RHODIUM(I)-CATALYZED CYCLOISOMERIZATION OF NITROGEN TETHERED ENE-ALLENES: FORMATION OF TETRAHYDROAZEPINES

by

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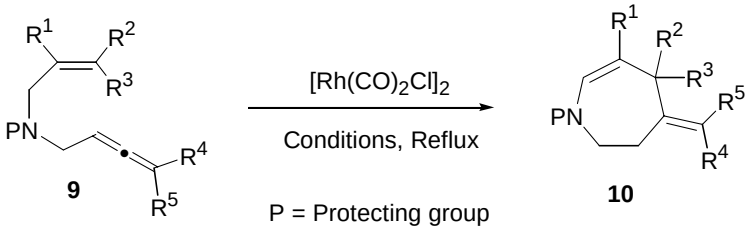

Abstract: A novel cycloisomerization process involving nitrogen-tethered 1,6-ene-allenes has been realized. Subjecting ene-allene **9** to rhodium biscarbonyl chloride dimer produces tetrahydroazepine **10** in moderate to high yields. Substituting the allene moiety with the bulky *tert*-butyl-group (R^4 = *t*-Bu), while employing a *trans*-alkene tether, afforded the corresponding azepines in the highest yields. This formal Alder-ene transformation tolerated not only a variety of alkyl-substituents on both the alkene and allene portions but also silyl-[R^2 = $SiMe_3$, $SiMe_2Bn$; R^4 = Si(*i*-Pr)$_3$] and phenyl-(R^2 = Ph, R^4 = Ph) substituents. A deuterium labeling study aided in the postulation of two possible mechanisms for this cycloisomerization. During the course of this investigation, a novel carbon monoxide insertion reaction was observed. Our findings to date are reported and discussed herein.

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LIST OF SCHEMES

ABBRIVIATIONS

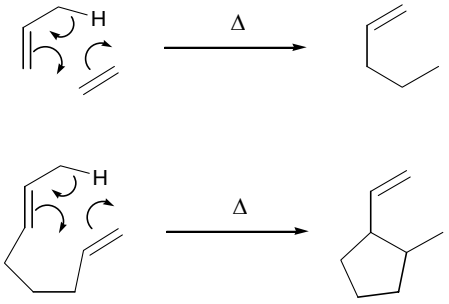
AcOH	Acetic acid
MeCN	Acetonitrile
PhH	Benzene
BBEDA	bis(benzylidene)ethylenediamine
9-BBN	9-Borabicyclo[3.3.1]nonane
Boc	*t*-butoxycarbonyl
TBS	*t*-butyldimethylsilyl
Cbz	Carbobenzyloxy
TMSCl	Chlorotrimethylsilane
DCE	Dichloroethane
DCM	Dichloromethane
DCC	Dicyclohexylcarbodiimide
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DME	1,2-Dimethoxyethane
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
HMPA	Hexamethylphosphoramide
MeOH	Methanol
PPTS	Pyridinium-*p*-toluenesulfonate

TBAF	Tetrabutylammoniumfluoride
THF	Tetrahydrofuran
THP	Tetrahydro-2*H*-pyran
TLC	Thin Layer Chromatography
Ts	*p*-Toluenesulfonyl
Red-Al®	Sodium dihydro-*bis*-(2-methoxyethoxy)-aluminate

1.0 INTRODUCTION

1.1 THE ALDER-ENE REACTION

The Alder-ene reaction is the substitution onto a π-bond of a molecule involving an olefin possessing an allylic hydrogen (Scheme 1).[1] This "ene" reaction is one of such C-C bond forming transformations that may lead to a cyclic product if the "ene" and "enophile" are tethered to the same substrate (Scheme 1). Cycloisomerization reactions are important transformations in organic synthesis which find some of their highest utility in complex molecule development and natural product assemblage. This class of reactions displays absolute atom economy by dispensing with the need for added reagents and generation of stoichiometric by-products.

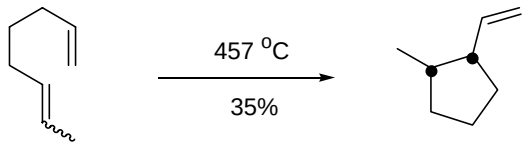


Scheme 1. The Alder-ene reaction

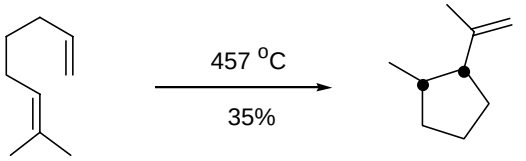
The Alder-ene reaction is a concerted six electron pericylic reaction, analogous to the Diels-Alder cycloaddition. Historically, it has been promoted by high temperatures with varying degrees of success.

1.2 THE THERMAL ALDER-ENE REACTION OF DIENES

Under thermal conditions, a 1,6-diene cyclizes to provide a 5-membered ring. Using a mixture of the *cis*- and *trans*-diene, Huntsman has shown that only the *cis*-cyclopentane product is formed (Eq. 1).[2] Furthermore, the *cis*-isomer is also obtained when employing a trisubstituted

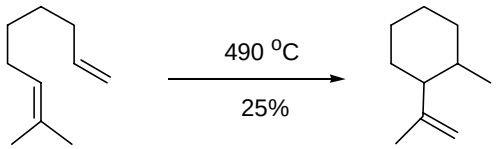


Eq. 1



Eq. 2

ene component (Eq. 2).[2] Reacting a 1,7-diene can afford either the 6 or 8-membered ring closure. The conversion of 1,7-diene **1** to cyclohexane **2** (Eq. 3) occurs in low yield under elevated temperature.[3] In thermal ene-reactions, formation of cyclohexane rings from 1,7-dienes versus cyclopentane rings from 1,6-dienes requires higher temperatures and provides the

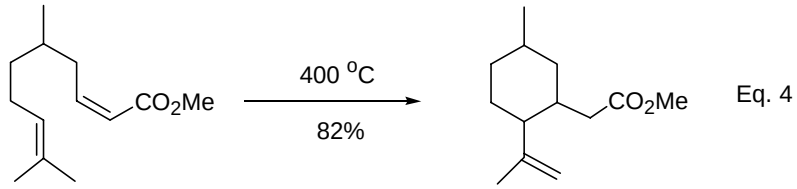


Eq. 3

1 **2**

cycloisomerized products in lower yields.[4] The scope of the thermal Alder-ene reaction was increased by using electron deficient enophiles. The reaction yields can be increased, and the temperature at which the cyclization is performed decreased, when implementing an unsaturated ester as the enophile (Eq. 4).[3] More recently the employments of transition metal catalysts have facilitated the Alder-ene reaction at much lower temperatures. Owing to the advent of these mild

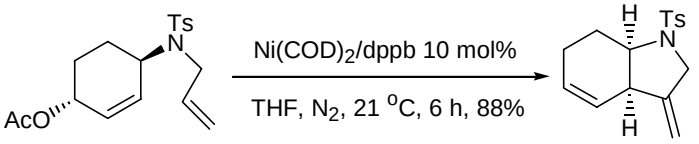
conditions, the Alder-ene reaction has been the focus of much attention due to its chemoselectivity and opportunity for fabrication of intricate cyclic skeletons.[1, 5]



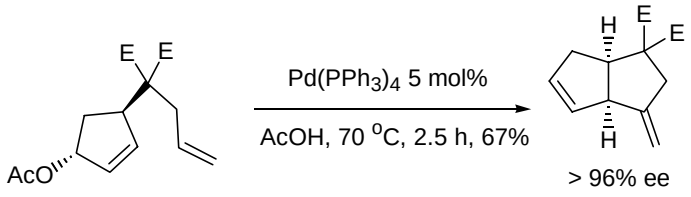
Eq. 4

1.3 THE METALLO-ENE REACTION

Many researchers have implemented the use of allylic leaving groups on their substrates which, upon exposure to the proper metal catalyst, form a π-allyl-metal complex that facilitates cyclization. Better known as the metallo-ene reaction, this transformation has gained extensive use in organic synthesis and provides access to frameworks which were previously unattainable by thermal cycloisomerization methods of dienes. The first of these metallo-ene reactions utilized nickel[6] and palladium[7,8] to accomplish a carbon-carbon bond formation and could be



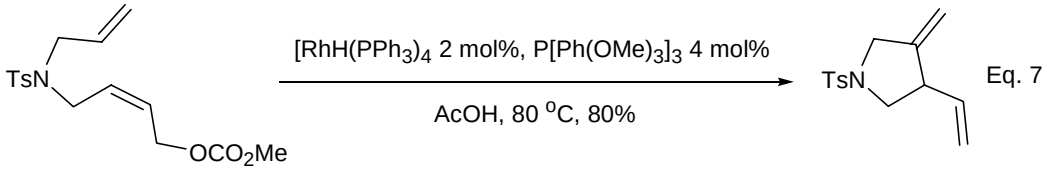
Eq. 5



Eq. 6

shown to operate in a diastereo-selective manner when using chiral nonracemic substrates (Eq. 5, 6). A short time after initial report of the metallo-ene reaction with nickel and palladium, Oppolzer demonstrated that the cyclization could also be performed with a rhodium catalyst

(Eq 7).[9] Milder conditions that do not require a protic acid are also described using $[Rh(COD)Cl]_2/Et_3N$ in MeCN solvent, but are reported to afford a lower yield (63%).

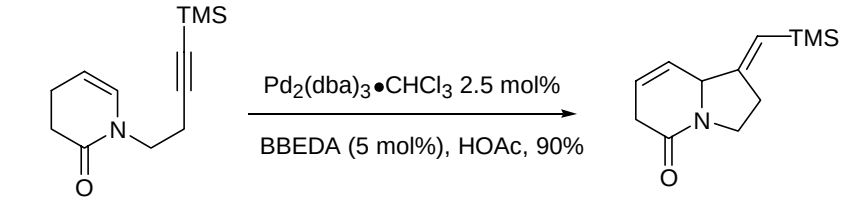


Eq. 7

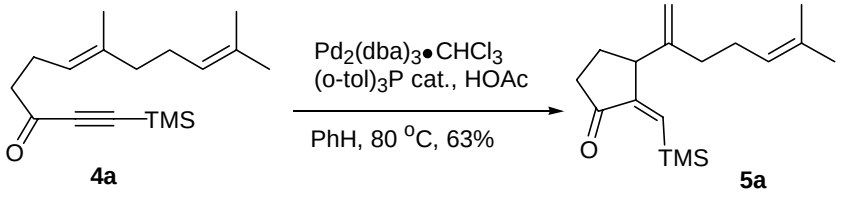
1.4 THE CATALYTIC ALDER-ENE REACTION OF ENYNES

1.4.1 Generality

Enynes have found widespread application as substrates in catalytic Alder-ene reactions within the realm of complex molecule synthesis. Transformations employing enynes result in predictable regiochemistry.[1,5] The major product of a 1,6-enyne cycloisomerization reaction is a 1,4-diene as long as there is opportunity for β-hydride elimination at the allylic position.[5] Substrate tolerance of this catalytic enyne cyclization has proven to be quite general for a range of molecules possessing electron donating or withdrawing groups on both the ene and enophile. A cyclic enamide cycloisomerizes with ease to give the 6,5-ring fused product in 90% yield (Eq. 8).[10] Alkynone **4a** also cyclizes to provide the *exo*-cyclic pentenone **5a** in a 63% yield.[11]



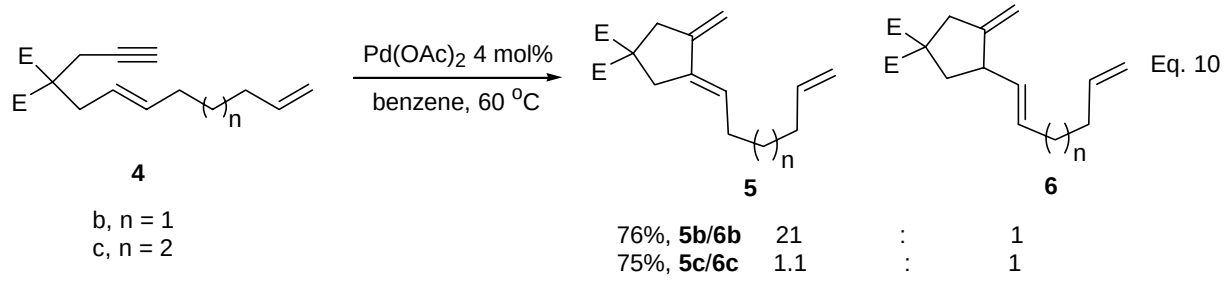
Eq. 8



Eq. 9

1.4.2 Predictability

A cyclized 1,3-diene is commonly formed as the minor product in cycloisomerizations of 1,6-enynes. The 1,3-diene has been observed as the major product in cases when the substrate possesses less substitution around the participating points of unsaturation. This 1,3-regioisomer product (**5**, Eq. 10) can be formed exclusively if there is coordination to the metal complex by remote sites of appended unsaturation, positioned at a proper distance, that direct β-hydride



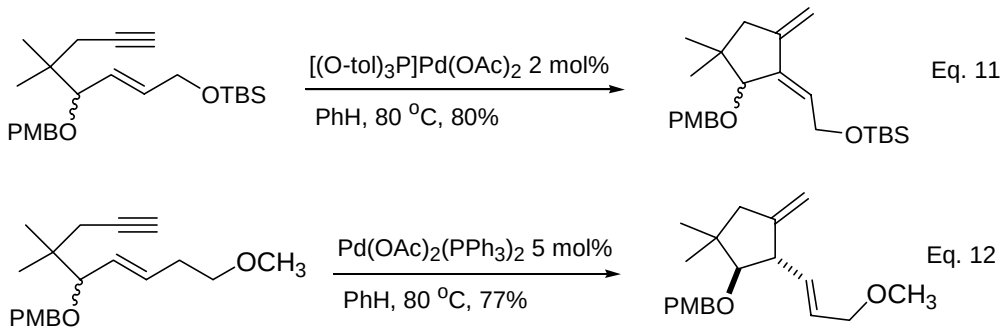
4

b, n = 1
c, n = 2

5 **6**

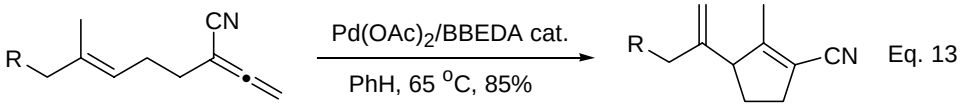
76%, **5b/6b** 21 : 1
75%, **5c/6c** 1.1 : 1

elimination.[12] For palladium, the highest degree of regioselectivity to form the 1,3-diene is achieved when there is a 3-carbon spacer between the reacting olefin and the tethered unsaturated moiety. Substitution patterns of the product can also be controlled by allylic heteroatom placement. An oxygen atom at the allylic position provides a 1,3-diene as product (Eq. 11).[13] Relocating oxygen to the homoallylic position affords the expected 1,4-diene (Eq. 12).[5]



1.5 THE ALDER-ENE REACTION OF ENE-ALLENES

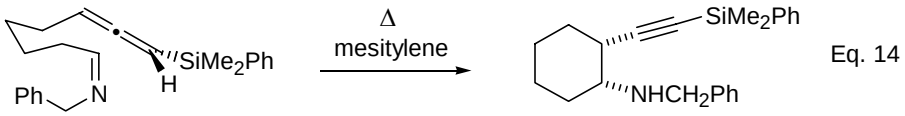
Until recently, the use of allenes in Alder-ene chemistry had been relatively unexplored. Trost has reported a cycloisomerization of a 1,5-ene-allene using palladium (Eq. 13) to afford a 5-membered ring product.[14] This product was an intermediate in the synthesis of petiodial. Due



Eq. 13

to the aprotic reaction conditions, the mechanistic pathway is likely to entail metallocycle formation (oxidative insertion) followed by β-hydride elimination and finally reductive elimination. The alternate pathway, under a protic environment, would involve hydrometallation followed by carbo-metallation, regenerating the metal-hydride species with a β-hydride elimination.

Weinreb has employed an imino-ene reaction with an allenyl-silane moiety to provide intermediates for enantioselective syntheses of (-)-montanine, (-)-coccinine, and (-)-pancracine.[15] The reaction was executed thermally and exhibited excellent stereocontrol (Eq. 14).



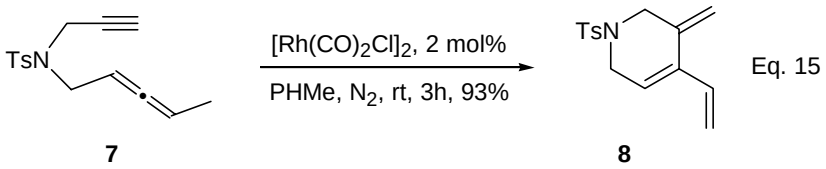
Eq. 14

1.6 DISCOVERY OF A NEW CYCLOISOMERIZATION REACTION

1.6.1 The motive behind discovery

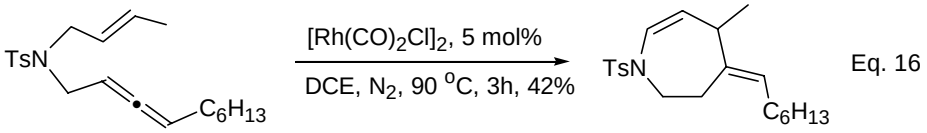
Our laboratory has been actively investigating the scope of a catalytic Alder-ene reaction involving allenynes of various tether lengths and substitution patterns. For example, subjecting

allenyne **7** to rhodium bis-carbonyl chloride dimer produces cross-conjugated triene **8** in 93% yield in 3 hours at room temperature (Eq. 15).[16] Malacria[17] and Sato[18] have reported on cross-

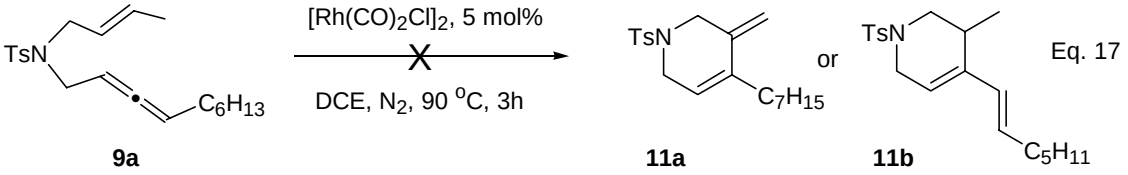


7 **8** Eq. 15

conjugated triene formation using allenynes, however these transformations require stoichiometric amounts of transition metal complex. Livinghouse[19] has also observed triene formation with allenyne substrates though they are produced as minor products under catalytic metal conditions. Our discovery of this rapid triene formation prompted us to employ ene-allenes as substrates to probe the possibility and/or selectivity of diene formation upon cyclization. Surprisingly, when ene-allene **9a** was subjected to modified conditions (heating to reflux) used for triene formation, a cycloisomerization occurred to form the azepine **10a** (Eq. 16)[20] and not the expected 6-membered ring dienes **11a** or **11b** (Eq. 17).



9a **10a** Eq. 16

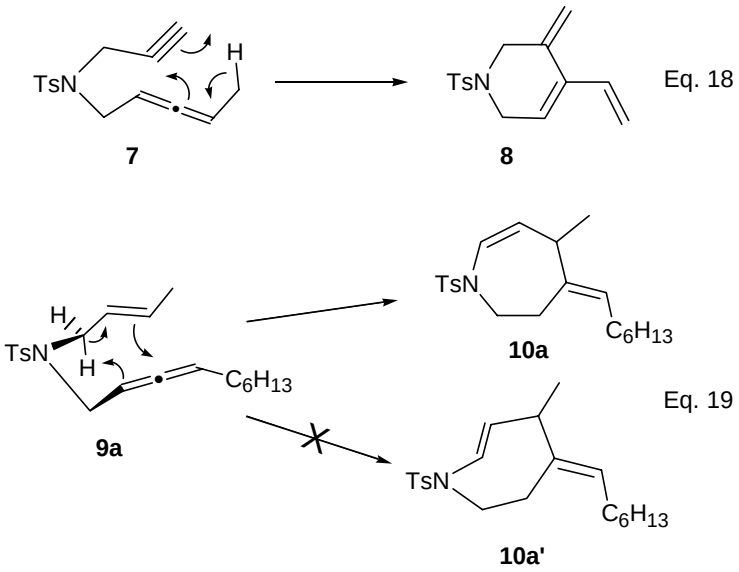


9a **11a** **11b** Eq. 17

1.6.2 Baldwin's rules

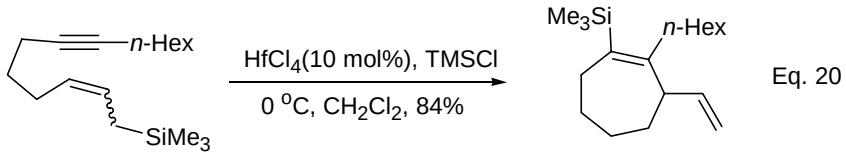
A novel aspect of this cycloisomerization was the reversal from *exo*-mode cyclization for allenyne substrates in triene formation (Eq. 15), to the exclusive *endo*-mode cyclization for ene-

allene tethers regarding production of azepines (Eq. 16). Without catalyst, these Alder-ene transformations can mechanistically be represented by equations 18 and 19. Upon inspection of

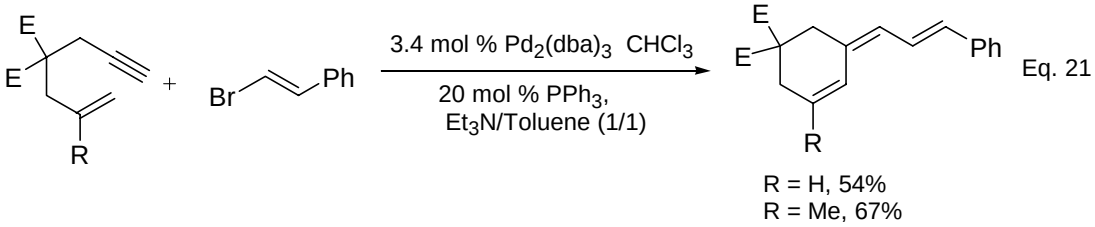


eq. 19, one realizes that *trans*-ring **10a′** should be the sole product due to the lack of orbital overlap between the allene and allylic hydrogen on the alkene tether to form the *cis*-ring **10a**. Formation of a *trans*-double bond in a 7-membered ring is unfavored and results in a highly strained molecule. The *trans*-geometry outcome can be avoided by employing a stepwise mechanism, which would be accessed through the use of Lewis acids and/or transition metals *vide infra*.

According to Baldwin,[21] 7-*endo-dig* ring closure is a stereoelectronically favored process; however in transition metal catalyzed Alder-ene reactions this mode of cyclization is not reported. An *endo-dig*-carbocyclization has been communicated by Yamamoto, though it is effected by allylsilane attack on an alkyne while using the catalyst as a Lewis acid (Eq. 20).[22]

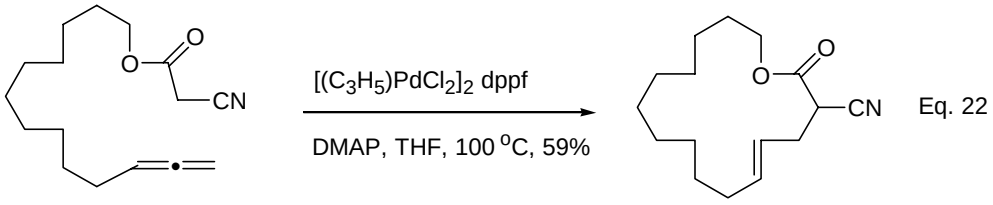


More often reported are 6-*endo-trig* cyclization of 1,6-enynes,[23,1] though these examples are very substrate dependent. In Trost's case, the substrates require a terminal alkyne and either a mono-substituted alkene or a 1,1-disubstituted alkene (Eq. 21).[23] Conversely, macrocyclization



Eq. 21

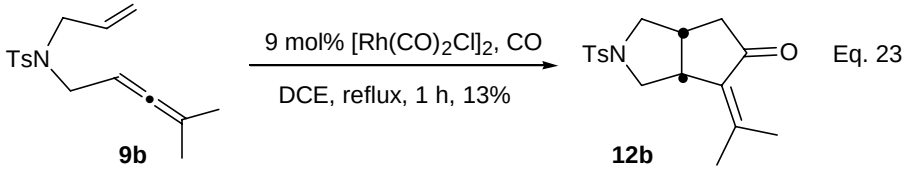
demonstrates a more general substrate tolerance towards *endo-trig* cyclization.[24] An oxaene *endo-trig* macro-cyclization using an allene has been reported by Trost under palladium catalyst conditions (Eq. 22).[25]



Eq. 22

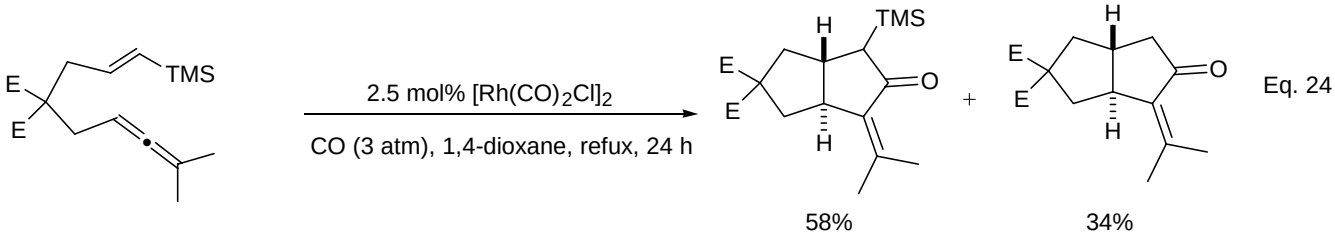
1.7 OBSERVATION OF A CARBON MONOXIDE INSERTION PRODUCT

Subjecting ene-allene **9b** to 9 mol% catalyst in DCE under a carbon monoxide environment produced the α-alkylidene cyclopentenone **12b** in a low 13% yield (Eq. 23).



Eq. 23

Insertion of carbon monoxide into an ene-allene system has been reported by Itoh,[26] under similar conditions, providing a single example (Eq. 24). To date, no reports have been



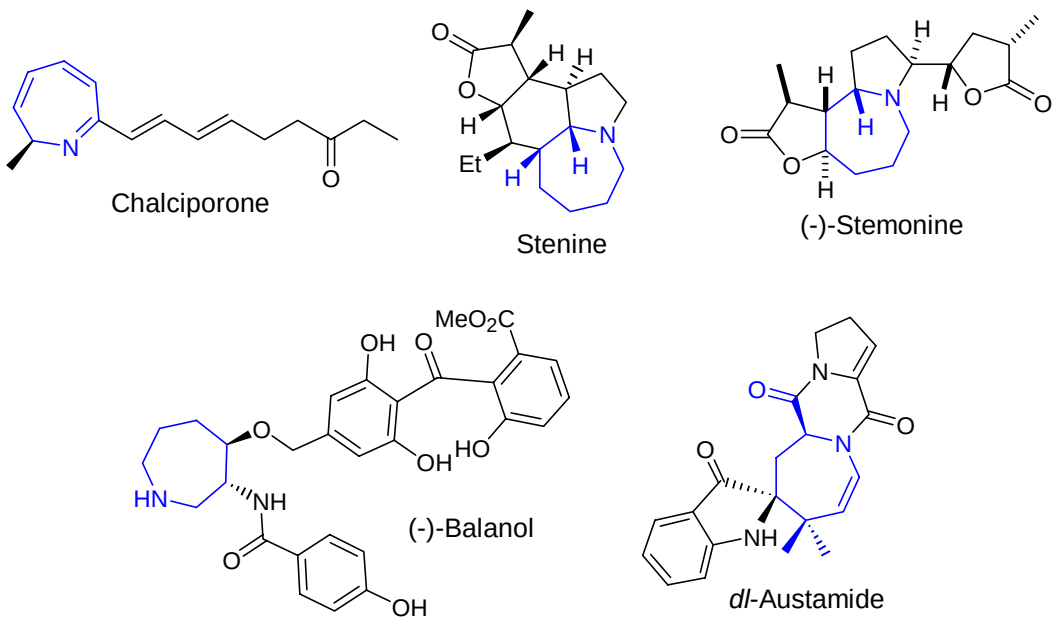
Eq. 24

communicated for carbon monoxide insertion of nitrogen tethered ene-allenes to form 4-alkylidenehexahydro-cyclopenta[c]pyrrol-5-one systems like that represented by **12b** (Eq. 23). Attempts at optimization of this insertion reaction will be discussed herein.

1.8 AZEPINE CONTAINING NATURAL PRODUCTS

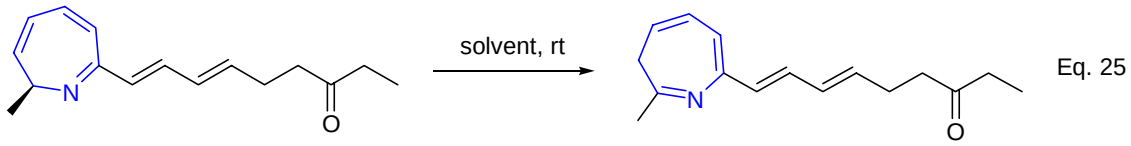
1.8.1 Chalciporone

A number of natural products possess the azepine skeleton as part of their core structure (highlighted in blue, List 1). The first of these alkaloids, chalciporone, is shown to be an antisectiside and very pungent to the taste.[27] It is a 2*H*-azepine and its biosynthesis is hypothesized to be the result of cyclization of a linear polyketide chain.[28] Thus far, no total syntheses have been communicated for the fully functionalized natural product.



List 1. Azepine containing natural products.

Steglich[29] has observed that the 2*H* azepine isomerizes, upon standing in organic solvent, to the more stable 3*H* isomer (Eq. 25). This isomerization phenomenon may pose a formidable challenge during synthesis.

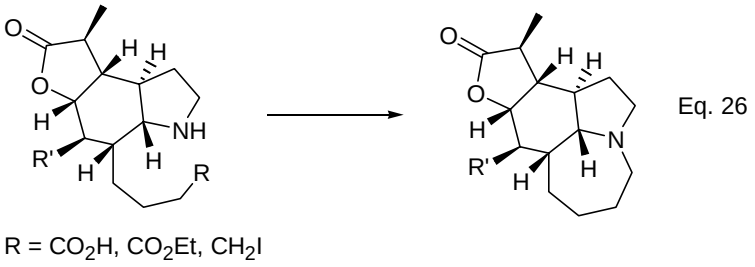


Eq. 25

1.8.2 Stenine and Stemonine

Stemona alkaloids (stenine and stemonine, List 1) have been the topic of intensive pursuit among synthetic organic chemists since their discovery.[30] Isolated from extracts of *Stemona japonica* and *Stemona tuberosa*, this class of alkaloids constitutes active components of the extracts which have been utilized as antitussives, antiparacitics, anthelmintics, and insecticides. The low quantities of pure stenine obtained from the extracts have compelled researchers[31,32,33,34] to

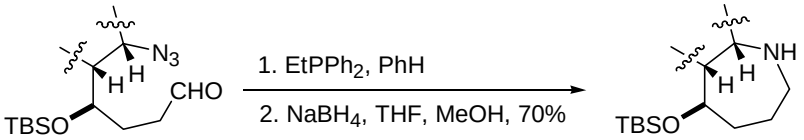
engage in its synthesis, not only for further biological studies but also for determination of its absolute stereochemistry. The azepine core is often the last ring to be formed in these syntheses. Wipf[32] (R = CO_2H, Eq. 26) and Hart[31] (R = CO_2Et, Eq. 26) utilized latamizations to install the azepine moiety while Morimoto[33] employed an *N*-alkylation with the corresponding iodide (R = CH_2I, Eq. 26).



Eq. 26

R = CO_2H, CO_2Et, CH_2I

Stemonine has also been the target of synthetic effort[35] for similar reasons. Williams[35] used a reductive amination approach to install the azepine core as the first ring in the synthesis of Stemonine (Eq. 27).

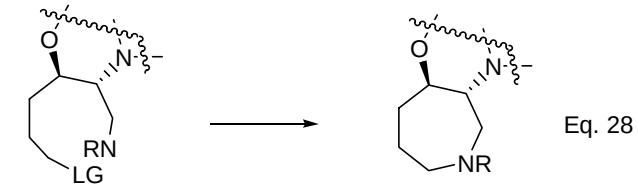


Eq. 27

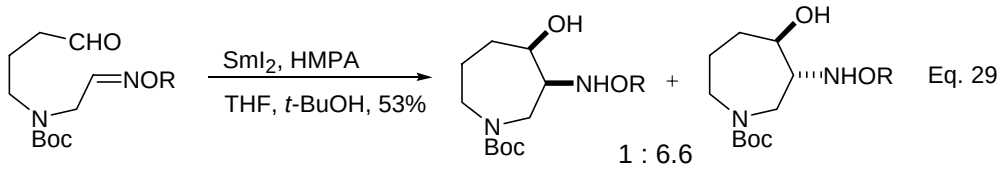
1.8.3 Balanol

Balanol is the most important of the five azepine natural products contained in list 1. Isolated from the fungi *Verticillium balanoides* and *Fusarium merismoides*, this alkaloid represents an exciting lead structure for inhibition of protein kinase C (PKC) which plays a critical role in regulating signal transduction pathways for many diseases like cancer, inflammation, cardiovascular dysfunctions, diabetic complications, asthma, central nervous system disorders, and HIV infection.[36] Balanol possesses IC_{50} values in the low nanomolar range but specificity

among PKC isoenzymes is poor.[37] Its synthesis has been actively explored by a number of research groups,[38,39,40,41] and derivation to analogs with higher specificity has also been examined.[42,43] To access the azepine ring Lampe and Hughes[39] begin from caprolactam which naturally provides this moiety. Nicolaou[38] and Tanner[41] both utilize similar *N*-alkylations (Eq. 28) while Naito[40] employs a novel radical cyclization (Eq. 29).



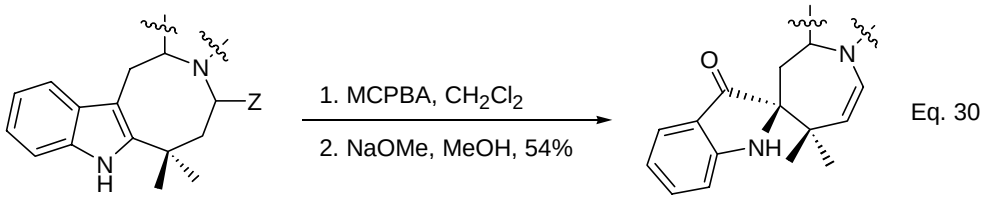
Eq. 28



Eq. 29

1.8.4 Austamide

Austamide (List 1) is a toxic metabolite produced from the fungus *Aspergillus ustus* which was first identified by Steyn.[44] It belongs to a class of alkaloids that is noted for their anthelmintic, paralytic, and insecticidal activities.[45] Biosynthetically, it is thought to arise from tryptophan, proline, and one isoprene unit.[46] Synthetically, its stereochemical elements pose a challenge, most notably the ψ-indoxyl spirocycle in conjunction with the azepine core. The first reported synthesis (racemic) was by Kishi[47] in 1979, and the second (enantioselective) was by Corey[48] twenty three years later. Kishi[47] and Corey[48] both formed the azepine ring through an oxidation-ring contraction process using the corresponding 8-membered ring (Eq. 30).



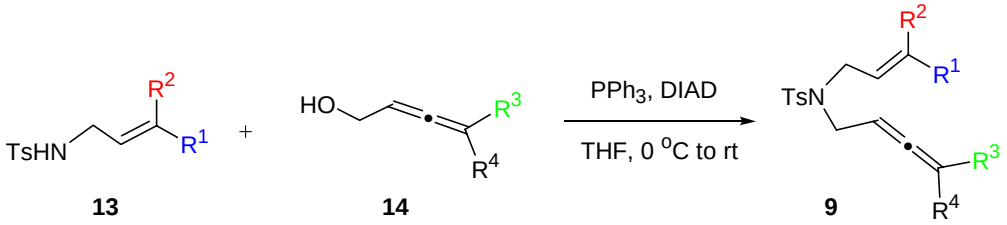
Eq. 30

2.0 RESULTS AND DISCUSSION

2.1 REACTIVITY TRENDS OBSERVED FOR THE MITSUNOBU REACTION BETWEEN ALLYLIC ALCOHOLS AND ALLYLIC TOSYLAMIDES

2.1.1 Coupling of allylic tosylamides with allylic-allenyl alcohols

Many cycloisomerization substrates in the current study were prepared via Mitsunobu reaction of the requisite alcohol with the corresponding *N*-allylic tosylamide (Tables 1 & 2).[19] Performing the Mitsunobu reaction between an allylic tosylamide **13** and an allylic allenyl-alcohol **14** provided ene-allenes **9** in yields ranging from 55-86%; avg = 64% (Table 1).



13 **14** **9**

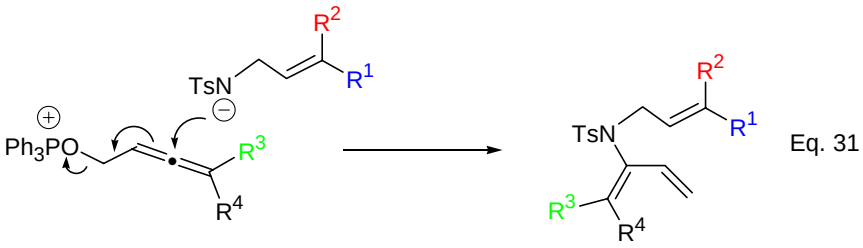
Table 1. Mitsunobu reaction of allylic allenyl-alcohols.

Entry	Tosylamide	Allylic alcohol	Yield (%)[a]	Ene-allene
1	**13a**; R^1 = Ph; R^2 = H	**14a**; R^3 = *t*-Bu; R^4 = H	60	**9c**
2	**13b**; R^1 = H; R^2 = Me	**14a**; R^3 = *t*-Bu; R^4 = H	55	**9d**
3	**13c**; R^1 = Me; R^2 = H	**14b**; R^3 = Ph; R^4 = H	55	**9e**
4	**13c**; R^1 = Me; R^2 = H	**14a**; R^3 = *t*-Bu; R^4 = H	60	**9f**
5	**13d**; R^1 = H; R^2 = H	**14c**; R^3 = R^4 = Me	86[b]	**9b**

[a]Indicates isolated yield. [b]Reaction was performed by Dr. Hongfeng Chen (ref. 20).

When the *tert*-butyl allylic allenyl-alcohol **14a** was employed, yields of 55-60% were observed for the coupling with **13a**, **13b**, and **13c** (entries 1, 2, 4). When employing the trisubstituted

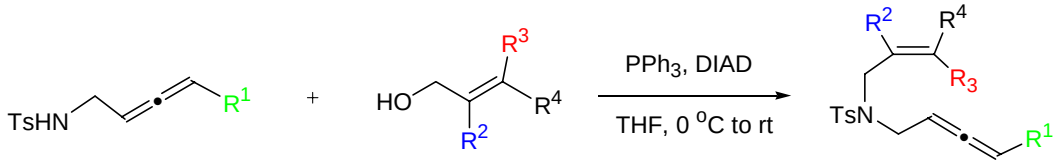
allene **14c** the highest yield was obtained for the series (86%, entry 5). Alcohol **14b** reacted to give **9e** in a 55% yield. A reason for the moderate yields for all but one entry (5) in table 1 is not exactly known but can be rationalized by considering the activated central carbon of the allene, which is electronically and stericly poised for S_N2' displacement of the leaving group. Displacing the leaving group in a S_N2' fashion would lead to an enamide by-product (Eq. 31) and reduce the overall yield of the desired ene-allene.



Eq. 31

2.1.2 Coupling of allylic-allenyl tosylamides with allylic alcohols

This allene reactivity hypothesis described above is further supported by the results observed for Mitsunobu reaction between allylic allenyl-tosylamides and allylic alcohols (Table 2) where the yields were consistently higher (67-90%; avg = 82%). Although substrates with allylic leaving



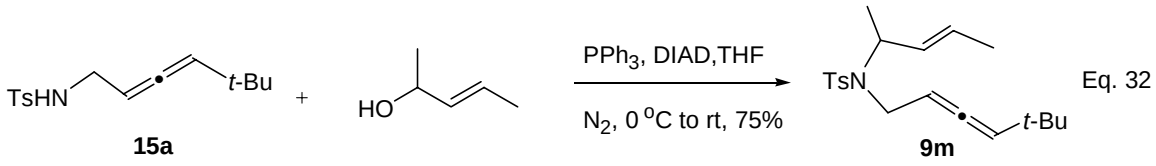
15 **16** **9**

Table 2. Mitsunobu reaction of allylic alcohols.

Entry	Tosylamide	Allylic alcohol	Yield (%)[a]	Ene-allene
6	**15a**; R^1 = *t*-Bu	**16a;** R^2 = Me, R^3 = R^4 = H	84	**9g**
7	**15a**; R^1 = *t*-Bu	**16b;** R^2 = H, R^3 = R^4 = Me	90	**9h**
8	**15a**; R^1 = *t*-Bu	**16c;** R^3 = H, R^2 = R^4 = -$(CH_2)_4$-	86	**9i**
9	**15a**; R^1 = *t*-Bu	**16d;** R^2 = R^3 = H, R^4 = $SiMe_3$	67	**9j**
10	**15a**; R^1 = *t*-Bu	**16e;** R^2 = R^3 = H, R^4 = $SiMe_2Bn$	79	**9k**
11	**15b**; R^1 = C_6H_{13}	**16f;** R^2 = R^3 = H, R^4 = C_3H_7	83	**9l**

[a]Indicates isolated yield.

groups can also undergo S_N2' reactions, steric hindrance at the 2-position (terminus) of **16** along with its less activated sp^2 carbon (verses the sp carbon of **14**) appear to be the cause for the observed chemo-selectivity and lack of S_N2' reactivity regarding the allylic alcohols submitted to Mitsunobu conditions. A secondary allylic alcohol also afforded the coupled amide in 75% yield as shown in eq. 32. On average, allylic allenyl-alcohols gave 18% lower yields when coupled

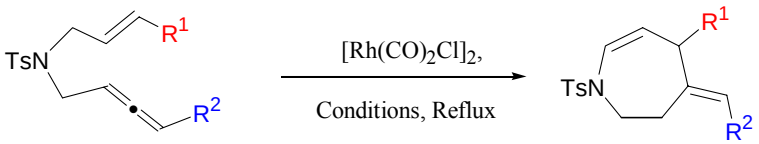


Eq. 32

to allylic tosylamides as opposed to using the alternate method of alkylating allylic allenyl-tosylamides with allylic alcohols. When possible, the latter method was employed over the former for substrate synthesis.

2.2 REACTIVITY OF ALKYL-SUBSTITUTED *TRANS*-ALKENE SUBSTRATES TOWARD CYCLOISOMERIZATION CONDITIONS

An investigation into the scope and limitations of this newly discovered rhodium catalyzed azepine forming reaction was initiated. The results for the alkyl-substituted *trans*-alkene substrates are illustrated in table 3 and summarized below.



9 **10**

Table 3. Reactivity of alkyl-substituted *trans*-alkenyl-substrates.

Entry	Ene-allene	Cat. (mol%)	Solvent	time (h)	Atmosphere	Yield (%)[a]	Azepine
12	**9n**; R^1 = Me; R^2 = H	10	1,4-dioxane	2	CO	0[b]	**10n**
13	**9a**; R^1 = Me; R^2 = C_6H_{13}	10	1,4-dioxane	0.22	Ar	54	**10a**
14	**9a**; R^1 = Me; R^2 = C_6H_{13}	10	DCE	2.5	Ar	50[c]	**10a**
15	**9f**; R^1 = Me; R^2 = *t*-Bu	5	DCE	1.5	Ar	95[c]	**10f**
16	**9f**; R^1 = Me; R^2 = *t*-Bu	5	1,4-dioxane	0.10	Ar	85	**10f**
17	**9f**; R^1 = Me; R^2 = *t*-Bu	2.5	1,4-dioxane	0.25	Ar	75	**10f**
18	**9e**; R^1 = Me; R^2 = Ph	9	DCE	1.3	Ar	0	**10e**
19	**9e**; R^1 = Me; R^2 = Ph	5	1,4-dioxane	0.12	Ar	45	**10e**
20	**9e**; R^1 = Me; R^2 = Ph	5	1,4-dioxane	0.25	CO	52	**10e**
21	**9e**; R^1 = Me; R^2 = Ph	5	THF	17.7	CO	41	**10e**
22	**9l**; R^1 = C_3H_7; R^2 = C_6H_{13}	17	DCE	2.5	Ar	28	**10l**
23	**9l**; R^1 = C_3H_7; R^2 = C_6H_{13}	6	1,4-dioxane	0.5	Ar	53	**10l**

[a]Isolated yield. [b]NMR shows a complex mixture. [c]Reaction was performed by Dr. Hongfeng Chen (ref. 20).

Placing methyl substitution on the alkene terminus fostered varying results, which were dependent on the substituent of the allene. Subjecting ene-allene **9n** with hydrogen as the allene substituent and a methyl group on the alkene terminus (R^1 = Me, R^2 = H; entry 12) to 10 mol% catalyst in 1,4-dioxane under a carbon monoxide atmosphere gave a complex mixture by ^{1}H NMR upon inspection of the crude material. No individual compound could be isolated by column chromatography. Replacing hydrogen with a hexyl-group on the allene terminus (R^1 = Me, R^2 = C_6H_{13}; entry 13) afforded azepine **10a** in 54% yield in 1,4-dioxane under an argon

atmosphere. The isolated yield for **10a** had decreased by only 4% (compare entry 13 to 14) when performing the reaction in DCE verses 1,4-dioxane though the reaction rate had decreased by 11 fold. Substituting the hexyl group on **9a** with a *t*-butyl moiety on the allene terminus (R^1 = Me, R^2 = *t*-Bu; entry 15) dramatically increased the yield by 45% under similar reaction conditions (compare entry 14 to 15). Exchanging DCE with 1,4-dioxane as solvent increased the reaction rate by 15 fold while decreasing the yield by 10% for conversion of **9f** to **10f** (compare entry 15 to 16). Performing the cycloisomerization of **9f** with half the catalyst loading (2.5 mol% vs. 5 mol%) actually decreased the reaction rate by 2 fold and the yield by 10% (compare entry 16 to 17). Success with this bulky *t*-butyl substituent on **9f** compelled our investigation to examine the tolerance of a phenyl ring on the allene terminus. In DCE solvent, no recognizable change of **9e** was observed after 1.3 hours at reflux with 9 mol% catalyst in an argon atmosphere (R^1 = Me, R^2 = Ph; entry 18). Simply replacing DCE with 1,4-dioxane afforded azepine **10e** in 45% yield (entry 19). Keeping 1,4-dioxane as solvent while exchanging argon with carbon monoxide increased the yield by 7% though decreased the reaction rate (compare entry 19 to 20). This same substrate **9e** also cyclized in THF solvent after prolonged refluxing to afford **10e** in 41% yield (entry 21).

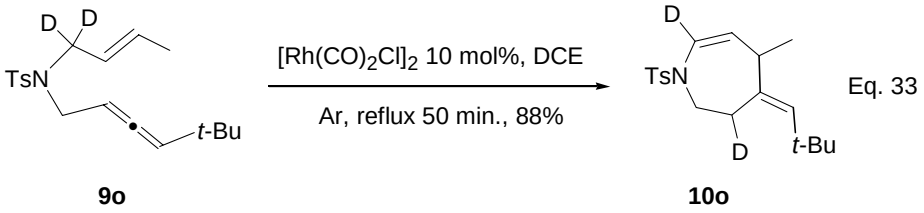
Lengthening the methyl group on the alkene to a propyl-group while maintaining the hexyl substituent on the allene (R^1 = C_3H_7, R^2 = C_6H_{13}; entry 22) reduced the yield to 28% even after employing a 17 mol% catalyst loading. Fortunately, product formation of **10l** could be increased to 53% by merely replacing DCE with 1,4-dioxane as solvent for the reaction (entry 23). Also noteworthy about this solvent change was the 5 fold increase on reaction rate and the 3-fold reduction of catalyst loading necessary for complete conversion (entry 23).

Generally, employing 1,4-dioxane as solvent verses DCE increased the reaction rates for all ene-allenes in table 3.

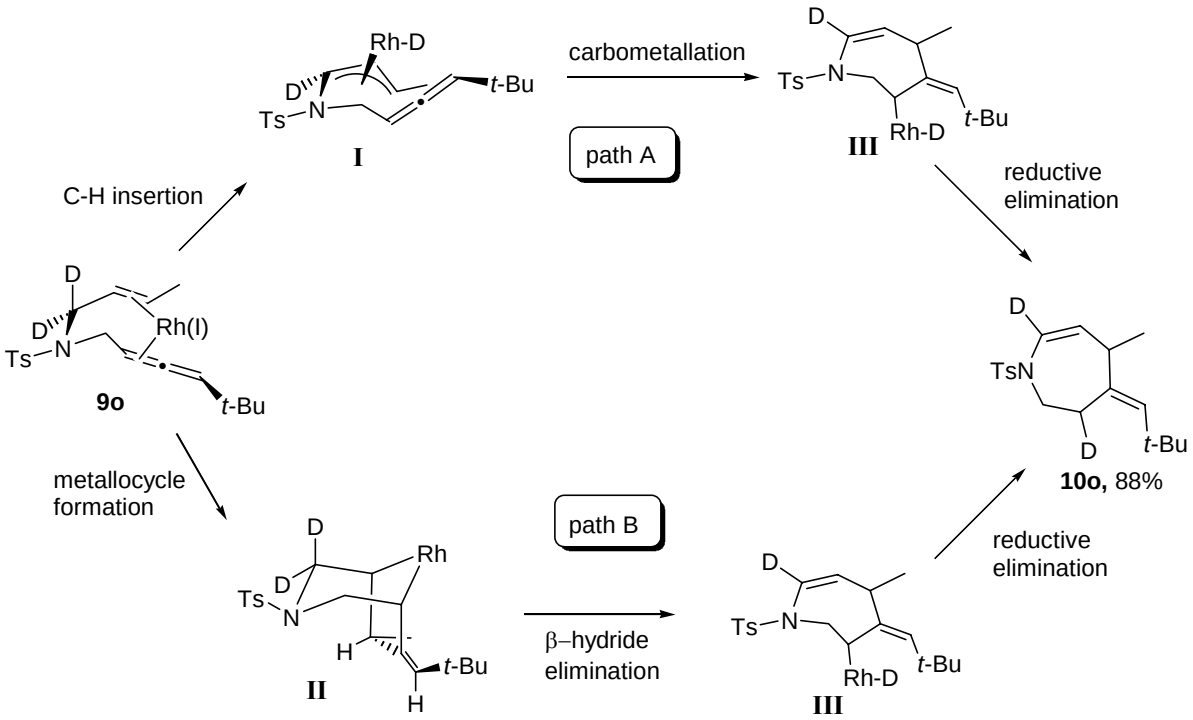
2.3 MECHANISM PROPOSALS FOR AZEPINE FORMATION

2.3.1 Evidence

Our discovery of this new azepine forming cycloisomerization reaction compelled us to investigate the mechanism by which transformation of ene-allenes to azepines was occurring. Ene-allene **9f** was chosen as the ideal substrate for this inquiry due to the success that was achieved for its cyclization. Modification of **9f** by substitution of the alkene tether with a tether that has been deuterated at the allylic position provided the necessary substrate **9o** (Eq. 33). Subjecting **9o** to 10 mol% catalyst in DCE under an argon atmosphere resulted in azepine **10o** in 88% yield after 50 minutes at reflux (Eq. 33).[20] Deuterium placement in the product azepine **10o** suggests two probable mechanisms which are illustrated in scheme 2. In path A (Scheme 2)



9o **10o**

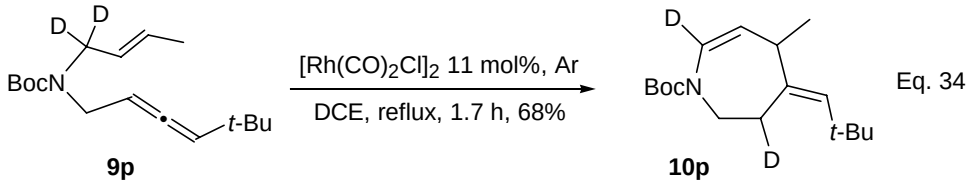


Scheme 2. C-H insertion and metallocycle mechanisms from deuterium labeling study (the ligands on rhodium have been omitted for clarity).

activation of the alkene moiety occurs *via* allylic C-D insertion of rhodium at the position α to nitrogen providing intermediate **I**, a π-allyl-Rh species.[49,50] This η-3 species (**I**) isomerizes to an η-1 species which then carbo-metallates onto the central carbon of the allene, effecting a 7-*endo*-*dig* cyclization resulting in intermediate **III**. The ensuing allylic-rhodium-hydride intermediate **III** then reductively eliminates to furnish the final product azepine **10o**. In path B (Scheme 2), rhodium oxidatively adds to the system after precoordination of ene-allene **9o** to furnish the bridged bicyclic intermediate **II**. The bicyclic complex **II** then undergoes β-deuteride elimination, resulting in intermediate **III**. Reductive elimination of **III** follows to arrive at the same deuterium labeled species **10o**.

Not surprising, a substrate with the same tethers on nitrogen but employing a Boc protecting group instead of a tosyl-group (**9p**) also underwent cyclization to result in identical

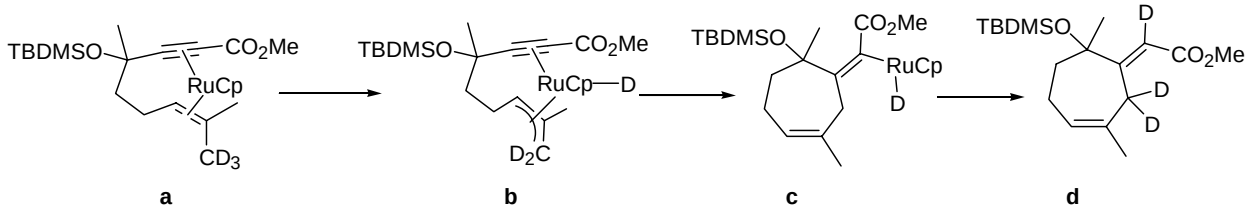
placement of deuterium in the product (**10p**), though in a lower 68% yield (Eq. 34). This lower yield may be attributed to a stronger complexation of the Boc group with the catalyst.



Eq. 34

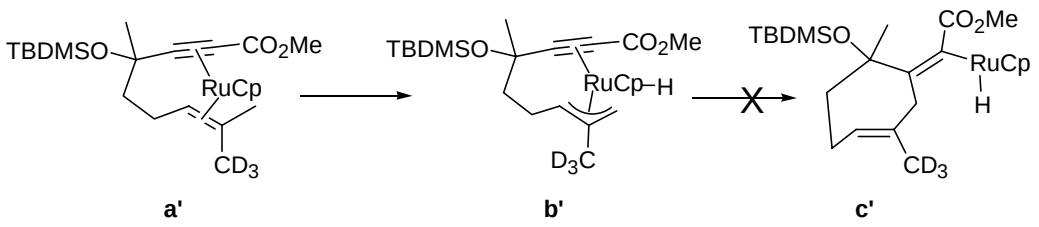
2.3.2 Precedence

In addition to C-H insertion of allylic amines reported by Tani and Otsuka,[49] Trost has communicated an allylic C-H insertion[51] to give 7-membered *exo*-alkylidenecycloheptenes from 1,6-enynes by employing a ruthenium catalyst (Scheme 3). In this mechanism (Scheme 3), which utilizes a deuterated substrate, Trost asserts that C-H activation must occur from the *cis*-alkenyl geometry (**a** → **b**) or isomerization from the *trans*- to the *cis*-geometry must happen after insertion (at intermediate **b**). The requirement for insertion into the *cis*-alkene moiety is



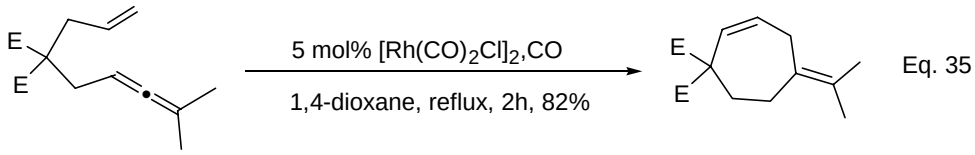
Scheme 3. *cis*-C-H insertion of enynes to form *exo*-alkylidenecycloheptenes.

rationalized by the strain that would ensue if *trans*-C-H insertion (**a′** → **b**,′ Scheme 4) occurred to provide, upon ring closure, a *trans*-double bond in a 7-membered ring (**c**,′ Scheme 4).



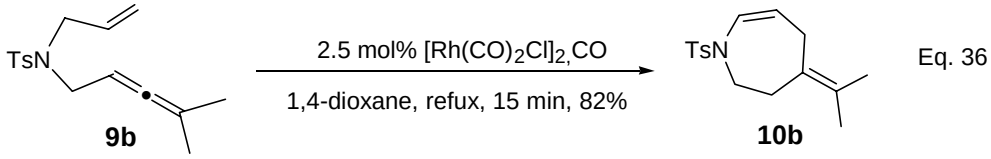
Scheme 4. Unlikely *trans*-C-H insertion model

Itoh has reported a similar cyclization to that of our azepine formation which resulted in construction of an *exo*-alkylidenecycloheptene carbocycle from a 1,6-ene-allene, though no



Eq. 35

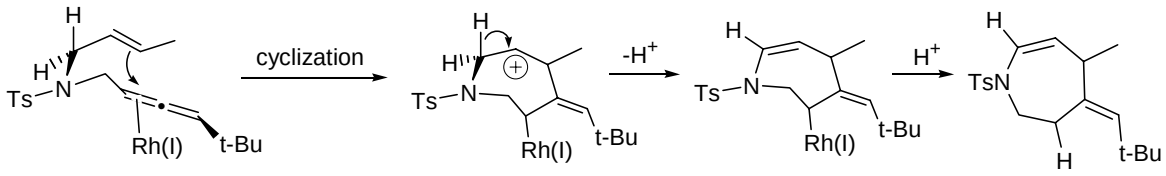
mechanism was proposed (Eq. 35).[52] The second of Itoh's communications[26] regarding 7-membered ring formation from 1,6-ene-allenes illustrated an identical azepine product **10b** (Eq. 36) as that described in our initial publication,[20] using similar conditions (2.5 mol% vs. 5 mol% cat., CO vs. Ar atmosphere, and 1,4-dioxane vs. DCE), but disclosing a single azepine entry.



Eq. 36

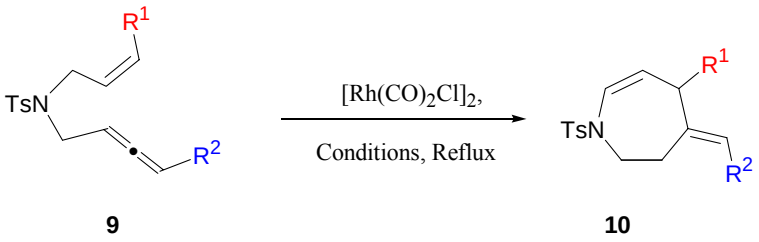
In this second publication by Itoh,[26] two possible mechanisms for *endo*-mode cyclization of 1,6-ene-allenes were postulated. The first proposal is the C-H insertion model which we initially supported by a deuterium labeling study (path A, Scheme 2) as described in our publication of this azepine forming reaction.[20] The second proposal from Itoh regarding 7-membered ring formation involves Lewis acid catalyzed attack of the olefin onto the allene center (Scheme 5). This Lewis acid catalyzed mechanism is criticized by Itoh to be unlikely due to the inability of

trapping the intermediate cationic species with D_2O or EtOD. Moreover, the reaction does not take place with Pt(II) which is an effective catalyst towards the cyclization of enynes involving a similar mechanism.[53,54,55]



Scheme 5. Lewis acid catalyzed cyclization of ene-allenes.

2.4 REACTIVITY OF ALKYL-SUBSTITUTED *CIS*-ALKENE SUBSTRATES TOWARD CYCLOISOMERIZATION CONDITIONS.



9 **10**

Table 4. Reactivity of alkyl-substituted *cis*-alkenyl substrates.

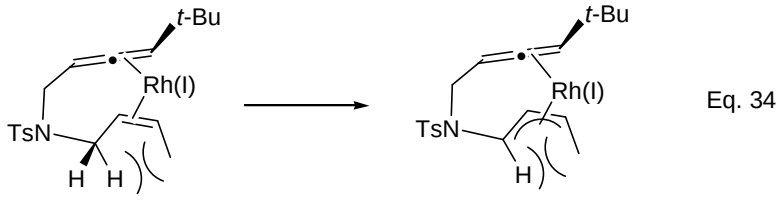
Entry	Ene-allene	Cat. (mol%)	Solvent	time (h)	Atmosphere	Yield (%)[a]	Azepine
24	**9q**; R^1 = Me; R^2 = C_6H_{13}	10	DCE	2.5	Ar	0[b]	**10q**
25	**9d**; R^1 = Me; R^2 = *t*-Bu	5	1,4-dioxane	2	Ar	43	**10f**
26	**9d**; R^1 = Me; R^2 = *t*-Bu	5	1,4-dioxane	0.17	Ar	36[c]	**10f**
27	**9d**; R^1 = Me; R^2 = *t*-Bu	5	DME	5	Ar	30	**10f**
28	**9d**; R^1 = Me; R^2 = *t*-Bu	10	DCE	0.9	Ar	29	**10f**

[a]Indicates isolated yield. [b]Reaction was performed by Dr. Hongfeng Chen. [c]Reaction was performed in the Personal Chemistry microwave oven at 140 °C in a sealed tube.

The *cis*-alkene substrate **9q** (R^1 = Me, R^2 = C_6H_{13}; entry 24) was unreactive when subjected to 10 mol% catalyst in dichloroethane solvent under an argon atmosphere. However, the *cis*-isomer

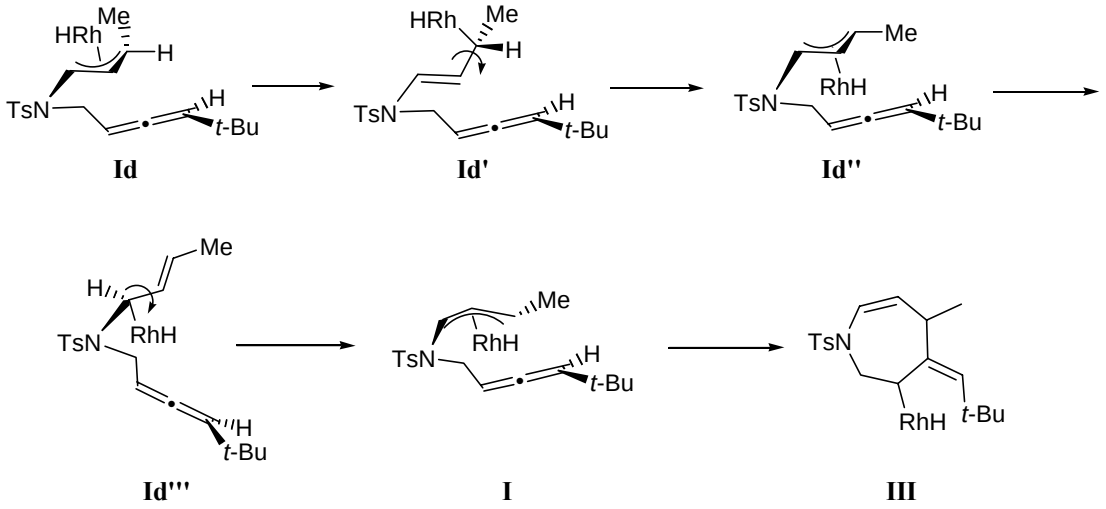
9d underwent conversion in 43% yield in 1,4-dioxane, 30% in DME, and 29% in DCE. In an attempt to improve product formation, cyclization of **9d** was also carried out in the microwave (entry 26) though this alteration only diminished the yield by 7% when compared to the reaction performed in an oil bath (entry 25). It is relatively surprising that ene-allene **9d** reacts in DCE (entry 28) considering the unreactivity of **9q** which completely failed to cyclize in DCE (entry 24).

The poor yield observed for the *cis*-alkene substrate **9d** can be rationalized by considering the mechanistic pathways postulated in scheme 2. When employing pathway A (Scheme 2) for the cyclization of *Z*-olefins verses *E*-olefins there is allylic strain that must be overcome in order to effect and maintain C-H insertion when forming the π-allyl-Rh complex (Eq. 34).



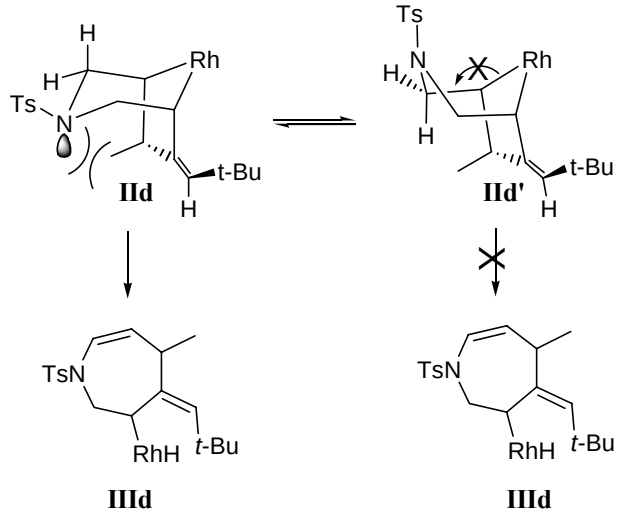
Eq. 34

Furthermore, in order to assume the reactive conformation **I** (Scheme 6) once C-H insertion has been achieved, the complex must progress from the η-3 coordination state **Id** to an η-1 state **Id′**. The carbon bearing rhodium in intermediate **Id′** must then rotate around the sp^2-sp^3 terminal C-C single bond and then isomerize back to an η-3 coordination state **Id″**. The π-allyl-rhodium intermediate **Id″** must then isomerizes to the η-1 intermediate **Id‴** in which another sp^2-sp^3 bond rotation must occur before the final isomerization back to an η-3 coordination state, resulting in intermediate **I**. The entire process illustrated in scheme 6 is an isomerization of the *cis*-alkene **9d** to its *trans*-alkene counterpart by way of π-allyl-rhodium intermediates **Id** and **Id″**, and η-1 alkyl intermediates **Id′** and **Id.‴**



Scheme 6. Isomerization of the π-allyl-rhodium intermediate **Ie**.

Implementing path B from scheme 2 shows that the methyl group from the *Z*-alkene in the bicyclic intermediate **IId** (Scheme 7) approaches a *syn*-pentane interaction with the lone pairs



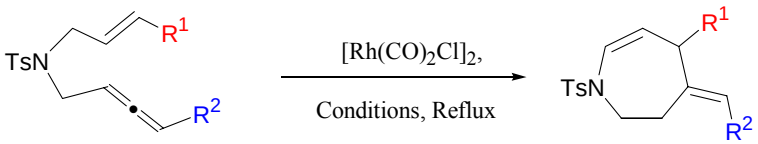
Scheme 7. Metallocycle intermediates in the mechanism for the *cis*-alkene substrate **9d.**

on nitrogen while the 6-membered ring is in the chair conformation. By adopting a boat configuration for the ring (**IId**,′ Scheme 7), the *syn*-pentane interaction is relieved though the β-hydrogen is now orthogonal to the Rh-C bond, preventing the complex from undergoing β-

hydride elimination. When one considers the mechanistic factors presented in both Scheme 6 and Scheme 7 regarding *cis*-isomer reactivity, the low conversion becomes reconcilable.

2.5 REACTIVITY OF PHENYL AND SILYL-SUBSTITUTED *TRANS*-ENE-ALLENES TOWARD CYCLOISOMERIZATION CONDITIONS

To further expand the scope of this azepine forming cycloisomerization reaction (**9** → **10**, table 5) our study employed the use of ene-allenes that have been substituted with either a phenyl or silyl-bearing substituent. The results of these substitutions regarding cyclization are depicted in table 5 and summarized below.



9 **10**

Table 5. Reactivity of phenyl and silyl-substituted *trans*-ene-allene substrates.

Entry	Ene-allene	Cat. (mol%)	Solvent	time (h)	Atmosphere	Yield (%)[a]	Azepine
29	**9c**; R^1 = Ph; R^2 = *t*-Bu	9	1,4-dioxane	8.5	CO	95	**10c**
30	**9c**; R^1 = Ph; R^2 = *t*-Bu	10	1,4-dioxane	0.5	Ar	79	**10c**
31	**9c**; R^1 = Ph; R^2 = *t*-Bu	5	DME	2	Ar	90	**10c**
32	**9c**; R^1 = Ph; R^2 = *t*-Bu	11	DCE	2.8	Ar	73	**10c**
33	**9r**; R^1 = Ph; R^2 = Si(*i*-pr)$_3$	6	1,4-dioxane	14.3	Ar	48[b]	**10r**
34	**9s**; R^1 = Me; R^2 = Si(*i*-pr)$_3$	6	1,4-dioxane	1.5	Ar	69	**10s**
35	**9t**; R^1 = $SiMe_3$; R^2 = C_6H_{13}	10	DCE	7	Ar	Trace	**10t**
36	**9j**; R^1 = $SiMe_3$; R^2 = *t*-Bu	10	DCE	1	Ar	82	**10j**
37	**9k**; R^1 = $SiMe_2Bn$; R^2 = *t*-Bu	10	DCE	1	Ar	97	**10k**

[a]Indicates isolated yield. [b]Gave a 40% yield but the starting material was contaminated with the *cis*-alkene isomer (~18%) which reacts slowly or not at all. The product was impure by ^{1}H NMR.

2.5.1 Phenyl-substituted alkene tethers

We first examined ene-allene **9c** (R^1 = Ph, R^2 = *t*-Bu; entry 29) which afforded an excellent 95% yield though a prolonged reaction time in carbon monoxide. Exchanging the carbon monoxide atmosphere used for entry 29 to one of argon caused a reduction in conversion of **9c** to **10c** by 16% but concomitantly fostered a 17-fold increase in reaction rate (compare entry 29 to 30). Maintaining argon as the atmosphere but substituting 1,4-dioxane for DME caused an 11% increase in yield but a 4-fold reduction in reaction rate (compare entry 30 to 34). Replacing DME with DCE and increasing the catalyst loading by 6% resulted in a 17% decrease in yield of **10c** (compare entry 31 to 32). Finally, in an effort to replace this esoteric *tert*-butyl group on the allene terminus with one that would be easier to remove after cyclization, we examined the affect of a triisopropylsilyl-substituted allenyl-tether on this phenyl-alkene series. Ene-allene **9r** (R^1 = Ph, R^2 = Si(*i*-pr)$_3$; entry 33) cyclized to give a 48% yield of azepine **10r** after a lengthy 14.3 hours at reflux in 1,4-dioxane blanketed with an argon atmosphere. Unfortunately, azepine **10r** was impure even after column chromatography.

2.5.2 Silyl substituted ene-allenes

The aim of employing silyl substituted ene-allenes **9r**, **9s**, **9t**, **9j**, and **9k** as substrates was 2-fold. First, this moiety would provide a handle on the product azepines that allows for facile derivitization. Second, a silyl group would be easier to remove on the product than an alkyl-group of similar steric demand. With this rationale in mind, syntheses of both allenyl- and vinyl-silane substrates were undertaken. Cyclization of **9r** (R^1 = Ph, R^2 = Si(*i*-pr)$_3$; entry 33) was described as affording not only a low yield but also an impure product. By changing the styryl-tether of **9r** to a crotyl-tether (R^1 = Me, R^2 = Si(*i*-pr)$_3$; entry 34), the reaction yield was increased

to 69%. Implementing a hexyl substituted allene with a vinyl-silane moiety (R^1 = $SiMe_3$, R^2 = C_6H_{13}; entry 35) provided only a trace of the desired azepine product **10t** by ^{1}H NMR. Replacing the hexyl substituent with the favored *t*-butyl group (R^1 = $SiMe_3$, R^2 = *t*-Bu; entry 36) had a drastic effect in that the cyclized product **10j** was isolated in 82% yield. Substituting the –$SiMe_3$ group on **9j** with a –$SiMe_2Bn$ group (R^1 = $SiMe_2Bn$, R^2 = *t*-Bu; entry 37) resulted in the highest yield of cycloisomerization observed to date (97%, **10k**) for nitrogen tethered ene-allenes.

2.6 REACTIVITY OF ALLYL-TETHERED ENE-ALLENES TOWARD CYCLOISOMERIZATION CONDITIONS

Allyl-tethered ene-allenes were the next class of substrates examined. The results for this facet of our cycloisomerization investigation are illustrated in table 6 and summarized below.

Employing an allyl-tether in conjunction with the hexyl-substituted allene moiety (R^1 = H, R^2 = C_6H_{13}; entry 38) provided azepines **10u** and **10u′** in a combined yield of 62%. Azepines **10u** and **10u′** are *E/Z* isomers about the exocyclic alkene, isolated as an inseparable mixture in a ratio of 1.3:1, respectively. Substituting the hexyl group on **9u** with a triisopropylsilyl-moiety caused an 11% increase in overall yield of **10v** and **10v′** while providing a marked escalation in

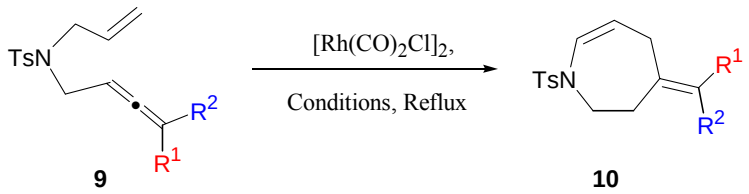


Table 6. Reactivity of allyl-tethered ene-allenes.

Entry	Ene-allene	Cat. (mol%)	Solvent	time (h)	Atmosphere	Yield (%)[a]	Azepine
38	**9u**; R^1 = H; R^2 = C_6H_{13}	10	DCE	4	Ar	62[b,c]	**10u; 10u′**
39	**9v**; R^1 = H; R^2 = Si(*i*-pr)$_3$	5	1,4-dioxane	0.3	Ar	73[d]	**10v; 10v′**
40	**9b**; R^1 = R^2 = Me	10	DCE	6	N_2	68[b]	**10b**
41	**9b**; R^1 = R^2 = Me	5	1,4-dioxane	0.25	CO/Ar	85	**10b**
42	**9w**; R^1 = R^2 = H	10	DCE	0.25	Ar	Trace	**10w**

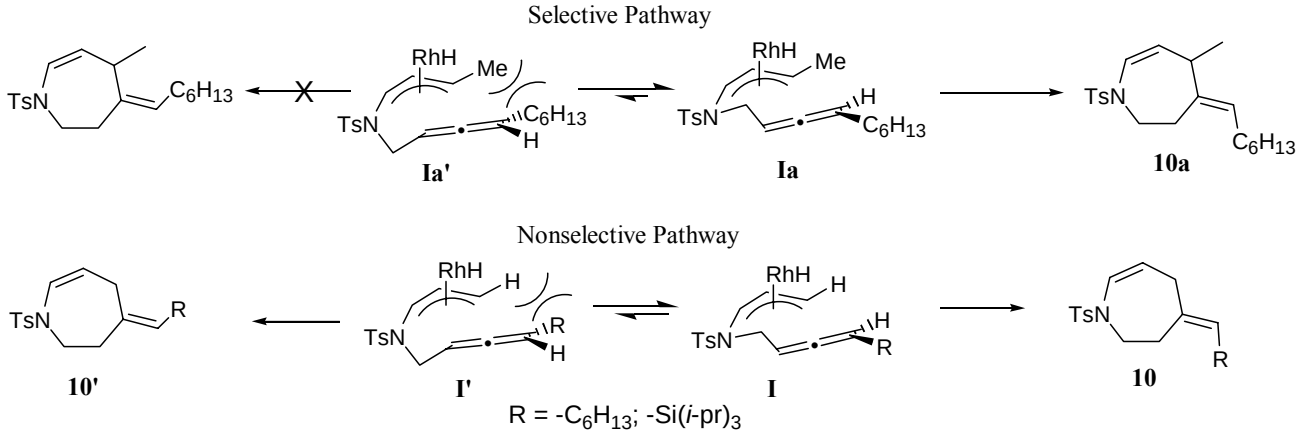
[a]Indicates isolated yield. [b]Reaction was performed by Dr. Hongfeng Chen (ref. 20). [c]*E/Z* isomers were obtained in a ratio of 1.3:1. [d]*E/Z* isomers were obtained in a ratio of 5.8:1.

E/Z ratio of 5.8:1 (compare entry 38 to 39). Replacing the hexyl chain on **9u** with a methyl group and further substituting the allene terminus with an additional methyl group (R^1 = R^2 = Me; entry 40) marginally improved the yield of the corresponding azepine **10b** by 6% (compare entries 38 and 40). Performing the cyclization of **9b** in 1,4-dioxane in a partial carbon monoxide/argon environment afforded a substantial improvement in yield of 85% compared to 68% in DCE and a nitrogen atmosphere (compare entry 40 to 41). Removing all substitution from the allene (R^1 = R^2 = H; entry 42) gave a rapid reaction with substantial decomposition. The azepine **10w** was only observed in trace amounts by crude ^{1}H NMR but was not isolable by silica gel chromatography.

2.6.1 Reasoning for observation of *E/Z* isomers

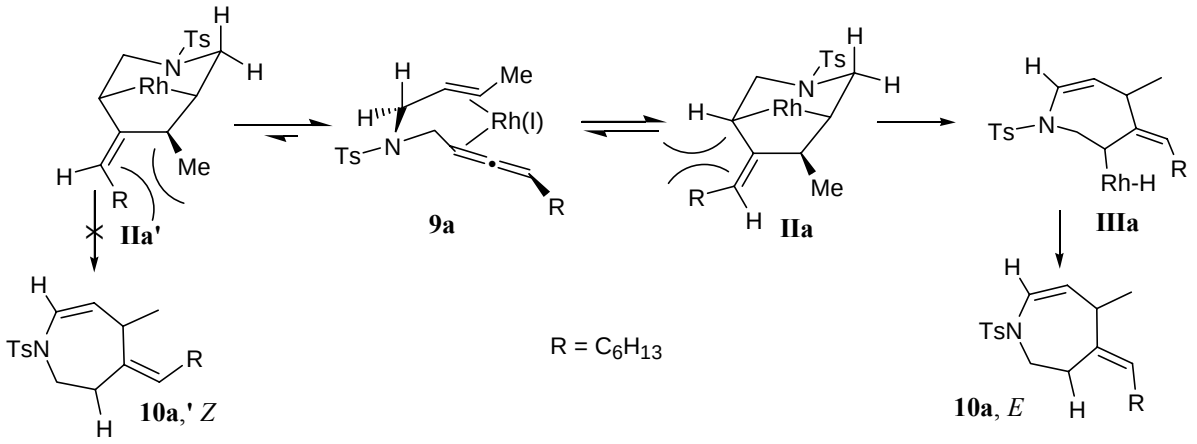
The prevalence of *E/Z*-isomers upon cyclization of **9u** (entry 38) and **9v** (entry 39) is postulated to originate from a lack of steric biasing in the transition state. When 1,2-distubstituted alkene tethers are used in substrates for cyclization, exclusive *E*-alkene products, with respect to the

exocyclic olefin, are observed (see tables 3, 4, & 5). This outcome can be rationalized while employing either path A or path B from scheme 2. The steric influence experienced in path A of scheme 2 is illustrated more clearly in scheme 8 below. Preferential formation of the *E*-isomer **10a**, indicated by the selective pathway (Scheme 8), is a result of the steric interaction between the alkene and allene termini (see **Ia′**). Exchange of the methyl group at the alkene terminus of **9a** with a hydrogen atom (ene-allene **9u**) reduces this steric biasing, denoted by the nonselective pathway (Scheme 8), which results in only a slight preference to form the *E*-isomer **10u** over the *Z*-isomer **10u′**. The steric bulk of the triisopropylsilyl group in conversion of **9v** to **10v** and **10v′** (table 6) increases this interaction, causing the product distribution to show a much higher



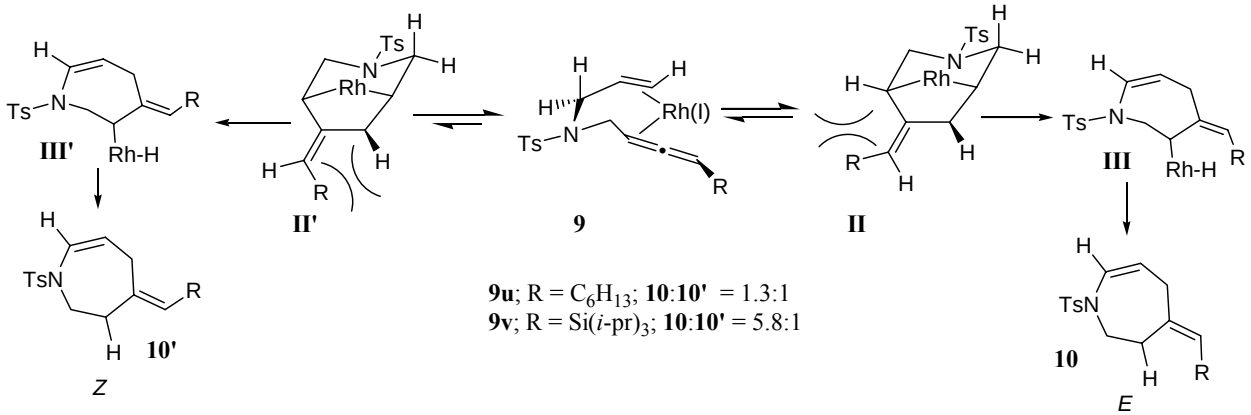
Scheme 8. Selective and nonselective cyclization employing C-H insertion mechanism (the ligands on rhodium have been omitted for clarity).

concentration of the *E*-isomer over the *Z*-isomer. When employing path B from scheme 2 (illustrated clearly in Scheme 9) a recognizable $A_{1,3}$ strain between the alkyl groups on the allene and alkene termini in intermediate **IIa′** is sufficient to drive the equilibrium towards formation of intermediate **IIa** which affords the *E*-alkene product **10a** over the *Z*-isomer **10a′** exclusively.



Scheme 9. Selective pathway of metallocycle mechanism
(the ligands on rhodium have been omitted for clarity).

When the alkene terminus is substituted with hydrogen and the allene terminus is substituted with a hexyl-group (**9u**), the similar $A_{1,3}$ strain experienced in both intermediates **II** and **II′** only slightly biases the equilibrium to prefer the *E*-isomer over the *Z*-isomer (Scheme 10). However, in the case of **9v** the steric encumberment is exacerbated by the bulkier triisopropylsilyl-group, conferring a substantial increase in *E/Z* ratio of 5.8:1 in the product isomers.

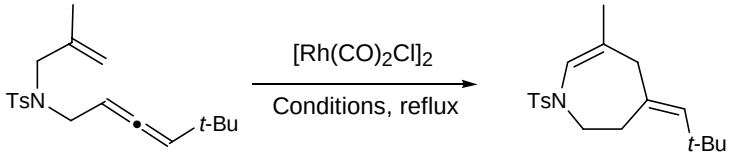


Scheme 10. Nonselective pathway of metallocycle mechanism
(the ligands on rhodium have been omitted for clarity).

2.7 REACTIVITY OF 1,1-DISUBSTITUTED AND TRISUBSTITUTED OLEFIN SUBSTRATES TOWARD CYCLOISOMERIZATION CONDITIONS

2.7.1 1,1-Disubstituted ene-allenes

Success with the cyclization of both allyl- and 1,2-disubstituted alkenyl-tethers directed our attention to the examination of 1,1-disubstituted alkenyl-tethers. The ene-allene chosen to probe this variation on substitution was **9g**. The results for the conversion of **9g** to **10g** are compiled in table 7 and digested below.



9g **10g**

Table 7. Reactivity of ene-allene **9g** to cycloisomerization conditions.

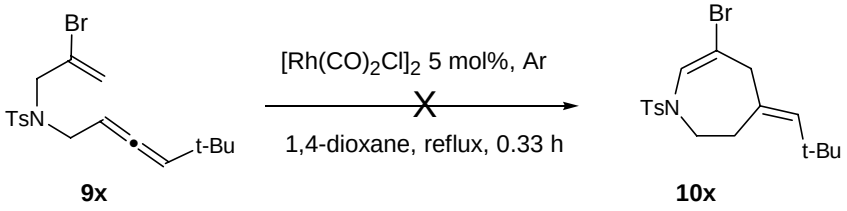
Entry	Cat. (mol%)	Solvent	time (h)	Atmosphere	Yield (%)[a]
43	5	1,4-dioxane	0.25	Ar	83
44	5	1,4-dioxane	0.33	Air[b]	86
45	5	DCE	0.25	Ar[c]	82
46	6	DCE	0.25	Ar[b]	73

[a]Indicates isolated yield. [b]The soln was not degassed prior to or after addition of catalyst. [c]The soln was degassed via freeze-pump-thaw method after the addition of catalyst.

Subjecting ene-allene **9g** to 5 mol% catalyst in 1,4-dioxane under an argon atmosphere afforded azepine **10g** in 83% yield (entry 43). We saw the reaction of **9g** as an opportunity to assess the effect of residual gas molecules in the solution at the time of cyclization. As an extreme example, the normal argon environment was replaced with air from the outside atmosphere. Surprisingly, the yield of azepine **10g** actually increased by 3% under air atmosphere conditions (compare entry 43 to 44). This finding suggests that the atmosphere in

which the reaction is ran, when utilizing 1,4-dioxane as solvent, does not have a large impact on the product yield. Switching the atmosphere from air to argon and the solvent back to DCE from 1,4-dioxane, while carefully degassing the solution after addition of catalyst, resulted in an 82% yield of **10g** (entry 45). Implementing these same conditions without degassing the solvent resulted in a 9% reduction in yield (compare entry 45 to 46). The data presented in entries 45 and 46 indicate that the residual gas concentration is a crucial factor when performing the cycloisomerization in DCE.

The encouraging results regarding transformation of **9g** to **10g** compelled our investigation to further examine the limits of substituent tolerance by replacing the alkenyl-methyl group on **9g** with a bromine atom (**9x**). When ene-allene **9x** was exposed to 5 mol% catalyst in an argon atmosphere and refluxed in 1,4-dioxane for 20 minutes the only observable phenomenon was substantial decomposition and no trace of the desired azepine **10x** (Eq. 35).



9x **10x** Eq. 35

Eight percent of the original starting material was recovered as an impure fraction after column chromatography. Performing the reaction with 13 mol% catalyst (added in 2 portions) in 1,4-dioxane under an argon atmosphere at 50 ºC instead of 110 ºC also promoted decomposition with no sign of azepine **10x**.

2.7.2 1,2,2-Trisubstituted ene-allenes

Our focus now shifted to substrates possessing trisubstituted alkenyl-tethers. The results for this series of ene-allenes towards cycloisomerization conditions are depicted in table 8 and synopsized in the proceeding paragraphs.

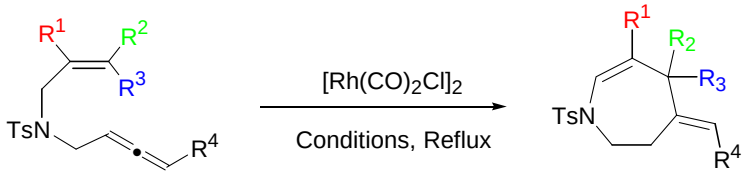


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Table 8. Reactivity of Trisubstituted Alkene Substrates

Entry	Ene-allene	Cat (mol%)	Solvent	time (h)	Atmosphere	Yield (%)[a]	Azepine
47	**9i**, $R^1 = R^2 = -(CH_2)_4-$; $R^3 = H$; $R^4 = t$-Bu	7	1,4-dioxane	13.3	Ar	78	**10i**
48	**9i**, $R^1 = R^2 = -(CH_2)_4-$; $R^3 = H$; $R^4 = t$-Bu	2.5	1,4-dioxane	1.6	Ar	66	**10i**
49	**9h**, $R^1 = H$; $R^2 = R^3 = Me$; $R^4 = t$-Bu	10	DCE	1.5	Ar	0	**10h**
50	**9h**, $R^1 = H$; $R^2 = R^3 = Me$; $R^4 = t$-Bu	11	1,4-dioxane	2.3	Ar	13[b]	**10h**
51	**9h**, $R^1 = H$; $R^2 = R^3 = Me$; $R^4 = t$-Bu	9	1,4-dioxane	6.7	CO	14[c]	**10h**
52	**9y**, $R^1 = H$; $R^2 = R^3 = R^4 = Me$	10	Toluene	3	Ar	0[d]	**10y**
53	**9z**, $R^1 = H$; $R^2 = R^3 = Me$; $R^4 = C_6H_{13}$	10	Toluene	13	Ar	0[d]	**10z**
54	**9A**, $R^1 = H$; $R^2 = R^3 = -(CH_2)_2-$; $R^4 = t$-Bu	10	1,4-dioxane	21.8	Ar	14[c]	**10A**

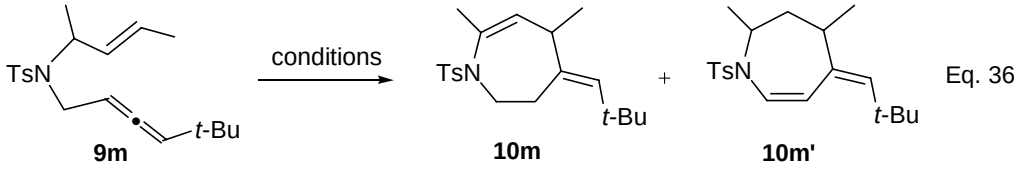
[a]Indicates isolated yield. [b]Determined by HPLC. [c]Determined by ^{1}H NMR. [d]Reaction was performed by Dr. Hongfeng Chen.

In 1,4-dioxane with 7 mol% catalyst surrounded by an argon atmosphere, ene-allene **9i** ($R^1 = R^2 = -(CH_2)_4-$, $R^3 = H$, $R^4 = t$-Bu; entry 47) which is a 1,1,2-trisubstituted alkene, reacted to provide azepine **10i** in a 78% yield. Reducing the catalyst loading to 2.5 mol% as opposed to 7 mol% caused a decrease in product yield of 12% (compare entry 47 to 48).

Substitution in the form of the 1,2,2-trisubstituted alkenyl-tether embodied in **9h** (R^1 = H, R^2 = R^3 = Me; R^4 = *t*-Bu; entry 49) was not tolerated under DCE/argon cycloisomerization conditions, as exemplified by this substrate's lack of reactivity. Exchanging the solvent to 1,4-dioxane facilitates the transformation, albeit in a poor 13% yield (entry 50). Replacing argon with carbon monoxide marginally increased the yield by 1% though caused a 3-fold reduction in rate (entry 51). Substituting the *t*-butyl group on the allene terminus of **9h** with a methyl group (R^1 = H, R^2 = R^3 = R^4 = Me; entry 52), while performing the reaction in toluene, was not a suitable alteration. Azepine **10y** was not observed upon attempted cyclization of ene-allene **9y**. When the methyl group on **9y** is replaced with a hexyl group (R^1 = H, R^2 = R^3 = Me, R^4 = C_6H_{13}; entry 53) and substrate **9z** is heated to reflux in toluene for 13 hours with 10 mol% catalyst under an argon atmosphere no azepine **10z** is observed. Given the low yields for conversion of **9h** to **10h** in 1,4-dioxane, it is assumed that both **9y** and **9z** would not react to an appreciable extent in this solvent. In an attempt to improve conversion of the 1,2,2-tribustituted alkene series by reducing the steric bulk of the alkene terminus, a cyclopropylidene moiety (R^1 = H, R^2 = R^3 = -$(CH_2)_2$-, R^4 = *t*-Bu; entry 54**)** was used but it too also provided the corresponding azepine **10A** in a low 14% yield.

2.8 REACTIVITY OF ENE-ALLENES SUBSTITUTED AT THE PROXIMAL ALLYLIC POSITION OF THE ALKENE

2.8.1 Monosubstitution at the proximal allylic position



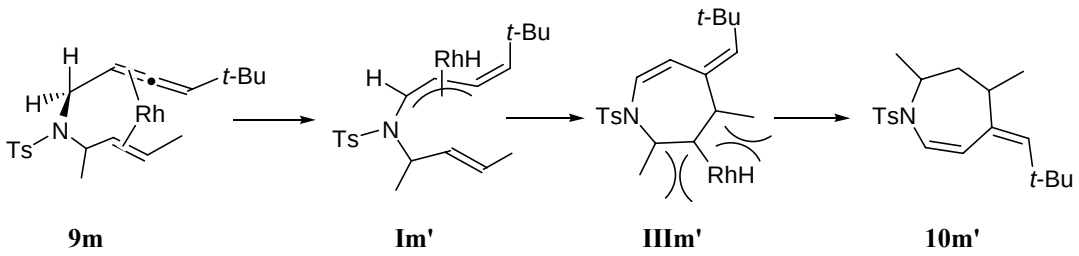
9m **10m** **10m'**

Solvent	Cat (mol%)	Time (h)	Yield (%)[a]	Ratio 10m:10m′
DCE	10	2.2	66	1.4:1
1,4-dioxane	6	0.72	50	1.3:1

[a]Indicates isolated yield. All reactions were performed in an argon environment.

When refluxing ene-allene **9m**, a substrate that is mono-substituted at the allylic position, in DCE with 10 mol% catalyst the two azepine products **10m** and **10m′** were isolated in a 1.4:1 ratio, respectively (Eq. 36). Nearly the same product ratio was also obtained when executing the reaction in 1,4-dioxane, meaning the product distribution is independent of solvent employed. Azepine **10m** is the major product and possesses the expected olefin regiochemistry that has been consistently obtained throughout the course of investigation. However, azepine **10m′** which was isolated as a single diastereomer has not been previously observed. The formation of **10m′** raises interesting mechanistic curiosities which are examined by implementing both reaction manifolds illustrated in scheme 2.

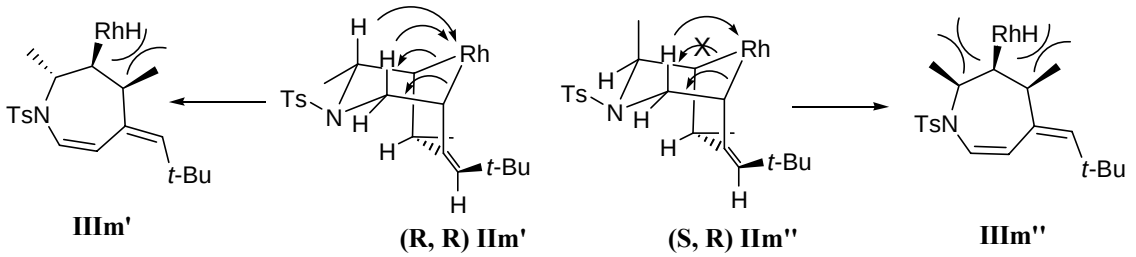
In order for C-H insertion to occur at the allenyl position of **9m** (adapted from Path A, Scheme 2) a rehybridization of both the allenic methylene carbon and the digonal central carbon



Scheme 11. C-H insertion mechanism for ene-allene **9m**.

of the allene must take place (**9m → Im**,′ Scheme 11). To the best of our knowledge, the π-allyl-Rh-alkylidene hydride species (or variants thereof) represented in **Im′** has not been previously reported.[56,57] Subsequently, intermediate **Im′** must undergo carbometallation onto the less activated alkene tether, providing **IIIm′**. Depending on both the diastereomer undergoing reaction and the rate of reductive elimination, the alkyl-Rh-H species **IIIm′** has the possibility of bearing substantial $A_{1,2}$ strain. This $A_{1,2}$ strain experienced in **IIIm′** would explain why a single diastereomer **10m′** is obtained, for it is likely that only one set of diastereomers (the enantiomeric pair) participate in the reaction, or isomerization of the unpreferred diastereomers occurs at some point during the course of the mechanism.

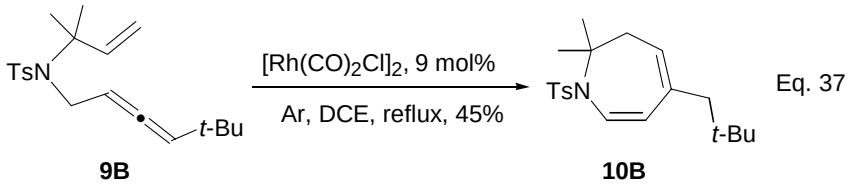
Applying path B of scheme 2 to substrate **9m** shows that the allenyl methylene hydrogens are more accessible for β-hydride elimination than the allylic methine hydrogen, regardless of the reacting diastereomer (**IIm′** and **IIm**,″ Scheme 12). The subsequent intermediates **IIIm′** and **IIIm″** are subject to the same $A_{1,2}$ strain as described for path A (above). This strain causes biasing which leads one to assume a preference of **IIIm′** over **IIIm″** due to its reduced steric interaction. An experiment incorporating a diastereomerically pure ene-allene would provide further insight towards the operative mechanism.



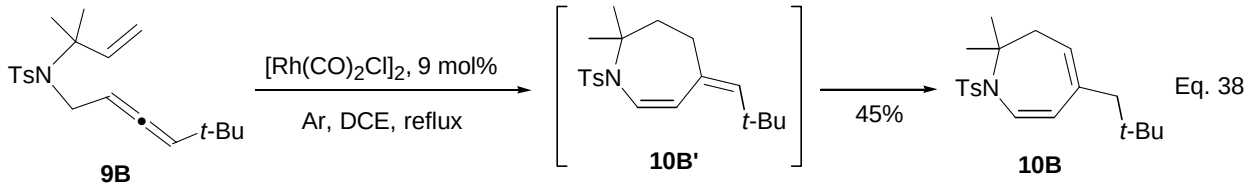
Scheme 12. Intermediates **II** and **III** of the metallocycle mechanism for conversion of **9m** to **10m′**.

2.8.2 Disubstitution at the proximal allylic position

To probe the effect of additional substitution at the allylic position, substrate **9B** was subjected to the reaction conditions listed in eq. 37. Azepine **10B** was obtained as the only isolable product



which is assumed to be the result of the same type of cycloisomerization that produced azepine **10m′** from **9m** (Schemes 11 and 12). However, the difference in olefin regiochemistry between azepines **10B** and **10m′** is thought to arise from an *in situ* Rh-catalyzed alkene isomerization on the initial product **10B′** (Eq. 38).

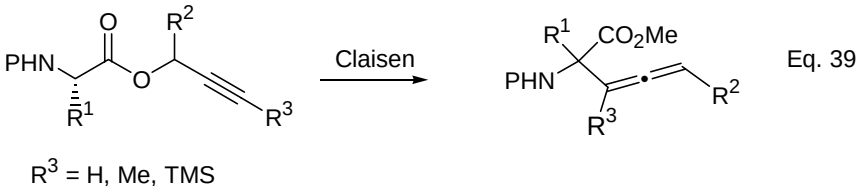


The production of **10B** was surprising in that cycloisomerization of all other ene-allenes in the current study never resulted in a conjugated dihydroazepine. The *gem*-dimethyl groups on the assumed intermediate **10B′** may facilitate the isomerization from **10B′ → 10B** (Eq. 38) by

providing an ideal conformation for Rh-reinsertion, due to steric interactions. The fact that azepine **10m′** did not undergo the same type olefin isomerization suggests the difficulty of this reinsertion by rhodium when there is a substituent at the allylic position within the ring.

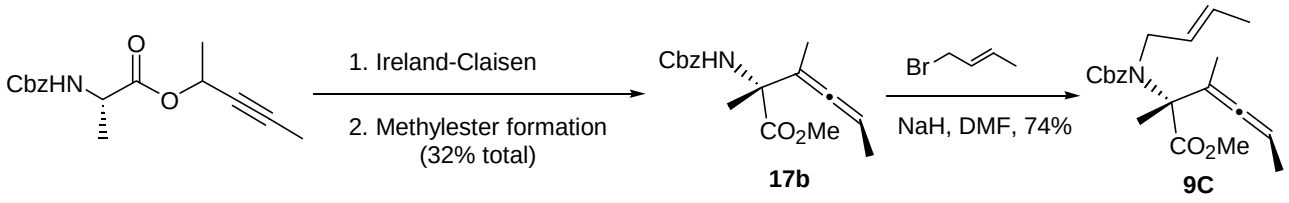
2.9 EFFECT OF SUBSITUTION AT THE PROXIMAL POSITION OF THE ALLENE AND AT THE ALLYLIC SITE OF THE ALLENYL-TETHER ON CYCLOISOMERIZATION

During the course of investigation towards applying the allenic Pauson-Kand reaction to library development,[58] the formation of allenes via Ireland-Claisen rearrangement[59,60] had been



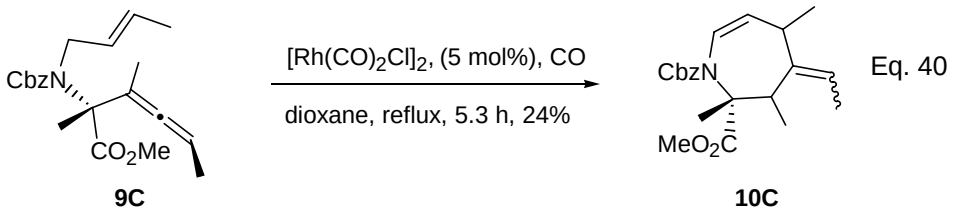
Eq. 39

extensively employed (Eq. 39). We envisioned ene-allene **9C** (Scheme 13) as being an ideal substrate for exploring the effect of further substitution on both the allylic allenyl-position and on the allene itself. This substrate was easily accessed through an Ireland-Claisen rearrangement followed by methylation of the resulting carboxylic acid and an alkylation of nitrogen (Scheme 13).



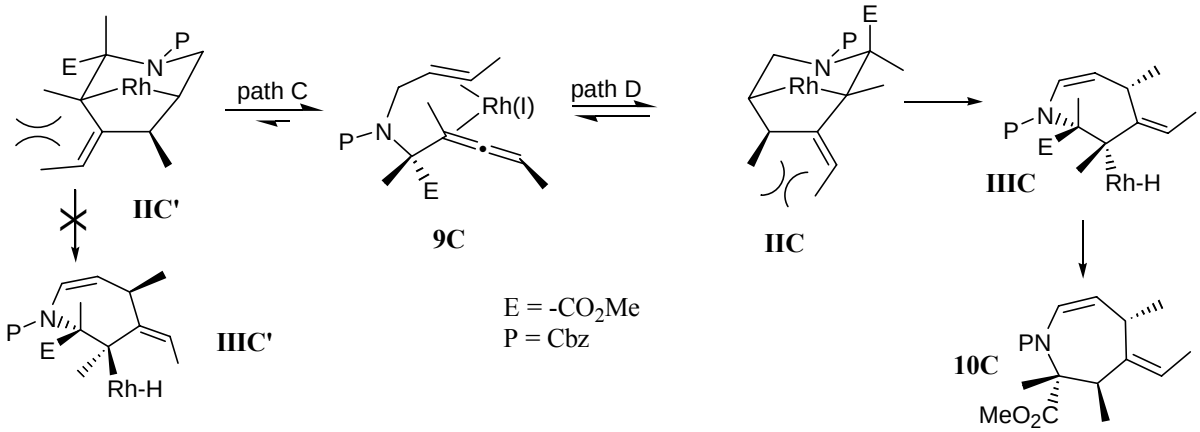
Scheme 13. Synthesis of ene-allene **9C.**

Upon refluxing ene-allene **9C** in 1,4-dioxane with 5 mol% catalyst under a carbon monoxide atmosphere, a reaction was observed that afforded azepine **10C** as a single diastereomer in a 24% yield (Eq. 40).[1] A probable explanation for this poor yield can be rationalized by implementing either path A or B of scheme 2.



9C **10C** Eq. 40

The intermediates for path B of scheme 2 are clearly depicted in the reaction manifold presented in scheme 14. The energy value of the allylic strain that metallocycle **IIC′** experiences



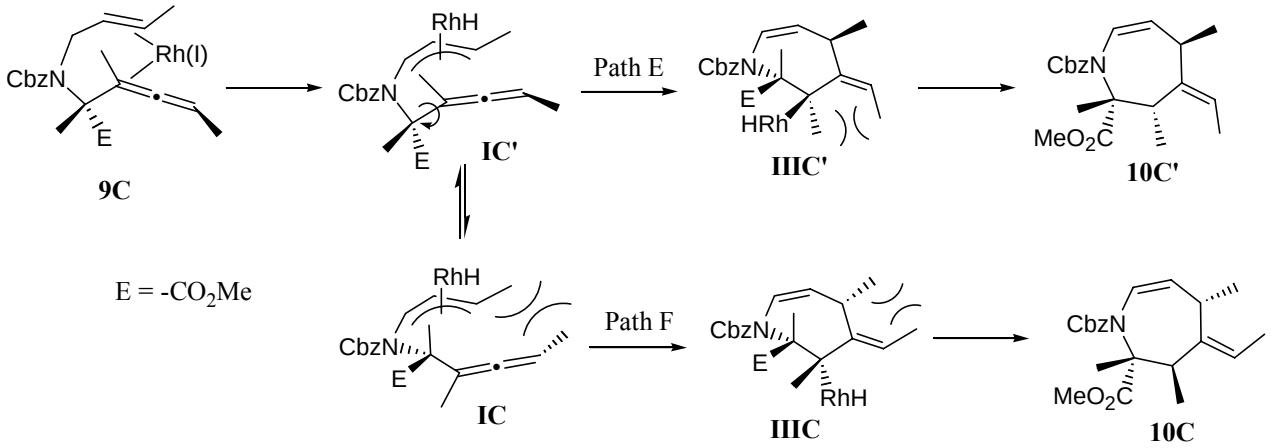
Scheme 14. Metallocycle mechanism for ene-allene **9C**.

(>4 kcal/mol) is substantially larger than that of **IIC** (~0.8 kcal/mol) which serves to bias path D over path C (Scheme 14). However, the overall strain in path D must also include the gauche interactions caused by the substituents both α and β to nitrogen.

[1] Yield was determined by NMR. The absolute configuration and olefin geometry remain to be determined.

This high energy intermediate **IIC** poses a formidable activation barrier for the reaction, which may have been the basis for its poor yield.

In path A of scheme 2, represented clearly in scheme 15, the steric interactions are dependent on the reacting conformation. The steric contribution is minimized for the conformation shown as **9C** in scheme 15. Ene-allene **9C** can then undergo C-H insertion, resulting in **IC′** which carbometallates onto the allenic portion of the molecule to provide



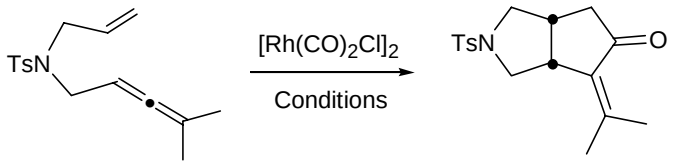
Scheme 15. C-H insertion mechanism for ene-allene **9C.**

intermediate **IIIC**.′ The allylic strain shown in **IIIC′** is an eclipsing interaction with a an energy value >4 kcal/mol. This interaction can be avoided by carbometallating the opposite side of the allene. Rotating the sp^3-sp^2 bond in intermediate **IC′** (as illustrated) generates a steric interaction in the reacting conformer of **IC** which must be overcome in order to proceed with the carbometallation that results in **IIIC**. The methyl groups responsible for the allylic strain illustrated in **IIIC** do not lie in a plain but possess a dihedral angle of ~60,° which is approximately equivalent to a gauche interaction (~0.8 kcal/mol). Biasing for either path E or F (Scheme 15) relies in the energy value of the steric interaction depicted in intermediate **1D**.

If this value, in addition to the allylic strain in **IIIC**, is larger than the allylic strain in **IIIC**,′ then path E would be favored. In either case, the steric demand for conversion of **9C** to **10C** or **10C**′ in scheme 15 is high and provides a rationale for the low product yield.

2.10 CARBON MONOXIDE INSERTION INTO AN ENE-ALLENE: FORMATION OF AN α-ALKYLIDENE CYCLOPENTENONE

Upon performing the reaction for conversion of **9b** to **10b** (Table 6), an interesting result was observed. Insertion of carbon monoxide had taken place to afford an α-alkylidene cyclopentenone in a poor but isolable 13% yield (entry 55, Table 9). Attempts at optimization of this result by employing various reaction conditions are represented in table 9 and summarized below.



9b **12b**

Table 9. Optimization Attempts for CO Insertion.

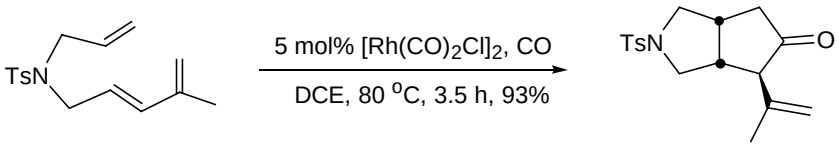
Entry	Solvent	Catalyst Loading (mol%)	Atmosphere	Yield (%)[a]
55	DCE	9	CO	13
56	DCE	10	CO/Ar	18
57	1,4-dioxane	5	CO	14
58	1,4-dioxane	6	CO/Ar	17

[a]Indicates isolated yield.

Employing a partial carbon monoxide/argon atmosphere, while maintaining DCE as solvent, improved the yield by only 5% (compare entry 55 to 56). Utilizing a complete carbon monoxide atmosphere and exchanging DCE for 1,4-dioxane as solvent decreased the yield by 4% (compare entry 56 to 57). Keeping 1,4-dioxane and implementing a partial carbon monoxide/argon atmosphere improved the yield by 3% (compare entry 57 to 58).

Overall, the optimized conditions (entry 56) only improved the yield by 5% in comparison to the conditions employed (entry 55) upon original discovery of this carbon monoxide insertion product **12b**.

Only a single report of carbon monoxide insertion using ene-allenes is present in the literature (Eq. 26).[26] Wender has communicated a related transformation utilizing diene-enes with the identical catalyst (Eq. 41).[61] He asserts that further substitution on the diene moiety causes formation of multiple products with isolation of only a moderate amount of the desired carbon monoxide insertion product.

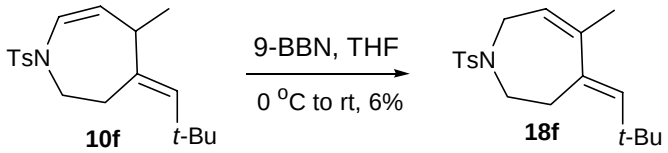


Eq. 41

2.11 ELABORATION OF AZEPINES

2.11.1 Hydroboration

Efforts to demonstrate the usefulness of these tetrahydroazepines for the construction of complex molecules are underway. Hydroboration of **10f** with 9-BBN was slow and did not consume the majority of starting material. The only isolable compound **18f** (6% yield) indicated hydroboration followed by elimination (Eq. 42).

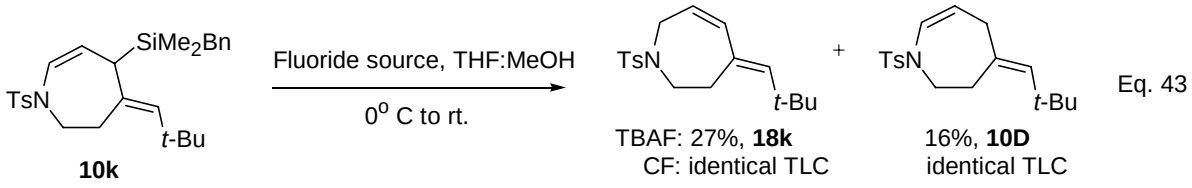


10f **18f**

Eq. 42

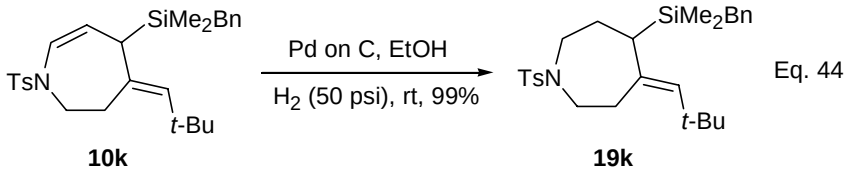
2.11.2 Tamao-Fleming oxidation

Upon treatment with a fluoride source as the initial step in a Tamao-Fleming oxidation of azepine **10k,** only protodesilation was witnessed to provide azepines **18k** and **10D** in 27% and 16% yields, respectively (Eq. 43).

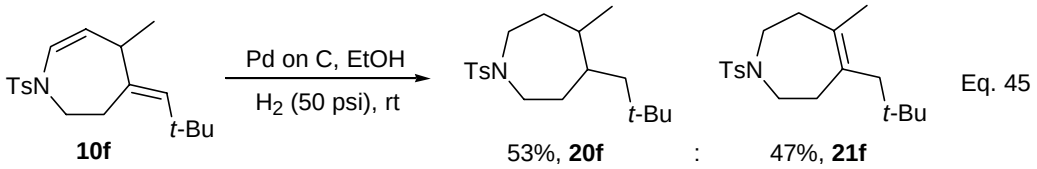


2.11.3 Reduction

Reduction of azepine **10k** with Palladium on carbon under a hydrogen atmosphere (50 psi) selectively reduced the endocyclic enamide moiety, proceeding in 99% yield and leaving the exocyclic olefin intact (Eq. 44). Trials using 1 atm of hydrogen lead to decomposition along with the desired product.

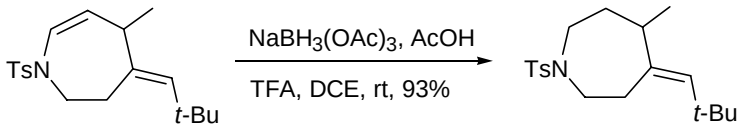


Reduction of azepine **10f** under identical conditions as those utilized for **10k** afforded the fully reduced hexahydroazepine **20f** and a partially reduced tetrahydroazepine **21f** in a 1.1:1 ratio, respectively (Eq. 45). Azepine **21f** is a result of enamide reduction followed by isomerization of the exocyclic olefin into the ring. Reduction under 1 atm of hydrogen revealed similar results.



10f 53%, **20f** : 47%, **21f** Eq. 45

Selective reduction of the enamide functionality of **10f** could be achieved with modified reductive amination conditions to furnish the desired hexahydroazepine **19f** in 93% yield (Eq. 46). The procedure was tedious and required constant addition of reagents to achieve complete consumption of the starting material. An endeavor to simplify the method by using AcOH/$NaBH_3CN$ displayed the same reaction trend and also did not improve the yield (57%).



10g **19g** Eq. 46

3.0 CONCLUSIONS

Mitsunobu reactions provided key substrates in higher yields when employing allenyl-tosylamides as nucleophiles with allylic alcohols as pro-electrophiles. Yields were diminished when allylic tosylamides were utilized as nucleophiles with allenyl-allylic alcohols as pro-electrophiles.

A novel carbon-carbon bond forming cycloisomerization reaction resulting in tetrahydroazepines was discovered which proved to be tolerable to a host of various substrates. Long alkyl-chain ene-allene tethers reacted in lower yields compared to their branched alkyl-counterparts. Vinyl-silane and styryl-derived substrates reacted in high yield when employing a *tert*-butyl substituted allene. Phenyl substitution on the allene (ene-allene **9e**) only provided azepine products in ethereal solvents. The substrate possessing an olefin with 1,1,2-trisubstitution, ene-allene **9i**, provided the azepine in an acceptable 78% yield while 1,2,2-trisubstituted alkenyl-substrates, ene-allenes **9h** and **9A**, reacted with poor conversion (14% and 14%, respectively).

Three major factors contributed to the efficiency of this azepine forming cycloisomerization: steric bulk of the alkene and allene substituents, solvent, and atmosphere. The yield of cyclization is surprisingly higher when the substrate possesses bulkier substituents at the alkene and allene termini. This enhanced reactivity due to steric bulk is limited however to 1,2-disubstituted alkenyl- and 1,3-disubstituted allenyl-substrates. Implementing the use of

ethereal solvents, 1,4-dioxane particularly, facilitated the reaction by increasing both the rate and yield of cyclization. In the cases of substrates **9d** and **9f**, utilizing 1,4-dioxane allowed cyclization to occur when is was not previously observed or observed in trace amounts in DCE. The lower boiling point solvents THF and DME were acceptable solvents for the cycloisomerization, but did prolong the reaction time when compared to 1,4-dioxane. Similarly, carbon monoxide retarded reaction progression and argon accelerated substrate conversion. A higher catalyst loading increases product formation and accelerates the reaction time.

A deuterium labeling study aided in the postulation of two working mechanisms (Scheme 2). The first activates the olefin moiety by allylic C-H insertion then closes down on the central carbon of the allene to result in 7-*endo*-*dig* cyclization followed by reductive elimination. The second mechanism effects transformation by way of a bridged metallocycle which undergoes β-hydride elimination followed by reductive elimination.

During the course of our examination of this cycloisomerization reaction, a novel carbon monoxide insertion was observed for ene-allene **9b** to afford α-alkylidene cyclopentenone **12b** in an 18% yield (Table 9). Efforts to improve the yield were not met with success. Selective reduction of the enamide moiety was achieved for azepines **10k** and **10f**, under differing conditions, to provide azepines **19k** and **19f** in 99% and 93% yield, respectively.

Further substrate exploration is necessary for application of this azepine forming methodology to library development or natural product synthesis. Ideally, additional investigation into this cycloisomerization reaction would lead to the development of milder conditions (room temperature verses reflux) and broader substrate tolerance.

APPENDIX A

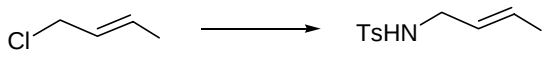
EXPERIMENTAL

Unless otherwise noted, all reactions were carried out in flame dried glassware under a nitrogen atmosphere and commercially available compounds were used as received. Solvent column purification under a nitrogen atmosphere employing alumina and activated Q5 material was utilized to purify tetrahydrofuran (THF) and diethyl ether (ether). Dichloromethane (DCM) was purified with an alumina column under a nitrogen atmosphere. Toluene and dichloroethane (DCE) were freshly distilled from CaH_2 prior to use. 1,4-Dioxane and 1,2-dimethoxyethane (DME) were freshly distilled from $LiAlH_4$ prior to use. Methanol (MeOH), acetonitrile (MeCN), and dimethylformamide (DMF) were dried with and stored over 4Å molecular sieves. Purification of compounds by flash chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size). Analyses by TLC were performed on silica gel 60 F_{254} plates with a 250 μm thickness layer. Gas chromatography was performed on a gas chromatograph with a 15 ft RTX-5 column containing 5% diphenyl-crossbonds and a 95% dimethylpolysiloxane stationary phase with an internal diameter of 0.25 mm and film thickness of 0.25 μm. Purification by HPLC was performed using a silica gel column (5 μm packing, 250 mm x 10 mm). Nuclear magnetic resonance spectra (^{1}H and ^{13}C) were obtained on a 300 MHz instrument, reporting chemical shifts (δ) relative to their respective residual solvent peak. All NMR spectra were obtained at room temperature unless otherwise specified. Infrared spectra were obtained on

an FT-IR instrument. Mass spectrometry (EI) was performed on a high resolution mass spectrometer. Stereoisomers obtained are denoted with a superscript and a description at the bottom of the page. When possible, diastereomeric ratios are reported according to their relative integration in the ^{1}H NMR spectrum or as a result of HPLC separation. Designation of ^{1}H NMR splitting patterns are as follows: b = broad, d = doublet, h =heptet, m = multiplet, p = pentet, q = quartet, s = singlet, t = triplet. All melting points are uncorrected.

A.1 SYNTHESIS OF ENE-ALLENES

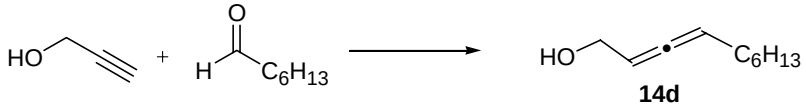
The synthesis of each ene-allene is described sequentially, including an explanation of the synthes(is/ese) of the requisite precursor(s) for each substrate.



13c

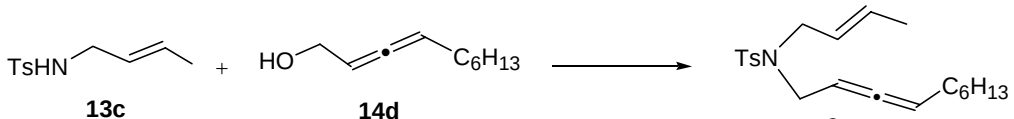
***N*-[(*E*)-2-Butenyl]-4-methylbenzenesulfonamide (13c):**[62] To a solution of *p*-toluenesulfonamide (11.89 g, 69.44 mmol) in MeCN (180 mL) was added K_2CO_3 (36.89 g, 266.9 mmol) and the slurry heated to 50 °C whereupon (*E*)-1-chloro-2-butene (5.2 mL, 53 mmol) was added dropwise. After 27 h of heating at 50 °C, the solution was concd in vacuo and the crude solid partitioned between ethyl acetate/H_2O (200 mL/250 mL). The aqueous layer was separated and extracted with ethyl acetate (2 x 200 mL), acidified to pH 8 using HCl (3 M), and re-extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with brine (2 x 200 mL), dried over $MgSO_4$, and concd in vacuo. The crude solid was purified via silica gel chromatography (ethyl acetate-hexanes 1:13-1:2) to afford 6.35 g of tosylamide **13c** as an off-white solid in 53% yield (mp 57-60 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.32 (1/2 AA′XX′ d, J = 8.5 Hz, 2H), 5.58 (dqt, J = 15.2, 6.5, 1.3 Hz, 1H), 5.34

(dtq, *J* = 15.2, 6.4, 1.6 Hz, 1H), 4.38-4.37 (bm, 1H), 3.51 (tdq, *J* = 6.3, 1.2, 1.2 Hz, 2H), 2.44 (s, 3H), 1.61 (ddt, *J* = 6.4, 1.4, 1.3 Hz, 3H).



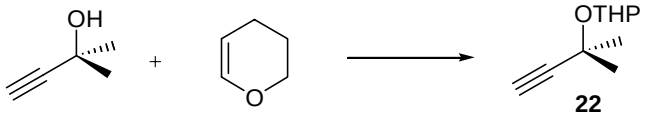
14d

2,3-Decadien-1-ol (14d):[63] To a solution of diisoproplyamine (14 mL, 100 mmol) in 1,4-dioxane (305 mL) at rt was added CuBr (4.31 g, 30 mmol) and heptaldehyde (14 mL, 100 mmol). The solution was subsequently heated to 90 °C for 30 min to result in a light blue color. To this solution was added propargyl alcohol (15 mL, 250 mmol) and it was heated to 110 °C for 24 h whereupon substantial precipitate had formed. Upon cooling to rt, the mixture was vacuum filtered and the filtrate concd in vacuo. The resulting brown oil was dissolved in ethyl acetate (300 mL) and washed with HCl aq (4 M, 50 mL), H_2O (2 x 75 mL), and saturated $NaHCO_3$ (50 mL) whereupon a precipitate had formed. The solids were removed *via* vacuum filtration and the organic layer was washed with H_2O (50 mL), dried over Na_2SO_4, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:3) to afford 2.28 g of alcohol **14d** as a light yellow oil in 15% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.36-5.27 (m, 2H), 4.12 (dd, *J* = 5.4, 3.3 Hz, 2H), 2.07-1.99 (m, 2H), 1.43-1.28 (m, 8H), 0.91-0.87 (m, 3H).



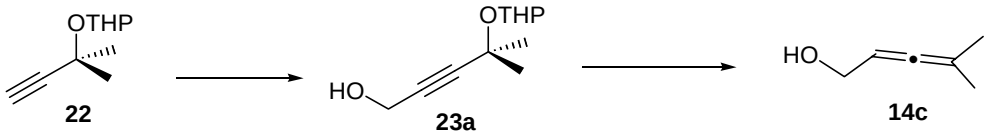
13c **14d** **9a**

***N*-[(*E*)-2-butenyl]-*N*-(2,3-decadienyl)-4-methylbenzenesulfonamide (9a):** Preparation of ene-allene **9a** has previously been described.[20]



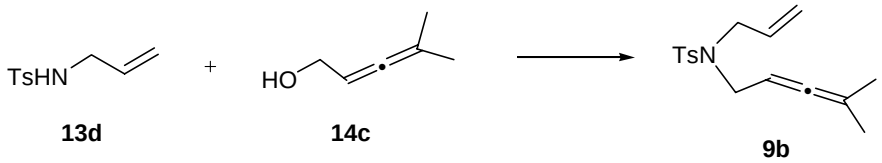
22

2-(1,1-Dimethyl-2-propynyloxy)-tetrahydropyran (22):[64] To a solution of 2-methyl-3-butyn-2-ol (11.5 mL, 119 mmol) in DCM (200 mL) was added 3,4-dihydro-2*H*-pyran (11.4 mL, 125 mmol) followed by PPTS (1.50 g, 5.97 mmol). After 31 h at rt excess 3,4-dihydro-2*H*-pyran (2.17 mL, 23.7 mmol) was added and after an additional 16 h the solution was washed with (½) saturated brine (3 x 30 mL), brine (40 mL), dried over Na_2SO_4, and carefully concd in vacuo (bath temp 0 °C). The residual DCM was removed by simple distillation and the THP-ether **22** was distd in vacuo (28 torr, 76 °C) to afford a 3.00 g fraction (91% pure by ^{1}H NMR) and a 14.47 g fraction (88% pure by ^{1}H NMR) to give a combined amount of 17.47 g in a calcd 77% yield. ^{1}H NMR (C_6D_6) δ: 5.38-5.35 (m, 1H), 3.87 (ddd, J = 11.2, 8.2, 3.4 Hz, 1H), 3.42-3.35 (m, 1H), 2.07 (s, 1H), 1.79-1.61 (m, 4H), 1.62 (s, 3H), 1.51 (s, 3H), 1.37-1.20 (m, 2H).



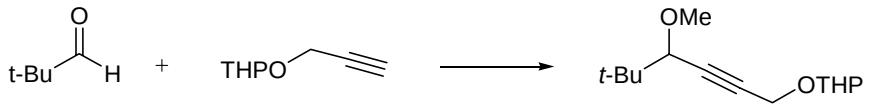
2,3-Pentadien-1-ol (14c):[65] To a solution of THP-ether **22** (89% purity, 17.47 g, 91.96 mmol) in THF (163 mL) at -78 °C was added *n*-butyllithium (1.6 M in hexanes, 92 mL, 147 mmol) dropwise. This solution was held at -78 °C for 30 min whereupon *p*-formaldehyde (undried, 5.88 g, 196 mmol) was added in portions. The mixture was slowly allowed to warm to rt and TLC analysis 24 h after *p*-formaldehyde addition indicated reaction completion. The solution was concd in vacuo and partitioned between ether/saturated NH_4Cl (300 mL/50 mL). The organic layer was washed with saturated NH_4Cl (2 x 40 mL), brine (2 x 50 mL), dried over Na_2SO_4, and concd in vacuo to afford 19.47 g of propargyl alcohol **23a** in quantitative yield (^{1}H NMR was contaminated with minor impurities). ^{1}H NMR (300 MHz, C_6D_6) δ: 5.42-5.38 (m, 1H), 3.93 (d, J = 6.1 Hz, 1H), 3.46-3.86 (m, 1H), 3.37-3.30 (m, 1H), 1.83-1.50 (m, 3H), 1.64 (s, 3H), 1.53 (s, 3H), 1.40-1.15 (m, 3H). To a suspension of $LiAlH_4$ (670 mg, 17.7 mmol) in ether

(30 mL) at 0 °C was added a solution of the crude alcohol **23a** (3.49 g, 17.6 mmol) in ether (8 mL) dropwise. The slurry was held at 0 °C until no further gas evolution whereupon it was heated at reflux for 4.3 h. The slurry was then cooled to 0 °C and carefully quenched with H_2O (Caution! Rapid gas evolution!). The solids were removed *via* vacuum filtration and the filtrate was dried over $MgSO_4$ and concd in vacuo to afford 1.24 g of allene **14c** in a 72% yield (^{1}H NMR contained minor impurities).[66] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.19 (th, J = 2.8, 2.8 Hz, 1H), 4.07 (d, J = 5.6 Hz, 2H), 1.73 (s, 3H), 1.72 (s, 3H), 1.43 (bs, 1H).



13d **14c** **9b**

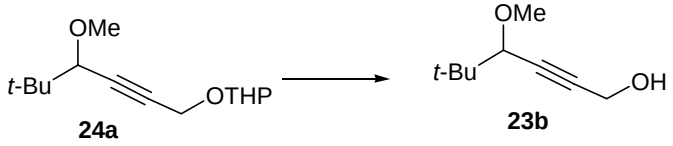
***N*-Allyl-*N*-(4-methyl-2,3-pentadienyl)-4-methylbenzenesulfonamide (9b):** Preparation of ene-allene **9b** has previously been described.[20]



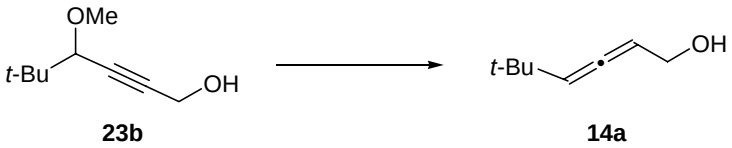
24a

2-(5,5-Dimethyl-4-methoxy-2-hexynyloxy)-tetrahydropyran (24a):[67] To a solution of *n*-butyllithium (1.6 M in hexanes, 20.0 mL, 32.0 mmol) in THF (81 mL) at -78 °C was added a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (4.0 mL, 28 mmol) in THF (15 mL). After 20 min at -78 °C trimethylacetaldehyde (3.1 mL, 28 mmol) was added as a solution in THF (8 mL). After 30 additional min at -78 °C neat methyliodide (7.0 mL, 0.11 mol) was added and the cold bath was removed. Upon reaching -20 °C HMPA (8.0 mL, 46 mmol) was added and TLC analysis indicated complete conversion after 45 min at rt. The solution was concd in vacuo and poured into brine (150 mL). The aqueous layer was extracted with ether (3x 100 mL) and the combined organic layer was washed with H_2O (3 x 100 mL), brine (100 mL), dried over K_2CO_3

and concd in vacuo to afford 7.23 g of the crude THP-ether **24a** as a yellow oil in quantitative yield.

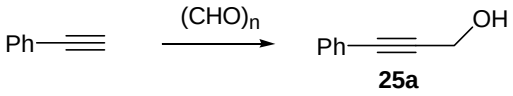


5,5-Dimethyl-4-methoxy-2-hexyn-1-ol (23b):[67] To a solution of crude **24a** (6.8 g, 28 mmol) in MeOH (40 mL) was added *p*-toluenesulfonic acid mono-hydrate (713 mg, 3.45 mmol) in one portion. After 3.6 h at rt, another portion of *p*-toluenesulfonic acid mono-hydrate was added (71 mg, 0.37 mmol) and the solution was quenched with saturated $NaHCO_3$ (3.4 mL) after an additional 1.8 h. The mixture was concd in vacuo and poured into 100 mL of H_2O. The aqueous layer was extracted with ether (2 x 60 mL, then 25 mL) and the combined organic layers were dried over K_2CO_3, and concd in vacuo to afford 4.54 g of alcohol **23b** in quantitative yield (^{1}H NMR possessed a slight amount of ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.34 (d, J = 1.5 Hz, 2H), 3.54 (t, J = 1.6 Hz, 1H), 3.41 (s, 3H), 0.98 (s, 9H).



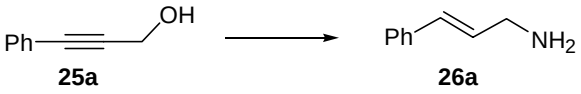
5,5-Dimethyl-2,3-hexadien-1-ol (14a):[67] To a suspension of $LiAlH_4$ (989 mg, 26.1 mmol) in ether (250 mL) was added 5,5-dimethyl-4-methoxy-2-hexyn-1-ol **23b** (1.00 g, 6.40 mmol) as a solution in ether (10 mL) dropwise. Ether (200 mL) was then added and the suspension was subsequently cooled to -78 °C whereupon I_2 (4.87 g, 19.2 mmol) was added in one portion. After an additional 3.5 h at -78 °C the suspension was quenched with saturated Rochelle's salt aq (25 mL) and saturated $Na_2S_2O_3$ aq (25 mL) whereupon it was allowed to warm to 0 °C. After 45 min at 0 °C the organic layer was decanted off and the aqueous layer was extracted with ether (2 x 30 mL). The combined organic layers were dried over K_2CO_3 and concd in vacuo. The crude

oil was purified by silica gel chromatography (ether-pentane 1:3-1:2) to afford 500 mg of alcohol **14a** as a clear oil in 62 % yield (^{1}H NMR possessed impurities). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.41 (q, *J* = 5.9 Hz, 1H), 5.33 (dt, *J* = 6.1, 3.0 Hz, 1H), 4.12 (ddd, *J* = 5.8, 5.8, 2.9 Hz, 1H), 1.44 (t, *J* = 6.0 Hz, 1H), 1.06 (s, 9H).



25a

3-Phenyl-2-propyn-1-ol (25a):[II] A 250 mL round bottom flask was charged with phenyl acetylene (5.00 g, 49.0 mmol) and THF (100 mL). To the solution at -78 °C was added *n*-butyllithium (1.6 M in hexanes, 40 mL, 64 mmol) dropwise *via* syringe. To the solution after 40 min at -78 °C was added paraformaldehyde (2.94 g, 98.0 mmol) in one portion. TLC analysis indicated reaction completion after an additional 5.3 h whereupon it was quenched with saturated NH_4Cl (20 mL) and concd in vacuo. The crude residue was extracted with ether (3 x 50 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concd in vacuo to afford **25a** as a yellow oil.

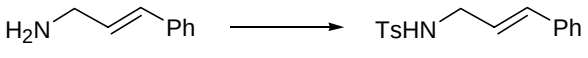


25a **26a**

***N*-[(*E*)-3-Phenyl-2-propenyl]amine (26a):**[II] To a solution of alcohol **25a** (~49 mmol) and triethylamine (9.6 mL, 69 mmol) in DCM (200 mL) at 0 °C was added methanesulfonyl chloride (4.6 mL, 59 mmol) dropwise. Reaction completion was observed by TLC after 2.8 h whereupon it was quenched with saturated NH_4Cl (20 mL), washed with brine (30 mL), 1:1 brine/saturated $NaHCO_3$ (2 x 30 mL), and again with brine (30 mL). The organic layer was dried over $MgSO_4$ and concd in vacuo to provide a yellow oil. To this oil dissolved in DMF (50 mL) was added NaN_3 (10.0 g, 154 mmol). The resulting solution was held at rt for 1 h followed by 40 °C

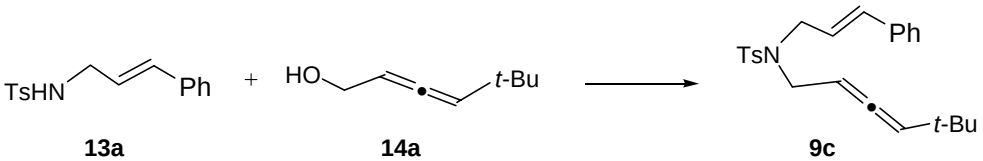
[II] Reaction sequence was performed by Dr. Hongfeng Chen. References were not provided.

heating overnight. To the solution was added H_2O (200 mL) and the mixture was extracted with ether (5 x 100 mL). The combined organic layers were washed with H_2O (5 x 20 mL), brine (3 x 20 mL), dried over $MgSO_4$, and concd in vacuo to give the crude azide as a yellow oil. To this oil dissolved in ether (150 mL) at 0 °C was slowly added $LiAlH_4$ (10.0 g, 256 mmol) in portions. After 4 h, NaOH aq (1 N) was cautiously added followed by H_2O until the precipitate became white. The solids were removed by vacuum filtration and the filtrate was dried over Na_2SO_4 followed by concn in vacuo to afford 2.48 g of amine **26a** in 38% yield (3 steps).



26a **13a**

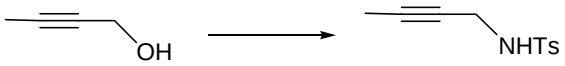
***N*-[(*E*)-3-Phenyl-2-propenyl]-4-methylbenzenesulfonamide (13a):**[II] To a solution of amine **26a** (2.48 g, 18.6 mmol) and triethylamine (7.1 mL, 51 mmol) in DCM (50 mL) at 0 °C was added *p*-toluenesulfonyl chloride (3.24 g, 17.0 mmol) in one portion. The temperature was then slowly raised to rt. Upon reaction completion (TLC), the solvent was removed in vacuo and the crude residue partitioned between ethyl acetate (200 mL) and saturated NH_4Cl/H_2O (1:12, 30 mL). The organic layer was washed with saturated NH_4Cl (30 mL), brine (2 x 30 mL), dried over Na_2SO_4, and concd in vacuo to afford **13a** as a pale yellow solid (mp 80-94 °C, yield not determined). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.79 (d, J = 8.2 Hz, 2H), 7.37-7.22 (m, 7H), 6.44 (d, J = 15.8 Hz, 1H), 6.02 (dt, J = 15.9, 6.3 Hz, 1H), 4.75 (t, J = 6.1 Hz, 1H), 3.76 (ddd, J = 6.3, 6.3, 1.0 Hz, 2H), 2.42 (s, 3H).



13a **14a** **9c**

General Procedure for the Mitsonobu Reaction: *N*-(5,5-Dimethyl-2,3-hexadienyl)-*N*-[(*E*)-3-phenyl-2-propenyl]-4-methylbenzenesulfonamide (9c):[19] To a solution of 5,5-dimethyl-2,3-

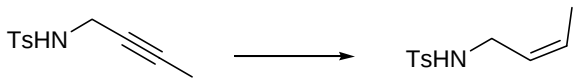
hexadien-1-ol **14a** (98 mg, 0.773 mmol) in THF (2.28 mL) was added *N*-[(*E*)-3-phenyl-2-propenyl]-4-methylbenzenesulfonamide **13a** (290 mg, 1.01 mmol) and PPh_3 (263 mg, 0.900 mmol). The flask was then cooled to 0 °C and DIAD (197 μL, 1.00 mmol) was added dropwise over a period of 15 min. At this rate the yellow color intensity dissipated after each drop. After 16 h, the solvent was removed under reduced pressure and the crude residue purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:6) to afford 182 mg of ene-allene **9c** as a white solid (mp 90-99 ^{o}C) in 60% yield. The ^{1}H NMR showed 8% of the *cis*-alkene impurity. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74 (d, *J* = 8.2 Hz, 2H), 7.34-7.21 (m, 7H), 6.45 (d, *J* = 15.9 Hz, 1H), 5.96 (dt, *J* = 15.8, 6.7 Hz, 1H) 5.15 (dt, *J* = 6.2, 2.4 Hz, 1H), 4.99 (dt, *J* = 7.0, 6.5 Hz, 1H), 4.02 (d, *J* = 6.7 Hz, 2H), 3.91 (1/2 AB ddd, *J* = 15.2, 6.6, 2.4 Hz, 1H), 3.82 (1/2 AB ddd, *J* = 15.2, 7.2, 2.2 Hz, 1H), 2.42 (s, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.6, 143.2, 137.7, 136.3, 133.9, 129.7, 128.5, 127.8, 127.2, 126.4, 123.8, 104.6, 88.3, 48.6, 46.6, 31.8, 30.1, 21.5; IR (KBr pellet) 3088, 3053, 3032, 3022, 2955, 2925, 2868, 1957, 1598, 1500, 1445, 1363, 1342 cm^{-1}; MS *m/z* (%) 91 (43), 117 (100), 212 (34), 286 (32), 338 (29), 380 (26), 395 (17); EI-HRMS calcd for $C_{24}H_{29}NO_2S$ [M+] *m/z*: 395.1919, found: 395.1938.



27

***N*-(2-Butynyl)-4-methylbenzenesulfonamide (27):**[II] To a solution of 2-butyn-1-ol (5.34 mL, 71.4 mmol) and triethylamine (14.3 mL, 103 mmol) in DCM (150 mL) at 0 °C was added methanesulfonyl chloride (5.52 mL, 71.3 mmol) dropwise. To the slurry after 1 h at 0 °C was added saturated NH_4Cl (20 mL) and the organic layer was washed with saturated $NaHCO_3$:brine:H_2O (1:2:1, 3 x 100 mL), brine (2 x 50 mL), dried over $MgSO_4$ and concd in vacuo to afford a yellow oil. To this oil that was dissolved in DMF (100 mL) at 0 °C was added NaN_3 (9.27 g, 143 mmol) and the solution was allowed to warm to rt. After an additional 1 h the

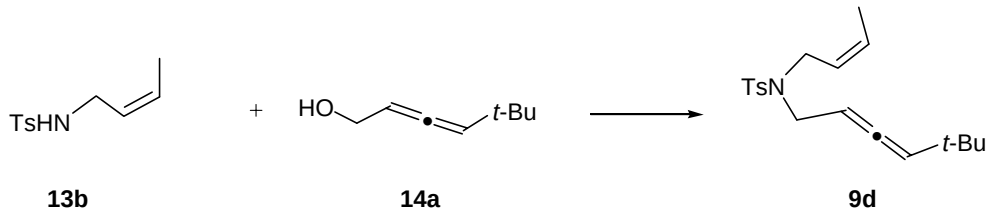
solution was heated to 45 °C for 13.5 h whereupon it was diluted with H_2O (200 mL) and extracted with ether (5 x 100 mL). The combined organic layers were washed with H_2O (2 x 100 mL), dried over $MgSO_4$, and concd in vacuo to afford a crude oil. To this oil dissolved in ether (50 mL) at 0 °C was added $LiAlH_4$ (0.60 g, 16 mmol) in portions. After 2 h at 0 °C the slurry was quenched with minimal H_2O. The slurry was filtered and the filter cake was washed with ether (30 mL). The organic layer was carefully concd in vacuo to afford a yellow liquid. To this liquid dissolved in DCM (30 mL) at 0 °C was added triethylamine (3.7 mL, 27 mmol) and p-toluenesufonylchloride (2.00 g, 10.5 mmol) whereupon it was allowed to warm to rt. After 4 h at rt the solvent was removed in vacuo and the crude residue was partitioned between ethyl acetate/H_2O (100 mL/20 mL), washed with brine (2 x 20 mL), dried over Na_2SO_4, and concd in vacuo. The resulting residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:4-1:1) to afford 1.34 g of tosylamide **27** in 8% yield (4 steps). ^{1}H NMR $CDCl_3$ δ: 7.78 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.35-7.29 (m, 2H), 4.52-4.47 (bm, 1H), 3.77 (dq, J = 6.0, 2.4 Hz, 2H), 2.44 (s, 3H), 1.61 (t, J = 2.4 Hz, 3H).



27 **13b**

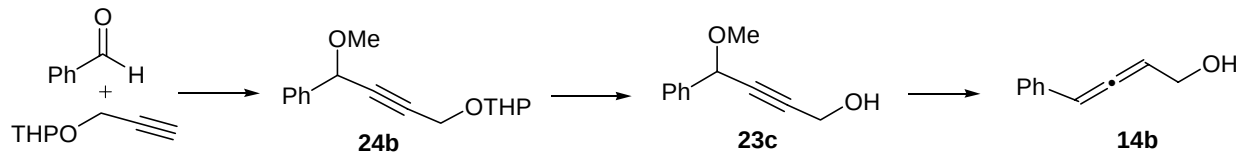
***N*-[(*Z*)-2-Butenyl]-4-methylbenzenesulfonamide (13b):**[68] A suspension of Lindler's catalyst (5% Pd on $CaCO_3$ poisoned with Pb, 65 mg, 0.031 mmol) and *N*-(2-butynyl)-4-methylbenzenesulfonamide **27** (1.29 g, 5.78 mmol) in MeOH (20 mL) was evacuated and charged with H_2 (5x). To the suspension was added ethylenediamine (0.46 mL, 7.6 mmol) and the suspension was then evacuated and charged with H_2. After 25 h at rt the suspension was filtered and the filter cake was washed with MeOH. The solution was concd in vacuo and the crude residue was purified by silica gel chromatography to afford 1.26 g of tosylamide **13b** in a

yield of 94%.[III] ^{1}H NMR $CDCl_3$ δ: 7.77 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.32 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.58 (dqt, *J* = 10.8, 6.9, 1.4 Hz, 1H), 5.30 (dtq, *J* = 10.8, 7.0, 1.7 Hz, 1H), 4.38-4.35 (bm, 1H), 3.62 (bt, *J* = 6.4 Hz, 2H), 2.44 (s, 3H), 1.57-1.53 (m, 3H).



13b **14a** **9d**

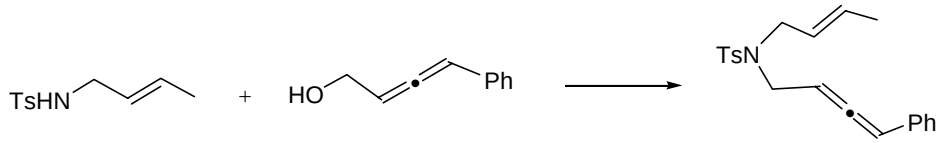
***N*-[(*Z*)-2-Butenyl)]-*N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9d)**: The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-[(*Z*)-2-butenyl]-4-methylbenzenesulfonamide **13b** (154 mg, 0.683 mmol), PPh_3 (188 mg, 0.718 mmol), DIAD (140 μL, 0.711 mmol), and 5,5-dimethyl-2,3-hexadien-1-ol **14a** (69 mg, 0.549 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 102 mg of ene-allene **9d** as a clear oil in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.29 (1/2 AA′XX′ d, *J* = 8.1 Hz, 2H), 5.60 (dqt, *J* = 10.9, 6.9, 1.6 Hz, 1H), 5.27 (dtq, *J* = 10.8, 6.9, 1.7 Hz, 1H), 5.14 (dt, *J* = 6.2, 2.4 Hz, 1H), 5.00 (dt, *J* = 7.4, 6.2 Hz, 1H), 3.90 (d, *J* = 6.8 Hz, 2H), 3.89 (1/2 AB ddd, *J* = 15.0, 6.2, 2.5 Hz, 1H), 3.71 (1/2 AB ddd, *J* = 15.0, 7.5, 2.2 Hz, 1H), 2.42 (s, 3H), 1.62 (dd, *J* = 6.9, 0.8 Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.4, 143.0, 137.9, 129.8, 128.3, 127.1, 124.9, 104.4, 88.8, 46.7, 43.1, 31.8, 30.0, 21.4, 12.9; IR (neat) 3027, 2960, 2925, 2863, 1969, 1611, 1455, 1342 cm^{-1}; MS *m/z* (%) 91 (100), 110 (49), 155 (85), 184 (95), 238 (53), 333 (11); EI-HRMS calcd for $C_{19}H_{27}NO_2S$ [M+] *m/z*: 333.1763, found: 333.1748.



24b **23c** **14b**

[III] The sample possessed 3% ethyl acetate by ^{1}H NMR.

4-Phenyl-2,3-butadien-1-ol (14b): Compound **24b** was prepared as described for preparation of **24a** (p. 53) using tetrahyro-2-(2-propynyloxy)-2*H*-pyran (3.00 mL, 21.3 mmol), benzaldehyde (2.15 mL, 21.2 mmol), *n*-butyllithium (1.6 M in hexanes, 14.7 mL, 23.5 mmol), iodomethane (5.3 mL, 85 mmol), HMPA (6.0 mL, 35 mmol), and THF (80 mL) to afford 5.87 g of the crude ether in quantitative conversion. Compound **23c** was prepared as described for preparation of **23b** (p. 54) using *p*-toluenesulfonic acid monohydrate (405 mg, 2.13 mmol) and MeOH (30 mL) to result in 4.04 g of the crude alcohol in quantitative conversion. Compound **14b** was prepared as described for preparation of **14a** (p. 54) using $LiAlH_4$ (1.028 g, 27.1 mmol), alcohol **23c** (1.34 g, 6.98 mmol), and ether (520 mL), which after purification by silica gel chromatography (ether-pentanes 1:3-1:2) afforded 296 mg of the alcohol in a calculated yield of 27%.[IV] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39-7.17 (m, 5H), 6.33 (dt, *J* = 6.2, 3.1 Hz, 1H), 5.80 (q, *J* = 6.0 Hz, 1H), 4.28-4.26 (m, 2H), 1.52 (bt, *J* = 5.8 Hz, 1H).

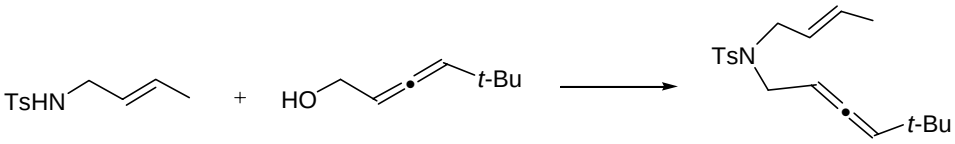


13c **14b** **9e**

***N*-[(*E*)-2-Butenyl]-*N*-(4-phenyl-2,3-butadienyl)-4-methylbenzenesulfonamide (9e)**: The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-[(*E*)-2-butenyl]-4-methyl-benzenesulfonamide **13c** (635 mg, 2.82 mmol), PPh_3 (665 mg, 2.53 mmol), DIAD (500 μL, 2.53 mmol), and 4-phenyl-2,3-butadien-1-ol **14b** (275 mg, 1.88 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:6) to afford 366 mg of ene-allene **9e** as a cloudy oil in 55% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.33-7.26 (m, 4H), 7.23-7.16 (m, 3H), 6.12 (dt, *J* = 6.4, 2.4 Hz, 1H), 5.55 (dqt, *J* = 15.2, 6.5, 1.2 Hz, 1H), 5.38 (q, *J* = 6.7 Hz, 1H), 5.28 (dtq, *J* = 15.2, 6.7, 1.6

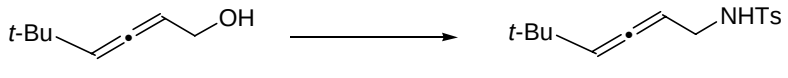
[IV] The sample possessed 7% of ether by ^{1}H NMR.

Hz, 1H), 3.96-3.90 (m, 2H), 3.81 (bd, J = 6.7 Hz, 2H), 2.42 (s, 3H), 1.60 (ddt, J = 6.4, 1.5, 1.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.1, 143.2, 137.6, 133.6, 130.8, 129.6, 128.6, 127.2, 127.2, 126.8, 125.1, 95.9, 90.7, 48.8, 45.3, 21.5, 17.6; IR (neat) 3086, 3063, 3032, 2925, 2858, 1947, 1729, 1602, 1496, 1450, 1342, 1158 cm^{-1}; MS *m/z* (%) 55 (100), 91 (71), 115 (100), 128 (63), 130 (78), 155 (84), 184 (73), 238 (95), 353 (23); EI-HRMS calcd for $C_{21}H_{23}NO_2S$ [M+] *m/z*: 353.1450, found: 353.1436.



13c **14a** **9g**

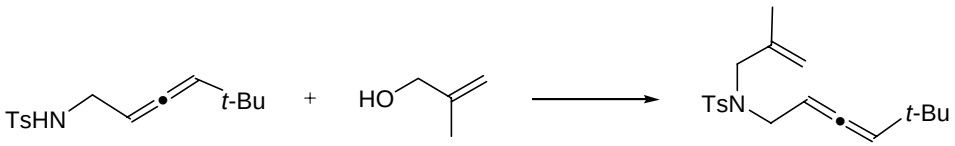
***N*-[(*E*)-2-Butenyl]-*N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9f)**: The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-[(*E*)-2-butenyl]-4-methyl-benzenesulfonamide **13c** (822 mg, 3.65 mmol), PPh_3 (958 mg, 3.65 mmol), DIAD (720 μL, 3.66 mmol), and 5,5-dimethyl-2,3-hexadien-1-ol **14a** (354 mg, 2.81 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 561 mg of ene-allene **9f** as a clear oil in 60% yield. ^{1}H NMR matched that previously reported in the literature.[20]



14a **15a**

N-(5,5-Dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (15a): To a soln. of 5,5-dimethyl-2,3-hexadien-1-ol **14a** (364 mg, 2.89 mmol) and triethylamine (570 μL, 4.09 mmol) in DCM (14.5 mL) at -30 °C was added methansulfonyl chloride (270 μL, 3.49 mmol) dropwise. Precipitation was observed after 10 min and TLC analysis indicated reaction completion after 20 min. The crude solution was washed with H_2O (2 x 15 mL), brine (15 mL), dried over $MgSO_4$, and concd in vacuo to afford 531 mg of crude mesylate as a light yellow oil in 90% yield.[69] This

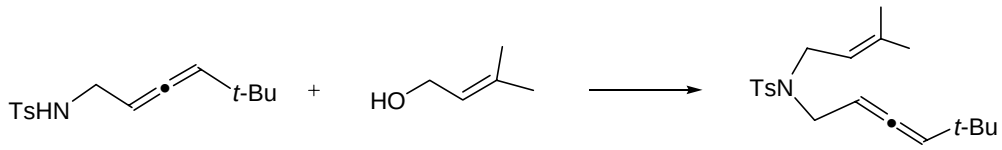
crude oil was dissolved in MeCN (8.7 mL) and transferred *via* cannula to a flask charged with *p*-toluenesulfonamide (666 mg, 3.89 mmol) and K_2CO_3 (anhyd, 1.80 g, 13.0 mmol). The mixture was heated to 50 °C for 13 h, whereupon TLC analysis indicated complete consumption of starting material. The mixture was then concd in vacuo and partitioned between H_2O/ethyl acetate (50 mL/50 mL). The aqueous layer was extracted with ethyl acetate (2 x 25 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:7) to afford 501 mg of allene **15a** as a white solid (mp 47-50 ˚C) in 69% yield (^{1}H NMR possessed a slight amount of impurities).[62] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 7.29 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 5.19 (dt, *J* = 6.2, 3.0 Hz, 1H), 5.10 (q, *J* = 6.0 Hz, 1H), 4.61 (bt, *J* = 5.6 Hz, 1H), 3.54 (ddd, *J* = 5.9, 5.9, 3.0 Hz, 2H), 2.41 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.8, 143.4, 137.1, 129.6, 127.1, 106.4, 89.4, 42.1, 31.8, 30.0, 21.4; IR (thin film) 3257, 2960, 2930, 2858, 1962, 1711, 1604, 1460, 1424, 1327, 1158 cm^{-1}; MS *m/z* (%) 91 (100), 155 (91), 184 (70), 264 (45), 279 (45); EI-HRMS calcd for $C_{15}H_{21}NO_2S$ [M+] *m/z*: 279.1293, found: 279.1291.



15a **16a** **9g**

***N*-(5,5-Dimethyl-2,3-hexadienyl)-*N*-(2-methyl-2-propenyl)-4-methylbenzenesulfonamide (9g):** The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide **15a** (99 mg, 0.35 mmol), PPh_3 (120 mg, 0.456 mmol), DIAD (90 μL, 0.46 mmol), and 2-methyl-2-propen-1-ol **16a** (40 μL, 0.47 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-

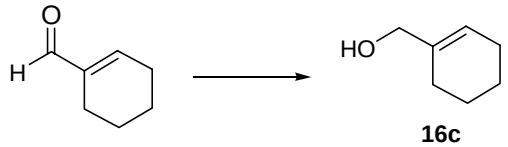
hexanes 1:19-1:9) to afford 99 mg of ene-allene **9g** as a colorless oil in 84% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.27 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.06 (dt, *J* = 6.2, 2.3 Hz, 1H), 4.90-4.83 (m, 3H), 3.84 (1/2 AB ddd, *J* = 15.3, 6.6, 2.3 Hz, 1H), 3.74 (s, 2H), 3.73 (1/2 AB ddd, *J* = 15.2, 7.4, 2.3 Hz, 1H), 2.40 (s, 3H), 1.69 (s, 3H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.4, 143.0, 140.0, 137.6, 129.6, 127.1, 114.2, 104.2, 87.7, 52.4, 46.4, 31.7, 30.0, 21.4, 19.8; IR (neat) 3078, 2960, 2930, 2904, 2963, 1962, 1655, 1593, 1445, 1342, 1163 cm^{-1}; MS *m/z* (%) 82 (69), 91 (100), 155 (56), 238 (68), 276 (31), 333 (22); EI-HRMS calcd for $C_{19}H_{27}NO_2S$ [M+] *m/z*: 333.1763, found: 333.1759.



15a **16b** **9h**

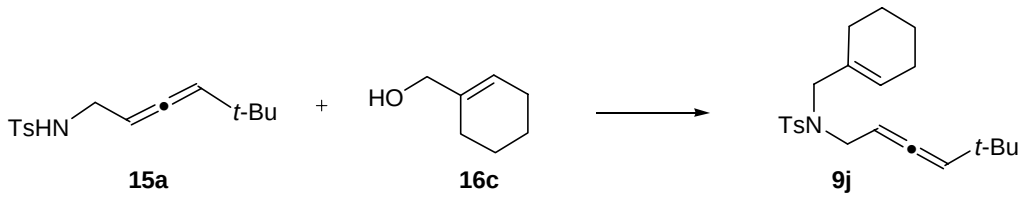
***N*-(5,5-Dimethyl-2,3-hexadienyl)-*N*-(3-methyl-2-butenyl)-4-methylbenzenesulfonamide (9h)**: The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide **15a** (157 mg, 0.562 mmol), PPh_3 (192 mg, 0.734 mmol), DIAD (145 μL, 0.736 mmol), and 3-methyl-2-buten-1-ol **16b** (74 μL, 0.73 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 176 mg of ene-allene **9h** as a colorless oil in 90% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.66 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.31 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.15 (dt, *J* = 6.2, 2.4 Hz, 1H), 5.05-4.93 (m, 2H), 3.84 (1/2 ddd, *J* = 15.1, 6.3, 2.6 Hz, 1H) 3.83-3.79 (m, 1H), 3.69 (1/2 AB ddd, *J* = 15.0, 7.5, 2.3 Hz, 1H), 2.42 (s, 3H), 1.66 (d, *J* = 0.9 Hz, 3H), 1.62 (bs, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.2, 142.9, 137.8, 136.7, 129.5, 127.1, 118.9, 104.4, 88.7, 46.4, 44.3, 31.8, 30.0, 25.7, 21.4, 17.8; IR (neat) 2960, 2925, 2863, 1962, 1916, 1777, 1670, 1598, 1445, 1347 cm^{-1}; MS *m/z* (%) 69 (100), 91 (51), 110

(40), 155 (45), 184 (80), 238 (28), 252 (32), 347 (12); EI-HRMS calcd for $C_{20}H_{29}NO_2S$ [M+] *m/z*: 347.1919, found: 347.1905.



16c

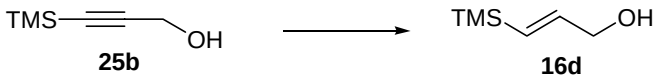
1-Cyclohexenylmethanol (16c):[70] To a solution of 1-cyclohexenecarboxaldehyde (100 μL, 0.877 mmol) in DCM (9.0 mL) at -78 °C was added diisobutylaluminum hydride (1.0 M in hexanes, 970 μL, 0.970 mmol) dropwise. To the solution after 15 min at -78 °C was added MeOH (100 μL) dropwise and it was allowed to warm to rt. Upon reaching rt H_2O (2 mL) was added followed by HCl aq (1N, 20 mL) and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concd in vacuo to afford 97 mg of crude alcohol **16c** in 99% yield.



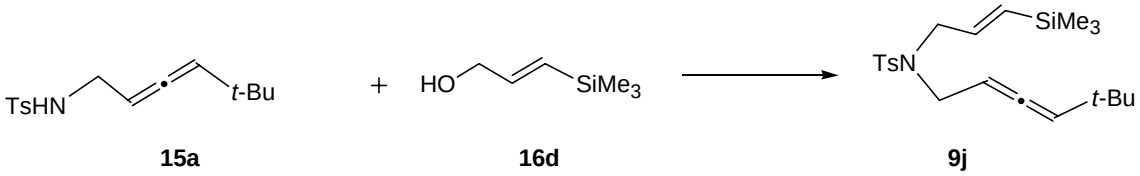
15a **16c** **9j**

***N*-(5,5-Dimethyl-2,3-hexadienyl)-*N*-(methyl-1-cyclohexenyl)-4-methylbenzenesulfonamide (9i):** The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide **15a** (160 mg, 0.573 mmol), PPh_3 (196 mg, 0.746 mmol), DIAD (147 μL, 0.746 mmol), and 1-cyclohexenylmethanol **16c** (97 mg, 0.87 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 184 mg of ene-allene **9i** as a colorless oil in 86% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 7.26 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.57 (bs, 1H), 5.05 (dt, *J* = 6.2, 2.2 Hz, 1H), 4.86 (dt, *J* = 7.3, 6.4 Hz, 1H), 3.83 (1/2 AB ddd, *J* = 15.3, 6.4, 2.3 Hz, 1H), 3.68 (1/2 AB ddd, *J* = 15.3, 7.6, 2.2 Hz, 1H), 3.67 (bs, 2H), 2.39

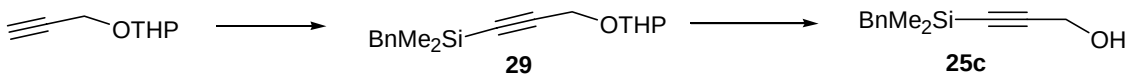
(s, 3H), 1.98-1.86 (m, 4H), 1.61-1.46 (m, 4H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.3, 142.8, 137.8, 132.3, 129.4, 127.1, 126.4, 104.1, 88.0, 53.0, 46.1, 31.6, 30.0, 25.9, 25.1, 22.4, 22.2, 21.4; IR (neat) 3027, 2960, 2930, 2858, 2383, 1962, 1598, 1496, 1440, 1347 cm^{-1}; MS *m/z* (%) 91 (37), 95 (100), 155 (31), 184 (20), 278 (21), 316 (18), 373 (36); EI-HRMS calcd for $C_{22}H_{31}NO_2S$ [M+] *m/z*: 373.2076, found: 373.2076.



(*E*)-3-(Trimethylsilyl)-2-propen-1-ol (16d): Compound **16d** was prepared as described in the literature[71] using 3-trimethylsilyl-2-propyn-1-ol **25b** (2.30 mL, 15.5 mmol), Red-Al®(65% wt in toluene, 7.2 mL, 25.2 mmol), and ether (19 mL) to afford 506 mg of the allylic alcohol that possessed 4% ether by ^{1}H NMR to afford a calculated yield of 24%. The ^{1}H NMR spectra matched that of the reported compound.

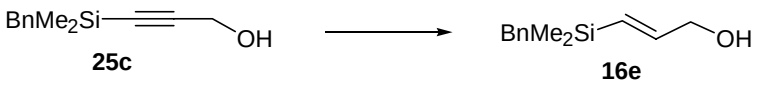


***N*-(5,5-Dimethyl-2,3-hexadienyl)-*N*-[(*E*)-3-(trimethylsilyl)-2-propenyl]-4-methylbenzene-sulfonamide (9j):** Preparation of ene-allene **9j** has previously been described.[20]



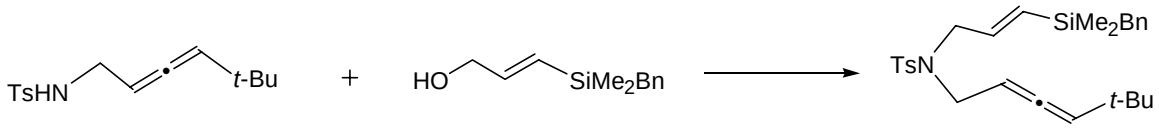
3-(Benzhydryldimethylsilyl)-2-propyn-1-ol (25c): The procedure as described in the literature[72] was followed using tetrahydro-2-(2-propynyloxy)-2*H*-pyran (340 μL, 2.42 mmol), benzylchlorodimethylsilane (500 μL, 2.66 mmol), *n*-butyllithium (1.51 mL, 2.42 mmol), and THF (4.8 mL) to provide THP-ether **29** in quantitative conversion after the first step. The second

step utilized crude ether **29** (2.42 mmol), *p*-toluenesulfonic acid monohydrate (13 mg, 0.050 mmol), and MeOH (4.8 mL) to provide alcohol **25c** in quantitative conversion.



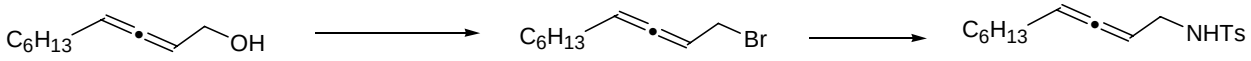
25c **16e**

(*E*)-3-(Benzhydryldimethylsilyl)-2-propen-1-ol (16e): The procedure as described in the literature[72] was followed using alcohol **25c** (2.42 mmol), Red-Al®(65% wt in toluene, 1.53 mL, 4.91 mmol), and ether (7.4 mL) to provide, after purification by silica gel chromatography (ether-pentane 1:3-1:2), 399 mg of alcohol **16e** as a slightly yellow oil in 80% yield. The ^{1}H NMR spectra matched that of the reported compound.



15a **16e** **9k**

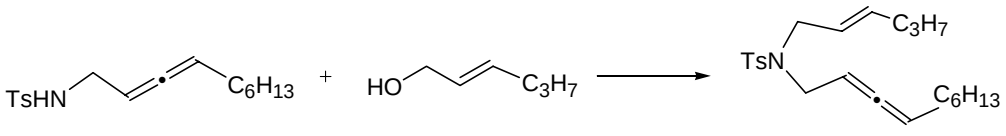
***N*-[(*E*)-3-(Benzyldimethylsilyl)-2-propenyl]-*N*-(5,5-Dimethyl-2,3-hexadienyl)-4-methyl-benzenesulfonamide (9k):** Preparation for ene-allene **9k** has previously been described.[20]



14d **28a** **15b**

***N*-(2,3-Decadienyl)-4-methylbenzenesulfonamide (15b):**[73] To a solution of alcohol **14d** (2.28 g, 14.8 mmol) and CBr_4 (5.40 g, 16.2 mmol) in DCM (50 mL) was added PPh_3 (4.27 g, 16.3 mmol) in portions. Within 5 min a brown color change was noted and TLC inspection indicated reaction completion after 10 min whereupon it was quenched with H_2O (6 mL) and concd in vacuo. The crude oil was extracted with ether-hexanes (1:1, 2 x 100 mL) and the decanted organic phases were combined and concd in vacuo to give the crude allylic bromide **28a** (yield not determined). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.44-5.31 (m, 2H), 3.94 (dd, J = 7.9, 2.0 Hz,

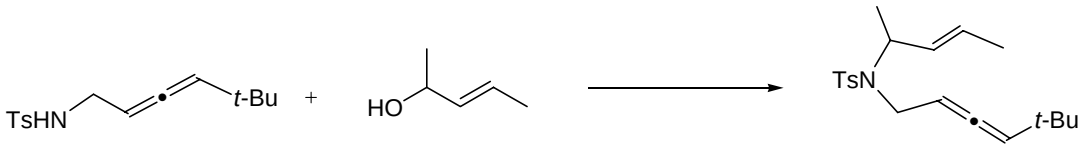
2H), 2.03 (dtd, J = 6.8, 6.8, 3.0 Hz, 2H), 1.45-1.19 (m, 8H), 0.90 (t, J = 6.8 Hz, 3H). The subsequent alkylation was carried out in the manner as that described for the formation of **13c** (p. 50) using bromide **28a** (1.24 g, 5.71 mmol), *p*-toluenesulfonamide (874 mg, 5.10 mmol), K_2CO_3 (3.53 g, 25.5 mmol) and MeCN (18 mL). The crude residue was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:2) to afford 537 mg of pure allene **15b** as a slightly yellow oil in 34% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.31 (1/2 AA′XX′ d, J = 8.5 Hz, 2H), 5.25-5.15 (m, 1H), 5.08-4.99 (m, 1H), 4.48 (bs, 1H), 3.56 (ddd, J = 5.9, 5.9, 3.1 Hz, 2H), 2.43 (s, 3H), 1.94 (dtd, J = 7.0, 7.0, 3.0 Hz, 2H), 1.40-1.25 (m, 8H), 0.91-0.85 (m, 3H).



15b **16f** **9l**

***N*-(2,3-Decadienyl)-*N*-[(*E*)-2-hexenyl]-4-methylbenzenesulfonamide (9l):** The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(2,3-decadienyl)-4-methyl-benzenesulfonamide **15b** (160 mg, 0.519 mmol), PPh_3 (217 mg, 0.828 mmol), DIAD (163 μL, 0.828 mmol), and 2-hexen-1-ol **16f** (92 μL, 0.78 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:6) to give 167 mg of ene-allene **9l** as a clear oil in 83% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.74 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.25 (1/2 AA′XX′ d, J = 8.0 Hz, 2H), 5.44 (bdt, J = 15.3, 6.6 Hz, 1H), 5.29 (dtt, J = 15.3, 6.5, 1.2 Hz, 1H), 5.05-4.94 (m, 2H), 3.98-3.92 (m, 2H), 3.91-3.86 (m, 2H), 1.91-1.73 (m, 7H), 1.31-1.36 (m, 10H), 0.89-0.83 (m, 3H), 0.77 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.4, 143.1, 142.8, 136.0, 129.7, 127.3, 124.1, 92.6, 86.4, 48.4, 46.0, 34.4, 31.8, 29.3, 28.9, 28.8, 22.7, 22.3, 21.6, 14.2, 13.8; IR (neat) 2955, 2925, 2853, 1957, 1772, 1445, 1347,

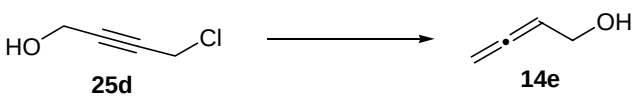
1163 cm^{-1}; MS *m/z* (%) 83 (100), 91 (77), 155 (81), 184 (100), 254 (37), 266 (38), 277 (20), 389 (20); EI-HRMS calcd for $C_{23}H_{35}NO_2S$ [M+] *m/z*: 389.2389, found: 389.2388.



15a **9m**

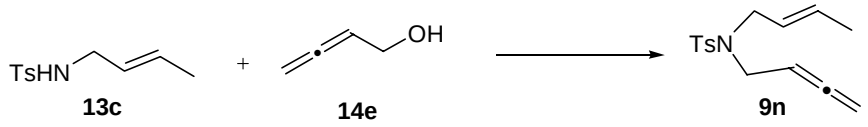
***N*-(5,5-Dimethyl-2,3-hexadienyl)-*N*-[(*E*)-1-methyl-2-butenyl]-4-methylbenzenesulfonamide (9m)**: The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide **15a** (184 mg, 0.659 mmol), PPh_3 (236 mg, 0.900 mmol), DIAD (175 μL, 0.842 mmol), and 1-methyl-2-buten-1-ol (100 μL, 0.979 mmol). The soltuion was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:7) to afford 171 mg of ene-allene **9m** as a colorless oil in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.4 Hz, $4H^a$), 7.27 (1/2 AA′XX′ d, *J* = 8.5 Hz, $4H^a$), 5.47 (m, $2H^a$), 5.32 (m, $1H^b$), 5.28 (m, $1H^b$), 5.19 (m, $4H^a$), 4.47 (m, $2H^a$), 3.76 (m, $4H^a$), 2.41 (s, $6H^a$), 1.61 (dd, *J* = 2.9, 1.5 Hz, $3H^b$), 1.59 (dd, *J* = 2.9, 1.5 Hz, $3H^b$), 1.23 (d, *J* = 1.7 Hz, $3H^b$), 1.21 (d, *J* = 1.7 Hz, $3H^b$), 1.03 (s, $9H^b$), 1.02 (s, $9H^b$); ^{13}C NMR (75 MHz, $CDCl_3$)[c] δ: 201.3, 143.0, 138.7, 131.0, 130.7, 129.6, 128.5, 127.9, 127.7, 127.3, 104.8, 104.6, 92.1, 54.8, 43.8, 32.3, 30.3, 21.6, 19.2, 18.8, 17.9; IR (neat)[c] 3027, 2960, 2930, 2863, 1962, 1598, 1496, 1455, 1342 cm^{-1}; MS[c] *m/z* (%) 69 (100), 184 (55), 91 (40), 155 (35), 252 (32), 347 (16), 332 (13), 348 (9); EI-HRMS calcd for $C_{20}H_{29}NO_2S$ [M+] *m/z*:[c] 347.1923, found: 347.1919.

[a]Spin set is a mixture of diastereomers. [b]Spin set results from resonance of one diastereomer. [c]Spectrum is reported as a mixture of diastereomers.

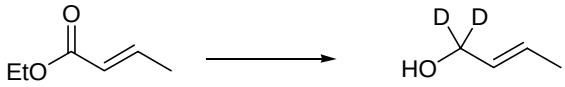


25d **14e**

2,3-Butadiene-1-ol (14e):[74] To a solution of alcohol **25d** (3.97 g, 37.9 mmol) in ether (95 mL) at -4 °C (NaCl ice bath) was added $LiAlH_4$ (1.40 g, 37.0 mmol) in portions over a period of 15 min. The cold bath was then removed and the slurry was heated to reflux for 2.5 h once it had warmed to rt. The slurry was then cooled to 0 °C and a small amount of H_2O was added to quench the remaining hydride. The solid was removed via vacuum filtration (washing with ether) and the filtrate was concd in vacuo to afford alcohol **14e** as a brown liquid (yield not determined). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.40-5.31 (m, 1H), 4.86 (ddd, *J* = 6.1, 3.1 3.1 Hz, 2H), 4.15 (ddd, *J* = 6.3, 3.0, 3.0 Hz, 2H).

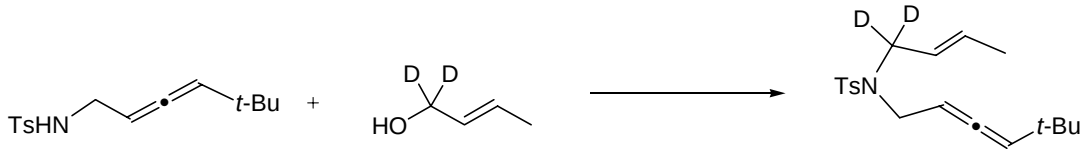


***N*-(2,3-Butadienyl)-*N*-[(*E*)-2-butenyl]-4-methylbenzenesulfonamide (9n):** The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-[(*E*)-2-butenyl]-4-methylbenzenesulfonamide **13c** (320 mg, 1.42 mmol), PPh_3 (520 mg, 1.98 mmol), 2,3-butadiene-1-ol **14e** (160 mg, 2.28 mmol)), and DIAD (390 μL, 1.98 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:9-1:6) to afford 268 mg of ene-allene **9n** in 68% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.69 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.29 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 5.65-5.52 (m, 1H), 5.33-5.22 (m, 1H), 4.88 (dt, *J* = 6.8, 6.8 Hz, 1H), 4.68 (dt, *J* = 6.5, 2.5 Hz, 2H), 3.83 (dt, *J* = 7.0, 2.5 Hz, 2H), 3.77 (bd, *J* = 6.7 Hz, 2H), 2.42 (s, 3H), 1.65 (bd, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, C_6D_6) δ: 209.4, 142.7, 138.5, 130.2, 129.5, 127.3, 125.6, 86.0, 75.7, 48.7, 45.4, 20.9, 17.4; IR (neat) 3063, 3027, 2966, 2919, 2859, 1952, 1716, 1670, 1598, 1491, 1440, 1342 cm^{-1}; MS *m/z* (%) 55 (62), 91 (100), 155 (100), 184 (70), 238 (49), 255 (43), 262 (31), 277 (40); EI-HRMS calcd for $C_{15}H_{19}NO_2S$ [M+] *m/z*: 277.1137, found: 277.1139.



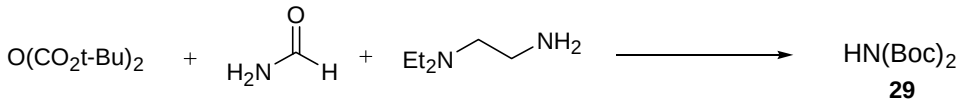
16g

(*E*)-2-Buten-1-ol-1,1-d_2 (16g): Compound **16g** was prepared as described in the literature[75] using ethyl crotonate (5.4 mL, 44 mmol), $LiAlD_4$ (1.83 g, 43.6 mmol), $AlCl_3$ (5.81 g, 43.6 mmol), and ether (220 mL) to afford 3.60 g of the crude alcohol in a calculated 86% yield.[V] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.79-5.67 (m, 2H), 1.72 (d, J = 4.9 Hz, 3H).



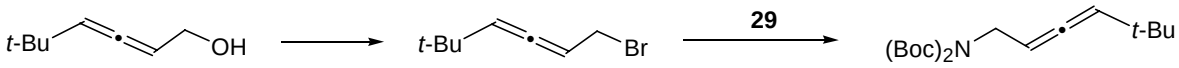
15a **16g** **9o**

***N*-[(*E*)-2-Butenyl-1,1-d_2]-*N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9o):** Preparation of ene-allene **9o** has previously been described.[20]



29

Di-*t*-butyliminodicarbonate (29): Compound **29** was prepared as described in the literature[76] using di-*t*-butyldicarbonate (24.8 g, 114 mmol), DMAP (630 mg, 5.16 mmol), formamide (2.05 mL, 51.6 mmol), *N*,*N*-diethylethylenediamine (8.85 mL, 61.8 mmol), and MeCN (26 mL) to afford 10.07 g of **29** as a white solid (mp 118-120 ˚C) in 90% yield (^{1}H NMR contained minor impurities). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.72 (s, 1H), 1.49 (s, 18H).

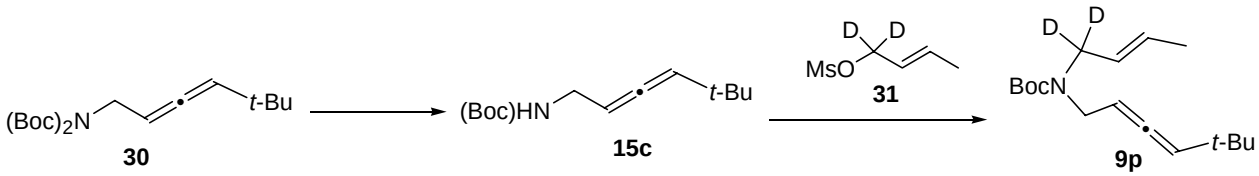


14a **28b** **30**

***N*-(5,5-Dimethyl-2,3-hexadienyl)-di-*t*-butyliminodicarbonate (30):** To a solution of imidazole (897 mg, 9.85 mmol) and triphenylphosphonium bromide (4.16 g, 9.85 mmol) in DCM (125 mL)

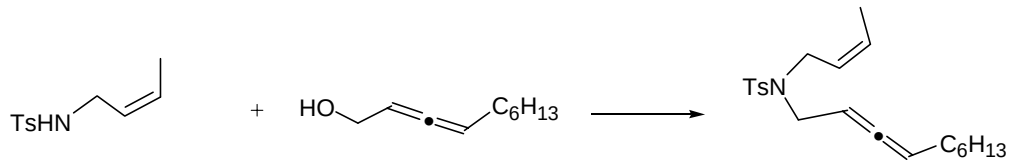
[V] The sample was contaminated with ethanol and exhibited 77% purity by ^{1}H NMR.

at 0 °C was added a solution of alcohol **14a** (832 mg, 6.59 mmol) in DCM (5mL) dropwise. After 4.3 h at rt excess triphenylphosphonium bromide (835 mg, 1.98 mmol) was added and the reaction showed completion by TLC after an additional 1.5 h. To the crude solution was added silicon dioxide (1 g) whereupon the mixture became orange. The mixture was then concd in vacuo and the crude gel was triturated with pentane. The decanted organic solution was concd in vacuo to yield 741 mg of bromide **28b** in 59% yield (^{1}H NMR contained minor impurities). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.48 (td, J = 8.0, 6.1 Hz, 1H), 5.36 (dt, J = 6.1, 1.8 Hz, 1H), 3.96 (dt, J = 8.0, 1.7 Hz, 2H), 1.07 (s, 9H).[77] To a solution of iminocarbonate **29** (29 mg, 0.13 mmol) in DMF (1.33 mL) at rt was added KH (35% wt in mineral oil, 20 mg, 0.17 mmol). After 30 min at rt neat bromide **28b** (23 μL, 0.13 mmol) was added dropwise and precipitation was noted within 5 min of addition. The slurry was held at rt for 2.3 h then diluted with ethyl acetate and poured into H_2O (15 mL). The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organic layers were washed with H_2O (4 x 15 mL), dried over $MgSO_4$, and concd in vacuo to furnish 39 mg of allenyliminocarbonate **30** as a slightly yellow oil in 90% yield (^{1}H NMR contained mineral oil). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.29-5.18 (m, 2H), 4.21 (1/2 AB ddd, J = 15.4, 5.1, 3.3 Hz, 1H), 4.12 (1/2 AB ddd, J = 15.5, 5.5, 2.9 Hz, 1H), 1.50 (s, 18H), 1.03 (s, 9H).



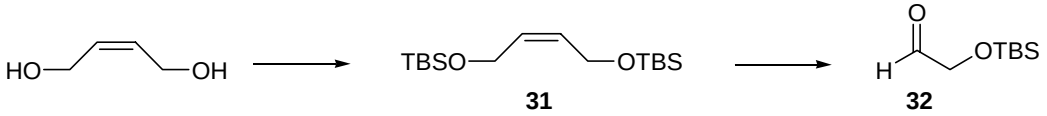
***N*-[(*E*)-2-Butenyl-1,1-d_2]-*N*-(5,5-dimethyl-2,3-hexadienyl)-*t*-butoxycarbonylamine (9p):** To a solution of **30** (60 mg, 0.19 mmol) in DCM (1.5 mL) at rt was added trifluoroacetic acid (27 μL, 0.35 mmol) dropwise. After 12 h at rt the solution was quenched with saturated $NaHCO_3$ (3 mL)

and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concd in vacuo afford 40 mg of carbamate **15c** in 96% yield.[78] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.30-5.19 (m, 2H), 4.58 (bs, 1H), 3.80-3.65 (m, 2H), 1.44 (s, 9H), 1.04 (s, 9H). To a solution of alcohol **16g** (51 μL, 0.58 mmol) and triethylamine (120 μL, 0.861 mmol) in DCM (2.9 mL) at -30 °C was added methansulfonyl chloride (54 μL, 0.70 mmol) dropwise. Precipitation was observed after 10 min and the slurry was held at -50 °C for 2 h. Upon warming to rt pentane (1 mL) was added and the precipitate filtered and washed with pentane (10 mL). The filtrate was washed with H_2O (5 mL), brine (5 mL), dried over $MgSO_4$, and concd in vacuo to afford 55 mg of crude mesylate **31** as a light yellow oil in 62% yield.[69] To a solution of carbamate **15c** (104 mg, 0.460 mmol) in DMF (1.9 mL) at rt was added KH (35% wt in mineral oil, 54 mg, 0.47 mmol) and the resulting slurry held at rt for 1 h. To the slurry was added a solution of the crude mesylate **31** (55 mg, 0.36 mmol) in DMF (1.0 mL) dropwise. After 2 h the slurry was poured into H_2O (10 mL) and extracted with ethyl acetate (4 x 10 mL). The combined organic layers were washed with H_2O (4 x 10 mL), brine (10 mL), dried over $MgSO_4$, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 53 mg of ene-allene **9p** as a clear oil in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.55 (dq, J = 15.2, 6.3 Hz, 1H), 5.39 (d, J = 15.4 Hz, 1H), 5.18 (dt, J = 6.2, 2.8 Hz, 1H), 5.11 (q, J = 6.2 Hz, 1H), 3.91-3.65 (m, 2H), 1.68 (dd, J = 6.2, 1.5 Hz, 3H), 1.45 (s, 9H), 1.03 (s, 9H).



13b **14d** **9q**

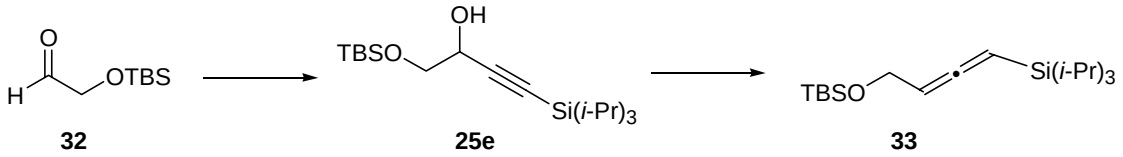
***N*-[(*Z*)-2-Butenyl)]-*N*-(2,3-decadienyl)-4-methylbenzenesulfonamide (9q)**:[VI] The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-[(*Z*)-2-butenyl]-4-methylbenzenesulfonamide **13b** (304 mg, 1.35 mmol), PPh_3 (470 mg, 1.79 mmol), 2,3-decadien-1-ol **14d** (267 mg, 1.73 mmol), and DIAD (350 μL, 1.78 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:9) to afford 339 mg of ene-allene **9q** in 69% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.29 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.61 (dqt, *J* = 10.8, 7.0, 1.5 Hz, 1H), 5.28 (dtq, *J* = 10.8, 6.9, 1.7 Hz, 1H), 5.11 (tdt, *J* = 6.8, 6.4, 2.3 Hz, 1H), 4.90 (dtt, *J* = 6.9, 6.5, 2.8 Hz, 1H), 3.90 (d, *J* = 6.9 Hz, 2H), 3.85 (1/2 AB ddd, *J* = 15.1, 6.6, 2.4 Hz, 1H), 3.75 (1/2 AB ddd, *J* = 15.0, 7.2, 2.3 Hz, 1H), 2.42 (s, 3H), 1.95 (dtd, *J* = 7.3, 6.9, 2.9 Hz, 2H), 1.65-1.61 (m, 3H), 1.41-1.23 (m, 8H), 0.91-0.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.1, 143.0, 129.6, 128.3, 127.2 (2C), 125.0, 92.6, 86.7, 46.5, 43.0, 31.6, 29.1, 28.7, 28.6, 22.6, 21.4, 14.0, 12.8.



2-*t*-butyldimethylsiloxyethanal (32): To a solution of *t*-butyldimethylsilylchloride (35.08 g, 232.7 mmol) and 4-(dimethylamino)pyridine (694 mg, 5.68 mmol) in DCM (380 mL) was added 2-buten-1,4-diol (9.30 mL, 113 mmol) dropwise. After 1 h at rt TLC analysis indicated complete consumption of starting material. The solution was diluted with DCM (100 mL), washed with H_2O (2 x 300 mL) and brine (300 mL), dried over $MgSO_4$, and concd in vacuo. The crude oil was dissolved in pentane whereupon the solids were filtered and the filtrate was concd in vacuo to afford 35.39 g of silyl ether **31** in 99% yield.[79] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.55 (s, 2H), 4.23 (s, 4H), 0.90 (s, 18H), 0.067 (s, 12H). To a solution of silyl ether **31** (3.01 g, 9.49 mmol) in

[VI] Reaction was performed by Dr. Hongfeng Chen.

DCM (19 mL) at -78 °C was bubbled a stream of O_3 for 15 min whereupon the solution turned blue. This solution was held at -78 °C and purged with N_2 until it became colorless. To the solution at -78 °C was added triphenylphosphine (2.49 g, 9.50 mmol) and it was then allowed to warm to rt. After 1 h at rt it was concd in vacuo and purified by silica gel chromatography (ether-pentane 1:9) to afford 2.27 g of aldehyde **32** in 63% yield.[VII] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.70 (s, 1H), 4.21 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H).

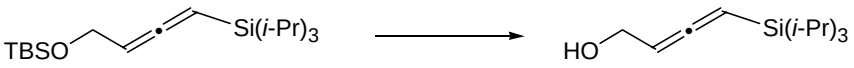


32 **25e** **33**

4-(Triisopropylsilyl)-2,3-butadienyl-*t*-butyldimethylsilylether (33): To a solution of triisopropylsilylacetylene (1.23 mL, 5.48 mmol) in THF (26 mL) at -78 °C was added n-butyllithium (1.6 M, 3.45 mL, 5.52 mmol) dropwise. To the solution, after 30 min at -78 °C, was added aldehyde **32** (1.00 g, 5.24 mmol) as a solution in THF (9 mL) dropwise. After an additional 40 min at -78 °C acetic acid (350 μL) was added and the mixture was allowed to warm to rt whereupon it was concd in vacuo and partitioned between H_2O/ether (100 mL/75 mL). The aqueous layer was washed with ether (75 mL) and the combined organic layers were washed with saturated $NaHCO_3$ (30 mL), dried over $MgSO_4$ and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:4) to afford propargyl alcohol **25e** in 74% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 4.42 (dd, J = 6.5, 3.9 Hz, 1H), 3.77 (dd, J = 9.9, 3.9 Hz, 1H), 3.65 (dd, J = 9.9, 6.5 Hz, 1H), 1.09 (s, 21H), 0.91 (s, 9H), 0.097 (s, 6H). To a solution of alcohol **25e** (442 mg, 1.24 mmol) and PPh_3 (650 mg, 2.48 mmol) in THF (8.4 mL) at -15 °C was added DEAD (390 μL, 2.48 mmol) dropwise. Immediately following was addition of *o*-nitrobenzenesulfonyl hydrazide (540 mg, 2.48 mmol) as a solution in THF (4.0 mL) at a

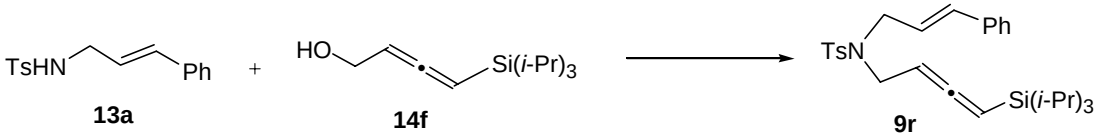
[VII] The yield discrepancy is due to the sample only being 91% pure by NMR.

rapid dropwise rate. This solution was allowed to slowly warm to rt and the reaction did not progress further after 17 h. The solution was then concd to a volume of ~5 mL where it was triturated with ice-cold hexanes, filtered, and concd in vacuo. The crude residue was purified by silica gel chromatography (hexanes) to afford 199 mg of allenyl ether **33** in 47% yield as a clear oil.[80] ^{1}H NMR (300 MHz, C_6D_6) δ: 5.00 (q, *J* = 6.8 Hz, 1H), 4.94 (dt, *J* = 6.9, 3.7 Hz, 1H), 4.24 (dd, J = 6.6, 3.1 Hz, 2H), 1.08 (s, 21H), 0.98 (s, 9H), 0.08 (s, 6H).



33 **14f**

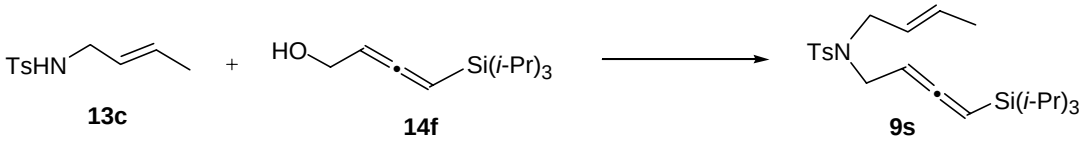
4-(Triisopropylsilyl)-2,3-butadien-1-ol (14f):[81] To an emulsion of silylether **33** (221 mg, 0.648 mmol) in THF/H_2O (1:1, 3.6 mL) was slowly added AcOH (5.4 mL), at which point the emulsion became a solution. After 12 h at rt the solution was poured into H_2O (100 mL) and extracted with ethyl acetate (75 mL, 2 x 60 mL). The combined organic layers were washed with H_2O (30 mL), brine (40 mL), dried over $MgSO_4$, and concd in vacuo. The residual AcOH was azeotroped with *n*-heptane (3 x 60 mL) to afford 147 mg of allenic alcohol **14f** in quantitative yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 4.92 (dt, *J* = 6.8, 3.3 Hz, 1H), 4.86 (q, *J* = 6.7 Hz, 1H), 3.96 (dd, *J* = 6.5, 3.3 Hz, 2H), 1.05 (s, 21H).



13a **14f** **9r**

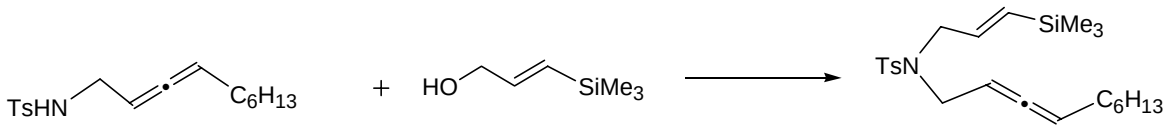
***N*-[(*E*)-3-Phenyl-2-propenyl]-*N*-[4-(triisopropylsilyl)-2,3-butadienyl]-4-methylbenzene-sulfonamide (9r):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 4-(triisopropylsilyl)-2,3-butadien-1-ol **14f** (86 mg, 0.38 mmol), THF (1.5 mL), *N*-[(*E*)-3-phenyl-2-propenyl]-4-methylbenzenesulfonamide **13a** (220 mg, 0.766 mmol), PPh_3 (201 mg, 0.765 mmol), and DIAD (150 μL, 0.762 mmol). The solution was concd in vacuo and purified by

silica gel chromatography (ethyl acetate-hexanes 1:32-1:13) to afford 68 mg of ene-allene **9r** as a clear oil in 36% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.76 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.18-6.99 (m, 5H), 6.75 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 6.34 (d, J = 15.8 Hz, 1H), 6.00 (ddd, J = 15.8, 7.2, 6.1 Hz, 1H), 4.81-4.66 (m, 2H), 4.24-4.00 (m, 2H), 4.01-3.79 (m, 2H), 1.86 (s, 3H), 0.97-0.93 (m, 21H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 211.5, 143.8, 138.0, 136.8, 134.0, 131.8, 130.1, 128.8, 127.5, 126.7, 124.3, 78.5, 77.9, 48.9, 46.6, 21.6, 18.5, 11.5; MS *m/z* (%) 91 (56), 117 (100), 183 (42), 294 (46), 452 (81), 495 (9); EI-HRMS calcd for $C_{29}H_{41}NO_2SiS$ [M+] *m/z*: 495.2627, found: 495.2639.



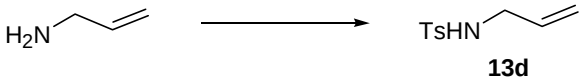
13c **14f** **9s**

***N*-[(*E*)-2-butenyl]-*N*-[4-(triisopropylsilyl)-2,3-butadienyl]-4-methylbenzene-sulfonamide (9s):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 4-(triisopropylsilyl)-2,3-butadien-1-ol **14f** (59 mg, 0.26 mmol), THF (1.1 mL), *N*-[(*E*)-2-butenyl]-4-methylbenzenesulfonamide **13c** (116 mg, 0.517 mmol), PPh_3 (137 mg, 0.521 mmol), and DIAD (103 μL, 0.523 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 29 mg of ene-allene **9s** as a clear oil in 26% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.75 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.75 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.51-5.37 (m, 1H), 5.35-5.24 (m, 1H), 4.80-4.75 (m, 1H), 4.71-4.63 (m, 1H), 4.22-4.12 (m, 1H), 4.03-3.95 (m, 1H), 3.88-3.74 (m, 2H), 1.85 (s, 3H), 1.42 (bd, J = 6.29 Hz, 3H), 1.00 (s, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 211.1, 143.0, 137.8, 130.5, 129.6, 127.2, 125.2, 78.1, 77.2, 48.1, 45.5, 21.5, 18.4, 17.7, 11.1; IR (neat) 2942, 2897, 2964, 1932, 1597, 1462, 1348, 1160 cm^{-1}; MS *m/z* (%) 55 (63), 59 (73), 91 (81), 338 (31), 390 (100); EI-HRMS calcd for $C_{29}H_{41}NO_2SiS$ [M+] *m/z*: 390.1923, found: 390.1918.



15b **16d** **9t**

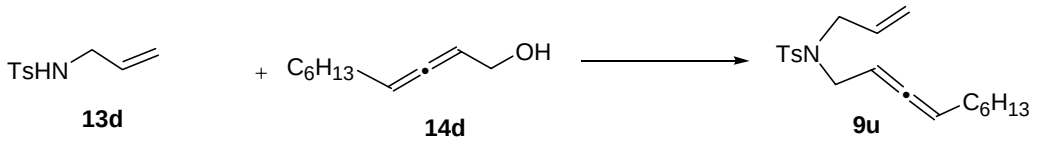
***N*-(2,3-Decadienyl)-*N*-[(*E*)-3-(trimethylsilyl)-2-propenyl]-4-methylbenzenesulfonamide (9t):** The general procedure for the Mitsunobu reaction (p. 56) was followed using PPh_3 (79 mg, 0.30 mmol), *N*-(2,3-decadienyl)-4-methylbenzenesulfonamide **15b** (67 mg, 0.22 mmol), (*E*)-3-(trimethylsilyl)-2-propen-1-ol **16d** (44 μL, 0.29 mmol), and DIAD (58 μL, 0.30 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:6) to afford 63 mg of ene-allene **9t** in 74% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.72 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.77 (1/2 AA′XX′ d, *J* = 8.1 Hz, 2H), 5.87 (dt, J = 18.6, 5.3 Hz, 2H), 5.74 (d, J = 18.7 Hz, 1H), 5.04-4.94 (m, 2H), 4.00-3.87 (m, 4H), 1.89 (s, 3H), 1.88-1.81 (m, 2H), 1.29-1.18 (m, 8H), 0.90-0.84 (m, 3H), -0.01 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 205.1, 143.4, 139.8, 137.9, 134.5, 129.6, 127.0, 92.4, 86.1, 46.5, 31.6, 29.6, 29.0, 28.7, 28.4, 22.5, 21.1, 13.7, -1.9; IR (thin film) 2955, 2926, 2855, 1963, 1618, 1599, 1458, 1350, 1305, 1248, 1161.



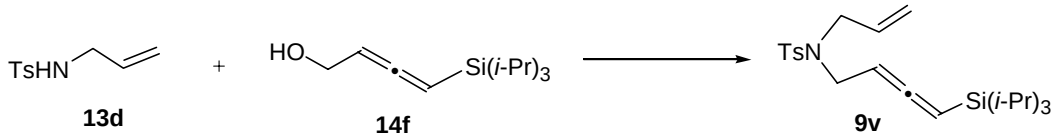
13d

***N*-(2-Propenyl)-4-methylbenzenesulfonamide (13d):** To neat allylamine (8.1 mL, 0.11 mol) at 0 °C was cautiously added *p*-toluenesulfonylchloride (3.00 g, 0.0157 mol) in portions (Reaction exotherms upon each addition!). Analysis by TLC showed reaction completion after 1.25 h whereupon the allyl amine was removed in vacuo and the solid was partitioned between ethyl acetate/H_2O (1:1, 200 mL). The organic layer was washed with H_2O (100 mL), brine (100 mL), dried over $MgSO_4$, and concd in vacuo to afford 3.27 g pure allylic tosylamide **13d** in 99% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 7.31 (1/2 AA′XX′ d, *J* =

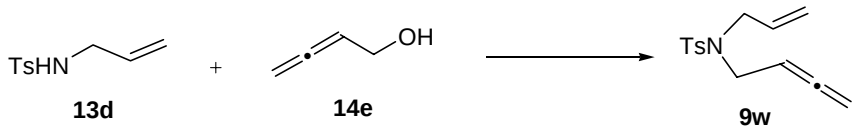
8.2 Hz, 2H), 5.72 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.17 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.10 (dd, *J* = 10.0, 0.9 Hz, 1H), 4.38-4.36 (bm, 1H), 3.59 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.43 (s, 3H).



***N*-(2,3-Decadienyl)-*N*-(2-propenyl)-4-methylbenzenesulfonamide (9u):** Preparation for ene-allene **9u** has previously been described.[20]

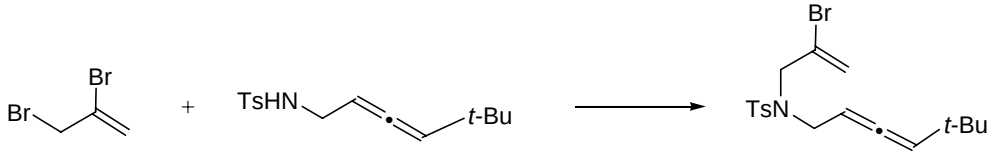


***N*-(2-Propenyl)-*N*-[4-(triisopropylsilyl)-2,3-butadienyl]-4-methylbenzenesulfonamide (9v):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 4-(triisopropylsilyl)-2,3-butadien-1-ol **14f** (74 mg, 0.33 mmol), THF (1.3 mL), *N*-(2-propenyl)-4-methylbenzenesulfonamide **13d** (136 mg, 0.645 mmol), PPh_3 (173 mg, 0.658 mmol), and DIAD (130 μL, 0.660 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:13) to afford 34 mg of ene-allene **9v** as a clear oil in 25% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.76 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 5.67-5.54 (m, 1H), 5.07-4.98 (m, 1H), 4.95-4.89 (m, 1H), 4.80-4.74 (m, 1H), 4.69-4.61 (m, 1H), 4.16-4.06 (m, 1H), 3.99-3.90 (m, 1H), 3.85-3.74 (m, 2H), 1.87 (s, 3H), 1.00 (s, 21 H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 211.4, 143.7, 138.0, 133.2, 130.0, 127.4, 118.7, 78.4, 77.8, 49.3, 46.3, 21.6, 18.5, 11.5; IR (neat) 2942, 2889, 2864, 1933, 1594, 1462, 1348, 1166; MS *m/z* (%) 59 (28), 91 (55), 324 (34), 376 (100); EI-HRMS calcd for $C_{23}H_{37}NO_2SiS$ [M+] *m/z*: 419.2314, found: 419.2325.



13d **14e** **9w**

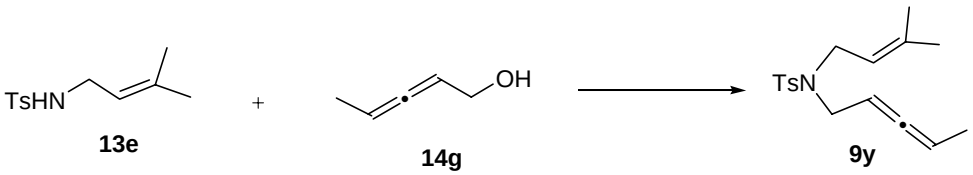
***N*-(2-Propenyl)-*N*-(2,3-butadienyl)-4-methylbenzenesulfonamide (9w):** The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(2-propenyl)-4-methylbenzenesulfonamide **13d** (102 mg, 0.484 mmol), PPh_3 (173 mg, 0.660 mmol), 2,3-butadiene-1-ol **14e** (50 mg, 0.71 mmol), and DIAD (129 μL, 0.655 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 92 mg of ene-allene **9w** in 72% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.28 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 5.66 (ddt, *J* = 17.4, 9.8, 6.4 Hz, 1H), 5.22-5.14 (m, 2H), 4.90 (dt, *J* = 6.8, 6.8 Hz, 1H), 4.70 (dt, *J* = 6.6, 2.5 Hz, 2H), 3.89-3.83 (m, 4H), 2.44 (s, 3H).



15a **9x**

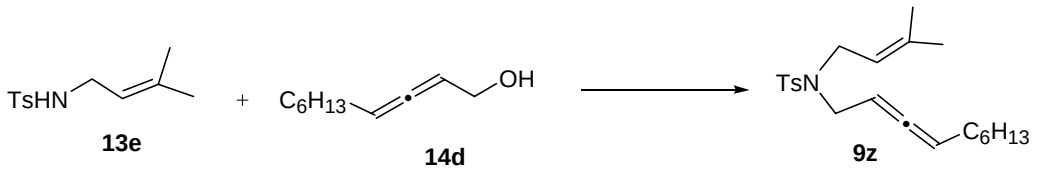
***N*-(2-Bromo-2-propenyl)-*N*-(5,5-Dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide (9x):**[62] To a flask charged with *N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide **15a** (99 mg, 0.35 mmol) and K_2CO_3 (244 mg, 1.77 mmol) was added MeCN (1.2 mL) and 2,3-dibromo-1-propene (103 μL, 1.05 mmol). After 4 h of heating at reflux, TLC analysis indicated complete consumption of starting material. The slurry was concd in vacuo and partitioned between ethyl acetate/H_2O (1:1, 20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and concd in vacuo. Purification by silica gel chromatography afforded 114 mg of pure ene-allene **9x** as a slightly yellow oil in 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (1/2 AA′XX′

d, *J* = 8.2 Hz, 2H), 7.30 (1/2 AA′XX′ d, *J* = 8.4 Hz, 2H), 5.87-5.85 (m, 1H), 5.61-5.59 (m, 1H), 5.13 (dt, *J* = 6.2, 2.3 Hz, 1H), 4.96-4.88 (m, 1H), 4.08 (s, 2H), 3.89 (1/2 AB ddd, *J* = 15.2, 6.9, 2.1 Hz, 1H), 3.82 (1/2 AB ddd, *J* = 15.2, 7.4, 2.3 Hz, 1H), 2.43 (s, 3H), 1.00 (s, 9H).



13e **14g** **9y**

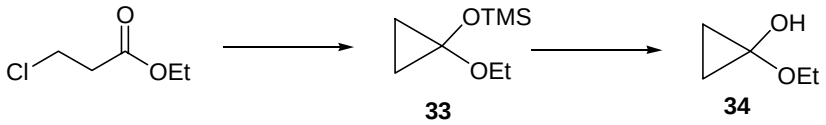
***N*-(3-Methyl-2-butenyl)-*N*-(2,3-pentadienyl]-4-methylbenzene-sulfonamide (9y):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 2,3-pentadien-1-ol **14g** (145 mg, 1.68 mmol), THF (10 mL), *N*-(3-methyl-2-butenyl)-4-methylbenzenesulfonamide **13e** (310 mg, 1.29 mmol), PPh_3 (458 mg, 1.75 mmol), and DIAD (340 μL, 1.73 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 220 mg of ene-allene **9y** as a clear oil in 56% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (1/2 AA′XX′ d, *J* = 8.6 Hz, 2H), 7.29 (1/2 AA′XX′ d, *J* = 8.9 Hz, 2H), 5.12-5.01 (m, 2H), 4.92-4.81 (m, 1H), 3.83 (bd, *J* = 7.2 Hz, 2H), 3.79 (dd, *J* = 6.9, 2.2 Hz, 2H), 2.43 (s, 3H), 1.68-1.62 (m, 6H), 1.61 (dd, *J* = 7.1, 3.1 Hz, 3H).



13e **14d** **9z**

***N*-(2,3-Decadienyl)-*N*-(3-methyl-2-butenyl)-4-methylbenzene-sulfonamide (9z):** The general procedure for the Mitsunobu reaction (p. 56) was followed using 2,3-decadien-1-ol **14d** (578 mg, 3.75 mmol), THF (10 mL), *N*-(3-methyl-2-butenyl)-4-methylbenzenesulfonamide **13e** (690 mg, 2.88 mmol), PPh_3 (1.02 g, 3.89 mmol), and DIAD (766 μL, 3.89 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 612 mg of ene-allene **9z** as a clear oil in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (1/2

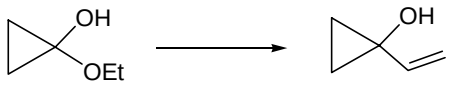
AA′XX′ d, *J* = 8.3 Hz, 2H), 7.28 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 5.10 (qt, *J* = 6.4, 2.4 Hz, 1H). 5.08-5.01 (m, 1H), 4.88 (ddt, J = 6.3, 6.3, 2.9 Hz, 1H), 3.84 (1/2 AB ddd, J = 15.4, 6.2, 2.4 Hz, 1H), 3.84 (bd, J = 7.7 Hz, 2H), 3.75 (1/2 AB ddd, J = 15.1, 7.2, 2.3 Hz, 1H), 2.42 (s, 3H), 1.95 (dtd, J = 6.8, 6.8, 2.8 Hz, 2H), 1.67 (d, J = 0.9 Hz, 3H), 1.63 (d, J = 0.5 Hz, 3H), 1.41-1.24 (m, 8H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.0, 142.9, 136.6, 129.5, 127.3, 127.3, 119.2, 92.5, 86.9, 46.4, 44.3, 31.6, 29.2, 28.7, 28.6, 25.7, 22.6, 21.4, 17.8, 14.0.



33 **34**

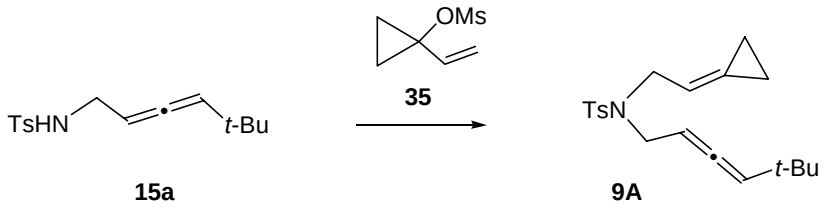
1-Ethoxycyclopropane-1-ol (34):[82] To a flask charged with sodium (s, 1.51g, 65.5 mg-atom), cut in small 5 mm cubes and washed with hexanes (2 x 10 mL), was added ether (28 mL) and the mixture was subsequently cooled to 0 °C before addition of chlorotrimethylsilane (3.65 mL, 28.8 mmol) and 3-chloropropionate (3.55 mL, 28.6 mmol). The flask was immersed in an ultrasonic cleaning bath[VIII] and held at 0 °C for 2.5 h then 2.2 h at rt whereupon a GC trace indicated complete conversion. The suspension was filtered over celite (30mL) and concd in vacuo to give 2.82 g of the crude cyclopropane silylacetal **33** as an oil in 57% yield. To the crude silylacetal **33** dissolved in MeOH (7.2 mL) was added one drop of saturated HCl (in MeOH) and TLC indicated complete consumption of starting material after 2 h. The residual MeOH was carefully removed in vacuo (20 °C, 34 torr) and the crude residue was distilled (60 °C, 34 torr) to afford 178 mg of alcohol **34** as a colorless oil in 11% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 3.61 (q, *J* = 7.1 Hz, 2H), 2.54 (bs, 1H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.86-0.80 (m, 2H), 0.77-0.72 (m, 2H).

[VIII] Branson 2510 cleaning bath, 100 W, 42 KHz.



34 **16h**

1-vinylcyclopropanol (16h):[83] To a flask containing vinylmagnesium bromide (5.6 mmol) in THF (5.6 mL) at reflux was added 1-Ethoxycyclopropane-1-ol **34** (178 mg, 1.75 mmol) in THF (200 µL) *via* cannulae. After 40 min the solution was cooled to rt then rapidly poured into saturated NH_4Cl (10 mL) and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and carefully concd in vacuo (bath temp 17 ˚C) to give 118 mg of crude cyclopropanol **16h** in a calculated 24% yield.[IX] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.61 (dd, *J* = 17.1, 10,6 Hz, 1H), 5.28 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.07 (dd, *J* = 10.6, 1.0 Hz, 1H), 4.75 (s, 1H), 1.10-1.04 (m, 2H), 0.76-0.71 (m, 2H).

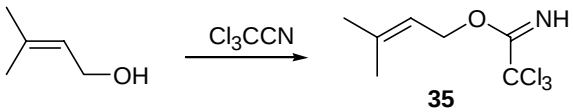


15a **9A**

***N*-(Ethyl-2-cyclopropylidene)-*N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzene-sulfonamide (9A):**[84] To a solution of alcohol **16h** (118 mg, 1.40 mmol) and triethylamine (270 µL, 1.94 mmol) at -30 °C in DCM (7.0 mL) was added methansulfonyl chloride (130 µL, 1.68 mmol) dropwise. After 45 min at -30 °C the slurry was warmed to rt and was poured into a separatory funnul with ice/water (20 mL) and the organic layer was drawn off. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layers dried over $MgSO_4$ and concd in vacuo to afford crude mesylate **35**. To a solution of *N*-(5,5-Dimethyl-2,3-hexadienyl)-4-methylbenzenesulfonamide **15a** (112 mg, 0.401 mmol) in THF (1mL) at rt was

[IX] Sample possessed 70% ethanol by ^{1}H NMR.

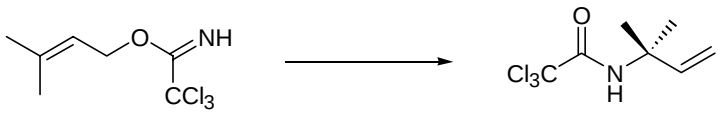
added NaH (60 wt., 17 mg, 0.43 mmol) and it was held at rt until no further gas evolution was observed. The solvent was evaporated *via* N_2 stream followed by addition of a solution of mesylate **35**, $Pd(PPh_3)_4$ (19 mg, 0.016 mmol), and DMSO (570 μL) in THF (2.30 mL) *via* cannulae. After 18.5 h the mixture was concd in vacuo and partitioned between ethyl acetate/(½) saturated brine (20 mL/20 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried over $MgSO_4$, and concd in vacuo. Purification of the crude residue by silica gel chromatography afforded 35 mg of pure ene-allene **9A** as a colorless oil in 25% overall yield (2 steps, ^{1}H NMR showed minor impurities). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.27 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 5.68-5.60 (m, 1H), 5.10 (dt, *J* = 6.2, 2.4 Hz, 1H), 5.00 (dt, *J* = 7.2, 6.3 Hz, 1H), 3.98 (bd, *J* = 6.6 Hz, 2H), 3.87 (1/2 AB ddd, *J* = 15.0, 6.3, 2.5 Hz, 1H), 3.72 (1/2 AB ddd, *J* = 15.0, 7.4, 2.3 Hz, 1H), 2.41 (s, 3H), 1.07-1.01 (m, 4H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 202.7, 143.7, 138.5, 130.0, 127.5, 127.4, 113.3, 104.8, 89.2, 48.5, 47.1, 32.1, 30.2, 21.6, 2.7, 2.2; IR (neat) 3060, 2961, 2925, 2901, 2865, 1960, 1598, 1494, 1475, 1461, 1438, 1345, 1305, 1159; EI-HRMS calcd for $C_{20}H_{27}NO_2S$ [M+Na^+] *m/z*: 368.1660, found: 368.1631.



35

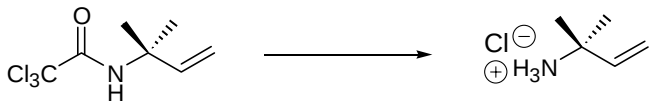
3-Methyl-2-butenyl-2,2,2-trichloroethanimidate (35):[85] A round bottom flask was charged with sodium hydride (60% wt in mineral oil, 28 mg, 0.12 mmol) and the emersion was washed with hexanes (3 mL). To the flask was added ether (33 mL) and 3-methyl-2-buten-1-ol (590 μL, 5.81 mmol) as a solution in ether (11 mL). Another portion of sodium hydride (60% wt in mineral oil, 27 mg, 0.12 mmol) was added and the slurry was cooled to -5 °C. Neat trichloroacetonitrile (580 μL, 5.78 mmol) was then added and after 4 h at -5 °C the suspension

was poured into pentanes (75 mL) containing MeOH (100 μL) and filtered. The filter cake was washed with pentanes (50 mL) and the filtrate concd in vacuo to give 1.066 g of crude imidate **35** in 80% yield (^{1}H NMR showed an impurity). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (bs, 1H), 5.51-5.44 (m, 1H), 4.79 (d, *J* = 7.0 Hz, 2H), 1.79 (s, 3H), 1.74 (s, 3H).



35 **13f**

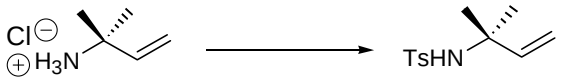
***N*-(1,1-Dimethyl-2-propenyl)-2,2,2-trichloroacetamide (13f):**[85] To a solution of 3-methyl-2-butenyl-2,2,2-trichloroethanimidate **35** (212 mg, 0.921 mmol) in THF (4.6 mL) at -78 °C was added mercuric trifluoroacetate (87 mg, 0.19 mmol) in one portion under positive N_2. The cold bath was removed after 10 min and the solution was allowed to warm to rt. After 1 h a solution of $NaBH_4$ in DME (1 M, 200 μL) was added dropwise and the slurry was concd in vacuo. Purification by silica gel chromatography (ethyl acetate-hexanes 1:19-1:14; column was pretreated with 1% TEA/hexanes) afforded 134 mg of pure trichloroacetamide **13f** in 63% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.58 (bs, 1H), 6.01 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.21 (d, *J* = 17.4 Hz, 1H), 5.15 (d, *J* = 10.7 Hz, 1H), 1.52 (s, 6H).



13f **26b**

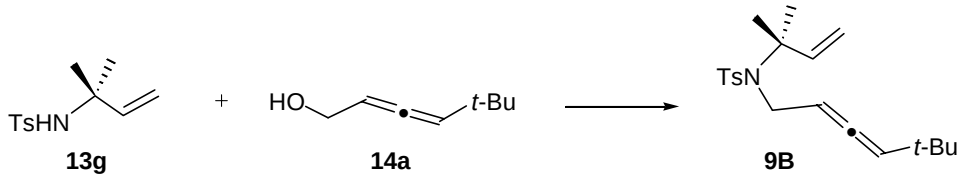
***N*-(1,1-Dimethyl-2-propenyl)aminehydrochloride (26b):**[86] To a solution of *N*-(1,1-dimethyl-2-propenyl)-2,2,2-trichloroacetamide **13f** (390 mg, 1.69 mmol) in EtOH (9.0 mL) was added a solution of NaOH aq (6 M, 8.5 mL, 51 mmol). After 18 h the solution was extracted with ether (3 x 30 mL) and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 (a small amount of $MgSO_4$ was added to clarify the solution) and filtered. The filter

cake was washed with ether (15 mL) and the filtrate was acidified by bubbling HCl (g) through the solution for 6 min. The resulting suspension was concd in vacuo and washed with benzene to afford 200 mg of pure aminehydrochloride salt **26b** in 97% yield. ^{1}H NMR (300 MHz, D_2O) δ: 6.02 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.34 (d, *J* = 17.6 Hz, 1H), 5.33 (d, *J* = 10.8 Hz, 1H), 1.48 (s, 6H).



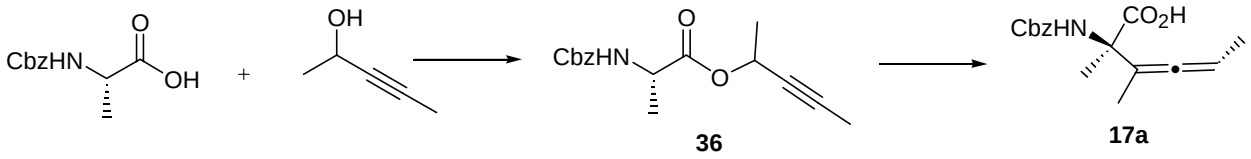
26b **13g**

***N*-(1,1-Dimethyl-2-propenyl)-4-methylbenzenesulfonamide (13g):** To a flask charged with *N*-(1,1-dimethyl-2-propenyl)aminehydrochloride **26b** (170 mg, 1.40 mmol) was added DCM (7 mL) and *p*-toluenesulfonylchloride (323 mg, 1.70 mmol). To the suspension at 0 °C was added triethylamine (590 μL, 4.23 mmol) dropwise and it was then warmed to rt. After 18.7 h the mixture was concd in vacuo and the crude semisolid was partitioned between H_2O/ethyl acetate (20 mL/15 mL). The aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:9-1:4) to afford 191 mg of tosylamide **13g** as a slightly yellow oil in 57% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.27 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.73 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.10 (d, *J* = 17.3 Hz, 1H), 4.96 (d, *J* = 10.7 Hz, 1H), 4.54 (bs, 1H), 2.42 (s, 3H), 1.30 (s, 6H).



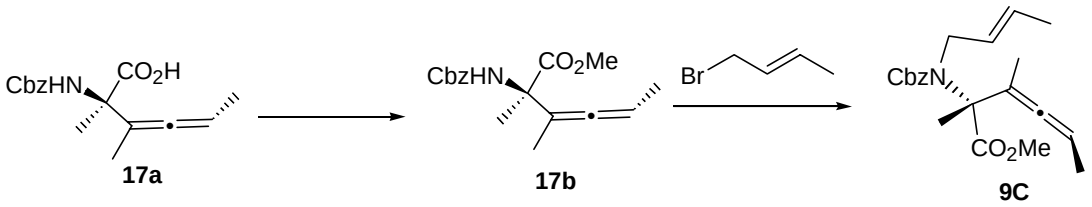
13g **14a** **9B**

***N*-(1,1-Dimethyl-2-propenyl)-*N*-(5,5-dimethyl-2,3-hexadienyl)-4-methylbenzene-sulfonamide (9B)**: The general procedure for the Mitsunobu reaction (p. 56) was followed using *N*-(1,1-Dimethyl-2-propenyl)-4-methylbenzenesulfonamide **13g** (192 mg, 0.796 mmol), PPh_3 (291 mg, 1.14 mmol), DIAD (277 μL, 1.41 mmol), and 5,5-Dimethyl-2,3-hexadien-1-ol **14a** (133 mg, 1.05 mmol). The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:6) to afford 47 mg of ene-allene **9B** as a colorless oil in 17% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.25 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.93 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.40 (q, *J* = 6.6, 1H), 5.18 (dt, *J* = 6.3, 2.4 Hz, 1H), 5.07 (d, *J* = 17.7 Hz, 1H), 5.02 (dd, *J* = 10.8, 0.5 Hz, 1H), 4.03 (1/2 AB ddd, *J* = 16.0, 6.4, 2.4 Hz, 1H), 3.92 (1/2 AB ddd, *J* = 16.0, 7.0, 2.4 Hz, 1H), 2.41 (s, 3H), 1.41 (s, 6H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.2, 144.3, 142.6, 141.1, 129.3, 127.0, 112.7, 104.4, 92.7, 62.6, 46.4, 32.1, 30.1, 26.9, 26.8, 21.5; IR (neat) 3083, 2960, 2930, 2863, 1962, 1598, 1455, 1327 cm^{-1}; MS *m/z* (%) 69 (86), 91 (48), 155 (57), 184 (100), 252 (53), 347 (11); EI-HRMS calcd for $C_{20}H_{29}NO_2S$ [M+] *m/z*: 347.1919, found: 347.1928.



2-Benzyloxycarbonylamino-2,3-dimethyl-3,4-hexadienoic acid (17a):[58] To a solution of 3-pentyn-1-ol (556 mg, 6.61 mmol) in DCM (10 mL) was added DCC (1.507 g, 7.30 mmol) and DMAP (810 mg, 6.63 mmol) followed by *N*-Cbz-alanine (1.56 g, 6.97 mmol) (an exothermic reaction was noted). After 1.5 h at rt the suspension was diluted with hexanes (7 mL) and filtered through a plug of silica (30 mL) which was washed with ethyl acetate-hexanes (1:1, 100 mL). The filtrate was concd in vacuo and purified by silica gel chromatography (ethyl-acetate-

hexanes 1:9-1:4) to afford 1.40 g of amino ester **36** in 73% yield. To a solution of diisopropylamine (580 μL, 4.15 mmol) in THF (4.2 mL) at -25 °C was added n-butyllithium (1.6 M in hexanes, 2.57 mL, 4.11 mmol) dropwise. The solution was then cooled to -78 °C whereupon amino ester **36** (475 mg, 1.64 mmol) was added as a solution in THF (4.0 mL). To the solution was added $ZnCl_2$ (0.5 M in THF, 4.0 mL, 2.0 mmol) and it was then allowed to warm to rt overnight whereupon it was diluted with ether (75 mL) and quenched with HCl aq (1 M, 20 mL). The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic layers were washed with HCl aq (1 M, 20 mL), brine (30 mL), dried over $MgSO_4$ and concd in vacuo to afford 403 mg of amino acid **17a** in 85% yield.

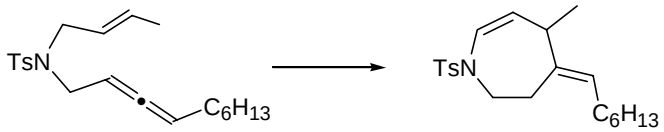


2-[(*E*)-Benzyloxycarbonyl-2-butenylamino]-2,3-dimethyl-3,4-hexadienoic acid methyl ester (9C):[58] To a solution of **17a** (403 mg, 1.39 mmol) in DMF (3.5 mL) was added $KHCO_3$ (349 mg, 3.49 mmol) and iodomethane (175 μL, 2.81 mmol). After 2.3 h at rt the suspension was poured into H_2O (75 mL). The aqueous layer was extracted with ethyl acetate (3 x 80 mL) and the combined organic layers were washed with H_2O (75 mL), brine (75 mL), dried over $MgSO_4$ and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:7) to afford amino ester **17b** in 38% yield. To a solution of amino ester **17b** (99 mg, 0.33 mmol) in DMF (1.7 mL) at rt was added NaH (60% wt in mineral oil, 21 mg, 0.53 mmol) in one portion. After 20 min at rt crotylbromide (67 μL, 0.65 mmol) was added and TLC analysis indicated a complete reaction after 6 min. The slurry was poured into H_2O (20 mL) and the aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layers

were washed with H_2O (3 x 15 mL), brine (15 mL), dried over $MgSO_4$, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:13-1:7) to afford 87 mg of ene-allene **9C** as a clear oil in 74% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.28 (m, 5H), 5.62-5.44 (m, 2H), 5.24-5.14 (m, 1H), 5.11 (s, 2H), 4.16-3.99 (m, 1H), 3.85-3.51 (m, 4H), 1.77-1.72 (m, 3H), 1.65-1.61 (m, 5H), 1.59-1.55 (m, 4H).

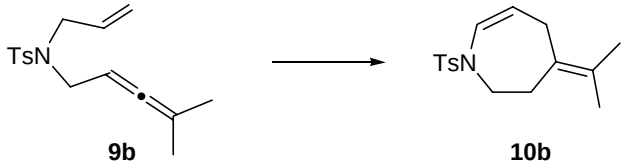
A.2 CYCLIZATION OF ENE-ALLENES TO FORM AZEPINES

The cycloisomerization of each ene-allene to form its corresponding azepine(s) is described sequentially.



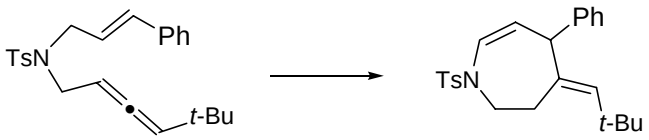
9a **10a**

5-[(*E*)-Heptylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10a; entry 14, Table 3): Cycloisomerization of ene-allene **9a** has previously been described.[20]



9b **10b**

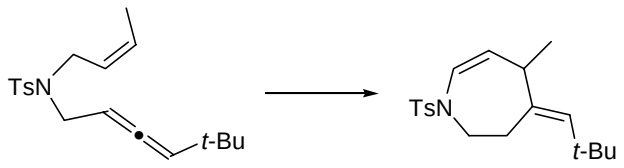
1-(4-Methylbenzenesulfonyl)-5-(1-methylethylidene]-4,5,6,7-tetrahydro-1*H*-azepine (10b; entry 40, Table 6): Cycloisomerization of ene-allene **9b** has previously been described.[20]



9c **10c**

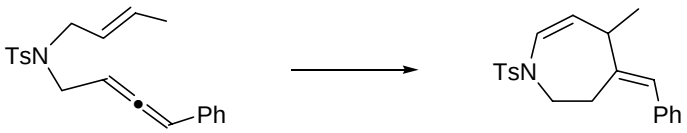
The General Procedure for Azepine Formation: 5-[(*E*)-2,2-Dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4-phenyl-4,5,6,7-tetrahydro-1*H*-azepine (10c; entry 31, Table 5):

Ene-allene **9c** (20 mg, 0.052 mmol) was dissolved in 1,2-dimethoxyethane (510 μL) and twice degassed via freeze-pump-thaw method followed by addition of $[Rh(CO)_2Cl]_2$ (2.0 mg, 0.0051 mmol) under an argon atmosphere. It was heated to reflux (95 °C) and reaction progress was monitored by TLC (benzene), reaching completion after 2 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 18 mg of azepine **10c** as a colorless oil 90% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.65 (1/2 AA′XX′ d, *J* = 8.1 Hz, 2H), 7.21-7.06 (m, 4H), 7.05-6.98 (m, 1H), 6.94 (d, *J* = 9.4 Hz, 1H), 6.73 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.35 (s, 1H), 4.91 (dd, *J* = 9.1, 7.9 Hz, 1H), 3.90 (d, *J* = 7.5 Hz, 1H), 3.45-3.28 (m, 2H), 2.81 (ddd, *J* = 20.7, 10.8, 5.0 Hz, 1H), 1.94 (bd, *J* = 16.9 Hz, 1H), 1.86 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 144.3, 143.9, 140.4, 137.1, 137.0, 130.2, 128.8, 128.6, 127.7, 127.1, 126.4, 112.7, 47.0, 32.7, 31.1, 29.2, 21.6; IR (thin film) 3058, 3022, 2955, 2899, 2863, 1649, 1598, 1491, 1450, 1352, 1332 cm^{-1}; MS *m/z* (%) 91 (100), 121 (84), 184 (49), 240 (43), 338 (60), 395 (30); EI-HRMS calcd for $C_{24}H_{29}NO_2S$ [M+] *m/z*: 395.1919, found: 395.1921.



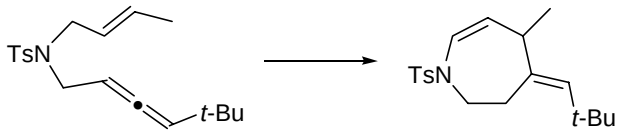
9d **10f**

5-[(*E*)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10f; entry 25, Table 4): The general procedure for azepine formation (p. 88) was followed using ene-allene **9e** (29 mg, 0.086 mmol), $[Rh(CO)_2Cl]_2$ (2.0 mg, 0.0051 mmol), and 1,4-dioxane (860 μL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 2 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 12 mg of azepine **10f** as a colorless oil 43% yield. The ^{1}H NMR spectrum was identical to the product previously reported.[20]



9e **10e**

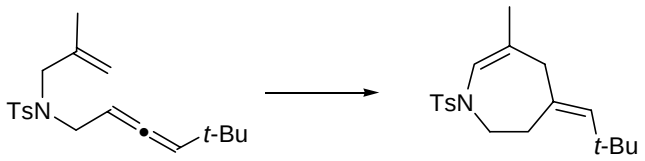
4-Methyl-1-(4-methylbenzenesulfonyl)-5-[(*E*)-1-phenylmethylidine]-4,5,6,7-tetrahydro-1*H*-azepine (10e; entry 20, Table 3). The general procedure for azepine formation (p. 88) was followed using ene-allene **9e** (23 mg, 0.065 mmol), $[Rh(CO)_2Cl]_2$ (1.4 mg, 0.0036 mmol), 1,4-dioxane (650 μL), under a carbon monoxide atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 15 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 11 mg of azepine **10e** as a clear oil in 52% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.57 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.32-7.26 (m, 2H), 7.23-7.19 (m, 1H), 7.16 (1/2 AA′XX′ d, J = 8.1 Hz, 2H), 7.07 (bd, J = 7.07 Hz, 1H), 6.40 (dd, J = 9.2, 1.6 Hz, 1H), 6.27 (s, 1H), 4.91 (dd, J = 9.2, 5.1 Hz, 1H), 3.72-3.66 (m, 2H), 3.33-3.22 (m, 1H), 2.69-2.65 (m, 2H), 2.35 (s, 3H), 1.24 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 144.1, 142.6, 138.0, 137.0, 130.0, 129.2, 128.4, 127.1, 126.9, 126.7, 125.4, 118.7, 47.9, 40.2, 30.8, 21.7, 20.9; IR (neat) 3053, 3022, 2960, 2925, 2879, 1721, 1644, 1598, 1491, 1455, 1347 cm^{-1}; MS *m/z* (%) 91 (100), 129 (38), 169 (36), 198 (72), 338 (17), 353 (16); EI-HRMS calcd for $C_{21}H_{23}NO_2S$ [M+] *m/z*: 353.1450, found: 353.1454.



9f **10f**

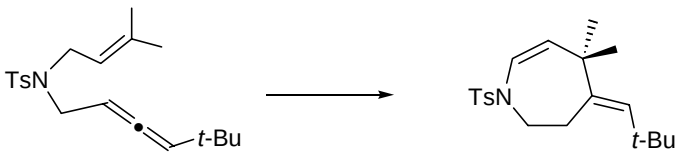
5-[(*E*)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10f; entry 17, Table 3): The general procedure for azepine formation (p. 88) was followed using ene-allene **9f** (118 mg, 0.355 mmol), $[Rh(CO)_2Cl]_2$ (3.4 mg, 0.0088 mmol), and

1,4-dioxane (2.60 mL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 6 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 89 mg of azepine **10f** as a colorless oil 75% yield. The ^{1}H NMR spectrum was identical to the product previously reported.[20]



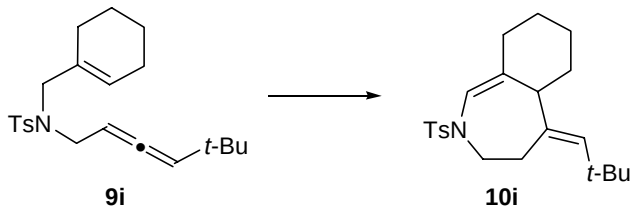
9g **10g**

5-[(*E*)-2,2-Dimethylpropylidene]-3-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10g; entry 43, Table 7): The general procedure for azepine formation (p. 88) was followed using ene-allene **9g** (17 mg, 0.051 mmol), $[Rh(CO)_2Cl]_2$ (1.0 mg, 0.0026 mmol), and 1,4-dioxane (510 μL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 15 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 14 mg of azepine **10g** as a colorless oil in 83% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.74 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 6.76 (1/2 AA′XX′ d, J = 8.4 Hz, 2H), 6.39 (s, 1H), 5.18 (s, 1H), 3.49-3.43 (m, 2H), 2.46 (s, 2H), 2.45-2.39 (m, 2H), 1.87 (s, 3H), 1.45 (d, J = 0.7 Hz, 3H), 0.97 (s, 9H), ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 143.9, 137.9, 137.2, 133.2, 130.1, 128.6, 127.1, 126.1, 122.6, 48.5, 43.7, 43.4, 32.4, 31.2, 32.1, 22.7, 21.6; IR (neat) 3027, 2955, 2925, 2963, 1665, 1593, 1434, 1342, 1158 cm^{-1}; MS *m/z* (%) 57 (72), 91 (100), 93 (71), 108 (77), 122 (70), 178 (65), 333 (68); EI-HRMS calcd for $C_{19}H_{27}NO_2S$ [M+] *m/z*: 333.1763, found: 333.1769.



9h **10h**

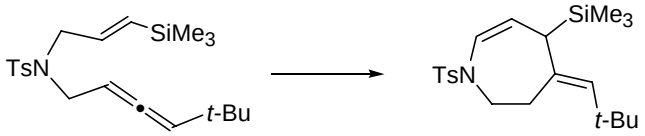
4,4-Dimethyl-5-[(*E*)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10h; entry 50, Table 8): The general procedure for azepine formation (p. 88) was followed using ene-allene **9h** (70 mg, 0.20 mmol), $[Rh(CO)_2Cl]_2$ (7.6 mg, 0.020 mmol), and 1,4-dioxane (2.0 mL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 2.3 h. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 17 mg of impure azepine **10h** as a slightly yellow oil. An HPLC purification of the impure sample provided 8 mg of pure product indicating a 13% overall yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.65 (1/2 AA′XX′ d, J = 8.4 Hz, 2H), 7.32 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 6.15 (d, J = 9.7 Hz, 1H), 5.30 (s, 1H), 4.70 (d, J = 9.8 Hz, 1H), 3.50-3.44 (m, 2H), 2.61-2.55 (m, 2H), 2.41 (s, 3H), 1.08 (s, 6H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 144.1, 141.9, 136.1, 134.1, 130.0, 127.4, 125.9, 122.4, 50.1, 42.7, 32.4, 31.7, 30.7, 27.3, 21.6; IR (neat) 2960, 2868, 1650, 1598, 1465, 1347 cm^{-1}; MS *m/z* (%) 57 (56), 85 (59), 91 (92), 136 (51), 192 (49), 290 (83), 332 (100), 333 (32), 347 (34); EI-HRMS calcd for $C_{20}H_{29}NO_2S$ [M+] *m/z*: 347.1919, found: 347.1925.



9i **10i**

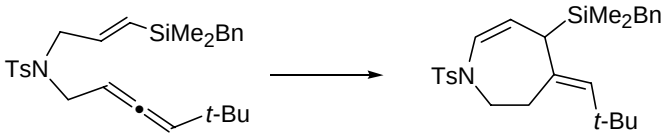
5-[(*E*)-2,2-Dimethylpropylidene)]-2-(4-methylbenzenesulfonyl)-3,4,5,5a,6,7,8,9-octahydro-1*H*-benzo[c]azepine (10i; entry 47, Table 8): The general procedure for azepine formation (p. 88) was followed using ene-allene **9i** (30 mg, 0.080 mmol), $[Rh(CO)_2Cl]_2$ (2.2 mg, 0.0057 mmol), and 1,4-dioxane (780 μL) under an argon atmosphere. The crude solution was concd after 13.3 h and purified by silica gel chromatography (benzene), to afford 23 mg of azepine **10i** as a colorless oil in 78% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.67 (1/2 AA′XX′ d, J = 8.4 Hz,

2H), 7.32 (1/2 AA′XX′ d, J = 8.0 Hz, 2H), 6.09 (s, 1H), 5.32 (s, 1H), 3.68 (1/2 AB ddd, J = 13.0, 6.7, 4.8 Hz, 1H), 3.40 (1/2 AB ddd, J = 13.1, 9.2, 5.5 Hz, 1H), 2.98 (ddd, J = 14.6, 9.2, 6.8 Hz, 1H), 2.64-2.56 (m, 1H), 2.42 (s, 3H), 2.23-2.11 (m, 2H), 2.01-1.88 (m, 1H), 1.87-1.72 (m, 2H), 1.66-1.59 (m, 1H), 1.49-1.39 (m, 2H), 1.28-1.17 (m, 1H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 143.9, 138.5, 137.5, 136.9, 132.9, 130.0, 127.3, 119.9, 54.8, 50.6, 35.8, 35.6, 32.5, 31.5, 29.4, 28.0, 27.0, 21.6; IR (neat) 2930, 2858, 1660, 1598, 1445, 1347, 1168 cm^{-1}; MS *m/z* (%) 57 (78), 91 (100), 133 (43), 148 (54), 160 (70), 162 (80), 218 (98), 316 (26), 373 (26); EI-HRMS calcd for $C_{22}H_{31}NO_2S$ [M+] *m/z*: 373.2076, found: 373.2093.



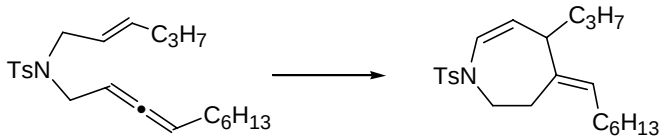
9j **10j**

5-(2,2-Dimethylpropylidene)-1-(4-methylbenzenesulfonyl)-4-(trimethylsilyl)-4,5,6,7-tetrahydro-1*H*-azepine (10j; entry 36, Table 5): Cycloisomerization of ene-allene **9j** has previously been described.[20]



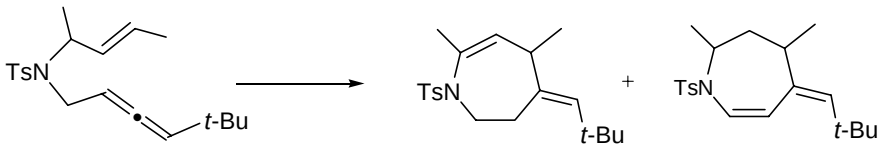
9k **10k**

4-(Benzhydryldimethylsilyl)-5-(2,2-dimethylpropylidene)-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10k; entry 37, Table 5): Cycloisomerization of ene-allene **9k** has previously been described.[20]



9l **10l**

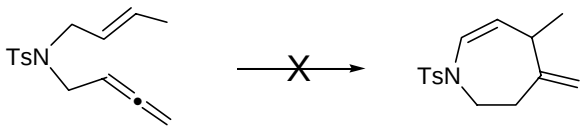
4-Propyl-5-[(*E*)-heptylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10l; entry 23, Table 3): The general procedure for azepine formation (p. 88) was followed using ene-allene **9l** (27 mg, 0.068 mmol), $[Rh(CO)_2Cl]_2$ (1.6 mg, 0.0041 mmol), and 1,4-dioxane (680 μL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 33 min. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 14 mg of azepine **10l** as a colorless oil 53% yield. ^{1}H NMR (300 MHz, CD_2Cl_2) δ: 7.66 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 7.31 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 9.3 Hz, 1H), 5.13 (bt, *J* = 7.1 Hz, 1H), 4.96 (dd, *J* = 9.3, 6.3 Hz, 1H), 3.64 (1/2 AB ddd, *J* = 13.8, 8.9, 4.0 Hz, 1H), 3.51 (1/2 AB ddd, *J* = 13.8, 6.6, 4.4 Hz, 1H), 2.78-2.71 (m, 1H), 2.62-2.50 (m, 1H), 2.41 (s, 3H), 2.24-2.15 (m, 1H), 1.82-1.72 (m, 2H), 1.43-1.17 (m, 12H), 0.90-0.85 (m, 3H), 0.84 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 144.0, 137.1, 137.0, 130.0, 127.7, 127.1, 126.5, 118.9, 48.7, 47.4, 37.4, 32.1, 30.0, 29.4, 28.4, 27.8, 23.0, 21.6, 21.1, 14.2, 14.1; IR (neat) 3042, 2955, 2920, 2853, 1726, 1650, 1593, 1455, 1343, 1163 cm^{-1}; MS *m/z* (%) 91 (65), 346 (100), 347 (28), 389 (19); EI-HRMS calcd for $C_{23}H_{35}NO_2S$ [M+] *m/z*: 389.2389, found: 389.2373.



9m **10m** **10m'**

2,4-Dimethyl-5-[(*E*)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10m; Eq. 36); 5,7-Dimethyl-4-[(*E*)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10m;′ Eq. 36): The general procedure for azepine formation (p. 88) was followed using ene-allene **9m** (84 mg, 0.242 mmol), $[Rh(CO)_2Cl]_2$ (9.3 mg, 0.0239 mmol), and DCE (1.20 mL) under an argon atmosphere. Reaction

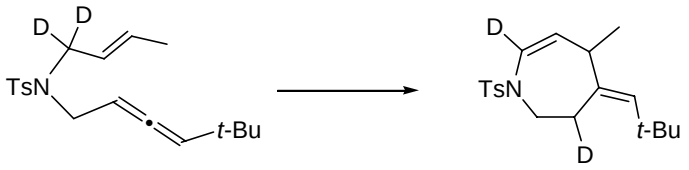
progress was monitored by TLC (benzene), reaching completion after 2.3 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 33 mg of azepine **10m** as a clear oil in 39% yield and azepine **10m′** as a white solid (mp 109-112 ^{o}C) in 27% yield. ^{1}H NMR **10m** (300 MHz, C_6D_6) δ: 7.80 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.76 (1/2 AA′XX′ d, *J* = 7.9 Hz, 2H), 5.20 (bs, 1H), 4.96-4.91 (m, 1H), 3.74 (ddd, *J* = 13.7, 6.1, 4.5 Hz, 1H), 3.07 (ddd, *J* = 13.7, 8.3, 4.2 Hz), 2.66-2.55 (m, 1H), 2.54-2.43 (m, 2H), 1.95 (t, *J* = 1.25 Hz, 3H), 1.88 (s, 3H), 1.03 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR **10m** (75 MHz, CD_2Cl_2) δ: 143.4, 138.7, 136.8, 135.5, 134.1, 131.2, 129.6, 127.0, 49.3, 31.8, 31.3, 31.0, 21.8, 21.3, 19.2; IR **10m** (neat) 2950, 2919, 2853, 1731, 1660, 1593, 1455, 1347 cm^{-1}; MS *m/z* (%) 57 (73), 68 (100), 91 (66), 122 (67), 192 (52), 332 (24), 347 (8); EI-HRMS calcd for **10m** $C_{20}H_{29}NO_2S$ [M+] *m/z*: 347.1919, found: 347.1918. ^{1}H NMR **10m′** (300 MHz, C_6D_6) δ: 7.73 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.72 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.58 (d, *J* = 9.15 Hz, 1H), 5.87 (dd, *J* = 9.1, 1.1 Hz, 1H) 5.17 (d, *J* = 1.1 Hz, 1H), 4.53-4.39 (m, 1H), 2.40-2.27 (m, 1H), 2.12 (ddd, *J* = 13.2, 8.5, 5.8 Hz, 1H), 1.84 (s, 3H), 1.07 (s, 9H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.90-0.80 (m, 1H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR **10m′** (75 MHz, CD_2Cl_2) δ: 144.2, 138.3, 137.4, 135.3, 130.1, 127.1, 123.0, 115.6, 45.8, 37.7, 32.6, 31.2, 21.6, 20.4, 19.7; IR **10m′** (thin film) 2955, 2919, 2853, 1737, 1639, 1598, 1455, 1347 cm^{-1}; MS *m/z* (%) 57 (100), 71 (56), 85 (38), 91 (40), 177 (25), 347 (21); EI-HRMS calcd for **10m′** $C_{20}H_{29}NO_2S$ [M+] *m/z*: 347.1919, found: 347.1910.



9n **10n**

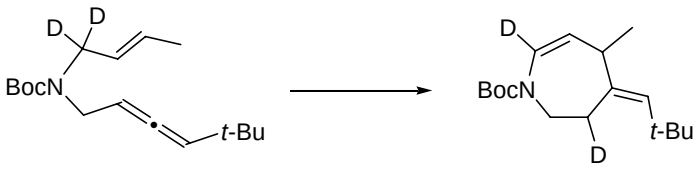
Attempted cycloisomerization of ene-allene 9n (entry 12, Table 3): The general procedure for azepine formation (p. 88) was followed using ene-allene **9n** (51 mg, 0.184 mmol), $[Rh(CO)_2Cl]_2$ (7.2 mg, 0.0185 mmol), and DCE (920 μL) under a carbon monoxide atmosphere.

Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), showing complete consumption of starting material after 3.3 h. After cooling to rt the solution was diluted with hexanes and purified by silica gel chromatography (ethyl acetate-hexanes 1:9; column was pretreated with 1% triethylamine/hexanes) to afford 3.4 mg of an impure, unidentifiable material.



9o **10o**

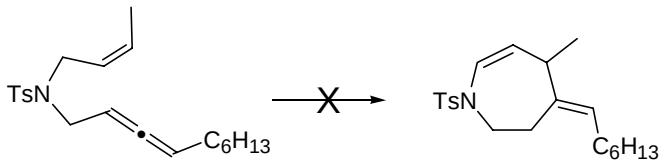
5-[(*E*)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine-2,6-d_2 (10o; Eq. 33): Cycloisomerization of ene-allene **9o** has previously been described.[20]



9p **10p**

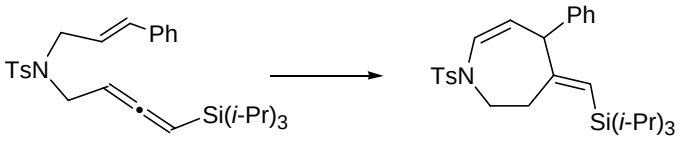
1-Carboxylicacid-*t*-butylester-5-[(*E*)-2,2-dimethylpropylidene]-4-methyl-4,5,6,7-tetrahydro-1*H*-azepine-2,6-d_2 (10p; Eq. 34). The general procedure for azepine formation (p. 88) was followed using ene-allene **9p** (53 mg, 0.18 mmol), DCE (940 μL), and $[Rh(CO)_2Cl]_2$ (7.5 mg, 0.019 mmol) under an argon atmosphere. Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), reaching completion after 1.7 h. The solution was diluted with hexanes (1.5 mL) and purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 36 mg of azepine **10p** as a colorless oil 68% yield. ^{1}H NMR [300 MHz, $(CD_3)_2SO$, 60 °C] δ: 5.24 (bs, 1H), 4.74 (bd, J = 4.9 Hz, 1H), 3.70 (dd, J = 13.9, 5.2 Hz, 1H), 3.59 (dd, J = 13.9, 7.5 Hz, 1H), 3.08-2.97 (m, 1H), 2.66 (bt, J = 5.6 Hz, 1H), 1.40 (s, 9H), 1.11

(d, J = 7.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR [75 MHz, $(CD_3)_2SO$, 60 °C] δ: 152.0, 138.7, 134.7, 127.3 (t), 118.1, 79.4, 69.0, 31.0, 30.9, 30.8, 28.2 (t), 27.6; IR (thin film) 2959, 2925, 2869, 1705, 1634, 1458, 1391, 1366, 1347, 1252, 1206, 1171, 1140.



9q **10q**

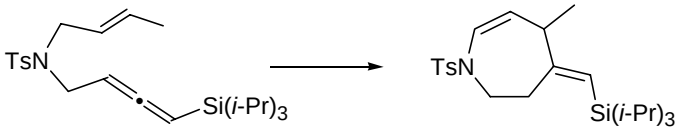
Attempted cycloisomerization of ene-allene 9q (entry 24, Table 4):[VI] The general procedure for azepine formation was followed (p. 88) using ene-allene **9q** (37 mg, 0.10 mmol), DCE (500 μL), and $[Rh(CO)_2Cl]_2$ (2.0 mg, 0.0051 mmol) under an argon atmosphere. Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), where the starting material was completely consuming after 23 h. A crude ^{1}H NMR displayed no signs of the desired azepine **10q**.



9r **10r**

1-(4-Methylbenzenesulfonyl)-5-[(*E*)-methylidene-1-(triisopropylsilyl)]-4-phenyl-4,5,6,7-tetrahydro-1*H*-azepine (10r; entry 33, Table 5): The general procedure for azepine formation (p. 88) was followed using ene-allene **9r** (23 mg, 0.046 mmol), 1,4-dioxane (460 μL), and $[Rh(CO)_2Cl]_2$ (1.1 mg, 0.0028 mmol) under an argon atmosphere. Monitering the reaction by TLC (benzene) showed a halt in progress after 14.3 h of heating. The solution was concd in vacuo after 5 h of additional heating and purified by silica gel chromatography (benzene; column was pretreated with 1% triethylamine/hexanes) to afford 9.0 mg of azepine **10r** as a slightly yellow oil in 40% yield (^{1}H NMR contained impurities). ^{1}H NMR (300 MHz, C_6D_6) δ: 7.63 (1/2

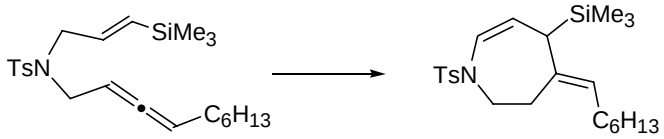
AA′XX′ d, *J* = 8.3 Hz, 2H), 7.23-6.97 (m, 5H), 6.90 (d, *J* = 9.5 Hz, 1H), 6.72 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.41 (s, 1H), 4.90 (dd, *J* = 9.5, 7.2 Hz, 1H), 4.23 (d, *J* = 7.1 Hz, 1H), 3.44 (dt, *J* = 13.7, 4.6 Hz, 1H), 3.32 (ddd, *J* = 13.6, 10.3, 3.6 Hz, 1H), 2.70 (ddd, *J* = 15.3, 10.2, 4.9 Hz, 1H), 2.37-2.29 (m, 1H), 1.84 (s, 3H), 1.15-1.08 (m, 21H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 157.4, 144.3, 143.3, 136.4, 130.2, 129.1, 128.6, 127.9, 127.2, 126.5, 125.0, 112.0, 56.5, 47.0, 34.9, 21.6, 19.1, 12.6; IR (neat) 3060, 3023, 2942, 2886, 2864, 2357, 2332, 1655, 1594, 1488, 1465, 1401, 1349, 1164; EI-HRMS calcd for $C_{29}H_{41}NO_2SiS$ [M+Na^+] *m/z*: 518.2525, found: 518.2535.



9s **10s**

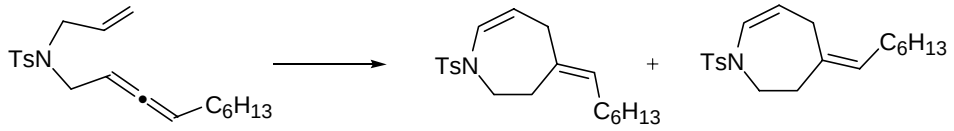
4-Methyl-1-(4-methylbenzenesulfonyl)-5-[(*E*)-methylidene-1-(triisopropylsilyl)]-4,5,6,7-tetrahydro-1*H*-azepine (10s; entry 34, Table 5): The general procedure for azepine formation (p. 88) was followed using ene-allene **9s** (14 mg, 0.032 mmol), 1,4-dioxane (500 μL), and $[Rh(CO)_2Cl]_2$ (0.8 mg, 0.0021 mmol) under an argon atmosphere. Reaction progress was monitered by TLC (benzene), reaching completion after 1.3 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene; column was pretreated with 1% triethylamine/hexanes) to afford 33 mg of azepine **10s** as a clear oil in 69% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.67 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.73 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 6.57 (dd, *J* = 9.3, 1.2 Hz, 1H), 5.25 (s, 1H), 4.53 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.60 (ddd, *J* = 13.3, 6.8, 3.7 Hz, 1H), 3.39 (ddd, *J* = 13.5, 9.0, 3.4 Hz, 1H), 3.02-2.94 (m, 1H), 2.64 (ddd, *J* = 15.4, 9.0, 3.4 Hz, 1H), 2.42 (ddd, *J* = 15.3, 6.9, 2.5 Hz, 1H), 1.84 (s, 3H), 1.08 (s, 21H), 0.97 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 158.3, 143.6, 136.0, 129.8, 126.9, 126.0, 118.3, 118.1, 47.3, 41.4, 35.8, 21.5, 21.0, 18.9, 12.2; IR (neat) 2958, 2942, 2864, 2051, 1990, 1642, 1605, 1462,

1348, 1170; MS *m/z* (%) 59 (27), 91 (40), 163 (27), 390 (100), 391 (30); EI-HRMS calcd for $C_{24}H_{39}NO_2SiS$ [M+(-*i*-Pr)] *m/z*: 390.1923, found: 390.1923.



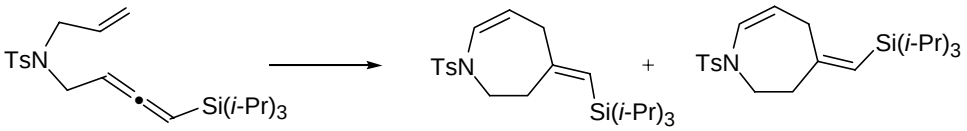
9t **10t**

5-[(*E*)-Heptylidene]-1-(4-methylbenzenesulfonyl)-4-(trimethylsilyl)-4,5,6,7-tetrahydro-1*H*-azepine (10t; entry 35, Table 5): The general procedure for azepine formation was followed (p. 88) using ene-allene **9t** (28 mg, 0.068 mmol), $[Rh(CO)_2Cl]_2$ (1.1 mg, 0.0028 mmol), and DCE (400 μL) under an argon atmosphere. Reaction progress was monitored by GC (Col. temp: 225 °C, inj. temp: 250 °C, det. temp: 250 °C), where the starting material was completely consumed after 7 h. The solution was concd in vacuo and a crude ^{1}H NMR showed a trace amount of azepine **10t**. ^{1}H NMR (300 MHz, C_6D_6) δ: 4.90 (t, *J* = 7.2 Hz, 1H), 4.70 (dd, *J* = 10.0, 6.6 Hz, 1H), 4.17-4.09 (m, 2H), 2.42 (d, *J* = 6.5 Hz, 1H).



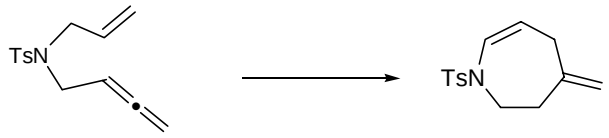
9u **10u** **10u'**

5-[(*E*)-Heptylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10u; entry 38, Table 6); 5-[(*Z*)-Heptylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10u;′ entry 38, Table 6): Cycloisomerization of ene-allene **9u** has previously been described.[20]



9v **10v** **10v'**

1-(4-Methylbenzenesulfonyl)-5-[(*E*)-1-(triisopropylsilyl)-methylidene]-4,5,6,7-tetrahydro-1*H*-azepine (10v; entry 39, Table 6); 1-(4-Methylbenzenesulfonyl)-5-[(*E*)-1-(triisopropylsilyl)-methylidene]-4,5,6,7-tetrahydro-1*H*-azepine (10v;′ entry 39, Table 6): The general procedure for azepine formation (p. 88) was followed using ene-allene **9v** (17 mg, 0.040 mmol), 1,4-dioxane (400 μL), and $[Rh(CO)_2Cl]_2$ (0.8 mg, 0.0021 mmol) under an argon atmosphere. Reaction progress was monitered by TLC (benzene), reaching completion after 20 min. The solution was concd in vacuo and purified by silica gel chromatography to afford azepines **10v** and **10v′** as an inseparable mixture in a combined yield of 73%. ^{1}H NMR undicated a ratio of 10w:10w′ of 5.8:1. ^{1}H NMR **10v** (300 MHz, C_6D_6) δ: 7.65 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.74 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 6.58 (d, J = 9.4 Hz, 1H), 5.23 (s, 1H), 4.69 (dt, J = 9.2, 5.8 Hz, 1H), 3.45 (dd, J = 5.8, 5.8 Hz, 2H), 2.72 (d, J = 5.7 Hz, 2H), 2.50 (bdd, J = 5.7, 4.6 Hz, 2H), 1.86 (s, 3H), 1.09-1.07 (m, 21H); ^{13}C NMR **10v** (300 MHz, CD_2Cl_2) δ: 155.1, 144.2, 136.6, 130.6, 127.8, 127.1, 122.0, 103.6, 47.4, 39.4, 37.1, 21.6, 19.1, 12.5; IR (neat)[X] 3052, 2942, 2889, 2864, 2725, 1673, 1652, 1613, 1577, 1463, 1348, 1166 cm^{-1}; ^{1}H NMR **10v′** (300 MHz, C_6D_6) δ: 7.43 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.65 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 5.85 (d, J = 8.0 Hz, 1H), 5.23 (s, 1H), 4.81 (dd, J = 9.6, 8.0 Hz, 1H), 3.14 (bt, J = 4.4 Hz, 2H), 2.27-2.23 (m, 2H), 1.77 (s, 3H), 1.04-1.01 (m, 21H). EI-HRMS calcd for $C_{23}H_{37}NO_2SiS$ [M+Na$^+$] *m/z*: 442.2212, found: 442.2171.

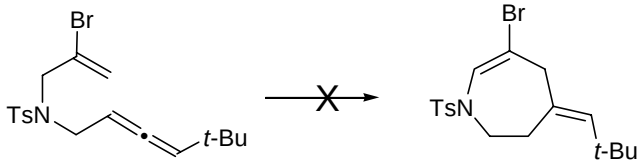


9w **10w**

Attempted cycloisomerization of ene-allene 9w (entry 42, Table 6): The general procedure for azepine formation (p. 88) was followed using ene-allene **9w** (74 mg, 0.28 mmol), DCE (940

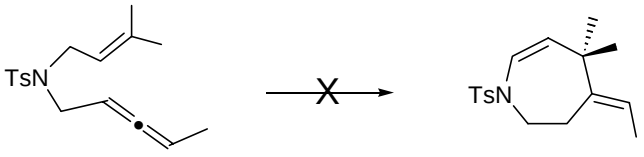
[X] Spectrum is of the *E/Z* mixture.

μL), and $[Rh(CO)_2Cl]_2$ (19 mg, 0.049 mmol) under an argon atmosphere. Reaction progress was monitored by TLC (ethyl acetate-hexanes), where the starting material was completely consumed after 2 h. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:7; column was pretreated with 1% triethylamine/hexanes) to afford 7 mg of material that possessed a trace amount of the desired azepine **10w** by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 7.30 (1/2 AA′XX′ d, *J* = 8.1 Hz, 2H), 6.44 (d, J = 9.2 Hz, 1H), 5.03 (dt, J = 9.0, 5.4 Hz, 1H), 3.66 (dd, J = 5.9, 5.9 Hz, 2H), 2.84 (d, J = 5.4 Hz, 2H), 2.47 (dd, J = 6.0 Hz, 2H), 2.43 (s, 3H).



9x **10x**

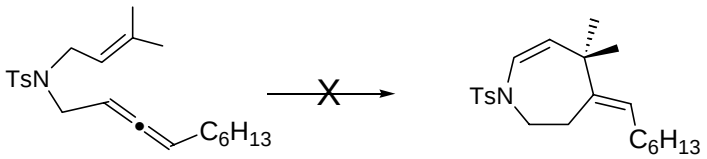
Attempted cycloisomerization of ene-allene 9x (Eq. 35): The general procedure for azepine formation was followed (p. 88) using ene-allene **9x** (37 mg, 0.093 mmol), 1,4-dioxane (930 μL), and $[Rh(CO)_2Cl]_2$ (1.7 mg, 0.0044 mmol) under an argon atmosphere. The reaction was monitered by TLC (benzene), where substantial decomposition was observed after 20 min. The solution was concd in vacuo and purified by silica gel chromatography to afford two fractions of 1.9 mg and 2.9 mg of unidentifiable material.



9y **10y**

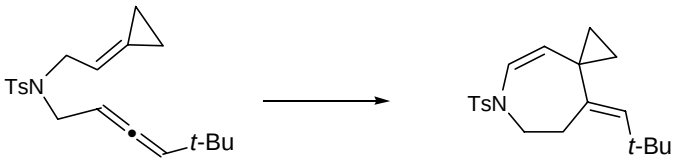
Attempted cycloisomerization of ene-allene 9y (entry 52, Table 8):[VI] The general procedure for azepine formation was followed (p. 88) using ene-allene **9y** (30 mg, 0.10 mmol), toluene (1.0 mL), and $[Rh(CO)_2Cl]_2$ (3.9 mg, 0.010 mmol) under an argon atmosphere. The solution was

heated to 90 °C for 3 h and was not refluxed. The solution was cooled to rt, diluted with hexanes, and filtered through a plug of silica gel, eluting with ethyl acetate/hexanes (1:4) to afford 16 mg of starting material (53% recovery) with no trace of the desired azepine **10y**.



9z **10z**

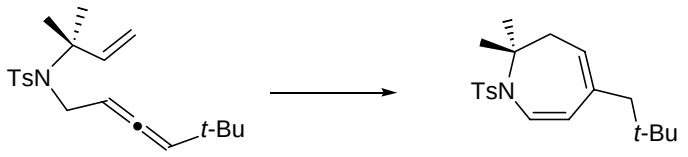
Attempted cycloisomerization of ene-allene 9z (entry 53, Table 8):[VI] The general procedure for azepine formation (p. 88) was followed using ene-allene **9z** (32 mg, 0.10 mmol), toluene (1.0 mL), and $[Rh(CO)_2Cl]_2$ (3.3 mg, 0.0085 mmol) under an argon atmosphere. The solution was heated to 90 °C for 13 h and was not refluxed. The solution was cooled to rt, diluted with hexanes, and filtered through a plug of silica gel, eluting with ethyl acetate/hexanes (1:4) to afford 22 mg of starting material (69% recovery) with no trace of the desired azepine **10z**.



9A **10A**

9-[(*E*)-2,2-Dimethylpropylidene]-6-(4-methylbenzenesulfonyl)-6-azaspiro[2.6]non-4-ene (10A; entry 54, Table 8): The general procedure for azepine formation (p. 88) was followed using ene-allene **9A** (16 mg, 0.047 mmol), $[Rh(CO)_2Cl]_2$ (1.0 mg, 0.0026 mmol), and 1,4-dioxane (460 μL) under an argon atmosphere. To the solution was added $[Rh(CO)_2Cl]_2$ (0.8 mg, 0.002 mmol) after 20.3 h of heating and TLC analysis showed reaction completion after an additional 1.5 h at reflux. The crude solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 6.8 mg of azepine **10A** as a clear oil in a calculated yield of

14%.[XI] ^{1}H NMR (300 MHz, C_6D_6) δ: 7.70 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 1H), 6.73 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.57 (d, *J* = 8.9 Hz, 1H), 5.38 (s, 1H), 3.62 (dd, *J* = 6.3, 6.3 Hz, 2H), 1.83 (s, 3H), 1.47 (d, *J* = 5.9 Hz, 1H), 1.45 (d, *J* = 6.5 Hz, 1H), 1.04 (s, 9H), 0.51-0.46 (m, 2H), 0.060-0.035 (m, 2H); IR (neat) 2956, 2925, 2860, 1638, 1597, 1459, 1352, 1295, 1164; EI-HRMS calcd for $C_{20}H_{27}NO_2S$ [M+Na^+] *m/z*: 368.1660, found: 368.1634.

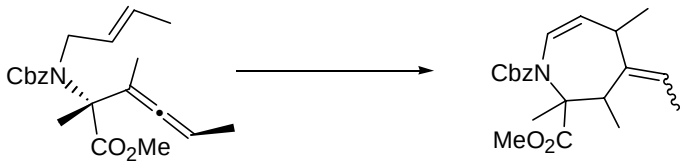


9B **10B**

4-(2,2-Dimethylpropyl)-7,7-dimethyl-1-(4-methylbenzenesulfonyl)-6,7-dihydro-1*H*-azepine (10B; Eq. 37). The general procedure for azepine formation (p. 88) was followed using ene-allene **9B** (22 mg, 0.064 mmol), $[Rh(CO)_2Cl]_2$ (2.3 mg, 0.0059 mmol), and dichloroethane (320 μL) under an argon atmosphere. Reaction progress was monitored by TLC (benzene), reaching completion after 1.5 h. The solution was concd in vacuo and purified by silica gel chromatography (benzene) to afford 7.5 mg of azepine **10B** as a clear oil. A mixed fraction was purified by HPLC (silica column, ethyl acetate-hexanes 1:32) to afford an additional 2.6 mg of **10B** for a combined yield of 45%. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.69 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 9.4 Hz, 1H), 6.70 (1/2 AA′XX′ d, *J* = 8.6 Hz, 2H), 5.39 (bt, *J* = 6.7 Hz, 1H), 5.51 (d, *J* = 9.4 Hz, 1H), 1.95 (d, *J* = 6.7 Hz, 2H), 1.86 (s, 3H), 1.75 (s, 2H), 1.63 (s, 6H), 0.69 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 143.4, 138.5, 130.0, 129.7, 129.2, 128.9, 127.3, 120.2, 50.6, 44.3, 31.3, 29.9, 29.6, 29.2, 21.3; IR (neat) 3027, 2950, 2904, 2868, 1644, 1598, 1470, 1337 cm^-

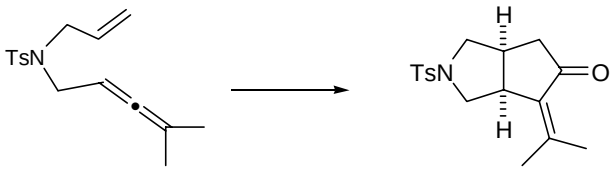
[XI] The sample possessed 34% of azepine **10B** by ^{1}H NMR.

[1]; MS *m/z* (%) 91 (33), 136 (32), 192 (100), 347 (27); EI-HRMS calcd for $C_{20}H_{29}NO_2S$ [M+] *m/z*: 347.1919, found: 347.1916.



9C **10C**

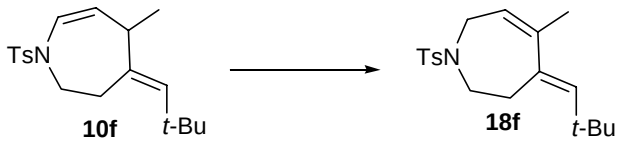
5-Ethylidene-3,5-dimethyl-2,3,4,5-tetrahydro-1*H*-azepine-1,2-carboxylic acid-2-methyl-1-benzyl ester (10C; Eq. 40): The general procedure for azepine formation (p. 88) was followed using ene-allene **9C** (21 mg, 0.059 mmol), $[Rh(CO)_2Cl]_2$ (1.2 mg, 0.0031 mmol), and 1,4-dioxane (590 μL) under a carbon monoxide atmosphere. Reaction progress was monitored by TLC (ethyl acetate-hexanes), reaching completion after 17 h. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:19-1:9) to afford 5.1 mg of azepine **10C** as a colorless oil in a calculated yield of 24%.[XII] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36-7.29 (m, 5H), 6.37 (bd, *J* = 9.3 Hz, 1H), 5.45 (qd, *J* = 6.9, 1.9 Hz, 1H), 5.13 (s, 2H), 4.82 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.63 (bs, 3H), 3.22 (bq, *J* = 7.0 Hz, 1H), 3.17-3.06 (m, 1H), 1.64 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.44 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.18 (d, *J* = 7.1 Hz, 3H); IR (neat) 3032, 2945, 2879, 1742, 1716, 1670, 1450, 1378, 1312, 1276 cm^{-1}; MS *m/z* (%) 91 (100), 222 (61), 254 (41), 298 (28), 357 (17).



9b **12b**

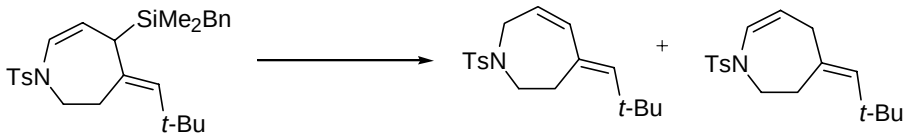
[XII] Composition of a 2.8 mg mixed fraction was determined by ^{1}H NMR.

4-Isopropylidene-2-(4-methylbenzenesulfonyl)-hexahydrocyclopenta[c]pyrrol-5-one (12b; entry 56, Table 9): The general procedure for azepine formation (p. 88) was followed using ene-allene **9b** (20 mg, 0.070 mmol), $[Rh(CO)_2Cl]_2$ (2.7 mg, 0.0070 mmol), and dichloroethane (350 μL) in a carbon monoxide/argon atmosphere (approximately 10%/90%). Reaction progress was monitered by TLC (ethyl acetate-hexanes), reaching completion after 45 min. The solution was concd in vacuo and purified by silica gel chromatography (ethyl acetate-hexanes 1:9-1:1.5) to afford 4 mg of **12b** as a slightly yellow solid in 18% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.78 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 3.43 (dd, *J* = 9.3, 9.3 Hz, 1H), 3.04 (dd, *J* = 10.0, 6.6 Hz, 1H), 2.82 (dd, *J* = 9.7, 6.6 Hz, 1H), 2.76 (dd, *J* = 10.0, 3.3 Hz, 1H), 2.72-2.62 (m, 1H), 2.04 (s, 3H), 2.02 (dd, *J* = 17.4, 9.0, 1H), 1.94-1.81 (m, 1H), 1.87 (s, 3H), 1.70 (dd, *J* = 17.5, 7.5 Hz, 1H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.0, 151.0, 143.9, 133.1, 132.3, 129.7, 127.8, 54.0, 53.4, 44.4, 44.2, 35.2, 24.8, 21.6, 20.6; IR (neat) 2955, 2919, 2853, 1706, 1624, 1593, 1342 1168 cm^{-1}; MS *m/z* (%) 65 (67), 79 (56), 91 (100), 135 (81), 164 (93), 319 (39); EI-HRMS calcd for $C_{17}H_{21}NO_3S$ [M+] *m/z*: 319.1242, found: 319.1231.



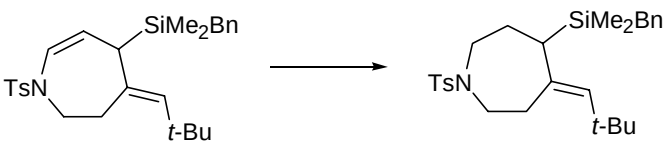
5-[(*E*)-2,2-Dimethylpropylidene]-4-methyl-1-(4-methylbenzenesulfonyl)-2,5,6,7-tetrahydro-1*H*-azepine (18f; Eq. 42):[87] To a solution of azepine **10f** (24 mg, 0.071 mmol) in THF (20 μL) at 0 °C was added 9-BBN (0.5 M in THF, 143 μL, 0.072 mmol) dropwise, whereupon the cold bath was removed. After 52 h at rt the solution was concd in vacuo and purified by silica gel chromatography (ethyl-acetate-hexanes 1:19-1:4; column was pre-treated with 1% triethylamine in hexanes) to afford 1.3 mg of azepine **18f** in 6% yield (^{1}H NMR was contaminated with impurities). ^{1}H NMR C_6D_6 δ: 7.70 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.76 (1/2 AA′XX′ d, *J* = 8.4

Hz, 2H), 5.28 (bs, 1H), 5.16 (bt, *J* = 5.2 Hz, 1H), 3.75 (bd, *J* = 5.6 Hz, 2H), 3.33 (t, *J* = 6.3 Hz, 2H), 2.23 (t, *J* = 6.3 Hz, 2H), 1.91 (s, 3H), 1.58 (d, *J* = 0.9 Hz, 3H), 0.95 (s, 9H).



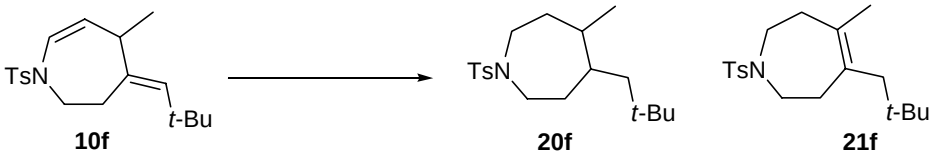
9k **18k** **10D**

5-[(*E*)-2,2-Dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-2,5,6,7-tetrahydro-1*H*-azepine (18k; Eq. 43); 5-[(*E*)-2,2-Dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-4,5,6,7-tetrahydro-1*H*-azepine (10D; Eq. 43):[88] To a solution of the azepine **9k** (18 mg, 0.038 mmol) in MeOH (150 μL) at 0 °C was added TBAF (1.0 M in THF, 150 μL, 0.150 mmol) dropwise and it was then warmed to rt. After 39 h at rt the solution was concd in vacuo and partitioned between ethyl acetate/H_2O (2 mL/2mL). The aqueous layer was extracted with ethyl acetate (3 x 5 mL), and the combined organic layers were dried over $MgSO_4$ and concd in vacuo. The residue was purified by silica gel chromatography (ethyl acetate-hexanes 1:32-1:9) to afford 3.3 mg of azepine **18k** as a colorless oil in 27% yield and 1.9 mg of azepine **10D** as a colorless oil in 16% yield (^{1}H NMR was contaminated with impurities). ^{1}H NMR **18k** (300 MHz, C_6D_6) δ: 7.70 (1/2 AA′XX′ d, *J* = 8.2 Hz, 2H), 6.78 (1/2 AA′XX′ d, *J* = 8.0 Hz, 2H), 5.82-5.76 (m, 1H), 5.27 (bs, 1H), 5.10 (dt, *J* = 11.5, 5.0 Hz, 1H), 3.77 (dd, *J* = 5.0, 1.4 Hz, 2H), 3.25 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.39 (dd, *J* = 5.6, 5.6 Hz, 2H), 1.90 (s, 3H), 0.91 (s, 9H). ^{1}H NMR **10D** (300 MHz, C_6D_6) δ: 7.68 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.73 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.63 (d, *J* = 9.1 Hz, 1H), 5.12 (s, 1H), 4.70 (dt, *J* = 9.1, 5.6 Hz, 1H), 3.47 (dd, *J* = 5.7, 5.7 Hz, 2H), 2.51 (bd, *J* = 5.7 Hz, 2H), 2.41-2.35 (m, 2H), 1.86 (s, 3H), 0.93 (s, 9H).



10k **19k**

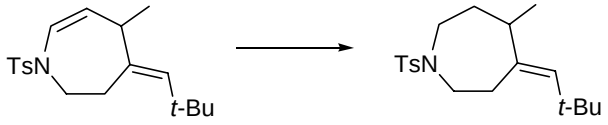
5-(Benzhydryldimethylsilyl)-4-[(*E*)-2,2-dimethylpropylidene]-1-(4-methylbenzenesulfonyl)-2,3,4,5,6,7-hexahydro-1*H*-azepine (19k; Eq. 44): To a solution of tetrahydroazepine **10k** (48 mg, 0.102 mmol) in ethanol (2.5 mL) was added Palladium on carbon (10% wt, 9.5 mg, 0.0089 mmol). The system was pressurized and evacuated with H_2 (3 x 30 psi) before being fully pressurized to 50 psi on a Parr hydrogenator apparatus. It was shaken vigorously and indicated complete conversion after 4 h (TLC). The slurry was filtered over celite and concd in vacuo to give 48 mg of pure azepine **19k** in 99% yield. ^{1}H NMR (300 MHz, CD_2Cl_2): 7.62 (1/2 AA′XX′ d, J = 8.3 Hz, 2H), 7.32 (1/2 AA′XX′ d, J = 8.0 Hz, 2H), 7.22-7.15 (m, 2H), 7.08-7.01 (m, 1H), 6.99-6.94 (m, 2H), 5.09 (s, 1H), 3.86-3.75 (m, 2H), 2.79 (ddd, J = 14.1, 6.3, 2.0 Hz, 1H), 2.71-2.56 (m, 2H), 2.41 (s, 3H), 2.13-1.99 (m, 3H), 1.96-1.86 (m, 1H), 1.78-1.61 (m, 2H), 1.06 (s, 9H), -0.12 (s, 6H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 143.7, 140.5, 137.6, 137.5, 136.8, 130.0, 128.6, 128.5, 127.4, 124.4, 51.4, 49.4, 37.2, 32.0, 31.0, 30.1, 28.8, 24.3, 21.6, -4.4, -4.6; IR (neat) 3078, 3058, 3022, 2950, 2925, 2853, 1598, 1491, 1450, 1363, 1342 cm^{-1}; MS *m/z* (%) 121 (38), 149 (68), 378 (100), 426 (74), 454 (74), 469 (15); EI-HRMS calcd for $C_{27}H_{39}NO_2SSi$ [M+] *m/z*: 469.2471, found: 469.2467.



4-(2,2-Dimethylpropyl)-5-methyl-2,3,4,5,6,7-hexahyro-1*H*-azepine (20f; Eq. 45); 4-(2,2-Dimethylpropyl)-5-methyl-2,3,6,7-tetrahyro-1*H*-azepine (21f; Eq. 45): The procedure for reduction of **10k** was followed using azepine **10f** (23 mg, 0.069 mmol), Palladium on carbon (10% wt, 4.6 mg, 0.0043), and ethanol (1.72 mL) to afford 20 mg of product as a colorless oil. Separation via HPLC afforded azepines **20f** and **21f** in 1.1:1 ratio to result in 46% and 40% yields, respectively. ^{1}H NMR **20f** (300 MHz, C_6D_6) δ: 7.72 (d, J = 8.3 Hz, 2H^a), 7.68 (d, J = 8.3

Hz, 2H[a]), 6.84 (d, J = 8.2 Hz, 2H[a]), 6.81 (d, J = 9.1 Hz, 2H[a]) 3.23-2.94 (m, 8H[b]), 2.12-2.07 (m, 2H[a]) 2.06-2.01 (m, 2H[a]), 1.93 (s, 3H[a]), 1.90 (s, 3H[a]) 1.59-1.25 (m, 12H[b]), 0.98 (d, J = 4.6 Hz, 3H[a]), 0.79 (s, 9H[a]), 0.76-0.71 (m, 12H[b]); MS *m/z* **20f** (%) 57 (97), 91 (100), 182 (77), 277 (22), 280 (39); EI-HRMS calcd for **20f** $C_{19}H_{31}NO_2S$ [M+] *m/z*: 337.2076, found: 337.2073. ^{1}H NMR **21f** (300 MHz, $CDCl_3$) δ: 7.62 (1/2 AA′XX′ d, J = 8.2 Hz, 2H), 7.29 (1/2 AA′XX′ d, J = 8.2 Hz, 2H), 3.12-3.06 (m, 4H), 2.42 (s, 3H), 2.36-2.29 (m, 4H), 1.93 (s, 2H), 1.62 (s, 3H), 0.85 (s, 9H). ^{13}C NMR **21f** (75 MHz, $CDCl_3$) δ: 143.1, 135.1, 134.2, 134.1, 129.6, 127.3, 48.5, 47.3, 46.6, 36.6, 36.2, 33.6, 30.2, 22.6, 21.5; IR **21f** (neat) 2950, 2858, 1598, 1455, 1363, 1337 cm^{-1}.

[a]Spin set is absorption of a single diastereomer. [b]Spin set is a mixture of diastereomers.



10f **19f**

4-[(*E*)-2,2-Dimethylpropylidene]-5-methyl-1-(4-methylbenzenesulfonyl)-2,3,4,5,6,7-hexahydro-1*H*-azepine (19f; Eq. 46):[89] To a solution of tetrahydroazepine **10f** (21 mg, 0.064 mmol) in dichloroethane (220 μL) was added acetic acid (3.7 μL, 0.065 mmol). To the solution after 5 min was added sodium triacetoxyborohydride (20 mg, 0.093 mmol). No change in starting material was observed after 1.3 h, whereupon acetic acid (6.4 μL, 0.109 mmol) and sodium triacetoxyborohydride (14 mg, 0.064 mmol) were added. No change in starting material was observed after and additional 1h, at which point acetic acid (7.4 μL, 0.13 mmol), sodium triacetoxyborohydride (27 mg, 0.13 mmol) and dichloroethane (100 μL) were again added. Analysis by TLC showed minimal change after 12 h (a faint lower spot). To the slurry was added trifluoroacetic acid (10.0 μL, 0.13 mmol) which resulted in a homogeneous solution. Within 1 h substantial conversion was observed (TLC) but the reaction did not progress after that point. During the course of the next 24 h, trifluoroacetic acid (15 μL, 0.19 mmol), and sodium

triacetoxyborohydride (41 mg, 0.19 mmol) were added in portions. Upon complete conversion the mixture was quenched with NaOH aq (1N, 400 μL), diluted with water (5 mL), and extracted with DCM (4 x 5 mL). The combined organic layers were washed with saturated $NaHCO_3$ (7 mL), brine (7 mL), dried over Na_2SO_4, and concd in vacuo. The crude residue was purified by silica gel chromatography (ethylacetate-hexanes 1:19-1:9) to afford 20 mg of pure hexahydroazepine **19f** in 93% yield. ^{1}H NMR (300 MHz, C_6D_6) δ: 7.71 (1/2 AA′XX′ d, *J* = 8.3 Hz, 2H), 6.82 (1/2 AA′XX′ d, *J* = 8.5 Hz, 2H), 5.20 (s, 1H), 3.43 (ddd, *J* = 12.6, 7.2, 4.4 Hz, 1H), 3.35 (ddd, *J* = 13.8, 8.1, 3.2 Hz, 1H), 2.94 (ddd, *J* = 12.5, 7.6, 4.4 Hz, 1H), 2.77 (ddd, *J* = 13.8, 7.8, 3.3 Hz, 1H), 2.34 (1/2 AB ddd, *J* = 14.4, 7.5, 4.4 Hz, 1H), 2.25 (1/2 AB ddd, *J* = 14.4, 7.1, 4.5 Hz, 1H), 2.13-1.98 (m, 1H), 1.91 (s, 3H), 1.69 (dddd, *J* = 14.2, 8.1, 5.7, 3.3 Hz, 1H), 1.30-1.16 (m, 1H), 1.00, (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ: 143.5, 140.4, 136.9, 136.8, 130.0, 127.4, 49.7, 47.5, 41.5, 36.9, 32.7, 31.7, 29.8, 21.7, 21.6; IR (neat) 2955, 2863, 1598, 1460, 1332, 1158 cm^{-1}; MS *m/z* (%) 91 (82), 124 (89), 180 (100), 320 (29), 335 (36); EI-HRMS calcd for $C_{19}H_{29}NO_2S$ [M+] *m/z*: 335.1919, found: 335.1917.

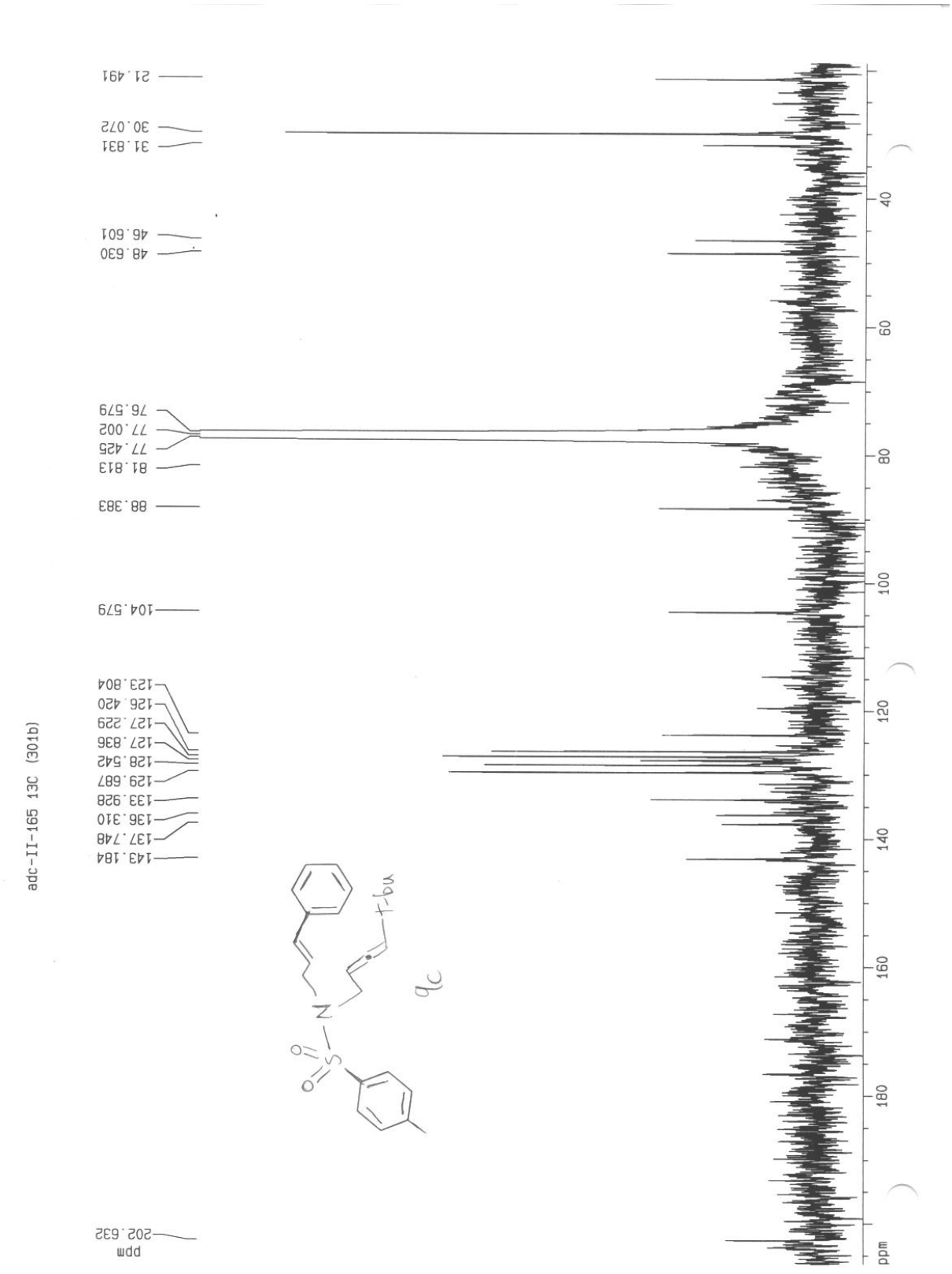
APPENDIX B

NMR SPECTRA

B.1 ENE-ALLENES

The ^{1}H and ^{13}C NMR spectra for each ene-allene are reported sequentially.

adc-II-165 (301b)
ppm
Integral
TsN
Ph
t-bu
9c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143.184
137.748
136.310
133.928
129.687
128.542
127.836
127.229
126.420
123.804
104.579
88.383
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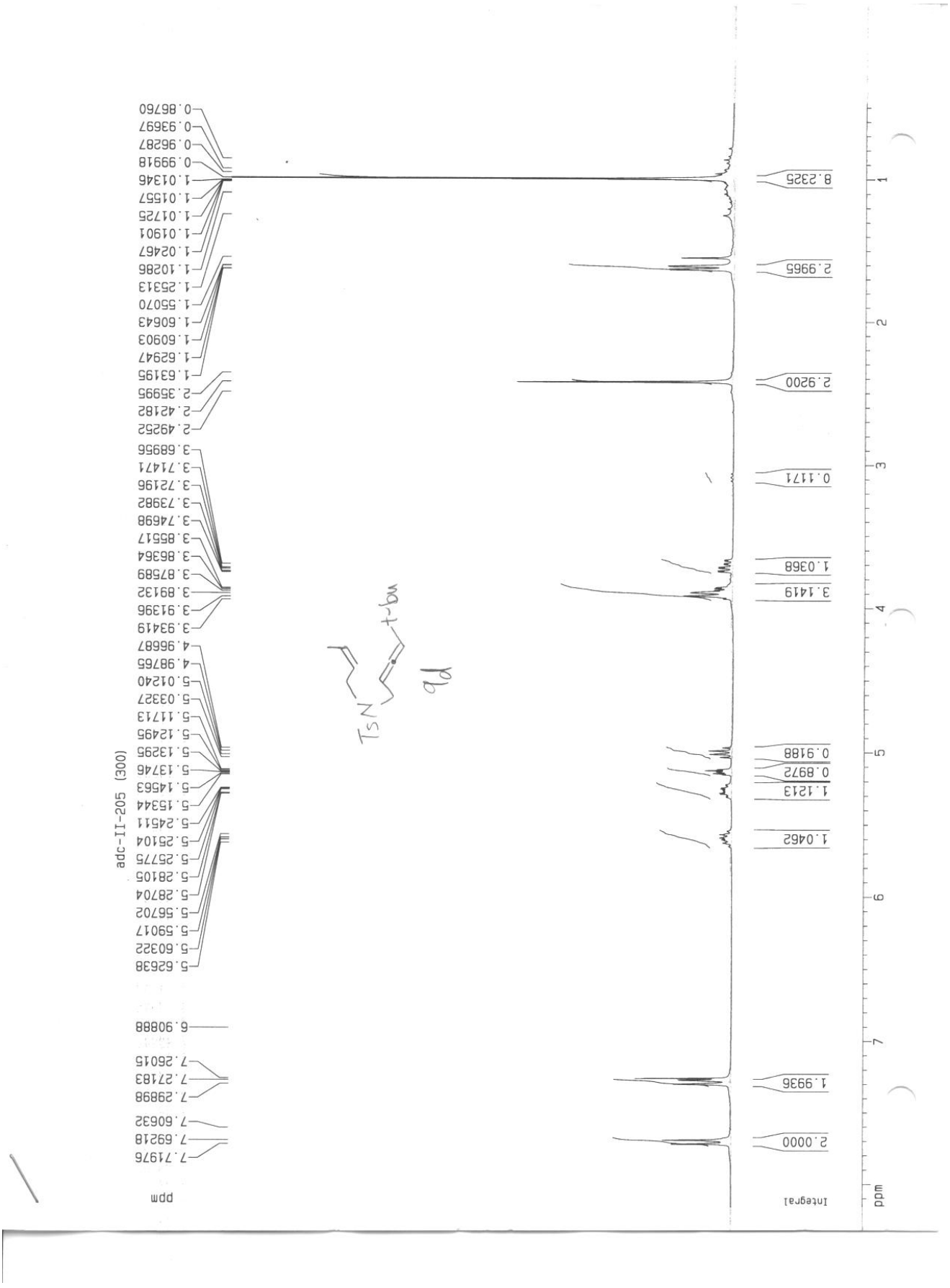
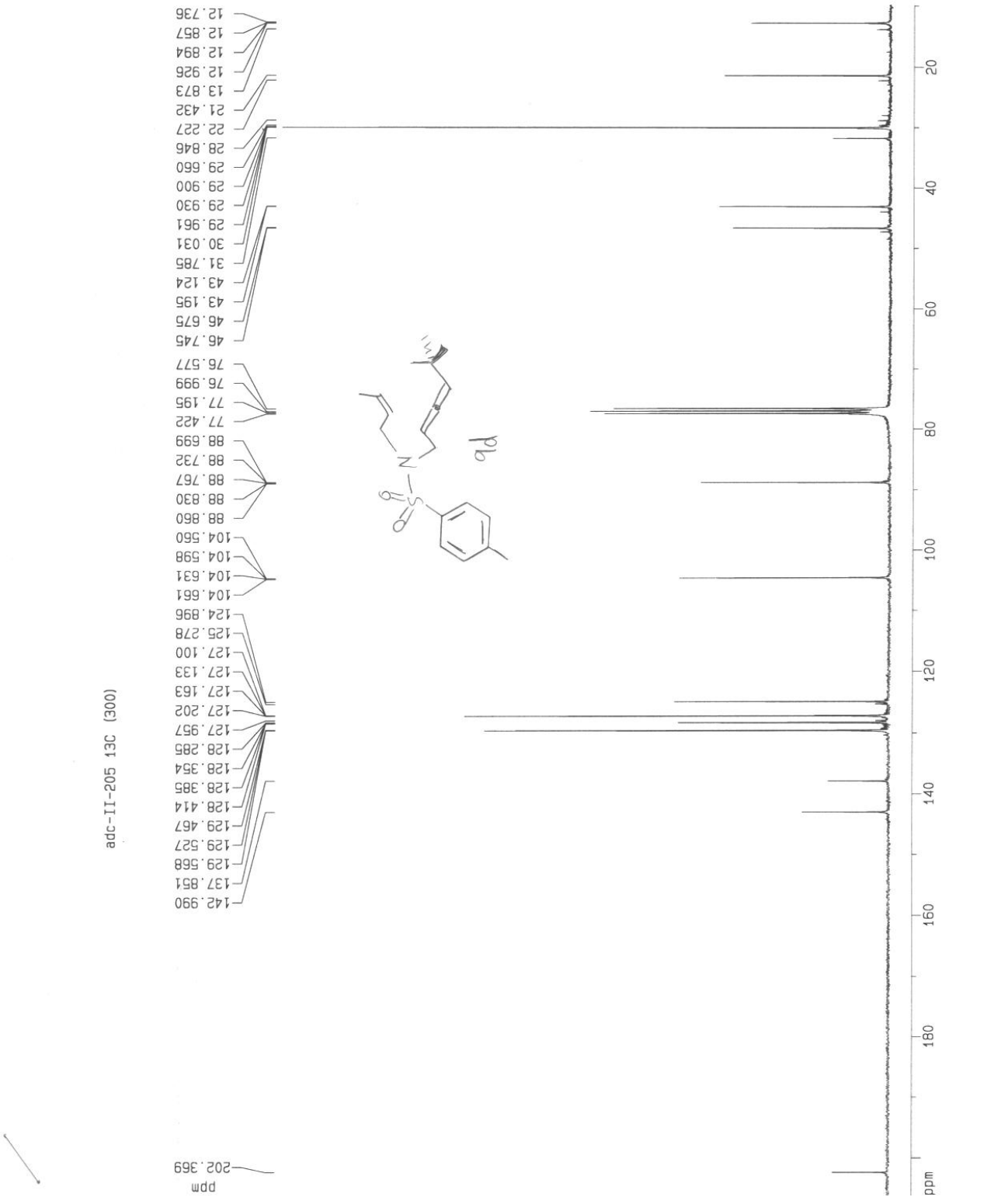
31.831
30.072
21.491
202.632
ppm
t-bu
qc


adc-II-205 (300)
ppm
Integral
TsN
t-bu
9d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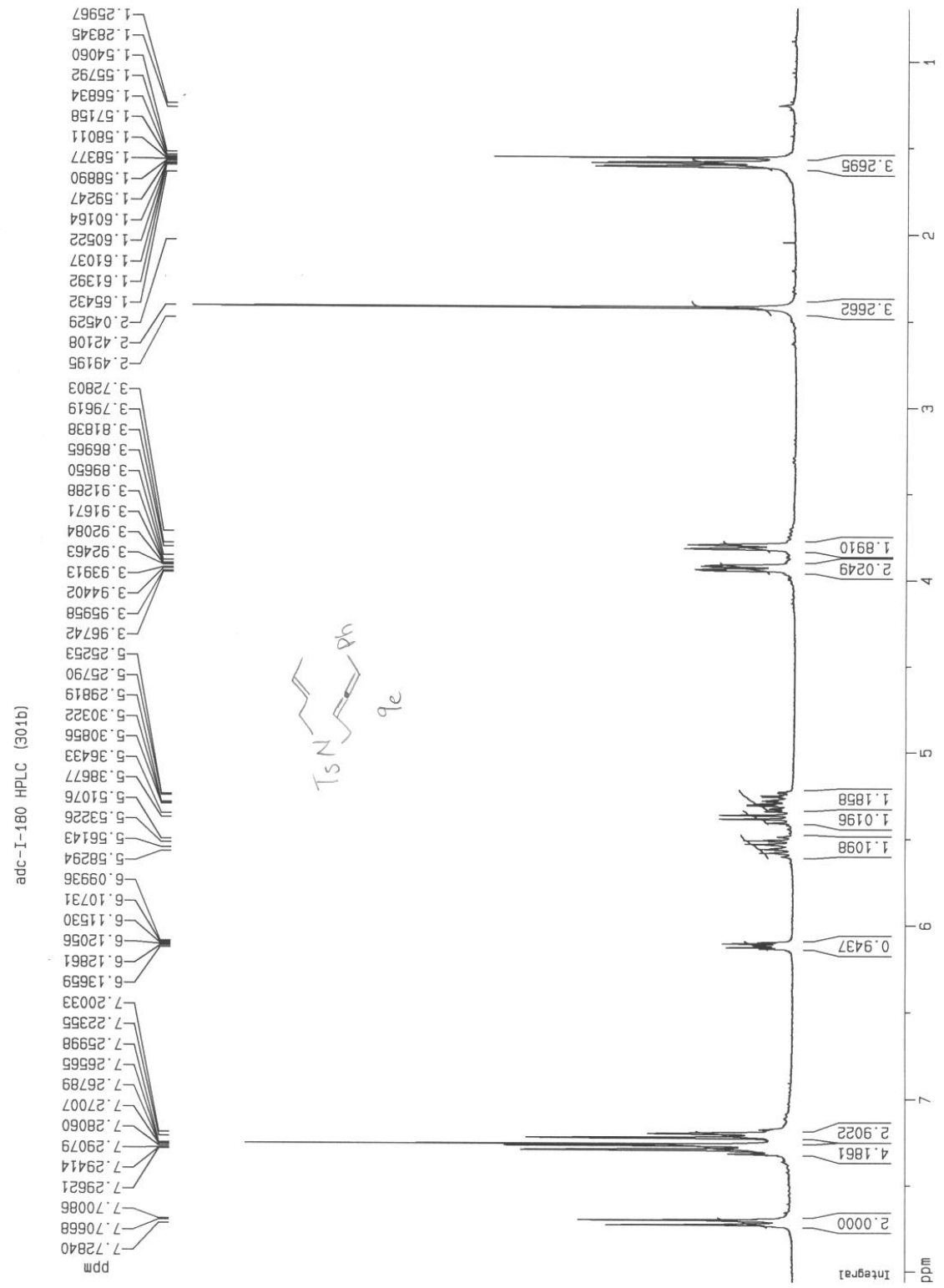
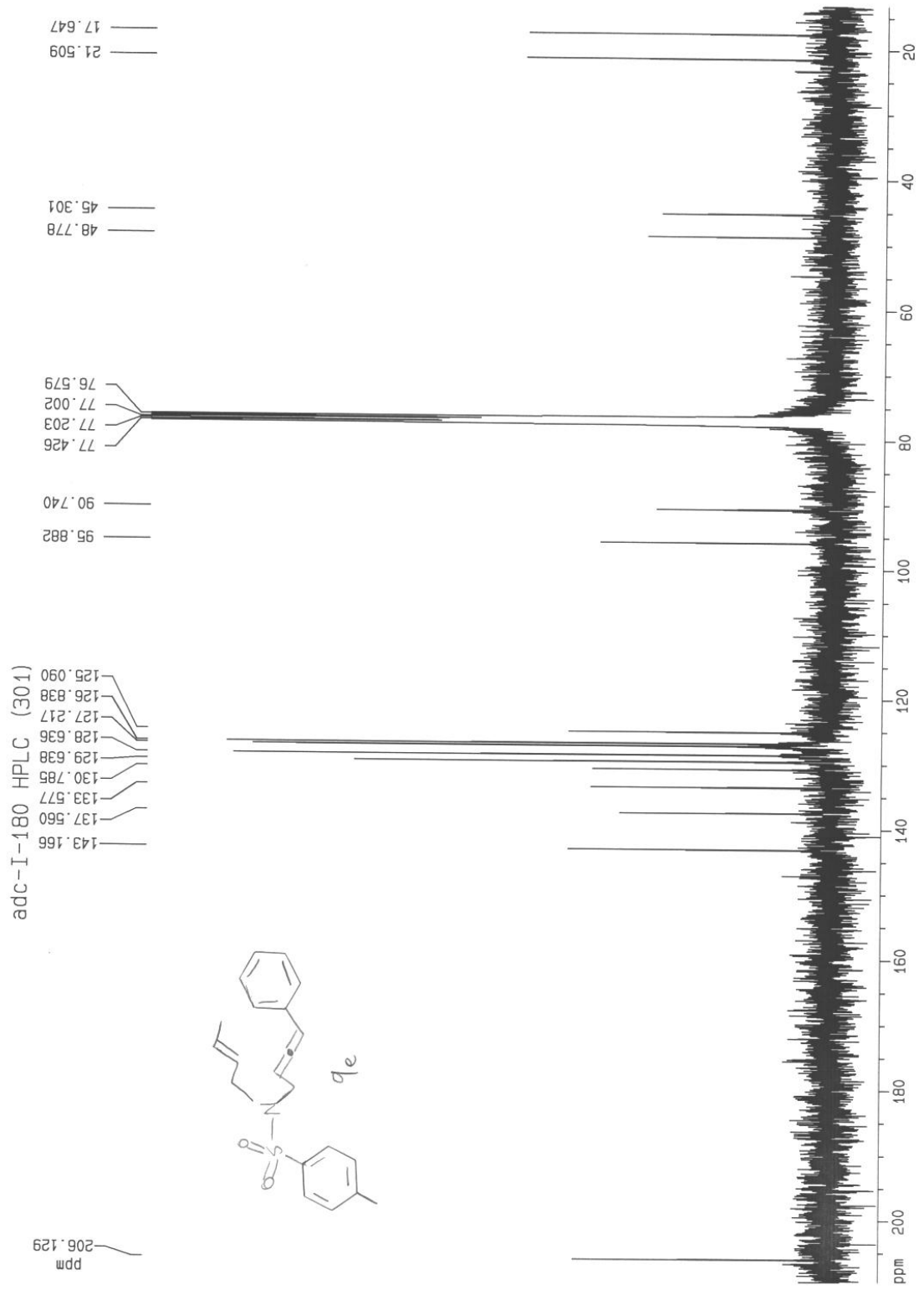
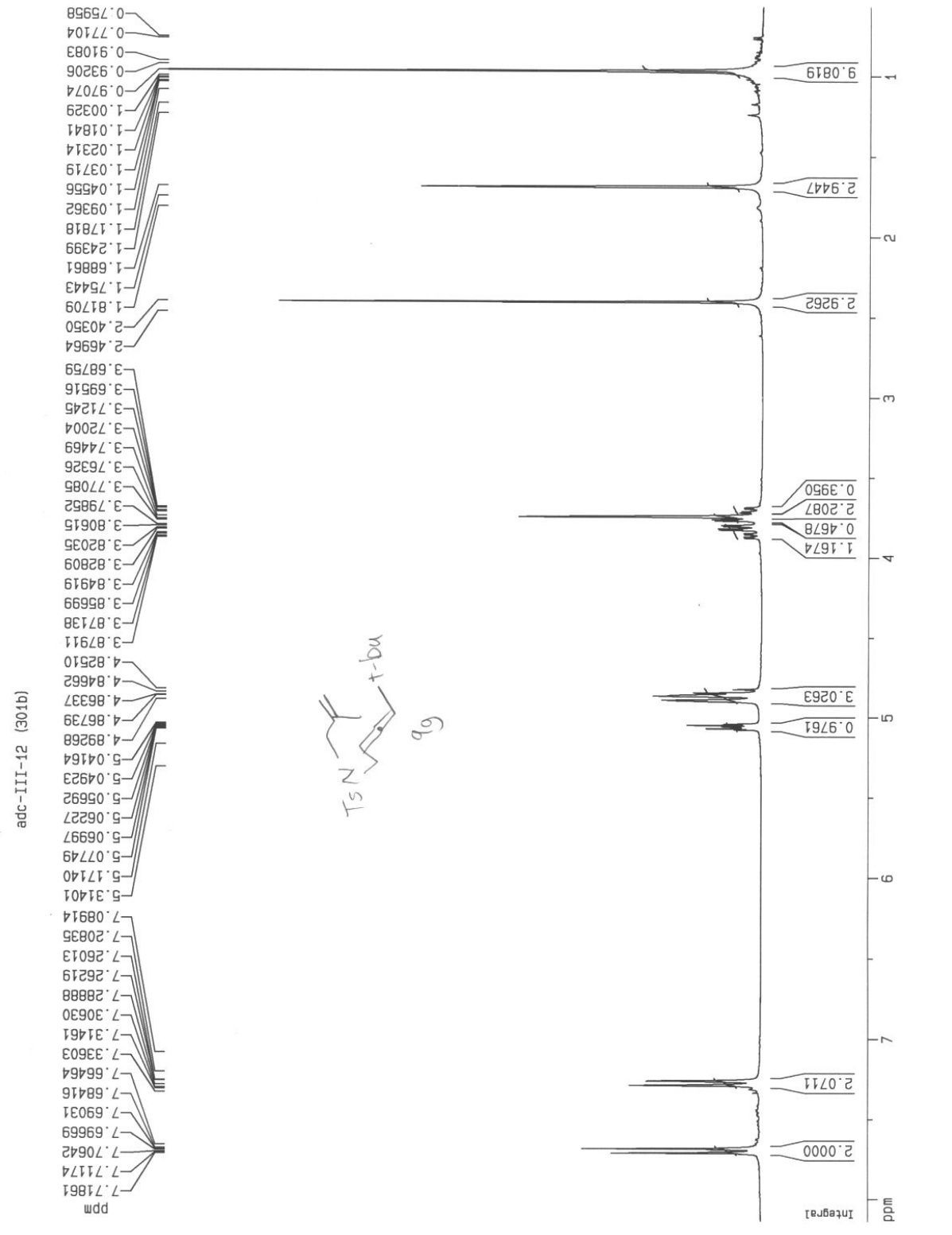
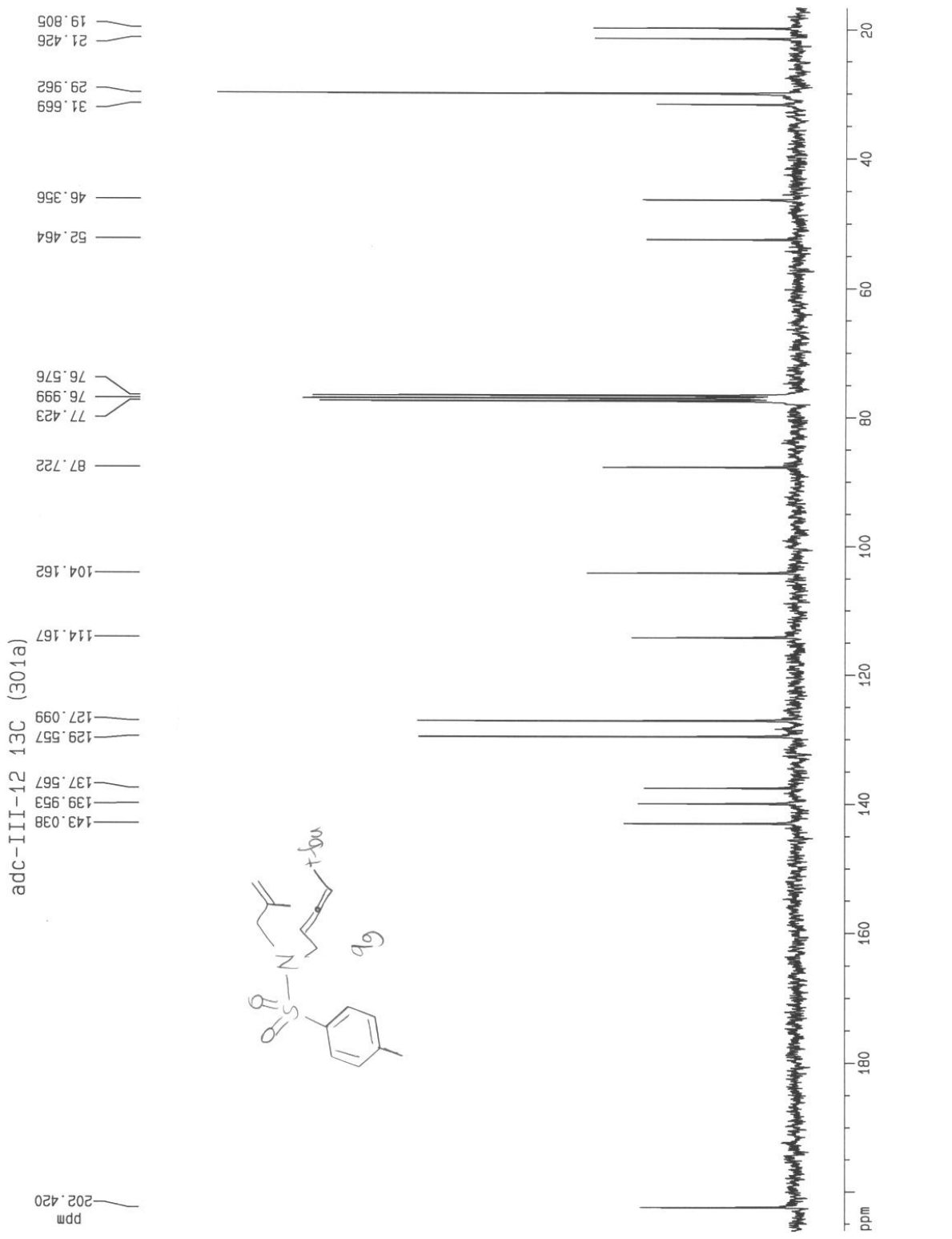
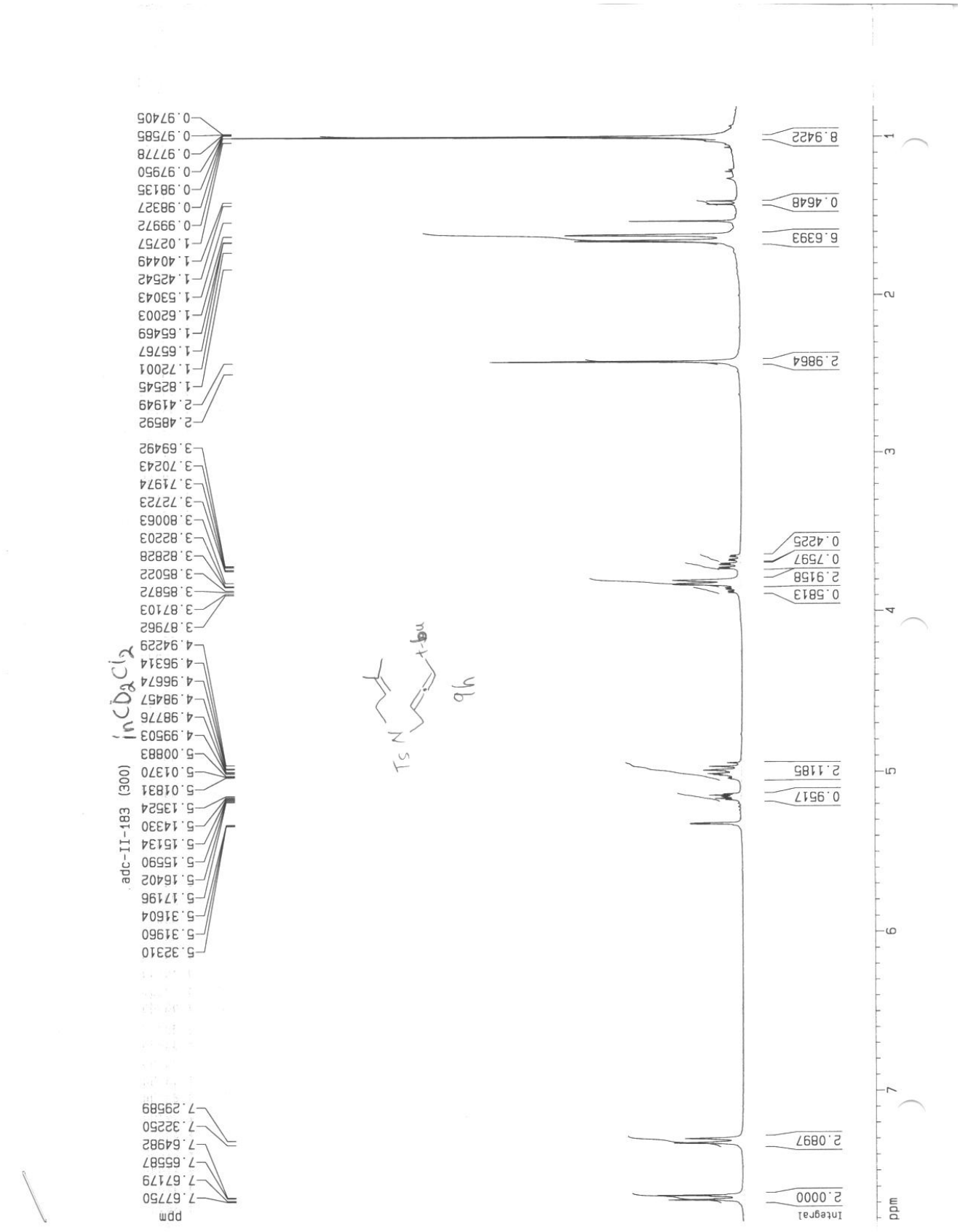
12.736
12.857
12.894
12.926
13.873
21.432
22.227
28.846
29.660
29.900
29.930
29.961
30.031
31.785
43.124
43.195
46.675
46.745
76.577
76.999
77.195
77.422
88.699
88.732
88.767
88.830
88.860
104.560
104.598
104.631
104.661
124.896
125.278
127.100
127.133
127.163
127.202
127.957
128.285
128.354
128.385
128.414
129.467
129.527
129.568
137.851
142.990
202.369
ppm
9d
20
40
60
80
100
120
140
160
180
ppm


adc-I-180 HPLC (301b)
ppm
Integral
TsN
Ph
9e
2.0000
4.1861
2.9022
0.9437
1.1098
1.0196
1.1858
2.0249
1.8910
3.2662
3.2695

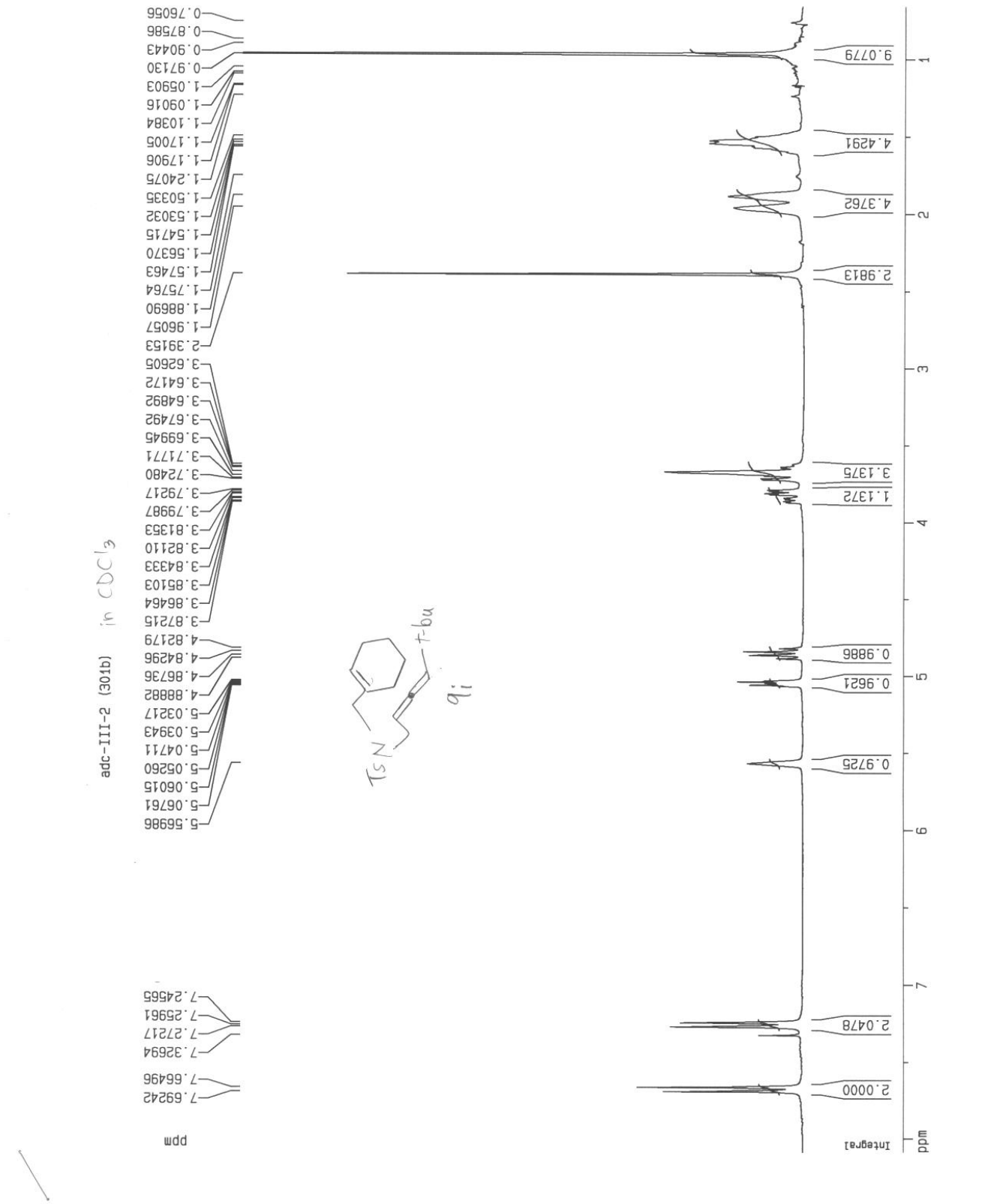

adc-I-180 HPLC (301)
17.647
21.509
45.301
48.778
76.579
77.002
77.203
77.426
90.740
95.882
125.090
126.838
127.217
128.636
129.638
130.785
133.577
137.560
143.166
206.129
ppm
9e

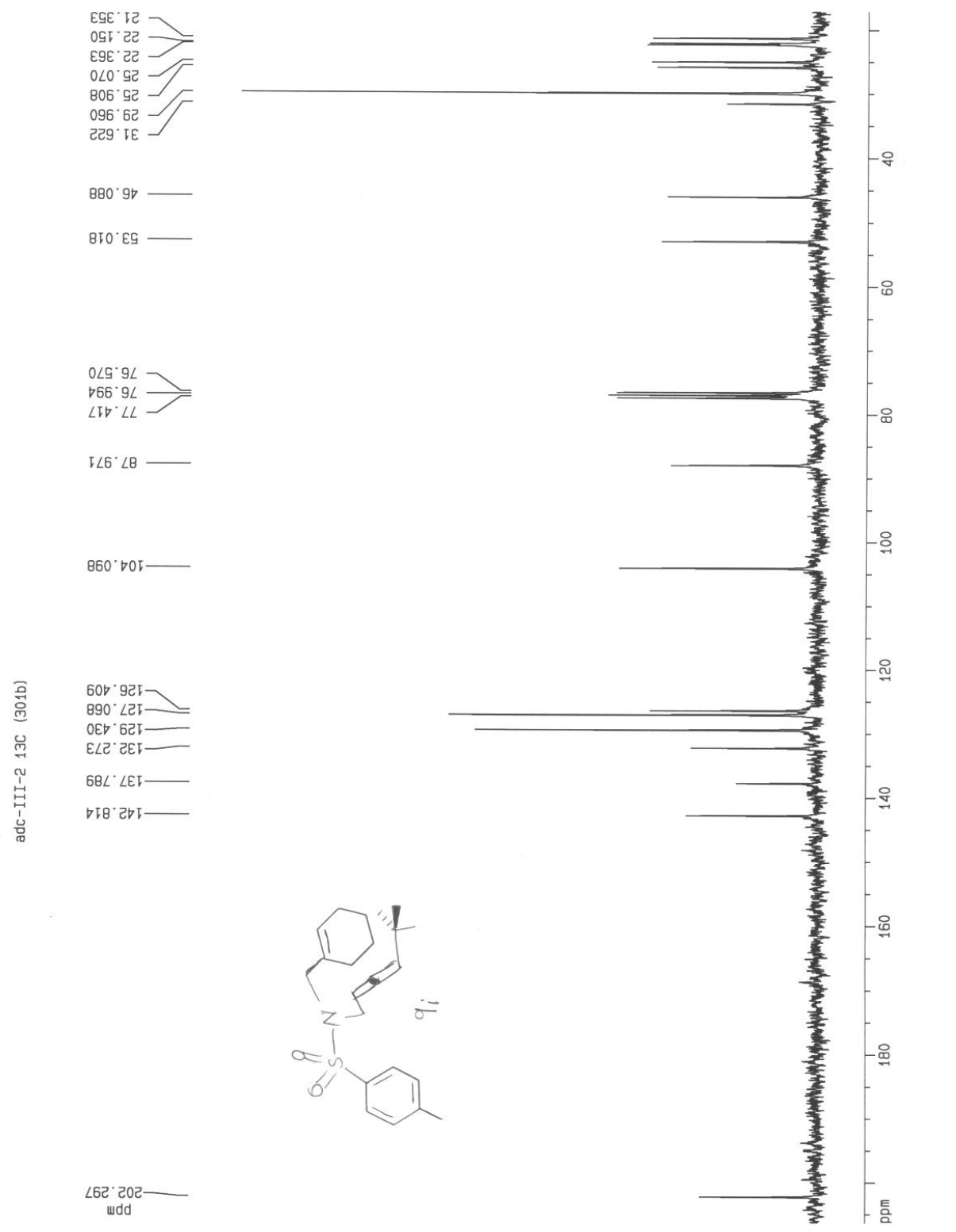

adc-III-12 (301b)
ppm
Integral
TsN
t-bu
9g

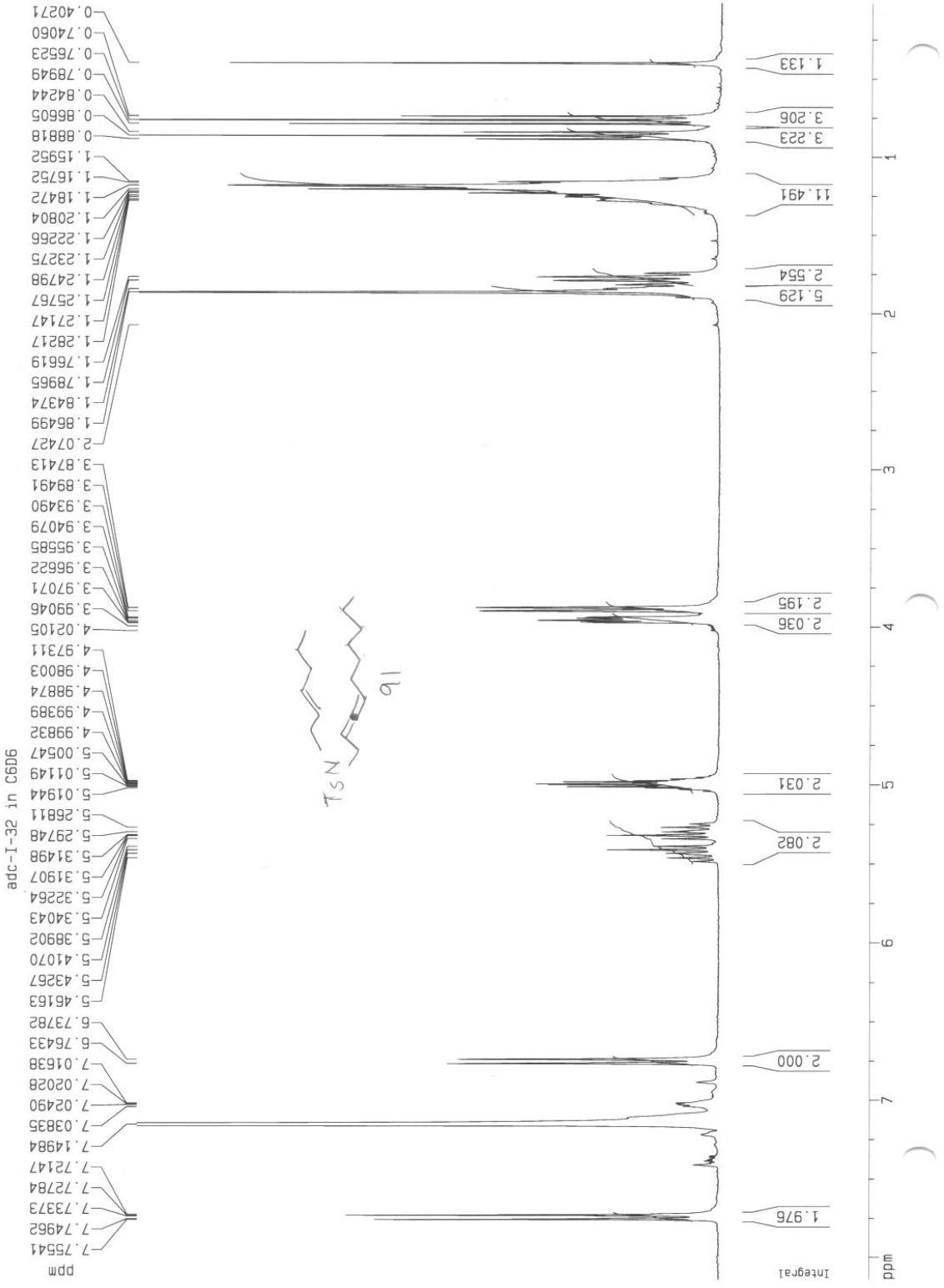

adc-III-12 13C (301a)
ppm
202.420
143.038
139.953
137.567
129.557
127.099
114.167
104.162
87.722
77.423
76.999
76.576
52.464
46.356
31.669
29.962
21.426
19.805
20
40
60
80
100
120
140
160
180
ppm
9g

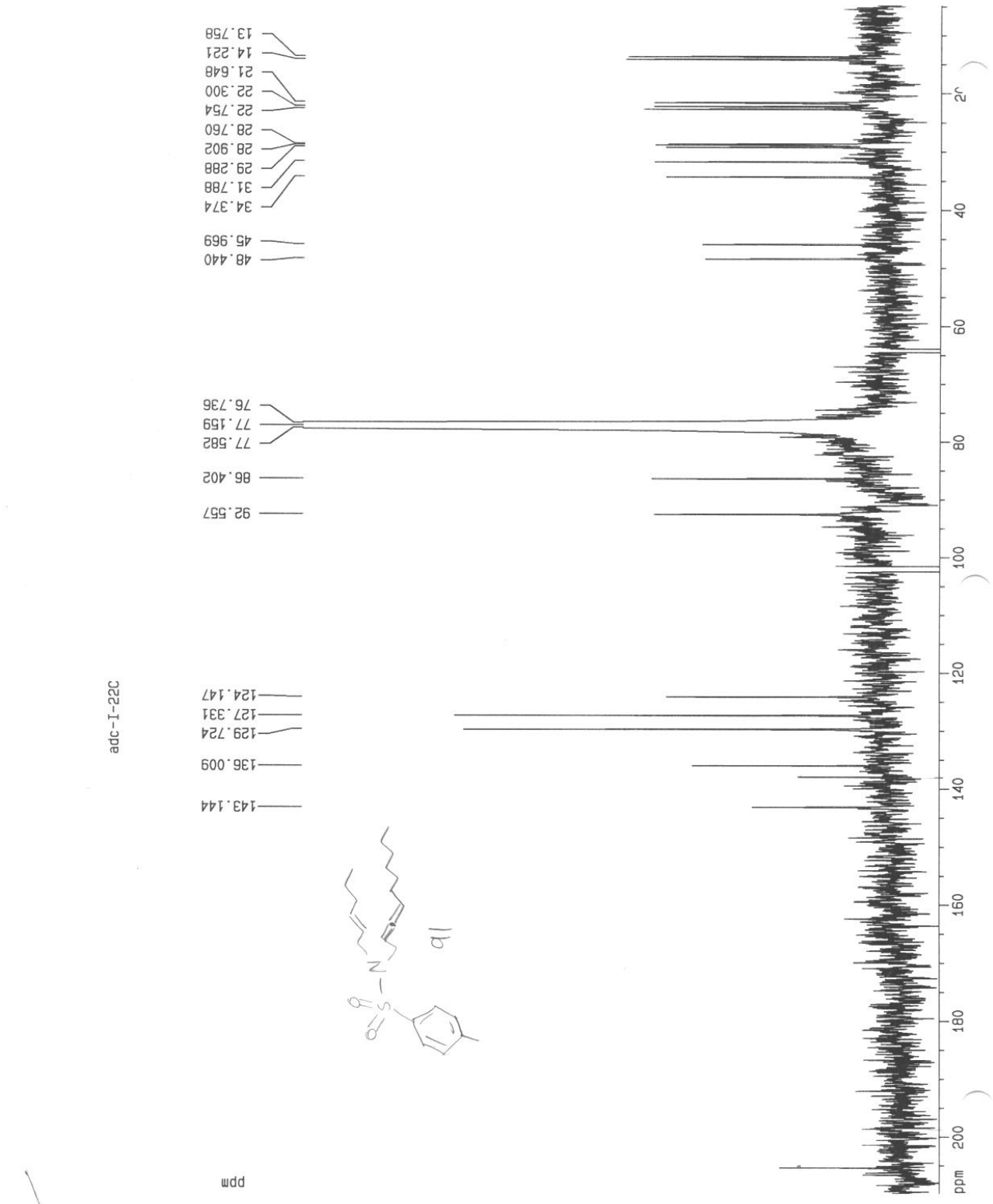

adc-II-183 (300)
InCl3Cl2
9h
Ts
N
t-Bu
ppm
Integral
8.9422
0.4648
6.6393
2.9864
0.4225
0.7597
2.9158
0.5813
2.1185
0.9517
2.0897
2.0000

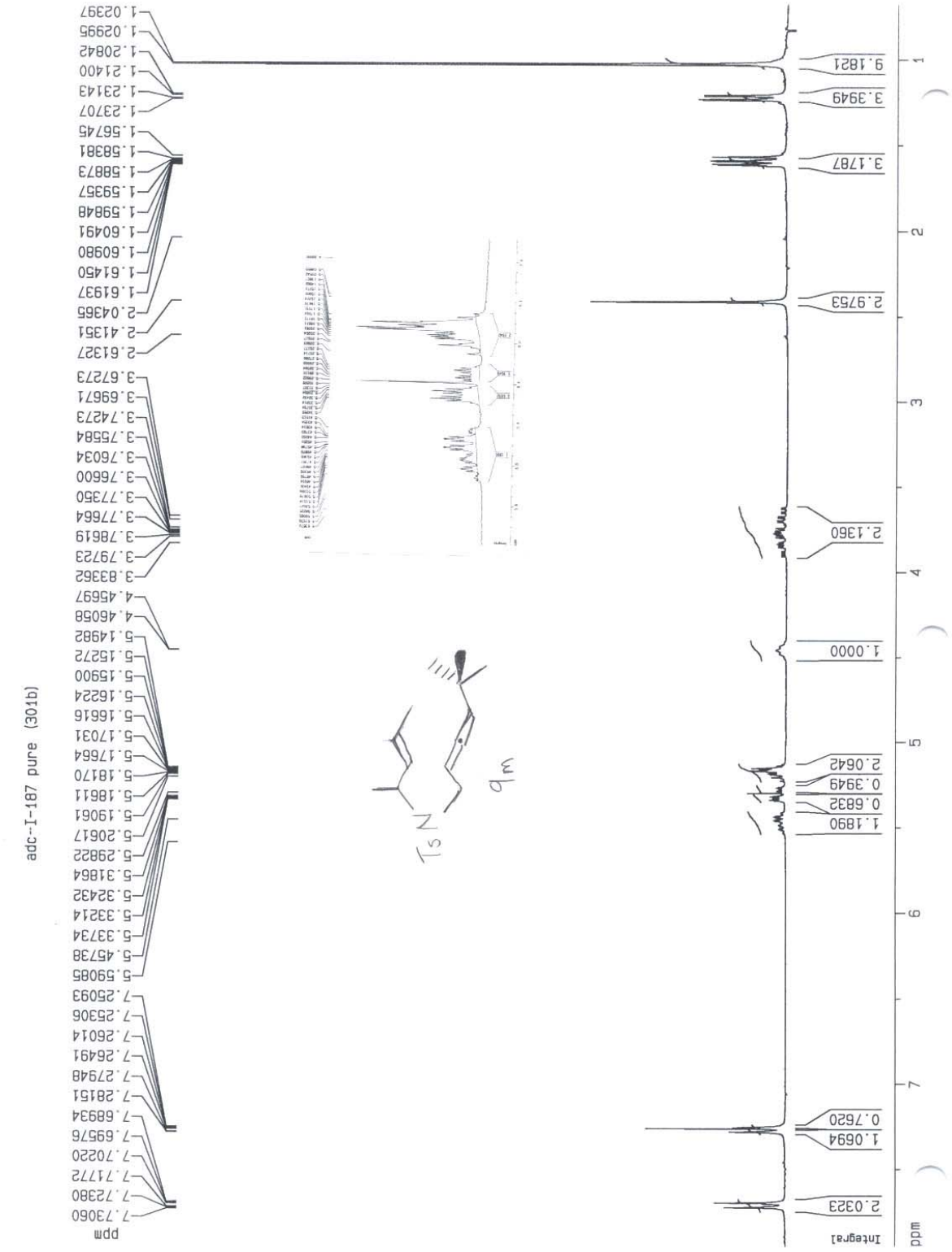
adc-II-183 13C (301b)
ppm
202.214
142.884
137.760
136.657
129.536
129.508
129.470
129.432
127.173
127.135
127.097
118.865
104.399
88.705
77.425
77.001
76.578
46.441
44.262
31.751
30.075
30.046
30.015
29.978
29.940
25.730
25.694
21.528
21.430
17.809
t-bu
9h
20
40
60
80
100
120
140
160
180
ppm

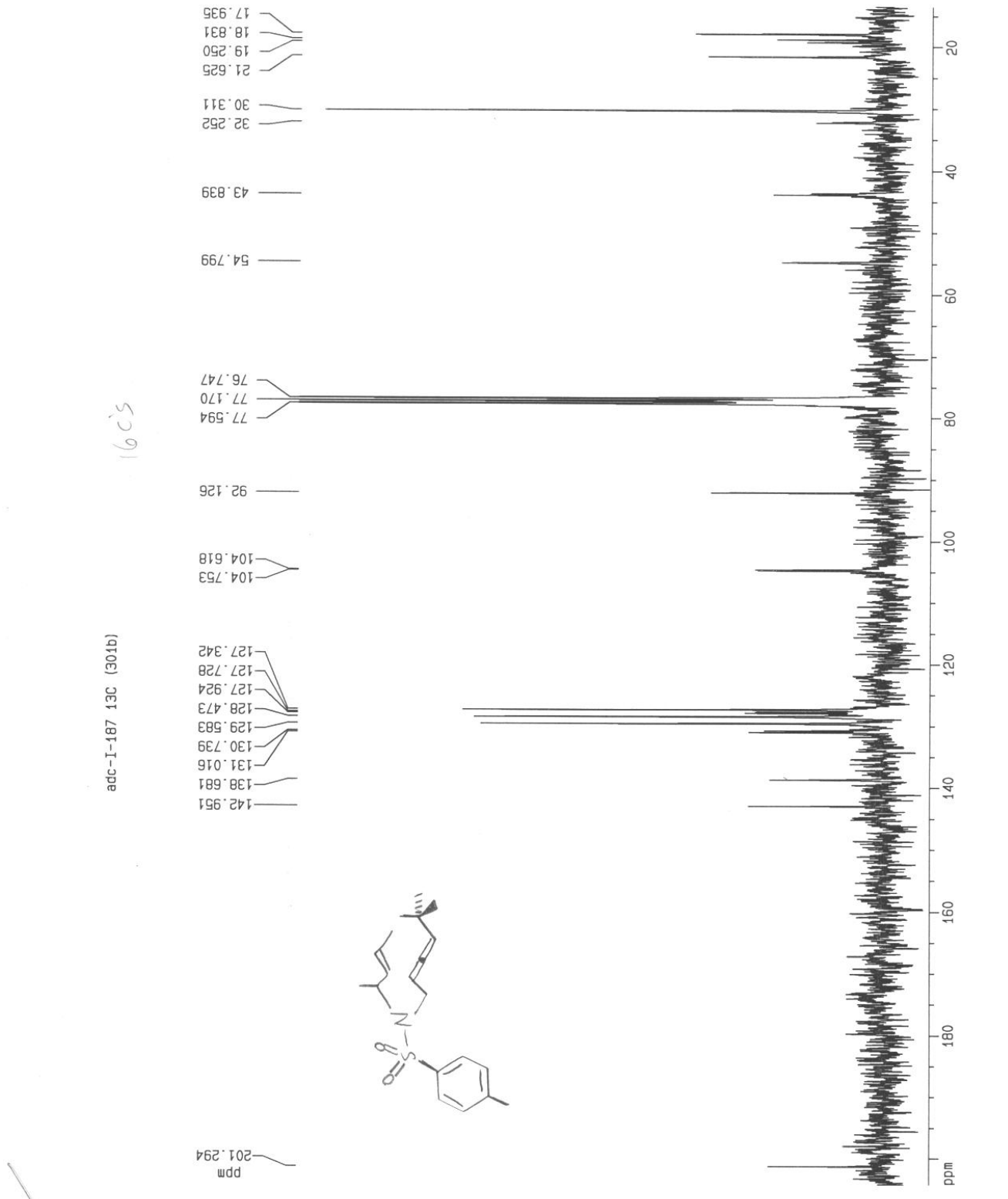

adc-III-2 (301b) in CDCl3
ppm
Integral
2.0000
2.0478
0.9725
0.9621
0.9886
3.1375
1.1372
2.9813
4.3762
4.4291
9.0779
7.69242
7.66496
7.32694
7.27217
7.25961
7.24565
5.69886
5.06761
5.06015
5.05260
5.04711
5.03943
5.03217
4.88882
4.86736
4.84296
4.82179
3.87215
3.86464
3.85103
3.84333
3.82110
3.81353
3.79987
3.79217
3.72480
3.71771
3.69945
3.67492
3.64892
3.64172
3.62605
2.39153
1.96057
1.88690
1.75764
1.57463
1.56370
1.54715
1.53032
1.50335
1.24075
1.17906
1.17005
1.10384
1.09016
1.05903
0.97130
0.90443
0.87586
0.76056
Ts N
t-bu
9i

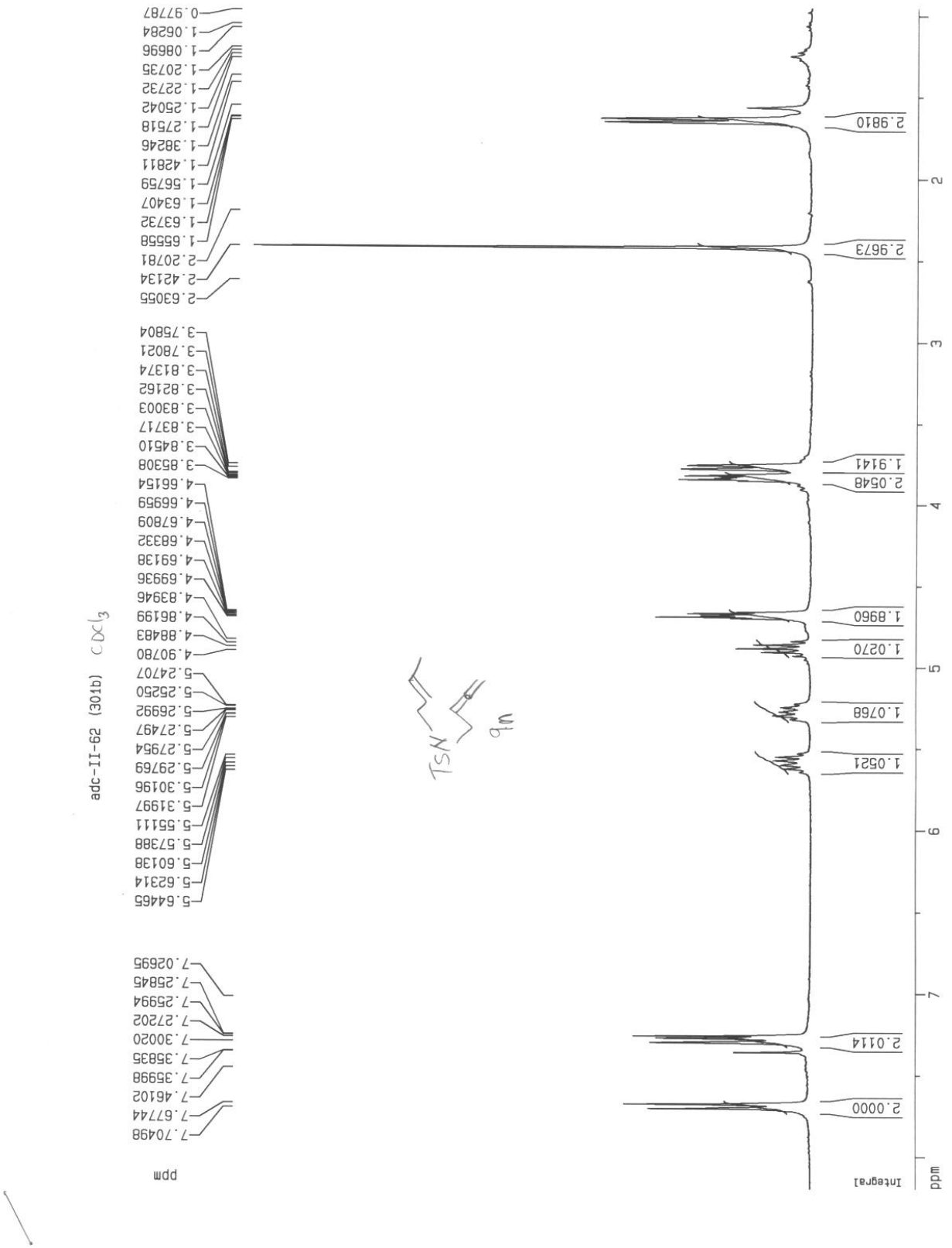

adc-III-2 13C (301b)
21.353
22.150
22.363
25.070
25.908
29.960
31.622
46.088
53.018
76.570
76.994
77.417
87.971
104.098
126.409
127.068
129.430
132.273
137.789
142.814
202.297
ppm
9i
ppm

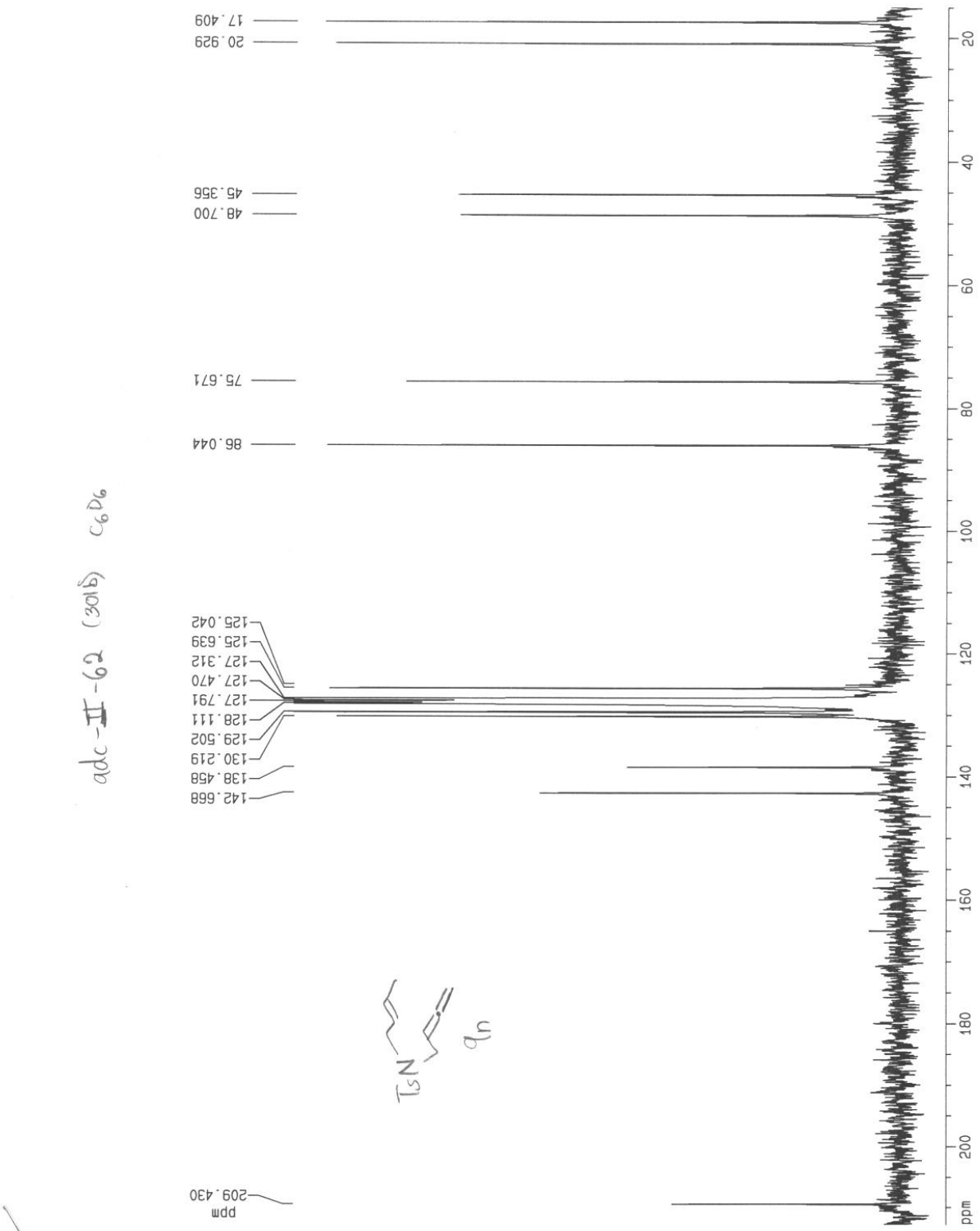

adc-I-32 in C6D6
ppm
Integral
TsN
91

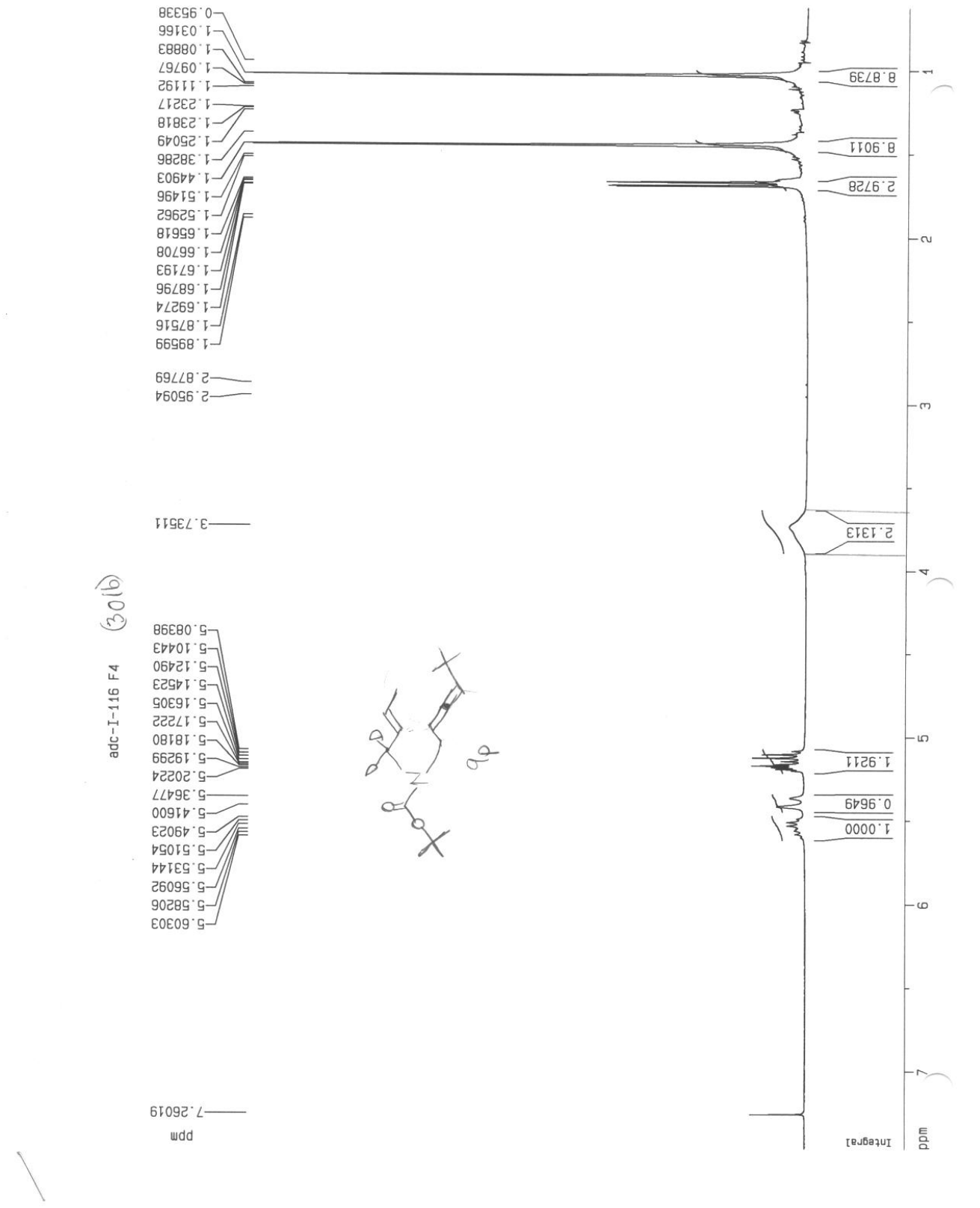

adc-I-22C
ppm
13.758
14.221
21.648
22.300
22.754
28.760
28.902
29.288
31.788
34.374
45.969
48.440
76.736
77.159
77.582
86.402
92.557
124.147
127.331
129.724
136.009
143.144
1b
91


adc-I-187 pure (301b)
ppm
Integral
Ts
N
9.1821
3.3949
3.1787
2.9753
2.1360
1.0000
2.0642
0.3949
0.6832
1.1890
0.7620
1.0694
2.0323

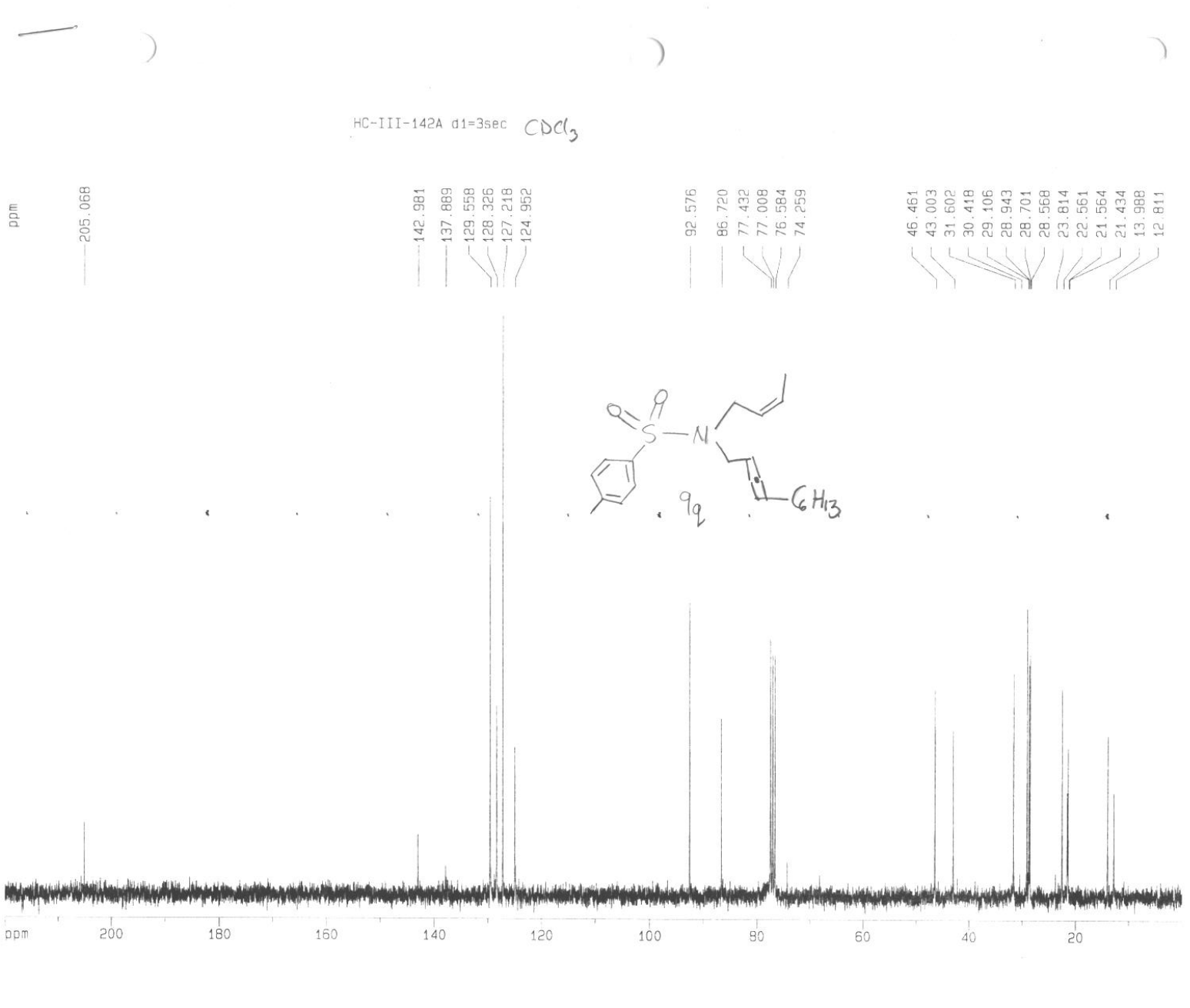

adc-I-187 13C (301b)
ppm
201.294
142.951
138.681
131.016
130.739
129.583
128.473
127.924
127.728
127.342
104.753
104.618
92.126
77.594
77.170
76.747
54.799
43.839
32.252
30.311
21.625
19.250
18.831
17.935
20
40
60
80
100
120
140
160
180
ppm

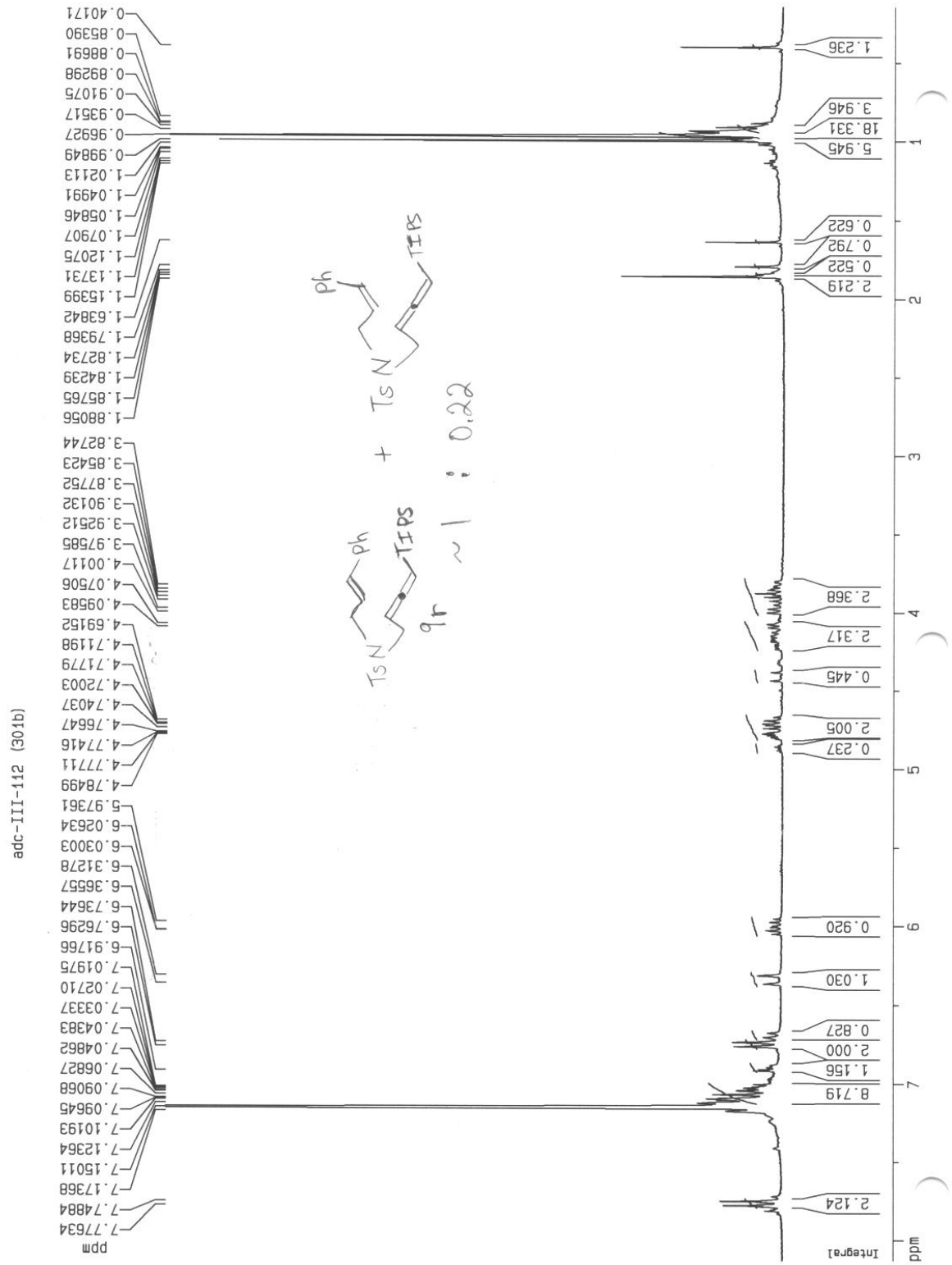

adc-II-62 (301b) CDCl3
ppm
Integral
TsN
9b


adc-II-62 (301b) C6D6
17.409
20.929
45.356
48.700
75.671
86.044
125.042
125.639
127.312
127.470
127.791
128.111
129.502
130.219
138.458
142.668
209.430
ppm
20
40
60
80
100
120
140
160
180
200
ppm
Ts
N
n

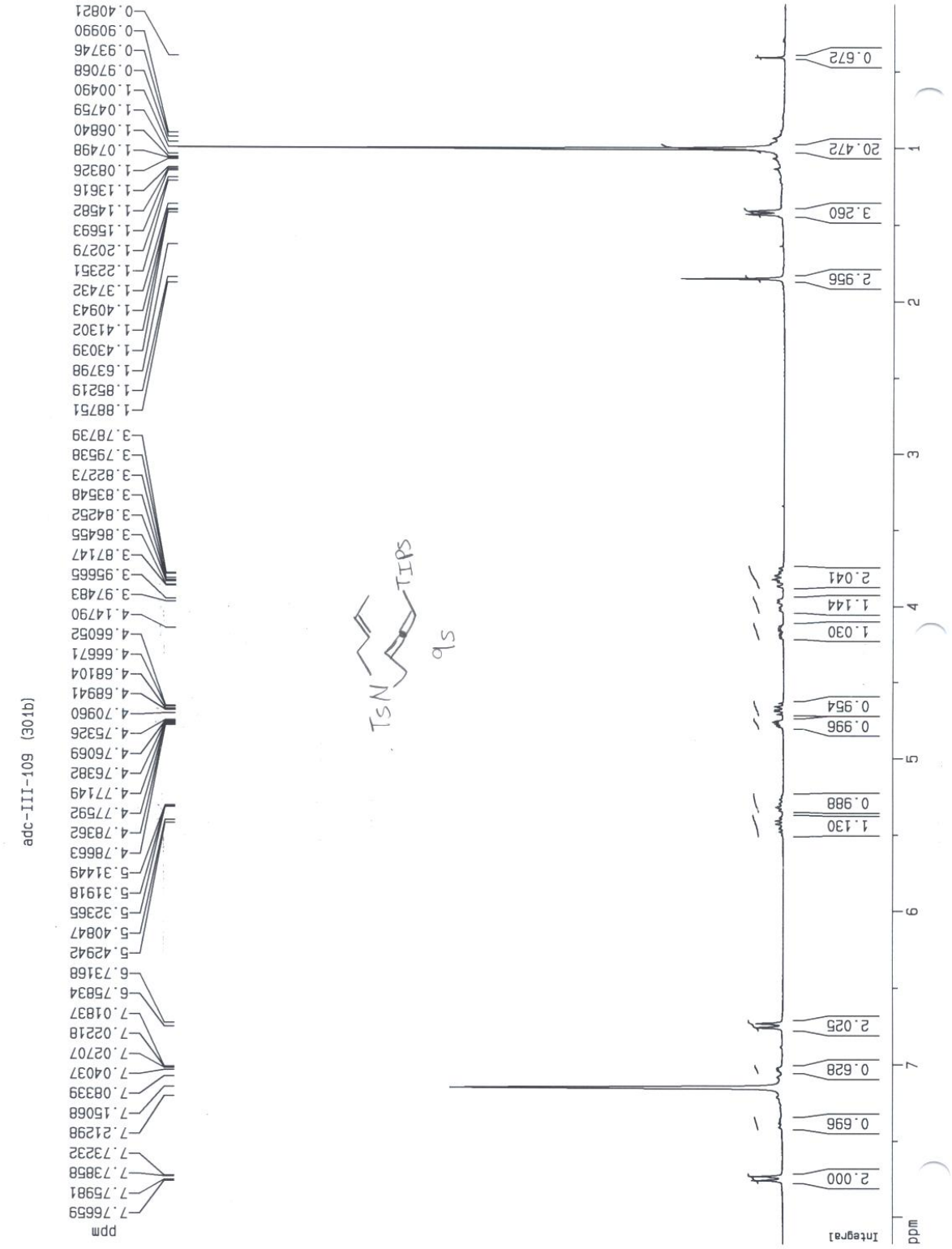

adc-I-116 F4
(30b)
ppm
Integral
7.26019
5.60303
5.58206
5.56092
5.53144
5.51054
5.49023
5.41600
5.36477
5.20224
5.19299
5.18180
5.17222
5.16305
5.14523
5.12490
5.10443
5.08398
3.73511
2.95094
2.87769
1.89599
1.87516
1.69274
1.68796
1.67193
1.66708
1.65618
1.52962
1.51496
1.44903
1.38286
1.25049
1.23818
1.23217
1.11192
1.09767
1.08883
1.03166
0.95338
8.8739
8.9011
2.9728
2.1313
1.9211
0.9649
1.0000
9p

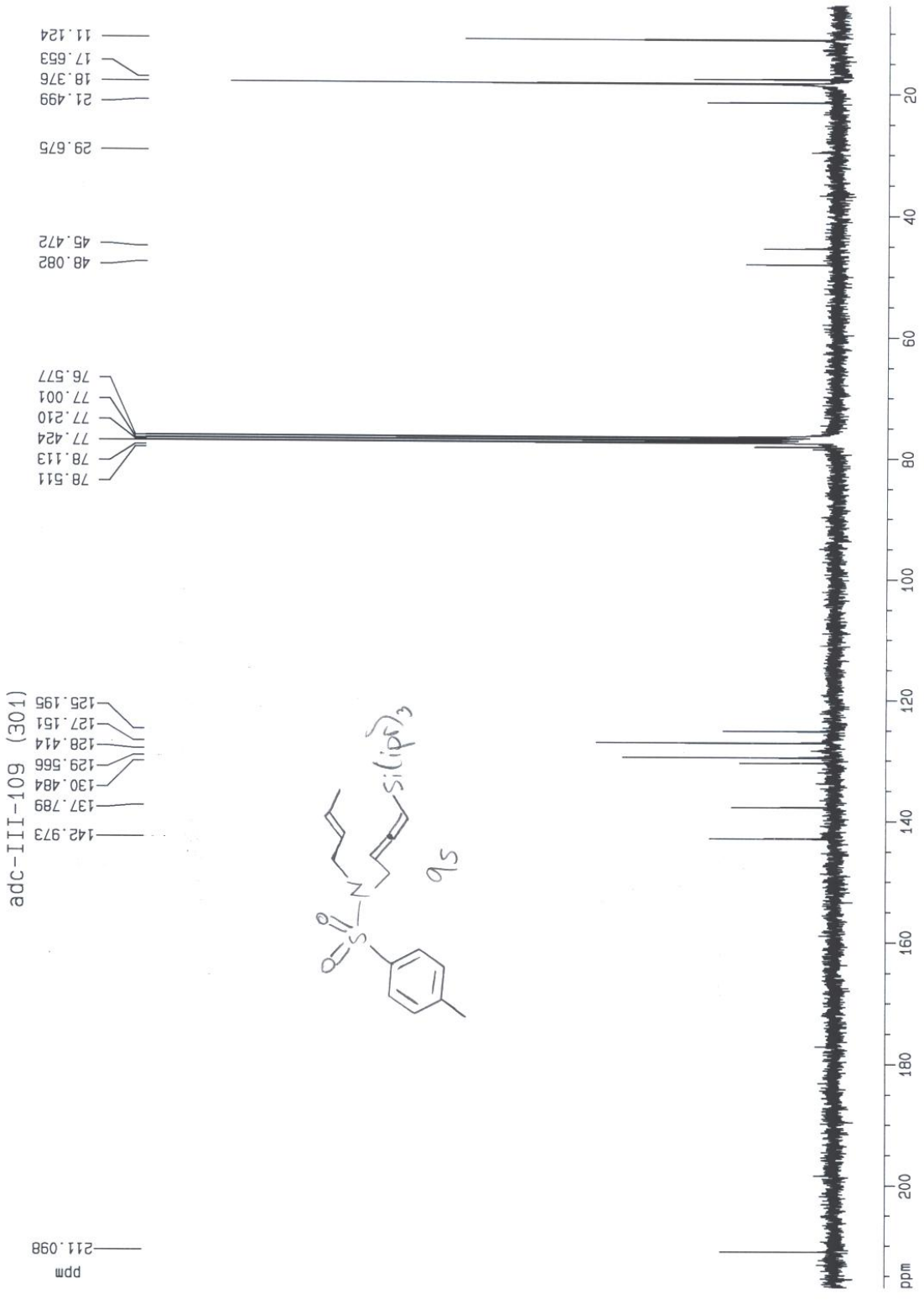
HC-III-142A dt=10sec
ppm
integral
0.85570
0.87910
0.90061
1.24923
1.26342
1.26491
1.28073
1.29771
1.32582
1.42408
1.44500
1.61498
1.61791
1.62064
1.63810
1.64097
1.64365
1.93130
1.94067
2.42485
3.76403
3.77163
3.78812
3.79571
3.81488
3.82286
3.83674
3.84476
3.89074
3.91377
4.89013
4.90164
4.92217
4.93339
5.09467
5.11612
5.25852
5.26464
5.29468
5.30060
5.58165
5.60475
7.27118
7.27693
7.30349
7.54894
7.69733
7.70324
7.71930
7.72503
7.73143
3.593
10.281
1.693
3.178
2.085
3.000
2.241
2.023
1.038
1.039
1.305
1.023
2.201
2.107
TsN
C6H13
9q

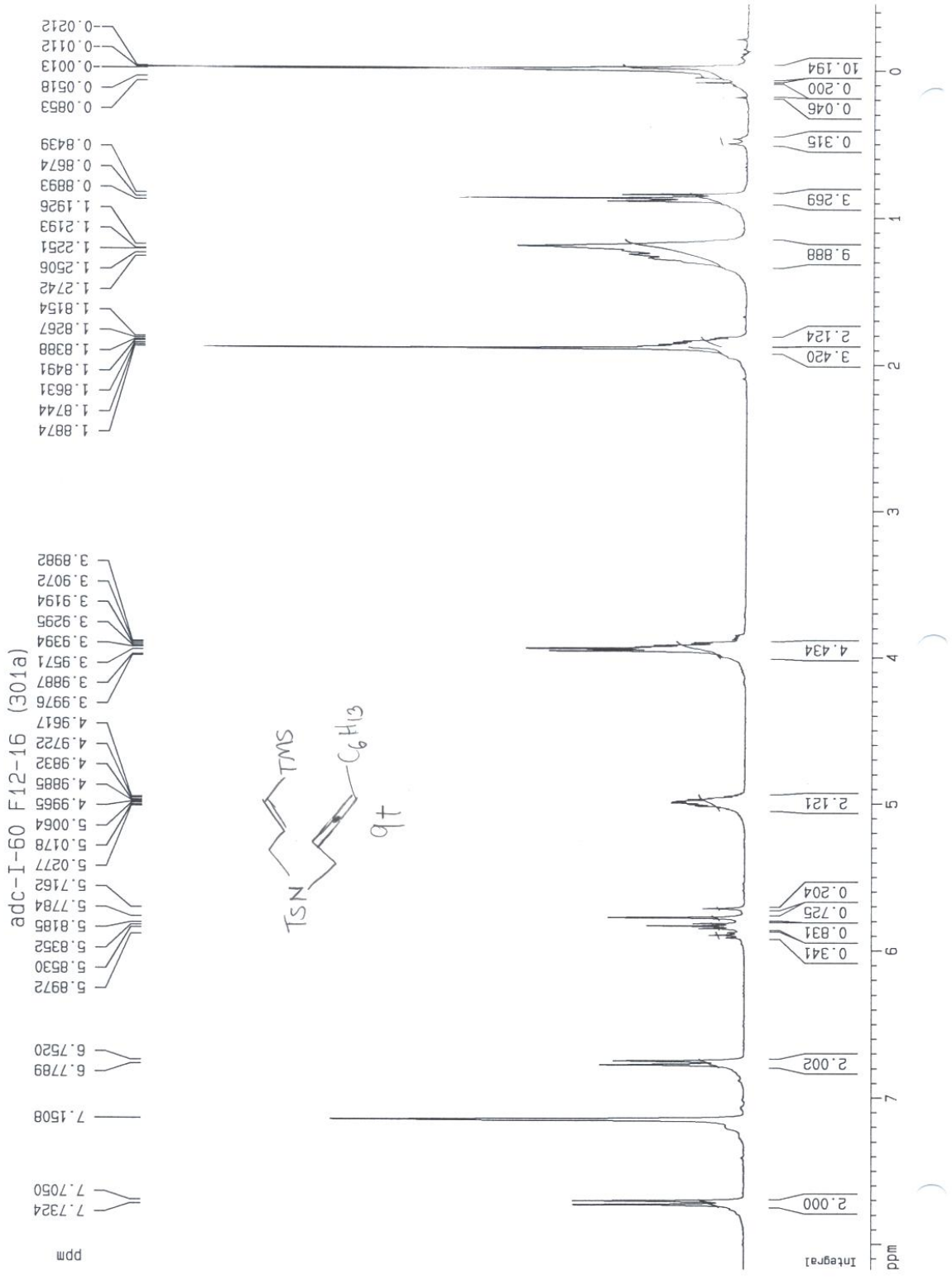

HC-III-142A d1=3sec CDCl3
ppm
205.068
142.981
137.889
129.558
128.326
127.218
124.952
92.576
86.720
77.432
77.008
76.584
74.259
46.461
43.003
31.602
30.418
29.106
28.943
28.701
28.568
23.814
22.561
21.564
21.434
13.988
12.811
C6H13
9q
ppm
200
180
160
140
120
100
80
60
40
20

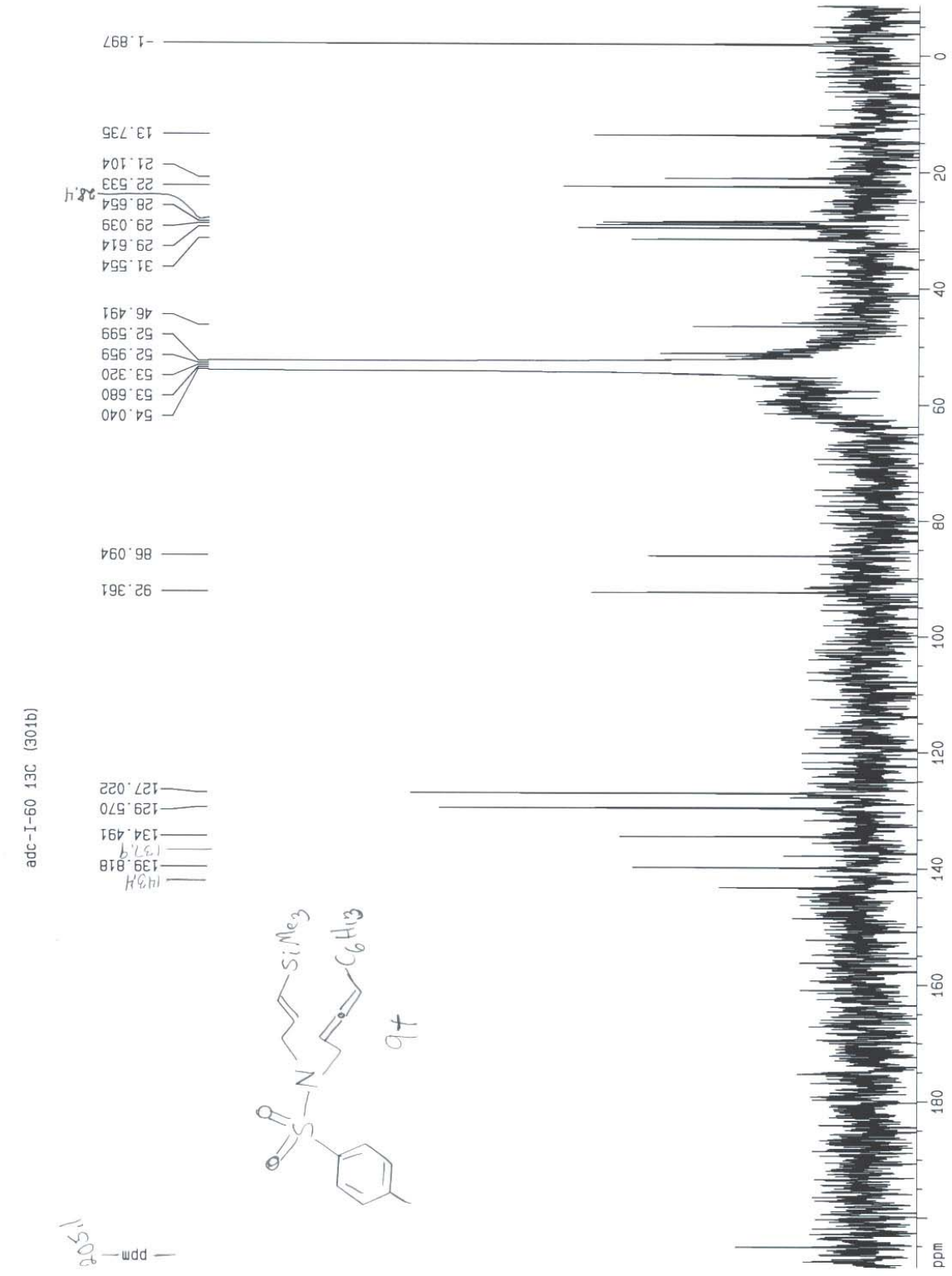

adc-III-112 (301b)
ppm
Integral
TsN
Ph
TIPS
+
TsN
Ph
TIPS
9r ~ 1 : 0.22

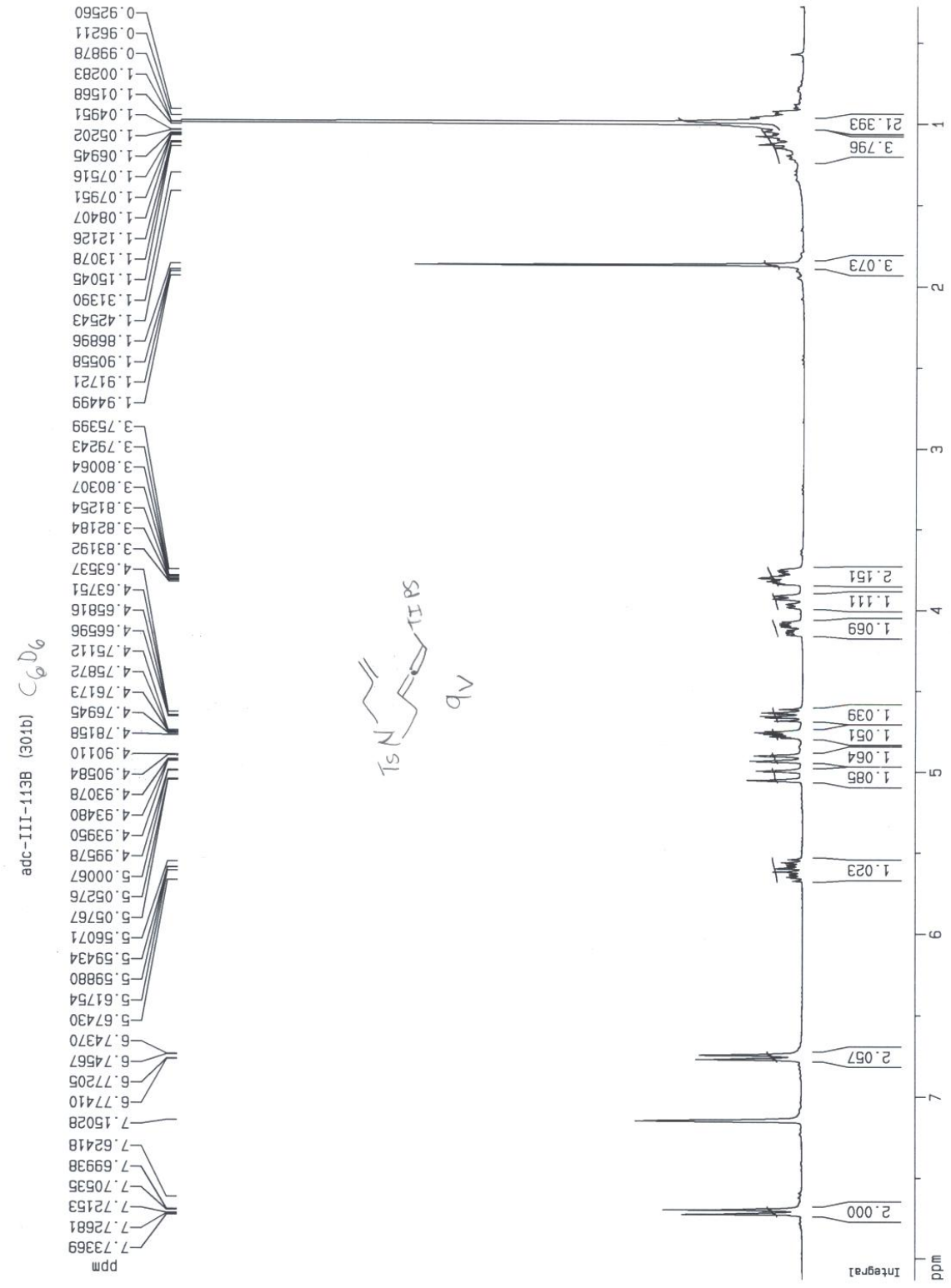
adc-III-112 13C (301)
ppm
211.530
211.460
144.054
143.795
138.008
136.754
134.031
131.807
130.071
129.897
128.842
128.772
128.638
128.577
128.413
128.110
128.009
127.475
126.729
124.295
82.163
78.516
78.263
77.877
54.520
54.160
53.799
53.438
53.078
48.879
46.563
21.592
21.510
18.695
18.536
11.551
11.513
11.475
TIPS
TIPS
0.22 : 1
ppm

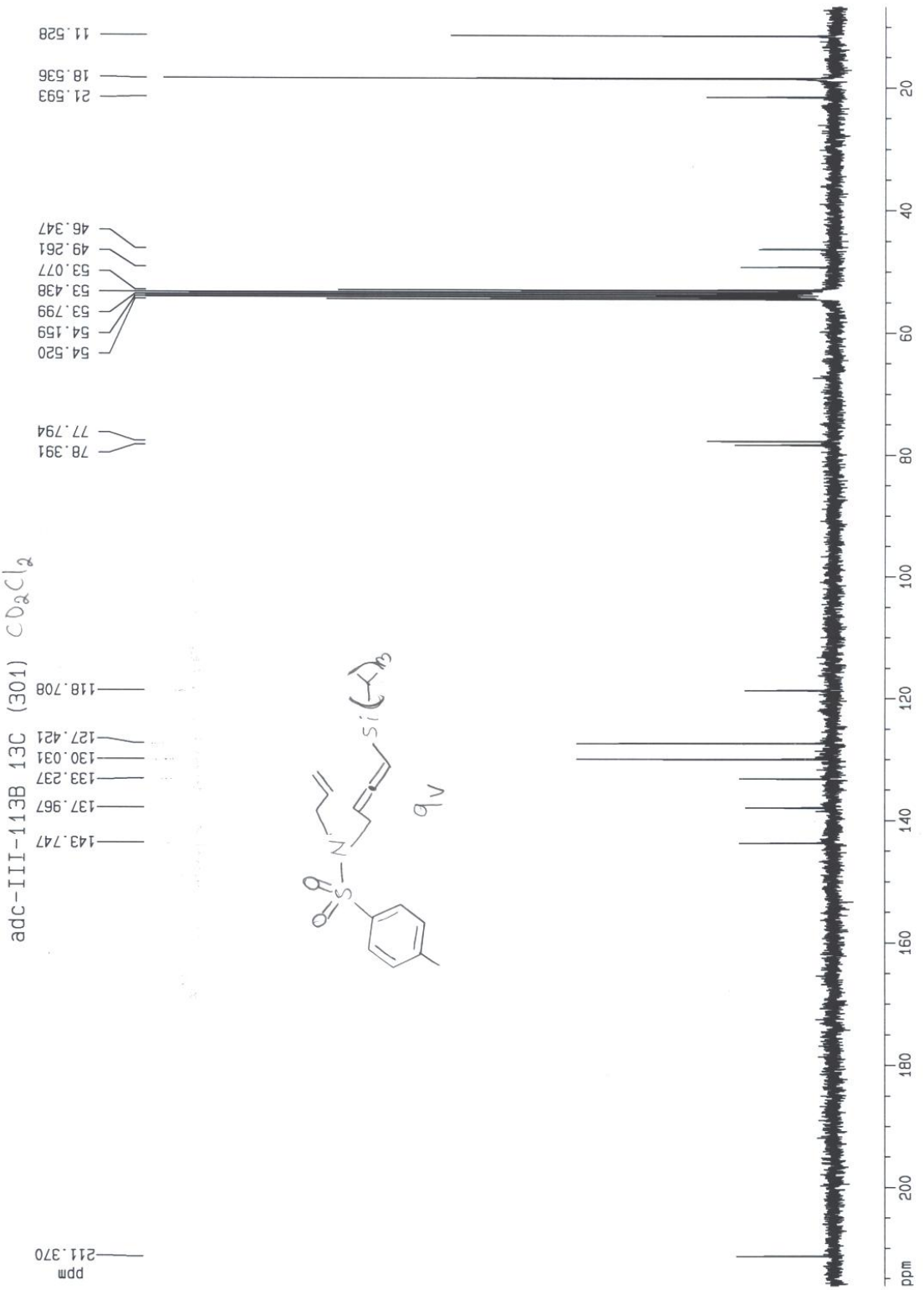

adc-III-109 (301b)
ppm
Integral
TsN
TIPS
9s

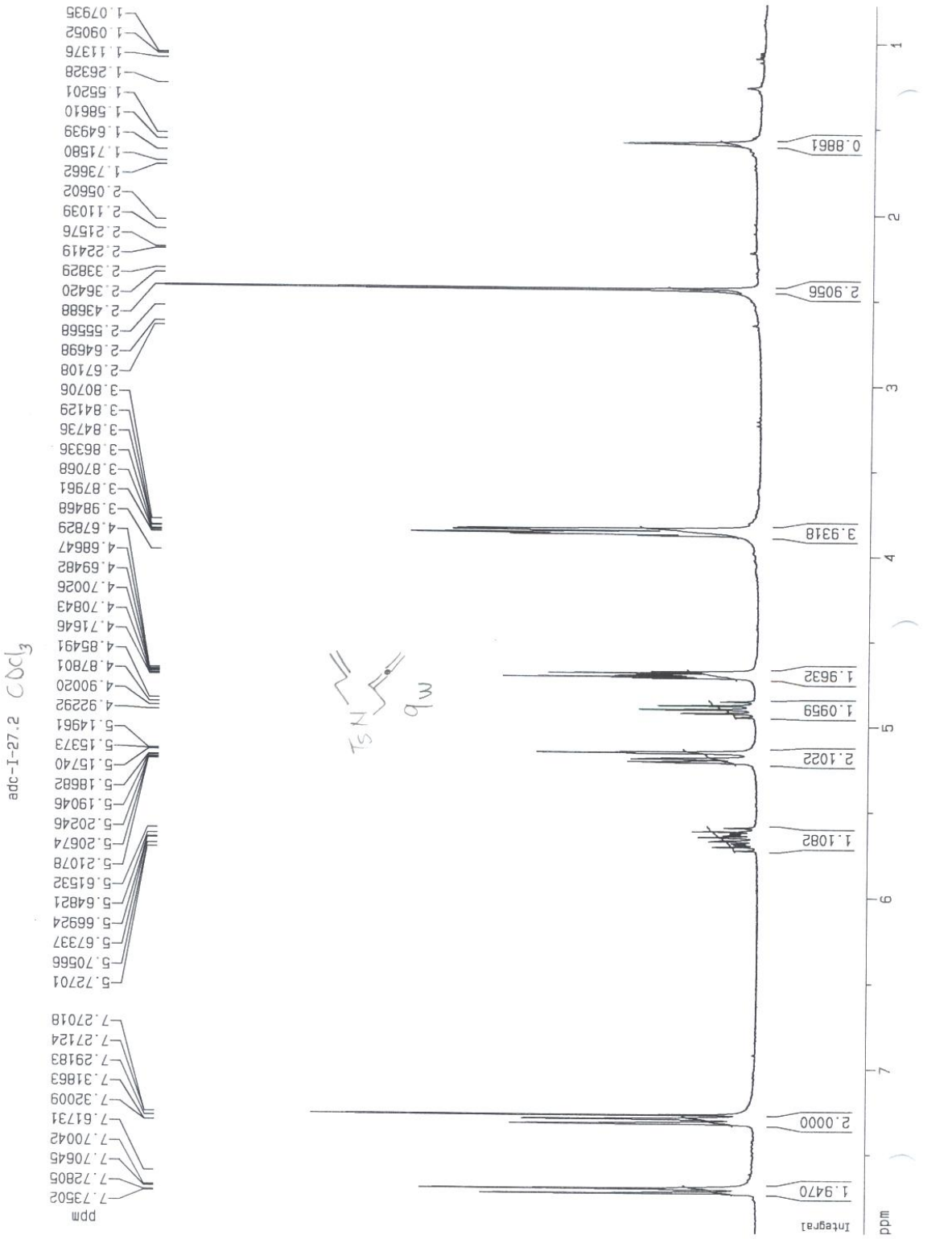

adc-III-109 (301)
ppm
211.098
142.973
137.789
130.484
129.566
128.414
127.151
125.195
78.511
78.113
77.424
77.210
77.001
76.577
48.082
45.472
29.675
21.499
18.376
17.653
11.124
Si(iPr)3
9s
ppm

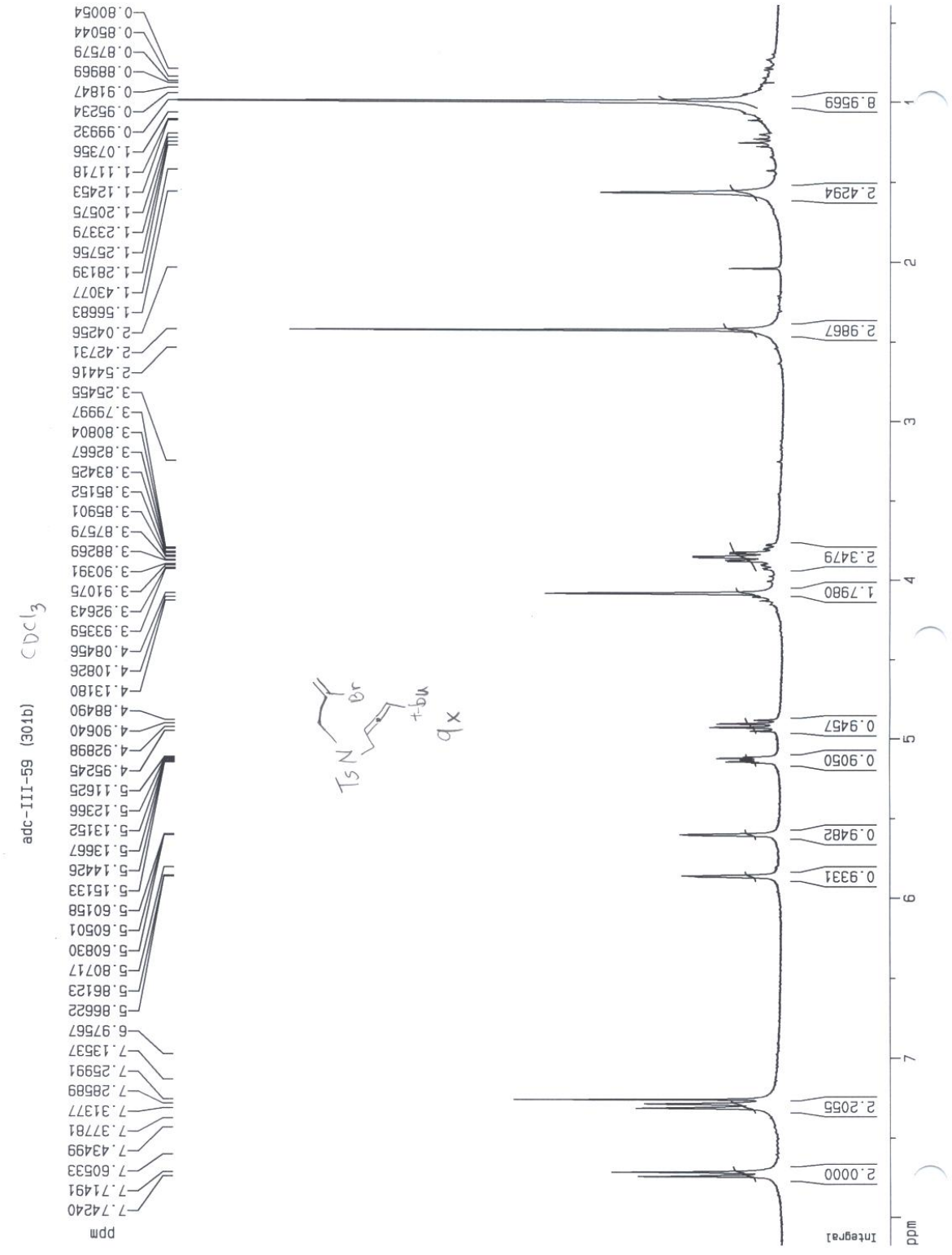

adc-I-60 F12-16 (301a)
ppm
Integral
TMS
C_6H_{13}
TsN
qt


adc-I-60 13C (301b)
-1.897
13.735
21.104
22.533
28.654
29.039
29.614
31.554
46.491
52.599
52.959
53.320
53.680
54.040
86.094
92.361
127.022
129.570
134.491
137.9
139.818
143.3H
ppm
SiMe3
C6H13
9t


adc-III-113B (301b) C6D6
ppm
7.73369
7.72681
7.72153
7.70535
7.69938
7.62418
7.15028
6.77410
6.77205
6.74567
6.74370
5.67430
5.61754
5.59880
5.59434
5.56071
5.05767
5.05276
5.00067
4.99578
4.93950
4.93480
4.93078
4.90584
4.90110
4.78158
4.76945
4.76173
4.75872
4.75112
4.66596
4.65816
4.63751
4.63537
3.83192
3.82184
3.81254
3.80307
3.80064
3.79243
3.75399
1.94499
1.91721
1.90558
1.86896
1.42543
1.31390
1.15045
1.13078
1.12126
1.08407
1.07951
1.07516
1.06945
1.05202
1.04951
1.01568
1.00283
0.99878
0.96211
0.92560
TsN
TIPS
9v
Integral
2.000
2.057
1.023
1.085
1.064
1.051
1.039
1.069
1.111
2.151
3.073
3.796
21.393
ppm

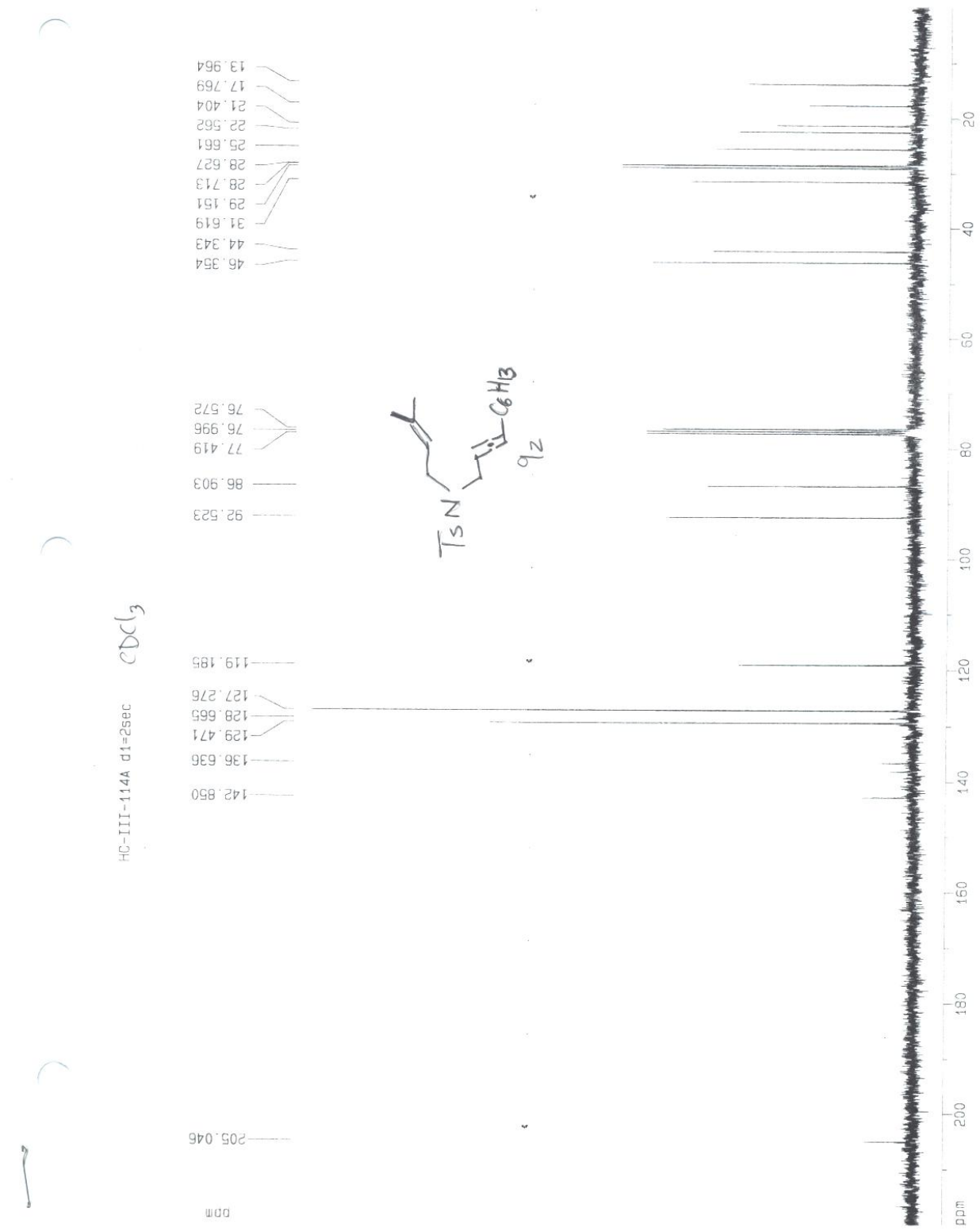

adc-III-113B 13C (301) CD_2Cl_2
ppm
211.370
143.747
137.967
133.237
130.031
127.421
118.708
78.391
77.794
54.520
54.159
53.799
53.438
53.077
49.261
46.347
21.593
18.536
11.528
ppm
20
40
60
80
100
120
140
160
180
200
9v

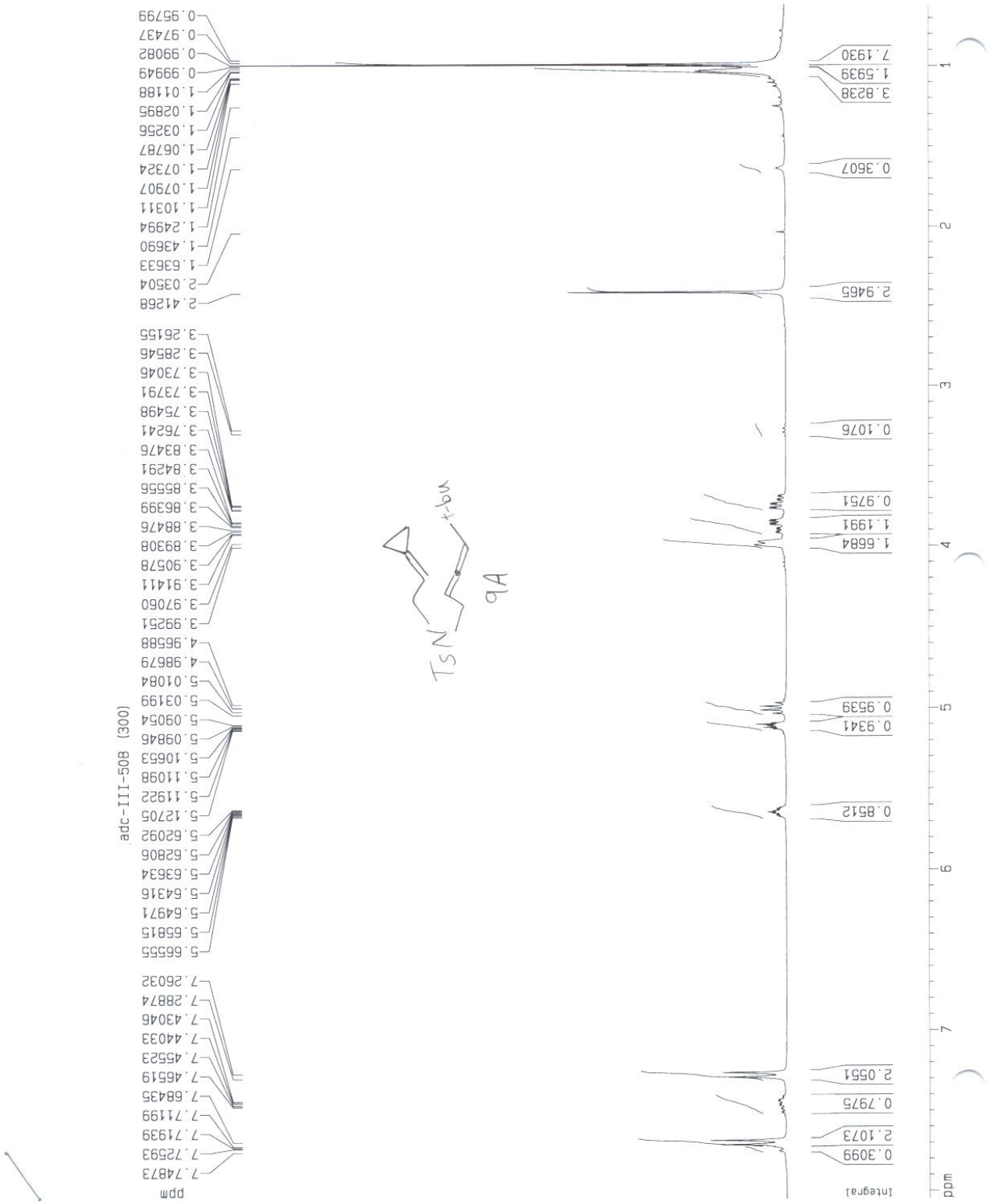

adc-I-27.2 CDCl3
TsN
9w
ppm
Integral
0.8861
2.9056
3.9318
1.9632
1.0959
2.1022
1.1082
2.0000
1.9470


adc-III-59 (301b)
CDCl3
ppm
Integral
2.0000
2.2055
0.9331
0.9482
0.9050
0.9457
1.7980
2.3479
2.9867
2.4294
8.9569
Ts N
Br
+Bu
9x

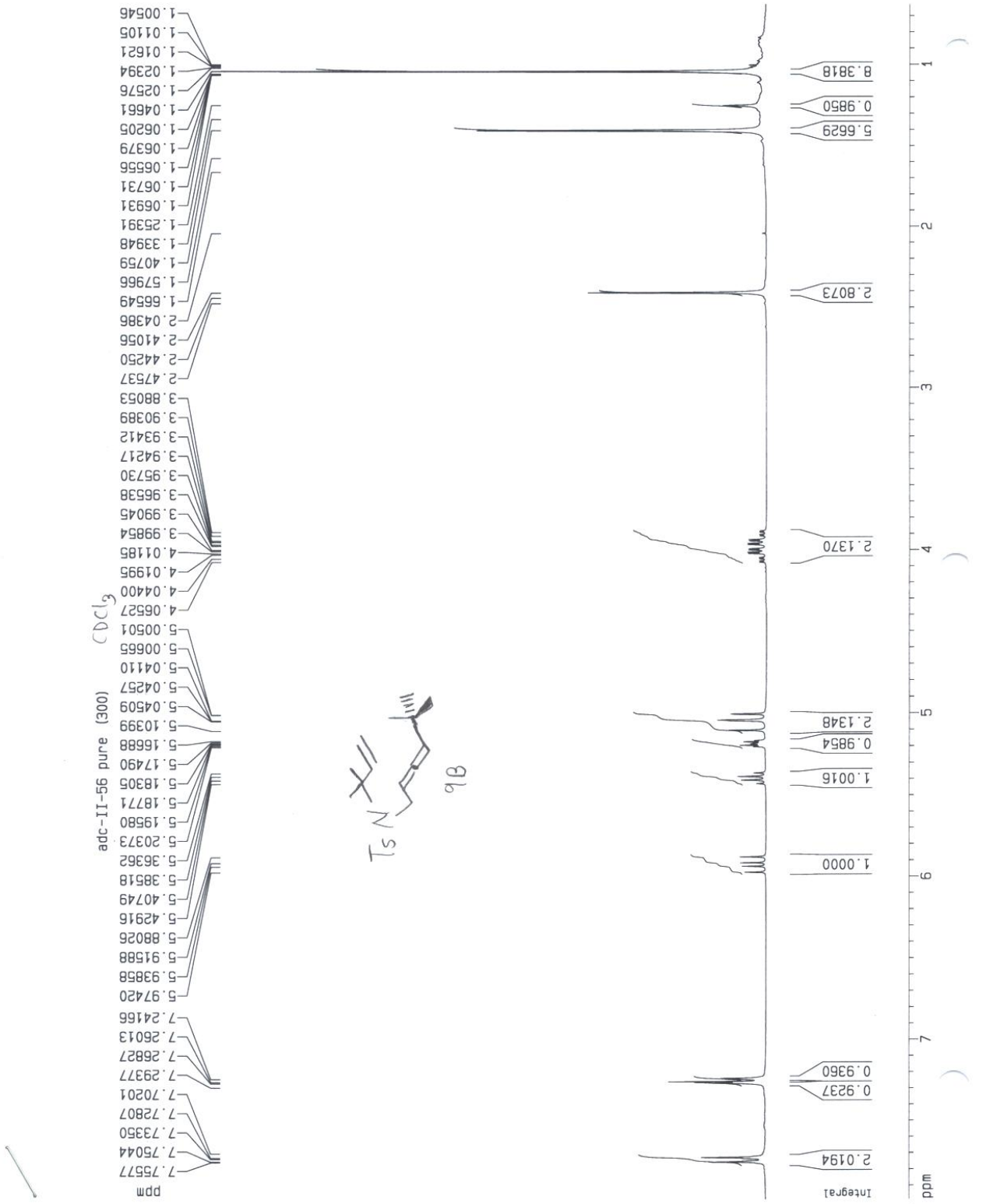
HC-III-084A d1=6sec
ppm
integral
0.87168
1.26053
1.42625
1.44717
1.57726
1.57894
1.58051
1.58234
1.58640
1.59785
1.60263
1.60831
1.62161
1.63158
1.65843
1.67326
2.42501
3.77562
3.78286
3.79840
3.80597
3.82063
3.84446
4.84960
4.86046
4.87122
4.88178
5.01707
5.03154
5.03614
5.04070
5.04527
5.05070
5.05985
5.06454
5.06818
5.08111
5.08342
5.10454
7.22238
7.27040
7.29994
7.67269
7.68157
7.68834
7.69426
7.70014
7.71016
7.71602
6.0714
2.9812
3.0000
3.8693
0.7992
1.8132
2.1025
1.8764
Ts
N
Ph

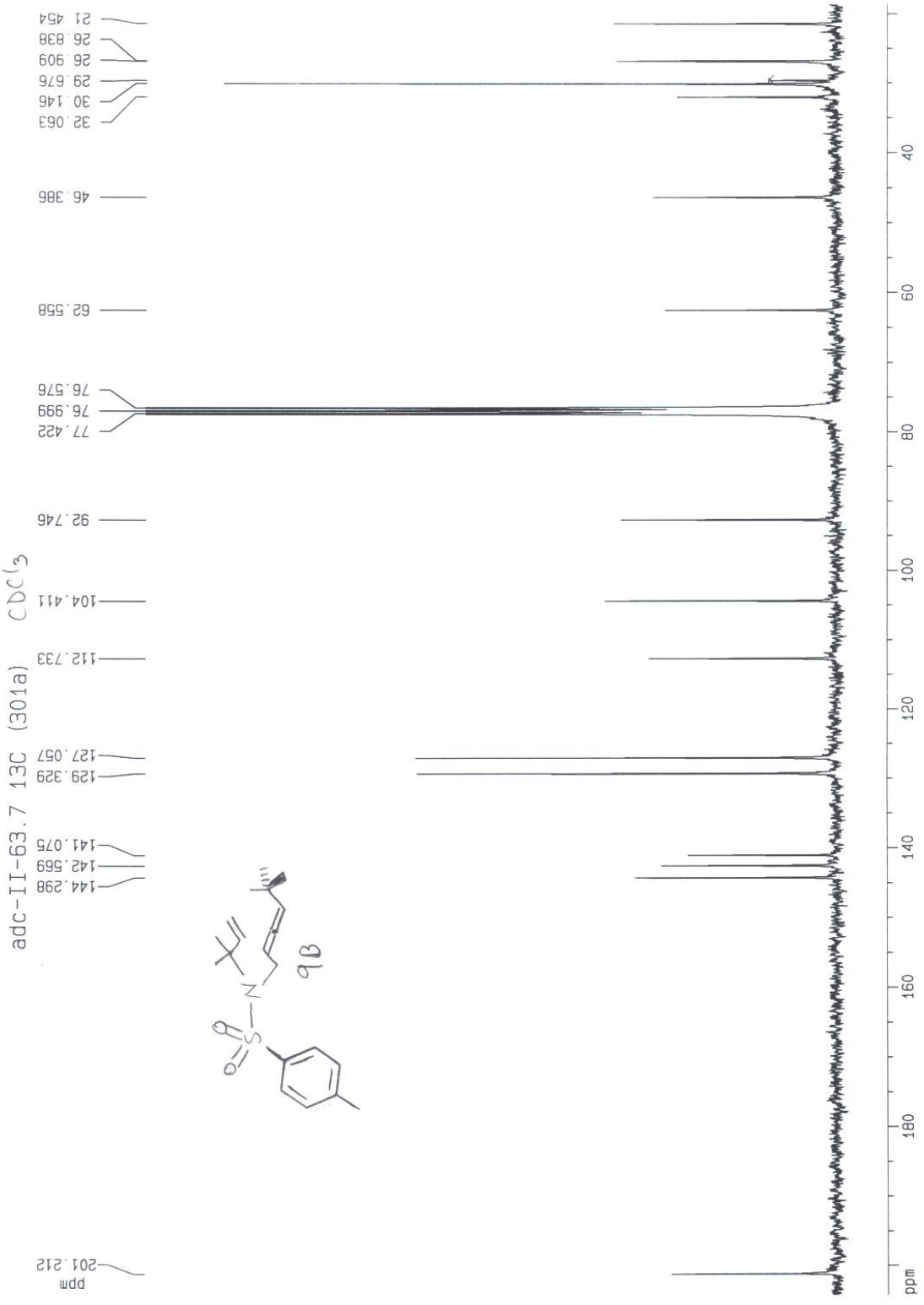
HC-III-114A d1=6sec
ppm
Integral
7.72208
7.71554
7.70972
7.69388
7.68786
7.68146
7.33737
7.33311
7.32401
7.29760
7.27024
5.11050
5.08918
5.06617
5.04693
5.04228
5.03760
5.01877
4.90316
4.89152
4.88011
3.84814
3.82874
3.82237
3.80797
3.79985
3.79364
3.78582
3.76970
3.76197
2.42498
1.95735
1.94198
1.93275
1.67279
1.66993
1.63000
1.62829
1.35307
1.32827
1.30093
1.28487
1.27409
1.26897
1.26615
1.25271
0.90401
0.89712
0.88208
0.85887
3.2641
9.6496
6.2458
2.0824
3.0000
4.2873
0.9979
1.9920
2.2055
1.9785
TsN
C6H13
9z

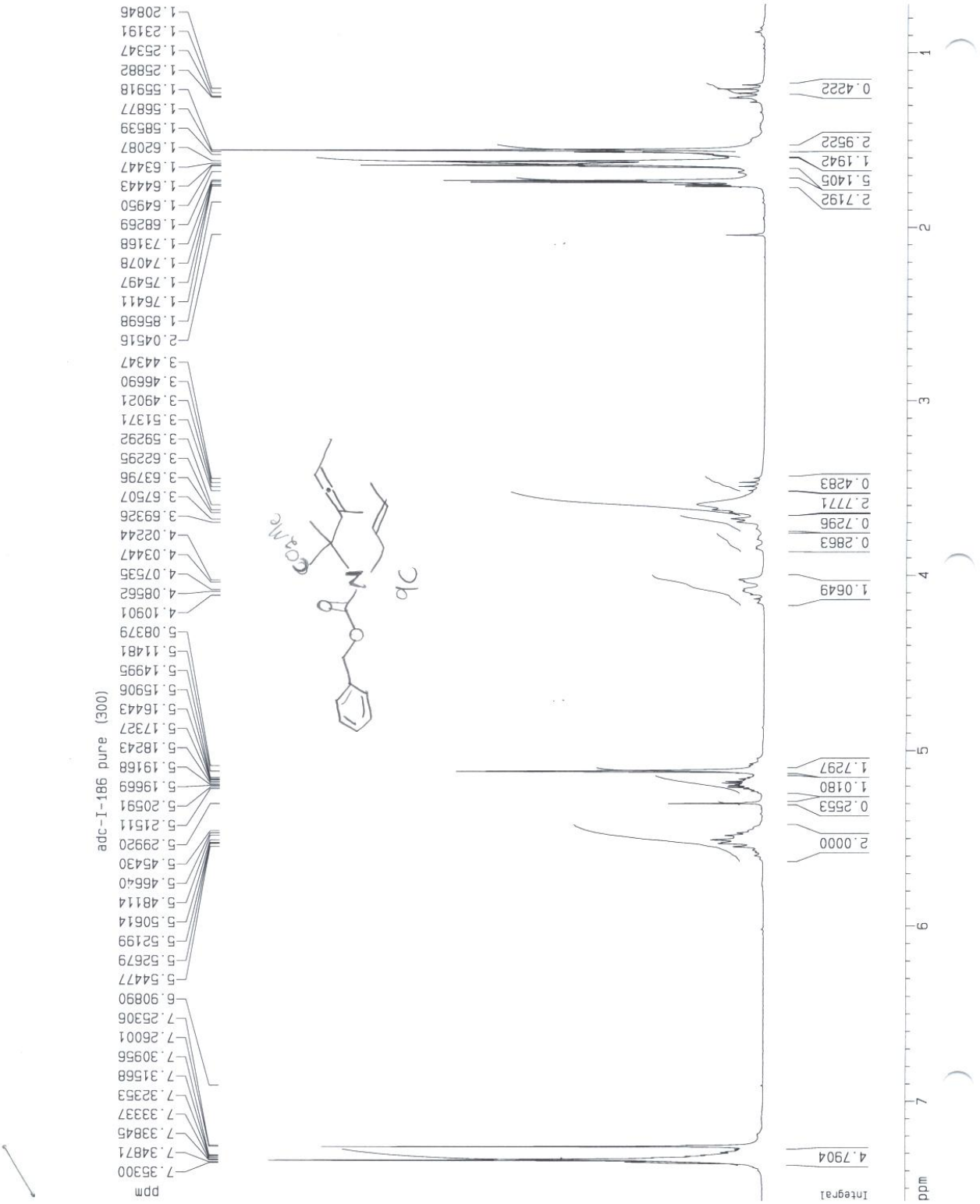

HC-III-114A d1=2sec
CDCl3
205.046
142.850
136.636
129.471
128.665
127.276
119.185
92.523
86.903
77.419
76.996
76.572
46.354
44.343
31.619
29.151
28.713
28.627
25.661
22.562
21.404
17.769
13.964
TsN
C6H13
9z
ppm


adc-III-50B (300)
ppm
Integral
TsN
t-bu
9A

adc-III-50B
CD_2Cl_2
ppm
202.737
143.660
138.474
132.699
132.559
131.989
131.951
130.019
129.002
128.838
127.726
127.636
127.604
127.572
127.534
127.439
113.348
104.856
104.785
89.178
54.520
54.160
53.800
53.440
53.080
48.515
47.332
47.109
42.071
32.098
30.406
30.345
30.315
30.282
30.222
30.153
30.121
30.063
30.033
29.971
21.615
13.790
2.672
2.219
t-bu
9A
ppm

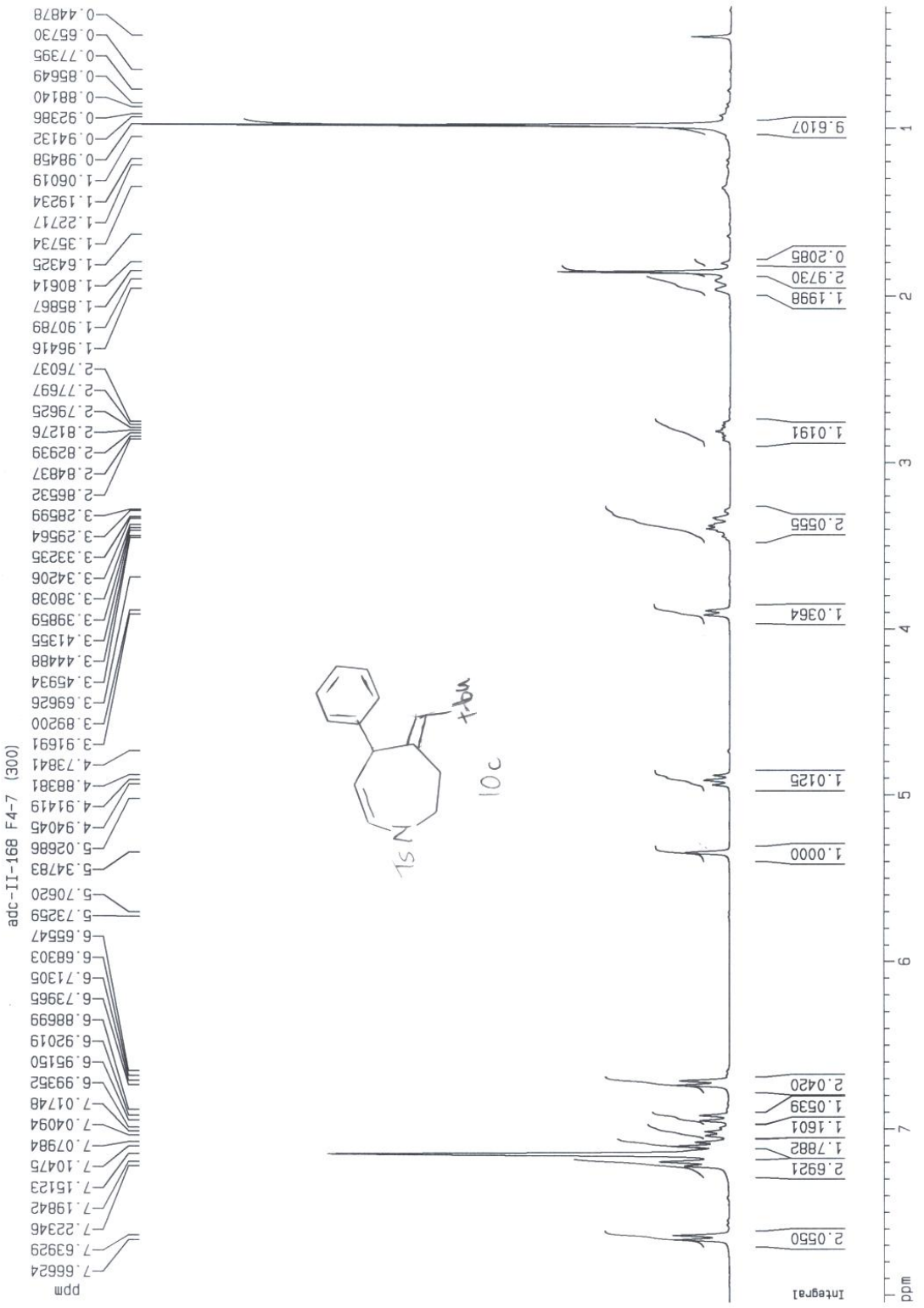

adc-II-56 pure (300)
CDCl3
ppm
Integral
9B
Ts
N

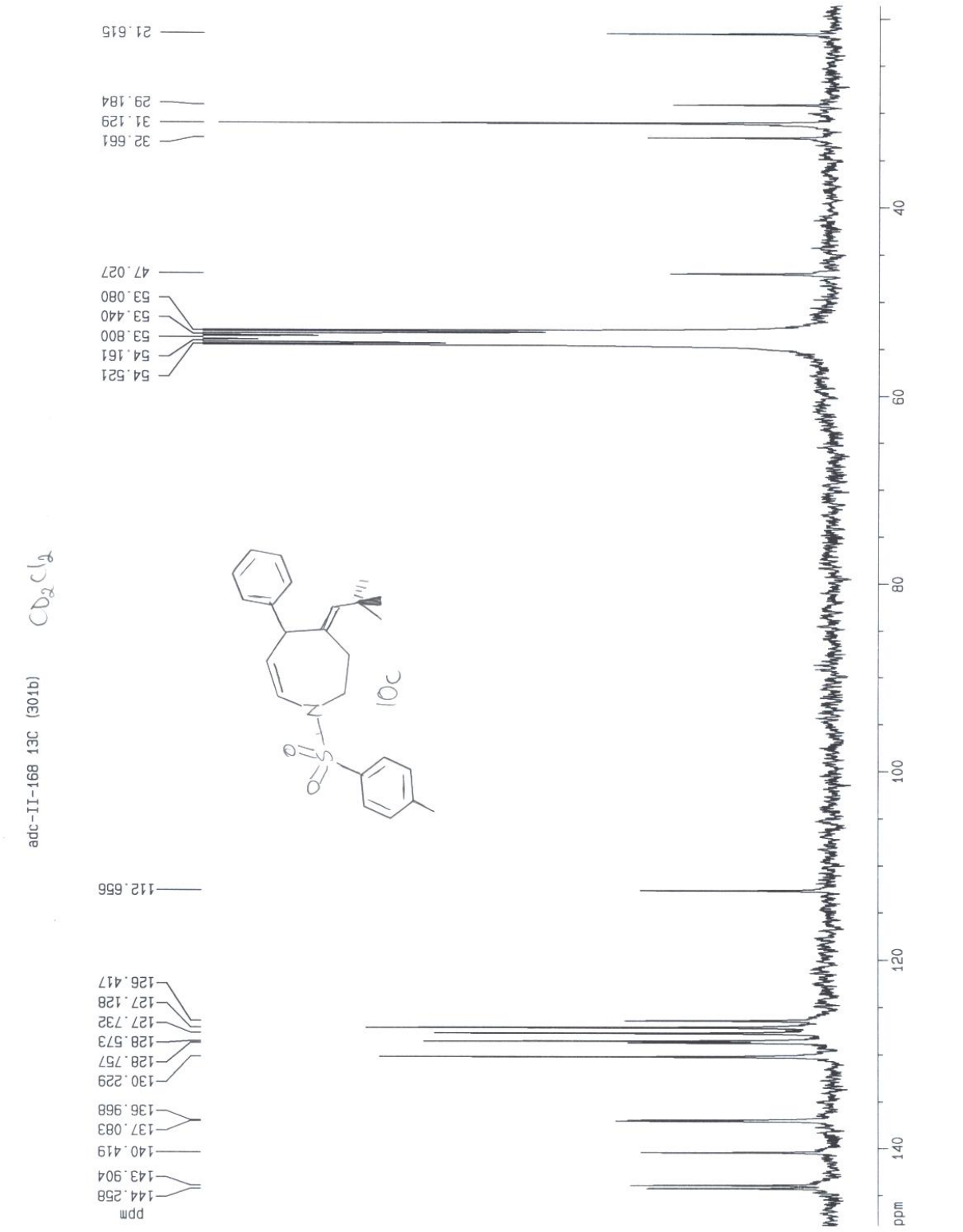

adc-II-63.7 13C (301a) CDCl3
201.212
144.298
142.569
141.075
129.329
127.057
112.733
104.411
92.746
77.422
76.999
76.576
62.558
46.386
32.063
30.146
29.676
26.909
26.838
21.454
ppm
9B

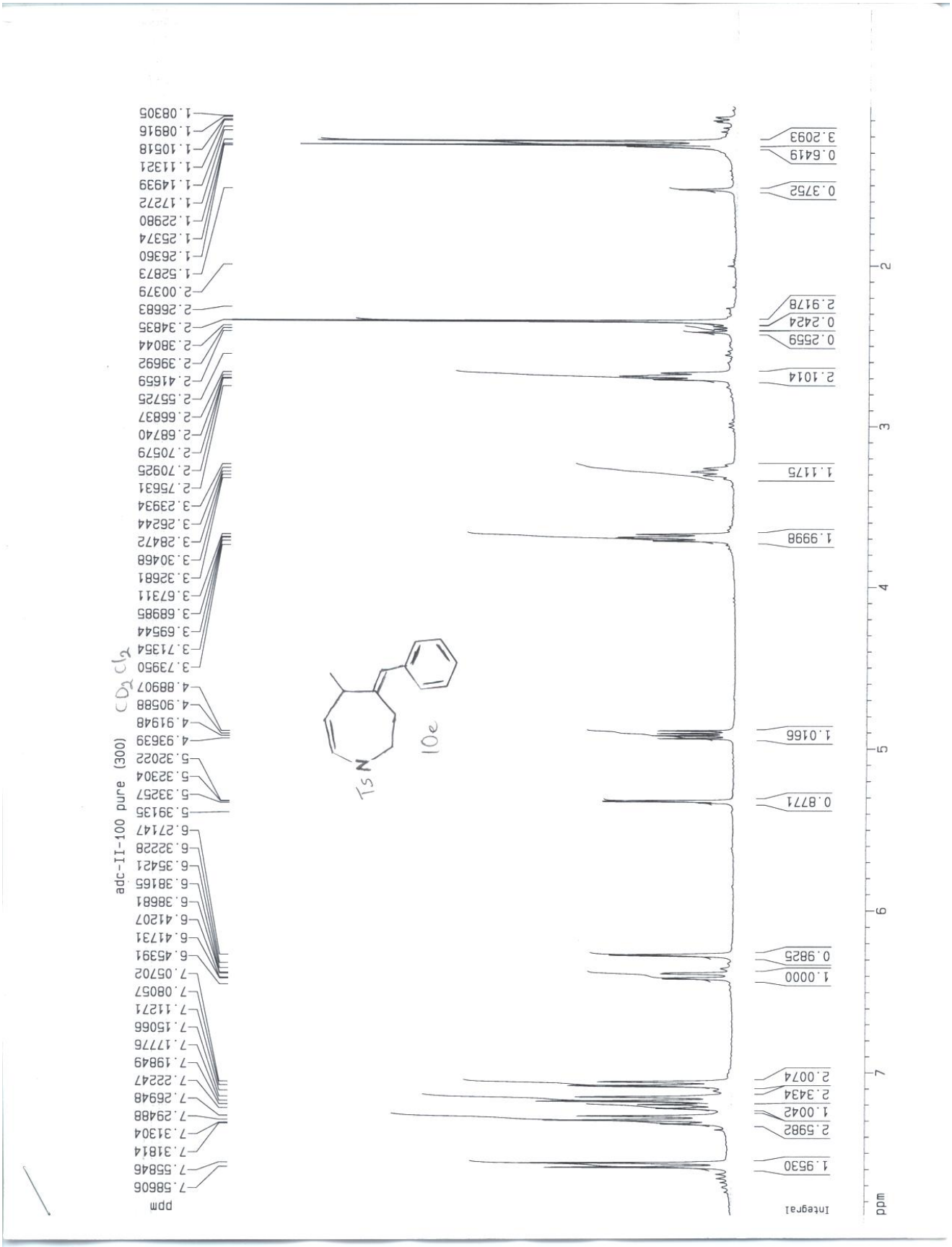

adc-I-186 pure (300)
ppm
Integral
9c
CO2Me

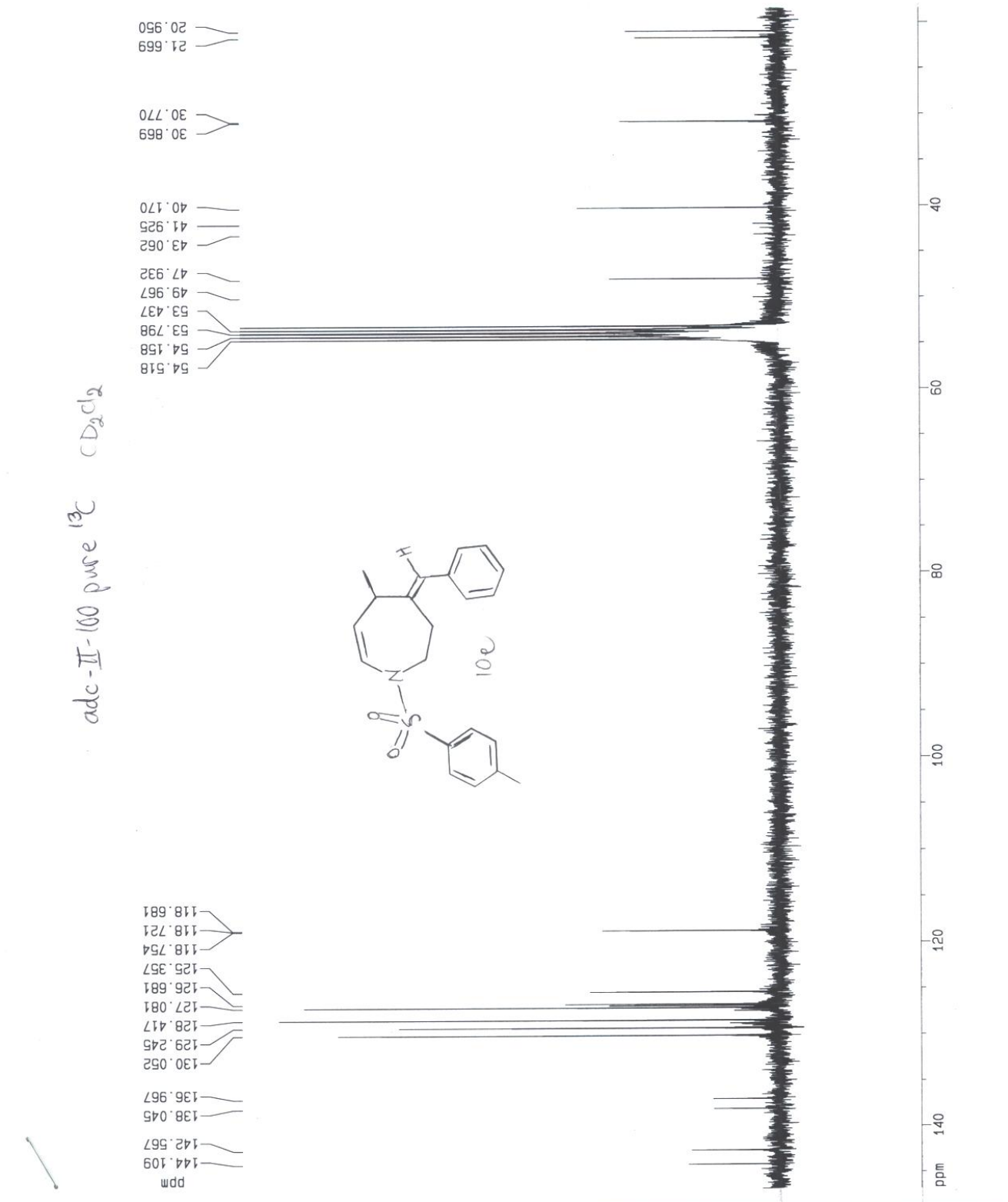
B.2 AZEPINES

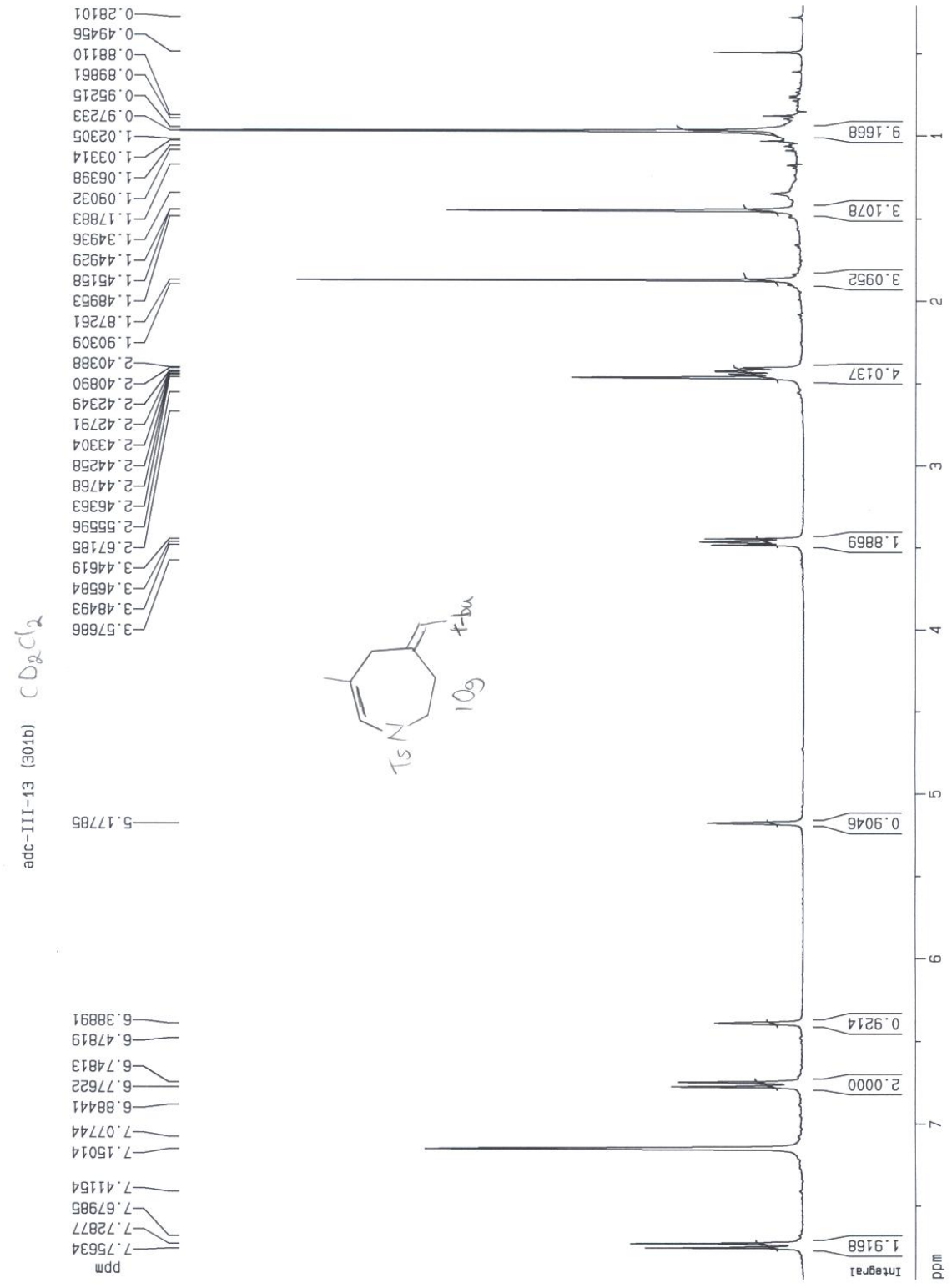
The ^{1}H NMR and ^{13}C spectra for each azepine are reported sequentially.


adc-II-168 F4-7 (300)
ppm
7.66624
7.63929
7.22346
7.19842
7.15123
7.10475
7.07984
7.04094
7.01748
6.99352
6.95150
6.92019
6.88699
6.73965
6.71305
6.68303
6.65547
5.73259
5.70620
5.34783
5.02686
4.94045
4.91419
4.88381
4.73841
3.91691
3.89200
3.69626
3.45934
3.44488
3.41355
3.39859
3.38038
3.34206
3.33235
3.29564
3.28599
2.86532
2.84837
2.82939
2.81276
2.79625
2.77697
2.76037
1.96416
1.90789
1.85867
1.80614
1.64325
1.35734
1.22717
1.19234
1.06019
0.98458
0.94132
0.92386
0.88140
0.85649
0.77395
0.65730
0.44878
Integral
9.6107
0.2085
2.9730
1.1998
1.0191
2.0555
1.0364
1.0125
1.0000
2.0420
1.0539
1.1601
1.7882
2.6921
2.0550
ppm
1
2
3
4
5
6
7
10c

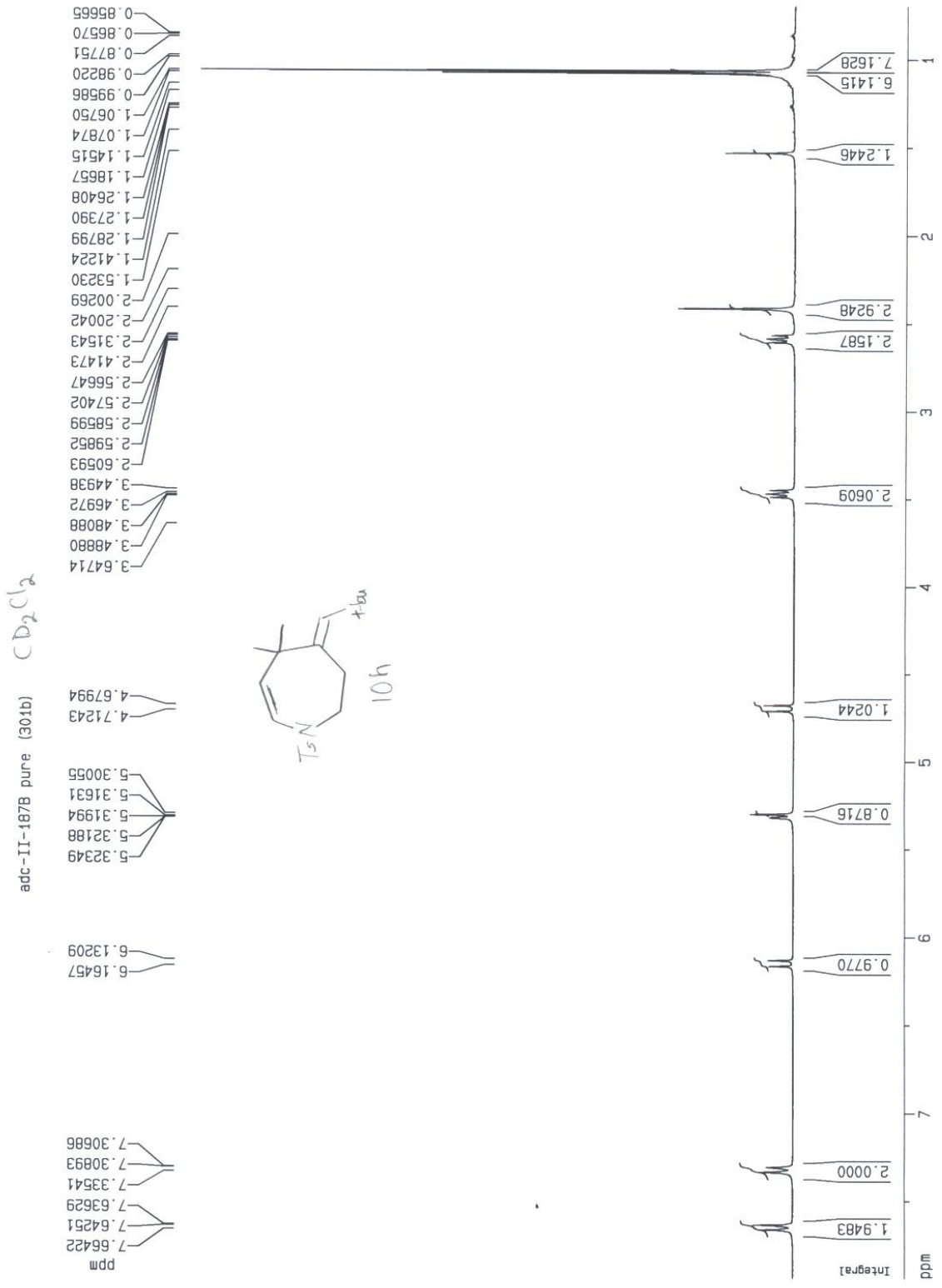

adc-II-168 13C (301b)
CD2Cl2
10c
ppm
144.258
143.904
140.419
137.083
136.968
130.229
128.757
128.573
127.732
127.128
126.417
112.656
54.521
54.161
53.800
53.440
53.080
47.027
32.661
31.129
29.184
21.615
ppm
140
120
100
80
60
40


adc-II-100 pure (300)
CD2Cl2
ppm
Integral
TsN
10e


adc-II-100 pure 13C (D2Cl2
10e
ppm
144.109
142.567
138.045
136.967
130.052
129.245
128.417
127.081
126.681
125.357
118.754
118.721
118.681
54.518
54.158
53.798
53.437
49.967
47.932
43.062
41.925
40.170
30.869
30.770
21.669
20.950
ppm 140
120
100
80
60
40


adc-III-13 (301b) CD_2Cl_2
ppm
Integral
1.9168
0.9214
2.0000
0.9046
5.17785
1.8869
4.0137
3.0952
3.1078
9.1668
Ts
N
t-Bu
10g

adc-III-13 CD2Cl2
ppm
143.895
137.944
137.222
133.174
130.082
128.647
127.091
126.115
122.928
122.618
122.575
122.268
54.518
54.157
53.796
53.696
53.664
53.435
53.336
53.244
53.075
52.945
52.461
48.481
43.713
43.394
32.623
32.353
31.300
31.214
31.121
30.052
22.747
21.904
21.606
21.545
ppm
140
120
100
80
60
40
tbu
10g


adc-II-187B pure (301b)
CD2Cl2
Integral
ppm
1.9483
2.0000
0.9770
0.8716
1.0244
4.7243
4.6799
2.0609
3.4938
2.1587
2.9248
1.2446
6.1415
7.1628
10h

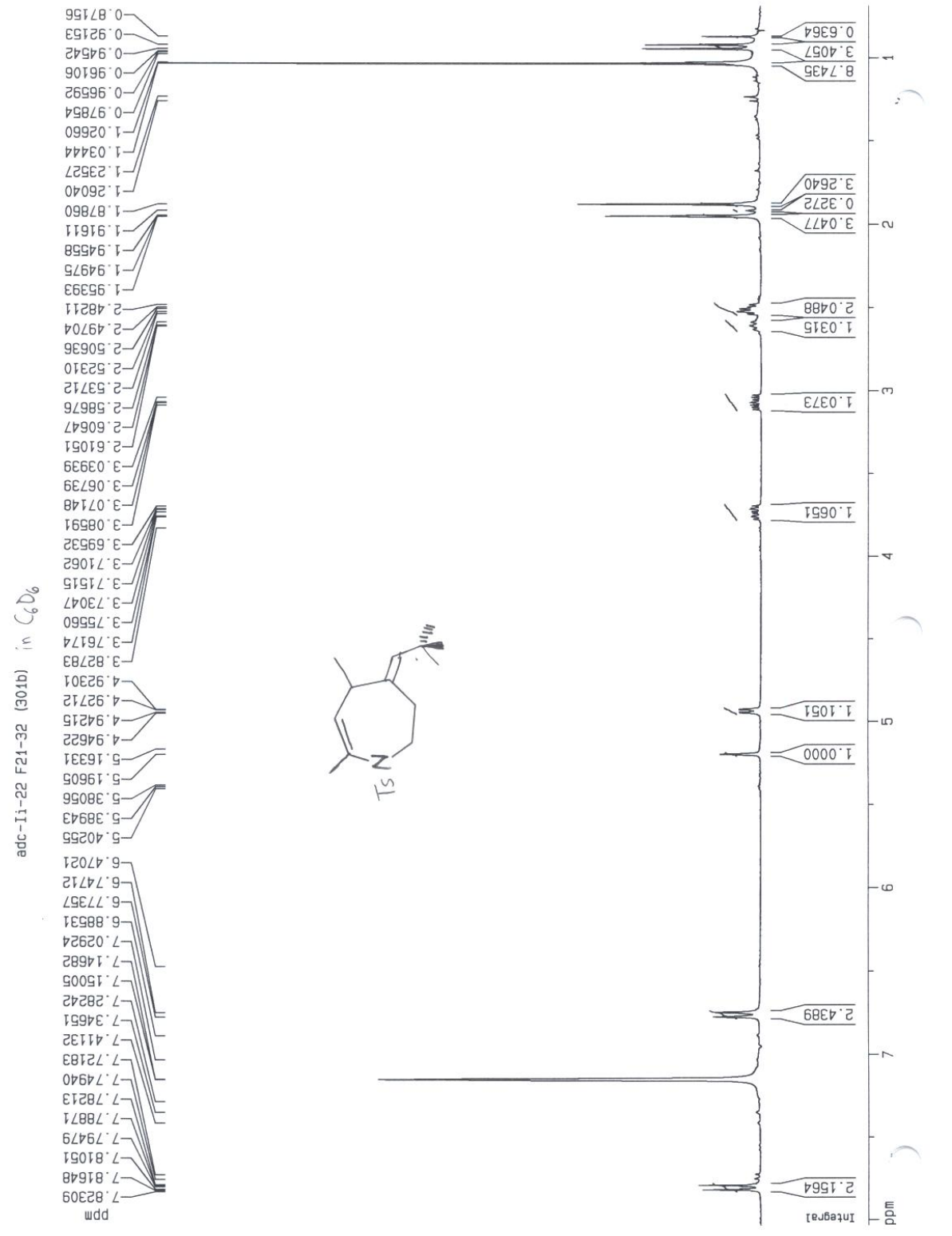
adc-II-187B pk3 13C (301) CD2Cl2
10h
ppm
144.141
141.909
136.099
134.108
130.008
127.373
125.916
122.388
54.520
54.159
53.799
53.438
53.078
50.135
42.680
32.393
31.744
30.670
27.303
21.596
ppm
140
120
100
80
60
40

adc-III-6.13 (301b) in CD_2Cl_2
ppm
7.68844
7.68185
7.67585
7.66018
7.65396
7.62773
7.37613
7.36023
7.33458
7.33332
7.30795
7.30646
7.13260
7.06422
6.12538
6.09167
6.00374
5.88957
5.74995
5.72976
5.55642
5.50493
5.43145
5.32379
5.31982
5.31679
5.19029
3.72563
3.68223
3.66601
3.65991
3.64381
3.44983
3.43160
3.41912
3.40094
3.37562
2.98450
2.61090
2.41836
2.22106
2.21706
2.18470
2.17233
2.16771
2.15087
2.13756
1.93494
1.80316
1.79356
1.78529
1.78052
1.77525
1.54275
1.54213
1.45849
1.43187
1.42639
1.41831
1.08102
0.91550
Integral
1.9294
2.0000
0.9100
1.2722
0.9880
0.9834
0.9946
1.0157
3.0162
2.2930
1.3444
2.3149
1.2091
2.2154
1.7215
8.7669
0.2921
0.2815
ppm
1
2
3
4
5
6
7
TsN
10i
t-Bu

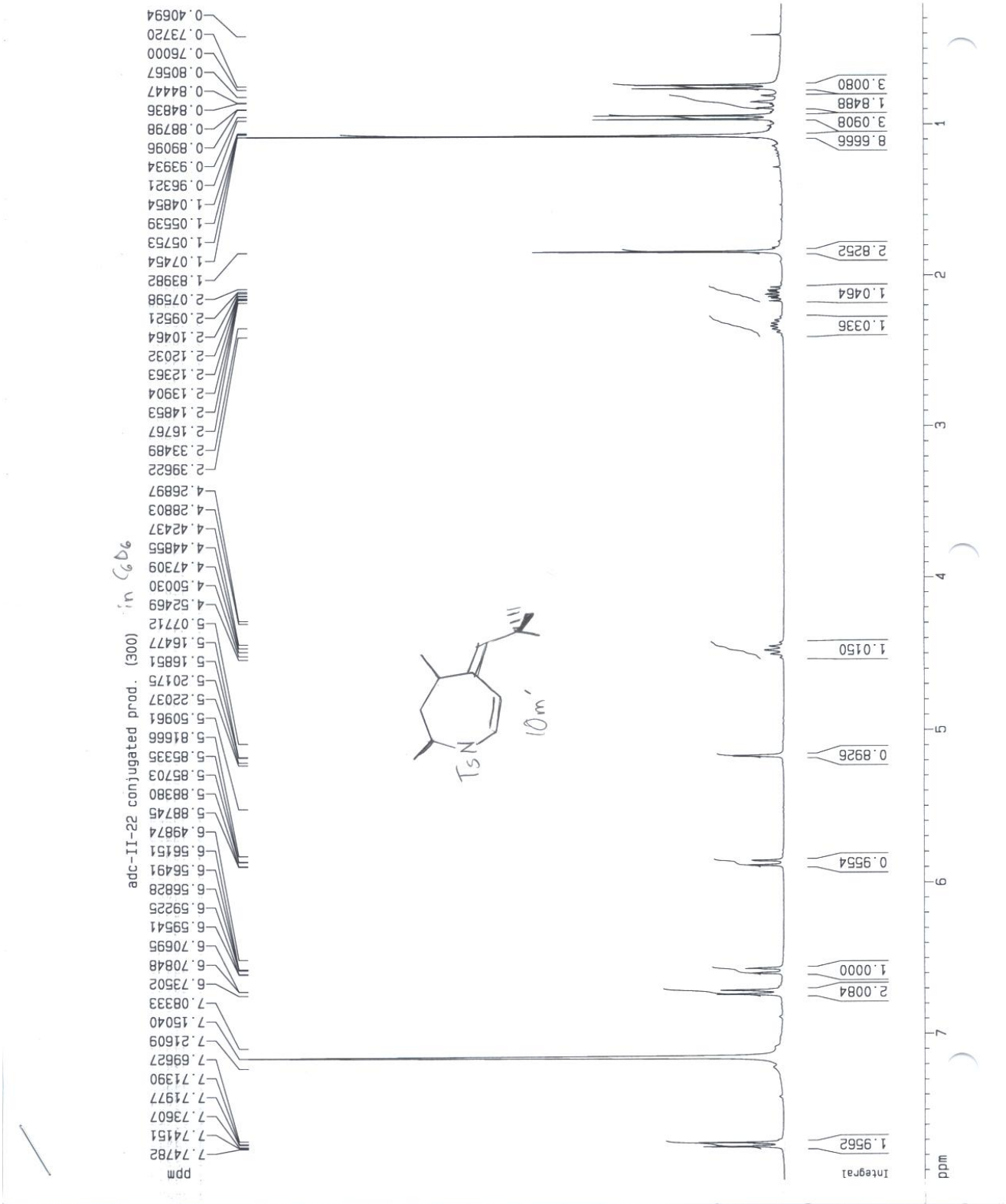
adc-III-6.13A 13C (301) CD2Cl2
10i
ppm
143.860
138.536
137.540
136.861
132.896
130.008
127.284
119.886
54.849
54.519
54.159
53.798
53.437
53.077
50.550
35.754
35.557
32.463
31.460
29.394
27.983
26.954
21.588
ppm
40
60
80
100
120
140

adc-I-25 (301b)
CD_2Cl_2
ppm
7.87465
7.84715
7.68138
7.67466
7.65323
7.64684
7.52491
7.51095
7.32530
7.29699
7.20490
6.36051
6.32967
5.60939
5.51931
5.42831
5.40000
5.32287
5.31994
5.31638
5.21805
5.15071
5.12670
5.10335
4.98153
4.96039
4.95057
4.92956
3.64252
3.62887
3.61204
3.59910
3.54906
3.53466
3.52710
3.51235
2.77376
2.74948
2.61075
2.56034
2.54428
2.52855
2.41092
2.21758
1.80479
1.78220
1.76370
1.52816
1.34837
1.32950
1.32473
1.30222
1.28696
1.23850
1.20009
0.89737
0.87533
0.86223
0.85195
0.83837
0.81463
Integral
6.714
14.158
2.585
2.783
1.248
3.159
1.297
1.132
1.154
1.134
1.030
1.046
0.985
2.055
2.000
ppm
1
2
3
4
5
6
7
Ts
N
101

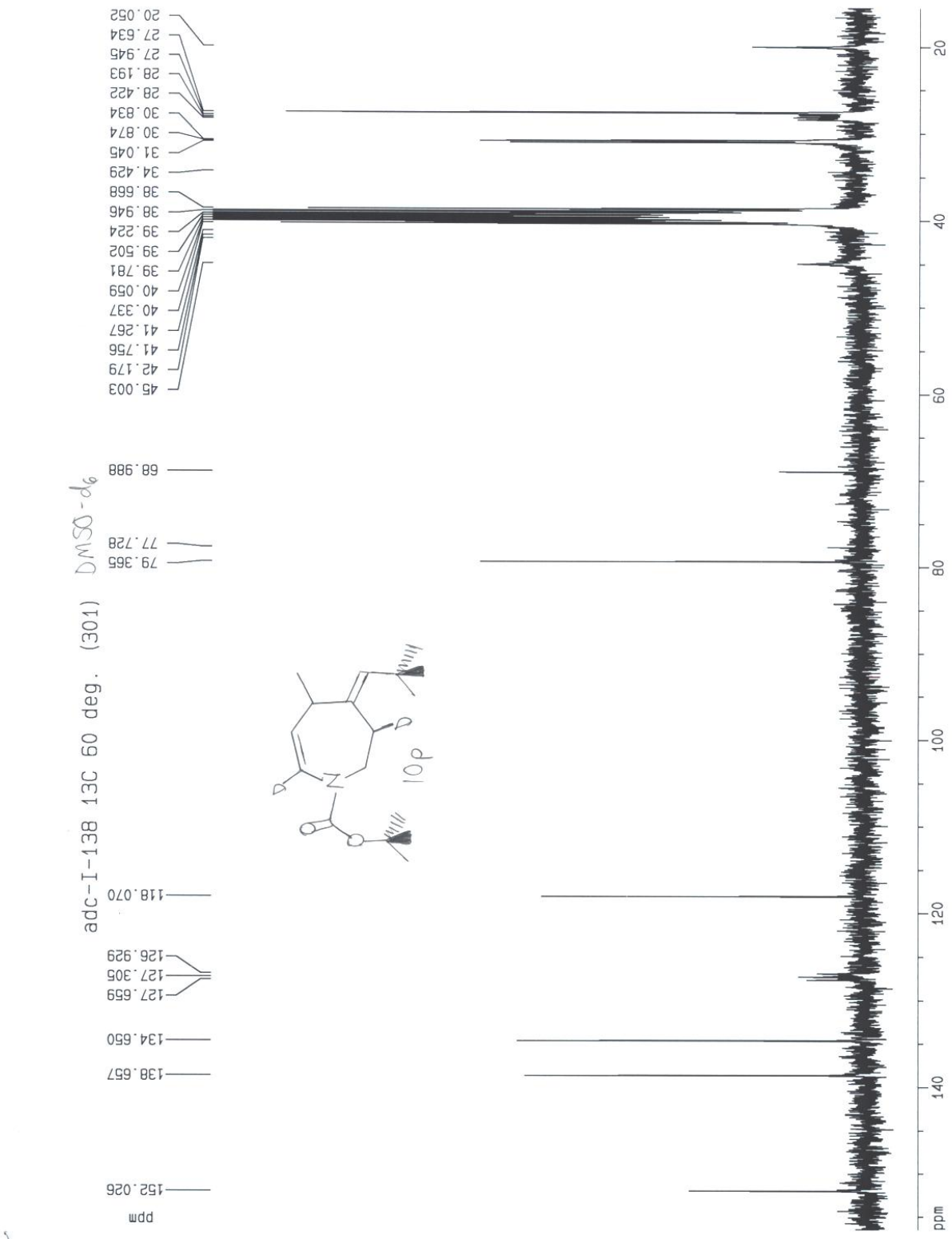
adc-I-25 13C (301) CD_2Cl_2
101
ppm
144.019
137.142
130.038
127.673
127.134
126.461
118.896
54.524
54.163
53.803
53.642
53.442
53.312
53.081
48.662
47.358
37.443
32.095
29.964
29.351
28.365
27.771
23.005
21.590
21.060
14.212
14.057
ppm
20
40
60
80
100
120
140

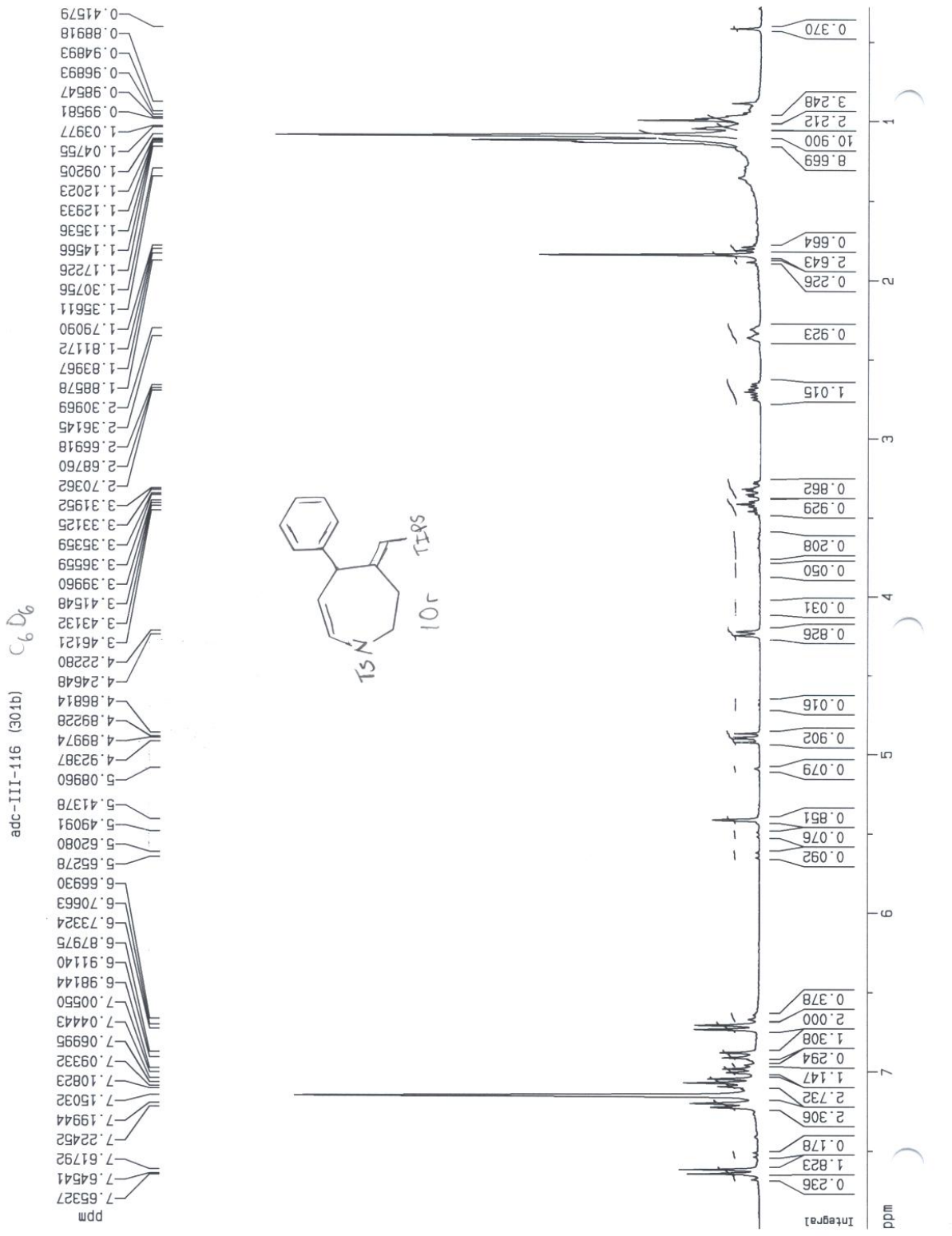

adc-Ii-22 F21-32 (301b) in C6D6
ppm
Integral
2.1564
2.4389
1.0000
1.1051
1.0651
1.0373
1.0315
2.0488
3.0477
0.3272
3.2640
8.7435
3.4057
0.6364
Ts
N

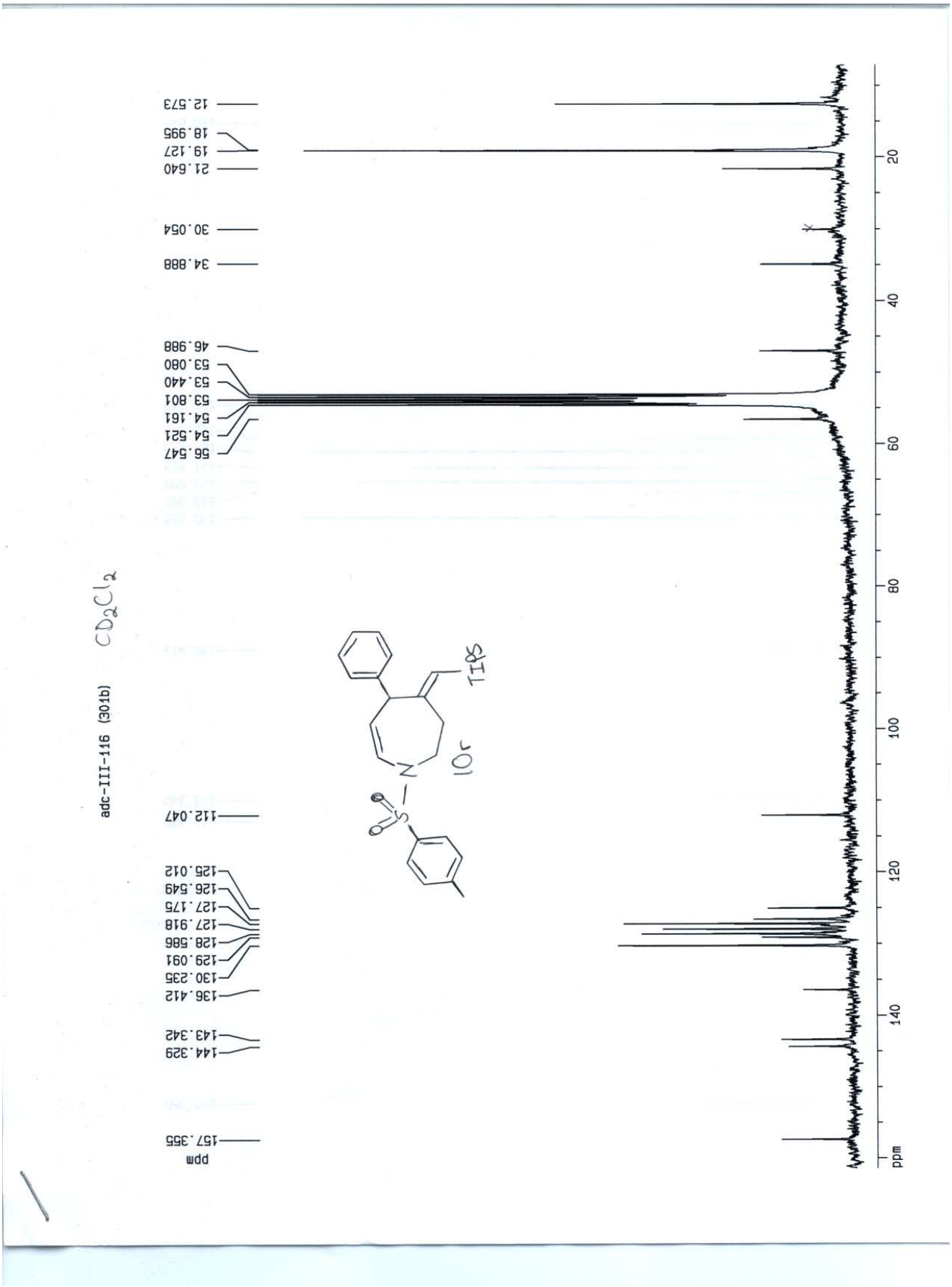
adc-II-22 F21-32 (301b) CD2Cl2
ppm
143.371
138.734
136.840
135.504
134.075
131.175
129.593
128.389
127.027
62.349
54.243
53.883
53.523
53.163
52.802
49.251
39.781
31.782
31.346
31.023
29.550
21.790
21.296
19.222
CDCl3
ppm 140 120 100 80 60 40 20

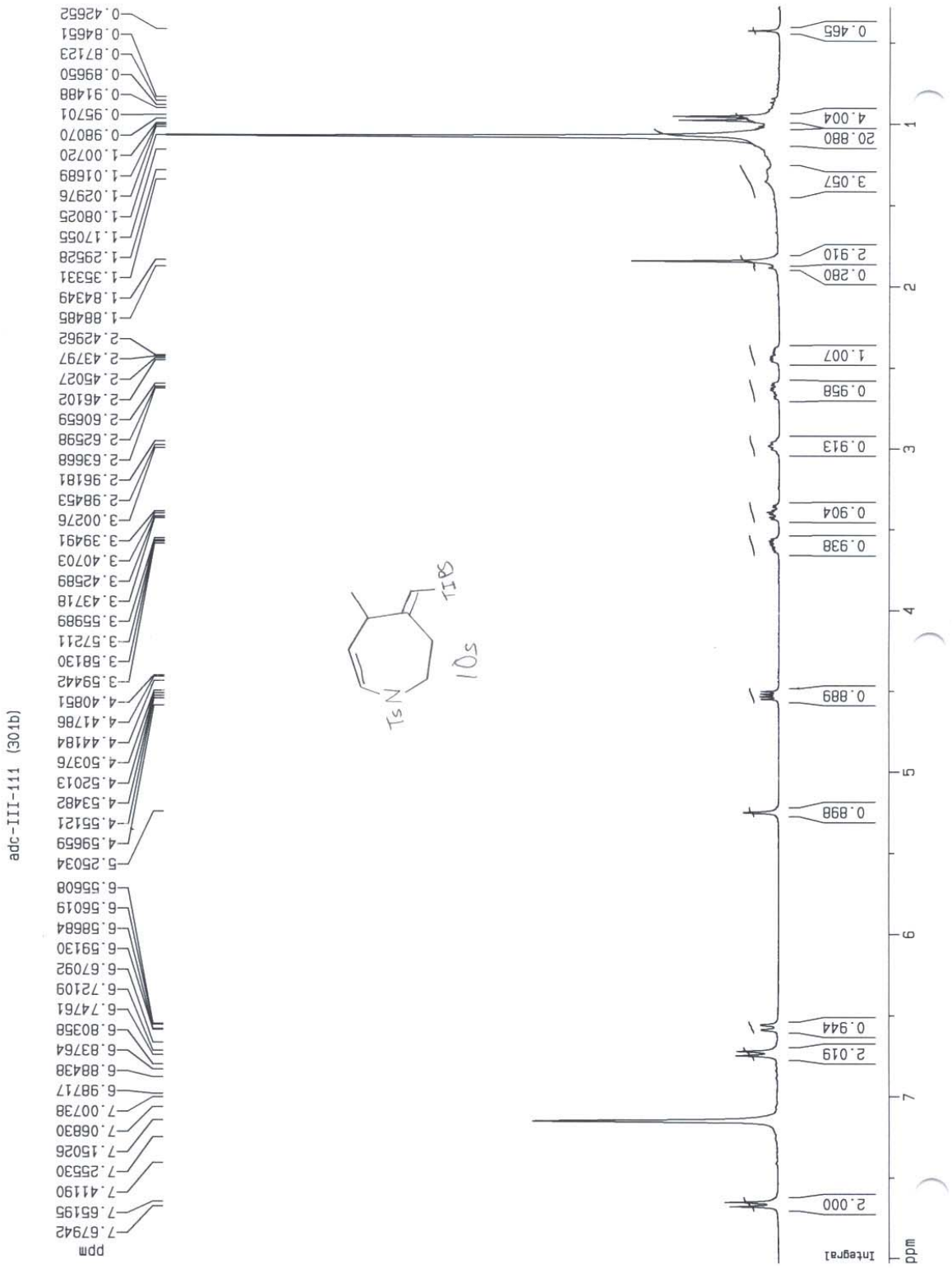

adc-II-22 conjugated prod. (300) in C6D6
ppm
7.7478
7.7415
7.7360
7.7197
7.7139
7.6962
7.2160
7.1504
7.0833
6.7502
6.7084
6.7069
6.5954
6.5922
6.5682
6.5649
6.5615
6.4987
5.8874
5.8838
5.8570
5.8533
5.8166
5.5096
5.2203
5.2017
5.1685
5.1647
5.0771
4.5246
4.5003
4.4730
4.4485
4.2423
4.2880
4.2689
2.3962
2.3348
2.1676
2.1485
2.1390
2.1236
2.1203
2.1046
2.0952
2.0759
1.8398
1.0754
1.0575
1.0553
1.0485
0.9632
0.9393
0.8909
0.8879
0.8483
0.8444
0.8056
0.7600
0.7372
0.4069
Integral
1.9562
1.0000
2.0084
0.9554
0.8926
1.0150
1.0336
1.0464
2.8252
8.6656
3.0908
1.8488
3.0080
ppm
1
2
3
4
5
6
7
Ts
N
10m'

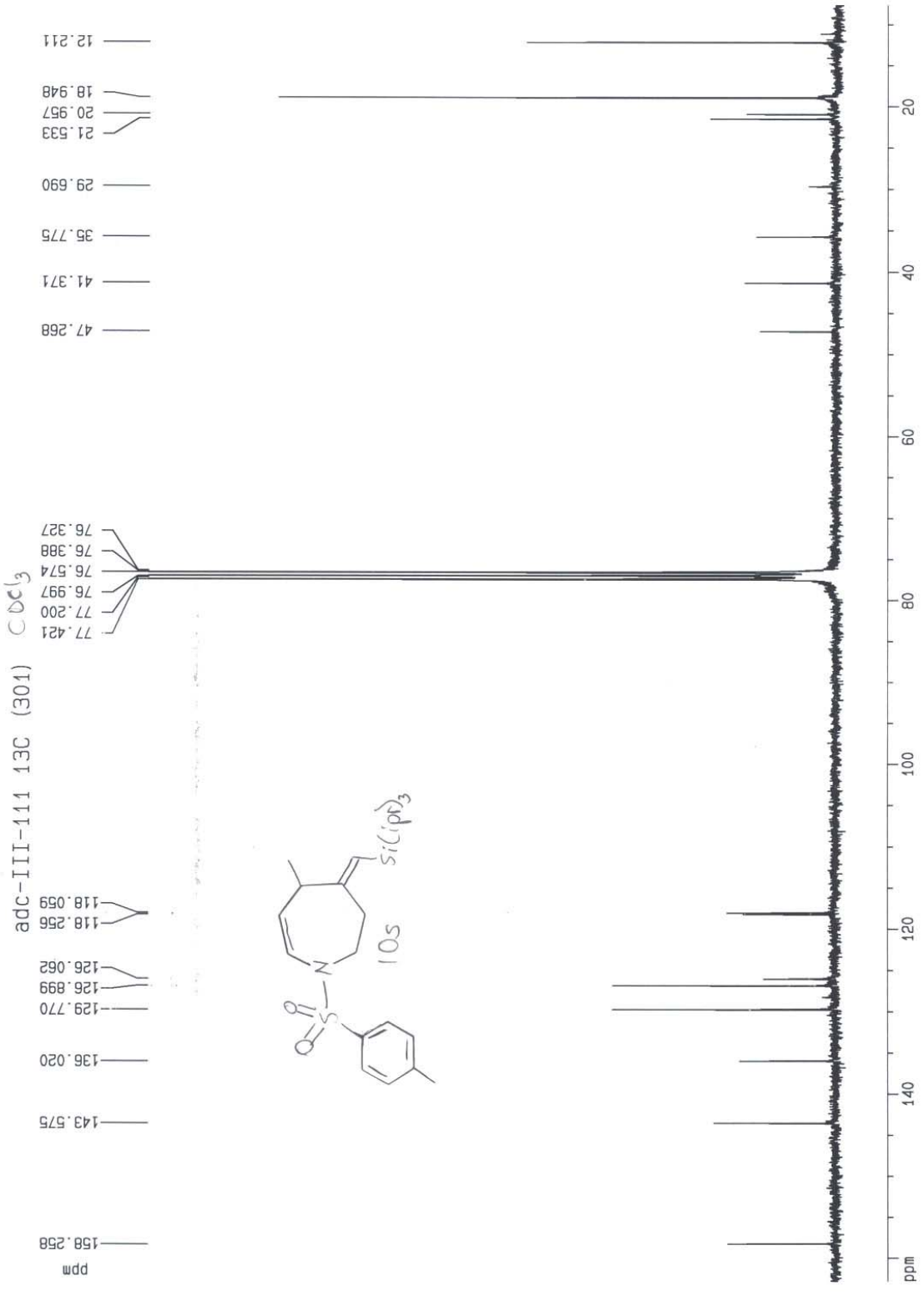
adc-III-138 60 deg. (301) DMSO-d6
ppm
5.24503
1.40191
1.21269
1.09754
1.06363
Integral
1.000
0.872
2.281
0.267
1.098
1.021
DMSO
13.067
9.712
10p
tbu
Boc
N

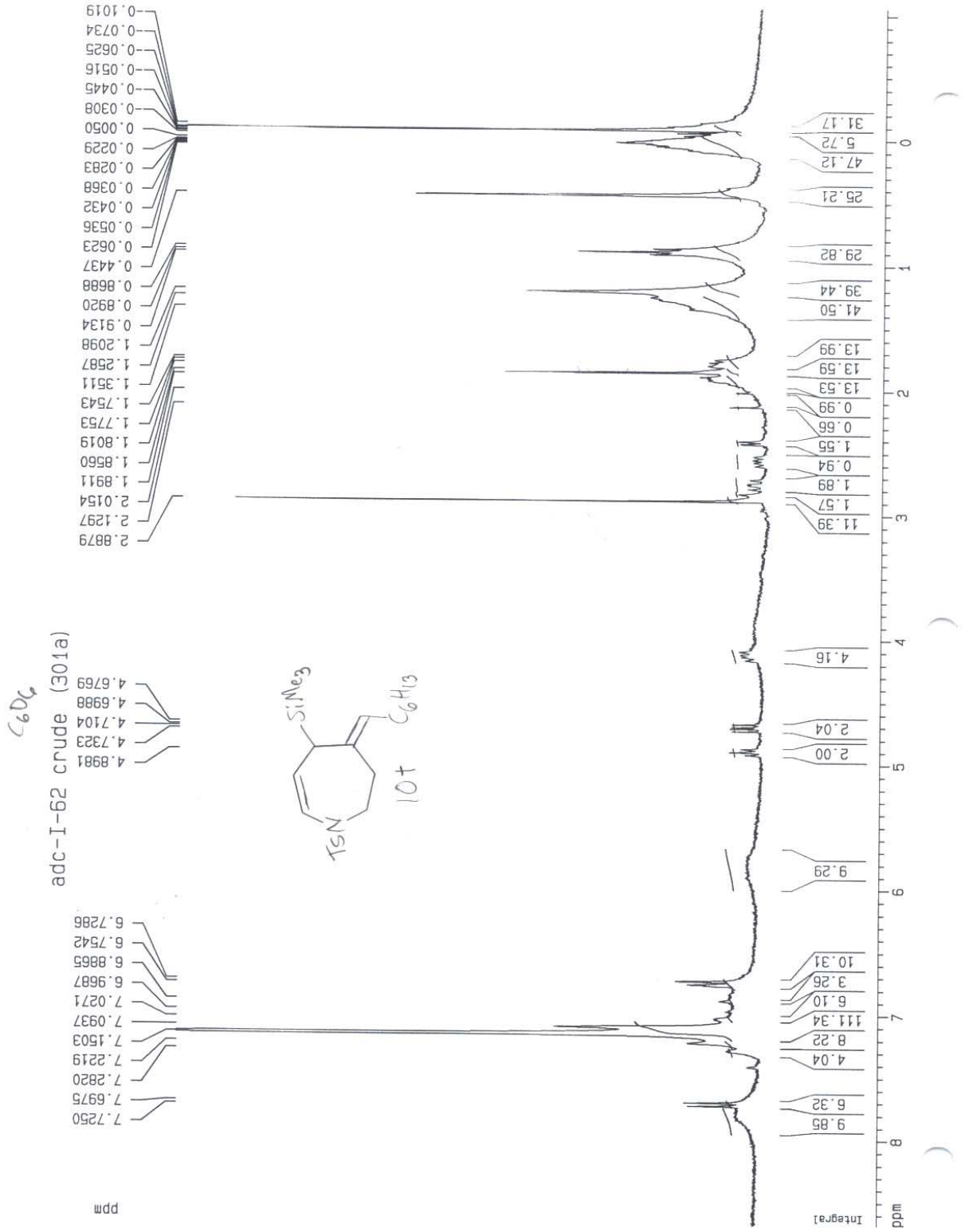

adc-I-138 13C 60 deg. (301)
DMSO-d_6
10p
ppm
152.026
138.657
134.650
127.659
127.305
126.929
118.070
79.365
77.728
68.988
45.003
42.179
41.756
41.267
40.337
40.059
39.781
39.502
39.224
38.946
38.668
34.429
31.045
30.874
30.834
28.422
28.193
27.945
27.634
20.052
ppm

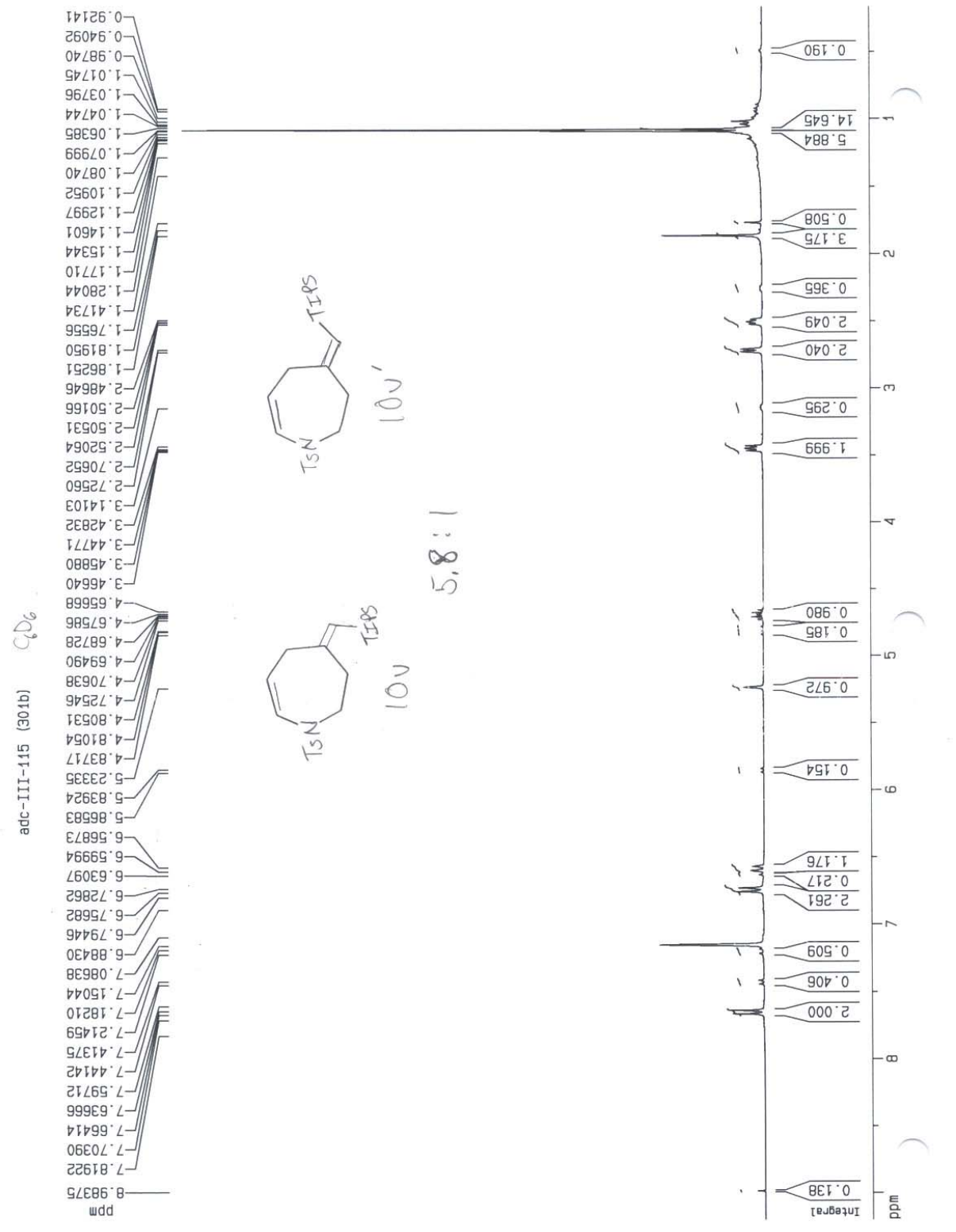

adc-III-116 (301b) C6D6
ppm
Integral
TIPS
TsN
10r

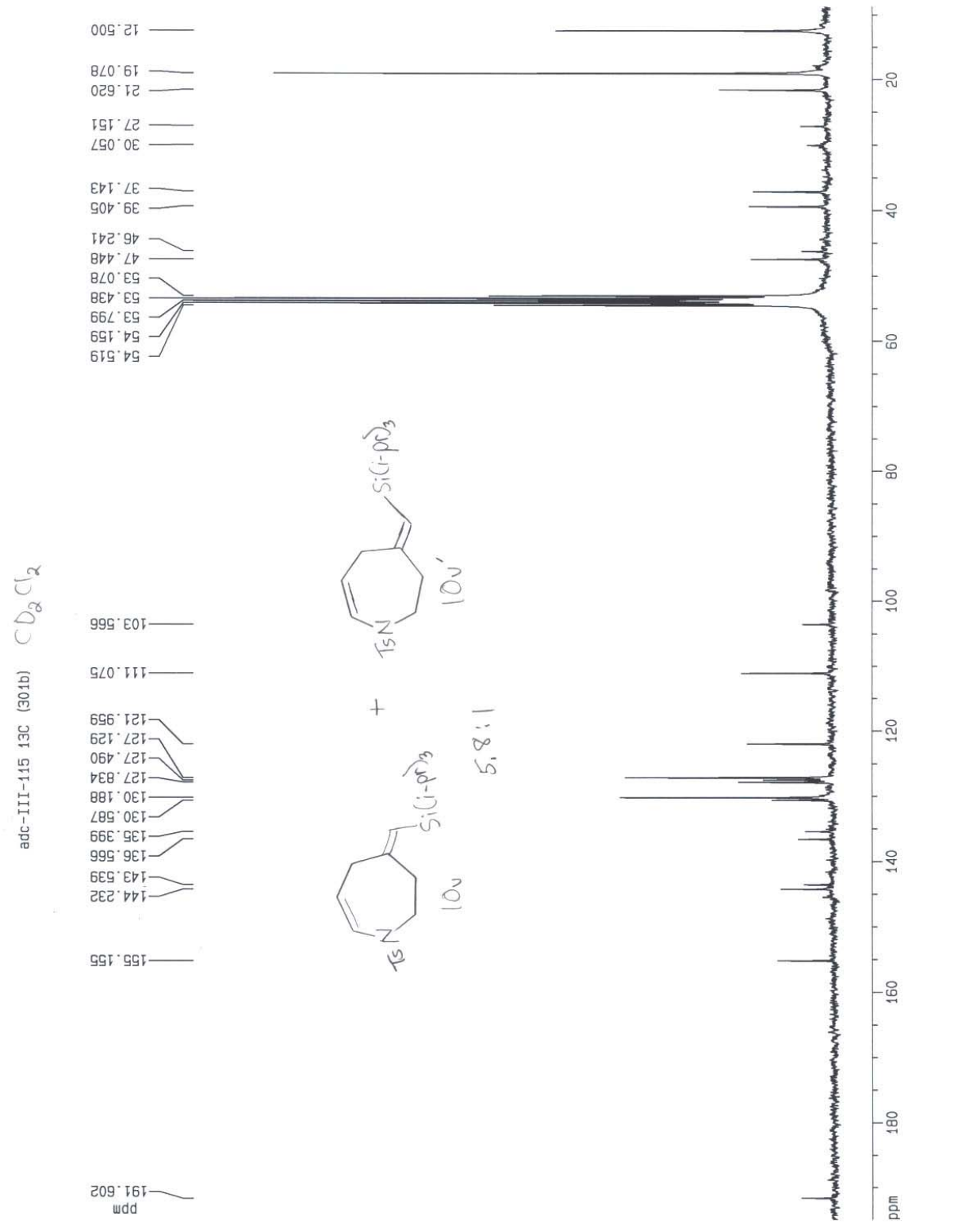

adc-III-116 (301b)
CD2Cl2
TIPS
10r
ppm
157.355
144.329
143.342
136.412
130.235
129.091
128.586
127.918
127.175
126.549
125.012
112.047
56.547
54.521
54.161
53.801
53.440
53.080
46.988
34.888
30.054
21.640
19.127
18.995
12.573
ppm
20
40
60
80
100
120
140


adc-III-111 (301b)
ppm
Integral
TsN
TIPS
10s


adc-III-111 13C (301) CDCl3
77.421
77.200
76.997
76.574
76.388
76.327
158.258
143.575
136.020
129.770
126.899
126.062
118.256
118.059
47.268
41.371
35.775
29.690
21.533
20.957
18.948
12.211
ppm
20
40
60
80
100
120
140
ppm
Si(ipr)3
10s


adc-I-62 crude (301a)
C6D6
SiMe3
C6H13
TsN
10t
ppm
Integral


adc-III-115 (301b)
C6D6
ppm
Integral
TIPS
TsN
10v'
10v
5.8:1


adc-III-115 13C (301b) CD_2Cl_2
ppm
191.602
155.155
144.232
143.539
136.566
135.399
130.587
130.188
127.834
127.490
127.129
121.959
111.075
103.566
54.519
54.159
53.799
53.438
53.078
47.448
46.241
39.405
37.143
30.057
27.151
21.620
19.078
12.500
20
40
60
80
100
120
140
160
180
ppm
Si(i-Pr)3
TsN
10v
+
Si(i-Pr)3
TsN
10v'
5.8:1

ppm
7.79107
7.76338
7.73609
7.71906
7.69145
7.47474
7.45923
7.44982
7.33233
7.31133
7.28445
7.26979
6.45233
6.42155
5.22798
5.22334
5.16752
5.13485
5.13051
5.04780
5.01793
4.67306
4.51267
4.50806
3.82801
3.80656
3.78436
3.68141
3.66232
3.64190
3.23397
3.21006
2.84852
2.83040
2.49178
2.47201
2.45153
2.43382
2.31957
2.20917
2.17991
2.05570
1.87233
1.73750
1.71574
1.65320
1.64915
1.63175
1.56079
1.54454
1.43534
1.42534
1.30181
1.26244
1.13396
1.09025
1.07963
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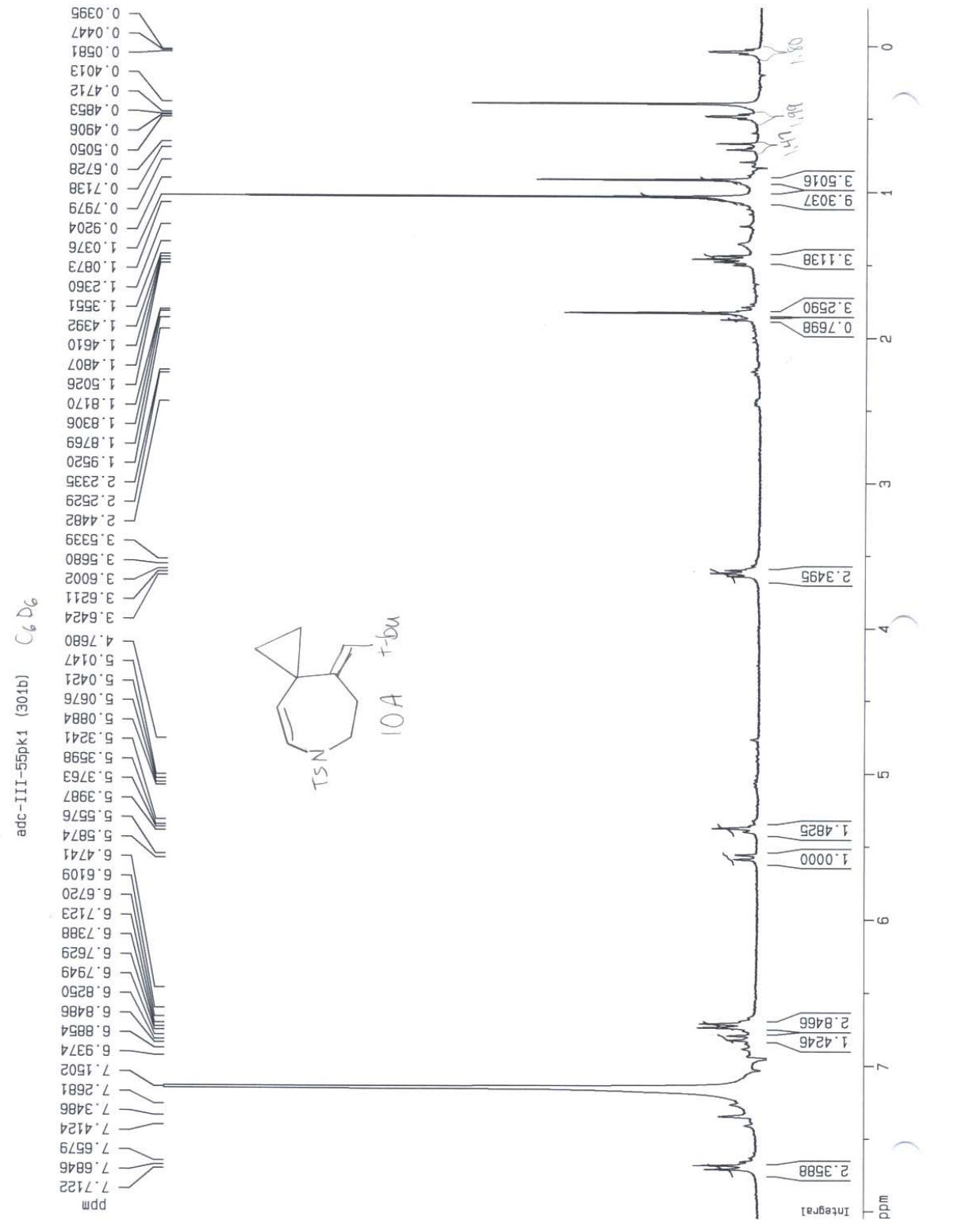
0.77745
Ts N
10 w
ppm
0
1
2
3
4
5
6
7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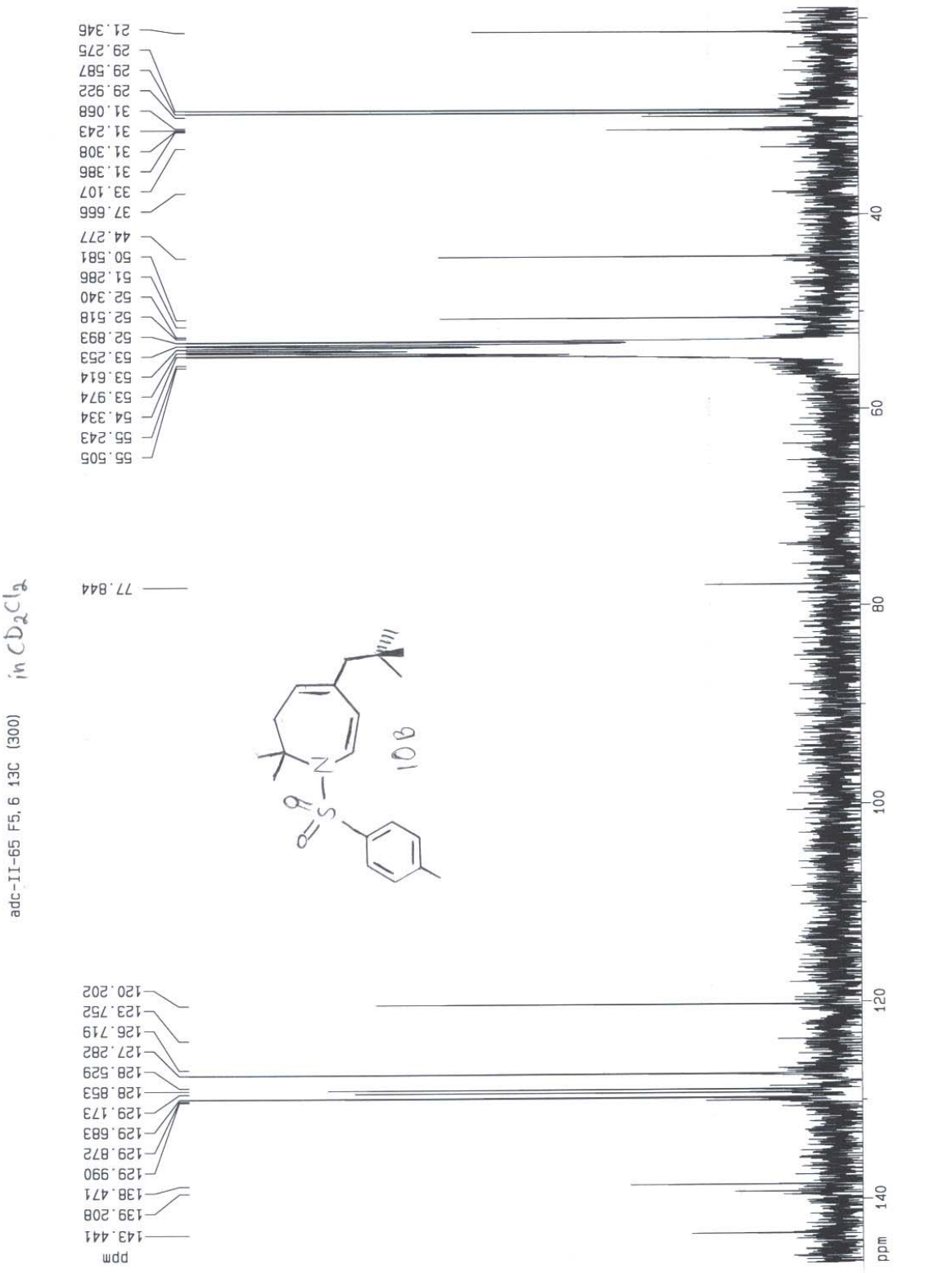
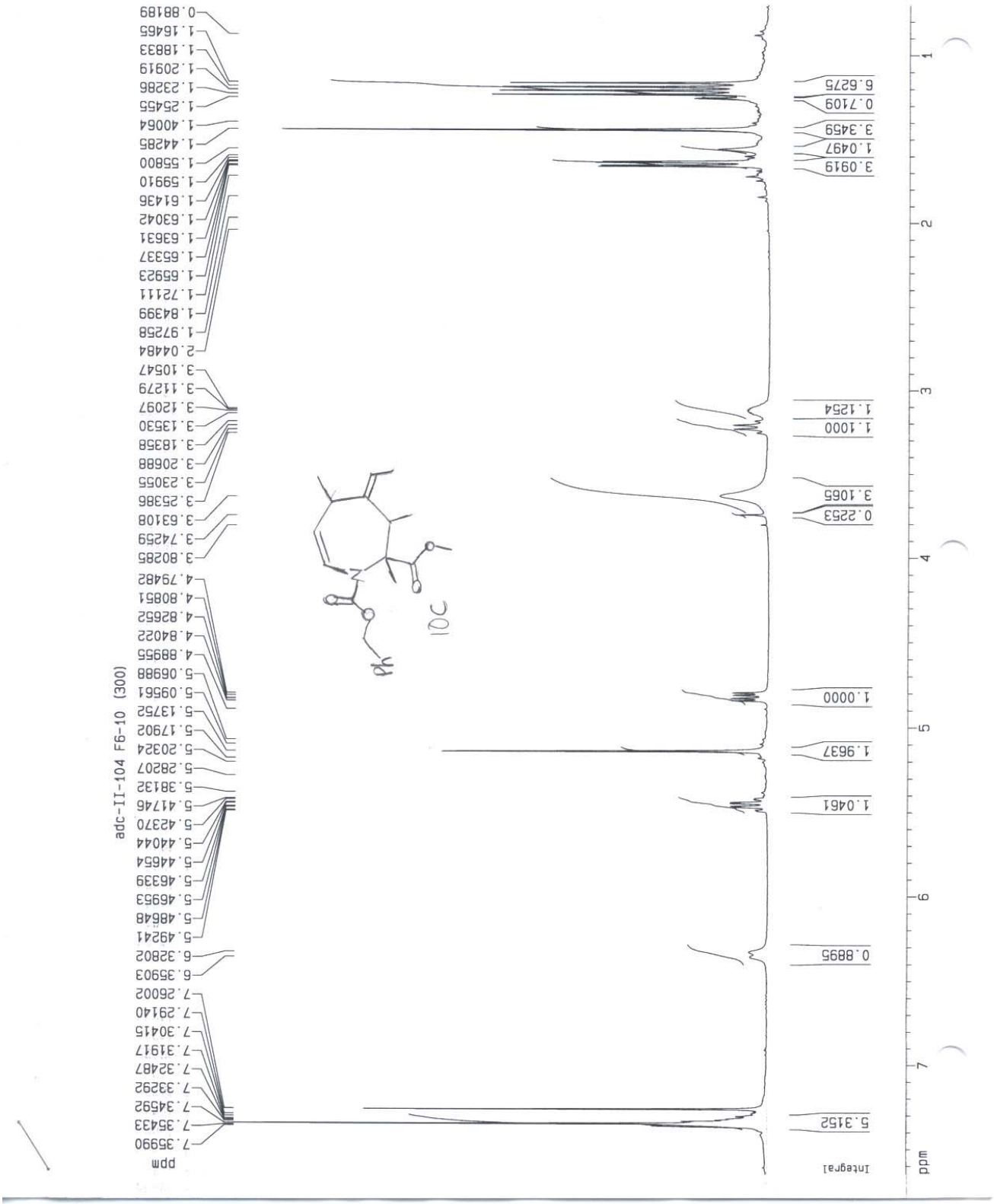
C6 D6
TsN
t-Bu
10A
ppm
Integral


adc-II-65 F5, 6 13C (300) in CD_2Cl_2
143.441
139.208
138.471
129.990
129.872
129.683
129.173
128.853
128.529
127.282
126.719
123.752
120.202
77.844
55.505
54.334
53.974
53.614
53.253
52.893
52.518
52.340
51.286
50.581
44.277
37.666
33.107
31.386
31.308
31.243
31.068
29.922
29.587
29.275
21.346
ppm
140
120
100
80
60
40
10B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ppm
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7.35433
7.34592
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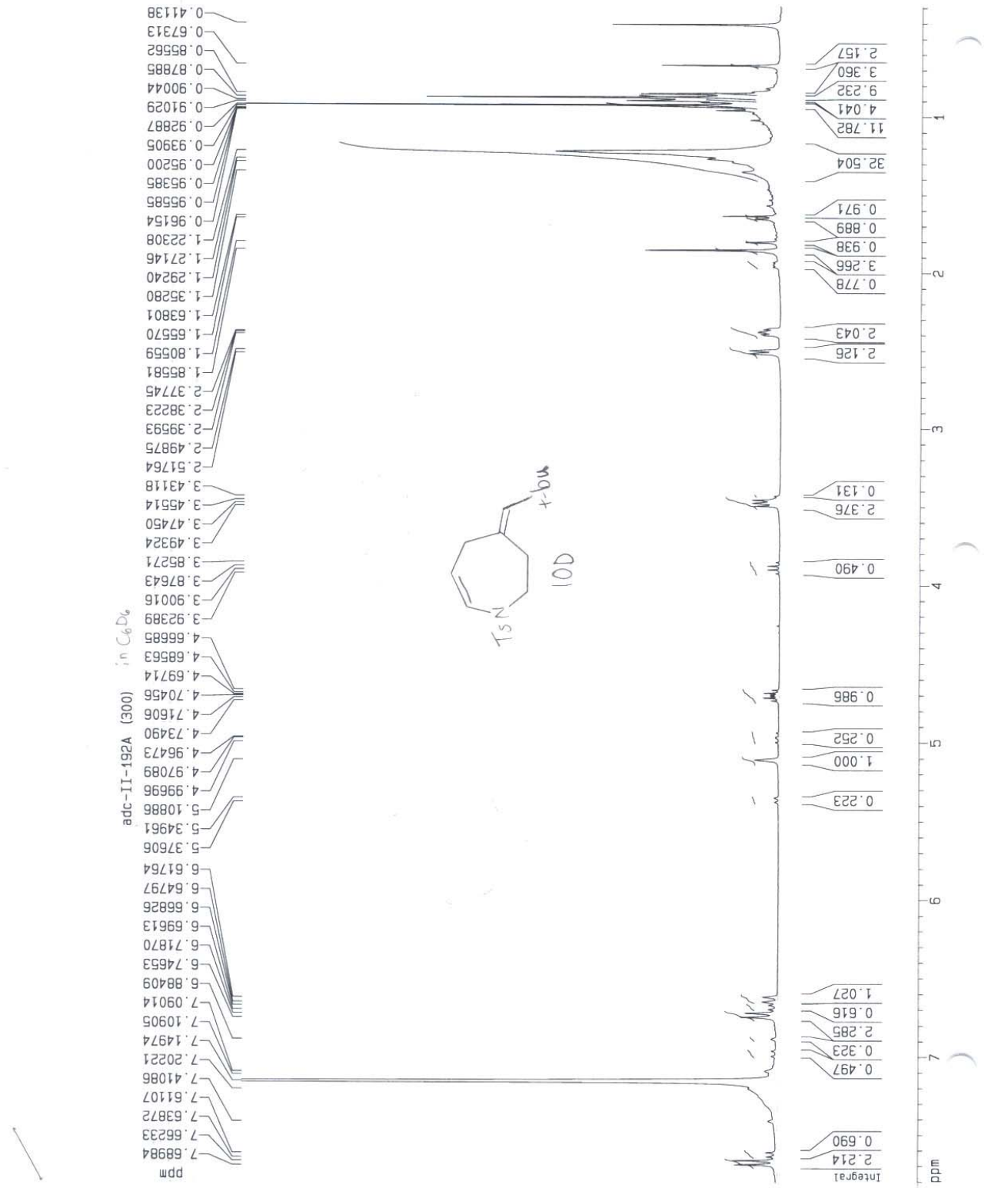
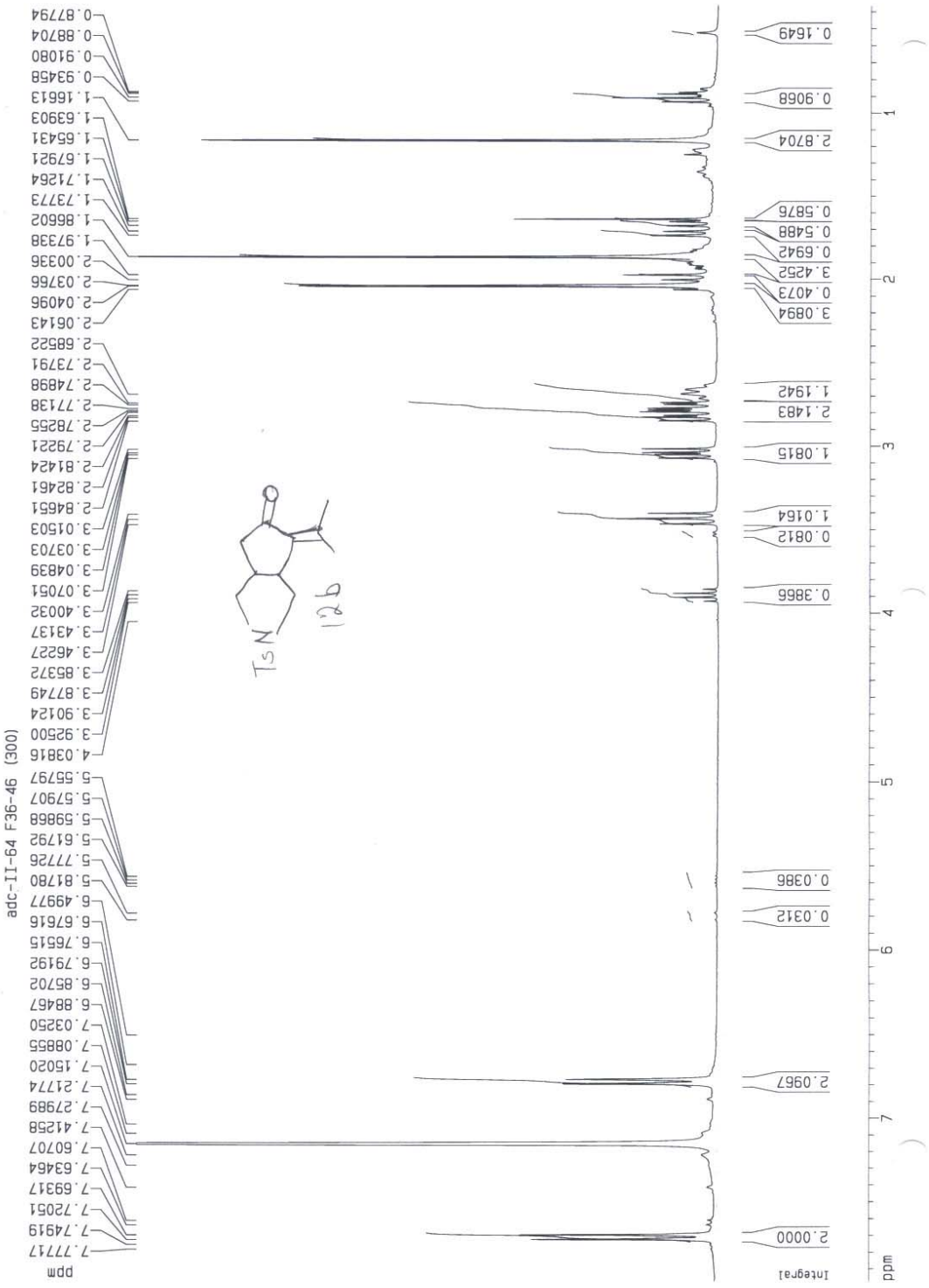
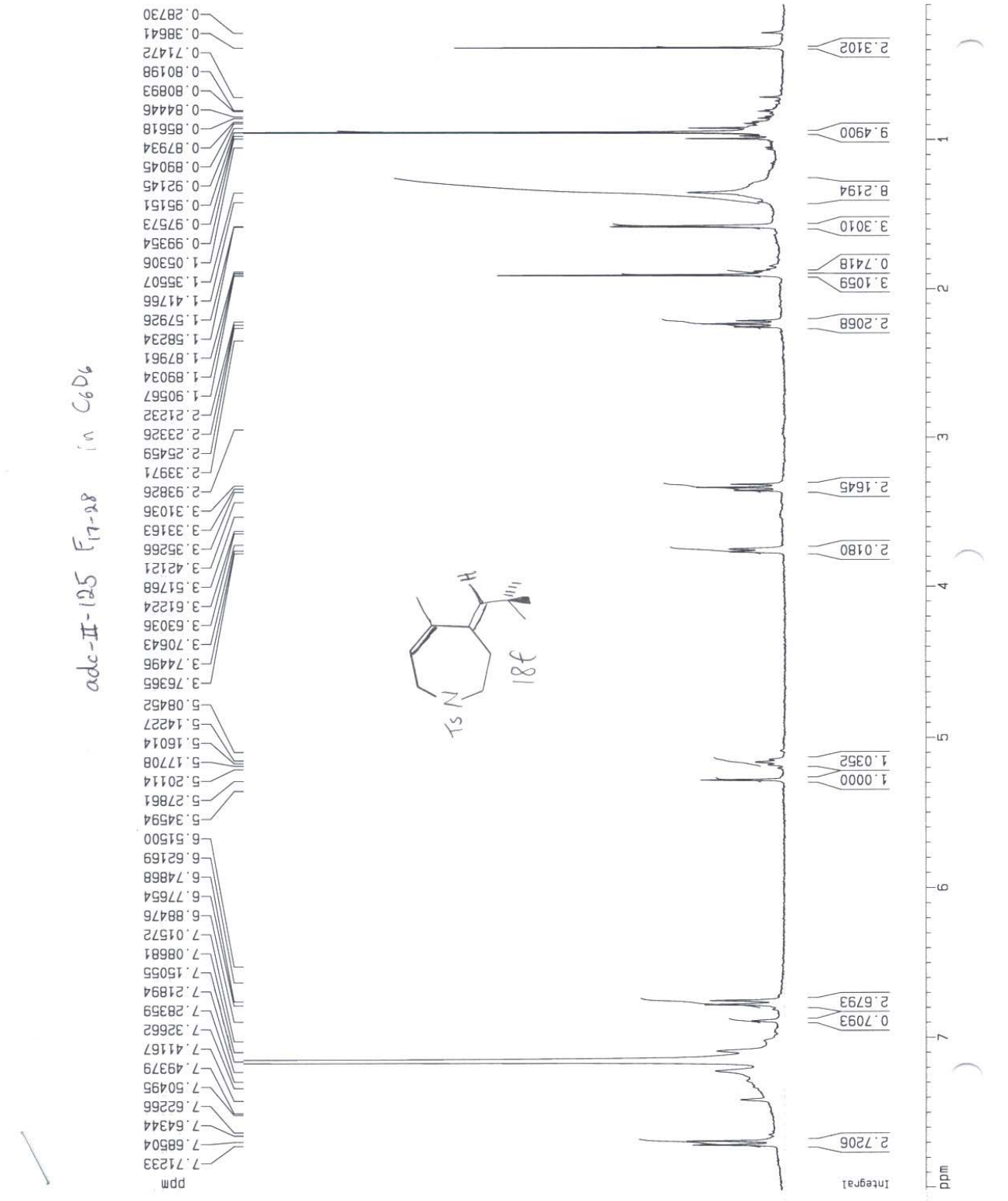
7.31917
7.30415
7.29140
7.26002
6.35903
6.32802
5.49241
5.48648
5.46953
5.46339
5.44654
5.44044
5.42370
5.41746
5.38132
5.28207
5.20324
5.17902
5.13752
5.09561
5.06988
4.88955
4.84022
4.82652
4.80851
4.79482
3.80285
3.74259
3.63108
3.53864
3.23055
3.20688
3.18358
3.13530
3.12097
3.11279
3.10547
2.04484
1.97258
1.84399
1.72111
1.65923
1.65337
1.63631
1.63042
1.61436
1.59910
1.55800
1.44285
1.40064
1.25455
1.23286
1.20919
1.18833
1.16465
0.88189
Integral
5.3152
0.8895
1.0461
1.9637
1.0000
0.2253
3.1065
1.1000
1.1254
3.0919
1.0497
3.3459
0.7109
6.6275
ppm
1
2
3
4
5
6
7
10C

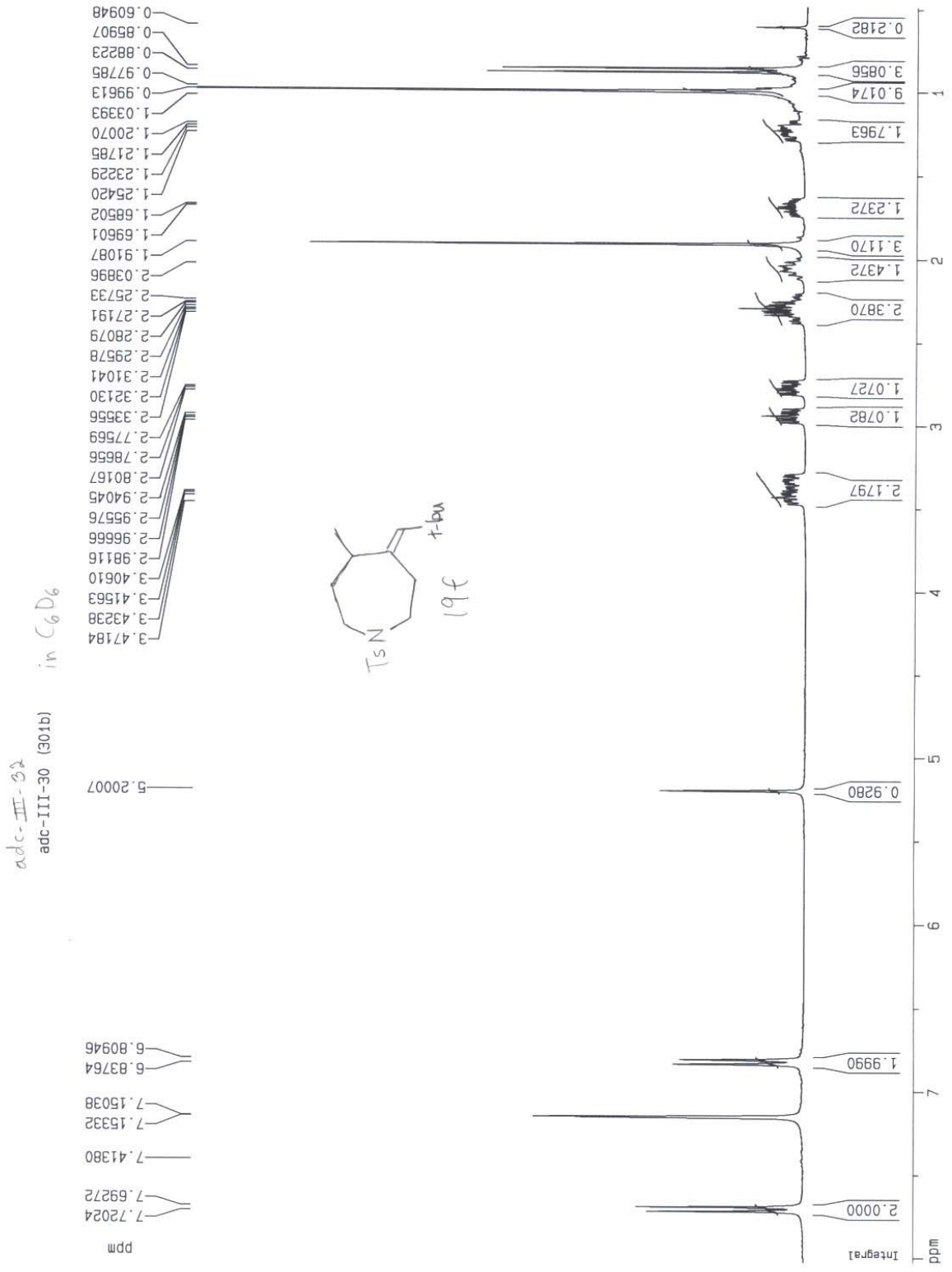

adc-II-192A (300) in C6D6
ppm
Integral
10D


adc-II-64 F36-46 (300)
ppm
Integral
TsN
12b

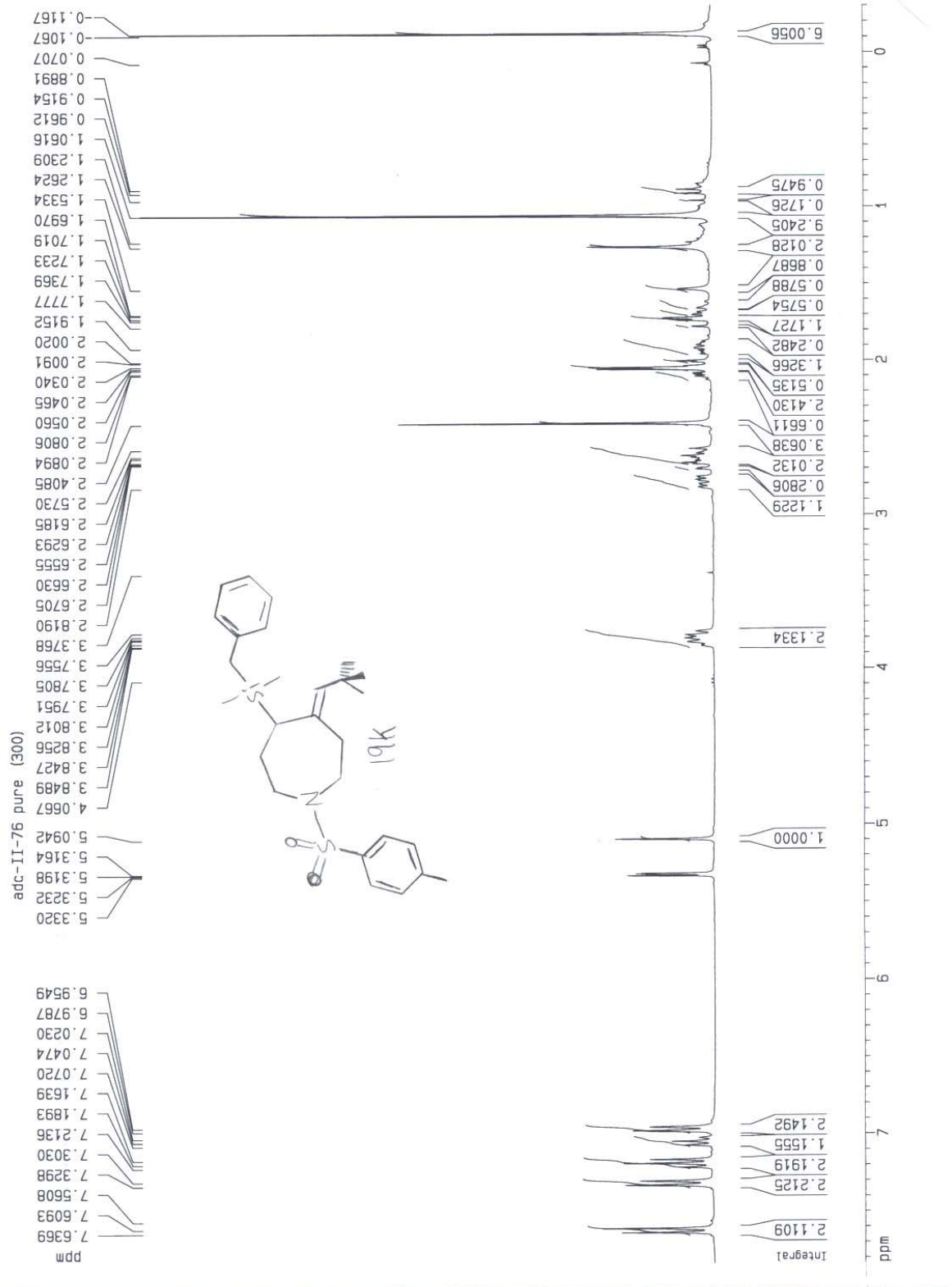
adc-II-64 F36-46 13C (301b)
205.034
151.040
143.859
133.072
132.313
129.732
127.795
77.420
76.997
76.574
53.979
53.372
44.382
44.182
35.218
24.793
21.559
20.608
ppm
40
60
80
100
120
140
160
180
200
ppm
12g

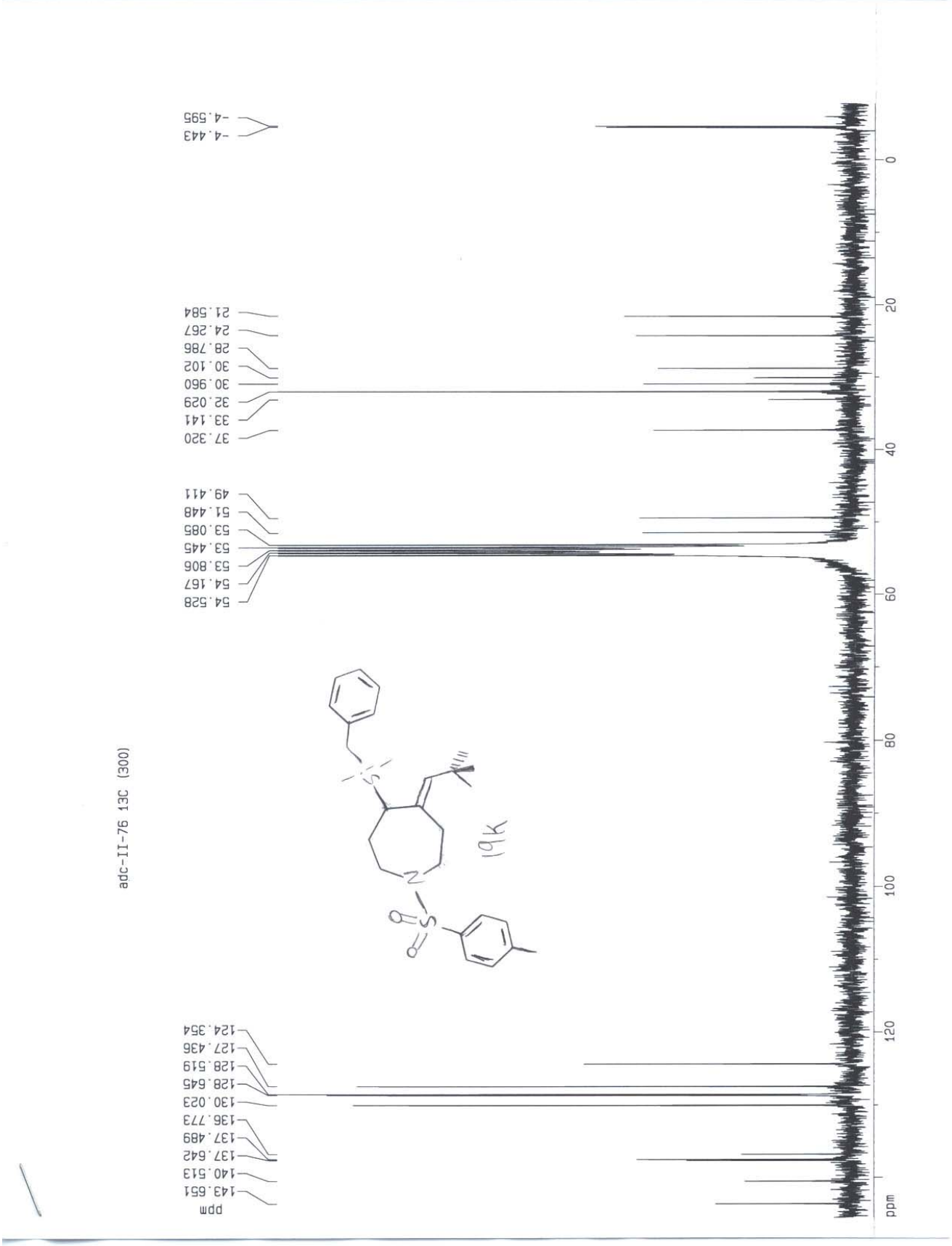

adc-II-125 F17-28 in C6D6
18f
Ts
N
H
ppm
Integral
7.71233
7.68504
7.64344
7.62266
7.50495
7.49379
7.41167
7.32662
7.28359
7.21894
7.15055
7.08681
7.01572
6.88476
6.77654
6.74868
6.62169
6.51500
5.34594
5.27861
5.20114
5.17708
5.16014
5.14227
5.08452
3.76365
3.74496
3.70643
3.63036
3.61224
3.51768
3.42121
3.35266
3.33163
3.31036
2.93826
2.33971
2.25459
2.23326
2.21232
1.90567
1.89034
1.87961
1.58234
1.57926
1.41766
1.35507
1.05306
0.99354
0.97573
0.95151
0.92145
0.89045
0.87934
0.85618
0.84446
0.80893
0.80198
0.71472
0.38641
0.28730
2.7206
0.7093
2.6793
1.0000
1.0352
2.1645
2.0180
2.2068
3.1059
0.7418
3.3010
8.2194
9.4900
2.3102

adc-II-192B (300)
ppm
Integral
18K
t-bu
Ts
N


adc-III-32
adc-III-30 (301b)
in C6D6
19f
Ts
N
t-Bu
ppm
Integral
0.2182
3.0856
9.0174
1.7963
1.2372
3.1170
1.4372
2.3870
1.0727
1.0782
2.1797
0.9280
1.9990
2.0000
7.72024
7.69272
7.41380
7.15332
7.15038
6.83764
6.80946
5.20007
3.47184
3.43238
3.41563
3.40610
2.98116
2.96666
2.95576
2.94045
2.80167
2.78656
2.77569
2.33556
2.32130
2.31041
2.29578
2.28079
2.27191
2.25733
2.03896
1.91087
1.69601
1.68502
1.25420
1.23229
1.21785
1.20070
1.03393
0.99613
0.97785
0.88223
0.85907
0.60948

adc-III-32 (300)
CD_2Cl_2
19f
ppm
143.551
140.333
136.938
136.896
136.833
129.988
129.883
127.441
127.411
127.368
54.518
54.158
53.798
53.438
49.697
47.554
41.490
41.453
41.413
36.928
32.731
31.768
31.736
31.694
29.795
21.703
21.671
21.580
140
120
100
80
60
40


adc-II-76 pure (300)
ppm
Integral
19k


adc-II-76 13C (300)
19K
ppm
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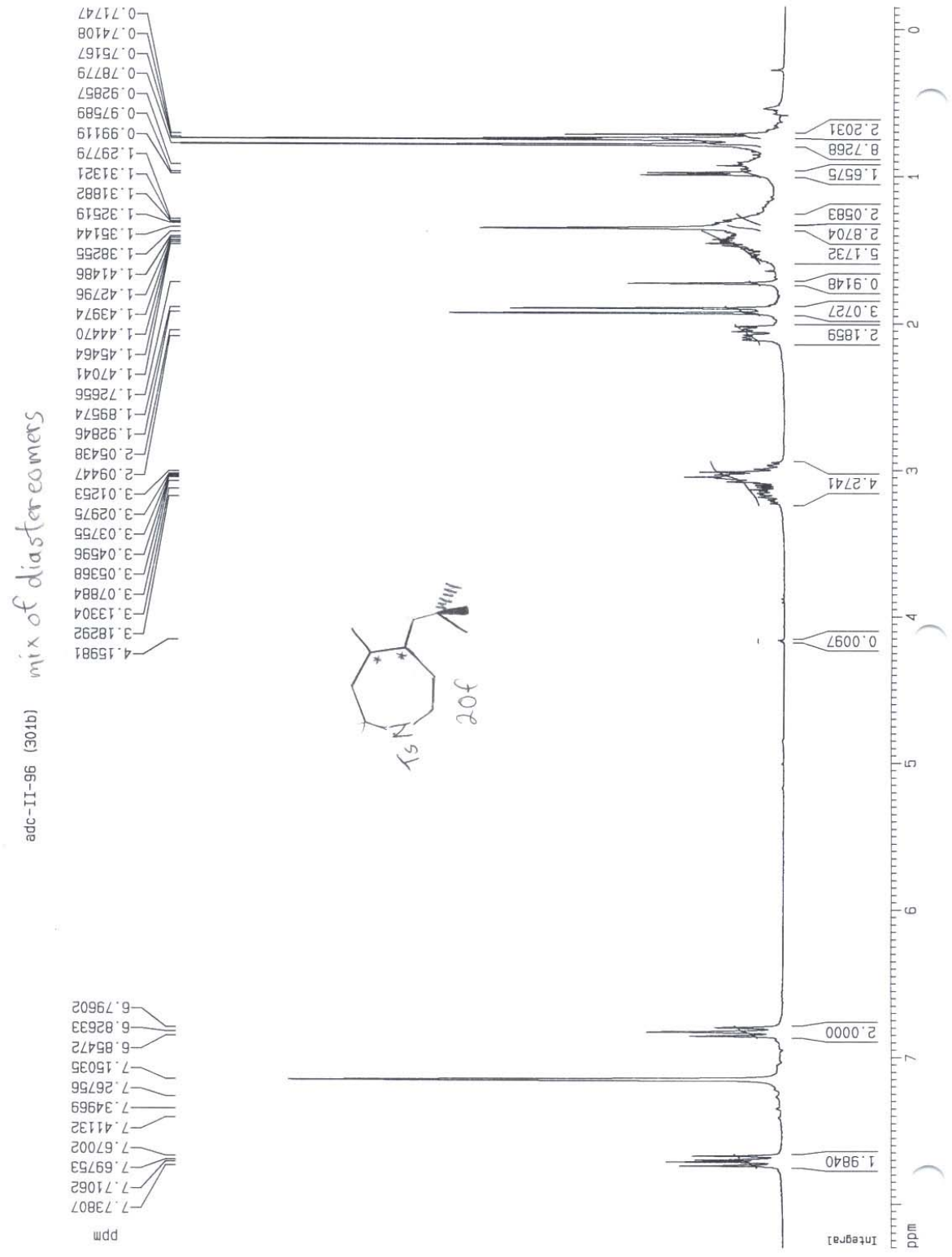
140.513
137.642
137.489
136.773
130.023
128.645
128.519
127.436
124.354
54.528
54.167
53.806
53.445
53.085
51.448
49.411
37.320
33.141
32.029
30.960
30.102
28.786
24.267
21.584
-4.443
-4.595


adc-II-96 (301b)
mix of diastereomers
ppm
Integral
1.9840
2.0000
0.0097
4.2741
2.1859
3.0727
0.9148
5.1732
2.8704
2.0583
1.6575
8.7268
2.2031
Ts
N
2of

adc-II-96 pk2 (301a) CDCl3
ppm
7.63680
7.60940
7.30604
7.27884
7.26070
3.11715
3.10616
3.09841
3.09024
3.08238
3.07180
2.41773
2.35432
2.33203
2.32038
2.29732
1.93177
1.62452
1.05039
1.00553
0.92473
0.90326
0.84516
Integral
2.0000
2.1487
3.8256
2.8089
3.8785
1.6770
2.5058
8.1845
ppm
1
2
3
4
5
6
7
15N
21f

adc-II-96 pk2 (301a) CDCl3
21f
ppm
143.057
135.059
134.173
134.086
129.579
127.282
77.422
76.998
76.575
48.480
47.339
46.632
36.643
36.155
33.639
30.167
22.565
21.497
20
40
60
80
100
120
140

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