the formation of the products in scheme **7**, it is necessary to show a mechanistic scheme for the reaction. Our proposed mechanism for this process is shown in scheme **13**. It is apparent that the deprotonation at the α-position in **1.19** by the cyclohexylamine was faster than the nucleophilic addition to the carbonyl carbon atom. This prototropic rearrangement of **1.19** to the allenyl ketone **1.33** (scheme **13**) initiated the sequence of reactions that led to the observed product. The allenyl ketone **1.33** thus formed is short lived. In the presence of the weakly acidic silica gel it rapidly undergoes the thermally allowed conrotatory ring closure to the cyclic cation that can be represented by the resonance structures shown in scheme **13**. It is noteworthy here to mention that resonance structure **1.35** (scheme **13**), being a secondary carbocation, offers little or no contribution to the overall stabilization energy. Carbocation formation α to silyl groups



Scheme 13

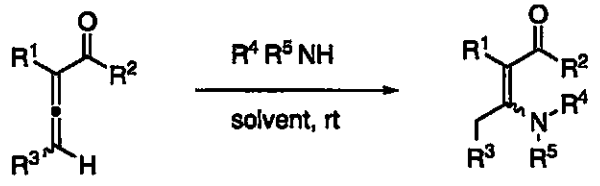
is disfavored, although not unknown,[33] whereas carbocation formation β to the silicon is favored (the β-effect). The reaction can thus be terminated as shown in scheme **13**. Cyclohexylamine, being a nucleophilic primary amine, intercepts cation **1.36** to give enol **1.37** which rapidly tautomerizes to ketone **1.38**. Due to the presence of excess base alkene migration takes place to give the observed product.

Likewise, deprotonation at the α-position in enones **1.22** and **1.23** (scheme **14**) leads to allenyl ketones **1.39** and **1.40** which rapidly undergo the thermally allowed 4π conrotatory ring closure to the cationic intermediates represented by resonance structures shown in scheme **14**. In the presence of triethylamine, a non-nucleophilic tertiary aminethe reaction is terminated by proton loss to enols **1.47** and **1.48** which tautomerize to ketones **1.49** and **1.50** under the same reaction conditions. Alkene migration produces **1.24** in the case of **1.49** whereas olefin migration is followed by proteodesilylation to give **1.25** in the case of **1.50**.



Scheme 14

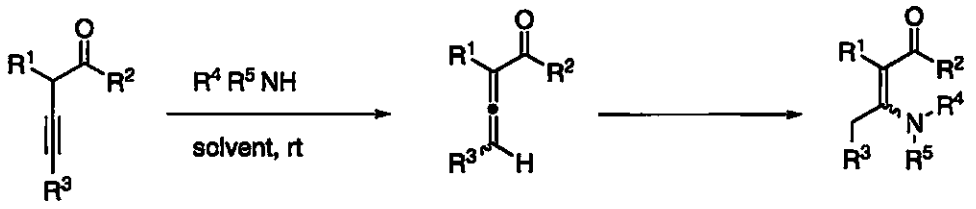
Vereshchagin and co-workers have studied the behavior of α-allenic ketones and β-acetylenic ketones in nucleophilic addition reactions with amines.[34] During these investigations, they discovered that addition of both aromatic and aliphatic primary and secondary amines to α-allenic ketones takes place with the formation of aminovinyl ketones (scheme 15). In the case of β-acetylenic ketones similar aminovinyl ketones



1.51 1.52

Scheme 15

were obtained. This was only possible if the amines isomerized the β-acetylenic ketones to allenic ketones (scheme **16**). Nucleophilic addition then followed to give the observed aminovinyl ketones. One can therefore anticipate a similar process in



1.53 **1.54** **1.55**

Scheme 16

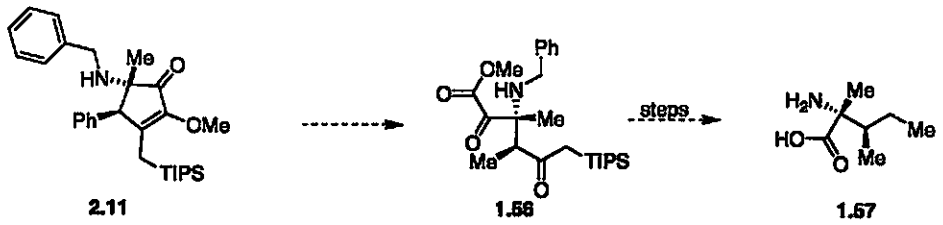
reactions of aliphatic and aromatic primary and secondary amines with **1.19, 1.22** or **1.23**. Aminovinyl ketones were not observed during the Nazarov cyclization process as shown by TLC and ^{1}H NMR analysis of crude products. The intermediate allenyl ketones undergo spontaneous cyclization in the presence of the weakly acidic silica gel.

1.5. α,α-Disubstituted α-Amino Acids

The aminocyclopentannelation reaction outlined in scheme **7** offers an attractive route to α,α-disubstituted amino acids bearing a variety of groups at the α-position. α,α-Disubstituted α-amino acids are nonproteinogenic modified amino acids, in which the hydrogen atom at the α-position is replaced by an alkyl substituent.[35] The substituents in disubstituted amino acids severely restrict conformational freedom of peptides containing such residues. In this way the amino acids are used as a probe to investigate the biologically active conformation,[36] to study the secondary structure of peptides,[37] and to search the origin of chirality.[38] Moreover, α,α-disubstituted α-amino acids appear to be powerful enzyme inhibitors, and thus promising drug candidates in

the field of medicinal chemistry.[39] The lack of availability of these compounds from natural sources necessitates the development of efficient methods for their synthesis.[40]

Our method for the preparation of these compounds would involve cleavage of aminocyclopentenone **2.11** by ozonolysis to give **1.56** (scheme **17**). Further functionalizations would ultimatey lead to the amino acid **1.57**.



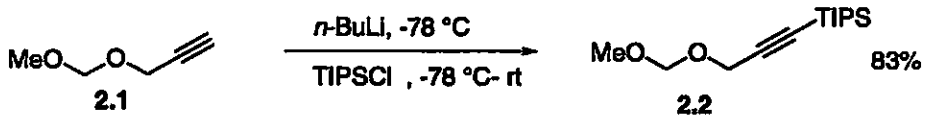
Scheme 17

As an extension of this work, the aminocyclopentannelation reaction can also be applied to the synthesis of enantiomerically pure α,α-disubstituted α-amino acids by using the camphor, or sugar derived chiral auxiliaries developed in our group.

2. Results and Discussion

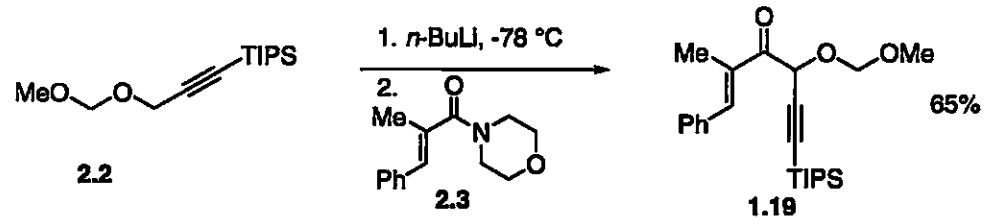
2.1. Synthesis

The starting point for the interrupted Nazarov reaction was triisopropyl(3-(methoxymethylmethoxy)prop-1-ynyl)silane **2.2,** which was prepared by deprotonating 3-(methoxymethoxy)prop-1-yne **2.1** with *n*-BuLi followed by quenching with triisopropyl chloride (scheme **18**). Under these conditions **2.2** was obtained in 83% yield. The MOM ether **2.1** was prepared according to a method that



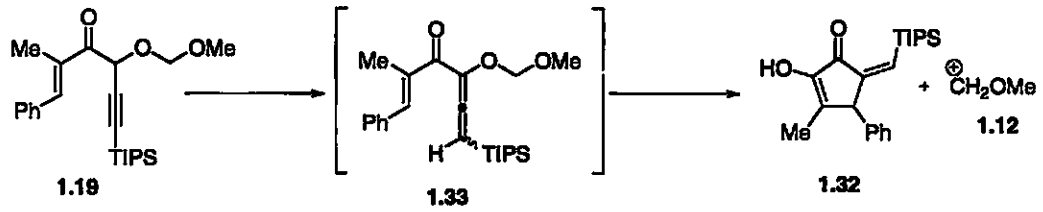
Scheme 18

has been described in the literature.[41] Treatment of **2.2** with 1 equiv of *n*-BuLi and addition of the anion generated to enamide **2.3** (scheme **19**) gave enone **1.22** in 65% yield after column chromatography on silica gel. Loss of **1.19** was observed during



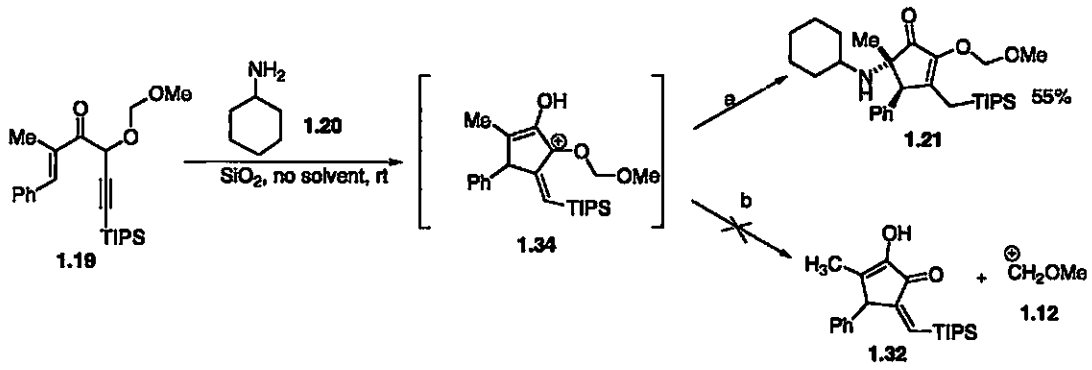
Scheme 12

silica gel chromatography. Under these conditions **1.19** isomerizes to the allenyl ketone **1.33** which then cyclizes to cyclopentenone **1.32** (scheme **12**).[18c] Loss of the methoxymethyl cation leads to the observed product. To avoid this loss, the crude product was used during the cyclization process. Column chromatography on neutral alumina led to the complete decomposition of **1.19**.



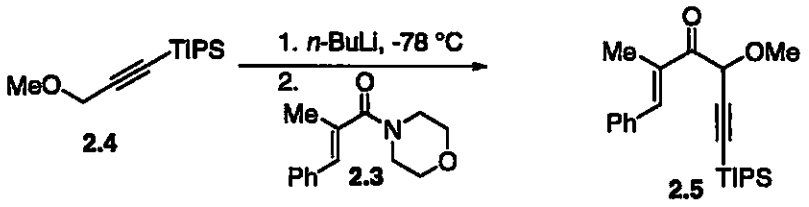
Scheme 12

A number of different reaction conditions for the interrupted Nazarov cyclization were examined and the use of 1.2 equiv of the amine and 16 equiv of silica gel gave the best results. Exposure of enone **1.19** to dry activated silica gel that had been thoroughly mixed with cyclohexylamine provided aminocyclopentenone



Scheme 20

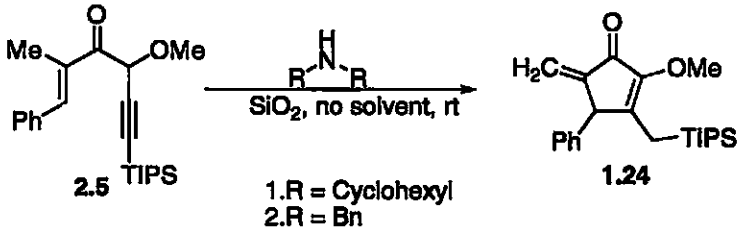
1.21 in 55% yield under these conditions (scheme **20**). To avoid possible competition reactions between termination by amine addition (route **a**) and loss of the methoxymethyl cation (route **b**, although the product from this reaction pathway was not observed under these conditions) we decided to use enone **2.5** (scheme **21**) for all



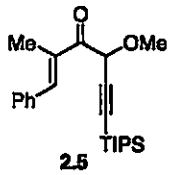
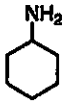
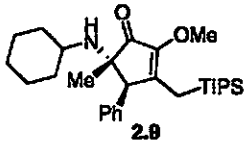
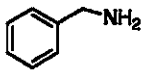
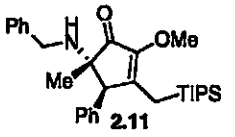
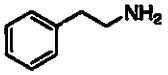
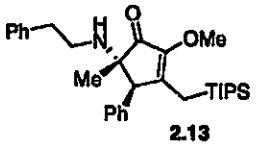
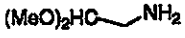
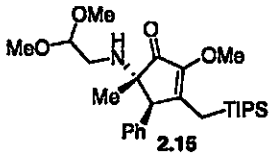
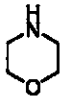
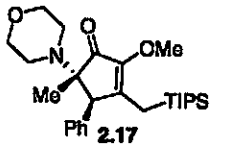
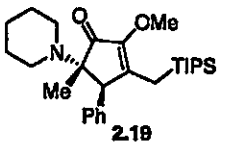
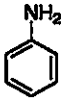
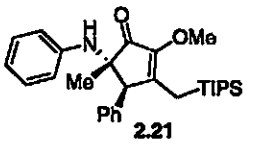
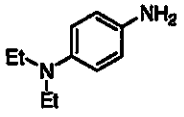
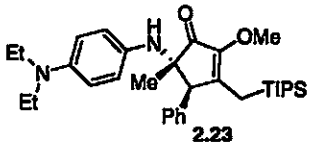
Scheme 21

the reactions. The ether **2.4** is derived from the commercially available methyl-propargyl ether. It was obtained by using the same procedure outlined in scheme **18**.

In order to determine the scope of the interrupted Nazarov reaction a number of different amines were screened with ketone **2.5**. The reaction with liquid aliphatic primary and less bulky secondary amines in the absence of solvent in all cases led to good yields of products. The results for the aminocyclopentannelation reaction are shown in table **1**. Product stereochemistry in all cases is governed by approach of the amine nucleophile from the least hindered face of the intermediate cation,[42] thus forming aminocyclopentenones with complete diastereoselectivity. The mildness of reaction conditions for the cyclization made it possible to employ 2,2-dimethoxyethylamine (Table **1**, entries **4**, **12** and **17**). No hydrolytic cleavage products of the acetal were detected under these conditions. The reaction with aromatic amines (aniline and 4-diethyl aminoaniline) gave rise to multiple products, including the anticipated aminocyclopentenones in low yields (table **1**, entries **7** and **8**). The low yields can be attributed to competition between N-alkylation vs C-alkylation (i.e Friedel-Crafts alkylation). The use of sterically hindered secondary amines such as dicyclohexylamine led exclusively to termination by proton loss (scheme **22**). Dibenzylamine also gave the same product. We then reasoned that tertiary amines

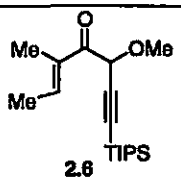
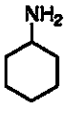
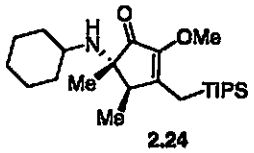
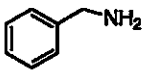
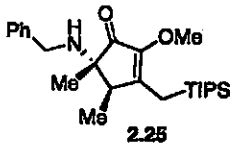
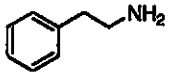
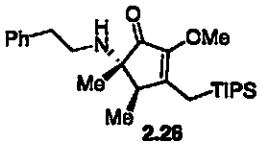
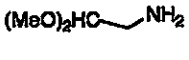
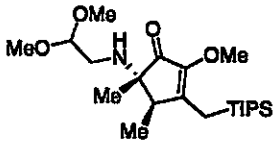
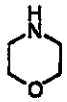
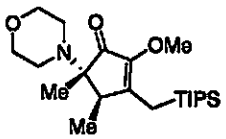
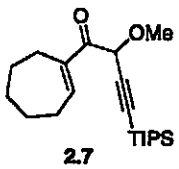
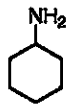
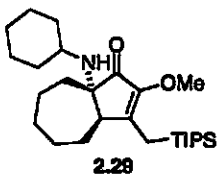
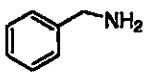
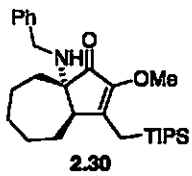


Scheme 22

Entry	Enone	Amine	Aminocyclopentenone	Yield[a]
1	 **2.5**	 **1.20**	 **2.9**	65%
2		 **2.10**	 **2.11**	60%
3		 **2.12**	 **2.13**	63%
4		 **2.14**	 **2.15**	67%
5		 **2.16**	 **2.17**	70%
6		 **2.18**	 **2.19**	58%
7		 **2.20**	 **2.21**	25%
8		 **2.22**	 **2.23**	20%

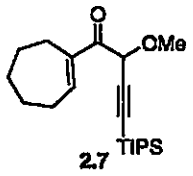
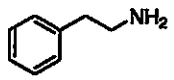
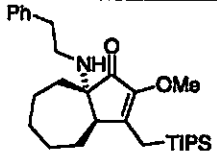
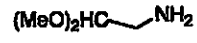
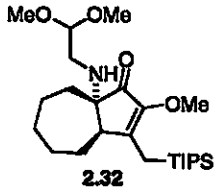
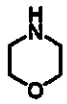
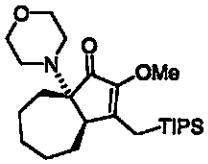
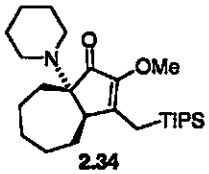
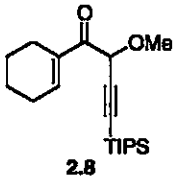
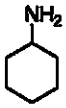
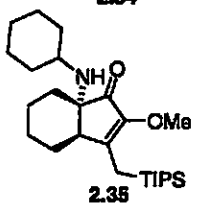
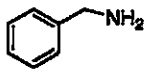
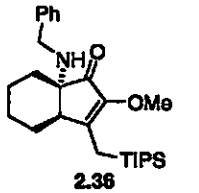
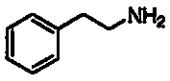
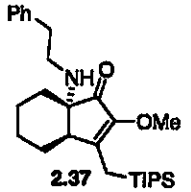
[a]Yields of aminocyclopentenones are for two steps, addition of **2.2** to enamide and cyclization.

Table 1. α-Aminocyclopentenones

Entry	Enone	Amine	Aminocyclopentenone	Yield[a]
9	 **2.6**	 **1.20**	 **2.24**	63%
10		 **2.10**	 **2.25**	64%
11		 **2.12**	 **2.26**	55%
12		 **2.14**	 **2.27**	51%
13		 **2.15**	 **2.28**	66%
14	 **2.7**	 **1.20**	 **2.29**	68%[b]
15		 **2.10**	 **2.30**	75%[c]

[b]13%,[c]4% of **2.39** was obtained.

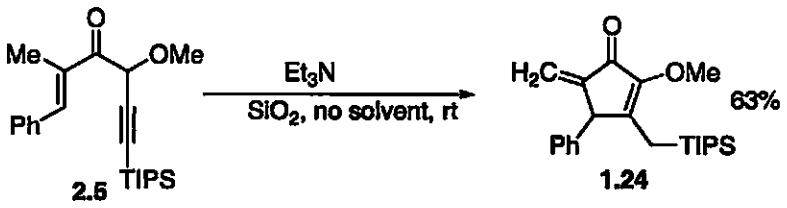
Table 1. (Continued) α-Aminocyclopentenones

Entry	Enone	Amine	Aminocyclopentenone	Yield[a]
16	 **2.7**	 **2.12**	 **2.31**	71%[d]
17		 **2.14**	 **2.32**	60%[e]
18		 **2.16**	 **2.33**	61%[f]
19		 **2.18**	 **2.34**	59%[g]
20	 **2.8**	 **1.20**	 **2.35**	59%[h]
21		 **2.10**	 **2.36**	60%[h]
22		 **2.12**	 **2.37**	64%[h]

[d]4%, [e]10%, [f]20%, [g]51% of **2.39** was obtained. [h]Elimination product was formed in varying amounts in all reactions of **2.8** but was not isolated.

Table 1. (Continued) α-Aminocyclopentenones

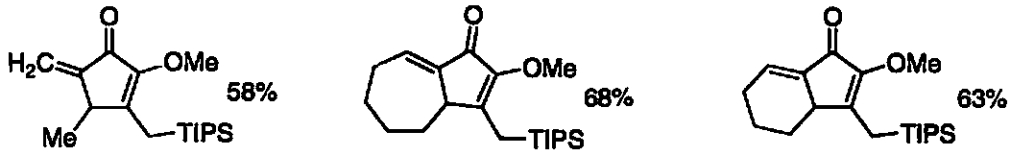
would also give the elimination product exclusively. This proved to be the case with triethylamine (scheme **23**). The reaction, however did not work when Hűnig's base was used. The process leading to allenyl ketone **1.33** (scheme **12**) seems to be slow with this amine.



2.5 **1.24**

Scheme 23

A few examples of this process were tried with enones **2.6**, **2.7** and **2.8** and the results are shown in Figure 1. The aminocyclopentannelation reaction seems to be



2.38 **2.39** **2.40**

Figure 1. Cross-conjugated cyclopentenones

limited to liquid amines. The use of solid amines did not give the desired aminocyclopentenones as shown by TLC and ^{1}H NMR of the crude products. It was also necessary to quench the reaction outlined in schemes **19** and **21** with 1 M HCl to get rid of all the morpholine, an amine byproduct of the reaction, which if carried over would participate in the aminocyclopentannelation process and also subsequently lead to decomposition of **1.19** or **2.5** upon storage. To examine the generality of the aminocyclopentannelation process we carried out the reactions using different enones.

Enones **2.6**, **2.7**, **2.8**, (table 1) are derived from morpholino amides **2.41**, **2.42** and **2.43** respectively (Figure 2). Enamides **2.3**

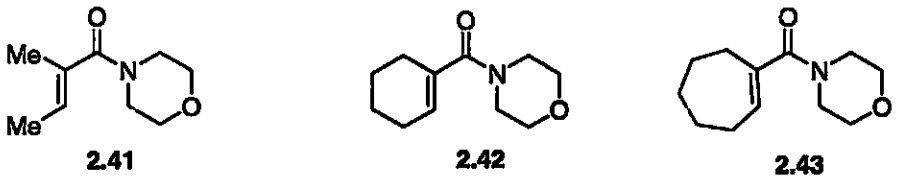
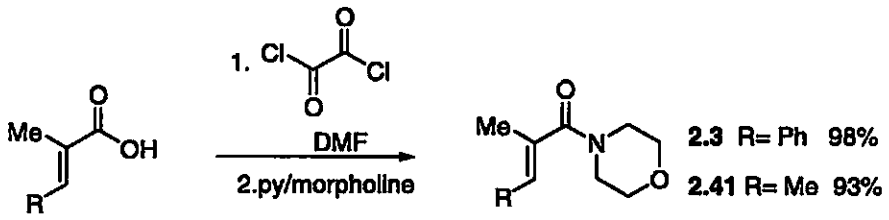


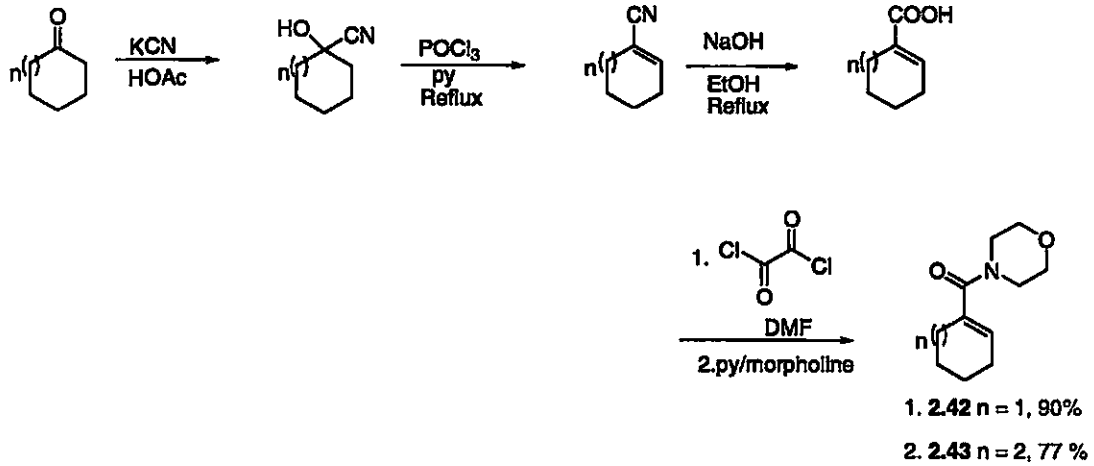
Figure 2. Morpholino amides

and **2.41** were prepared from the commercially available carboxylic acids in two steps (scheme **24**). Exposure to oxalyl chloride and catalytic DMF led to acid chlorides that



Scheme 24

were treated with morpholine and pyridine to give the amides in quantitative yields. Amides **2.42** and **2.43** were prepared from cyclohexanone and cycloheptanone, respectively (scheme **25**).

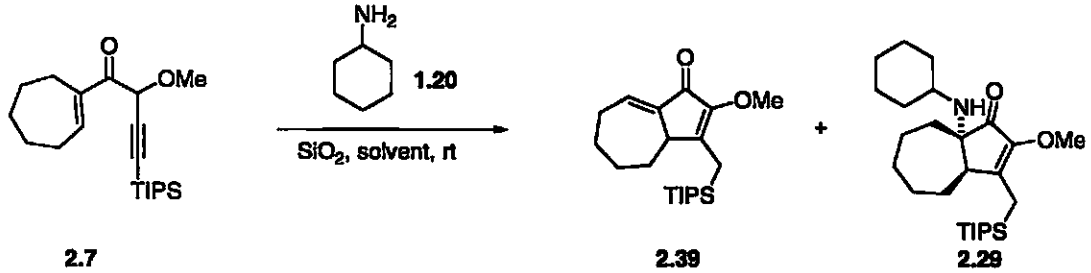


Scheme 25

The ketones were first converted to the corresponding cyanohydrins with potassium cyanide and acetic acid and then dehydrated with phosphorus oxychloride according to a procedure that has been published in the literature.[43] The resulting α,β-unsaturated nitriles were hydrolyzed to the corresponding carboxylic acids by exposure to aqueous ethanolic sodium hydroxide at reflux in the presence of catalytic tetra-*n*-butylammonium hydrogen sulfate. The carboxylic acids were converted to enamides in the same way as **2.3** and **2.41**.

The reaction of enones **2.7** and **2.8** revealed to us yet another important aspect of the reaction. Competition between addition and elimination processes was observed in their reactions with nucleophilic primary and secondary amines (Table **1** entries **14-22**). The amount of the elimination product increased in reactions with secondary amines. The elimination products were not observed in reactions of **2.5** and **2.6** with primary and secondary amines. This result clearly indicates the ease with which elimination occurs with branching at the α-enone substituent. Elimination is also likely to be favored by increasing the steric requirement of the α-substituent of the enone.

After the success of the solid phase reaction we then went on to investigate the outcome of the reaction in the presence of solvent. Thus enone **2.7** was treated with



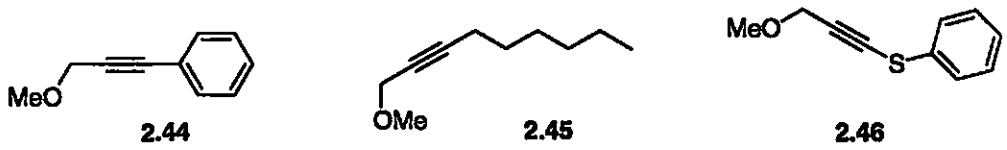
Scheme 26

activated silica gel in the presence of solvent (scheme **26**). Aminocyclopentenone **2.29** and cyclopentenone **2.39** were obtained in 55% and 35% yield, respectively, when reactions were carried out in dichloromethane. Changing the solvent to THF gave **2.29** and **2.39** in 48% and 25% respectively. It appears that proton elimination from the intermediate cation occurs more readily in the presence of solvent. This led to the diminished yields of **2.29**.

2.2. Conclusions

We have demonstrated the first example of an interrupted Nazarov cyclization that is terminated by N-alkylation. The aminocyclopentannelation reaction is fairly general and provides structurally diverse α-aminocyclopentenones in good yields. No methodology exists that allows for such a rapid assembly of complex aminocyclopentenones. The reaction also proceeds under very mild conditions. Synthesis of the aminocyclopentenones by any other means would be challenging and require several discrete steps. The other beauty of this reaction is that it can be carried out in the absence of solvent. Minimization of organic solvents during synthesis is encouraged for reasons of economy as well as to reduce any adverse environmental impact. The α- aminocyclopentannelation reaction therefore conforms to the principles of *green chemistry*. Mechanistically, it is surprising that one can trap a highly reactive intermediate cation such as **1.36** in a bimolecular nucleophilic process in the absence of solvent. It therefore seems likely that the close proximity of the amine and propargyl ketone that is required in order for isomerization to take place ensures the success of the nucleophilic addition because the reactive intermediate is generated only in the proximity of the amine.[44] Another puzzling result is the formation of cyclopentenones **1.24** and **1.25** from **1.22** and **1.23** respectively (scheme **8**). In this reaction it is possible to get competition between termination through the elimination process or by loss of the methoxymethyl cation **1.12**, however the product from the latter reaction pathway was not observed in both cases. This therefore suggests that the elimination reaction occurs much faster than loss of the methoxymethyl cation. The full scope of the reaction, however, remains to be

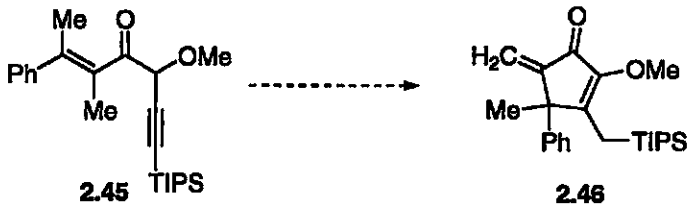
explored. A number of parameters are yet to be varied for the α-aminocyclopentannelation process. For example the use of substituted propargyl ethers shown in Fugure **3** is yet to be investigated. The fate of the elimination process



2.44 **2.45** **2.46**

Figure 3: Propargyl ethers

in the presence of α-aryl substituents and sterically hindered α-substituents is yet to be investigated. The failure of the reaction with solid amines might have been due to solubility problems. Carrying out the reaction in solution might solve this problem. Another interesting feature worth probing is the intramolecular version of the amine trapping reaction. The execution of the intramolecular reaction poses a great challenge since the intermediate enone is not stable in the presence of a free base. Whilst we have succeeded in intercepting the Nazarov intermediate with amines, it remains to be shown that the same can be done with carbon nucleophiles. Such nucleophiles could include silyl enol ethers, allyl silanes and activated aromatic compounds. The success of such a process might be increased by utilizing enamides that have α-aryl substituents, as competition with the elimination process is unlikely in these substrates. The methodology has potential use in the synthesis of natural products that have a stereocenter at the β-position and an α-quaternary carbon bearing a nitrogen atom. The elimination process (scheme **23**) presents another way of generating β-quaternary carbon centers in cyclopentenones (scheme **27**) if the reaction outlined in scheme **21** is carried out using a tetrasubstituted enamide. Such a process if carried out asymmetrically would furnish chiral cyclopentenones bearing a β-quaternary

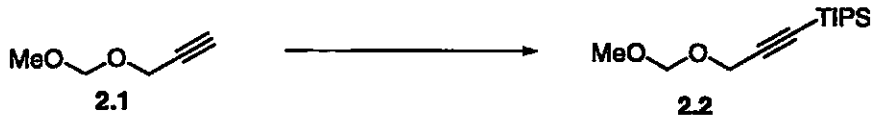


Scheme 27

carbon atom. The synthesis of quaternary centers is a great challenge when all the substituents are carbon atoms.[45] The use of the methodology in this endeavor is yet to investigated. Research in this direction is currently underway.

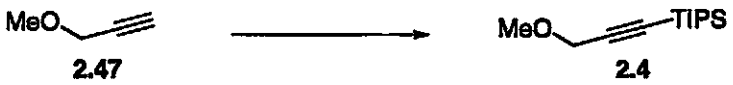
3. Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Mercury Plus 300 operating at 300 MHz (^{1}H) or 75 MHz (^{13}C) or on a Varian Unity Inova 500 operating at 500 MHz (^{1}H) or 126 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e 7.26/77.0 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded on a Perkin Elmer IR 1430 spectrometer. Electron impact mass spectra were recorded on a VG-70SE mass spectrometer. Thin layer chromatography (TLC) was performed on Sigma-Aldrich TLC plates, 250 μm, particle size 5-17 μm, pore size 60 Å. Flash column chromatography was performed on Natland International Corporation silica gel, 200-400 mesh and Sorbent technologies, premium R_f, 60 Å, 40-75 μm. Purity and homogeneity of all materials was determined from TLC, ^{1}H NMR, and ^{13}C NMR. Anhydrous THF was taken from a GlassContour (www.glasscontour.com) solvent purification system. The silica gel was activated by heating under vacuum at 160 °C for 16 h. The amines were distilled and stored over potassium hydroxide before use. All moisture sensitive reactions were performed under a static atmosphere of nitrogen or argon atmosphere in oven dried or flame dried glassware.



2.1 2.2

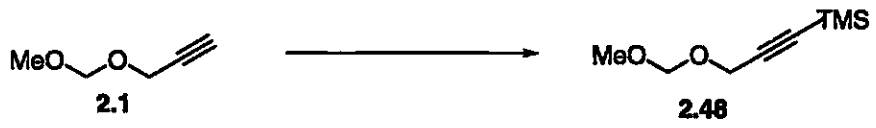
To a solution of 3-(methoxymethoxy)prop-1-yne **2.1** (1.5 g, 15 mmol) in THF (15 ml) at -78 °C was added *n*-BuLi (6 ml, 2.5 M, 15 mmol). The reaction mixture was stirred at this temperature for 30 min and then neat chlorotriisopropylsilane (3.5 ml, 16.4 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 12 hours. The reaction was diluted with water and ether and the aqueous layer was extracted with ether (3X). The combined organic extracts were washed with brine (1X), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography on silica gel (2% EtOAc in hexanes) gave triisopropyl(3-(methoxymethylmethoxy)prop-1-ynyl)silane **2.2** (3.2 g, 83% yield) as a colorless oil: R_f= 0.26 (2% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.74 (s, 2 H), 4.25 (s, 2 H), 3.38 (s, 3 H), 1.06 (s, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.0, 94.5, 87.6, 55.7, 54.9, 18.7, 11.3; IR (film) 2980, 2100, 1490 1340 cm^{-1}; EIMS *m/z* (%) 183 (100), 155(43) 141 (31); HREIMS calcd for $C_{14}H_{28}O_2Si$ 256.1859, found 256.1887.



2.47 2.4

To a solution of methyl-propargyl ether **2.47** (1.05 g, 15 mmol) in THF (15 ml) at -78 °C was added n-BuLi (6 ml, 2.5 M, 15 mmol). The reaction mixture was stirred at this temperature for 30 min and then neat chlorotriisopropylsilane (3.5 ml, 16.4 mmol) was added dropwise. The reaction mixture was then allowed to warm up to room temperature and stirred at this temperature for 12 hours. The reaction was then diluted with water and ether and the aqueous layer was extracted with ether (3X).

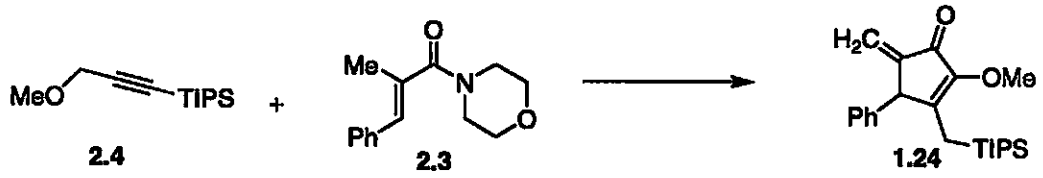
The combined organic extracts were washed with brine (1X), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography on silica gel (1.5% EtOAc in hexanes) gave triisopropyl(3-methoxyprop-1-ynyl)silane **2.4** (2.80 g, 85% yield) as a colorless oil: R_f = 0.26 (1.5% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 2 H), 3.10 (s, 3 H), 0.78 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.1, 87.6, 60.4, 57.2, 18.5, 11.1; IR (film) 2983, 2120, 1495 1350 cm^{-1}; EIMS *m/z* (%) 226 (M^+, 10) 183 (100), 155(21); HREIMS calcd for $C_{13}H_{26}O_2Si$ 226.1753, found 226.1777.



2.1 **2.48**

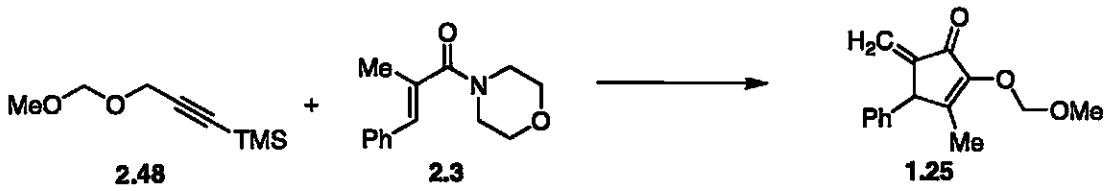
To a solution of 3-(methoxymethoxy)prop-1-yne **2.1** (1.5g, 15 mmol) in THF (15 ml) at -78 °C was added *n*-BuLi (6 ml, 2.5 M, 15 mmol). The reaction mixture was stirred at this temperature for 30 min and then a solution of chlorotriisopropylsilane (2.1 ml, 16.4 mmol) in triethyl amine was added dropwise (the TMSCl (3 ml) was mixed with TEA (3 ml) and centrifuged to separate the triethyl amine hydrochloride salt). The reaction mixture was allowed to warm to room temperature and stirred for 4 hours. The reaction was diluted with water and ether and the aqueous layer was extracted with ether (3X). The combined organic extracts were washed with brine (1X), dried over $MgSO_4$ and concentrated. Purification by flash column chromatography on silica gel (2% EtOAc in hexanes) gave triisopropyl(3-(methoxymethylmethoxy)prop-1-ynyl)silane **2.48** (2.3 g, 88% yield) as a colorless oil: R_f = 0.28 (2% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.66 (s, 2 H), 4.16 (s, 2 H), 3.33 (s, 3 H), 0.13 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.9, 94.7, 91.1, 55.4, 54.8, 0.3; IR (film) 2985, 2128, 1495 1350 cm^{-1}; EIMS *m/z* (%) 127 (100), 111(26), 97 (50), 73 (72); HREIMS calcd for $C_8H_{16}O_2Si$ 172.0920, found 172.0915.

A general method for the preparation of cyclopentenone **1.24** is described below. The general method was applied to the synthesis of **1.25**, **2.28**, **2.39** and **2.40**.

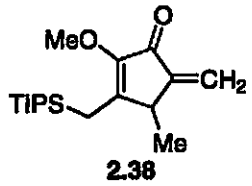


To a solution of ether **2.5** (147 mg, 0.65 mmol) in THF (3 ml) at -78 °C was added *n*-BuLi (0.25 ml, 0.63 mmol, 2.5 M in hexanes). After 30 min, a solution of enamide **2.3** (125 mg, 0.54 mmol) in THF (1 ml) was added dropwise via cannula. The reaction was stirred at -78 °C for 1 h, quenched with 1M HCl and diluted with ether. The aqueous phase was extracted with Et_2O (3X) and the combined organic extracts were washed with brine (1X), dried over $MgSO_4$, and concentrated under reduced pressure. Removal of trace solvent was done under high vacuum for 1 h. The crude product was transferred to a 4-dram vial charged with two glass beads. To a separate 4-dram vial containing activated silica gel (540 mg, 9.00 mmol) was added triethylamine (90 μl, 66 mg, 0.65 mmol). The mixture was stirred for 10 min and then transferred to the vial that contained crude enone **2.5**. The reaction was stirred at room temperature for 3 h. Direct purification of the reaction mixture by flash column chromatography on silica gel (5% EtOAc in hexanes) gave cyclopentenone **2.44** as colorless oil (126 mg, 63% yield): R_f = 0.33 (5% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.18 (m, 4 H), 7.14-7.04 (m, 1 H), 5.93 (s, 1 H), 4.98 (s, 1 H), 4.22 (s, 1 H), 4.08 (s, 3 H), 2.21 (d, J = 12.0 Hz, 1 H), 1.31 (d, J = 12.0 Hz, 1 H), 1.03-0.93 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.4, 156.3, 153.4, 145.9. 140.2, 128.7, 127.7, 127.1, 116.2, 57.8, 49.6, 18.3, 12.1, 11.8; IR (film) 2943, 2866, 1688,

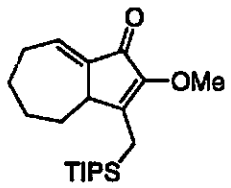
1656, 1605, 1447, 1385, 1342 cm^{-1}; EIMS *m/z* (%) 370 (M^+, 7), 346 (5), 327 (18), 197 (25); HREIMS calcd for $C_{23}H_{34}O_2Si$ 370.2328, found 370.2315.



Isolated as a white crystalline solid (105 mg, 68%): mp = 70-71°C, R_f = 0.28 (20% diethyl ether in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.34 (m, 3 H), 7.10-7.16 (m, 2 H), 6.09 (s, 1 H), 5.41 (s, 2 H), 5.13 (s, 1 H), 4.24 (s, 1 H), 3.52 (s, 3 H), 1.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0, 152.9, 152.1, 145.7, 140.8, 129.0, 128.1, 127.5, 118.2, 95.3, 56.8, 50.1, 12.7; IR (neat) 2953, 1695, 1663, 1626, 1453, 1409 cm^{-1}; EIMS *m/z* (%) 244 (M^+, 66), 229 (63), 213 (38), 184 (42), 115 (72), 84 (100); HREIMS calcd for $C_{15}H_{16}NO_3Si$ 244.1099, found 244.1106.



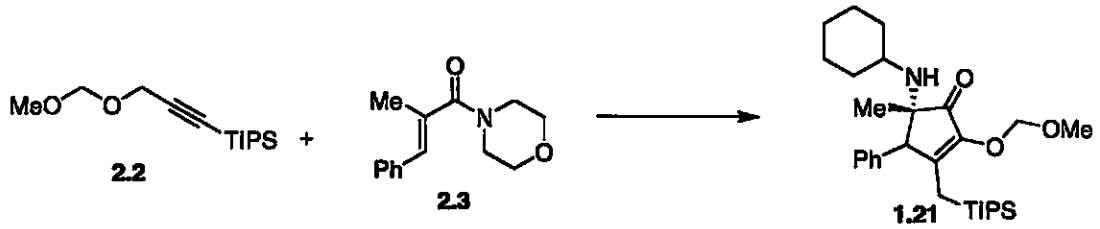
Isolated as a colorless oil (116 mg, 58%): R_f = 0.28 (20% diethyl ether in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 5.22 (s, 1 H), 3.98 (s, 3 H), 3.11 (q, J = 7.2 Hz, 1 H), 2.27 (d, J = 12.0 Hz, 1 H), 1.62 (d, J = 12.0 Hz, 1 H), 1.23 (d, J = 7.2 Hz, 1 H) 0.98-1.10 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 159.0, 151.8, 146.6, 114.0. 57.6, 37.2, 18.4, 18.3, 11.8, 11.2; IR (neat) 2943, 2867, 1691, 1655, 1607, 1451 cm^{-1}; EIMS *m/z* (%) 308 (M^+, 46), 265 (51), 251 (51), 250 (61), 69 (100); HREIMS calcd for $C_{18}H_{32}O_2Si$ 308.2172, found 308.2190.



2.39

Isolated as a colorless oil (136 mg, 68% yield): $R_f = 0.31$ (3% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (ddd, J = 8.4, 4.5, 1.5 Hz, 1 H), 3.99 (s, 3 H), 3.00 (d, J = 11.7 Hz, 1 H), 2.52-2.38 (m, 1 H), 2.27 (d, J = 12.3 Hz, 1 H), 2.24-2.08 (m, 3 H), 1.92-1.80 (m, 1 H), 1.67 (d, J = 12.3 Hz, 1 H), 1.60-1.56 (m, 1 H), 1.32-1.18 (m, 2 H), 1.18-1.00 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 156.5, 152.2, 141.8, 133.0, 57.7, 43.7, 31.4, 30.5, 28.4, 26.4, 18.4, 11.7, 10.7; IR (film) 2940, 2866, 1692, 1664, 1610, 1445 cm^{-1}; EIMS: *m/z* (%) 348 (M^+, 100), 305 (41), 290 (90), 131 (56); HREIMS calcd for $C_{21}H_{36}O_2Si$ 348.2485, found 348.2478.

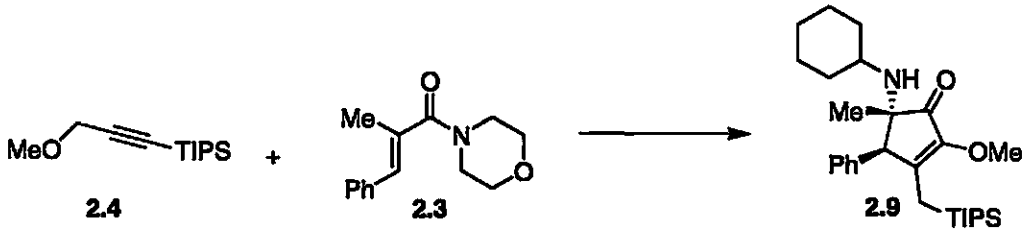
A general procedure for the preparation of all aminocyclopentenones is illustrated for the case of **1.21**.



2.2 **2.3** **1.21**

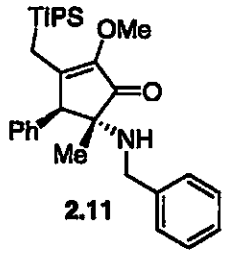
To a solution of ether **2.2** (167 mg, 0.65 mmol) in THF (3 ml) at -78 °C was added *n*-BuLi (0.25 ml, 0.63 mmol, 2.5 M in hexanes). After 30 min, a solution of enamide **2.3** (125 mg, 0.54 mmol) in THF (1 ml) was added dropwise via cannula. The reaction was stirred at -78 °C for 1 h, quenched with 1 M HCl and diluted with ether. The aqueous phase was extracted with Et_2O (3X) and the combined organic extracts were washed with brine (1X), dried over $MgSO_4$, and concentrated under

reduced pressure. Removal of trace solvent was done under high vacuum for 1 h. The crude product was transferred to a vial charged with two glass beads. To a separate vial containing activated silica gel (540 mg, 9.00 mmol) was added cyclohexylamine (74 μl, 64 mg, 0.65 mmol). The mixture was stirred for 10 min and then transferred to the vial that contained crude enone **1.19**. The reaction was stirred at room temperature for 3 h. Direct purification of the reaction mixture by flash column chromatography on silica gel (10% EtOAc in hexanes) gave aminocyclopentenone **1.21** (148 mg, 55 % yield) as a white crystalline solid: mp 87-90°C, R_f = 0.30 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.19 (m, 4 H), 7.04 (bs, 1 H), 5.57 (d, J = 6.0 Hz, 1 H), 4.97 (d, J = 6.0 Hz, 1 H), 3.93 (s, 3 H), 3.49 (s, 1 H), 2.36 (d, J = 12.0 Hz, 1 H), 2.31-2.20 (m, 1 H), 1.98-1.70 (m, 2 H), 1.70-1.42 (m, 3 H), 1.54 (d, J = 12.0 Hz, 1 H), 1.30-0.82 (m, 27 H), 0.55 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 160.8, 147.7, 136.9, 128.2, 126.9, 95.0, 64.8, 56.7, 53.8, 53.1, 37.2, 35.0, 25.6, 25.3, 22.8, 18.2, 12.8, 11.7; IR (film) 2927, 2866, 1701, 1627, 1453, 1367, 1331 cm^{-1}; EIMS *m/z* (%) 499 (M^+, 50), 454 (65), 313 (20), 264 (100); HREIMS calcd for $C_{30}H_{49}NO_3Si$ 499.3482, found 499.3491.



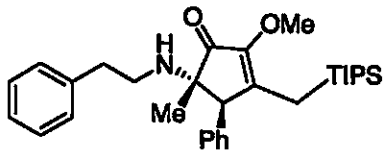
Isolated as a colorless oil (165 mg, 65% yield): R_f = 0.33 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 4 H), 7.08 (bs, 1 H), 4.00 (s, 3 H), 3.90 (s, 1 H), 2.35 (d, J = 12.0 Hz, 1 H), 2.36-2.26 (m, 1 H), 1.96-1.82 (m, 2 H), 1.74-1.62 (m, 2 H), 1.52 (d, J = 12.0 Hz, 1 H), 1.60-1.48 (m, 1 H), 1.30-1.12 (m, 3 H),

1.12-0.92 (m, 23 H), 0.57 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4, 157.9, 150.2, 137.7, 128.2, 126.7(2), 64.6, 57.7, 54.1, 52.4, 37.8, 35.6, 25.7, 25.4, 23.1, 18.3, 12.5, 11.6; IR (film) 2924, 2866, 1670, 1624, 1451, 1366, 1334 cm^{-1}; EIMS *m/z* (%) 469 (M^+, 83), 426 (12), 372 (4), 312 (33), 84 (100); HREIMS calcd for $C_{29}H_{47}NO_2Si$ 469.3376, found 469.3343.



2.11

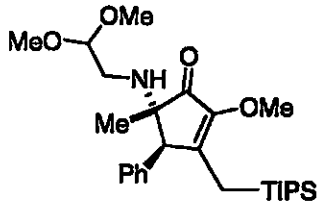
Isolated as a colorless oil (155 mg, 60% yield): R_f = 0.33 (6% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.14 (m, 10 H), 3.98 (s, 3 H), 3.92 (s, 1 H), 3.64 (s, 2 H), 2.31 (d, *J* = 12.0 Hz, 1 H), 1.46 (d, *J* = 12.0 Hz, 1 H), 1.02-0.80 (m, 21 H), 0.64 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 158.8, 150.2, 139.8, 137.8, 128.3 (2), 128.2 (2), 127.0, 126.9, 64.6, 57.8, 54.1, 47.6, 21.9, 18.3, 12.9, 11.8; IR (film) 3027, 2942, 2866, 1698, 1621, 1452, 1335 cm^{-1}; EIMS *m/z* (%) 477 (M^+, 1), 372 (7), 131 (81), 103 (75), 75 (100); HREIMS calcd for $C_{30}H_{43}NO_2Si$ 477.3063, found 477.3049.



2.13

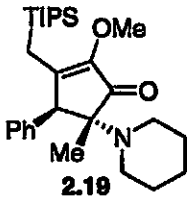
Isolated as colorless oil (167mg, 63% yield): R_f = 0.23 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (m, 8 H), 6.99 (bs, 2 H), 4.04 (s, 3 H), 3.81 (s, 1 H), 2.90-2.74 (m, 4 H), 2.37 (d, *J* = 12.0 Hz, 1 H), 1.82 (bs, 1 H) 1.52

(d, J = 12.0 Hz, 1H), 1.08-0.92 (m, 21 H), 0.66 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 158.2, 149.9, 139.7, 137.9, 128.5, 128.2, 128.1, 128.0, 126.7, 125.9, 64.0, 57.7, 54.2, 44.6, 36.7, 21.9, 18.2, 12.6, 11.7; IR (film) 3026, 2942, 2865, 1696, 1621, 1495, 1453, 1335 cm^{-1}; EIMS *m/z* (%) 491 (M^+, 58), 400 (100), 372 (45), 157 (36), 115 (47); HREIMS calcd for $C_{31}H_{45}NO_2Si$ 491.3220, found 491.3224.



2.15

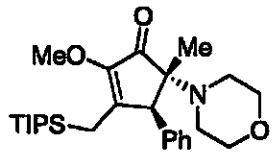
Isolated as a colorless oil (171 mg, 67% yield): R_f = 0.25 (45% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 4 H), 7.07 (bs, 1 H), 4.42 (t, J = 5.4 Hz, 1 H), 3.99 (s, 3 H), 3.83 (s, 1 H), 3.33 (s, 3 H), 3.32 (s, 3 H), 2.66 (dd, J = 11.7, 5.4 Hz, 1 H), 2.65 (dd, J = 11.7, 5.4 Hz, 1 H), 2.32 (d, J = 12.0 Hz, 1 H), 1.66 (bs, 1 H), 1.46 (d, J = 12.0 Hz, 1 H), 1.10-0.88 (m, 21 H), 0.61 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 157.8, 149.9, 139.9, 128.2, 126.8, 103.7, 63.7, 57.7, 54.6, 53.5, 53.0, 44.8, 21.4, 18.3, 12.6, 11.7; IR (film) 2943, 2868, 1697, 1624, 1452, 1367 cm^{-1}; EIMS *m/z* (%) 475 (M^+, 10), 400 (6), 84 (100); HREIMS calcd for $C_{27}H_{45}NO_4Si$ 475.3118, found 475.3113.



2.19

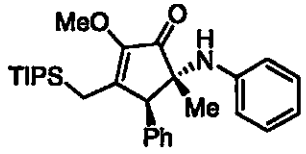
Isolated as a colorless oil (143 mg, 58% yield): R_f = 0.29 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.14 (m, 4 H), 6.82 (bs, 1 H), 4.03 (s, 3 H), 3.99 (s, 1 H), 2.60-2.40 (m, 4 H), 2.29 (d, J = 12.0 Hz, 1 H), 1.50-1.62 (m, 4 H),

1.40-1.49 (m, 2 H), 1.37 (d, J = 12.0 Hz, 1 H), 0.94-1.12 (m, 21 H), 0.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 158.5, 150.6, 139.1, 131.6, 128.1, 126.5, 68.5, 57.7, 50.9, 48.5, 26.2, 24.7, 18.9, 18.3, 12.7, 11.7; IR (film) 2938, 2865, 1701, 1632, 1453, 1336 cm^{-1}; EIMS *m/z* (%) 455 (M^+, 7), 103 (61), 131 (69); HREIMS calcd for $C_{28}H_{45}NO_2Si$ 455.3220, found 455.3209.



2.17

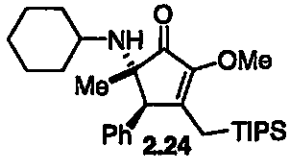
Isolated as a colorless oil (173 mg, 70% yield): R_f = 0.29 (15% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.34 (m, 4 H), 6.82 (bs, 1 H), 4.04 (s, 1 H), 3.99 (s, 3 H), 3.70 (m, 4 H), 2.59 (m, 4 H), 2.30 (d, J = 12.0 Hz, 1 H), 1.38 (d, J = 12.0 Hz, 1 H), 0.90-1.20 (m, 21 H), 0.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 159.0, 150.7, 138.7, 131.5, 128.4, 126.8, 68.0, 67.3, 57.8, 51.1, 47.8, 18.6, 18.4, 12.9, 11.9; IR (film) 2943, 2891, 2865, 1699, 1628, 1453, 1337 cm^{-1}; EIMS *m/z* (%) 457 (M^+, 94), 442 (29), 372 (67), 313 (49), 157 (69), 115 (100); HREIMS calcd for $C_{27}H_{43}NO_3Si$ 457.3012, found 457.3004.



2.21

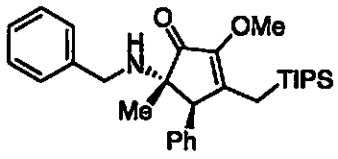
Isolated as a white solid (75 mg, 30% yield): mp 50-53 °C, R_f = 0.28 (7% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-7.36 (m, 4 H), 7.30-7.10 (m, 2 H), 6.94 (t, J = 7.2 Hz, 1 H), 6.78-6.72 (m, 2 H) 4.38 (s, 1 H), 4.18 (s, 3 H), 2.52 (d, J = 12.0 Hz, 1 H), 1.75 (d, J = 12.0 Hz, 1 H), 1.10-0.95 (m, 24 H); ^{13}C NMR (75

MHz, $CDCl_3$) δ 199.6, 157.1, 149.9, 143.1, 136.4, 129.0(2), 128.1, 126.9, 119.6, 116.0, 64.3, 57.7, 51.2, 24.2, 18.1, 12.6, 11.6; IR (neat) 3355, 2942, 2866, 1703, 1602, 1497, 1455, 1369, 1334 cm^{-1}; EIMS *m/z* (%) 463 (M^+, 20), 371(15), 160 (48), 131 (100), 103 (80); HREIMS calcd for $C_{29}H_{41}NO_2Si$ 463.2907, found 463.2934.



2.24

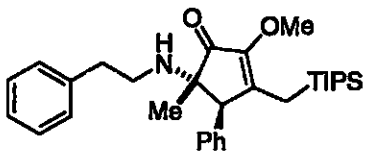
Isolated as a colorless oil (166 mg, 63% yield): R_f = 0.28 (25% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3 H), 2.70 (q, *J* = 7.2 Hz, 1 H), 2.25 (dd, *J* = 12.3, 1.2 Hz, 1 H), 2.82-2.65 (m, 1 H), 1.85-1.45 (m, 7 H), 1.59 (d, *J* = 12.3 Hz, 1 H), 1.13 (d, *J* = 7.2 Hz, 3 H), 1.10-1.04 (m, 24 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 161.2, 148.4, 68.9, 57.5, 52.5, 41.3, 37.5, 35.5, 25.6, 25.5, 25.3, 21.6, 18.4, 12.9, 11.8, 11.3; IR (film) 2926, 2866, 1696, 1622, 1448, 1377, 1337 cm^{-1}; EIMS *m/z* (%) 407 (M^+, 100), 392 (44), 310 (71), 250 (39); HREIMS calcd for $C_{24}H_{45}NO_2Si$ 407.3220, found 407.3240.



2.25

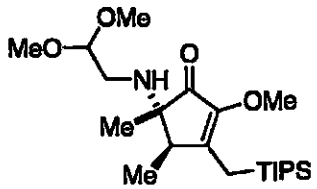
Isolated as a colorless oil (172 mg, 64% yield): R_f = 0.31 (15% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5 H), 3.93 (s, 3 H), 3.58 (d, *J* = 12.3 Hz, 1 H), 3.51 (d, *J* = 12.3 Hz, 1 H), 2.79 (q, *J* = 7.2 Hz, 1 H), 2.28 (dd, *J* = 12.0, 1.2 Hz, 1 H), 1.82 (bs, 1 H), 1.63 (d, *J* = 12.0 Hz, 1 H), 1.39 (d, *J* = 7.2 Hz, 3 H), 1.11 (s, 3 H), 1.01-1.10 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 161.8, 148.5,

140.4, 128.2, 127.9, 126.8, 63.9, 57.5, 47.7, 40.7, 20.9, 18.4, 13.2, 11.8, 11.5; IR (film) 2942, 2866, 1696, 1620, 1454, 1338 cm^{-1}; EIMS *m/z* (%) 415 (M^+, 10), 400 (16), 310 (100), 90 (90); HREIMS calcd for $C_{25}H_{41}NO_2Si$ 415.2907, found 415.2907.



2.26

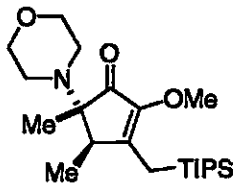
Isolated as a colorless oil (153 mg, 55% yield): R_f = 0.26 (25% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.33 (m, 3 H), 7.32-7.24 (m, 2 H), 4.00 (s, 3 H), 2.90-2.70 (m, 5 H), 2.36 (d, *J* = 12.3 Hz, 1 H), 1.82 (bs, 1 H) 1.72 (d, *J* = 12.3 Hz, 1 H), 1.26 (d, *J* = 7.5 Hz, 3 H), 1.20-1.10 (m, 24 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 161.7, 148.4, 139.5, 128.4, 128.2, 125.9, 63.2, 57.5, 44.6, 41.0, 36.8, 20.6, 18.3, 13.5, 11.7, 11.4; IR (film) 2942, 2866, 1694, 1620, 1456, 1337 cm^{-1}; EIMS *m/z* (%) 429 (M^+, 29), 414 (20), 338 (57), 310 (100); HREIMS calcd for $C_{26}H_{43}NO_2Si$ 429.3063, found 429.3088.



2.27

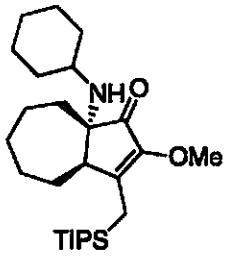
Isolated as a colorless oil (137 mg, 51% yield): R_f = 0.40 (40% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 4.37 (t, *J* = 5.7 Hz, 1 H), 3.88 (s, 3 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 2.65 (q, *J* = 7.5 Hz, 1 H), 2.51 (d, *J* = 5.7 Hz, 2 H), 2.25 (d, *J* = 12.0 Hz, 1 H), 1.80 (bs, 1 H), 1.60 (d, *J* = 12.0 Hz, 1 H), 1.13 (d, *J* = 7.5 Hz, 3 H), 1.02-1.08 (m, 24 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 161.3, 148.2, 103.4, 62.9,

57.4, 53.5, 52.7, 44.4, 41.1, 20.4, 18.3, 13.4, 11.7, 11.4; IR (film) 2943, 2867,1698, 1621, 1462, 1447 cm^{-1}; EIMS *m/z* (%) 413(M^+, 83), 381(19), 338 (39), 310 (100); HREIMS calcd for $C_{22}H_{43}NO_4Si$ 413.2961, found 413.2999.



2.28

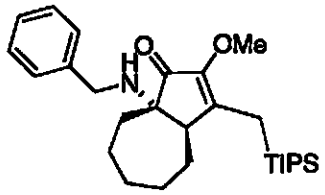
Isolated as a colorless oil (170 mg, 66% yield): R_f = 0.33 (40% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 3 H), 3.57-3.70 (m, 4 H), 2.80 (q, *J* = 7.2 Hz, 1 H), 2.60-2.50 (m, 2 H), 2.42-2.32 (m, 2 H), 2.20 (dd, *J* = 12.3, 1.2 Hz, 1 H), 1.56 (d, *J* = 12.3 Hz, 1 H), 1.10-0.98 (m, 27 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.6, 161.8, 148.7, 67.12, 67.08, 57.6, 47.2, 36.7, 18.4, 17.4, 14.8, 11.8, 11.3; IR (film) 2944, 2866, 1695, 1623, 1455, 1383, 1338 cm^{-1}; EIMS *m/z* (%) 395 (M^+, 6), 380 (6), 310 (30), 84 (100); HREIMS calcd for $C_{23}H_{41}NO_2Si$ 395.2856, found 395.2885.



2.29

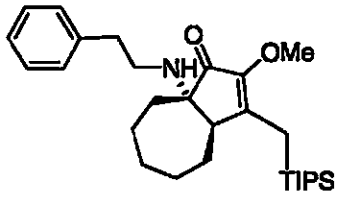
Isolated as a colorless oil (175 mg, 68% yield) R_f = 0.24 (10% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 2.60 (dd, *J* = 7.2, 3.0 Hz, 1 H), 2.29 (d, *J* = 12.0 Hz, 1 H), 2.28-2.20 (m, 1 H), 2.01-1.89 (m, 2 H), 1.80-1.40 (m, 14 H), 1.55 (d, *J* = 12.0 Hz, 1 H), 1.41-1.30 (m, 3 H), 1.15-1.00 (m, 22 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.4, 162.6, 150.5, 66.6, 57.7, 51.2, 49.2, 37.8, 36.0, 35.5, 31.0,

28.2, 25.9, 25.7, 25.6, 25.5, 23.5, 18.5, 11.9, 10.9; IR (film) 3322, 2926, 2865, 1694, 1651, 1622, 1446, 1335 cm^{-1}; EIMS *m/z* (%) 447 (M^+, 4), 388 (14), 351 (27), 350 (100), 264 (53); HREIMS calcd for $C_{27}H_{49}NO_2Si$ 447.3533, found 447.3561.



2.30

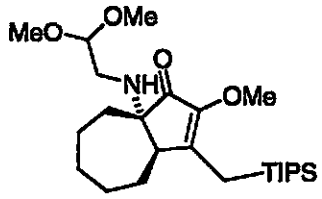
Isolated as a colorless oil (196 mg, 75% yield): R_f = 0.28 (5% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.16-7.30 (m, 5 H), 3.95 (s, 3 H), 3.55 (s, 2 H), 2.73 (dd, *J* = 7.5, 2.7 Hz, 1 H), 2.32 (d, *J* = 12.0 Hz, 1 H), 1.34-2.60 (m, 8 H), 1.58 (d, *J* = 12.0 Hz, 1 H), 1.18- 1.28 (m, 2 H), 0.98-1.12 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.8, 163.0, 150.4, 140.6, 128.2, 128.0, 126.7, 66.6, 57.7, 48.6, 47.1, 34.8, 31.0, 28.6, 25.9, 23.4, 18.4, 17.7, 11.9; IR (film) 2924, 2865, 1691, 1618, 1459, 1335; EIMS *m/z* (%) 351 (27), 350 (100), 335 (13), 291(23), 157 (24), 91 (61); HREIMS calcd for $C_{28}H_{45}NO_2Si$ 455.3220, found 447.3177.



2.31

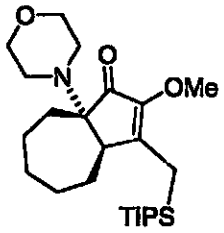
Isolated as colorless oil (190 mg, 71% yield): R_f = 0.30 (15 % EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.24 (m, 5 H), 4.02 (s, 3 H), 2.84-2.68 (m, 5 H), 2.40 (d, *J* = 12.0 Hz, 1 H), 3.40-2.20 (m, 1 H), 1.96-1.60 (m, 7 H), 1.62 (d, *J* = 12.0 Hz, 1 H), 1.54-1.42 (m, 2 H), 1.22-1.06 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 162.9, 150.5, 139.7, 128.5, 128.2, 125.9, 66.3, 57.7, 48.3, 44.5, 36.9, 35.1, 30.9, 28.4, 25.7, 23.5, 18.4, 11.8, 10.9; IR (film) 3026, 2923, 2864, 1690, 1618, 1496,

1449; EIMS *m/z* (%) 379 (13), 378 (46), 350 (79), 329 (28), 260 (100), 105 (41); HREIMS calcd for $C_{29}H_{47}NO_2Si$ 469.3376, found 469.3348.



2.32

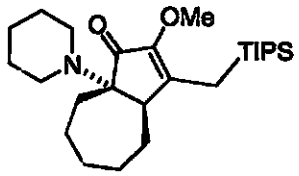
Isolated as a colorless oil (155 mg, 60% yield): R_f= 0.45 (40% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (t, *J* = 5.7 Hz, 1 H), 3.89 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 2.58 (d, *J* = 5.1 Hz, 1 H), 2.56 (dd, *J* = 11.7, 5.4 Hz, 1 H), 2.48 (dd, *J* = 11.7, 5.1 Hz, 1 H), 2.27 (d, *J* = 12.0 Hz, 1 H), 2.00-1.86 (m, 1 H), 1.54 (d, *J* = 12.0 Hz, 1 H), 1.42-1.82 (m, 7 H), 1.42-1.30 (m, 2 H), 1.09-1.00 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 162.3, 149.9, 103.7, 65.6, 57.6, 53.3, 52.9, 49.1, 43.9, 34.1, 30.9, 28.4, 25.9, 23.3 18.4, 11.8, 11.7; IR (film) 2935, 2866, 1698, 1623, 1446 cm^{-1}; EIMS *m/z* (%) 453 (M^+, 3), 422 (8), 378 (35), 350 (100); HREIMS calcd for $C_{25}H_{47}NO_4Si$ 453.3274 found, 453.3263.



2.33

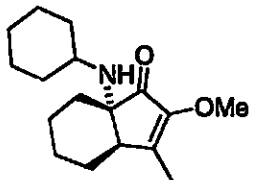
Isolated as a colorless oil (153 mg 61% yield): R_f = 0.17 (15% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 3.62-3.58 (m, 4 H), 2.90-2.80 (m, 1 H), 2.62-2.52 (m, 2 H), 2.41-2.30 (m, 2 H), 2.27 (d, *J* = 12.0 Hz, 1 H), 2.10-1.52 (m, 8 H), 1.51 (d, *J* = 12.0 Hz, 1 H), 1.10-0.98 (m, 23 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 163.4, 151.5, 70.2, 67.3, 57.8, 47.5, 43.9, 31.9, 31.0, 28.3, 25.0, 23.7, 18.5,

11.9, 10.9; IR (film) 2923, 2864, 1691, 1625, 1449, 1385, 1338 cm^{-1}; EIMS *m/z* (%) 392 (8), 351 (30), 350 (100), 291 (29), 115 (16); HREIMS calcd for $C_{25}H_{45}NO_3Si$ 435.3169, found 435.3169.



2.34

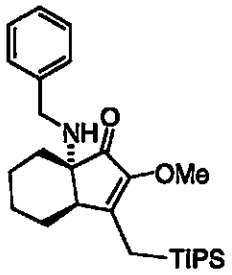
Isolated as a colorless oil (127 mg, 51% yield): R_f = 0.30 (10% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 2.86-2.78 (m, 1 H), 2.60-2.46 (m, 2 H), 2.48 (d, *J* = 12.0 Hz, 1 H), 2.28-2.20 (m, 2 H), 2.04-1.82 (m, 3 H), 1.52 (d, *J* = 12.0 Hz, 1 H), 1.80-1.30 (m, 11 H), 1.18-1.00 (m, 22 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.2, 163.3, 151.8, 71.1, 58.0, 48.4, 44.4, 32.6, 31.3, 28.7, 26.7, 25.5, 25.2, 24.1, 18.8, 12.2, 11.2; EIMS *m/z* (%) 433 (M^+, 1), 350 (38), 251 (36), 250 (100). HREIMS calcd for $C_{27}H_{47}NO_2Si$ 433.3376, found 433.3380.



2.35

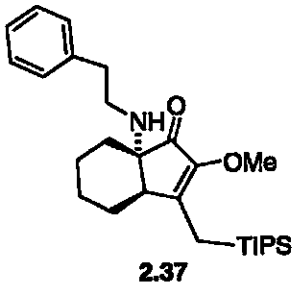
Isolated as a colorless oil (153 mg, 59% yield): R_f = 0.36 (9% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 2.64 (t, 1 H), 2.30 (d, *J* = 12.0 Hz, 1 H), 2.25-2.18 (m, 1 H), 1.55 (d, *J* = 12.0 Hz, 1 H), 1.85-1.40 (m, 14 H), 1.33-1.20 (m, 3 H), 1.12-1.02 (m, 22 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7, 160.8, 149.7, 63.2, 57.3, 52.0, 42.7, 37.3, 35.6, 31.2, 25.5, 25.4, 25.2, 22.7, 18.2, 17.7, 11.7, 11.2; IR (film) 2932, 2865, 1693, 1652, 1621, 1446 cm^{-1}; EIMS *m/z* (%) 433 (M^+, 4), 418

(2), 374 (13), 337 (25), 336 (100), 264 (48); HREIMS calcd for $C_{26}H_{47}NO_2Si$ 433.3376, found 433.3351.



2.36

Isolated as a colorless oil (158 mg, 60% yield): R_f = 0.30 (6% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.13 (m, 5 H), 3.90 (s, 3 H), 3.45 (d, J = 12.6 Hz, 1 H), 2.56 (d, J = 12.6 Hz, 1 H), 2.65 (t, J = 5.0 Hz, 1 H), 2.28 (d, J = 12.0 Hz, 1 H), 1.92-1.80 (m, 1 H), 1.76 (bs, 1 H), 1.54 (d, J = 12.0 Hz, 1 H), 1.64-1.46 (m, 5 H), 1.36-1.20 (m, 1 H), 1.04-0.97 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 161.5, 149.8, 140.4, 128.0, 127.7, 126.5, 63.4, 63.3, 57.4, 47.1, 42.2, 30.5, 22.8, 18.2, 17.5, 11.6, 11.3; IR (film) 2942, 2866, 1694, 1620, 1462 cm^{-1}; EIMS *m/z* (%) 336 (100), 337 (34), 91 (40), 277 (18); HREIMS calcd for $C_{27}H_{43}NO_2Si$ 441.3063, found 453.3036.



2.37

Isolated as a white solid (174 mg, 64% yield): mp 45-46 °C, R_f = 0.29 (9% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.31 (m, 3 H), 7.30-7.22 (m, 2 H), 3.99 (s, 3 H), 2.86-2.65 (m, 5 H), 2.38 (d, J = 12.0 Hz, 1 H), 2.06-1.92 (m, 1 H),

1.88 (bs, 1 H), 1.76-1.54 (m, 6 H), 1.30-1.48 (m, 2 H), 1.07-1.18 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.6, 161.7, 149.9, 139.5, 128.3, 128.1, 125.8, 62.8, 57.4, 44.1, 42.7, 36.7, 30.0, 22.8, 18.3, 17.8, 17.2, 11.7, 11.4; IR (neat) 2942, 2866, 1694, 1618, 1446 cm^{-1}; EIMS *m/z* (%) 337 (27), 364 (67), 336 (100); HREIMS calcd for $C_{28}H_{45}NO_2Si$ 453.3220, found 453.3185.

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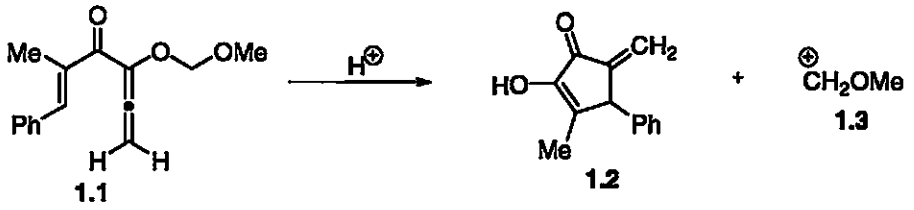
PART II:

TANDEM ALKYLATION-CYCLIZATION PROCESS VIA AN O,C DIANION

1. Introduction

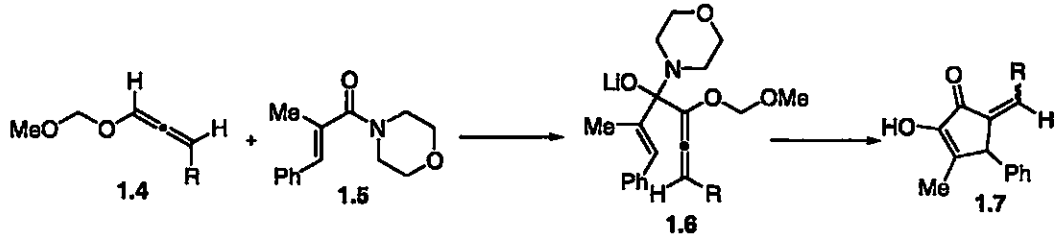
1.1. Background

The variant of the Nazarov reaction in which an allenyl ether function participates in conrotation has been a long standing research interest in our group.[1] The reaction leads to cross-conjugated cyclopentenones such as **1.2** (scheme 1) that possesses an exocyclic methylene.



Scheme 1

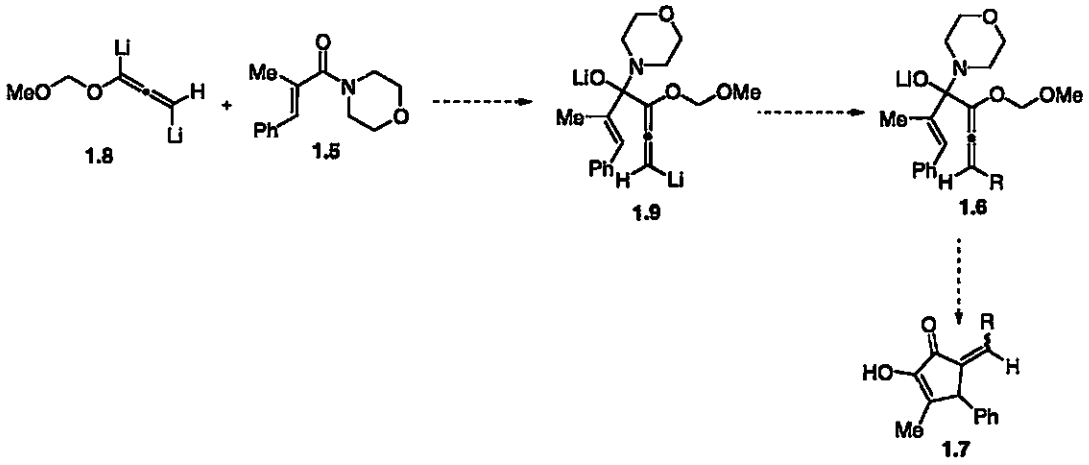
While a variety of cyclopentenones can be constructed in this way, a convenient method that leads to C6-substituted α-methylene cyclopentenones was needed. One approach to these compounds would involve the use of allene **1.4** (scheme 2). α-Lithiation of **1.4** followed by trapping the resulting anion with enamide **1.5** results in tetrahedral intermediate **1.6**, which collapses to cyclopentenone **1.7** upon acid workup.



Scheme 2

A more direct approach to the C6- substituted α-methylene cyclopentenones would be through α,γ-allene dianion **1.8** (scheme 3). Deprotonation of the γ-carbon atom would take place last making selective electrophilic trapping at that site a

possible.Whilst this approach provides the shortest possible route to C6- substituted α- methylene cyclopentenones, work done within our group to put this plan to practise plan failed.

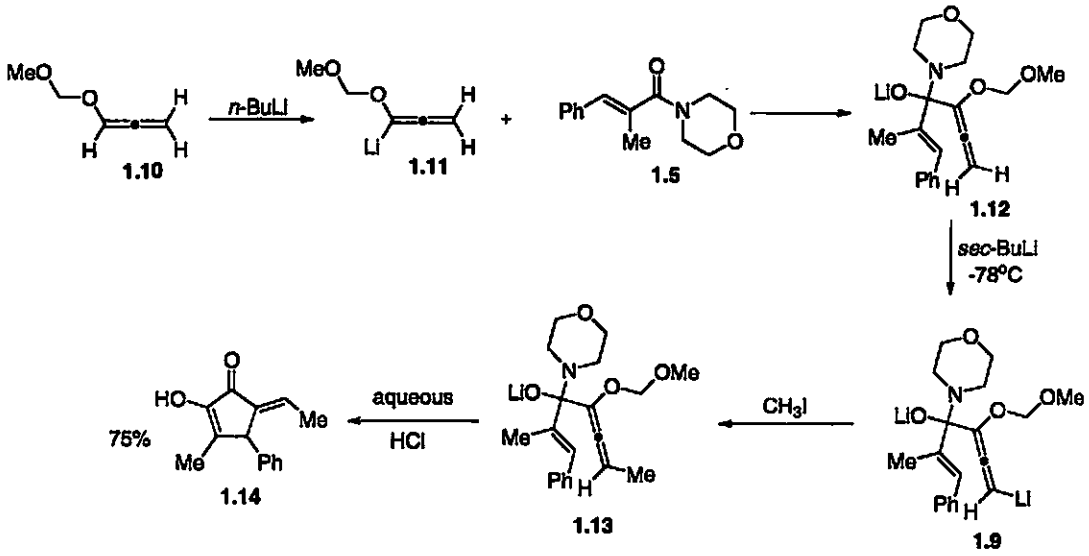


Scheme 3

The former method shown in scheme **2** was not satisfactory either. Whereas the preparation of **1.4** (R = H) is straightforward, the preparation of homologues of **1.4** (R = Alkyl) requires several additional steps, and is not always efficient.[2] Some allene substituents may interfere with the generation of the lithioallene **1.4**, or inhibit the clean addition of the morpholino enamide **1.5**.

The simple solution to this problem, developed within our group,[3] is summarized in scheme **4**. α-Lithiation of **1.10** followed by addition of the resulting anion **1.11** to enamide **1.5** gave the tetrahedral intermediate **1.12**. The γ-allenic protons in **1.12** are acidic, and exposure to *sec*-butyllithium led to an O,C-dianion **1.9**. Exposure of **1.9** to iodomethane followed by quenching the reaction with 5% HCl in ethanol gave **1.14** in 75% yield (scheme **4**). The process leading to **1.14** is triply convergent. It involves an allene, a morpholino amide, and an electrophile. As such it

may be useful for application to the synthesis of small molecule libraries. Reactions of enamide **1** and several electrophiles gave good yields of products.



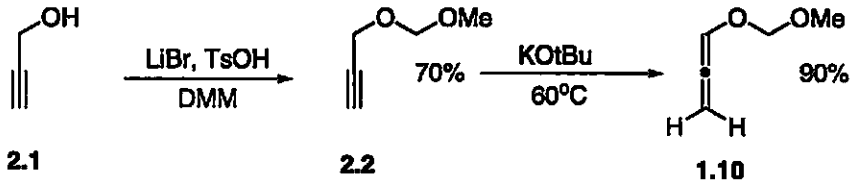
Scheme 4

As an extension of this work, we then sought to prove that the methodology is applicable to other mopholino enamides and electrophiles. Above all we wanted to be able to define the optimum conditions for the process.

2. Results and Discussion

2.1. Synthesis

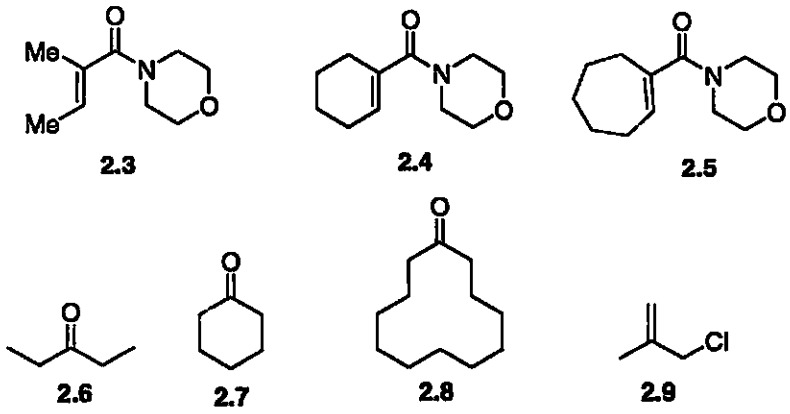
The starting point for the synthesis of the allene **1.10** was propargyl alcohol **2.1** which was converted to 3-(methoxymethoxy)prop-1-yne **2.2** according to a procedure that has been described in the literature (scheme **5**).[4] Isomerization of **2.2** according to



2.1 **2.2** **1.10**

Scheme 5

Brandsma's excellent methodology gave allene **1.10** in 90% yield.[5] With the allene precursor synthesized the cyclizations were carried out as shown in scheme **4** with different amides and nucleophiles (Figure **1**). The results for the cyclization process are shown in table **1**. Product yields within the synthetically useful range were obtained in all cases.



2.3 **2.4** **2.5** **2.6** **2.7** **2.8** **2.9**

Figure 1: Amides and Electrophiles

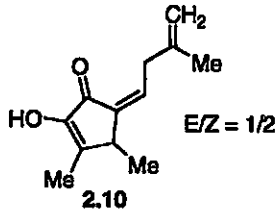
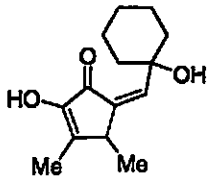
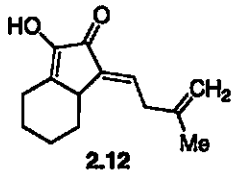
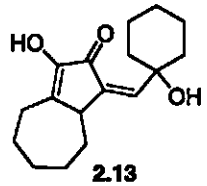
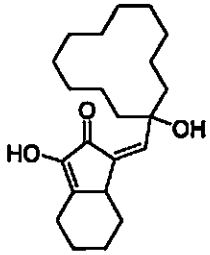
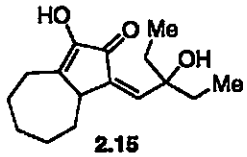
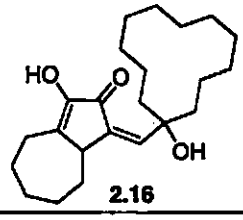
Entry	Cyclopentenone	Yield
1	 E/Z = 1/2 **2.10**	56%
2	 **2.11**	56%
3	 **2.12**	51%
4	 **2.13**	60%
5	 **2.14**	58%
6	 **2.15**	51%
7	 **2.16**	67%

Table 1: Cyclopentenones

During the execution of this research several observations that had an important bearing on the outcome of the reaction were made. In all cases amides were dried by azeotropic distillation with benzene, then stored in THF over 4 Å molecular sieves before use. Best results were obtained when fresh solutions of *sec*-butyllithium were used for the generation of O,C-dianion **1.9**. The use of aged solutions invariably led to erosion of the yield of product. Two reasons could have led to this observation. First, when the titer of the *sec*-butyllithium falls below 1 M, the volume of the solution to be added increases, as does the proportion of hydrocarbon solvent (cyclohexane) in the reaction medium (THF). This may have an effect on the kinetics of the subsequent steps leading to **1.9**. Second, reduction in titer of the *sec*-butyllithium is probably caused by introduction of a small amount of air through leaks in the septum closure. This suggests the presence of hydroperoxides in aged *sec*-butyllithium solutions that may be able to degrade O,C- dianion **1.9** through oxidative processes. The quality of the allene used for the preparation of **1.11** is important. Allene **1.10** undergoes some discoloration upon standing. Discolored samples were redistilled before use. The reactions with methallyl chloride were sluggish compared to reactions with ketones and iodomethane.[3,6] Addition of HMPA and several equivalents of LiI was necessary in order to achieve the results shown in Table 1. Liquid ketones such a cyclohexanone and 3-pentanone were distilled and dried over 4 Å molecular sieves before use. No such precaution was necessary in the case of cyclododecanone, a crystalline solid.

The kinetic products of the cyclization are the Z-isomers at the exocyclic double bond. Longer contact times with acid during cyclization can lead to isomerization to the E-isomer when it is thermodynamically favored. When the

substituent at C6 position has a large steric requirement, the Z isomer is often thermodynamically, as well as kinetically favored (Entries **2**, **4**, **5**, **6** and **7**, Table **1**). It is noteworthy that cyclopentenones **2.10** and **2.12** were isolated as skipped dienes. Conjugation of the terminal double bond on the sidechain did not take place. This result testifies to the mildness of the reaction conditions used for cyclization. All reaction products were fairly stable to storage under neutral conditions, however some decomposition took place upon standing at room temperature.

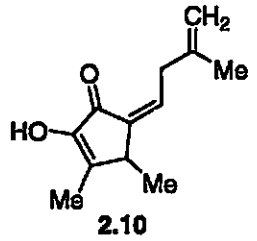
2.2. Conclusions

The scope of the tandem alkylation cyclization process for preparing highly substituted cyclopentenones was expanded. Preparation of the products shown in Table 1 by any other means would be challenging and require several discrete steps. The method leads to a large degree of molecular complexity in a single step. Applications to natural product total synthesis as well as to diversity-oriented synthesis can be anticipated.

3. Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Varian Mercury Plus 300 operating at 300 MHz (^{1}H) or 75 MHz (^{13}C) or on a Varian Unity Inova 500 operating at 500 MHz (^{1}H) or 126 MHz (^{13}C). Chemical shifts are reported in parts per million (δ) and are referenced to the solvent, i.e 7.26/77.0 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), or m (multiplet). Coupling constants (*J*) are reported in Hertz (Hz). Infrared spectra were recorded on a Perkin-Elmer IR 1430 spectrometer. Electron impact mass spectra were recorded on a VG-70SE mass spectrometer. Thin-layer chromatography (TLC) was performed on Sigma-Aldrich TLC plates, 250 μm, particle size 5 to 17 μm, pore size 60 Å. Flash column chromatography was performed on Natland International Corporation silica gel, 200-400 mesh and Sorbent Technologies silica gel, premium R_f, 60 Å, 40-75 μ. Anhydrous THF was taken from a solvent purification system from GlassContour (www.glasscontour.com). Reagents were purified as described in text or were used as received. All moisture sensitive reactions were performed under a static nitrogen or argon atmosphere in oven-dried or flame-dried glassware.

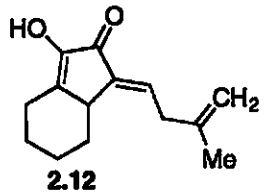
A general procedure for the preparation of **2.10** and **2.12** is described for the case of **2.10**.



2.10

To a solution of allene **1.10** (140 mg, 1.40 mmol) in 3 mL THF at –78 °C was added *n*-BuLi (0.63 ml, 2.32 M in hexanes, 1.45 mmol). After 45 min, a solution of amide **2.3** (169 mg, 1.00 mmol) in 2 mL THF was added at –78 °C via cannula. After 10 min at –78 °C, the reaction mixture was warmed from –78 °C to –30 °C over 30 min and stirred further for 30 min at –30 °C. *sec*-BuLi (1.21 ml, 1.4 M in cyclohexane, 1.7 mmol) was added dropwise at –78 °C. After 45 min, a solution of methallyl chloride (0.50 ml, 6.00 mmol), LiI (268 mg, 2.00 mmol), and HMPA (0.5 ml, 0.31 mmol) in 3 mL THF was added at –78 °C via cannula. The reaction mixture was warmed from –78 °C to –30 °C over 15 min and stirred further for 2 hr at –30 °C; then quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in EtOH (7 ml). After 10 min, it was neutralized with pH 7 buffer and extracted with EtOAc (3x). The combined organic extracts were washed with brine (2x) and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (15% EtOAc in hexanes) gave cyclopentenone **2.10** as a colorless oil (112 mg, 56% yield): R_f= 0.4 (20% EtOAc in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (td, J = 7.8, 1.2 Hz, 1 H), 4.72 (s, 1 H), 4.76 (s, 1 H), 3.54 (d, J = 7.8 Hz, 2 H), 3.02 (q, J = 7.2 Hz, 1 H), 1.96 (d, J = 1.2 Hz, 3 H), 1.75 (s, 3 H), 1.20 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.5, 150.9, 148.9, 144.3, 141.0, 137.1, 111.3, 38.6, 35.8, 22.9, 17.9,

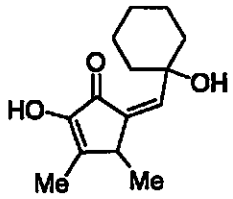
11.7; IR (neat): 3314, 2967, 2932, 2871, 1679, 1626, 1650, 1409, 1357 cm^{-1}; EIMS: *m/z* (%) 192 (M^+, 85), 177 (100) 159 (38) 131 (40); HREIMS calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1146.



2.12

Isolated as a colorless oil (104 mg, 51%): R_f = 0.28 (10% EtOAc in hexanes). ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (bs, 1 H), 5.99 (t, *J* = 7.8 Hz, 1 H), 4.76 (s, 1 H), 4.70 (s, 1 H) 3.53 (d, *J* = 7.8 Hz, 2 H), 2.97 (dd, *J* = 13.8, 4.2 Hz, 1 H), 2.82 (dd, *J* = 11.7, 5.4 Hz, 1 H) 2.26-2.14 (m, 1 H), 2.10-1.80 (m, 3 H), 1.74 (s, 3 H), 1.56-1.38 (m, 1 H), 1.36-1.15 (m, 1 H), 1.15-0.80 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 148.1, 144.3, 142.9, 136.8, 136.5, 111.3, 40.9, 35.7, 33.2, 25.5, 25.2, 25.1, 22.9; IR (film): 3315, 2933, 2855, 1687, 1623, 1445, 1400, 1361 cm^{-1}; EIMS: *m/z* (%); 218 (M^+, 16), 203 (15), 101 (87), 84 (100); HREIMS calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1334.

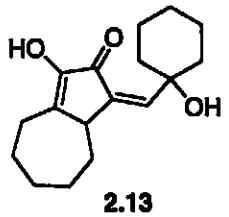
The preparation of **2.11** is described below. Compounds **2.13-2.16** were prepared according to the same procedure.



2.11

To a solution of allene **1.10** (145 mg, 1.45 mmol) in 3 mL THF at –78 °C was added *n*-BuLi (0.63ml, 2.32 M in hexanes, 1.45 mmol). After 45 min a solution of amide **2.3** (169 mg, 1.00 mmol) in 2 ml THF was added at –78 °C via cannula. After

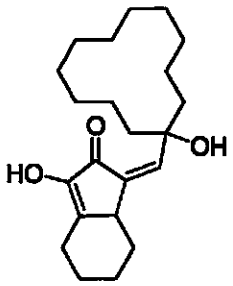
10 min at –78 °C, the reaction mixture was warmed from –78 °C to –30 °C over 30 min and stirred further for 30 min at –30 °C. *sec*-BuLi (1.21ml, 1.40 M in cyclohexane, 1.70 mmol) was added dropwise at –78 °C. After 45 min, a solution of cyclohexanone (0.62 ml, 6.00 mmol) in 2 ml THF was added at –78 °C via cannula. The reaction mixture was warmed from –78 °C to –30 °C over 15 min, and stirred further for 1 hr at –30 °C; then quenched by rapid addition through a large bore cannula to 5% (v/v) aqueous HCl in EtOH (7 ml). After 10 min, it was neutralized with pH 7 buffer, and extracted with EtOAc (3x). The combined organic extracts were washed with brine (2x) and dried over $MgSO_4$. Purification by flash column chromatography on silica gel (10% EtOAc in hexanes) gave cyclopentenone **2.11** as a colorless oil (123 mg, 56% yield); R_f= 0.32 (10% EtOAc in hexanes). ^{1}H NMR (300 MHz, C_6D_6) δ 6.64 (bs, 1 H), 6.14 (bs, 1 H), 5.89 (s, 1 H), 3.24-3.16 (m, 1 H), 3.14-3.06 (m, 1 H), 2.42-2.30 (m, 1 H), 2.08-1.90 (m, 3 H), 1.52 (s, 3 H), 1.50-1.38 (m, 3 H), 1.18-1.15 (m, 2 H), 0.69 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 150.8, 148.9, 144.2, 136.6, 71.7, 38.9, 37.9, 37.8, 25.6, 25.4, 22.3, 17.8, 12.0; IR (film): 3300, 2932, 2855, 1659, 1613, 1446, 1403, 1350 cm^{-1}; EIMS: *m/z* (%)236 (M^+, 12) 180 (100) 162 (21) 81(100); HREIMS calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1440.



2.13

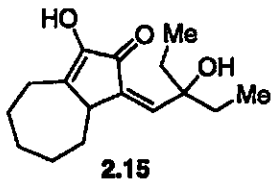
Isolated as a white crystalline solid. (157 mg, 60% yield): mp = 281-282 °C, R_f= 0.33 (20% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (d, J = 3 Hz,

1 H), 5.70 (bs, 1 H), 3.05-2.92 (m, 1 H), 2.83 (dd, J = 12.0, 5.4 Hz, 1 H), 2.26-1.05 (m, 17 H), 1.05 (qd, J = 12.6, 3.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 148.6, 147.9, 146.2, 135.3, 71.8, 41.1, 37.9 (2), 33.0, 25.6, 25.4 (2), 25.1, 22.3 (2); IR (neat): 3300, 2932, 2855, 1659, 1613, 1446, 1403, 1350 cm^{-1}; EIMS: m/z (%) = 262 (M^+, 100), 244 (56), 150 (79); HREIMS calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1572.



2.14

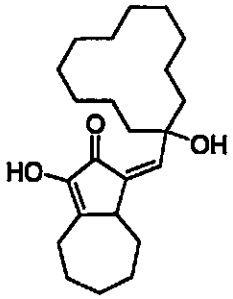
Isolated as a white crystalline solid (119 mg, 58% yield): mp = 154-156 °C, R_f = 0.30 (20% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (bs, 1 H), 6.19 (s, 1 H), 3.05-2.90 (m, 1 H), 2.81 (dd, J = 11.7, 5.4 Hz, 1 H), 2.24-0.80 (m, 29 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7, 148.8, 147.9,146.2, 134.9, 75.4, 41.2, 35.1, 35.0, 33.1, 26.6, 26.3, 25.4 (2), 25.1 (2), 22.7 (2), 22.3 (2), 20.2, 19.9; IR (neat): 3310, 2960, 1714, 1665, 1610, 1457, 1414, 1359 cm^{-1}; EIMS: m/z (%) = 346 (M^+, 100), 328 (51), 150 (86); HREIMS calcd for $C_{22}H_{34}O_3$ 346.2508, found 346.2487.



2.15

Isolated as a white crystalline solid (135 mg, 51% yield): mp 140-142°C, R_f= 0.3 (20% EtOAc in Hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.71 (s, 1 H), 6.09 (s,

1 H), 3.19 (dd, J = 10.2, 1.8 Hz, 1 H), 2.82-2.58 (m, 2 H), 2.10 (dd, J = 14.0, 2.7 Hz, 1 H), 2.00-1.80 (m, 3 H), 1.76-1.40 (m, 6 H), 1.38-1.20 (m, 2 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.0, 150.3, 149.9, 148.5, 137.2, 44.8, 35.6 (2), 34.2, 34.1, 30.8, 29.9, 28.5, 25.9, 8.5 (2); IR (neat): 3310, 2960, 1715, 1666, 1610, 1457,1415, 1359 cm^{-1}; EIMS: *m/z* (%) = 264 (M^+, 2), 246 (9), 235 (100); HREIMS calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1742.



2.16

Isolated as a white crystalline solid (120 mg, 67% yield): mp 160-162°C, R_f = 0.32 (20% EtOAc in Hexanes). ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.43 (bs, 1 H), 6.24 (s, 1 H), 5.65 (bs, 1 H), 3.14 (d, J = 9.9 Hz, 1 H), 2.82-2.58 (m, 2 H), 2.08 (d, J = 11.7 Hz, 1 H), 2.00-1.71 (m, 5 H), 1.70-1.57 (m, 3 H) 1.50-1.20 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.5, 150.2, 149.9, 149.1, 135.5, 75.1, 44.3, 35.1, 34.9, 34.8 (2), 30.6, 29.7, 28.3, 26.4 (2), 26.0, 25.6, 22.5 (2), 22.0, 19.9, 19.8; IR (neat): 3345, 2927, 2850, 1667, 1610, 1470, 1419 cm^{-1}; EIMS: *m/z* (%) 360 (M^+, 100), 342 (93), 332 (70), 178 (60); HREIMS calcd for $C_{23}H_{36}O_3$ 360.2664, found 360.2700.

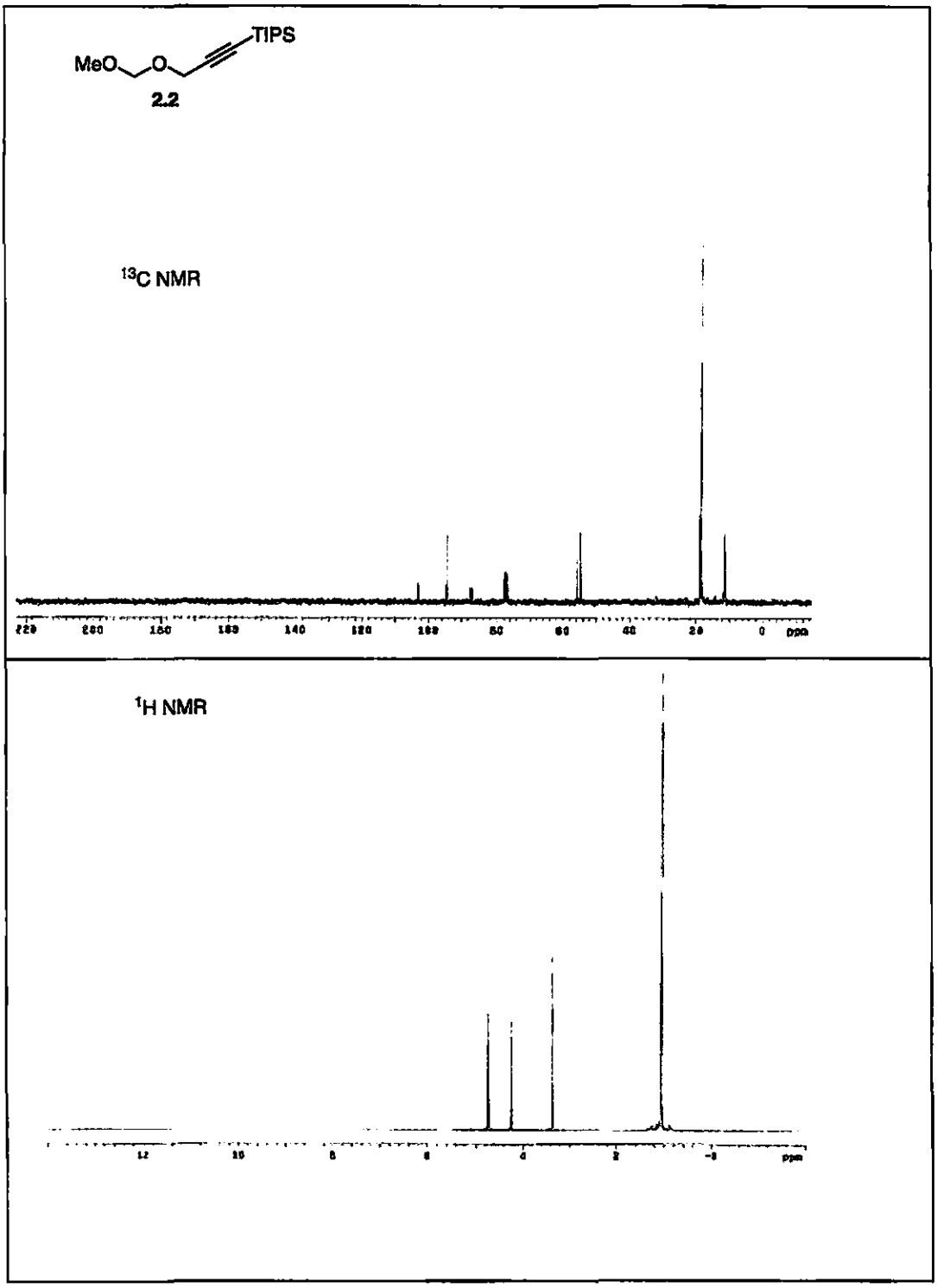
4. References

1. For an overview of work in this area, see: Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284-290 and references cited therein.
2. Tius, M. A.; Busch-Petersen, J.; Yamashita, M. *Tetrahedron Lett.* **1998**, *39*, 4219-4222.
3. Bee, C.; Tius, M. A. *Org lett.* **2003**, *5*, 1681-1684.
4. Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd Ed.; Elsevier: New York, 1988; pp 248-249.
5. Hoff, S.; Brandsma, L.; Arens, J. F. *Recl. Trav. Chim.* Pays-Bas **1968**, *87*, 916-924.
6. Banaag, A. R.; Berger, G. O.; Dhoro, F; delos Santos, D. B; Dixon, D. D; Mitchell, J. P.; Tokeshi, B. K.; Tius, M. A. *Tetrahedron* **2005**, *61*, 3419-3428.

APPENDIX

Spectral Data for Selected Compounds

Part I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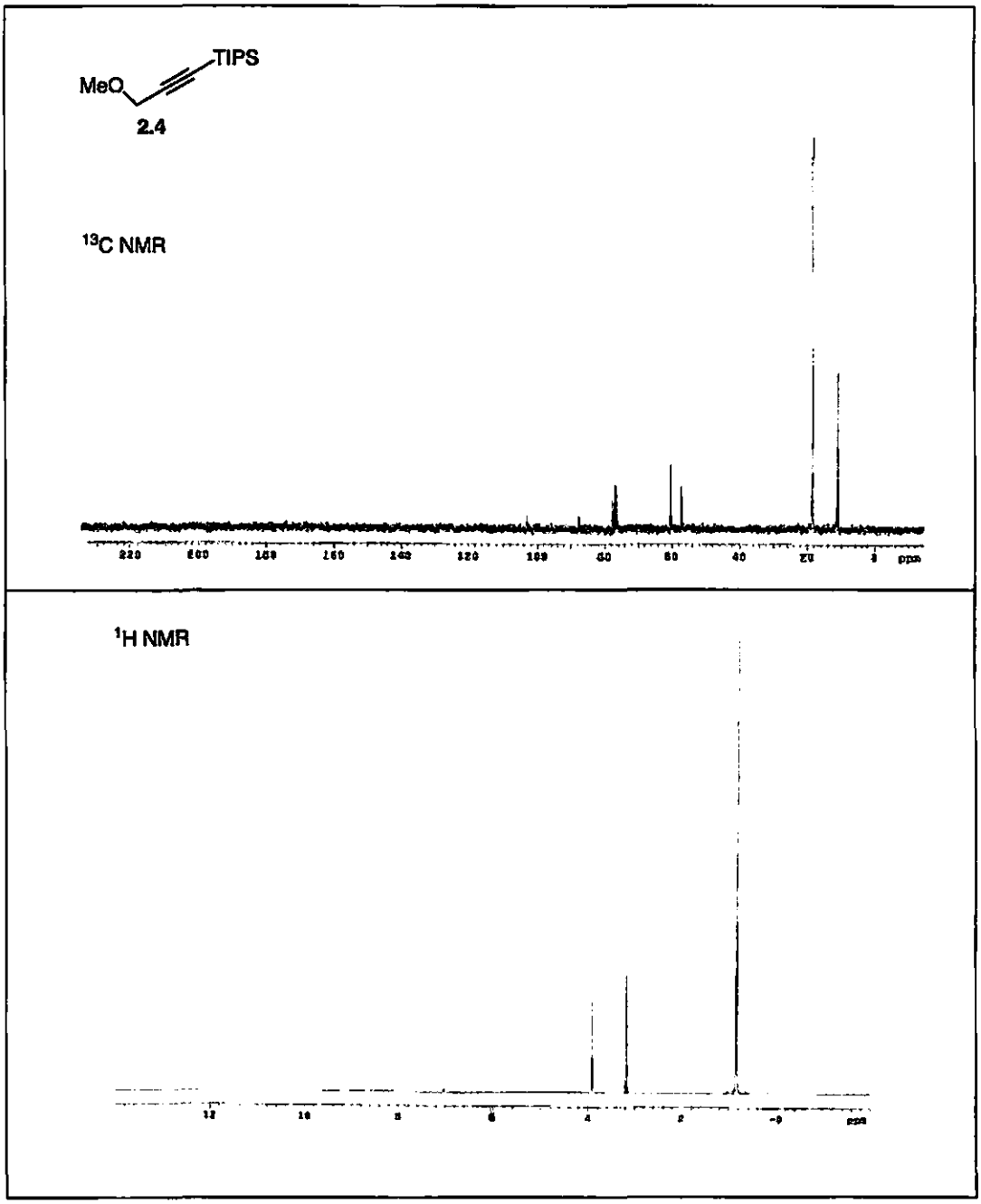
2.2
^{13}C NMR
ppm
^{1}H NMR
ppm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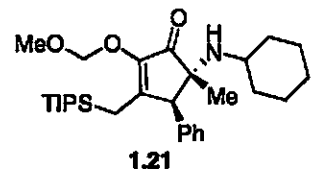
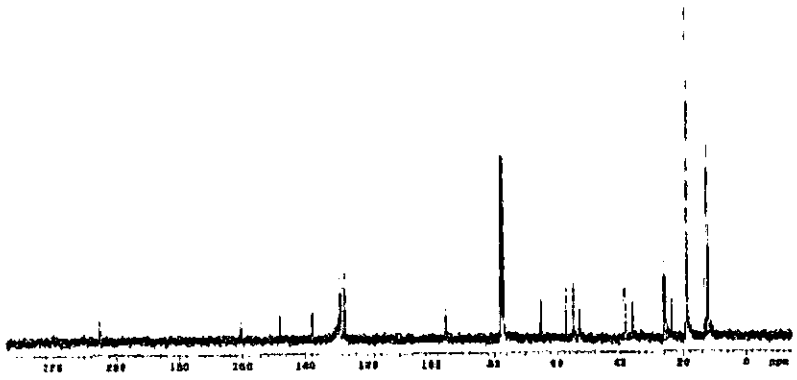
^{1}H NMR

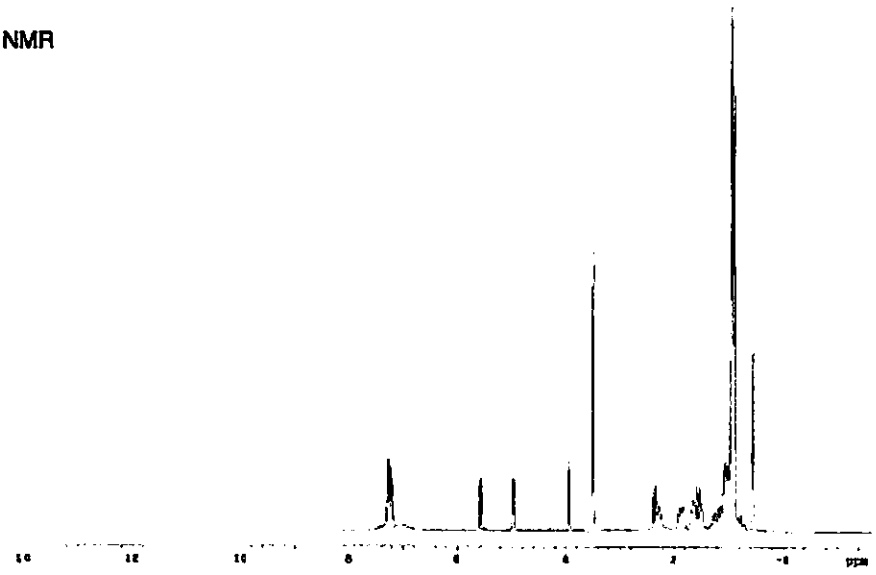


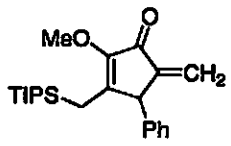
1.21

^{13}C NMR



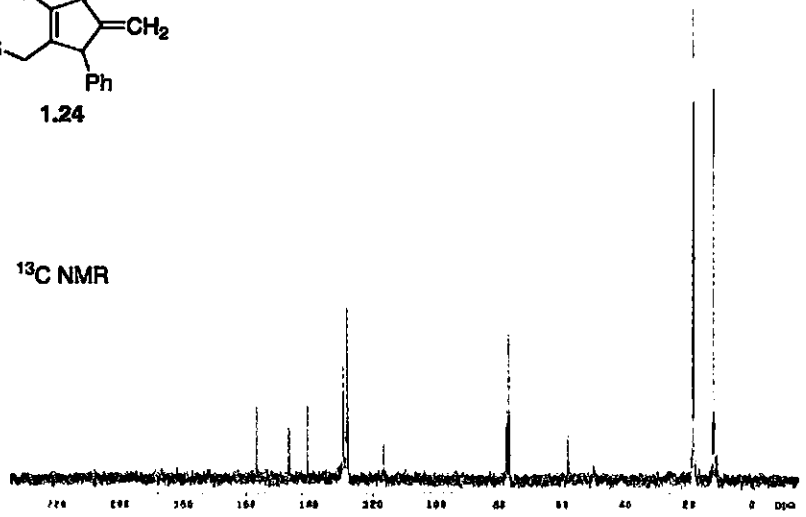
^{1}H NMR



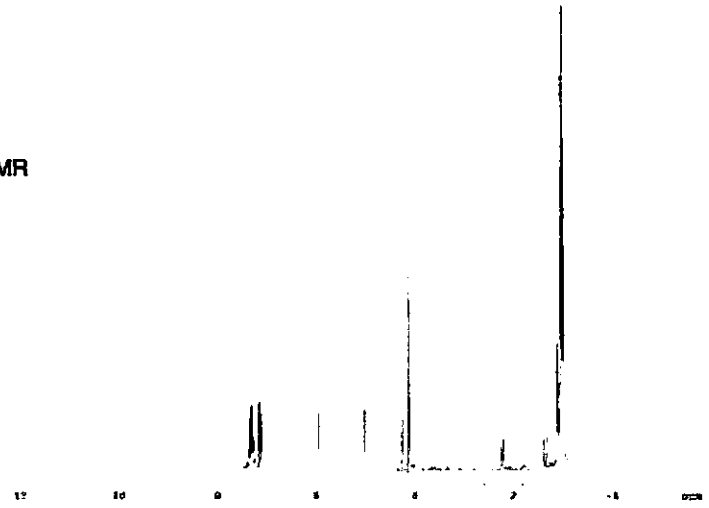


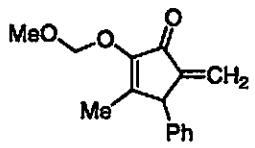
1.24

^{13}C NMR



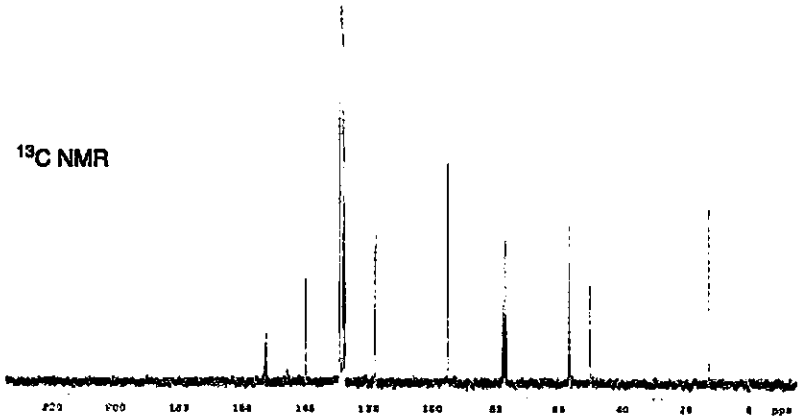
^{1}H NMR



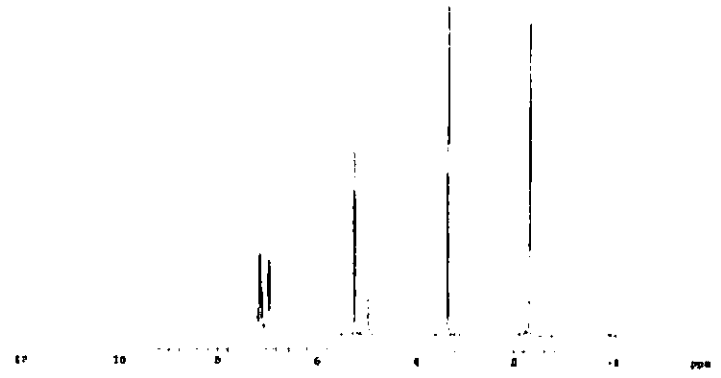


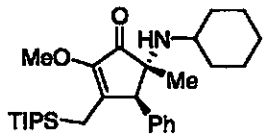
1.25

^{13}C NMR



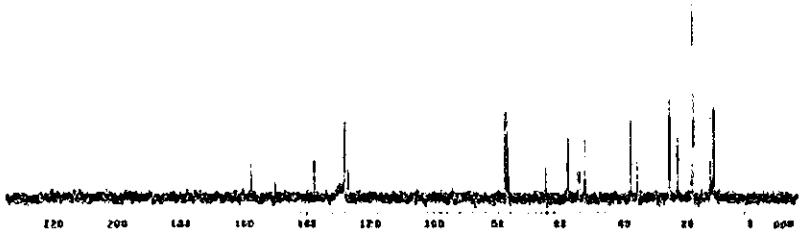
^{1}H NMR



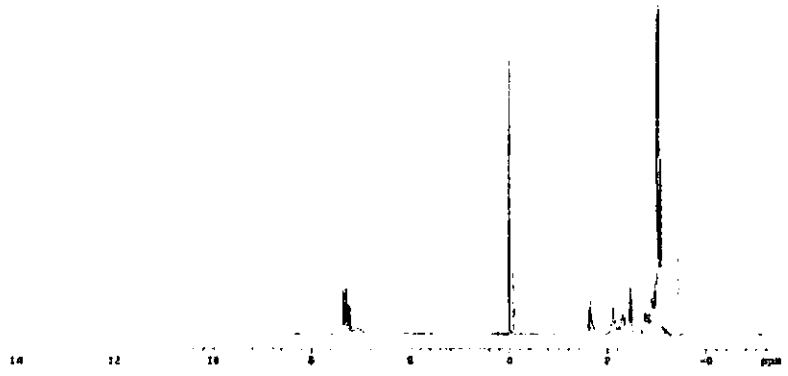


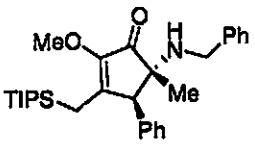
2.9

^{13}C NMR



^{1}H NMR





2.11

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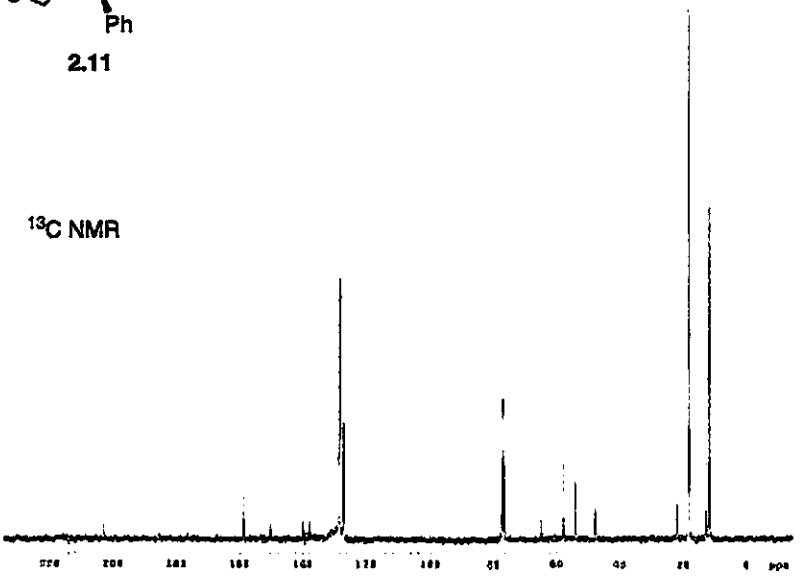

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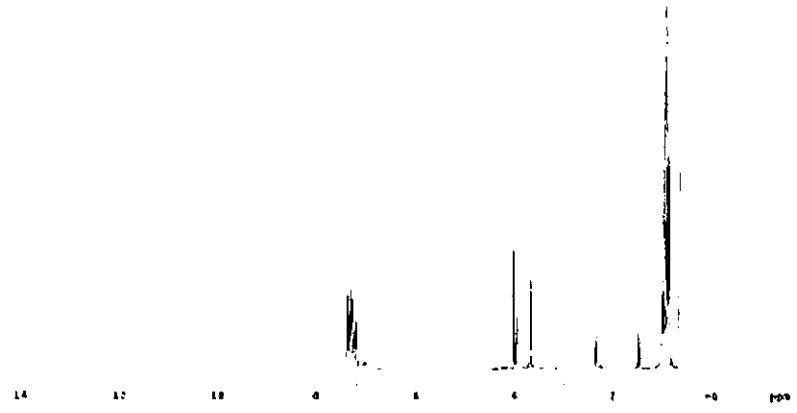

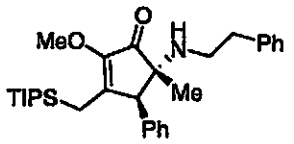

2.13

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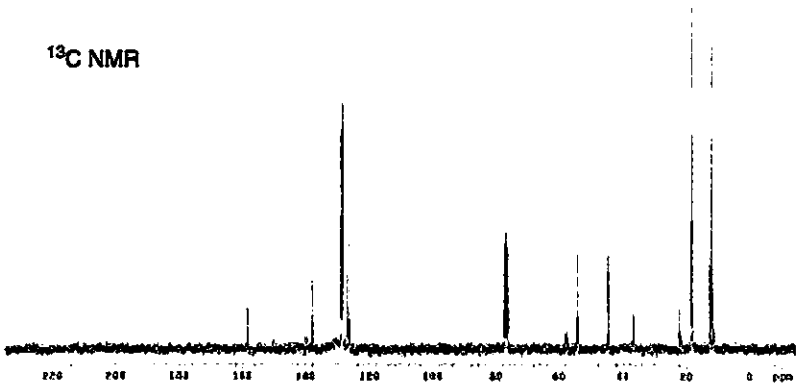

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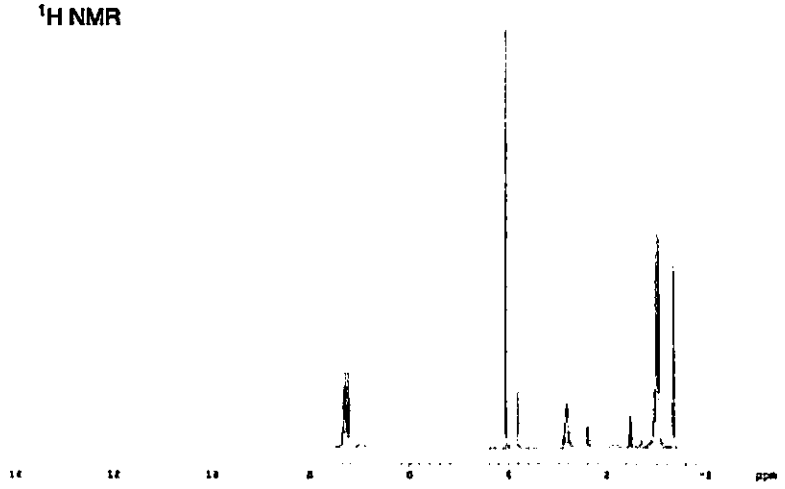

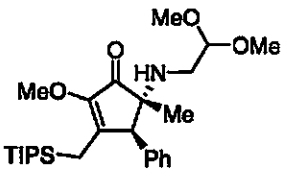

2.15

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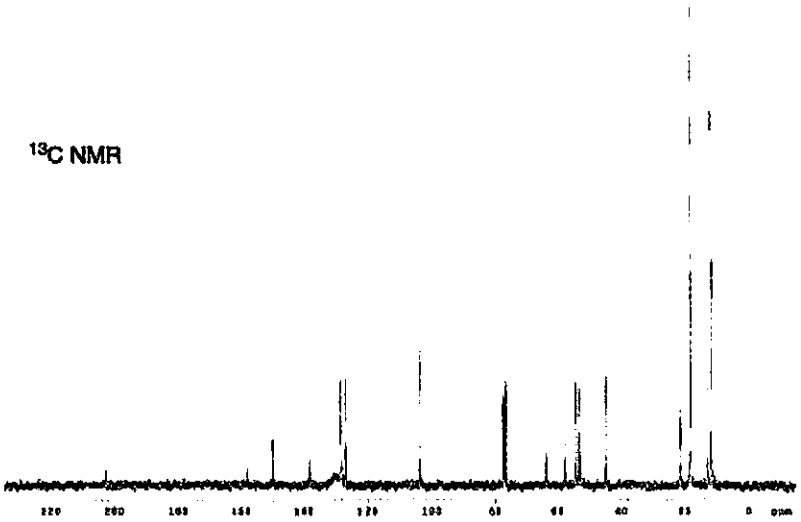
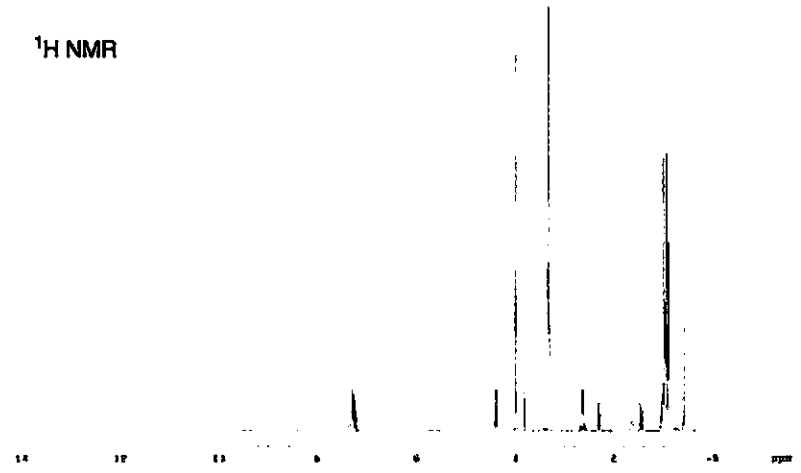
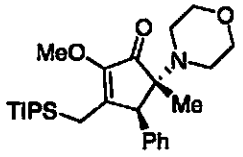


^{1}H NMR





2.17

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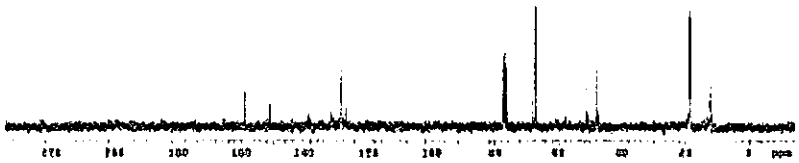

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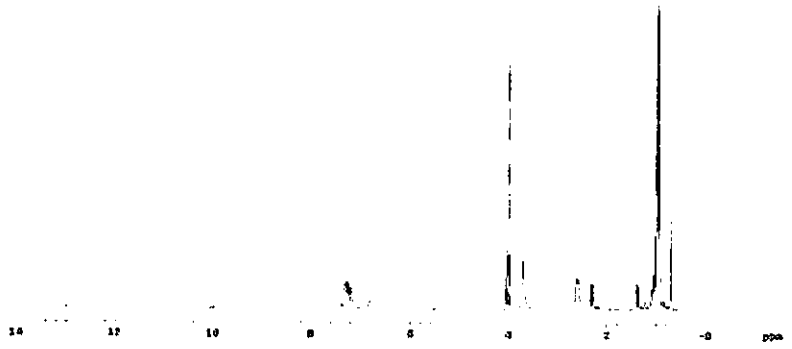

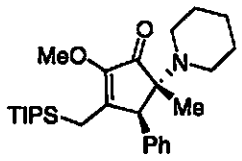

2.19

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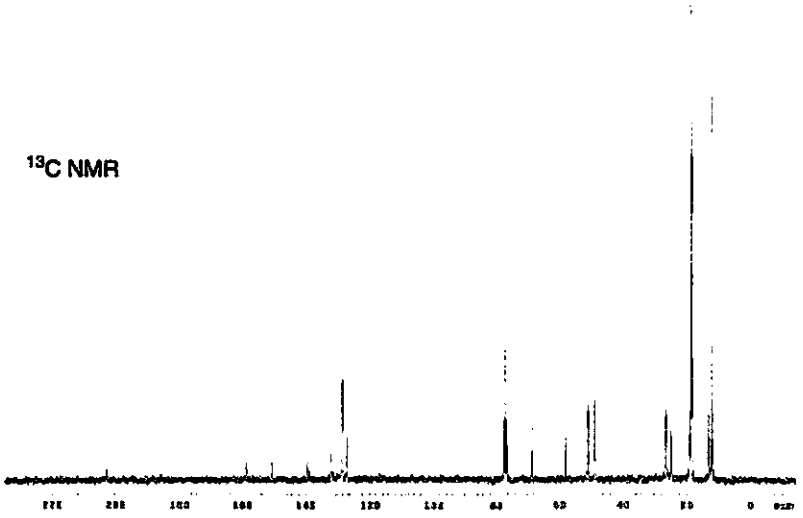

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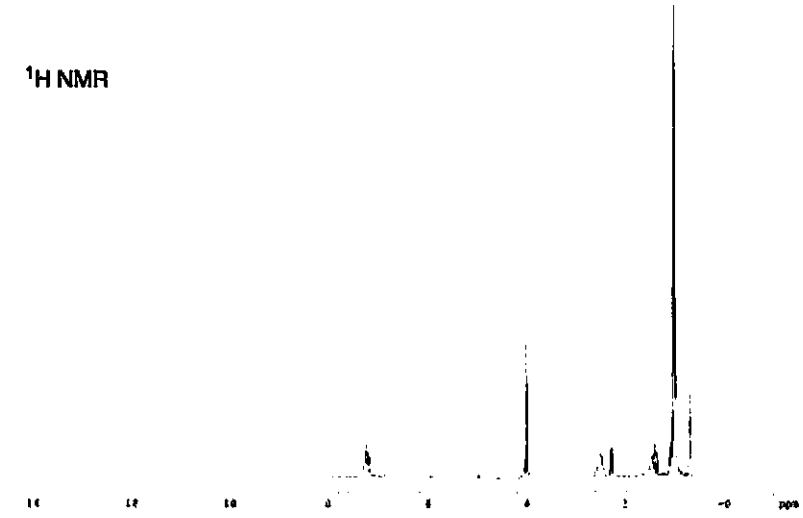
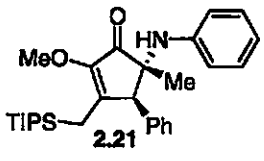
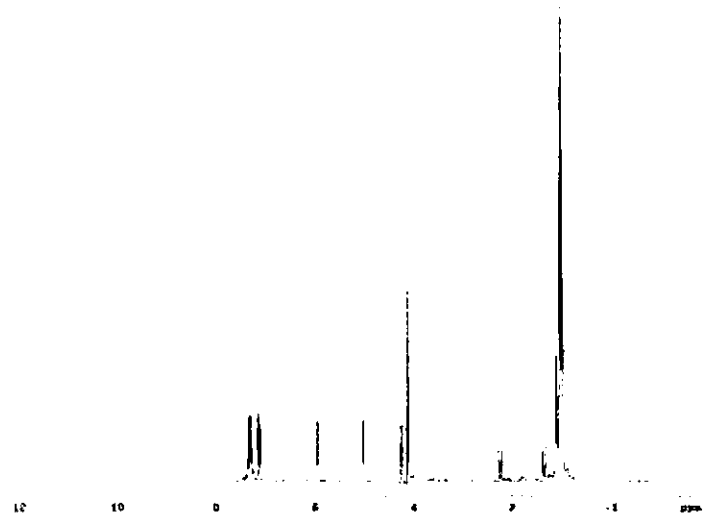


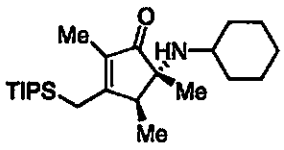


2.21

^{13}C NMR

^{1}H NMR





2.24

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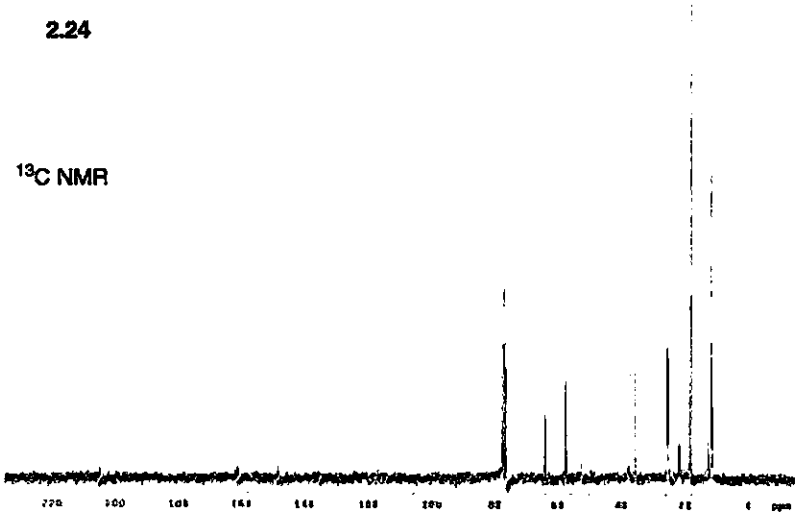

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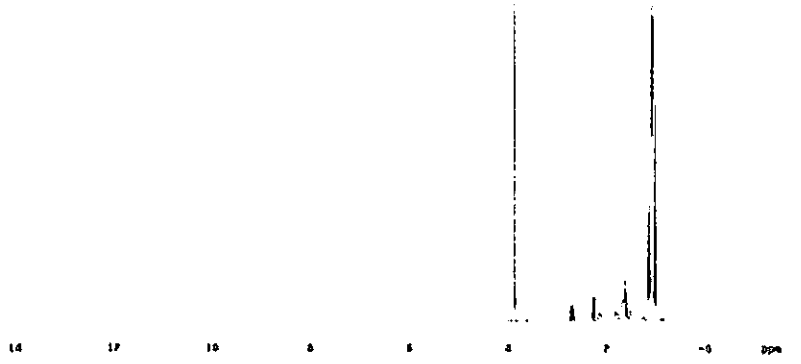

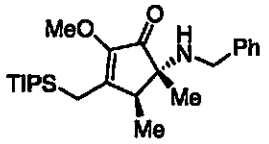

2.25

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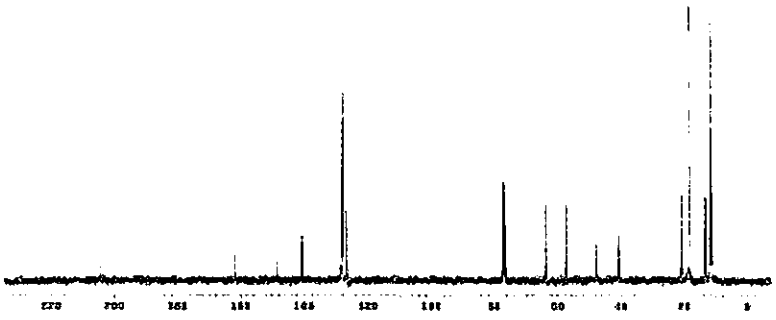

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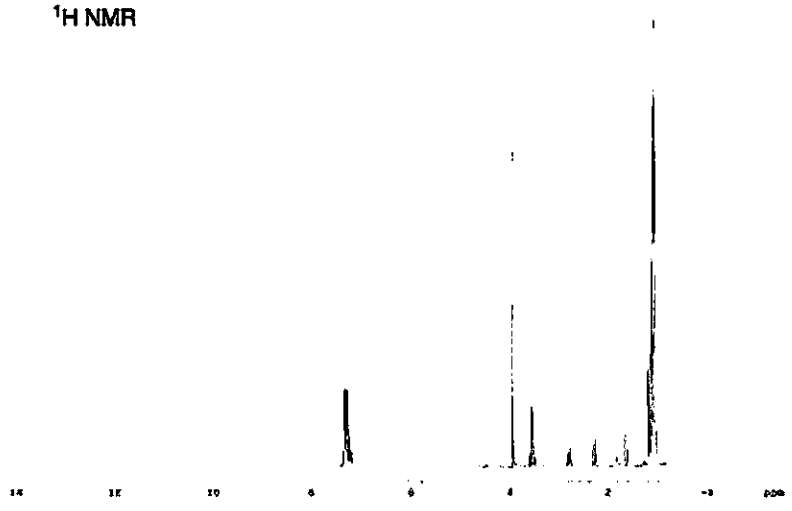

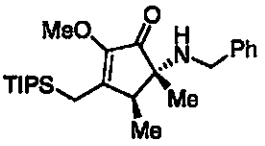

2.26

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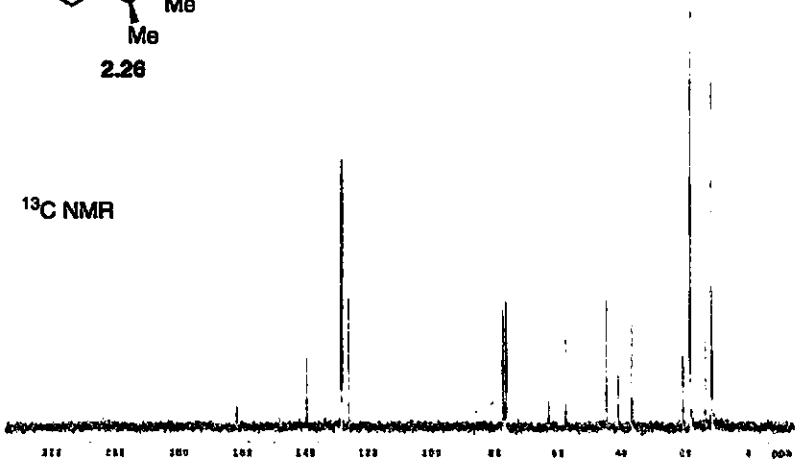

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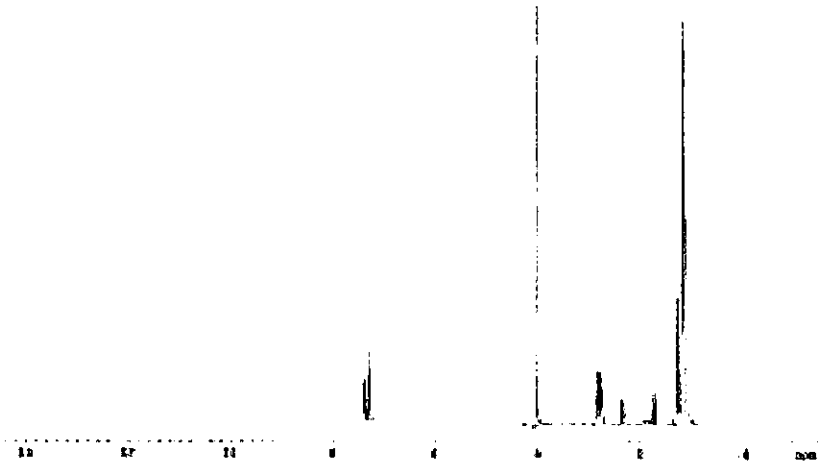

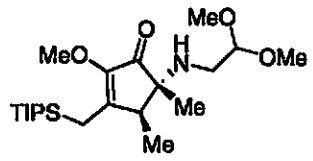

2.27

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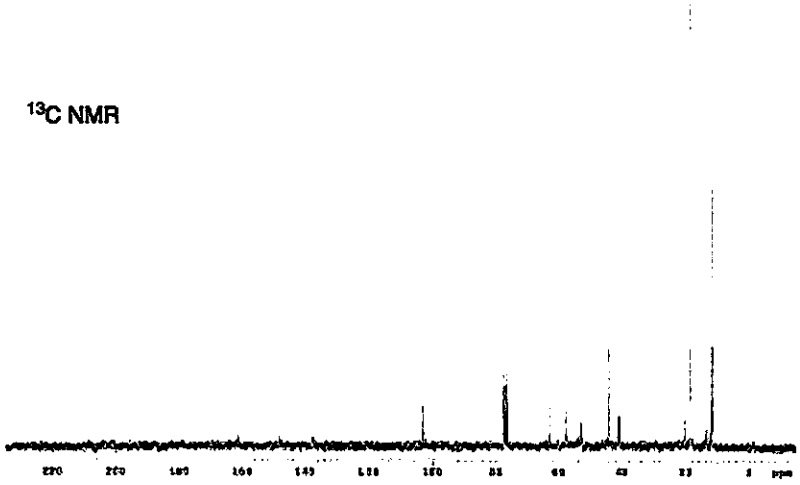

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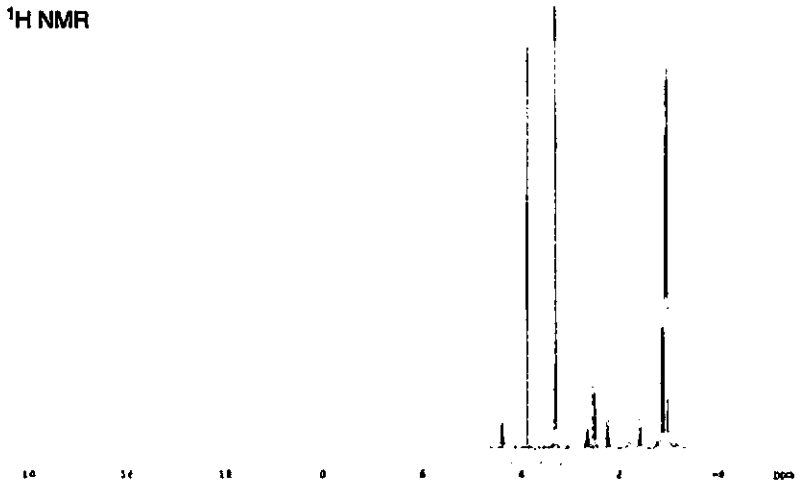

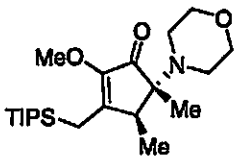

2.28

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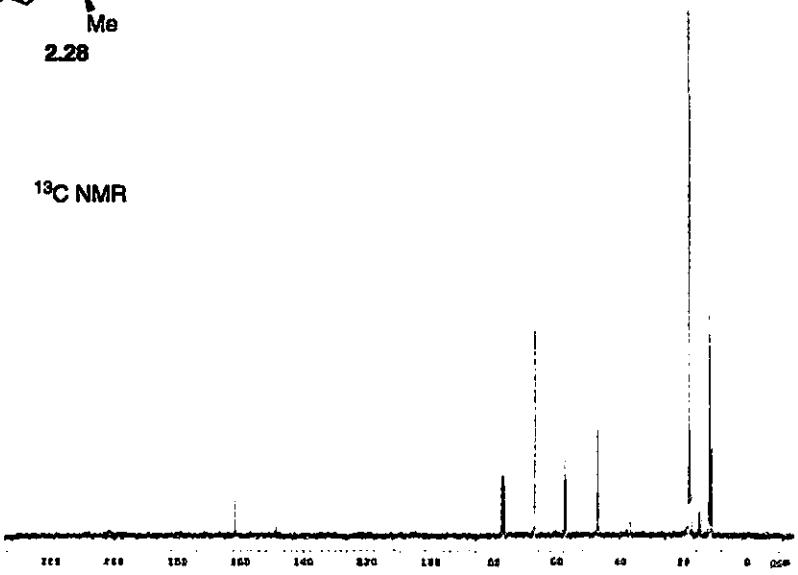

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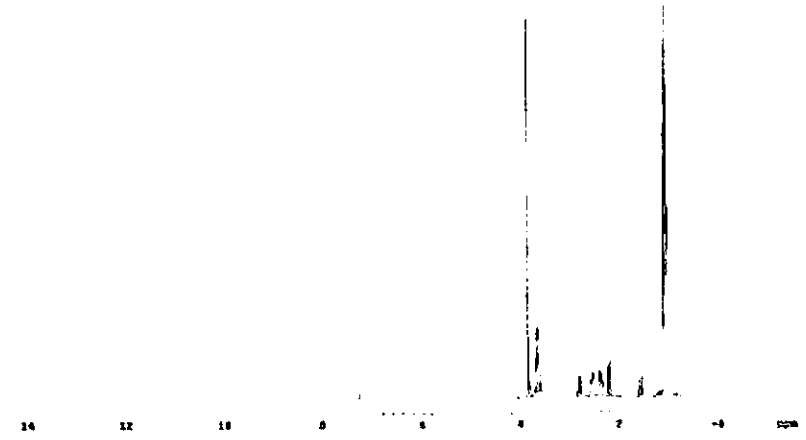

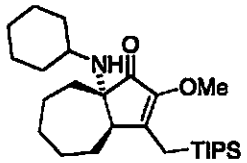

2.29

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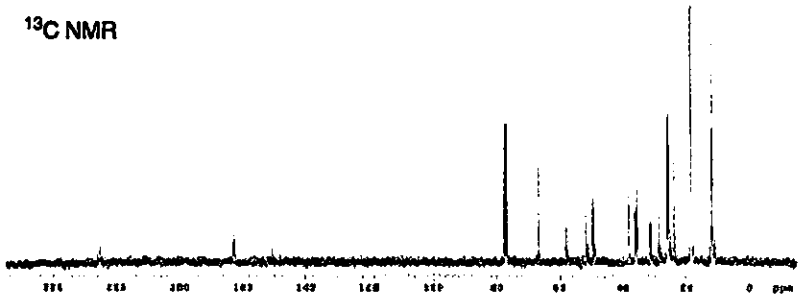

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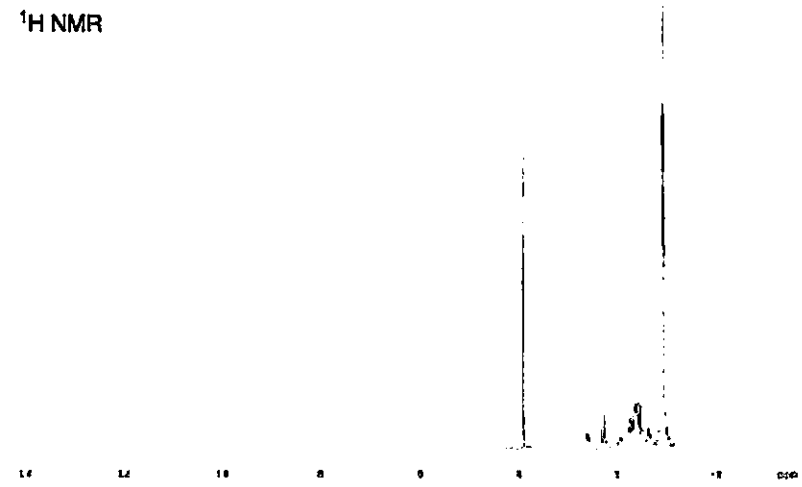

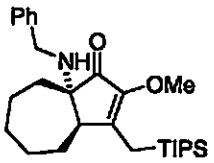

2.30

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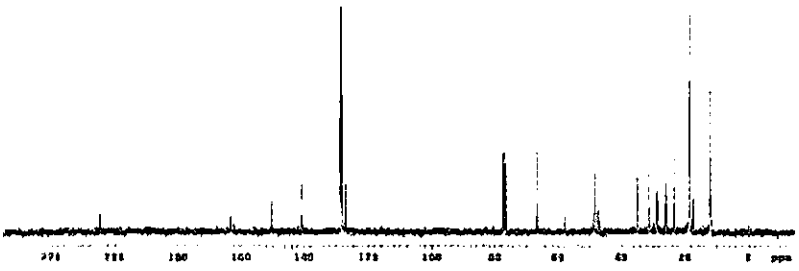
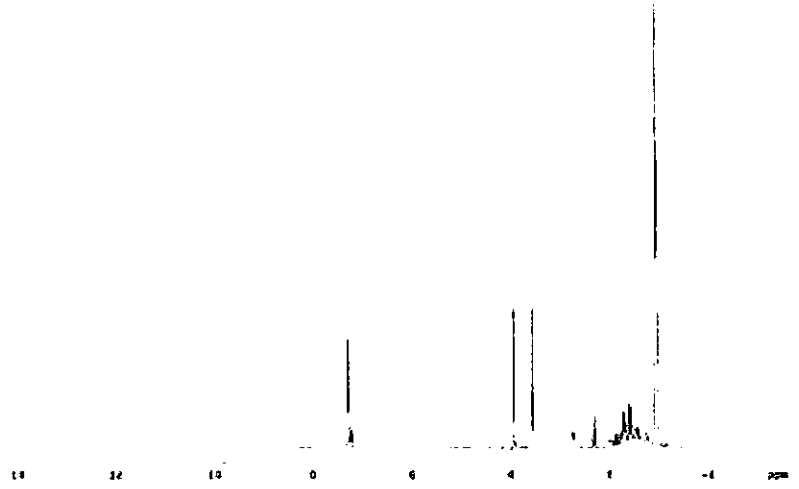
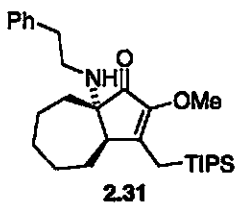


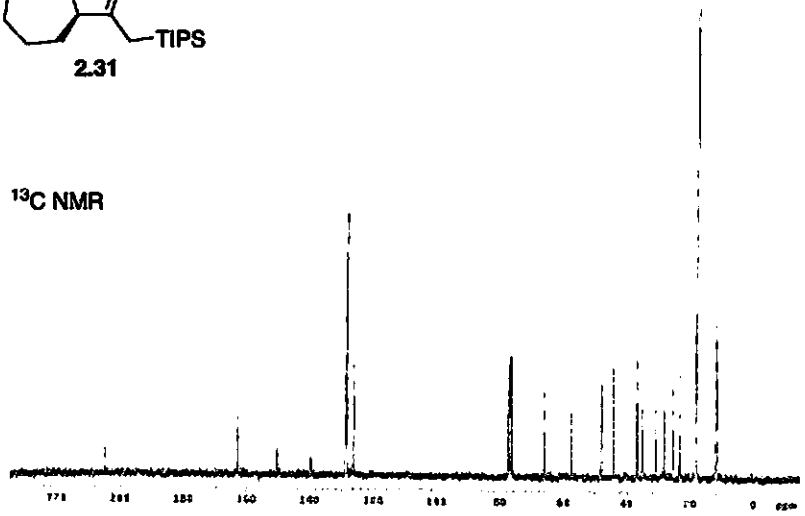
^{1}H NMR





2.31

^{13}C NMR



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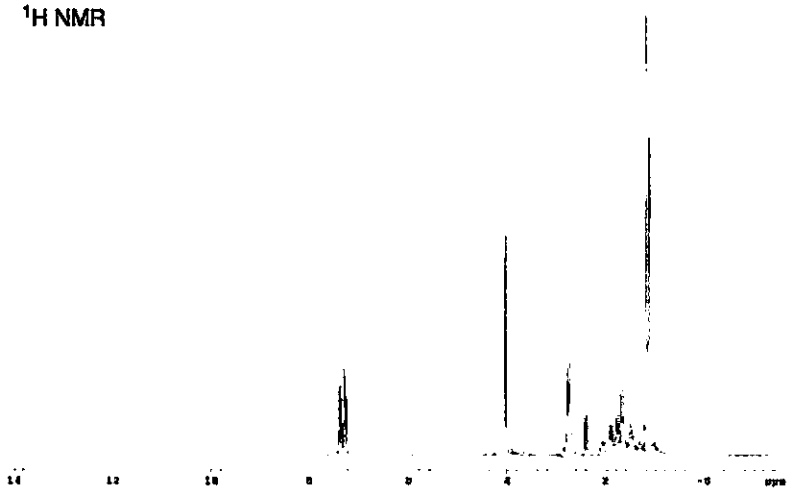

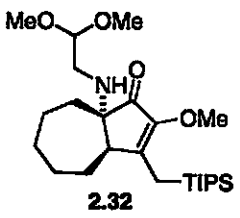

2.32

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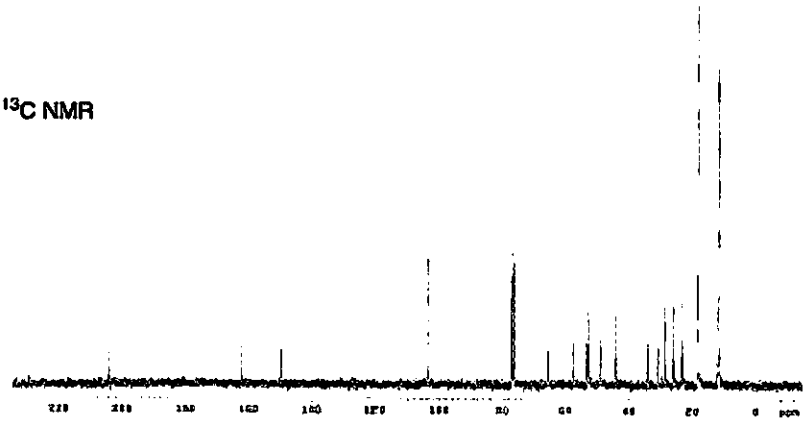

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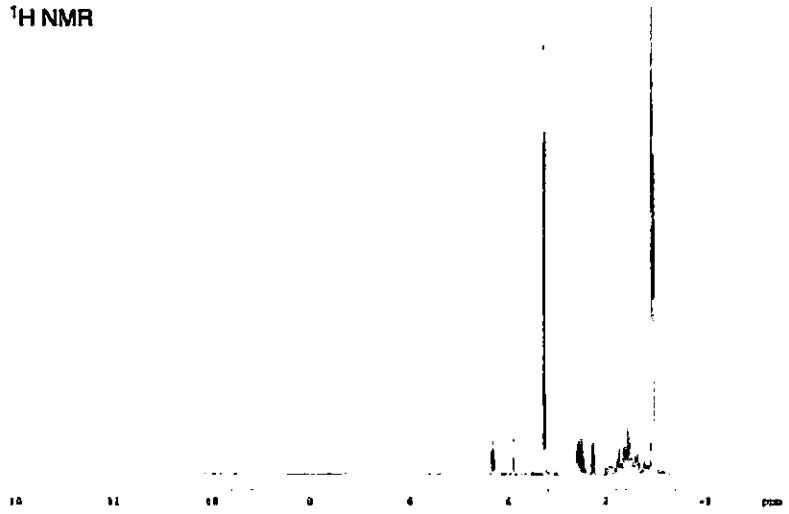
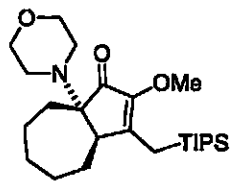
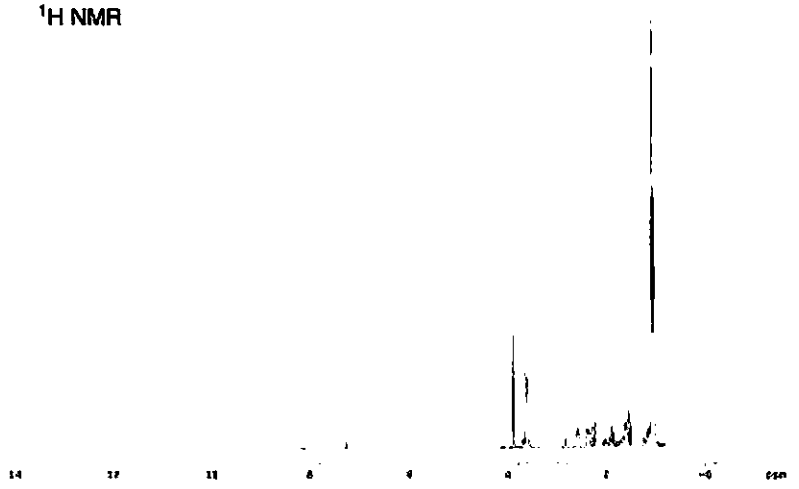


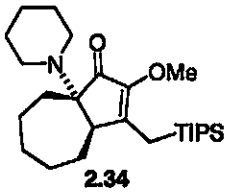


2.33

^{13}C NMR

^{1}H NMR





2.34

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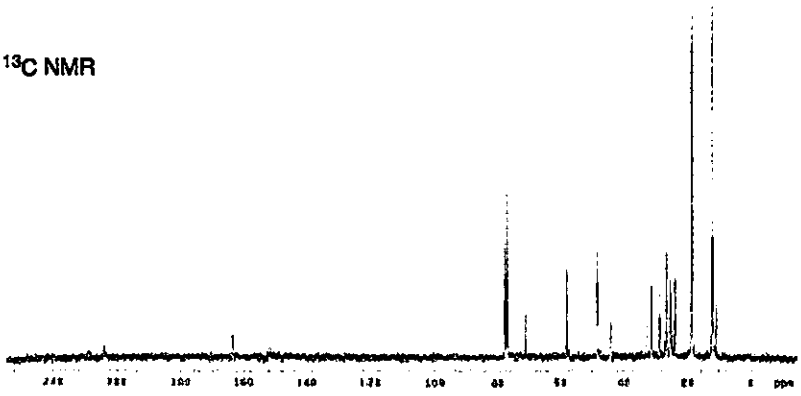
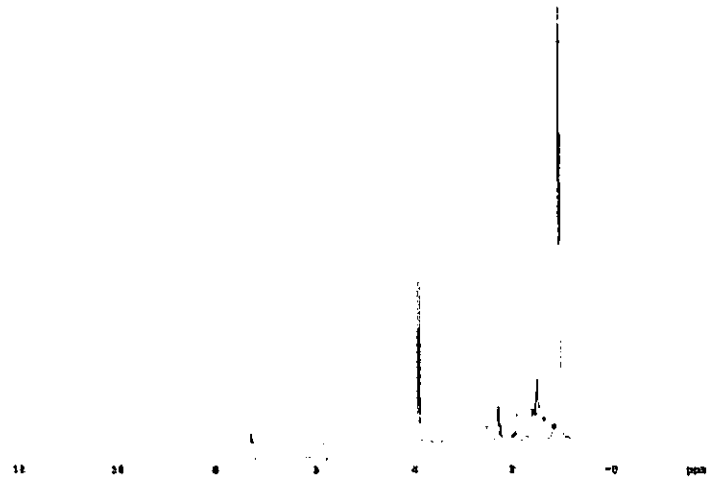
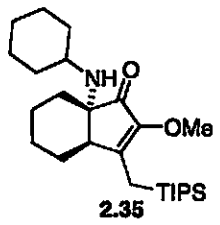


^{1}H NMR





2.35

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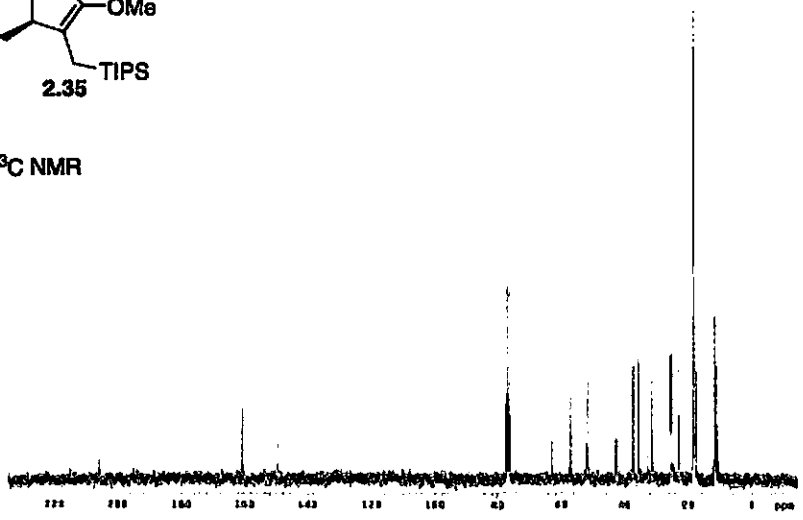
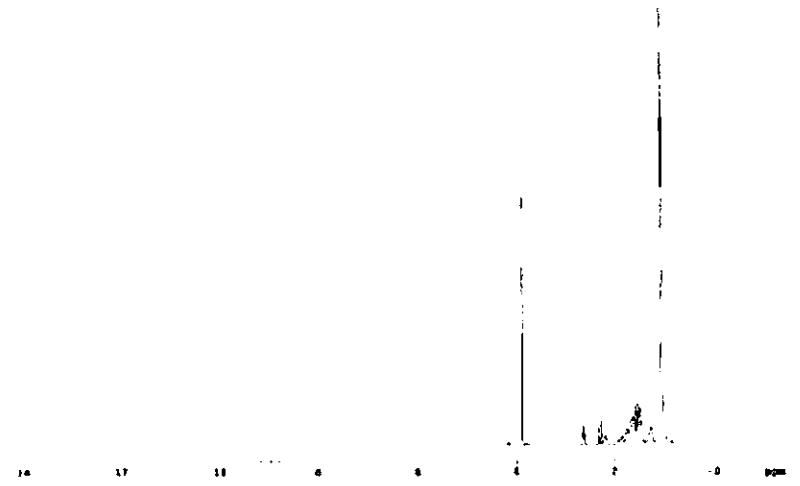
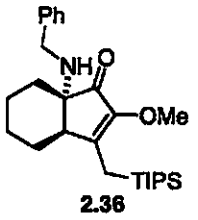


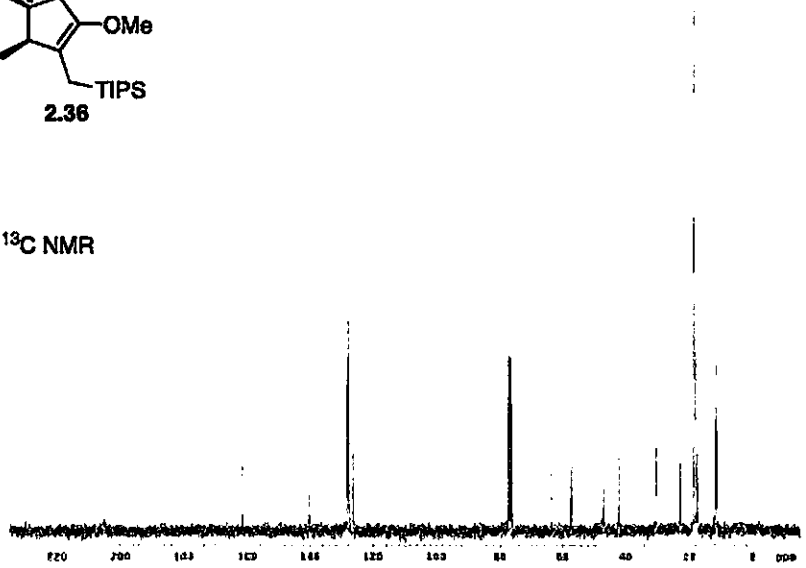
^{1}H NMR



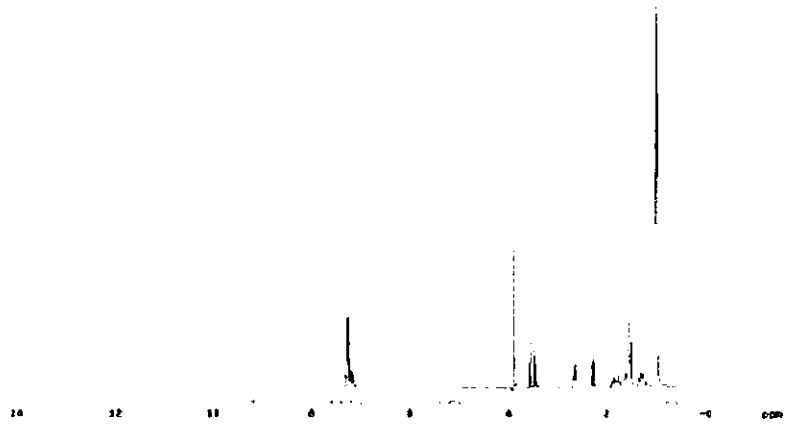


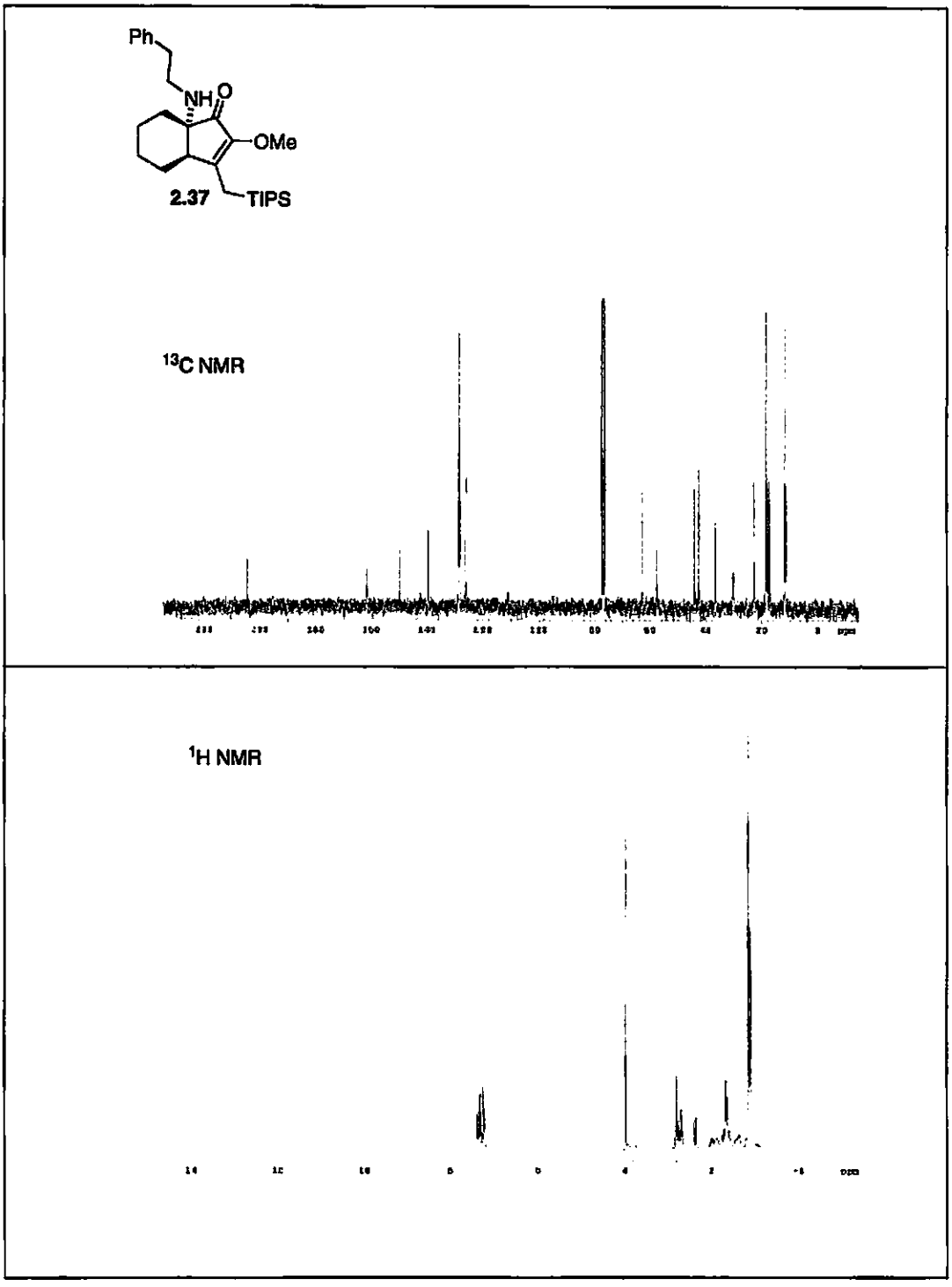
2.36

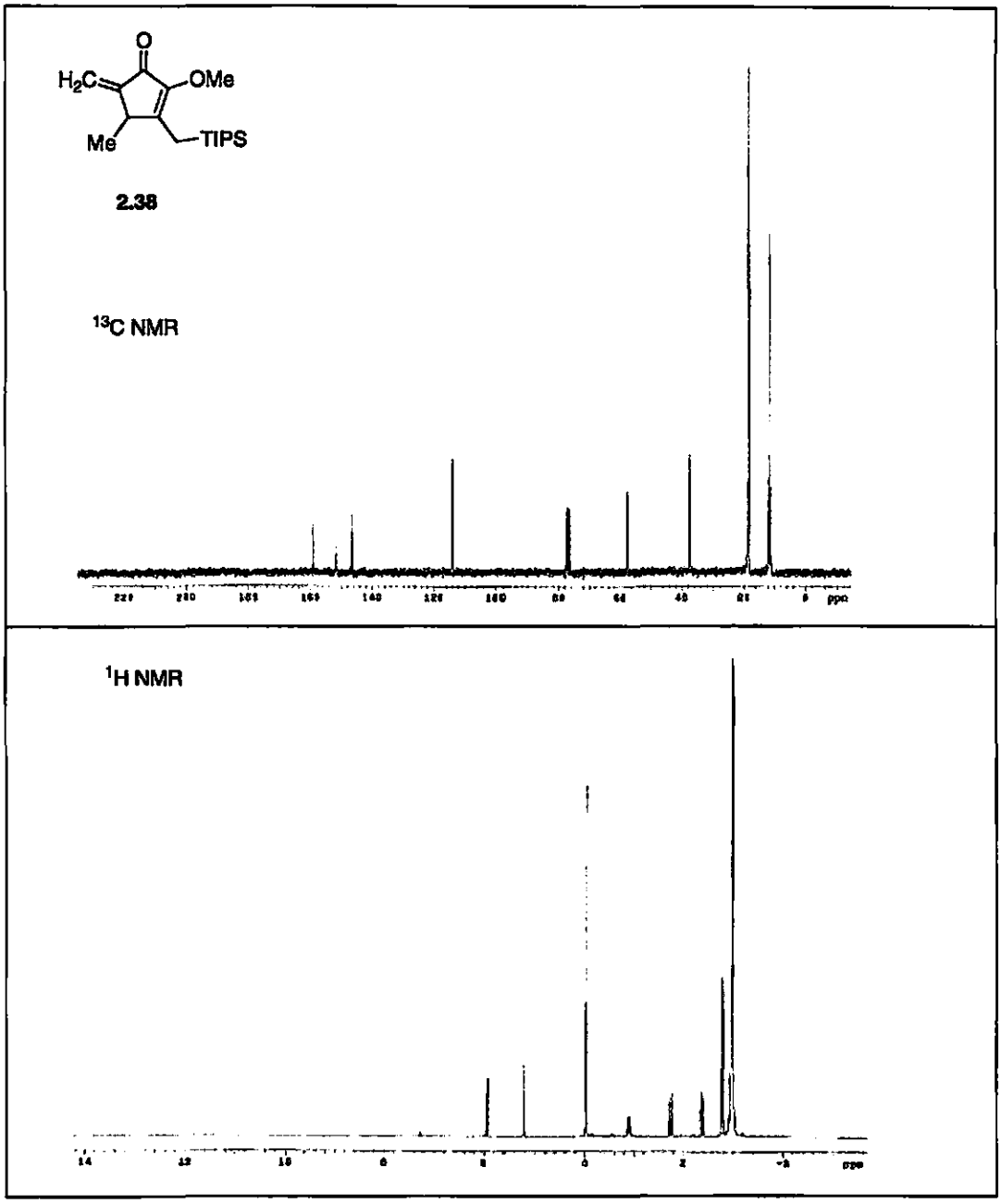
^{13}C NMR

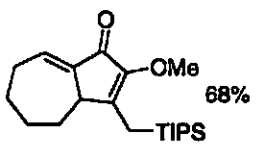


^{1}H NMR



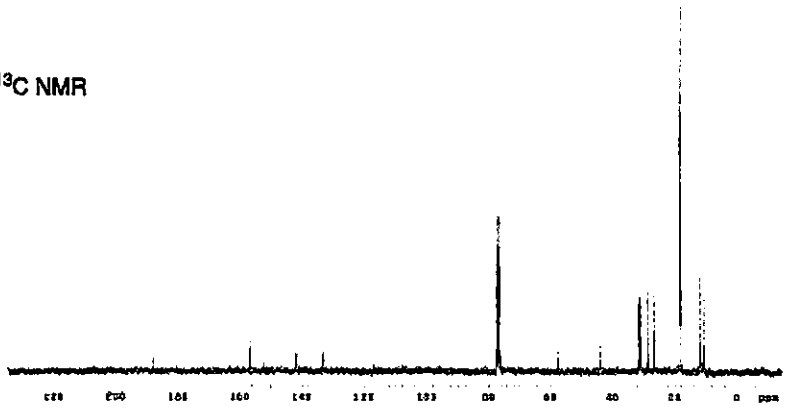

Ph
NH
O
OMe
2.37
TIPS
^{13}C NMR
^{1}H NMR


O
H2C
OMe
Me
TIPS
2.38
13C NMR
1H NMR

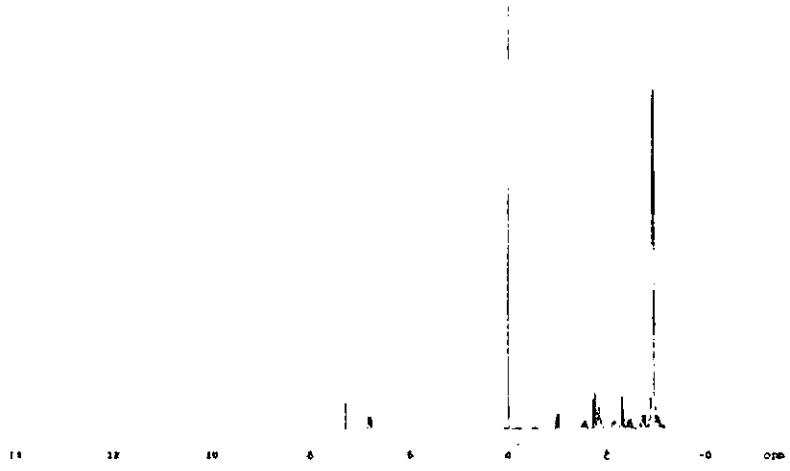


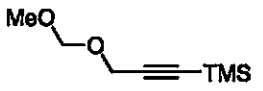
2.39

^{13}C NMR



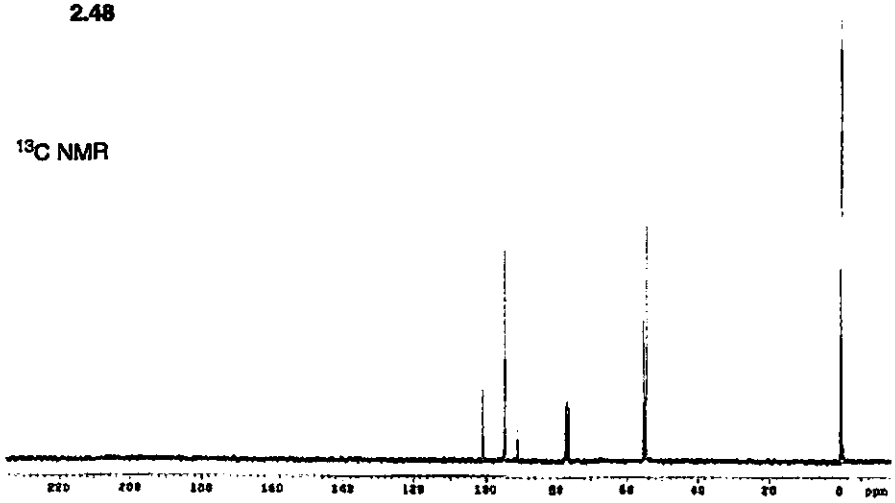
^{1}H NMR



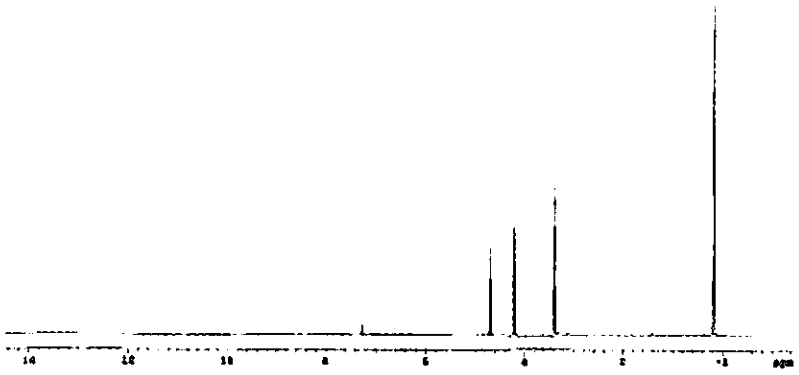


2.48

^{13}C NMR

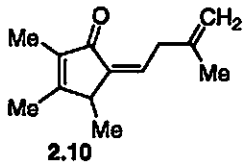


^{1}H NMR



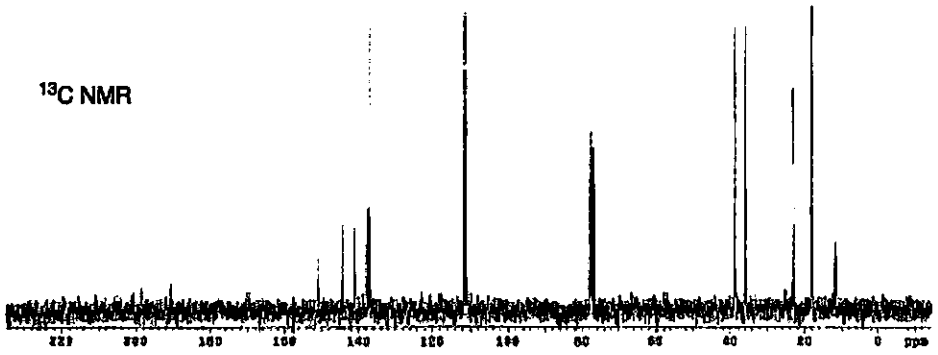
Spectral Data for Selected Compounds

Part II

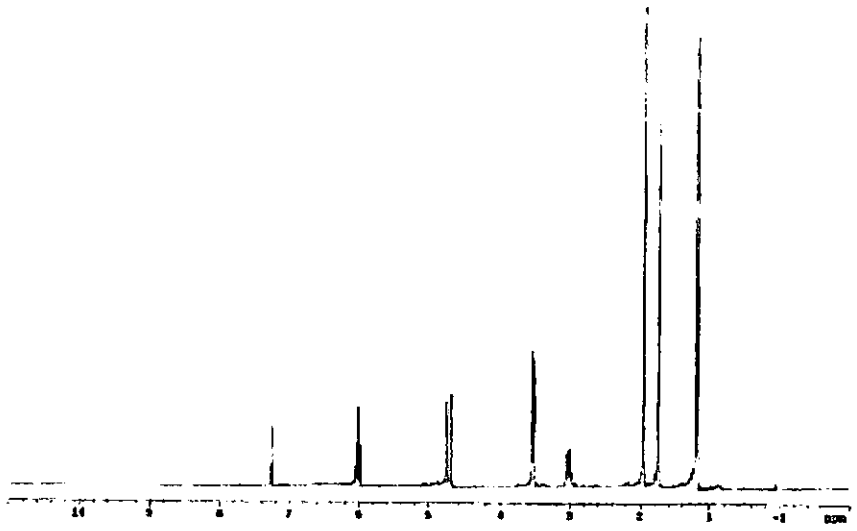


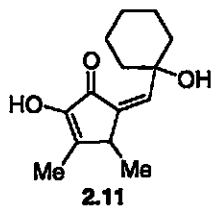
2.10

^{13}C NMR



^{1}H NMR

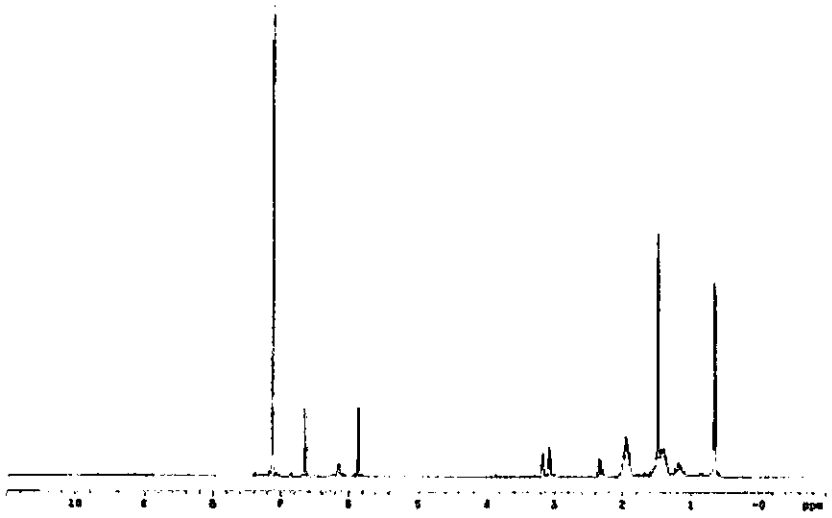


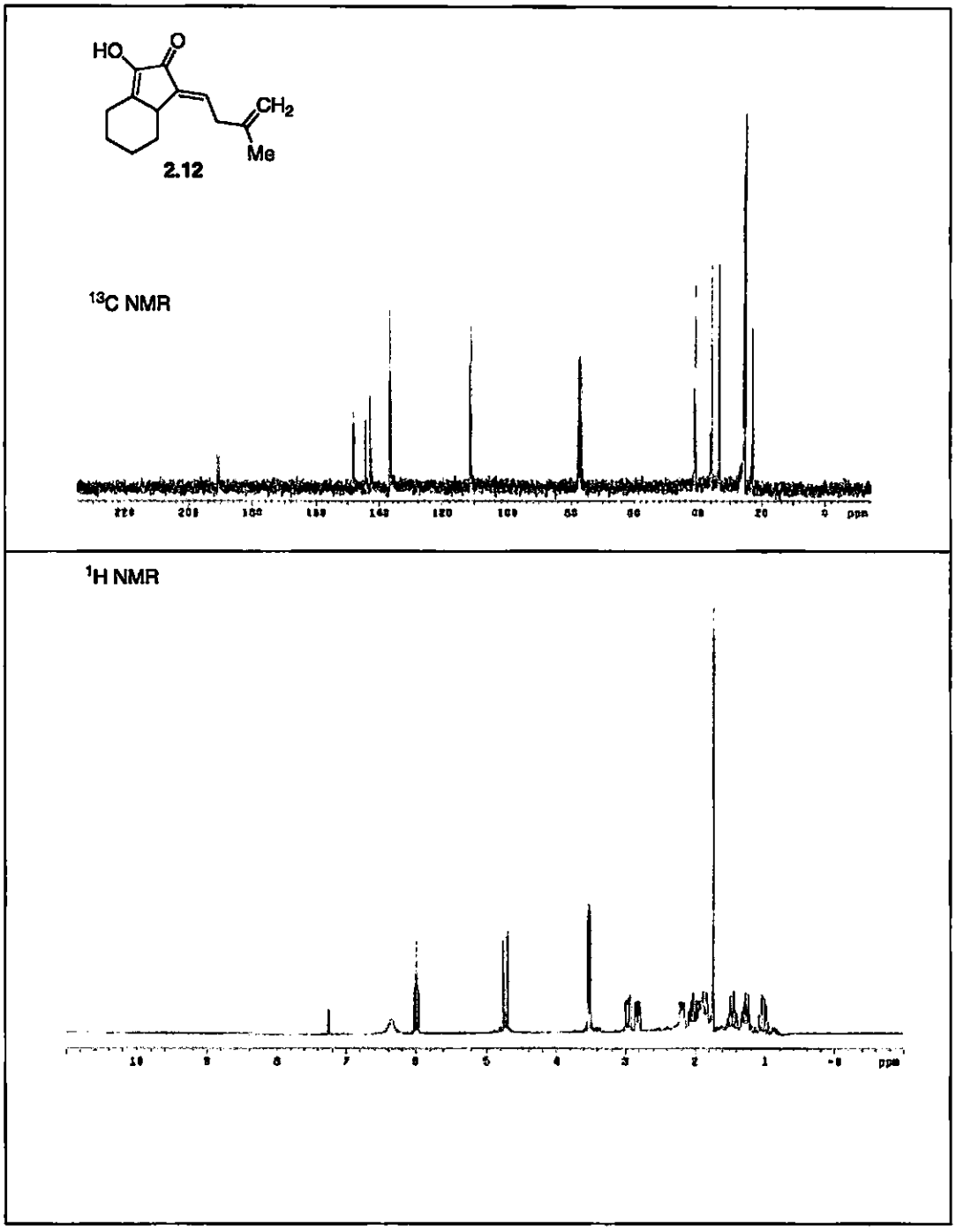


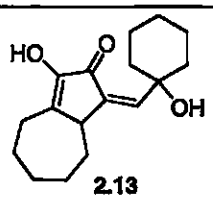
2.11

^{13}C NMR

^{1}H NMR

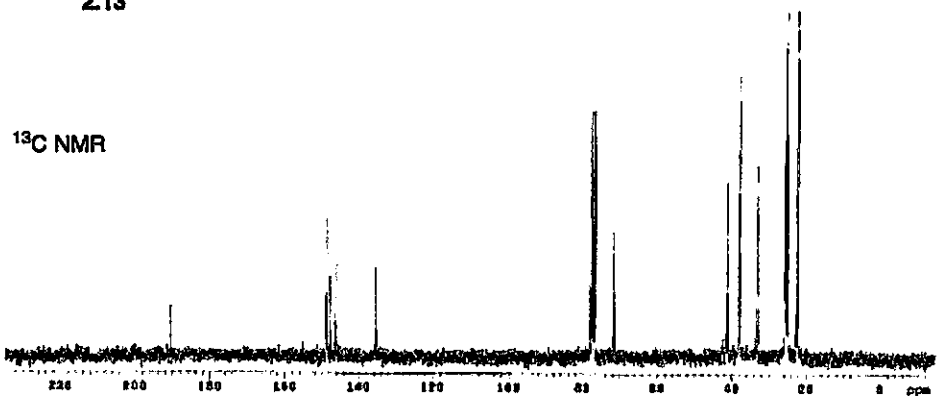



HO
O
CH2
Me
2.12
13C NMR
1H NMR

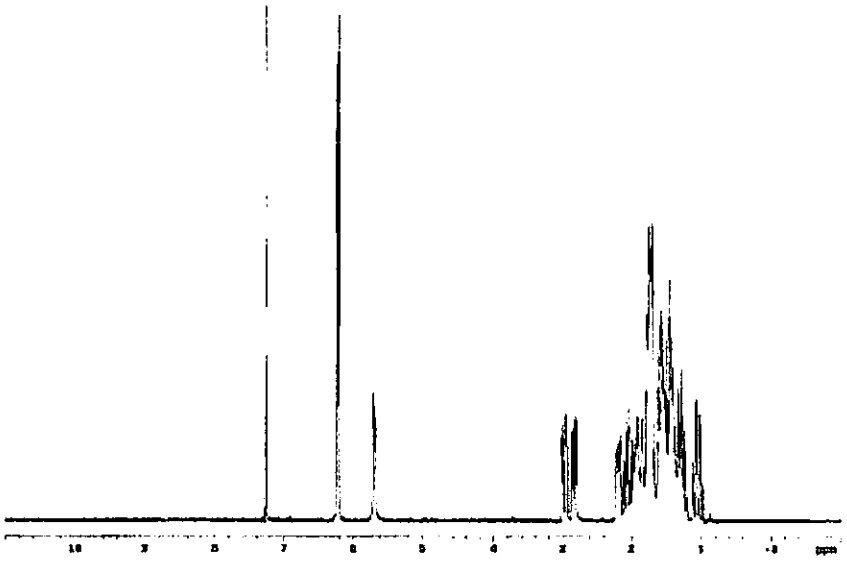


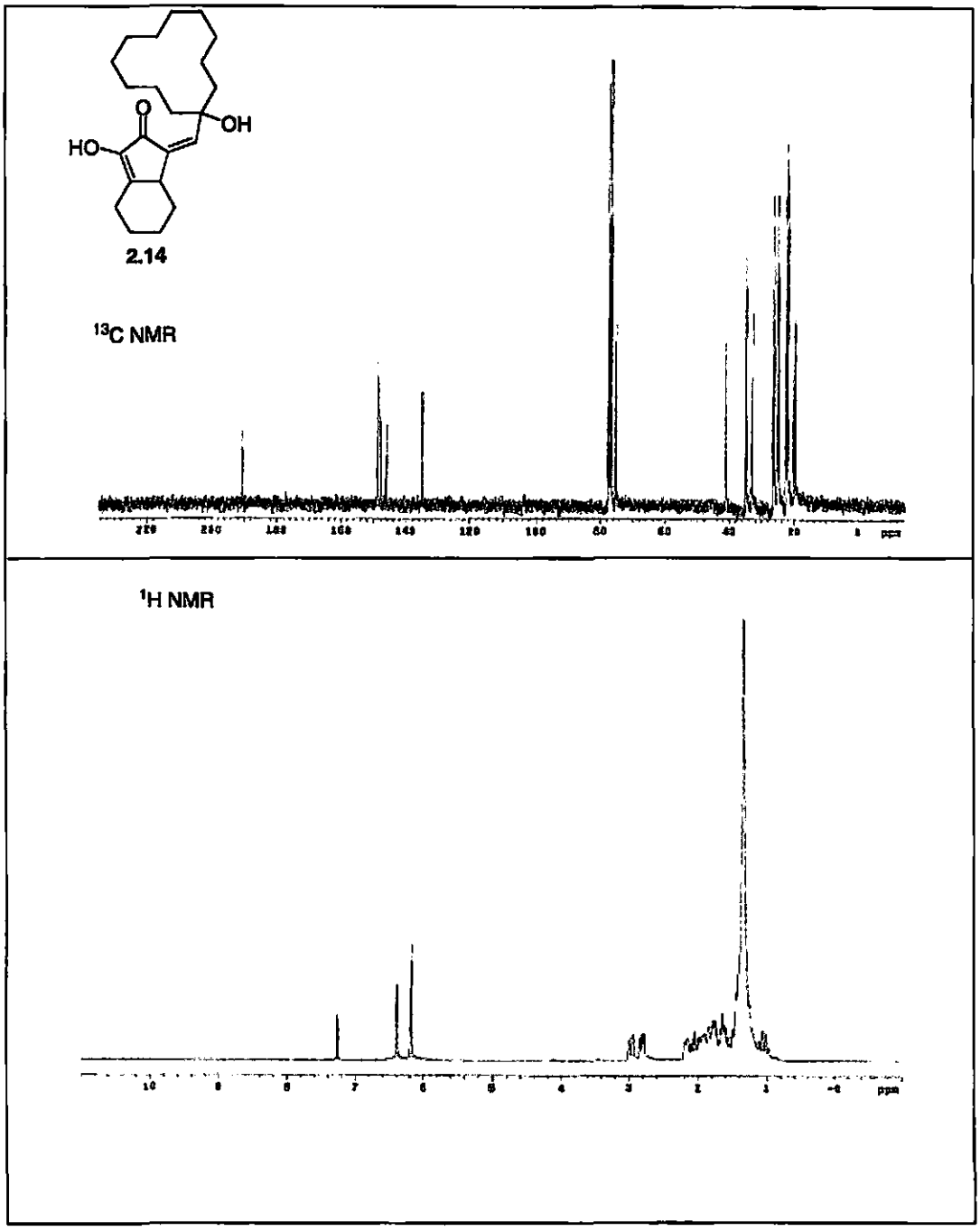
2.13

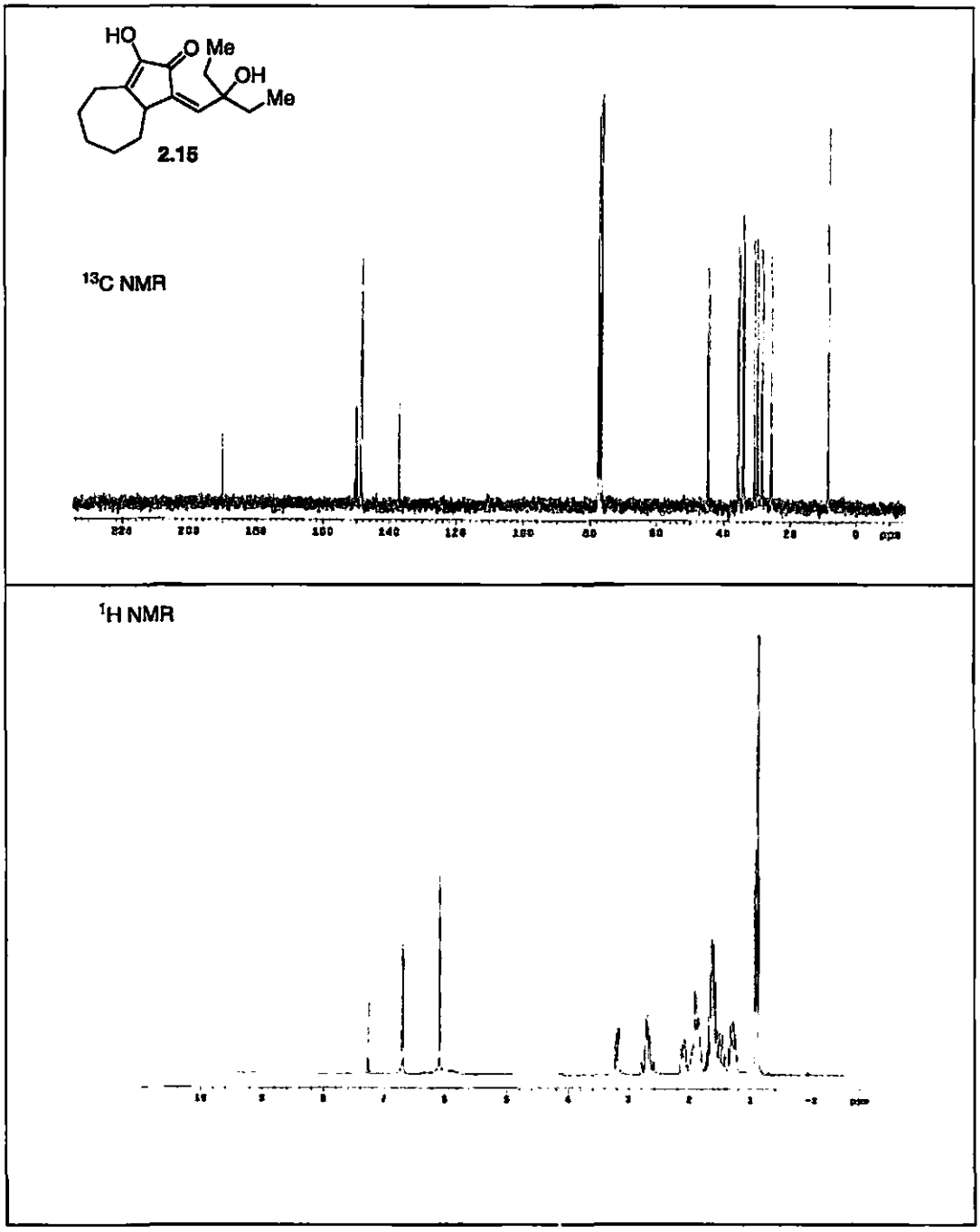
^{13}C NMR

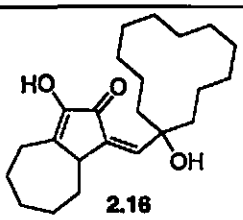


^{1}H NMR




HO
O
OH
2.14
^{13}C NMR
^{1}H NMR


HO
O
Me
OH
Me
2.15
^{13}C NMR
^{1}H NMR



2.16

^{13}C NMR

^{1}H NMR